National Institute for Health and Care Excellence

Consultation

Renal and Ureteric Stones: assessment and management

Pain management

NICE guideline

Intervention evidence review

July 2018

Consultation

This evidence review was developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Contents

1

1 Pain management

1.1 Review question: What is the clinical and cost-effectiveness of drugs in managing acute pain in people with symptomatic renal or ureteric stones?

1.2 Introduction

Pain relief is the first step in managing people with acute renal colic. Whilst NSAIDs are generally accepted as the first line treatment by health professionals, there is uncertainty in the efficacy of other treatment options such as muscle relaxants, and there are concerns surrounding the use of opioids, because of their significant side effects, and because of the potential risks of misuse of a controlled drug.

There are variations in practice with the method of administering pain relief, which has significant resource implications, particularly the use of intravenous or intramuscular methods requiring hospital attendance as well as variation in practice due to the patient's age . An intramuscular route is rarely used in children due to the distress this may cause, and an intravenous route is often preferred in young children who won't swallow medication on demand. There is currently a lack of guidance on an evidence-based step-by-step approach to pain relief for patients presenting with renal/ureteric colic.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People (adults, children and young people) with symptomatic renal or ureteric stones
Interventions	• NSAIDs • Opioids/Opiates • Paracetamol • Smooth muscle relaxant/antispasmodic
Comparisons	Compared to: • Each other (class comparison only; no within class comparison) • No treatment • Placebo

Outcomes	Critical outcomes:
	• Quality of life
	• Pain intensity (visual analogue scale, verbal ratings, descriptive scales, time to pain relief, need to rescue medication)
	• Adverse events
	  ○ Major: GI haemorrhage, acute kidney injury, respiratory depression, mortality, and cardiac event.
	  ○ Minor: GI disturbance without bleeding (vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention)
	Important outcomes:
	• Length of stay
	• Use of healthcare services

Study design	RCTs and systematic reviews of RCTs If no RCT evidence is available, search for non-randomised studies for children

1.4 Clinical evidence

1.4.1 Included studies

Thirty-eight studies were included in the review;[3, 4, 6, 9, 11, 15, 22, 27, 28, 31, 42, 48, 52, 53, 55, 61, 69, 70, 73, 76, 79, 81, 89, 92, 97, 98, 101, 112, 114, 118, 120, 121, 124, 127, 128, 131, 134, 142] these are summarised in Table 2 below. Twenty-two studies compared NSAIDS to opioids [4, 6, 9, 25, 27, 28, 48, 52, 53, 55, 69, 70, 79, 89, 98, 101, 112, 114, 118, 121, 131, 142], 3 studies compared NSAIDs to muscle relaxants [3, 31, 124],5 studies compared NSAIDs to paracetamol [6, 22, 61, 92, 101], 6 studies compared opioids to paracetamol [6, 11, 15, 81, 101, 120], 4 studies compared NSAIDs to placebo [3, 73, 76, 134], 2 studies compared opioid to muscle relaxants [97, 128], 1 study compared opioid to placebo [15], 1 study compared paracetamol to placebo [15], 1 study compared muscle relaxants to placebo [3] and 4 studies compared combinations of pain relief medications. [53, 92, 124, 127] Evidence from these studies is summarised in the clinical evidence summaries below in Table 3 to Table 11.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

Two Cochrane systematic reviews were identified, however both were excluded. Both were excluded due to deviation from the review protocol to include drugs that are excluded in this review.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Heterogeneity

For the comparison of NSAID versus opioid/opiate, there was substantial heterogeneity between the studies when they were meta-analysed for the outcomes of pain intensity, partial pain relief, complete pain relief, need for rescue medication, reduction in pain by 50% and minor adverse events including vomiting, nausea and dizziness. For the comparison of NSAID versus paracetamol there was substantial heterogeneity between the studies when they were meta-analysed for the outcome pain intensity. For the comparison of NSAID versus muscle relaxant/antispasmodic, there was substantial heterogeneity between the studies when they were meta-analysed for the outcome of need for rescue medication. For the comparison of NSAID versus placebo, there was substantial heterogeneity between the studies when they were meta-analysed for the outcomes of pain intensity and complete pain relief. For the comparison of opioid/opiate versus paracetamol, there was substantial heterogeneity between the studies when they were meta-analysed for the outcome of pain intensity. Where pre-specified subgroup analyses (see Appendix A:) were either unable to be performed, or did not explain the heterogeneity, a random effects meta-analysis was applied to these outcomes, and the evidence was downgraded for inconsistency in GRADE.

1.4.4 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Aganovic 2012[3]	Intervention (n=100): NSAID (diclofenac 75mg, intramuscularly) Comparison (n=100): muscle relaxant (butylscopolamin amp, intravenously) Comparison (n=100): placebo (distilled water, intravenously) In case the pain was not relieved, within 30 minutes an additional dose of the drug was administered or Tramal amp. 50 mg, and if the patient did not respond to either drug, a more invasive urological treatment was applied	n=300 People with renal colic Age not reported Gender not reported Bosnia and Herzegovina	Complete pain relief (30 minutes): number of participants cured or not cured (not defined) Minor adverse events (30 minutes): not specified	Unclear if diagnosis of renal colic is confirmed. Unclear if participants had any previous treatment
Al 2017[6]	Intervention (n=100): NSAID (dexketoprofen trometamol 50mg, intravenously) Comparison (n=100): paracetamol (10mg intravenously) Comparison (n=100): opioid (fentanyl 2µg/kg intravenously)	n=300 People with confirmed renal colic Age: mean 42.2 years (no SD) Male to female ratio 216:84 Turkey	Need for rescue medication (30 minutes) Partial pain relief pain (at discharge) Complete pain relief pain (at discharge) Minor adverse events (time-point not reported): vomiting, dizziness	Pain intensity outcomes reported after rescue medication given
al-Sahlawi 1996[4]	Intervention (n=50): NSAID (indomethacin, 100mg, intravenous)	n=100 People with acute renal colic Age >20 years	Pain relief (30 minutes): number of people with partial or complete relief	

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison (n=50): Opioid (pethidine 100mg, intravenous) A single dose of pethidine 100mg was given 30 minutes after treatment if pain had not been relieved at all	Male to female ratio 71:29 Kuwait	Need for rescue medication (30 minutes) Minor adverse events (time-point not reported): dizziness	
Ay 2014[9]	Intervention (n=26): NSAIDS (dexketoprofen trometamol, ampules of 50mg per 2ml, intravenous) Comparison (n=26): opioid (meperidine hydrochloride ampules of 100mg per 2ml, intravenous) A 50mg additional dose of meperidine was administered to patients with ongoing pain at 30 minutes	n=52 People with renal colic Aged 18-70 years Gender not reported Turkey	Pain (30 minutes): numerical rating scale (NRS), 0-10, high score is poor outcome Need for rescue medication (30 minutes) Minor adverse events (30 minutes): nausea/ vomiting	Unclear if participants had any previous treatment
Azizkhani 2013[11]	Intervention (n=62): Paracetamol (acetaminophen, 1g, intravenous) Comparison (n=62): Opioid (morphine 10mg, intravenous)	n=124 People with renal colic pain Age, mean (SD): paracetamol group 38.40 (11.60); opioid group 39.73 (11.62) Male to female ratio 68:32 Iran	Pain (30 minutes): VAS, 0-10, high score is poor outcome Minor adverse events (time-point not reported): dizziness, vomiting, arterial hypotension	
Bektas 2009[15]	Intervention (n=55): Paracetamol (1g in 100ml normal saline solution, intravenous) Comparison (n=55): Opioid (morphine, 0.1mg/kg in 100ml normal saline solution, intravenous)	n=165 People with acute flank pain and a diagnosis of suspected acute renal colic Age, years (mean, SD): paracetamol group 35 (10); morphine group 39	Pain (30 minutes): VAS, 0-100, high score is poor outcome Need for rescue medication (30 minutes)	

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison 2 (n=55): Placebo (100ml normal saline solution, intravenous) Those who had inadequate pain relief at 30 minutes received rescue fentanyl 0.75µg/kg intravenously	(11); placebo group 36 (10) Male to female ratio 90:56 Turkey	Major adverse events (time-point not reported): respiratory depression Minor adverse events (time-point not reported): nausea and vomiting, urinary retention	
Cenker 2017[22]	Intervention (n=100): NSAID (ibuprofen 800mg in 100ml normal saline, intravenous) Comparison (n=100): paracetamol (1g in 100ml normal saline, intravenous)	n=200 People with flank pain and confirmed renal colic Age, years (mean, SD): 36 (9) Male to female ratio 129:71 Turkey	Pain (30 minutes): VAS, 0-100, high score is poor outcome Need for rescue medication (30 minutes) Minor adverse events (time-point not reported): vomiting, epigastric pain, dizziness	
Collaborative group of the Spanish Society of Clinical Pharmacology 1991[42]	Intervention (n=116): NSAID (diclofenac sodium, 75mg, intramuscular) Comparison (n=118): Opioid (pethidine, 100mg, intramuscular) Rescue medication consisted of a single dose of pethidine 100mg, given 30 minutes after the treatment	n=234 People with acute renal colic Age, mean (SD): NSAID group 40.7 years (13.9); opioid group 41.4 years (12.7) Male to female ratio 124:110 13 hospitals in Spain	Need for rescue medication (30 minutes): defined as pain not decreasing by 25% Minor adverse events (60 minutes): dizziness, local pain, nausea, urinary retention, vomiting	40% had received pharmacological treatment before resorting to emergency service
Cordell 1996[27]	Intervention (n=51): NSAID (intravenous ketorolac, 60mg). Placebo (normal saline solution) was	n=102 People with renal colic and pain of	Pain (30 minutes): VAS, 0-100, high score is poor outcome	Participants were allowed one 200mg rectal dose of trimethobenaza mide

Study	Intervention and comparison	Population	Outcomes	Comments
	given to maintain blinding Comparison (n=51): opioid (intravenous meperidine 50mg). Placebo (normal saline solution) was given to maintain blinding	moderate or severe intensity Age, mean (SD): NSAID group 38.8 (10.2); opioid group 42.0 (11.24) Male to female ratio 58:13 United States	Need for rescue medication (30 minutes) Minor adverse events (2 hours): dizziness, sleepiness	hydrochloride for nausea or vomiting
Curry 1995[28]	Intervention (n=17): NSAID (tenoxicam, 40mg, intravenously) Comparison (n=24): Opioid (pethidine, 75mg, intravenously) If analgesia was inadequate after 30 minutes, a dose of pethidine 50mg was given	n=41 People with pain consistent with renal colic Age, mean (range): 40 years (18-74) Male to female ratio 31:10 New Zealand	Need for rescue medication (30 minutes) Minor adverse events (time-point not reported): not reported	Patients had intravenous metoclopramide 10mg before treatment Unclear if diagnosis of renal colic is confirmed. Unclear if participants had any previous treatment
Dawood Al-Waili 1998[31]	Intervention (n=25): NSAID (tenoxicam, 20mg, intravenously) Comparison (n=22): muscle relaxant/ antispasmodic (buscopan compositum, 20mg, intravenously) If there was no satisfactory response after the first hour, then 100mg was given	n=47 People with acute renal colic Age, mean (range): 36 years (20-45) Male to female ratio 40:7 United Arab Emirates	Need for rescue medication (60 minutes) Minor adverse events (time-point not reported): dry mouth, drowsiness	
Hetherington 1986[48]	Intervention (n=30): NSAID (diclofenac sodium 75mg, intramuscularly) Comparison (n=28): opioid (pethidine, 100mg, intramuscularly) A second injection of the same drug was	n=58 People with severe pain though to have acute renal colic Age, mean (range): 46 (19-85) Male to female ratio 41:17	Need for rescue medication (30 minutes) Minor adverse events (time-point not reported): not specified	Unclear if diagnosis of renal colic is confirmed.

Study	Intervention and comparison	Population	Outcomes	Comments
	offered after 30 minutes if the first had not been successful or if pain returned	UK		
Hosseini 2015[52]	Intervention (n=266): NSAID (diclofenac 100mg, rectal) Comparison (n=275): Opioids/opiates (pethidine 50mg, intramuscular injection)	n=541 People with renal colic Age not reported Male to female ratio 351:190 Iran	Reduction in pain by ≥50% (30 minutes)	Unclear if diagnosis of renal colic confirmed Unclear if previous treatment given Patients did not have VAS recorded up to 30 minutes if they responded to medication earlier and were discharged
Hosseininejad 2017[53]	Intervention (n=100): Combined NSAID and opioid/opiate (ketorolac 30mg, and morphine 0.1mg/kg, intravenous) Comparison (n=100): NSAID (ketorolac 30mg, intravenous) Comparison (n=100): Opioid/opiate (morphine 0.1mg/kg, intravenous)	n=300 People with acute renal colic and pain score of 5 or more measured by the 10-cm visual analogue scale Age (range): 18-55 years Male to female ratio morphine and ketorolac group 67:33; morphine group 72:28; ketorolac group 69:31 Iran	Pain (unclear time-point; 40 minutes): VAS, 0-10, high score is poor outcome Need for rescue medication (40 minutes) Minor adverse events (time-point not reported): nausea, vomiting, dizziness (vertigo)	
Indudhara 1990[55]	Intervention (n=33): NSAID (diclofenac sodium, 150mg orally) Comparison (n=31): Opioid (pethidine, 50mg intramuscularly)	n=94 People with acute renal colic Age (range): 19-57 years Male to female ratio 68:26	Pain relief (1 hour): number of people with no pain relief Adverse events (time-point not reported): not specified	

Study	Intervention and comparison	Population	Outcomes	Comments
		India		
Kaynar 2015[61]	Intervention (n=40): NSAID (diclofenac sodium, 75mg, single intramuscular injection) Comparison (n=42): Paracetamol (acetaminophen, 1g/100ml of serum saline, intravenous)	n=82 People with urolithiasis-driven renal colic Age, mean (range): NSAID group 37.98 (18-72); opioid group 46.3 (19-81) Male to female ratio 48:34 Turkey	Minor adverse events (time-point not reported): dizziness/ vomiting, abdominal burning	
Larkin 1999[69]	Intervention (n=33): NSAID (ketorolac, 60mg, intramuscularly) Comparison (n=37): Opioid (meperidine, patients weighing 50-90kg received 100mg, those weighing more than 90kg received 150mg, intramuscularly)	n=70 People with acute renal colic and confirmed ureterolithiasis Age, mean (SD): NSAID group 45.5 (16); opioid group 40.7 (13.3) Male to female ratio 53:17 United States	Need for rescue medication (20 minutes) Minor adverse events (90 minutes): nausea	Unclear if participants had any previous treatment
Lehtonen 1983[70]	Intervention (n=93): NSAID (indomethacin, 50mg in a 5ml intravenous injection) Comparison (n=31): opioid (pethidine, 50mg, in a 5ml intravenous injection)	n=124 People with ureteral colic Age, mean (range): NSAID group 44.6 (16-79); opioid group 39.5 (23-75) Male to female ratio 95:29 Four hospitals in Finland	Pain relief (30 minutes): number of people with no, partial or complete pain relief Need for rescue medication (30 minutes) Minor adverse events (time-point not reported): vomiting, nausea, dizziness, tiredness	

Study	Intervention and comparison	Population	Outcomes	Comments
Lundstam 1980[73]	Intervention (n=9): NSAID (diclofenac sodium, 50mg, intramuscular injection Comparison (n=10): placebo (saline, intramuscular injection) Patients who experienced significant pain 25 minutes after the injection were treated with 50mg diclofenac sodium intramuscularly	n=19 People with ureteral colic Age, range: NSAID group 25-62; placebo group 24-69 Male to female ratio 16:3 Sweden	Pain (25 minutes): VAS, 0-100, high score is poor outcome Pain relief (25 minutes): number of people with no relief, partial relief or complete relief Need for rescue medication (25 minutes)	Unclear if participants had any previous treatment
Magrini 1984[76]	Intervention (n=10): NSAID (ketoprofen, 200mg, intravenous) Comparison (n=10): placebo (intravenous injection, no further details) Patients were given further analgesia after 30 minutes if response was unsatisfactory	n=20 People with episodes of renal colic admitted to the emergency ward while in hospital for other reasons Age, median (range): NSAID group 48.5 (30-69); placebo group 42.5 (32-75) Male to female ratio 11:9 Italy	Pain relief (3 hours): VAS, 0-10, high is good outcome Need for rescue medication (3 hours)	
Marthak 1991[79]	Intervention (n=25): NSAID (diclofenac sodium, 3ml [75mg], by intramuscular injection) Comparison (n=25): opioid (pethidine, 3ml [75mg] by intramuscular injection) If no pain relief was achieved within 60 minutes, a second injection of pethidine was administered. Those receiving diclofenac received	n=50 People with renal or ureteric colic Age, mean (range): NSAID group 36.4 (22-65); opioid group 34 (24-62) Male to female ratio 37:13 India	Pain relief (30 minutes): number of patients with total, partial or no relief Minor adverse events (time-point not reported): nausea/ vomiting, dizziness, sleepiness	

Study	Intervention and comparison	Population	Outcomes	Comments
	another drug of the investigator's choice			
Masoumi 2014[81]	Intervention (n=55): paracetamol (acetaminophen, 1g in 100ml normal saline, intravenously, over 5-10 minutes) Comparison (n=55): opioid (morphine, 0.1mg/kg in 100ml normal saline, intravenously, over 5-10 minutes) After 30 minutes, if severity of pain was equal to or more than 5 VAS units, 1µgr/kg intravenous fentanyl was administered to the patient as rescue therapy	n=110 People with acute renal colic Age, mean (SD): paracetamol group 36.07 (9.7); opioid group 34.96 (8.94) Male to female ratio 82:28 Iran	Pain (30 minutes): VAS, 0-10, high score is poor outcome Need for rescue medication (30 minutes) Minor adverse events (time-point not reported): nausea, vomiting	
Mozafari 2017[89]	Intervention (n=32): Opioids/opiates (buprenorphine 2mg, sublingual tab, and 1 cc sterile water as placebo, intravenous) Comparison (n=31): NSAID (ketorolac tromethamine 30mg, intravenously and a sublingual tab as placebo)	n=63 People with acute renal colic because of renal stones and pain score >3 as determined by the visual analogue scale Age, mean (SD): 37.38 (1.83) Male to female ratio 52:11 Iran	Pain (40 minutes): VAS, 0-10, high score is poor outcome Need for rescue medication (40 minutes) Minor adverse events (Unclear time-point – 24 hours): nausea, vomiting, dizziness	Minor adverse events reported after rescue medication given
Narci 2012[92]	Intervention (n=25): Combined paracetamol and NSAID (acetaminophen 1000mg orally and 75 mg diclofenac sodium, intramuscular) Comparison (n=25): Paracetamol	n=75 People with clinical symptoms and signs of renal colic Age, mean (SD): acetominophen and diclofenac: 34 (12); acetaminophen: 35.8 (13); diclofenac: 39.6 (18)	Pain (30 minutes): VAS, 0-10, high score is poor outcome Need for rescue medication (30 minutes)	Minor adverse events and possibly pain intensity reported after rescue medication given

Study	Intervention and comparison	Population	Outcomes	Comments
	(acetaminophen, 1 gram, orally and placebo (i.m. normal saline)) Comparison (n=25): NSAID (diclofenac sodium, 75mg, intramusclular, and placebo (startch tablet, orally))	Male to female ratio 42:33 Turkey	Pain relief (Unclear time-point): number of patients with complete pain relief Minor adverse events (60 minutes): unspecified	
Oosterlinck 1976[97]	Intervention (n=20): muscle relaxant (buscopan compositum: 20mg hyoscine-N-butylbromide and 2.5g sodium phenyl-dimethyl-pyrazolon-methylaminomethane sulphonate, intravenously over 5 minutes) Comparison (n=20): opioid (meptazinol, 60mg, intravenously over 5 minutes)	n=40 People with severe pain provoked by an ureteral or renal stone Age, mean (SD not reported): muscle relaxant group 44.2; opioid group 44.8 Male to female ratio 30:10 Belgium	Pain relief (time-point not reported): number of people with complete pain relief Pain (5 minutes): pain relief within 5 minutes Pain (time-point not reported): number of people with no pain relief Minor adverse events (time-point not reported): dizziness, nausea and vomiting	Unclear if participants had any previous treatment
Oosterlinck 1990[98]	Intervention (n=84): NSAID (single dose of intramuscular ketorolac, 45 participants received 10mg (1ml of 1% solution) and 37 participants received 90mg (3ml of 3% solution)) Comparison (n=41): opioid (single dose of intramuscular	n=125 People with pain due to renal colic, and the pain was at least moderate on a 4-point verbal rating scale Age, median (range): NSAID group 40.5 (21-71); opioid group 39 (18-70) years	Pain (1 hour): VAS, 0-100, high score is poor outcome Pain relief (1 hour): defined as number of people with no pain on a 4-point verbal rating scale Need for rescue	Unclear if participants had any previous treatment

Study	Intervention and comparison	Population	Outcomes	Comments
	pethidine, 100mg (2ml of 5% solution))	Male to female ratio 90:31 UK	medication (10 hours) Minor adverse events (12 hours): vomiting, nausea, drowsiness, injection site pain	
Pathan 2016[101]	Intervention (n=548): NSAID (diclofenac 75mg in 3ml solution, intramuscularly) Comparison (n=548): opioid (morphine, 0.1mg/kg, intravenously over 2-5 minutes) Comparison (n=549): paracetamol (1g, intravenously over 3-5 minutes) Rescue analgesia was administered after 30 minutes as morphine 3 mg intravenously every 5 minutes	n=1645 People with renal colic of intensity on a Numerical pain Rating Scale (NRS 0 to 10) of 4 or more Age, median (IQR): NSAID group 35.1 (29.2-42.6); opioid group 34.7 (28.8-41.7); paracetamol group 34.4 (28.6-41.5) Stone size: ≤5mm 62%; >5mm 34% Male to female ratio 1362:283 Qatar	Pain (30 minutes): NRS, 0-10, high score is poor outcome Need for rescue medication (30 minutes) Persistent pain (60 minutes): NRS >2 Reduction in pain by ≥50% (30 minutes) Reduction in NRS of ≥3 (30 minutes) Minor adverse events (14 days): unspecified	Stone wasn't detected or imaging wasn't done in 20% participants
Safdar 2006[112]	Intervention (n=43): NSAID (ketorolac, 15mg at time 0 and 15mg at time 20 – total of 30mg in 20 minutes, intravenous) Comparison (n=43): Opioid (morphine, 5mg at time 0 and 5mg at time 20 – total of 10mg in 20 minutes, intravenous) People with persistent pain at 40	n=86 People with acute renal colic and pain of 5 or more on a 10 point VAS, or at least moderate pain on a 4 category scale Age, mean (SD): NSAID group 39.3 (9.9); opioid group 37.3 (10) Male to female ratio 58:28	Pain (40 minutes): VAS, 0-10, high score is poor outcome Need for rescue medication (40 minutes) Minor adverse events (time-point not reported): nausea, vomiting, dizziness	

Study	Intervention and comparison	Population	Outcomes	Comments
	minutes were given 5mg intravenous morphine	United States		
Salameh 2011[114]	Intervention (n=48): NSAID (diclofenac 75mg, intramuscular) Comparison (n=49): Opioids/opiates (tramadol 100mg, intramuscular)	n=100 People with renal colic , and moderate to severe pain (visual analogue scale score ≥4 based on 1-10 scale) Age (range): 18-65 years Male to female ratio 3:1 Israel	Pain (30 minutes): VAS, 1-10, high score is poor outcome Need for rescue medication (30 minutes) Major adverse events (time-point not reported): significant side effects	
Sandhu 1994[118]	Intervention (n=76): NSAID (ketorolac, 30mg, intramuscularly) Comparison (n=78): opioid (pethidine, 100mg, intramuscularly)	n=154 People with moderate to severe pain in the lumbar region due to renal colic Age, mean (SD): NSAID group 45.2 (14.6); opioid group 42.1 (14.6) Male to female ratio 117:37 UK	Need for rescue medication (24 hours) Minor adverse events (24 hours): nausea and vomiting, dizziness, sleepiness	Renal colic was confirmed in 72% of participants
Serinken 2012[120]	Intervention (n=40): paracetamol (1g in 100ml normal saline) Comparison (n=40): opioid (morphine, 0.1mg/kg in 100ml normal saline) Both drugs were given as a bolus infusion within 2-4 minutes	n=80 People with a clinical diagnosis of acute renal colic with moderate to severe pain Age, mean (SD): 30.2 (8.6) Male to female ratio 51:29 Turkey	Pain (30 minutes): VAS, 0-100, high score is poor outcome Need for rescue medication (time-point not reported) Major adverse events (time-point not reported):	

Study	Intervention and comparison	Population	Outcomes	Comments
			respiratory depression Minor adverse events(time-point not reported): nausea and vomiting, dizziness	
Shirazi 2015[121]	Intervention (n=40): opioid (tramadol, 50mg, intramuscularly) Comparison (n=40): NSAID (indomethacin, 100mg, rectally) Patients who had no satisfactory pain relief within 30 minutes, a second treatment were administrated	n=80 People with renal colic caused by urolithiasis Age, mean (SD): opioid group 39.1 (8.9); NSAID group 36.7 (9.2) Male to female ratio 45:35 Iran	Pain (30 minutes): VAS, 0-10, high score is poor outcome Pain relief (30 minutes): number of patients with complete pain relief Need for rescue medication (30 minutes)	
Snir 2008[124]	Intervention (n=29): muscle relaxant/ antispasmodic (papaverine hydrochloride, 120mg, intravenously in 100cc 0.9% saline infusion for a minimum of 3 minutes) Comparison (n=30): NSAID (sodium diclofenac, 75mg, intramuscularly) Comparison (n=27): muscle relaxant/ antispasmodic (papaverine hydrochloride, 120mg, intravenously in 100cc 0.9% saline infusion for a minimum of 3 minutes) + NSAID (sodium diclofenac, 75mg, intramuscularly)	n=86 People referred to the emergency department with renal colic Renal stone on imaging: muscle relaxant group 48.2%; NSAID group 53.3%; combination group 44.4% Stone size, mean: muscle relaxant group 4.12mm; NSAID group 4.9mm; combination group 6.1mm Age, mean (SD not reported): muscle relaxant group 46.2; NSAID group 44.1; combination group 43.9	Pain (40 minutes): VAS, 0-10, high score is poor outcome Need for rescue medication (40 minutes) Minor adverse events (time point not reported): dizziness, sleepiness	

Study	Intervention and comparison	Population	Outcomes	Comments
	People requiring further analgesia after 40 minutes were given 1mg/kg of intramuscular meperidine	Male to female ratio 68:18 Israel		
Song 2012[127]	Intervention (n=46): NSAID (ketorolac, 30 mg, intravenous) + opioid (morphine, 5mg intravenously, over 5 mins) + muscle relaxant (Butylscopolammonium bromide, 20mg, intravenously, diluted with 50 mL of normal saline) Comparison (n=43): NSAID (ketorolac, 30 mg, intravenous) + opioid (morphine, 5mg intravenously, over 5 mins) + placebo (normal saline solution, 50ml)	n=89 People presenting to the ED with flank pain consistent with an abrupt onset of severe paroxysmal unilateral location Age, mean (SD): muscle relaxant group 38.8 (9.8); placebo group 41.9 (9.6) Male to female ratio 72:17 Korea	Pain intensity (40 minutes): VAS Need for rescue medication (40 minutes) Major adverse events (40 minutes): respiratory depression Minor adverse events (40 minutes): nausea, vomiting, dizziness, sleepiness	19.1% had confirmed stone on CT and 40.4% had confirmed stone on IVP
Stankov 1994[128]	Intervention (n=35): opioid (tramadol, 100mg, intravenously) Comparison (n=33): antispasmodic (butylscopolamine, 20mg, intravenously) People with no adequate pain relief after 20 minutes, were given a second injection of the study medication	n=68 People with acute renal colic Age, mean (SD): 46.4 (16.2) years Male to female ratio 71:33 8 centres in Germany	Pain (20 minutes): VAS, 0-100, high score is poor outcome Need for rescue medication (20 minutes) Pain (20 minutes): time to pain relief Pain (time-point not reported): number of people with no pain relief, defined as non-responders	

Study	Intervention and comparison	Population	Outcomes	Comments
			Minor adverse events (time-point not reported): nausea, vomiting, dizziness	
Thompson 1989[131]	Intervention (n=29): NSAID (diclofenac, 100mg, rectally) Comparison (n=29): opioid (pethidine, 100mg, injection). Participants also received 12.5mg prochloperazine	n=58 People with presumed renal colic Age not reported Gender not reported UK	Pain (1 hour): number of patients pain free Need for rescue medication (time-point not reported) Minor adverse events (time-point not reported): nausea, vomiting, dizziness	Unclear if diagnosis of renal colic is confirmed.
Vignoni 1983[134]	Intervention (n=63): NSAID (sodium diclofenac, 75mg/3ml, intramuscular) Comparison (n=68): placebo (3ml saline in identical ampoules, intramuscular) Participants who still experienced significant pain 25 minutes after the first injection were treated with 75mg diclofenac sodium intramuscularly	n=131 People with ureteral colic Age, mean (SD): NSAID group 39.2 (14.74); placebo group 37.6 (11.69) Male to female ratio NSAID group 3.53:1; placebo group 3.42:1 Italy	Pain (25 minutes): VAS, 0-100, high score is poor outcome Pain relief (25 minutes): number of participants with complete pain relief Need for rescue medication (25 minutes)	Unclear if participants had any previous treatment
Zamanian 2016[142]	Intervention (n=79): NSAID (indomethiacin 100mg, suppository) Comparison (n=79): Opioids/opiates (morphine 10mg, suppository)	n=158 People with confirmed renal colic Age, mean (SD): NSAID group 37.3 (11.5); opioid group 37.2 (10.6)	Pain (40 minutes): numerical rating scale, 0-10, high score is poor outcome, change score Minor adverse events (time-	Patients were excluded if they had analgesics up to four hours prior to admission

Study	Intervention and comparison	Population	Outcomes	Comments
		Male to female ratio 102:56 Iran	point not reported): nausea, vomiting, dizziness	

See appendix D for full evidence tables

1.4.5 Quality assessment of clinical studies included in the evidence review

1.4.5.1 NSAID versus opioid/opiate

Table 3: Clinical evidence summary: NSAID versus opioid/opiate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with NSAID (95% CI)
Pain (VAS & NRS) [final and change scores] Scale from: 0 to 10.	1675 (8 studies) 30-60 minutes	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, inconsistency		The mean pain (vas & nrs) [final and change scores] in the control groups was 2.84	The mean pain (vas & nrs) [final and change scores] in the intervention groups was 0.35 lower (1.14 lower to 0.43 higher)
Pain (VAS 1-10) Scale from: 1 to 10.	97 (1 study) 30 minutes	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision		The mean pain (vas 1-10) in the control groups was 5.6	The mean pain (vas 1-10) in the intervention groups was 1.4 lower (2.5 to 0.3 lower)
Need for rescue medication	2769 (17 studies) 30-40 minutes	⊕⊖⊖⊖ VERY LOW1,3,4 due to risk of bias, inconsistency, imprecision	RR 0.77 (0.64 to 0.93)	Moderate	
				357 per 1000	82 fewer per 1000 (from 25 fewer to 129 fewer)
No pain relief	336 (4 studies) 30-60 minutes	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 1.52 (0.57 to 4.07)	32 per 1000	17 more per 1000 (from 14 fewer to 98 more)
Partial pain relief	474 (4 studies) 30 minutes or at discharge	⊕⊖⊖⊖ VERY LOW1,3,5 due to risk of bias, inconsistency, imprecision	RR 0.93 (0.73 to 1.17)	Moderate	
				555 per 1000	39 fewer per 1000 (from 150 fewer to 94 more)
Complete pain relief				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with NSAID (95% CI)
	715 (7 studies) 30-60 minutes or at discharge	⊕⊖⊖⊖ VERY LOW1,3,6 due to risk of bias, inconsistency, imprecision	RR 1.05 (0.78 to 1.42)	516 per 1000	26 more per 1000 (from 114 fewer to 217 more)
Persistent pain	1096 (1 study) 60 minutes	⊕⊕⊕⊕ HIGH	RR 0.64 (0.53 to 0.76)	377 per 1000	136 fewer per 1000 (from 90 fewer to 177 fewer)
Reduction in pain NRS score >3	1096 (1 study) 30 minutes	⊕⊕⊕⊕ HIGH	RR 1.05 (0.99 to 1.11)	781 per 1000	39 more per 1000 (from 8 fewer to 86 more)
Reduction in pain by 50%	1708 (3 studies) 30 minutes	⊕⊖⊖⊖ VERY LOW1,3,7 due to risk of bias, inconsistency, imprecision	RR 1.19 (0.91 to 1.54)	Moderate	
				610 per 1000	116 more per 1000 (from 55 fewer to 329 more)
Major adverse events (significant side effects)	97 (1 study) time-point not reported	⊕⊕⊖⊖ LOW1 due to risk of bias	Not estimable8	Moderate	
				0 per 1000	0 fewer per 1000 (from 39 fewer to 39 more)13
Minor adverse events (unspecified)	1259 (4 studies) 14 days	⊕⊕⊖⊖ LOW1,9 due to risk of bias, indirectness	RR 0.39 (0.22 to 0.7)	101 per 1000	62 fewer per 1000 (from 30 fewer to 79 fewer)
Minor adverse events (urinary retention)	234 (1 study) 60 minutes	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	Peto OR 0.14 (0 to 6.94)	9 per 1000	8 fewer per 1000 (from 9 fewer to 50 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with NSAID (95% CI)
Minor adverse events (nausea and vomiting)	206 (2 studies) 30 minutes - 24 hours	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision	RR 0.55 (0.32 to 0.93)	218 per 1000	98 fewer per 1000 (from 15 fewer to 148 fewer)
Minor adverse events (vomiting)	1290 (10 studies) Unclear time-point	⊕⊖⊖⊖ VERY LOW1,3,10 due to risk of bias, inconsistency, imprecision	RR 0.38 (0.18 to 0.81)	Moderate	
				108 per 1000	67 fewer per 1000 (from 21 fewer to 89 fewer)
Minor adverse events (nausea)	1160 (10 studies) Unclear time-point	⊕⊖⊖⊖ VERY LOW1,3,11 due to risk of bias, inconsistency, imprecision	RR 0.47 (0.25 to 0.88)	Moderate	
				191 per 1000	101 fewer per 1000 (from 23 fewer to 143 fewer)
Minor adverse events (dizziness)	1490 (12 studies) Unclear time-point	⊕⊖⊖⊖ VERY LOW1,3,12 due to risk of bias, inconsistency, imprecision	RR 0.29 (0.11 to 0.74)	Moderate	
				160 per 1000	114 fewer per 1000 (from 42 fewer to 142 fewer)
Minor adverse events (sleepiness)	758 (6 studies) 1-24 hours or not reported	⊕⊕⊕⊖ MODERATE1 due to risk of bias	RR 0.39 (0.27 to 0.56)	121 per 1000	74 fewer per 1000 (from 53 fewer to 88 fewer)
Minor adverse events (pain – injection site/local)	359 (2 studies) 12 hours	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision	RR 3.33 (1.19 to 9.29)	17 per 1000	40 more per 1000 (from 3 more to 141 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because heterogeneity, I2= 94%, p= > 0.1, unexplained by subgroup analysis
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with NSAID (95% CI)

4 Downgraded by 1 or 2 increments because heterogeneity, I2= 54%, p= > 0.1, unexplained by subgroup analysis
5 Downgraded by 1 or 2 increments because heterogeneity, I2= 60%, p= > 0.1, unexplained by subgroup analysis
6 Downgraded by 1 or 2 increments because heterogeneity, I2= 77%, p= > 0.1, unexplained by subgroup analysis
7 Downgraded by 1 or 2 increments because heterogeneity, I2= 93%, p= > 0.1, unexplained by subgroup analysis
8 Could not be calculated as there were no events in the intervention or comparison group
9 Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
10 Downgraded by 1 or 2 increments because heterogeneity, I2= 68%, p= > 0.1, unexplained by subgroup analysis
11 Downgraded by 1 or 2 increments because heterogeneity, I2= 65%, p= > 0.1, unexplained by subgroup analysis
12 Downgraded by 1 or 2 increments because heterogeneity, I2= 81%, p= > 0.1, unexplained by subgroup analysis
13 Risk difference calculated in Review Manager

1.4.5.2 NSAID versus paracetamol

Table 4: Clinical evidence summary: NSAID versus paracetamol

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with paracetamol	Risk difference with NSAID (95% CI)
Pain (NRS or VAS; 0-10) Scale from: 0 to 10.	1341 (3 studies) 30 minutes	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain (nrs or vas; 0-10) in the control groups was 3.7	The mean pain (nrs or vas; 0-10) in the intervention groups was 0.88 lower (2.01 lower to 0.25 higher)
Reduction in pain by 50%	1095 (1 study) 30 minutes	⊕⊕⊕⊕ HIGH	RR 1.02 (0.94 to 1.11)	664 per 1000	13 more per 1000 (from 40 fewer to 73 more)
Reduction in NRS pain score by >3	1095 (1 study) 30 minutes	⊕⊕⊕⊕ HIGH	RR 1 (0.95 to 1.06)	818 per 1000	0 fewer per 1000 (from 41 fewer to 49 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with paracetamol	Risk difference with NSAID (95% CI)
Persistent pain	1095 (1 study) 60 minutes	⊕⊕⊕⊖ MODERATE3 due to imprecision	RR 0.81 (0.66 to 0.99)	296 per 1000	56 fewer per 1000 (from 3 fewer to 101 fewer)
Partial pain relief	200 (1 study) at discharge	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision	RR 0.89 (0.7 to 1.12)	Moderate	
				610 per 1000	67 fewer per 1000 (from 183 fewer to 73 more)
Complete pain relief	250 (2 studies) discharge/ unclear time-point	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 1.15 (0.85 to 1.55)	Moderate	
				355 per 1000	53 more per 1000 (from 53 fewer to 195 more)
Need for rescue medication	1541 (4 studies) 30 minutes	⊕⊕⊕⊖ MODERATE1 due to risk of bias	RR 0.55 (0.44 to 0.68)	Moderate	
				221 per 1000	99 fewer per 1000 (from 71 fewer to 124 fewer)
Minor adverse events (unspecified)	1145 (2 studies) 1 hour - 14 days	⊕⊖⊖⊖ VERY LOW1,3,5 due to risk of bias, imprecision, indirectness	RR 1 (0.35 to 2.84)	6 per 1000	0 fewer per 1000 (from 4 fewer to 11 more)
Minor adverse events (vomiting)	476 (3 studies) 90 minutes or not reported	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 0.47 (0.13 to 1.66)	Moderate	
				25 per 1000	13 fewer per 1000 (from 22 fewer to 16 more)
Minor adverse events (abdominal pain)	80 (1 study) time point not reported	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	Peto OR 7.58 (0.47 to 123.37)	0 per 1000	50 more per 1000 (from 31 fewer to 131 more)
Minor adverse events (dizziness)	396 (2 studies) time point not reported	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	Peto OR 0.52 (0.05 to 4.98)	Moderate	
				10 per 1000	5 fewer per 1000 (from 9 fewer to 38 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with paracetamol	Risk difference with NSAID (95% CI)
Minor adverse events (epigastric pain)	196 (1 study) time point not reported	⨁⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	Peto OR 7.54 (0.15 to 380.22)	0 per 1000	10 more per 1000 (from 18 fewer to 38 more)4

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because heterogeneity, I2= 94%, p= > 0.1, unexplained by subgroup analysis
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
4 Risk difference calculated in Review Manager

5 Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

1.4.5.3 NSAID versus muscle relaxant/antispasmodic

Table 5: Clinical evidence summary: NSAID versus muscle relaxant/antispasmodic

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with muscle relaxant/antispasmodic	Risk difference with NSAID (95% CI)
Pain (pain intensity; VAS, 0-10) Scale from: 0 to 10.	59 (1 study) 40 minutes	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean pain (vas, 0-10) in the control groups was 3.65	The mean pain (vas, 0-10) in the intervention groups was 1.19 lower (2.51 lower to 0.13 higher)
Pain (complete pain relief)	200 (1 study) 30 minutes	⨁⨁⊖⊖ LOW4 due to indirectness	RR 3.33 (2.32 to 4.79)	240 per 1000	559 more per 1000 (from 317 more to 910 more)
Pain (need for rescue medication)	106 (2 studies) 40-60 minutes	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, imprecision, inconsistency	RR 0.42 (0.06 to 3.05)	338 per 1000	196 fewer per 1000 (from 318 fewer to 693 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with muscle relaxant/antispasmodic	Risk difference with NSAID (95% CI)
Minor adverse events (sleepiness)	106 (2 studies) time point not reported	⊕⊕⊕⊖ MODERATE1 due to risk of bias	Peto OR 0.02 (0.01 to 0.07)	517 per 1000	496 fewer per 1000 (from 447 fewer to 506 fewer)
Minor adverse events (dizziness)	59 (1 study) time point not reported	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	Peto OR 0.12 (0.01 to 1.22)	103 per 1000	89 fewer per 1000 (from 102 fewer to 20 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Downgraded by 1 or 2 increments because heterogeneity, I2= 81%, p= > 0.1, unexplained by subgroup analysis
4 Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

1.4.5.4 NSAID versus placebo

Table 6: Clinical evidence summary: NSAID versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with NSAID (95% CI)
Pain (pain intensity; VAS; 0-10) [change & final scores] Scale from: 0 to 10. Better indicated by lower scores	150 (2 studies) 25 minutes	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain intensity (0-10) in the control groups was 4.13	The mean pain intensity(0-10) in the intervention groups was 3.42 lower (6.28 to 0.56 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with NSAID (95% CI)
Pain (pain relief; VAS; 0-10) Scale from: 0 to 10. Better indicated by higher scores	20 (1 study) 180 minutes	⨁⨁⨁⊖ MODERATE1 due to risk of bias		The mean pain relief (0-10) in the control groups was 0.8	The mean pain relief (0-10) in the intervention groups was 7.8 higher (7.38 to 8.22 higher)
Pain (need for rescue medication)	170 (3 studies) 25 minutes	⨁⨁⊖⊖ LOW1 due to risk of bias	RR 0.39 (0.26 to 0.57)	900 per 1000	549 fewer per 1000 (from 387 fewer to 666 fewer)
Pain (no pain relief)	19 (1 study) 25 minutes	⨁⨁⨁⊖ MODERATE1 due to risk of bias	Peto OR 0.06 (0.01 to 0.36)	700 per 1000	577 fewer per 1000 (from 243 fewer to 677 fewer)
Pain (partial pain relief)	19 (1 study) 25 minutes	⨁⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 1.11 (0.3 to 4.17)	300 per 1000	33 more per 1000 (from 210 fewer to 951 more)
Pain (complete pain relief)	150 (3 studies) 25-30 minutes	⨁⊖⊖⊖ VERY LOW1,3,4 due to risk of bias, imprecision, inconsistency,	RR 5.74 (0.61 to 53.9)	60 per 1000	284 more per 1000 (from 23 fewer to 1000 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because heterogeneity, I2= 85%, p= > 0.1, unexplained by subgroup analysis
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
4 Downgraded by 1 or 2 increments because heterogeneity, I2= 95%, p= > 0.1, unexplained by subgroup analysis

1.4.5.5 Opioid/opiate versus paracetamol

Table 7: Clinical evidence summary: Opioid/opiate versus paracetamol

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Paracetamol	Risk difference with Opioid (95% CI)
Pain (VAS & NRS, 0-10) [final and change scores] Scale from: 0 to 10.	1497 (5 studies) 30 minutes	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain (vas & nrs, 0-10) [final and change scores] in the control groups was -0.174	The mean pain (vas & nrs, 0-10) [final and change scores] in the intervention groups was 0.36 higher (0.67 lower to 1.38 higher)
Reduction in pain by 50%	1097 (1 study) 30 minutes	⊕⊕⊕⊕ HIGH	RR 0.92 (0.84 to 1)	664 per 1000	53 fewer per 1000 (from 106 fewer to 0 more)
Need for rescue medication	1575 (5 studies) 30 minutes	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 1.11 (0.95 to 1.3)	Moderate	
				309 per 1000	34 more per 1000 (from 15 fewer to 93 more)
Reduction in pain NRS score >3	1097 (1 study) 30 minutes	⊕⊕⊕⊕ HIGH	RR 0.96 (0.9 to 1.01)	818 per 1000	33 fewer per 1000 (from 82 fewer to 8 more)
Persistent pain	1097 (1 study) 60 minutes	⊕⊕⊕⊖ MODERATE3 due to imprecision	RR 1.28 (1.08 to 1.51)	296 per 1000	83 more per 1000 (from 24 more to 151 more)
Partial pain relief	200 (1 study) discharge	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 1.13 (0.92 to 1.39)	Moderate	
				610 per 1000	79 more per 1000 (from 49 fewer to 238 more)
Complete pain relief				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Paracetamol	Risk difference with Opioid (95% CI)
	200 (1 study) discharge	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision	RR 0.79 (0.54 to 1.16)	390 per 1000	82 fewer per 1000 (from 179 fewer to 62 more)
Minor adverse events (nausea and vomiting)	168 (2 studies) time-point not reported	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 1.07 (0.46 to 2.46)	102 per 1000	7 more per 1000 (from 55 fewer to 149 more)
Minor adverse events (nausea)	108 (1 study) time-point not reported	⊕⊕⊕⊖ MODERATE1 due to risk of bias	Peto OR 8.5 (2.03 to 35.64)	0 per 1000	148 more per 1000 (from 49 more to 247 more)4
Minor adverse events (vomiting)	432 (3 studies) time-point not reported	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	Peto OR 4.99 (1.32 to 18.83)	Moderate	
				0 per 1000	111 more per 1000 (from 22 more to 200 more)4
Minor adverse events (unspecified)	1097 (1 study) 14 days	⊕⊕⊖⊖ LOW3,5 due to indirectness, imprecision	RR 2.71 (1.15 to 6.39)	13 per 1000	22 more per 1000 (from 2 more to 69 more)
Minor adverse events (dizziness)	397 (3 studies) time-point not reported	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	Peto OR 7.61 (3.51 to 16.47)	Moderate	
				0 per 1000	132 more per 1000 (from 83 more to 181 more)4
Minor adverse events (urinary retention)	95 (1 study) time-point not reported	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	Peto OR 6.95	0 per 1000	20 more per 1000 (from 35 fewer to 76 more)4

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Paracetamol	Risk difference with Opioid (95% CI)
			(0.14 to 350.96)		
Major adverse events (respiratory depression)	168 (2 studies) time-point not reported	⨁⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	Not estimable6	0 per 1000	0 fewer per 1000 (from 40 fewer to 40 more)4
Length of stay (discharged within 1 hour)	108 (1 study) 1 hour	⨁⨁⊖⊖ LOW1,3 due to risk of bias, imprecision	RR 0.8 (0.66 to 0.96)	907 per 1000	181 fewer per 1000 (from 36 fewer to 309 fewer)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because heterogeneity, I2= 87%, p= > 0.1, unexplained by subgroup analysis
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
4 Risk difference calculated in Review Manager
5 Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
6 Could not be calculated as there were no events in the intervention or comparison group

1.4.5.6 Opioid/opiate versus muscle relaxant/antispasmodic

Table 8: Clinical evidence summary: Opioid/opiate versus muscle relaxant/antispasmodic

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with muscle relaxant/antispasmodic	Risk difference with Opioid/opiate (95% CI)
Pain (pain intensity; VAS 0-10) Scale from: 0 to 10.	68 (1 study) 20 minutes	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain (0-10) in the control groups was -3.78	The mean pain (0-10) in the intervention groups was 0.22 higher (1.5 lower to 1.94 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with muscle relaxant/antispasmodic	Risk difference with Opioid/opiate (95% CI)
Pain (need for rescue medication)	68 (1 study) 20 minutes	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.11 (0.58 to 2.13)	333 per 1000	37 more per 1000 (from 140 fewer to 376 more)
Pain (complete pain relief)	40 (1 study) time-point not reported	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.67 (0.96 to 2.88)	450 per 1000	301 more per 1000 (from 18 fewer to 846 more)
Pain (no pain relief)	108 (2 studies) time-point not reported	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.95 (0.40 to 2.23)	131 per 1000	7 fewer per 1000 (from 79 fewer to 161 more)
Pain (time to pain relief within 5 minutes)	40 (1 study) time-point not reported	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.80 (1.13 to 2.86)	500 per 1000	400 more per 1000 (from 65 more to 930 more)
Pain (time to pain relief)	68 (1 study) time-point not reported	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain (time to pain relief) in the control groups was 16.22 minutes	The mean pain (time to pain relief) in the intervention groups was 1.08 higher (5.91 lower to 8.07 higher)
Minor adverse events (nausea and vomiting)	40 (1 study) time-point not reported	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.2 (0.44 to 3.3)	250 per 1000	50 more per 1000 (from 140 fewer to 575 more)
Minor adverse events (nausea)	68 (1 study) time-point not reported	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 6.98 (0.14 to 352.30)	0 per 1000	29 more per 1000 (from 48 fewer to 105 more)3
Minor adverse events (vomiting)	68 (1 study)	⨁⊖⊖⊖ VERY LOW1,2	Peto OR 0.13 (0 to 6.43)	30 per 1000	26 fewer per 1000 (from 30 fewer to 136 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with muscle relaxant/antispasmodic	Risk difference with Opioid/opiate (95% CI)
	time-point not reported	due to risk of bias, imprecision			
Minor adverse events (dizziness)	108 (2 studies) 12 hours or time-point not reported	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 2.97 (1.25 to 7.06)	115 per 1000	227 more per 1000 (from 29 more to 697 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Risk difference calculated in Review Manager

1.4.5.7 Opioid/opiate versus placebo

Table 9: Clinical evidence table: Opioid/opiate versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Opioid/opiate (95% CI)
Pain (pain intensity; VAS 0-10) [change score] Scale from: 0 to 10.	100 (1 study) 30 minutes	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean pain (0-10) in the control groups was -2.7	The mean pain (0-10) in the intervention groups was 1.3 lower (2.60 lower to 0.00 higher)
Pain (need for rescue medication)	100 (1 study) 30 minutes	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 0.73 (0.52 to 1.04)	667 per 1000	180 fewer per 1000 (from 320 fewer to 27 more)
Major adverse events (respiratory depression)	100 (1 study)	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Not estimable4	0 per 1000	0 fewer per 1000 (from 39 fewer to 39 more)3

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Opioid/opiate (95% CI)
	time-point not reported				
Minor adverse events (nausea and vomiting)	100 (1 study) time-point not reported	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 4.68 (1.06 to 20.6)	39 per 1000	144 more per 1000 (from 2 more to 764 more)
Minor adverse events (urinary retention)	100 (1 study) time-point not reported	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 7.7 (0.15 to 388.2)	0 per 1000	20 more per 1000 (from 34 fewer to 75 more)3

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Risk difference calculated in Review Manager
4 Could not be calculated as there were no events in the intervention or control arm

1.4.5.8 Paracetamol versus placebo

Table 10: Clinical evidence summary: Paracetamol versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Paracetamol (95% CI)
Pain (pain intensity; VAS, 0-10) [change score] Scale from: 0 to 10.	97 (1 study) 30 minutes	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean pain (0-10) in the control groups was -2.7	The mean pain (0-10) in the intervention groups was 1.6 lower (2.7 to 0.5 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Paracetamol (95% CI)
Pain (need for rescue medication)	97 (1 study) 30 minutes	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 0.68 (0.47 to 0.99)	667 per 1000	213 fewer per 1000 (from 7 fewer to 354 fewer)
Major adverse events (respiratory depression)	97 (1 study) time-point not reported	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Not estimable4	0 per 1000	0 fewer per 1000 (from 40 fewer to 40 more)3
Minor adverse events (nausea and vomiting)	97 (1 study) 30 minutes	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 3.88 (0.85 to 17.74)	39 per 1000	112 more per 1000 (from 6 fewer to 653 more)
Minor adverse events (urinary retention)	97 (1 study) time-point not reported	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Not estimable4	0 per 1000	0 fewer per 1000 (from 40 fewer to 40 more)3

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Risk difference calculated in Review Manager
4 Could not be calculated as there were no events in the intervention or control arm

1.4.5.9 Muscle relaxant/antispasmodic versus placebo

Table 11: Clinical evidence summary: Muscle relaxant/antispasmodic versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Muscle relaxant/antispasmodic (95% CI)
Pain (complete pain relief)	200 (1 study) 30 minutes	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness	RR 4 (1.71 to 9.36)	60 per 1000	180 more per 1000 (from 43 more to 502 more)
Adverse events (unspecified)	200 (1 study) 30 minutes	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness	RR 84 (11.93 to 591.6)	10 per 1000	830 more per 1000 (from 109 more to 1000 more)

1 Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

1.4.5.10 Combinations

Table 12: Clinical evidence summary: NSAID + muscle relaxant/ antispasmodic versus NSAID

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSAID	Risk difference with Combination: NSAID + muscle relaxant/ antispasmodic (95% CI)
Pain intensity (VAS) Scale from: 0 to 10.	57 (1 study) 40 minutes	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain intensity (vas) in the control groups was 2.46	The mean pain intensity (vas) in the intervention groups was 0.5 higher (0.95 lower to 1.95 higher)
Need for rescue medication	57 (1 study) 40 minutes	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 3.89 (0.88 to 17.13)	Moderate	
				67 per 1000	194 more per 1000 (from 8 fewer to 1000 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSAID	Risk difference with Combination: NSAID + muscle relaxant/ antispasmodic (95% CI)
Minor adverse events (dizziness)	57 (1 study) 40 minutes	⊕⊕⊕⊖ MODERATE1 due to risk of bias	Not estimable4	Moderate	
				0 per 1000	0 fewer per 1000 (from 66 fewer to 66 more)3
Minor adverse events (sleepiness)	57 (1 study) 40 minutes	⊕⊕⊕⊖ MODERATE1 due to risk of bias	Not estimable4	Moderate	
				0 per 1000	0 fewer per 1000 (from 66 fewer to 66 more)3

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Risk difference calculated in Review Manager
4 Could not be calculated as there were no events in the intervention or comparison group

Table 13: Clinical evidence summary: NSAID + muscle relaxant/ antispasmodic versus muscle relaxant/ antispasmodic

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with muscle relaxant/ antispasmodic	Risk difference with Combination: NSAID + muscle relaxant/ antispasmodic (95% CI)
Pain intensity (VAS) Scale from: 0 to 10.	56 (1 study) 40 minutes	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean pain intensity (vas) in the control groups was 3.65	The mean pain intensity (vas) in the intervention groups was 0.69 lower (2.22 lower to 0.84 higher)
Need for rescue medication	56 (1 study) 40 minutes	⊕⊕⊕⊖ MODERATE1 due to risk of bias	RR 0.58 (0.27 to 1.23)	Moderate	
				448 per 1000	188 fewer per 1000 (from 327 fewer to 103 more)
Minor adverse events (dizziness)	56 (1 study) 40 minutes	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	Peto OR 0.13 (0.01 to 1.35)	Moderate	
				103 per 1000	90 fewer per 1000 (from 102 fewer to 36 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with muscle relaxant/ antispasmodic	Risk difference with Combination: NSAID + muscle relaxant/ antispasmodic (95% CI)
Minor adverse events (sleepiness)	56 (1 study) 40 minutes	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	Peto OR 0.14 (0 to 7.33)	Moderate	
				35 per 1000	30 fewer per 1000 (from 35 fewer to 222 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 14: Clinical evidence summary: NSAID + opioid + muscle relaxant/ antispasmodic versus NSAID + opioid

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSAID + opioid	Risk difference with NSAID + opioid + muscle relaxant/ antispasmodic (95% CI)
Pain intensity (VAS) Scale from: 0 to 10.	89 (1 study) 40 minutes	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean pain intensity (vas) in the control groups was 2.5	The mean pain intensity (vas) in the intervention groups was 1.2 lower (2.15 to 0.25 lower)
Need for rescue medication	89 (1 study) 40 minutes	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 0.47 (0.21 to 1.05)	326 per 1000	173 fewer per 1000 (from 258 fewer to 16 more)
Major adverse events (respiratory depression)	89 (1 study) 40 minutes	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	Not estimable4	0 per 1000	0 fewer per 1000 (from 43 fewer to 43 more)3
Minor adverse events (vomiting)	89 (1 study) 40 minutes	⨁⨁⨁⨀ MODERATE1 due to risk of bias	Peto OR 0.13 (0 to 6.38)	23 per 1000	20 fewer per 1000 (from 23 fewer to 108 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSAID + opioid	Risk difference with NSAID + opioid + muscle relaxant/ antispasmodic (95% CI)
Minor adverse events (nausea)	89 (1 study) 40 minutes	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 0.13 (0 to 6.38)	23 per 1000	20 fewer per 1000 (from 23 fewer to 108 more)
Minor adverse events (dizziness)	89 (1 study) 40 minutes	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.87 (0.18 to 19.88)	23 per 1000	20 more per 1000 (from 19 fewer to 434 more)
Minor adverse events (sleepiness)	89 (1 study) 40 minutes	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	Peto OR 6.92 (0.14 to 349.65)	0 per 1000	22 more per 1000 (from 38 fewer to 81 more)3

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Risk difference calculated in Review Manager
4 Could not be calculated as there were no events in the intervention or control arm

Table 15: Clinical evidence summary: NSAID + opioid versus NSAID

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSAID	Risk difference with Combination: NSAID + opioid (95% CI)
Need for rescue medication	200 (1 study) 40 minutes	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.67 (0.38 to 1.18)	Moderate	
				240 per 1000	79 fewer per 1000 (from 149 fewer to 43 more)
Minor adverse events (nausea)	200 (1 study) time-point not reported	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.5 (0.09 to 2.67)	Moderate	
				40 per 1000	20 fewer per 1000 (from 36 fewer to 67 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSAID	Risk difference with Combination: NSAID + opioid (95% CI)
Minor adverse events (vomiting)	200 (1 study) time-point not reported	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1 (0.14 to 6.96)	Moderate	
				20 per 1000	0 fewer per 1000 (from 17 fewer to 119 more)
Minor adverse events (dizziness)	200 (1 study) time-point not reported	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 3 (0.32 to 28.35)	Moderate	
				10 per 1000	20 more per 1000 (from 7 fewer to 273 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 16: Clinical evidence summary: NSAID + opioid versus opioid

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with opioid	Risk difference with Combination: NSAID + opioid (95% CI)
Need for rescue medication	200 (1 study) 40 minutes	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.8 (0.44 to 1.45)	Moderate	
				200 per 1000	40 fewer per 1000 (from 112 fewer to 90 more)
Minor adverse events (nausea)	200 (1 study) time-point not reported	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.5 (0.09 to 2.67)	Moderate	
				40 per 1000	20 fewer per 1000 (from 36 fewer to 67 more)
Minor adverse events (vomiting)	200 (1 study) time-point not reported	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.5 (0.09 to 2.67)	Moderate	
				40 per 1000	20 fewer per 1000 (from 36 fewer to 67 more)
Minor adverse events (dizziness)				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with opioid	Risk difference with Combination: NSAID + opioid (95% CI)
	200 (1 study) time-point not reported	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.5 (0.13 to 1.94)	60 per 1000	30 fewer per 1000 (from 52 fewer to 56 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 17: Clinical evidence summary: NSAID + paracetamol versus NSAID

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSAID	Risk difference with Combination NSAID + paracetamol (95% CI)
Pain (VAS 0-10) Scale from: 0 to 10.	50 (1 study) 30 minutes	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain (vas 0-10) in the control groups was 3.02	The mean pain (vas 0-10) in the intervention groups was 1.66 lower (2.82 to 0.5 lower)
Need for rescue medication	50 (1 study) 30 minutes	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1 (0.15 to 6.55)	Moderate	
				80 per 1000	0 fewer per 1000 (from 68 fewer to 444 more)
Complete pain relief	50 (1 study) 60 minutes	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 2.5 (1.37 to 4.57)	Moderate	
				320 per 1000	480 more 1000 (from 118 more to 1000 more)
Minor adverse events (unspecified)	50 (1 study) 60 minutes	⊕⊕⊕⊖ MODERATE1 due to risk of bias	Not estimable4	Moderate	
				0 per 1000	0 fewer per 1000 (from 75 fewer to 75 more)3

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSAID	Risk difference with Combination NSAID + paracetamol (95% CI)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Risk difference calculated in Review Manager
4 Could not be calculated as there were no events in the intervention or comparison group

Table 18: Clinical evidence summary: NSAID + paracetamol versus paracetamol

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with paracetamol	Risk difference with Combination NSAID + paracetamol (95% CI)
Pain (VAS 0-10) Scale from: 0 to 10.	50 (1 study) 30 minutes	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain (vas 0-10) in the control groups was 4.28	The mean pain (vas 0-10) in the intervention groups was 2.92 lower (3.94 to 1.9 lower)
Need for rescue medication	50 (1 study) 30 minutes	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.33 (0.07 to 1.5)	Moderate	
				240 per 1000	161 fewer per 1000 (from 223 fewer to 120 more)
Complete pain relief	50 (1 study) Unclear time point	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 2.5 (1.37 to 4.57)	Moderate	
				320 per 1000	480 more 1000 (from 118 more to 1000 more)
Minor adverse events (unspecified)	50 (1 study) 60 minutes	⊕⊕⊕⊖ MODERATE1 due to risk of bias	Not estimable4	Moderate	
				0 per 1000	0 fewer per 1000 (from 75 fewer to 75 more)3

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with paracetamol	Risk difference with Combination NSAID + paracetamol (95% CI)
3 Risk difference calculated in Review Manager 4 Could not be calculated as there were no events in the intervention or comparison group					

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.5.3 Unit costs

Table 19: UK costs of pain drugs (not including method of administration)

Drug	Formulation	Unit cost	Dose per pain episode	Cost per episode[a]	Source of dosage
	NSAIDS				
Diclofenac sodium	MR tablets	75mg tablets, pack of 56 = £11.31	75 mg	£0.20	Clinical review
	Suppository	100mg suppository, pack of 10 = £2.04	50mg	£0.36	Clinical review
	Intramuscular	25mg/ml, 10 ampoules = £9.91	75mg	£2.97	Clinical review
Indomethacin	suppositories	100mg, pack of 10 = £17.61	100mg	£1.76	Clinical review
Ketorolac	30mg/1ml solution for injection ampules	5 ampoule = £6.56	30mg	£0.57	Clinical review
	OPIOIDS				
Pethidine	50mg/1ml solution for injection ampules	10 ampoule = £4.66	100 mg	£0.93	Clinical review
	Smooth muscle relaxants				
Hyoscine Butylbromide	20mg/1ml solution for injection ampoules	10 ampoule = £2.92	20mg	£0.29	Clinical review
Paracetamol	1g/100ml solution for infusion (vial)	10 vials = £3.96	1g	£0.40	Clinical review

Source: BNF NHS Drug Tariff, DATE; October 2017
(a) Daily cost estimate refers to single drug administration. Daily cost would be double or triple for additional drug administrations required in case pain persists
(b)The costs of meperidine, papaverine are not provided by BNF site

Table 20: Other resource use

Resource	Detail	Unit cost	Source
GP appointment	Per patient contact lasting 9.22 minutes	£38	PSSRU 2017{Curtis, 2017 #1576}
Emergency department attendance	Type 01 non admitted VB09Z Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	£119	NHS reference costs 2016/17{NHS Improvement, 2017 #1570}

1.6 Resource costs

The recommendations made by the committee based on this review (see section 1.8) may have a substantial impact on resources.

Additional costs could be incurred for the following reasons: the use of IV paracetamol requiring hospital attendance.

1.7 Evidence statements

1.7.1 Clinical evidence statements

NSAID versus opioid/opiate

Twenty-two studies compared NSAIDs to opioid/opiates. Eight studies reported the outcome pain intensity (VAS & NRS; 0-10) and evidence suggested no clinical difference between the two interventions (n=1675). One study reported the outcome pain intensity on a different scale (VAS; 1-10) and this evidence suggested no clinical difference between the two interventions (n=97). Pain was also reported in terms of the number of participants with no pain relief, partial pain relief and complete pain relief, and there was no clinical difference between the interventions (4-7 studies; n=336-715). The need for rescue medication was reported by 17 studies and showed a clinical benefit of NSAIDs compared to opioids/opiates (n=2769). One study reported pain in terms of a reduction in pain NRS score >3 and found no clinical difference between the interventions, but a clinical benefit of NSAID when pain was reported in terms of persistent pain after 1 hour (n=1096). Three studies reported pain in terms of a reduction in pain by 50%, and evidence showed a clinical benefit of NSAID (n=1708). One study reported major adverse events (defined as significant side effects) and found no clinical difference between the interventions (n=97). Minor adverse events were reported by a total of 18 studies. Two studies reported nausea and vomiting, 10 studies reported nausea, 10 studies reported vomiting, 6 studies reported the outcome sleepiness, 12 reported dizziness and 4 studies reported unspecified adverse events (n=206-1490). All showed a clinically important benefit of NSAIDs. There was no clinical difference between interventions in terms of urinary retention (1 study; n=234) or injection site or local pain (2 studies; n=359). The quality of the evidence ranged from High to Very Low. The main reasons for downgrading evidence included risk of bias, imprecision and in some cases, inconsistency.

NSAID versus paracetamol

Five studies compared NSAID to paracetamol. No clinical difference between interventions was found for the outcomes pain intensity, pain reported as a reduction in NRS pain score by >3, and a reduction in pain by 50% (1-3 studies; n=1095-1341). When pain was reported as need for rescue medication (4 studies; n=1541), persistent pain after 1 hour (1 study; n=1095) and complete pain relief (2 studies; n=250), the evidence demonstrated a clinical

benefit of NSAID. One study reported partial pain relief (n=200) and the evidence suggested a clinical benefit of paracetamol. Five minor adverse event outcomes were reported. There was no clinical difference between NSAIDs and paracetamol in terms of unspecified minor adverse events (2 studies, n=1145), vomiting (3 studies; n=476), dizziness (2 studies; n=396) or epigastric pain (1 study; n=196). One study found a clinical benefit of paracetamol in terms of the outcome abdominal pain (n=80). The quality of the evidence ranged from High to Very Low. The main reasons for downgrading evidence were risk of bias, imprecision and in some cases, inconsistency.

NSAID versus muscle relaxant/antispasmodic

Three studies compared NSAIDs to muscle relaxants/antispasmodics. No clinical difference was found between the interventions in terms of pain intensity (1 study; n=59). One study demonstrated a clinical benefit of pain reported as complete pain relief (n=200), and 2 studies demonstrated a clinical benefit of NSAID in terms of pain reported as need for rescue medication (n=106). Two minor adverse events were reported: 2 studies demonstrated a clinical benefit of NSAID in terms of drowsiness/sleepiness (n=106), and 1 study demonstrated a clinical benefit of NSAID in terms of dizziness (n=59). The quality of the evidence ranged from Moderate to Very Low. The main reasons for downgrading evidence were risk of bias, imprecision and in some cases, inconsistency and indirectness.

NSAID versus placebo

Four studies compared NSAIDs to placebo. A clinical benefit of NSAID was found for the outcomes of pain intensity, pain relief, need for rescue medication, the number of people with no pain relief, and the number of people with complete pain relief (1-3 studies; n=19-170). There was no clinical difference between interventions in terms of the number of people with partial pain relief (1 study; n=19). The quality of the evidence ranged from Moderate to Very Low. The main reasons for downgrading evidence were risk of bias, imprecision and in some cases, inconsistency.

Opioid/opiate versus paracetamol

Six studies compared opioids/opiates to paracetamol. There was no clinical difference between the interventions in terms of the following pain outcomes: pain intensity (5 studies; n=1497); the need for rescue medication (5 studies; n=1575); a reduction in pain NRS score >3 (1 study; n=1097); the major adverse event of respiratory depression (2 studies; n=168). A clinical benefit of paracetamol was found in terms of pain reported as a reduction in pain by 50%, persistent pain after 1 hour and complete pain relief (1 study; n=200-1097). There was a clinical benefit of opioid in terms of pain reported as partial pain relief (1 study; n=200). In terms of adverse events, there was no clinical difference between interventions for minor adverse events of nausea and vomiting, urinary retention, and unspecified minor adverse events (1-2 studies; n=95-1097), or for the major adverse events respiratory depression (2 studies; n=168). For the minor adverse events of nausea, vomiting and dizziness, a clinical benefit of paracetamol was found (1-3 studies; n=108-432). A clinical benefit of paracetamol was also found in terms of length of stay, when reported as the number of people discharged within 1 hour (1 study; n=108). The quality of the evidence ranged from High to Very Low. The main reasons for downgrading evidence were risk of bias and imprecision. There was inconsistency for the pain intensity outcome and indirectness for unspecified minor adverse events.

Opioid/opiate versus muscle relaxant/antispasmodic

Two studies compared opioids/opiates to muscle relaxants/antispasmodics. No clinical difference was found between the interventions in terms of pain intensity, the need for rescue medication, the number of people with no pain relief, and the time to pain relief (1-2 studies; n=68-108). A clinical benefit of opioids/opiates was found in terms of the number of people with complete pain relief, and the number of people with pain relief within 5 minutes (1 study; n=40). In terms of minor adverse events, there was no clinical difference between the

interventions in terms of nausea, and in terms of vomiting (1 study, n=68). There was a clinical benefit of muscle relaxant/antispasmodics in terms of nausea and vomiting as a single outcome, and dizziness (1-2 studies; n=40-108). The quality of the evidence ranged from Low to Very Low. The main reasons for downgrading evidence were risk of bias and imprecision.

Opioid/opiate versus placebo

One study compared opioids/opiates to placebo. There was no clinical difference between the interventions in terms of pain intensity, major adverse events (respiratory depression), or minor adverse events (urinary retention) (n=100). There was a clinical benefit for opioid/opiate in terms of need for rescue medication (n=100), and a clinical benefit for placebo in terms of the minor adverse event, nausea and vomiting. The quality of the evidence ranged from Low to Very Low. The main reasons for downgrading evidence were risk of bias and imprecision.

Paracetamol versus placebo

One study compared paracetamol to placebo. The evidence demonstrated a clinical benefit of paracetamol in terms of the outcomes pain intensity and need for rescue medication (n=97). There was no clinical difference between interventions in terms of the major adverse events outcome of respiratory depression, or for the minor adverse event outcome of urinary retention (n=97). There was a clinical benefit of placebo in terms of nausea and vomiting (n=97). The quality of the evidence ranged from Low to Very Low. The main reasons for downgrading evidence were risk of bias and imprecision.

Muscle relaxant/antispasmodic versus placebo

One study compared muscle relaxant/antispasmodics to placebo. There was a clinical benefit of muscle relaxant for the outcome of pain, reported as the number of people with complete pain relief (n=200), and there was a clinical benefit of placebo in terms of unspecified adverse events (n=200). The quality of the evidence was Very Low. The main reasons for downgrading the evidence were risk of bias and imprecision.

Combinations – NSAID + muscle relaxant versus NSAID

One study compared a combination of NSAID and muscle relaxant to NSAID only. There was a clinical benefit of the NSAID alone in terms of the need for rescue medication (n=57). There was no clinical difference between interventions in terms of pain intensity (VAS), dizziness and sleepiness (n=57). The quality of the evidence was Moderate to Very Low. The main reasons for downgrading the evidence were risk of bias and imprecision.

Combinations – NSAID + muscle relaxant versus muscle relaxant

One study compared a combination of NSAID and muscle relaxant to NSAID only. There was a clinical benefit of the NSAID + muscle relaxant combination in terms of the need for rescue medication and dizziness (n=56). There was no clinical difference between interventions in terms of pain intensity (VAS) and sleepiness (n=56). The quality of the evidence was Moderate to Low. The main reasons for downgrading the evidence were risk of bias and imprecision.

Combinations – NSAID + opioid + muscle relaxant versus NSAID + opioid

One study compared a combination of NSAID, opioid and muscle relaxant to NSAID and opioid. There was a clinical benefit of the NSAID, opioid and muscle relaxant combination in terms of the need for rescue medication (n=89). There was no difference between the two combinations in terms of pain intensity, vomiting, nausea, dizziness, sleepiness or the major adverse event respiratory depression (n=89). The quality of the evidence was Very Low. The main reasons for downgrading the evidence were risk of bias and imprecision.

Combinations – NSAID + opioid versus NSAID

One study compared a combination of NSAID and opioid to NSAID alone. There was a clinically important benefit found for NSAID + opioid in terms of the need for rescue medication (n=200). No clinical difference was found between interventions in terms of vomiting, nausea and dizziness (1 study; n=200). The quality of the evidence was Very Low. The main reasons for downgrading the evidence were risk of bias and imprecision.

Combinations – NSAID + opioid versus opioid

One study compared a combination of NSAID and opioid to opioid alone. There was no clinically important difference found between interventions for the following outcomes: need for rescue medication, nausea, vomiting and dizziness (1 study; n=200). The quality of the evidence was Very Low. The main reasons for downgrading the evidence were risk of bias and imprecision.

Combinations – NSAID + paracetamol versus NSAID

One study compared a combination of NSAID and paracetamol to NSAID alone. There was a clinically important benefit found for NSAID + paracetamol in terms of pain intensity and complete pain relief (n=50). No clinical difference was found between interventions in terms of need for rescue medication and minor adverse events (unspecified) (n=50). The quality of the evidence was Moderate to Very Low. The main reasons for downgrading the evidence were risk of bias and imprecision.

Combinations – NSAID + paracetamol versus paracetamol

One study compared a combination of NSAID and paracetamol to paracetamol alone. There was a clinically important benefit found for NSAID + paracetamol in terms of pain intensity, complete pain relief and need for rescue medication (n=50). No clinical difference was found between interventions in terms of minor adverse events (unspecified) (n=50). The quality of the evidence was Moderate to Very Low. The main reasons for downgrading the evidence were risk of bias and imprecision.

1.7.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.8 Recommendations

E1. Offer a non-steroidal anti-inflammatory drug (NSAID) by any route as first-line treatment for adults, children and young people with suspected renal colic.

E2. Offer intravenous paracetamol to adults, children and young people with suspected renal colic if NSAIDs are contraindicated or have not been effective.

E3. Do not offer opioids to adults, children and young people with suspected renal colic unless both NSAIDs and intravenous paracetamol are contraindicated or have not been effective.

E4. Do not offer muscle relaxants to adults, children and young people with suspected renal colic.

1.8.1 Research recommendations

Research question: What is the most clinically and cost effective route of administration for NSAID in the management of acute pain thought to be due to renal or ureteric stones?

1.9 Rationale and impact

1.9.1 Why the committee made the recommendations

Evidence showed that non-steroidal anti-inflammatory drugs (NSAIDs) reduced the need for rescue medication compared with opioids, muscle relaxants, and intravenous paracetamol. NSAIDs also reduced pain and had fewer adverse effects. NSAIDs had a better balance of benefits and costs, so the committee agreed that these should be offered as a first-line treatment for people with suspected renal colic.

The committee discussed the route of administration for NSAIDs, and noted that the evidence was heterogeneous in terms of the specific route used in the studies. They noted that most studies used intravenous or intramuscular NSAIDs. They agreed that the evidence does not reflect current practice, which has changed over time, as oral or rectal NSAIDs are more commonly used. . The committee were concerned that there was very little evidence that oral or rectal NSAIDs were as effective as intravenous or intramuscular NSAIDs, and were reluctant to recommend a significant change in practice that would have resource implications. Therefore, the committee were not able to specify a particular route of administration of NSAIDs, but did agree to make a research recommendation to inform future practice. Not specifying the route of administration also allows more flexibility for primary care staff, and people with recurrent stones or people who can manage their pain in the community.

Some evidence showed a benefit of paracetamol for pain relief when compared with opioids. The committee noted that most of the evidence was based on intravenous paracetamol. They agreed that intravenous paracetamol differed from other routes of paracetamol administration in terms of potency and speed of action, and therefore this benefit could not be generalised to other routes of administration, such as oral. This difference in mechanism of action was not believed to be as strong for other drugs such as NSAIDs. Therefore, the committee recommended that intravenous paracetamol should be offered if NSAIDs cannot be used or have not been effective.

Opioids showed a benefit compared with muscle relaxants in terms of pain relief, and there was no difference between opioids and most comparators in terms of adverse events. There was no benefit of opioids over NSAIDs or paracetamol. The committee also noted concerns around opioid use in terms of dependency and misuse. The committee agreed that opioids could only be offered if both NSAIDs and intravenous paracetamol were contraindicated or not effective.

Muscle relaxants offered no benefit in terms of pain relief when compared with NSAIDs. The committee also highlighted that in the studies muscle relaxants were given intravenously, whereas in clinical practice an oral route is often used for adults. The committee discussed how muscle relaxants can be more difficult to administer intravenously, because of an increased risk of adverse events and a need for intensive monitoring. They agreed that muscle relaxants should not be offered to people with suspected acute renal colic.

Very limited evidence for combinations of NSAIDS, opioids and muscle relaxants compared to NSAIDs and opioids, NSAIDs and muscle relaxants compared to either drug alone, and NSAIDs and oral paracetamol compared to either drug alone showed some benefit of a combination of NSAIDs and oral paracetamol, for pain relief, and no increase in adverse events. The committee considered that this was based on small, single studies. They noted that in practice, two drugs would not be given at the same time, but a second would usually be given if the first line drug hasn't worked, in a staged manner. They also noted that people with recurrent stones may self-manage with both oral paracetamol and NSAIDs and so it is important to ask people presenting with suspected renal colic about previous analgesia use.

Overall, they agreed that there was not enough convincing evidence for any of the combination treatments.

All the identified evidence was for adults with renal or ureteric stones. However, the committee agreed that it would be reasonable to extrapolate the evidence on pain relief to children and young people and to include this age group in the recommendations.

1.9.2 Impact of the recommendations on practice

Currently, intravenous paracetamol is not used routinely for managing pain in people with acute renal colic, but is used in other areas of secondary care (analgesia during surgery). Extending its use into other clinical areas (for example, emergency departments and surgical assessment units) will mean changes in policy and additional training for staff. Therefore this recommendation will require a change from current practice by most or all providers. The use of intravenous paracetamol may also have some implications for practice if more hospital attendances are required to administer the treatment..

1.10 The committee's discussion of the evidence

1.10.1 Interpreting the evidence

1.10.1.1 The outcomes that matter most

The committee agreed that quality of life, pain, major adverse events and minor adverse events were the outcomes that were critical for decision making. Length of stay in hospital and use of healthcare services were also considered as important outcomes.

Evidence was reported for pain, major adverse events, minor adverse events, and length of stay. There was no evidence for the critical outcome of quality of life, or for the important outcome of use of healthcare services.

1.10.1.2 The quality of the evidence

For the majority of evidence in this review, the quality ranged from a GRADE rating of moderate to very low. This was due to a lack of blinding, presence of selection bias in terms of a lack of adequate randomisation and allocation concealment, and risk of measurement bias, resulting in a high or very high risk of bias rating. Evidence was further downgraded due to the presence of imprecision for many outcomes, and heterogeneity for some outcomes. Six outcomes were given a high quality rating. This included pain in terms of reduction in pain by 50% and reduction in pain numerical rating scale (NRS) by >3, and came from a single large study of 1097 participants, in the opioid versus paracetamol comparison. In the NSAID versus paracetamol comparison, 2 outcomes (need for rescue medication and reduction in NRS pain score by >3) from the same study had a high quality rating, and in the NSAID versus opioid comparison the same study had high quality evidence for the persistent pain, and reduction in pain NRS score >3 outcomes.

1.10.1.3 Benefits and harms

Evidence for adults and children and young people was searched for, however none was identified for children and young people. The committee agreed that it would be appropriate for the recommendations to apply to both adults and children and young people based on consensus and current practice.

NSAID

The committee considered the evidence for NSAIDs and noted that the majority of the evidence was from studies that used an intravenous or intramuscular route of administration,

whereas only one study used an oral preparation, and 4 used rectal preparations. It was noted that this differs from current practice, where oral or rectal are currently more common, and therefore the results may not reflect practice in the UK.

When compared to placebo, the committee noted that all pain outcomes apart from partial pain relief showed a clinically important benefit of NSAID.

When compared to paracetamol, the committee noted that there was no difference between the interventions in terms of pain intensity, but there were benefits of NSAIDs in terms of need for rescue medication and the number of people with persistent pain. The committee noted that the majority of the studies used an intravenous route for paracetamol. Only one study used an oral route and this was a very small study of low quality. The committee discussed that the evidence for pain intensity did not reflect experience from clinical practice, and considered that this may be due to the use of an intravenous route of administration for paracetamol. The committee noted that intravenous paracetamol is very different to other routes of administration in terms of speed of action and potency, and that intravenous paracetamol is not part of usual practice. Because of this, the committee agreed that this evidence cannot be extrapolated other routes of administration.

The committee considered the evidence for NSAIDs compared to opioids and noted that in terms of pain, the majority of evidence suggested either a clinical benefit of NSAIDs or no difference between the 2 interventions. The committee agreed that overall the evidence for adverse events demonstrated a clinical benefit of NSAIDs. The committee concluded that the evidence demonstrates that NSAIDs are more effective in terms of reducing the need for additional rescue medication, reducing both pain intensity and length of pain episodes, and have fewer adverse events. The committee also discussed the difficulties of administering opioids in clinical practice, and therefore the potential benefits of using NSAIDs, such as potentially shorter hospital stays and quicker pain relief for patients. The committee also considered the implications of prolonged opioid use and potential misuse, and agreed based on clinical experience and expertise that NSAIDs are therefore a safer option.

The comparison of NSAID and muscle relaxants showed a benefit of NSAIDs for most pain and adverse events outcomes reported. There was no difference between the two interventions in terms of pain intensity, although the committee noted that this was a single study of low quality, and did show a trend towards a benefit of NSAIDs. The committee therefore agreed that overall, the evidence supported the use of NSAIDs over muscle relaxants.

Overall, the committee noted that the evidence demonstrated that NSAIDs were more clinically effective that placebo, opioids, paracetamol and muscle relaxants, and therefore NSAIDs should be recommended as a first line pain relief. The committee noted from clinical experience that NSAIDs carry risks such as acute kidney injury (AKI), and therefore all patients receiving NSAIDs should be monitored for this risk, as well as all other associated side effects and contraindications. The committee discussed specifying a particular route of administration for NSAIDs, but agreed that the evidence was too varied in terms of the administration route used in the studies. They agreed unlike paracetamol, the difference between the routes in terms of potency and speed of action is not as significant for NSAIDs and that experience from clinical practice suggests that they are all equally effective, They noted that head to head comparisons of route of administration was not part of the protocol and so this was not specifically looked for in the evidence. Overall, the committee agreed to specify in the recommendation that any route of administration could be used. This also allows the recommendation to be applicable to a community setting, where oral or rectal NSAID can be used, as recurrent stone formers in particular tend to manage their pain at home. The committee considered that many of the studies were over 15 years old, and may be reflective of standard practice at that time, when intravenous NSAIDs were often used. However, the committee agreed that standard practice for NSAIDs administration has changed and now an oral or rectal route of administration is used. This is not based on

evidence, but due to other factors such as changes in availability and ease of use. They therefore agreed that a research recommendation in this area would inform future practice.

Paracetamol

When compared to placebo, the committee noted that there was a benefit of paracetamol for both pain outcomes, and no difference or benefit of placebo in terms of adverse events. The committee noted that all evidence from this comparison came from a single study of 97 participants.

The committee also considered the evidence for NSAID versus paracetamol and opioid versus paracetamol. Overall, the committee agreed that the evidence suggested a benefit of paracetamol over placebo and opioids, but not when compared to NSAIDs. The committee therefore agreed that paracetamol should be recommended as a second line treatment where NSAIDs can't be used or have not been effective.

The committee noted that all evidence for paracetamol was from studies that used an intravenous route of administration, apart from one small study that used an oral route. They agreed that this data could not be used to extrapolate to other routes of administration. Therefore, the committee agreed to specify that if paracetamol is used, it should be given intravenously.

Opioid

The committee noted that when compared to placebo, there was a clinical benefit of opioids in terms of need for rescue medication, but no clinical difference in terms of pain intensity, and some adverse events. The committee agreed that this suggests that there is no benefit of opioids over placebo, but noted that all evidence from this comparison came from a single study of 100 people and was all of low or very low quality.

When compared to intravenous paracetamol, the committee noted that the evidence suggested a clinical benefit of paracetamol in terms of reduction in pain by 50%, persistent pain and some adverse events, and no clinical difference in pain intensity, need for rescue medication and major adverse events outcomes. The committee agreed that this suggests there is no benefit of opioids over paracetamol, and that intravenous paracetamol should be offered before considering the use of opioids.

When compared to muscle relaxants, the committee noted that there was no clinical difference between interventions for four of the six pain outcomes. The outcomes of complete pain relief and pain relief within 5 minutes outcomes showed a benefit of opioids in one study. The committee considered this evidence and agreed that there no clinical difference for many outcomes, and that overall the evidence also demonstrated there was no benefit of muscle relaxants over opioids.

The GC also discussed the harms associated with increased risk of opioid misuse, and noted opioids are often used as the last management option when the maximum dose of other analgesics have been prescribed.

Overall, the committee agreed that the evidence showed a benefit of opioid over placebo, but no benefit when compared to paracetamol or NSAIDs, and little benefit when compared to muscle relaxants. The committee therefore agreed that opioids should not be routinely offered as first or second line pain relief, and should only be given when other treatment has been ineffective or contraindicated. At this point a suspected diagnosis of renal colic might be reconsidered if NSAID and paracetamol pain relief is not effective.

Muscle relaxant

The committee considered the evidence for muscle relaxants compared to placebo and noted that there was a clinical benefit of muscle relaxants in terms of pain relief, and a

clinical benefit of placebo in terms of unspecified minor adverse events. The committee noted that although this appears to show a benefit of muscle relaxants in terms of pain, their use are not part of current practice, and further, all evidence came from a single study of 200 participants, and was of low and very low quality.

The committee also considered evidence from the comparisons of NSAID versus muscle relaxant and opioid versus muscle relaxant and agreed that overall, there was no benefit of muscle relaxants over opioids or NSAIDs. The committee also considered the difficulties in giving muscle relaxants in clinical practice, such as hypotension and tachycardia, and that all evidence in the review used an intravenous method of administration, whereas in clinical practice muscle relaxants are more likely to be given orally. The committee noted that as the intravenous route is expected to be the most effective route of administration, it is likely that other routes of administration, such as oral, would be even less effective. Based on this, the committee agreed that muscle relaxants should not be recommended.

Combinations

Four studies were included that compared combinations of pain relief drugs. One study compared NSAID + opioid + muscle relaxant to NSAID + opioid. The evidence demonstrated a clinical benefit of the 3 intervention combination in terms of the need for rescue medication, but no clinical difference between the groups in terms of pain intensity, or any adverse events. The committee considered this evidence and agreed that because the evidence came from a single, small study, was of very low and low quality for all but one outcome, and showed no clinical difference for all but one outcome, there was not enough convincing evidence to recommend this combination. It was further noted that the study used an intravenous route of administration for the muscle relaxant, which is not part of usual practice, and is associated with serious adverse cardiovascular events.

One study compared a combination of NSAID + muscle relaxant with NSAID alone, and with muscle relaxant alone. When compared with NSAID alone the committee noted that there were fewer people needing rescue medication in the NSAID alone group, and no difference for any other outcomes. Compared to muscle relaxant alone there were also fewer people needing rescue medication and fewer people experiencing dizziness. The committee agreed that this was not convincing evidence to recommend this combination, compared to either drug alone.

One study compared a combination of NSAID + opioid with NSAID alone, and with opioid alone. When compared with NSAID alone, the committee noted that there were fewer people needing rescue medication, and no difference between groups in terms of adverse events. There was no difference between any of the outcomes when the combination was compared to opioid alone. The committee considered that this evidence was based on a small number of participants and was very low quality. They agreed that there was no convincing evidence that there was any additional benefit of combined treatment with NSAIDs and opioid, compared to either drug alone.

One study compared a combination of NSAID + paracetamol to both NSAID alone and paracetamol alone. When compared with NSAID alone, the committee noted that there was a clinical benefit of the combination in terms of pain intensity, but no difference in terms of need for rescue medication or adverse events. When compared to paracetamol alone, there was a benefit of the combination for both pain related outcomes, and no difference for adverse events. The committee highlighted that the route of administration of paracetamol in this study was oral, and that there did seem to be some benefit of combined NSAID and oral paracetamol. The committee considered that an advantage of oral paracetamol is that it can be used to self-manage pain at home by recurrent stone formers, without the need to visit A&E. However, they noted that the route of administration for the NSAID in this study was intramuscular, which would probably require a hospital visit. They also noted that self-managing with paracetamol would have implications for the ability to give further analgesia with paracetamol, and that clinicians would need to assess previous paracetamol

consumption and wait for enough time to elapse before intravenous paracetamol could be administered. Overall, the committee considered that this was the only study using an oral preparation, and that it was very small and very low quality. They therefore agreed that there wasn't enough evidence to recommend this combination.

The committee also noted that in all combination studies, the drugs are given at the same time, whereas in a real world scenario, combinations would be given in a staggered manner.

1.10.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

Pain medication tends to be low cost. Unit costs presented to the committee as costs per single dose administration showed that this ranges from 20 pence to around £1. All trials from the clinical review used a single dose of pain medication as generally that is what would be required for an acute pain episode. Patients may then either take oral pain medication for further pain episodes or present to an emergency department (or in some cases GP) where they may be given pain relief in another form (intramuscular (IM)/intravenous (IV)).

Other resource use associated with administering pain relief depends on the type of drug and the method by which it is administered. IV administration will usually require an admission (or at least the patient being on a trolley in the hospital) and IM administration could be given by a GP. Therefore compared to oral administration, for which a patient could take a prescription away with them, IV or IM administration would require either a hospital or GP attendance to administer the drug every time the pain is unmanageable. Compared to providing other drugs intravenously, opioids require a longer hospital stay because patients need to be observed for longer periods before they can be discharged; for example, with IV paracetamol patients can be discharged more quickly. Anti-emesis is also usually given with opioids to combat the common side effect of nausea. Opioid prescribing can still be a controversial area due to the controlled nature of the drug, and the trade off from providing alleviation for significant pain but people often having to tolerate significant adverse events as a result.

In terms of what we can infer about cost effectiveness from the clinical review: when comparing the drugs to placebo, there was a clinical benefit on the pain outcomes demonstrating that the drugs work. The GC recognised that there is usually a large placebo effect with pain relief, particularly when delivered by the intravenous route. For acute pain episodes the period of time that quality of life would apply is very small because the pain episodes are short, therefore any QALY improvement will be very small, creating large ICERs. However, in spite of this it would not be ethical to deny people pain relief.

<u>For drugs compared to each other:</u>

NSAIDs versus opioids showed a clinical benefit for NSAIDs as they were associated with fewer minor adverse events and had less need for rescue medication, therefore the use of NSAIDs is expected to be less costly than opioids. Alongside this, NSAIDs are less likely to require other resource use such as staff time, making NSAIDs a dominant intervention compared to opioids.

NSAIDs versus paracetamol (predominantly IV paracetamol) gave contradictory results, as this comparison showed that patients who used NSAIDs needed less rescue medication, whereas paracetamol was associated with fewer adverse events of abdominal pain.

Opioids compared to (IV) paracetamol showed either benefit of paracetamol for pain or no difference, and also a shorter length of stay for paracetamol, (as more monitoring is required with opioids). There was also a benefit for paracetamol in terms of fewer adverse events. If paracetamol is also cheaper because of less resource use such as length of stay or staff time, then paracetamol is a dominant intervention compared to opioids.

The committee consensus, based on the clinical evidence, was that the analgesic role of opioids in this area is perhaps more prominent than it deserves to be. In current practice NSAIDs are the first drug of choice, and then usually IV morphine if this has not been effective. Patients might then also be given prescription NSAIDs to take away with them. The clinical evidence however suggested that both NSAIDs and paracetamol were more effective than opioids. The committee agreed on recommendations for NSAID as the first line analgesic, paracetamol (IV) as second line, and a 'do not use opioids' recommendation to stress that this should only be given when other treatment has been ineffective or contraindicated. At this point a suspected diagnosis of renal colic might be reconsidered if pain relief is not working.

Some evidence was identified for combination treatment, which would have a higher cost associated with it, particularly if different interventions are delivered using different routes of administration. However the committee did not feel confident making recommendations based on this evidence.

The committee discussed the different patient groups that might be affected by these recommendations. Recurrent stone formers who suspect that they have renal colic, if they are familiar with the symptoms, may present to their GP rather than the emergency department. A recommendation specifying a particular preparation to be used may result in this group of people being referred to hospital, whereas an oral or suppository preparation would be as effective, with advice that the patient could go to hospital if these did not relieve their pain. The GC therefore wanted to make a recommendation for NSAIDs, without specifying the form of administration, in order to provide clinicians with the flexibility to make a decision on the preparation that was appropriate for the clinical scenario. If someone has presented to their GP rather than to an emergency department, their pain may not be extreme. If pain relief is needed out of hours, then a preparation could be given in the patient's home without them needing to go to the hospital (e.g. IM).

There was discussion about the recommendation for IV paracetamol, because if this replaces current practice of using opioids, then this implies that a hospital attendance or admission is needed in order to have this administered (each time this is needed). This may be a change in practice if an oral form of an opioid could have been given instead. This may apply to recurrent stone formers who are more likely to be well managed in the community/primary care.

However, if someone was finding their pain unmanageable, they may go to hospital anyway because non-oral forms of pain relief are faster acting - and so some hospital attendances are likely to be considered necessary.

With new stone formers, a diagnosis of suspected renal colic will need to be confirmed, in which case a hospital attendance or possibly admission will be necessary. Diagnosis might be made at their first attendance to the hospital or they will come back within a certain timeframe, and further pain relief could be administered.

The committee acknowledged there is an element of flexibility in the recommendations to account for the different patient groups, making the resource impact variable depending on factors such as where people present (GP or hospital).

1.10.3 Other factors the committee took into account

The committee discussed the route of administration across all comparisons. It was noted that some comparisons included an intravenous route compared to an intramuscular route, and the committee discussed whether this comparison was appropriate, due to differences in the speed of action associated with these different routes. However, it was noted that the only studies reporting time to pain relief used an intravenous route in both arms. Further, there was only one study comparing an active drug to placebo that used an intravenous route in the placebo arm but not the drug arm.

When considering the evidence for paracetamol, the committee noted that intravenous paracetamol differed from other routes of paracetamol administration in terms of potency and speed of action. All the evidence for paracetamol apart from one small study, came from studies using an intravenous method. Therefore the committee agreed that based on the evidence, only an intravenous route of administration could be recommended.

Table 21: Route of administration

NSAID	OPIOID	Number of studies
IV	IV	8
IV	IM	1
IV	Subcutaneous	1
IV	Sublingual	1
IM	IV	1
IM	IM	7
Oral	IM	1
Rectal	IM	2
Rectal	Rectal	1
Rectal	'injection'	1
NSAID	**PARACETAMOL**	
IM	IV	2
IM	Oral	1
IV	IV	2
NSAID	**MUSCLE RELAXANT**	
IM	IV	2
IV	IV	1
NSAID	**PLACEBO**	
IM	IV	1
IM	IM	2
IV	IV	1
OPIOID	**PARACETAMOL**	
IV	IV	5
OPIOD	**MUSCLE RELAXANT**	
IV	IV	2
OPIOID	**PLACEBO**	
IV	IV	1
PARACETAMOL	**PLACEBO**	
IV	IV	1
MUSCLE RELAXANT	**PLACEBO**	
IV	IV	1
COMBINATIONS		
NSAID + MUSCLE RELAXANT	**NSAID**	
IM + IV	**IM**	**1**
NSAID + MUSCLE RELAXANT	**MUSCLE RELAXANT**	
IM + IV	**IV**	**1**
NSAID + OPIOID + MUSCLE RELAXANT	**NSAID + OPIOID**	
IV	IV	1
NSAID + OPIOID	**OPIOID**	

IV	IV	1
NSAID + OPIOID	**NSAID**	
IV	IV	1
NSAID + PARACETAMOL	**NSAID**	
IM + oral	IM	1
NSAID + PARACETAMOL	**PARACETAMOL**	
IM + oral	Oral	1

The committee considered the evidence for NSAIDs, and agreed that it was heterogeneous in terms of the type of NSAID used in the comparisons, and the route of administration used, making comparisons difficult to interpret. It was noted that when considering the NSAID evidence, the majority of studies used either an intravenous or intramuscular route of administration, whereas in current practice an oral or rectal route of administration is often used. Only one small study of 94 participants looked at an oral route of NSAID administration compared to intramuscular opioid, and the committee noted that this study demonstrated a clinical benefit of opioid for the outcomes of unspecified minor adverse events, but no difference in terms of the number of pain free participants. The committee noted that this study had a high risk of bias, very serious imprecision, and was over 15 years old and therefore unlikely to reflect current practice. Therefore, the committee agreed that there was not sufficient evidence to specify a particular route of administration within the recommendation, and that the appropriate route of administration to use would depend on the clinical situation.

When considering the evidence for opioids, the committee noted that pethidine is less commonly used for renal colic in current UK practice; however of the 24 studies comparing opioids, 10 of them used pethidine. The committee therefore considered that the evidence may not be representative of UK practice.

The committee noted that many people self-manage pain at home before going to hospital or to their GP. They therefore agreed that it is important for clinicians to ask people with suspected renal colic about any previous analgesia use at home, as there is a risk of overdose particularly for paracetamol.

The committee discussed current practice for the paediatric population. This includes NSAIDs, paracetamol and/or opioids. Therefore they concluded that the recommendations should apply to both adults and children. The committee noted however, that as with adults, children receiving NSAIDs should be closely monitored for AKI.

References

1. Abbasi S, Bidi N, Mahshidfar B, Hafezimoghadam P, Rezai M, Mofidi M et al. Can low-dose of ketamine reduce the need for morphine in renal colic? A double-blind randomized clinical trial. American Journal of Emergency Medicine. 2018; 36(3):376-9

2. Afshar K, Jafari S, Marks AJ, Eftekhari A, MacNeily AE. Nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioids for acute renal colic. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD006027. DOI: 10.1002/14651858.CD006027.pub2.

3. Aganovic D, Prcic A, Kulovac B, Hadziosmanovic O. Clinical decision making in renal pain management. Acta Informatica Medica. 2012; 20(1):18-20

4. al-Sahlawi KS, Tawfik OM. Comparative study of the efficacy of lysine acetylsalicylate, indomethacin and pethidine in acute renal colic. European Journal of Emergency Medicine. 1996; 3(3):183-6

5. Al-Waili NS, Saloom KY. Intramuscular piroxicam versus intramuscular diclofenac sodium in the treatment of acute renal colic: double-blind study. European Journal of Medical Research. 1999; 4(1):23-6

6. Al B, Sunar MM, Zengin S, Sabak M, Bogan M, Can B et al. Comparison of intravenous dexketoprofen trometamol, fentanyl, and paracetamol in the treatment of patients admitted to the emergency department for renal colic: a randomized controlled trial. American Journal of Emergency Medicine. 2017; 36(4):571-6

7. Anonymous. Renal colic in adults: NSAIDs and morphine are effective for pain relief. Prescrire International. 2009; 18(103):217-21

8. Asgari SA, Asli MM, Madani AH, Maghsoudi PA, Ghanaei MM, Shakiba M et al. Treatment of loin pain suspected to be renal colic with papaverine hydrochloride: a prospective double-blind randomised study. BJU International. 2012; 110(3):449-52

9. Ay MO, Sebe A, Kozaci N, Satar S, Acikalin A, Gulen M et al. Comparison of the analgesic efficacy of dexketoprofen trometamol and meperidine HCl in the relief of renal colic. American Journal of Therapeutics. 2014; 21(4):296-303

10. Aydogdu O, Burgu B, Gucuk A, Suer E, Soygur T. Effectiveness of doxazosin in treatment of distal ureteral stones in children. Journal of Urology. 2009; 182(6):2880-4

11. Azizkhani R, Pourafzali SM, Baloochestani E, Masoumi B. Comparing the analgesic effect of intravenous acetaminophen and morphine on patients with renal colic pain referring to the emergency department: a randomized controlled trial. Journal of Research in Medical Sciences. 2013; 18(9):772-6

12. Bahn Zobbe V, Rygaard H, Rasmussen D, Strandberg C, Krause S, Hartvig Hartsen S et al. Glucagon in acute ureteral colic: a randomized trial. European Urology. 1986; 12(1):28-31

13. Barry HC. Low-dose morphine less effective than diclofenac or acetaminophen for renal colic. American Family Physician. 2016; 94(8):665

14. Basar I, Bircan K, Tasar C, Ergen A, Cakmak F, Remzi D. Diclofenac sodium and spasmolytic drugs in the treatment of ureteral colic: a comparative study. International Urology and Nephrology. 1991; 23(3):227-30

15. Bektas F, Eken C, Karadeniz O, Goksu E, Cubuk M, Cete Y. Intravenous paracetamol or morphine for the treatment of renal colic: a randomized, placebo-controlled trial. Annals of Emergency Medicine. 2009; 54(4):568-74

16. Benyajati C. Comparative study of Baralgan and hyoscine-N-methyl bromide in the treatment of intestinal and renal colicy pain. Journal of the Medical Association of Thailand. 1986; 69(10):569-73

17. Bergus GR. Pain relief for renal colic. Journal of Family Practice. 1996; 43(5):438-40

18. Boubaker H, Boukef R, Claessens YE, Bouida W, Grissa MH, Beltaief K et al. Phloroglucinol as an adjuvant analgesic to treat renal colic. American Journal of Emergency Medicine. 2010; 28(6):720-3

19. Bultitude M, Rees J. Management of renal colic. BMJ. 2012; 345(e5499):1-8

20. Burrows PK, Hollander JE, Wolfson AB, Kurz MC, Richards L, DiFiore S et al. Design and challenges of a randomized clinical trial of medical expulsive therapy (tamsulosin) for urolithiasis in the emergency department. Contemporary Clinical Trials. 2017; 52:91-4

21. Caravati EM, Runge JW, Bossart PJ, Martinez JC, Hartsell SC, Williamson SG. Nifedipine for the relief of renal colic: a double-blind, placebo-controlled clinical trial. Annals of Emergency Medicine. 1989; 18(4):352-4

22. Cenker E, Serinken M, Uyanik E. Intravenous paracetamol vs ibuprofen in renal colic: a randomised, double-blind, controlled clinical trial. Urolithiasis. 2017; Epublication

23. Chaudhary A, Gupta RL. Double blind, randomised, parallel, prospective, comparative, clinical evaluation of a combination of antispasmodic analgesic Diclofenac + Pitofenone + Fenpiverinium (Manyana vs Analgin + Pitofenone + Fenpiverinium (Baralgan) in biliary, ureteric and intestinal colic. Journal of the Indian Medical Association. 1999; 97(6):244-5

24. Cohen E, Hafner R, Rotenberg Z, Fadilla M, Garty M. Comparison of ketorolac and diclofenac in the treatment of renal colic. European Journal of Clinical Pharmacology. 1998; 54(6):455-8

25. Comparative study of the efficacy of dipyrone, diclofenac sodium and pethidine in acute renal colic. Collaborative Group of the Spanish Society of Clinical Pharmacology. European Journal of Clinical Pharmacology. 1991; 40(6):543-6

26. Cordell WH, Larson TA, Lingeman JE, Nelson DR, Woods JR, Burns LB et al. Indomethacin suppositories versus intravenously titrated morphine for the treatment of ureteral colic. Annals of Emergency Medicine. 1994; 23(2):262-9

27. Cordell WH, Wright SW, Wolfson AB, Timerding BL, Maneatis TJ, Lewis RH et al. Comparison of intravenous ketorolac, meperidine, and both (balanced analgesia) for renal colic. Annals of Emergency Medicine. 1996; 28(2):151-8

28. Curry C, Kelly AM. Intravenous tenoxicam for the treatment of renal colic. New Zealand Medical Journal. 1995; 108(1001):229-30

29. Daljord OA, Barstad S, Norenberg P. [Ambulatory treatment of an acute attack in urinary calculi. A randomized study of the effects of Petidin, Fortralin, Temgesic and Confortid]. Tidsskrift for den Norske Laegeforening. 1983; 103(12):1006-8

30. Dash A, Maiti R, Akantappa Bandakkanavar TK, Arora P. Intramuscular drotaverine and diclofenac in acute renal colic: a comparative study of analgesic efficacy and safety. Pain Medicine. 2012; 13(3):466-71

31. Dawood Al-Waili NS, Saloom KY. Intravenous tenoxicam to treat acute renal colic: comparison with Buscopan Compositum. Journal of the Pakistan Medical Association. 1998; 48(12):370-2

32. Ebell MH. NSAIDs vs. opiates for pain in acute renal colic. American Family Physician. 2004; 70(9):1682

33. el-Sherif AE, Foda R, Norlen LJ, Yahia H. Treatment of renal colic by prostaglandin synthetase inhibitors and avafortan (analgesic antispasmodic). British Journal of Urology. 1990; 66(6):602-5

34. Elliott JP, Evans JW, Gordon JO, Platt LO. Butorphanol and meperidine compared in patients with acute ureteral colic. Journal of Urology. 1979; 122(4):455-7

35. Engeler DS, Ackermann DK, Osterwalder JJ, Keel A, Schmid HP. A double-blind, placebo controlled comparison of the morphine sparing effect of oral rofecoxib and diclofenac for acute renal colic. Journal of Urology. 2005; 174(3):933-6

36. Erden IA, Artukoglu F, Gozacan A, Ozgen S. Comparison of propofol/fentanyl and ketamine anesthesia in children during extracorporeal shockwave lithotripsy. Saudi Medical Journal. 2007; 28(3):364-8

37. Ergene U, Pekdemir M, Canda E, Kirkali Z, Fowler J, Coskun F. Ondansetron versus diclofenac sodium in the treatment of acute ureteral colic: a double blind controlled trial. International Urology and Nephrology. 2001; 33(2):315-9

38. Faridaalaee G, Mohammadi N, Merghati SZ, Khajeh FK, Naghipour B, Pouraghaei M et al. Intravenous morphine vs intravenous ketofol for treating renal colic; a randomized controlled trial. Emergency. 2016; 4(4):202-6

39. Firouzian A, Alipour A, Rashidian Dezfouli H, Zamani Kiasari A, Gholipour Baradari A, Emami Zeydi A et al. Does lidocaine as an adjuvant to morphine improve pain relief in patients presenting to the ED with acute renal colic? A double-blind, randomized controlled trial. American Journal of Emergency Medicine. 2016; 34(3):443-8

40. Fraga A, De Almeida M, Moreira-Da-Silva V, Sousa-Marques M, Severo L, Matos-Ferreira A et al. Intramuscular etofenamate versus diclofenac in the relief of renal colic: a randomised, single-blind, comparative study. Clinical Drug Investigation. 2003; 23(11):701-6

41. Galassi P, Vicentini C, Scapellato F, Laurenti C. [Use of indomethacin and metamizole administered intravenously in renal colic: Comparative study]. Minerva Urologica. 1983; 35(4):295-300

42. Garcća-Alonso F, Collaborative Group of the Spanish Society of Clinical Pharmacology. Comparative study of the efficacy of dipyrone, diclofenac sodium and pethidine in acute renal colic. European Journal of Clinical Pharmacology. 1991; 40(6):543-6

43. Glina S, Damiao R, Afif-Abdo J, Maria CFS, Novoa R, Cairoli CED et al. Efficacy and safety of parecoxib in the treatment of acute renal colic: a randomized clinical trial. International Brazilian Journal of Urology. 2011; 37(6):697-705

44. Gonzalez Ramallo VJ, Muino Miguez A, Rodriguez de Castro E, Lazaro Bermejo C. [Intramuscular buprenorphine in the symptomatic treatment of renal colic]. Revista Clinica Espanola. 1990; 186(8):414

45. Grissa MH, Claessens YE, Bouida W, Boubaker H, Boudhib L, Kerkeni W et al. Paracetamol vs piroxicam to relieve pain in renal colic: results of a randomized controlled trial. American Journal of Emergency Medicine. 2011; 29(2):203-6

46. Hatipoglu Z, Gulec E, Turktan M, Izol V, Aridogan A, Gunes Y et al. Comparative study of ultrasound-guided paravertebral block versus intravenous tramadol for postoperative pain control in percutaneous nephrolithotomy. BMC Anesthesiology. 2018; 18(24)

47. Hazhir S, Badr YA, Darabi JN. Comparison of intranasal desmopressin and intramuscular tramadol versus pethidine in patients with renal colic. Urology Journal. 2010; 7(3):148-51

48. Hetherington JW, Philp NH. Diclofenac sodium versus pethidine in acute renal colic. BMJ. 1986; 292(6515):237-8

49. Holdgate A, Pollock T. Nonsteroidal anti-inflammatory drugs (NSAIDS) versus opioids for acute renal colic. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD004137. DOI: 10.1002/14651858.CD004137.pub3.

50. Holdgate A, Pollock T. Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. BMJ. 2004; 328(1401):1-8

51. Holmlund D, Sjodin JG. Treatment of ureteral colic with intravenous indomethacin. Journal of Urology. 1978; 120(6):676-7

52. Hosseini MM, Yousefi A, Ghahramani L, Rastegari M, Ebrahimi AR. Comparison of the therapeutic effects of rectal diclofenac sodium and intramuscular pethidine injection in the treatment of acute renal colic: a randomized clinical trial. Journal of Clinical Trials. 2015; 5:3

53. Hosseininejad SM, Ahidashti HA, Bozorgi F, Khatir IG, Montazar SH, Jahanian F et al. Efficacy and safety of combination therapy with ketorolac and morphine in patient with acute renal colic; a triple-blind randomized controlled clinical trial. Bulletin of Emergency and Trauma. 2017; 5(3):165-70

54. Iguchi M, Katoh Y, Koike H, Hayashi T, Nakamura M. Randomized trial of trigger point injection for renal colic. International Journal of Urology. 2002; 9(9):475-9

55. Indudhara R, Vaidyanathan S, Sankaranarayanan A. Oral diclofenac sodium in the treatment of acute renal colic. A prospective randomized study. Clinical Trials Journal. 1990; 27(5):295-300

56. Ioannidis S, Kampantais S, Ioannidis A, Gkagkalidis K, Vakalopoulos I, Toutziaris C et al. Dermal scarification versus intramuscular diclofenac sodium injection for the treatment of renal colic: a prospective randomized clinical trial. Urolithiasis. 2014; 42(6):527-32

57. Jones JB, Dula DJ. The efficacy of sublingual hyoscyamine sulfate and intravenous ketorolac tromethamine in the relief of ureteral colic. American Journal of Emergency Medicine. 1998; 16(6):557-9

58. Jones JB, Giles BK, Brizendine EJ, Cordell WH. Sublingual hyoscyamine sulfate in combination with ketorolac tromethamine for ureteral colic: a randomized, double-blind, controlled trial. Annals of Emergency Medicine. 2001; 37(2):141-6

59. Jonsson PE, Olsson AM, Petersson BA, Johansson K. Intravenous indomethacin and oxycone-papaverine in the treatment of acute renal colic. A double-blind study. British Journal of Urology. 1987; 59(5):396-400

60. KandaSwamy GV, Dhanasekaran AK, Elangovan A, John B, Viswaroop B, Vedanayagam KS. Randomized double blinded placebo controlled trial comparing

diclofenac and piroxicam in management of acute renal colic and its clinical implications. Urology Journal. 2015; 12(2):2069-73

61. Kaynar M, Koyuncu F, Buldu, Tekinarslan E, Tepeler A, Karata T et al. Comparison of the efficacy of diclofenac, acupuncture, and acetaminophen in the treatment of renal colic. American Journal of Emergency Medicine. 2015; 33(6):749-53

62. Kekec Z, Yilmaz U, Sozuer E. The effectiveness of tenoxicam vs isosorbide dinitrate plus tenoxicam in the treatment of acute renal colic. BJU International. 2000; 85(7):783-5

63. Khalifa MS, Sharkawi MA. Treatment of pain owing to acute ureteral obstruction with prostaglandin-synthetase inhibitor: a prospective randomized study. Journal of Urology. 1986; 136(2):393-5

64. Kheirollahi AR, Tehrani M, Bashashati M. A comparison of the effect of intranasal desmopressin and intramuscular hyoscine N-butyl bromide combination with intramuscular hyoscine N-butyl bromide alone in acute renal colic. Journal of Research in Medical Sciences. 2010; 15(4):214-8

65. Kromann-Andersen B, Sommer P, Finnerup B, Lendorf A, Lyngdorf P, Mouritsen AL et al. Acute pain due to kidney/ureter stones treated with intramuscular Voltaren or Ketogan. Ugeskrift for Laeger. 1987; 149(49):3324-6

66. Kumar S, Behera NC, Sarkar D, Prasad S, Mandal AK, Singh SK. A comparative assessment of the clinical efficacy of intranasal desmopressin spray and diclofenac in the treatment of renal colic. Urological Research. 2011; 39(5):397-400

67. Laerum E, Ommundsen OE, Gronseth JE, Christiansen A, Fagertun HE. Intramuscular diclofenac versus intravenous indomethacin in the treatment of acute renal colic. European Urology. 1996; 30(3):358-62

68. Laerum E, Ommundsen OE, Grønseth JE, Christiansen A, Fagertun HE. Oral diclofenac in the prophylactic treatment of recurrent renal colic. A double-blind comparison with placebo. European Urology. 1995; 28(2):108-11

69. Larkin GL, Peacock WF, Pearl SM, Blair GA, D'Amico F. Efficacy of ketorolac tromethamine versus meperidine in the ED treatment of acute renal colic. American Journal of Emergency Medicine. 1999; 17(1):6-10

70. Lehtonen T, Kellokumpu I, Permi J, Sarsila O. Intravenous indomethacin in the treatment of ureteric colic. A clinical multicentre study with pethidine and metamizol as the control preparations. Annals of Clinical Research. 1983; 15(5-6):197-9

71. Lloret J, Munoz J, Monmany J, Puig X, Bonastre M, Brau J et al. Treatment of renal colic with dipyrone. A double-blind comparison trial with hyoscine alone or combined with dipyrone. Current Therapeutic Research - Clinical and Experimental. 1987; 42(6):1119-28

72. Lund PG, Jensen SK, Therkildsen MH, Olsen JH. Treatment of acute pain due to ureteral calculi with intravenous indomethacin or pethidine. Ugeskrift for Laeger. 1986; 148(26):1601-4

73. Lundstam S, Wahlander L, Kral JG. Treatment of ureteral colic by prostaglandin synthetase inhibition with diclofenac sodium. Current Therapeutic Research - Clinical and Experimental. 1980; 28(3 I):355-8

74. Lundstam SOA, Leissner KH, Wahlander LA, Kral JG. Prostaglandin-synthetase inhibition with diclofenac sodium in treatment of renal colic: comparison with use of a narcotic analgesic. Lancet. 1982; 1(8281):1096-7

75. Lupi A, Fierro A, Daniele E. The treatment of ureteral colic with intramuscular injection of pirprofen: a double-blind comparison trial with indomethacin. Current Therapeutic Research - Clinical and Experimental. 1986; 40(5):908-11

76. Magrini M, Pavesi G, Liverta C, Bruni G. Intravenous ketoprofen in renal colic: a placebo-controlled pilot study. Clinical Therapeutics. 1984; 6(4):483-7

77. Maldonado-Avila M, Garduno-Arteaga LM, Vela-Mollinedo RA, Jaspersen-Gastelum J, Virgen-Gutierrez F, Del Rosario-Santiago M et al. Comparison of three analgesic drug regimens with twelfth subcostal nerve block for pain control during extracorporeal shock wave lithotripsy. International Urology and Nephrology. 2018; 50(1):49-53

78. Mankongsrisuk T, Nualyong C, Tantiwong A, Taweemonkongsap T, Amornvesukit T, Chotikawanich E. Efficacy of nephrostomy tract infiltration with bupivacaine before and after tubeless percutaneous nephrolithotomy: a randomized control study. Journal of the Medical Association of Thailand. 2017; 100(3 Supplement 2):S138-43

79. Marthak KV, Gokarn AM, Rao AV, Sane SP, Mahanta RK, Sheth RD et al. A multi-centre comparative study of diclofenac sodium and a dipyrone/spasmolytic combination, and a single-centre comparative study of diclofenac sodium and pethidine in renal colic patients in India. Current Medical Research and Opinion. 1991; 12(6):366-73

80. Martin Carrasco C, Rodriguez Vazquez M, Palacios Garcia R. [A double-blind study of the analgesic efficacy in kidney colic of the combination of dipyrone and spasmolytic with ketorolac trometamol]. Archivos Españoles de Urología. 1993; 46(9):763-8

81. Masoumi K, Forouzan A, Darian AA, Feli M, Barzegari H, Khavanin A. Comparison of clinical efficacy of intravenous acetaminophen with intravenous morphine in acute renal colic: a randomized, double-blind, controlled trial. Emergency Medicine International. 2014; 2014:571326

82. Miano L, Galassi P, Goldoni S. Tyropramide versus butylscopolamine bromide administered intravenously in renal colic. A multicentre study. European Review for Medical and Pharmacological Sciences. 1986; 8(4):449-55

83. Miralles R, Cami J, Gutierrez J, Torne J, Garces JM, Badenas JM. Diclofenac versus dipyrone in acute renal colic: a double-blind controlled trial. European Journal of Clinical Pharmacology. 1987; 33(5):527-8

84. Montiel-Jarquín Á J, Rocha-Rocha VM, Solís-Mendoza HA, Romero-Figueroa MS, Etchegaray-Morales I, Alvarado-Ortega I. Management of ureteric colic with ketorolac and nifedipin vs. ketorolac and tamsulosin in the emergency room. Revista Medica del Instituto Mexicano del Seguro Social. 2017; 55 (Suppl 1):S20-5

85. Mora Durban MJ, Extramiana Cameno J, Arrizabalaga Moreno M, Paniagua Andres P, Camp Herrero J, Milla Santos J et al. [Flubiprofen vs dipyrone combined with hyoscine: the analgesic efficacy in renal colic]. Archivos Españoles de Urología. 1995; 48(9):867-73

86. Mortelmans LJM, Desruelles D, Baert JA, Hente KR, Tailly GG. Use of tramadol drip in controlling renal colic pain. Journal of Endourology. 2006; 20(12):1010-5

87. Morteza-Bagi HR, Amjadi M, Mirzaii-Sousefidi R. The comparison of apotel plus low dose of morphine and full dose of morphine in pain relief in patients with acute renal colic. Addiction & Health. 2015; 7(1-2):66-73

88. Moustafa F, Liotier J, Mathevon T, Pic D, Perrier C, Schmidt J. Usefulness of nefopam in treating pain of severe uncomplicated renal colics in adults admitted to emergency units: a randomised double-blind controlled trial. The 'INCoNU' study. Emergency Medicine Journal. 2013; 30(2):143-8

89. Mozafari J, Masoumi K, Forouzan A, Motamed H, Saki MA, Dezham M. Sublingual buprenorphine efficacy in renal colic pain relief: a randomized placebo-controlled clinical trial. Pain and Therapy. 2017; 6(2):227-34

90. Muriel-Villoria C, Zungri-Telo E, Diaz-Curiel M, Fernandez-Guerrero M, Moreno J, Puerta J et al. Comparison of the onset and duration of the analgesic effect of dipyrone, 1 or 2 g, by the intramuscular or intravenous route, in acute renal colic. European Journal of Clinical Pharmacology. 1995; 48(2):103-7

91. Muriel C, Ortiz P, Mella G, Arellano M, Pereiro M, Franco J et al. Efficacy of two different intramuscular doses of dipyrone in acute renal colic. Methods and Findings in Experimental and Clinical Pharmacology. 1993; 15(7):465-9

92. Narci H, Ugur M, Uzun H, Yandi M. Combining 1000 mg oral acetaminophen with 75 mg intramuscular diclofenac of analgesic efficacy for acute renal colic treatment. Scientific Research and Essays. 2012; 7(22):2017-21

93. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

94. Nicolas Torralba JA, Rigabert Montiel M, Banon Perez V, Valdelvira Nadal P, Perez Albacete M. [Intramuscular ketorolac compared to subcutaneous tramadol in the initial emergency treatment of renal colic]. Archivos Españoles de Urología. 1999; 52(5):435-7

95. O'Connor A, Schug SA, Cardwell H. A comparison of the efficacy and safety of morphine and pethidine as analgesia for suspected renal colic in the emergency setting. Journal of Accident and Emergency Medicine. 2000; 17(4):261-4

96. Oliveira JeSL, Scherber K, Cabrera D, Motov S, Erwin PJ, West CP et al. Safety and efficacy of intravenous lidocaine for pain management in the emergency department: a systematic review. Annals of Emergency Medicine. 2018; Epublication

97. Oosterlinck W, De Sy W. A double blind comparison between meptazinol (Wy 22811) and 'Buscopan' Compositum in renal colic. Current Medical Research and Opinion. 1976; 3(10):716-8

98. Oosterlinck W, Philp NH, Charig C, Gillies G, Hetherington JW, Lloyd J. A double-blind single dose comparison of intramuscular ketorolac tromethamine and pethidine in the treatment of renal colic. Journal of Clinical Pharmacology. 1990; 30(4):336-41

99. Pathan SA, Mitra B, Cameron PA. Titrated doses are optimal for opioids in pain trials - Authors' reply. Lancet. 2016; 388(10048):961-2

100. Pathan SA, Mitra B, Cameron PA. A systematic review and meta-analysis comparing the efficacy of nonsteroidal anti-inflammatory drugs, opioids, and paracetamol in the treatment of acute renal colic. European Urology. 2017; 73:583-95

101. Pathan SA, Mitra B, Straney LD, Afzal MS, Anjum S, Shukla D et al. Delivering safe and effective analgesia for management of renal colic in the emergency department: a double-blind, multigroup, randomised controlled trial. Lancet. 2016; 387(10032):1999-2007

102. Pavlik I, Suchy J, Pacik D, Bokr R, Sust M, Villoria J et al. Comparison of cizolirtine citrate and metamizol sodium in the treatment of adult acute renal colic: a randomized, double-blind, clinical pilot study. Clinical Therapeutics. 2004; 26(7):1061-72

103. Payandemehr P, Jalili M, Mostafazadeh Davani B, Dehpour AR. Sublingual buprenorphine for acute renal colic pain management: a double-blind, randomized controlled trial. International Journal of Emergency Medicine. 2014; 7(1):1-5

104. Pellegrino H, Di Girolamo G, Marti ML, De los Santos AR. Comparison of lysine clonixinate 200 mg versus diclofenac 75 mg in the treatment of renal colic pain. Prospective double-blind clinical trial in parallel groups. Prensa Medica Argentina. 1999; 86(10):1015-21

105. Persson NH, Bergqvist D, Melander A, Zederfelt B. Comparison of a narcotic (oxicone) and a non-narcotic anti-inflammatory analgesic (indoprofen) in the treatment of renal colic. Acta Chirurgica Scandinavica. 1985; 151(2):105-108

106. Phillips E, Hinck B, Pedro R, Makhlouf A, Kriedberg C, Hendlin K et al. Celecoxib in the management of acute renal colic: a randomized controlled clinical trial. Urology. 2009; 74(5):994-9

107. Porena M, Guiggi P, Balestra A, Micheli C. Pain killers and antibacterial therapy for kidney colic and stones. Urologia Internationalis. 2004; 72(Suppl 1):34-9

108. Porwal A, Mahajan AD, Oswal DS, Erram SS, Sheth DN, Balamurugan S et al. Efficacy and tolerability of fixed-dose combination of dexketoprofen and dicyclomine injection in acute renal colic. Pain Research and Treatment. 2012; 2012:295926

109. Quilez C, Perez-Mateo M, Hernandez P, Rubio I. [Usefulness of a non-steroid anti-inflammatory, sodium diclofenac, in the treatment of renal colic: Comparative study with a spasmolytic and an opiate analgesic]. Medicina Clínica. 1984; 82(17):754-5

110. Roberts G, Leslie R, Robb S, Siemens DR, Beiko D. Intraureteral lidocaine for ureteral stent symptoms post-ureteroscopy: a randomized, phase 2, placebo-controlled trial. Canadian Urological Association Journal. 2017; 11(10):326-30

111. Romics I, Molnár DL, Timberg G, Mrklic B, Jelakovic B, Köszegi G et al. The effect of drotaverine hydrochloride in acute colicky pain caused by renal and ureteric stones. BJU International. 2003; 92(1):92-6

112. Safdar B, Degutis LC, Landry K, Vedere SR, Moscovitz HC, D'Onofrio G. Intravenous morphine plus ketorolac is superior to either drug alone for treatment of acute renal colic. Annals of Emergency Medicine. 2006; 48(2):173-81, 181.e1

113. Sakr A, Salem E, Kamel M, Desoky E, Ragab A, Omran M et al. Minimally invasive percutaneous nephrolithotomy vs standard PCNL for management of renal stones in the flank-free modified supine position: single-center experience. Urolithiasis. 2017; 45(6):585-9

114. Salameh S, Hiller N, Antopolsky M, Ghanem F, Abramovitz Y, Stalnikowics R. Diclofenac versus tramadol in the treatment of renal colic: a prospective, randomized trial. Open Emergency Medicine Journal. 2011; 4:9-13

115. Sanahuja J, Corbera G, Garau J, Pla R, Carre MC. Intramuscular diclofenac sodium versus intravenous Baralgin in the treatment of renal colic. Annals of Pharmacotherapy. 1990; 24(4):361-4

116. Sanchez-Carpena J, Dominguez-Hervella F, Garcia I, Gene E, Bugarin R, Martin A et al. Comparison of intravenous dexketoprofen and dipyrone in acute renal colic. European Journal of Clinical Pharmacology. 2007; 63(8):751-60

117. Sanchez-Carpena J, Sesma-Sanchez J, Sanchez-Juan C, Tomas-Vecina S, Garcia-Alonso D, Rico-Salvado J et al. Comparison of dexketoprofen trometamol and dipyrone in the treatment of renal colic. Clinical Drug Investigation. 2003; 23(3):139-52

118. Sandhu DPS, Iacovou JW, Fletcher MS, Kaisary AV, Philip NH, Arkell DG. A comparison of intramuscular ketorolac and pethidine in the alleviation of renal colic. British Journal of Urology. 1994; 74(6):690-3

119. Sen H, Erturhan S, Sadioglu E, Bayrak O, Seckiner I. A comparison of efficacy of doxazosin 4 and 8 mg in medical expulsive therapy of distal ureteral stones: a prospective randomized clinical trial. Urolithiasis. 2017; 45(5):461-4

120. Serinken M, Eken C, Turkcuer I, Elicabuk H, Uyanik E, Schultz CH. Intravenous paracetamol versus morphine for renal colic in the emergency department: a randomised double-blind controlled trial. Emergency Medicine Journal. 2012; 29(11):902-5

121. Shirazi M, Salehipour M, Afrasiabi MA, Aminsharifi A. Analgesic effects and safety of desmopressin, tramadol and indomethacin in patients with acute renal colic: a randomized clinical trial. Bulletin of Emergency and Trauma. 2015; 3(2):41-5

122. Sjodin JG. Clinical experience of indomethacin in pain from ureteral stone. Scandinavian Journal of Urology and Nephrology. 1983; 75(Suppl):35-6

123. Slade N. Clinical blind trial of three drugs in the control of renal colic. British Journal of Urology. 1967; 39(1):22-5

124. Snir N, Moskovitz B, Nativ O, Margel D, Sandovski U, Sulkes J et al. Papaverine hydrochloride for the treatment of renal colic: an old drug revisited. A prospective, randomized study. Journal of Urology. 2008; 179(4):1411-4

125. Soleimanpour H, Hassanzadeh K, Vaezi H, Golzari SE, Esfanjani RM, Soleimanpour M. Effectiveness of intravenous lidocaine versus intravenous morphine for patients with renal colic in the emergency department. BMC Urology. 2012; 12:13

126. Sommer P, Kromann-Andersen B, Lendorf A, Lyngdorf P, Moller P. Analgesic effect and tolerance of Voltaren and Ketogan in acute renal or ureteric colic. British Journal of Urology. 1989; 63(1):4-6

127. Song SW, Kim K, Rhee JE, Lee JH, Seo GJ, Park HM. Butylscopolammonium bromide does not provide additional analgesia when combined with morphine and ketorolac for acute renal colic. Emergency Medicine Australasia. 2012; 24(2):144-50

128. Stankov G, Schmieder G, Zerle G, Schinzel S, Brune K. Double-blind study with dipyrone versus tramadol and butylscopolamine in acute renal colic pain. World Journal of Urology. 1994; 12(3):155-61

129. Stein A, Ben Dov D, Finkel B, Mecz Y, Kitzes R, Lurie A. Single-dose intramuscular ketorolac versus diclofenac for pain management in renal colic. American Journal of Emergency Medicine. 1996; 14(4):385-7

130. Supervia A, Peuro-Botet J, Nogues X, Echarte JL, Mingukz S, Iglesias ML et al. Piroxicam fast-dissolving dosage form vs diclofenac sodium in the treatment of acute renal colic: a double-blind controlled trial. British Journal of Urology. 1998; 81(1):27-30

131. Thompson JF, Pike JM, Chumas PD, Rundle JS. Rectal diclofenac compared with pethidine injection in acute renal colic. BMJ. 1989; 299(6708):1140-1

132. Torchi B, Villani U, Bruni G, Lavezzari M, Mandelli V. Intravenous indoprofen in the management of renal colic. International Journal of Clinical Pharmacology Research. 1983; 3(3):167-73

133. Udén P, Rentzhog L, Berger T. A comparative study on the analgesic effects of indomethacin and hydromorphinechloride-atropine in acute, ureteral-stone pain. Acta Chirurgica Scandinavica. 1983; 149(5):497-9

134. Vignoni A, Fierro A, Moreschini G, Cau M, Agostino A, Daniele E et al. Diclofenac sodium in ureteral colic: a double-blind comparison trial with placebo. Journal of International Medical Research. 1983; 11(5):303-7

135. Walden M, Lahtinen J, Elvander E. Analgesic effect and tolerance of ketoprofen and diclofenac in acute ureteral colic. Scandinavian Journal of Urology and Nephrology. 1993; 27(3):323-5

136. Warren MM, Boyce WH, Evans JW, Peters PC. A double-blind comparison of dezocine and morphine in patients with acute renal and ureteral colic. Journal of Urology. 1985; 134(3):457-9

137. Wolfson AB, Yealy DM. Oral indomethacin for acute renal colic. American Journal of Emergency Medicine. 1991; 9(1):16-19

138. Wood VM, Christenson JM, Innes GD, Lesperance M, McKnight D. The NARC (nonsteroidal anti-inflammatory in renal colic) trial. Single-dose intravenous ketorolac versus titrated intravenous meperidine in acute renal colic: a randomized clinical trial. Canadian Journal of Emergency Medical Care. 2000; 2(2):83-9

139. Xue P, Tu C, Wang K, Wang X, Fang Y. Intracutaneous sterile water injection versus oral paracetamol for renal colic during pregnancy: a randomized controlled trial. International Urology and Nephrology. 2013; 45(2):321-5

140. Yakoot M, Salem A, Yousef S, Helmy S. Clinical efficacy of Spasmofen suppository in the emergency treatment of renal colic: a randomized, double-blind, double-dummy comparative trial. Drug Design, Development and Therapy. 2014; 8:405-10

141. Yencilek F, Aktas C, Goktas C, Yilmaz C, Yilmaz U, Sarica K. Role of papaverine hydrochloride administration in patients with intractable renal colic: randomized prospective trial. Urology. 2008; 72(5):987-90

142. Zamanian F, Jalili M, Moradi-Lakeh M, Kia M, Aghili R, Aghili SM. Morphine suppository versus indomethacin suppository in the management of renal colic: randomized clinical trial. Pain Research and Treatment. 2016; 2016:4981585

143. Ziapor B, Motamed H, Verki MM, Norani H. Comparison of effect of morphine-chlorpheniramine combined versus morphine alone in alleviating acute renal colic pain: a randomized clinical trail. Jundishapur Journal of Natural Pharmaceutical Products. 2017; 12 (3):e15585

Appendices

Appendix A: Review protocols

Table 22: Review protocol: Pain management

Field	Content
Review question	What is the clinical and cost-effectiveness of drugs in managing acute pain in people with symptomatic renal or ureteric stones?
Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To find the most effective drug for managing acute pain in people with symptomatic renal and ureteric stones
Eligibility criteria – population / disease / condition / issue / domain	People (adults, children and young people) with symptomatic renal or ureteric stones
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• NSAIDs • Opioids/Opiates • Paracetamol • Buscopan
Eligibility criteria – comparator(s) / control or reference (gold) standard	Compared to: • Each other (class comparison only; no within class comparison) • No treatment • Placebo

Outcomes and prioritisation	Critical outcomes:
	• Quality of life
	• Pain intensity (visual analogue scale, verbal ratings, time to pain relief, need to rescue medication)
	• Adverse events
	  ○ Major: GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event
	  ○ Minor : GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention
	Important outcomes:
	• Length of stay
	• Use of healthcare services

Eligibility criteria – study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no RCT evidence is available, search for non-randomised studies for children
Other inclusion exclusion criteria	Bladder stones Open surgery for renal (kidney and ureteric) stones Laparoscopic nephrolithotomy and pyelolithotomy Non-English language studies
Proposed sensitivity / subgroup analysis, or meta-regression	Strata: • Adults (≥16 years) • Children and young people (<16 years) • Pregnant women

Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• Pairwise meta-analyses performed using Cochrane Review Manager (RevMan5). • GRADEpro used to assess the quality of evidence for each outcome • Endnote for bibliography, citations, sifting and reference management • Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library Date: all years Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2014 NHSEED, HTA – all years Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10033
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. [Consider exploring publication bias for review questions where it may be more common, such as pharmacological questions, certain disease areas, etc. Describe any steps taken to mitigate against publication bias, such as examining trial registries.]

Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Andrew Dickinson in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 23: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the individual review protocol above. • Studies must be of a relevant economic study design (cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G *[in the Full guideline]*.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the 2014 NICE guidelines manual.[93] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence

table will not be completed and it will not be included in the economic evidence profile.

- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the Committee if required. The ultimate aim is to include economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the Committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix M.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations.

Economic study type:

- Cost-utility analysis (most applicable).
- Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'.
- Studies published before 2002 will have been excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the economic analysis:

- The more closely the clinical effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review. [Add cross reference]

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Separate searches were run to identify studies about pain in adults and in children.

B.1.1 Adults

Table 24: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 21 March 2018	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 21 March 2018	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 3 of 12 CENTRAL to 2018 Issue 2 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/

19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	exp Analgesics/
28.	analgesic*.ti,ab.
29.	exp anti-inflammatory agents, non steroidal/
30.	((non-steroid* or nonsteroid*) adj (antiinflammatory or anti-inflammatory)).ti,ab.
31.	NSAID*.ti,ab.
32.	exp Ibuprofen/
33.	(ibuprofen or brufen or calprofen or cuprofen or ibucalm or ibuderm or ibugel or ibuleve or ibuspray or nurofen).ti,ab.
34.	Diclofenac/
35.	(diclofenac or Voltarol or Voltaren or Fenactol or Dicloflex or Diclomax or Motifene or Econac).ti,ab.
36.	Naproxen/
37.	(naproxen or Arthroxen or Naprosyn or Naprosin or Stirlescent or Vimovo or Napratec).ti,ab.
38.	exp Analgesics, Opioid/
39.	exp Opiate Alkaloids/
40.	Narcotics/
41.	(opioid* or opiate* or narcotic*).ti,ab.
42.	exp Morphine/
43.	(morphine or Sevredol or MST Continus or Morphgesic or MXL or Zomorph or Oramorph or Cyclimorph).ti,ab.
44.	Meperidine/
45.	(pethidine or meperidine).ti,ab.
46.	Tramadol/
47.	(tramadol or Zydol or Zamadol or Invodol or Mabron or Maneo or Marol or Oldaram or Tilodol or Tradorec or Tramulief or Zamadol or Zeridame or Maxitram or Tramquel).ti,ab.
48.	exp Codeine/
49.	(codeine or methylmorphine or Galcodine or Co-codamol or Codipar or Kapake or Solpadol or Zapain or Codipar or Paracodol or Tylex).ti,ab.
50.	Acetaminophen/
51.	(paracetamol or acetaminophen or Mandanol or Panadol or Paravict or Calpol or Perfalgan or Alvedon or Tramacet).ti,ab.
52.	Butylscopolammonium Bromide/
53.	(Buscopan or butylscopolammonium or N-butylscopolammonium or hyoscine or scopolamine or butylscopolamine).ti,ab.
54.	or/27-53
55.	26 and 54
56.	randomized controlled trial.pt.
57.	controlled clinical trial.pt.

58.	randomi#ed.ti,ab.
59.	placebo.ab.
60.	randomly.ti,ab.
61.	Clinical Trials as topic.sh.
62.	trial.ti.
63.	or/56-62
64.	Meta-Analysis/
65.	exp Meta-Analysis as Topic/
66.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
67.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
68.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
69.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
70.	(search* adj4 literature).ab.
71.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
72.	cochrane.jw.
73.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
74.	or/64-73
75.	63 or 74
76.	55 and 75

1 **Embase (Ovid) search terms**

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.

22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	exp analgesic agent/
26.	analgesic*.ti,ab.
27.	exp nonsteroid antiinflammatory agent/
28.	((non-steroid* or nonsteroid*) adj (antiinflammatory or anti-inflammatory)).ti,ab.
29.	NSAID*.ti,ab.
30.	ibuprofen/
31.	(ibuprofen or brufen or calprofen or cuprofen or ibucalm or ibuderm or ibugel or ibuleve or ibuspray or nurofen).ti,ab.
32.	diclofenac/
33.	(diclofenac or Voltarol or Voltaren or Fenactol or Dicloflex or Diclomax or Motifene or Econac).ti,ab.
34.	naproxen/
35.	(naproxen or Arthroxen or Naprosyn or Naprosin or Stirlescent or Vimovo or Napratec).ti,ab.
36.	exp narcotic analgesic agent/
37.	exp opiate/
38.	exp narcotic agent/
39.	(opioid* or opiate* or narcotic*).ti,ab.
40.	morphine/
41.	exp morphine derivate/
42.	(morphine or Sevredol or MST Continus or Morphgesic or MXL or Zomorph or Oramorph or Cyclimorph).ti,ab.
43.	pethidine/
44.	(pethidine or meperidine).ti,ab.
45.	tramadol/
46.	(tramadol or Zydol or Zamadol or Invodol or Mabron or Maneo or Marol or Oldaram or Tilodol or Tradorec or Tramulief or Zamadol or Zeridame or Maxitram or Tramquel).ti,ab.
47.	codeine/
48.	(codeine or methylmorphine or Galcodine or Co-codamol or Codipar or Kapake or Solpadol or Zapain or Codipar or Paracodol or Tylex).ti,ab.
49.	paracetamol/
50.	paracetamol plus tramadol/
51.	(paracetamol or acetaminophen or Mandanol or Panadol or Paravict or Calpol or Perfalgan or Alvedon or Tramacet).ti,ab.
52.	scopolamine butyl bromide/
53.	(Buscopan or butylscopolammonium or N-butylscopolammonium or hyoscine or scopolamine or butylscopolamine).ti,ab.
54.	or/25-53
55.	24 and 54
56.	random*.ti,ab.
57.	factorial*.ti,ab.
58.	(crossover* or cross over*).ti,ab.
59.	((doubl* or singl*) adj blind*).ti,ab.
60.	(assign* or allocat* or volunteer* or placebo*).ti,ab.

61.	crossover procedure/
62.	single blind procedure/
63.	randomized controlled trial/
64.	double blind procedure/
65.	or/56-64
66.	systematic review/
67.	meta-analysis/
68.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
69.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
70.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
71.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
72.	(search* adj4 literature).ab.
73.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
74.	cochrane.jw.
75.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
76.	or/66-75
77.	65 or 76
78.	55 and 77

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Urolithiasis] explode all trees
#2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s):ti,ab
#3.	((renal or kidney* or urinary or ureter* or urethra*) near/3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)):ti,ab
#4.	stone disease*:ti,ab
#5.	((calculi or calculus or calcium oxalate or cystine) near/3 (crystal* or stone* or lithiasis)):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Analgesics] explode all trees
#8.	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#9.	((non-steroid* or nonsteroid*) near (antiinflammatory or anti-inflammatory)):ti,ab
#10.	NSAID*:ti,ab
#11.	MeSH descriptor: [Ibuprofen] this term only
#12.	(ibuprofen or brufen or calprofen or cuprofen or ibucalm or ibuderm or ibugel or ibuleve or ibuspray or nurofen):ti,ab
#13.	MeSH descriptor: [Diclofenac] this term only
#14.	(diclofenac or Voltarol or Voltaren or Fenactol or Dicloflex or Diclomax or Motifene or Econac):ti,ab
#15.	MeSH descriptor: [Naproxen] this term only
#16.	(naproxen or Arthroxen or Naprosyn or Naprosin or Stirlescent or Vimovo or Napratec):ti,ab
#17.	MeSH descriptor: [Analgesics, Opioid] explode all trees
#18.	MeSH descriptor: [Opiate Alkaloids] explode all trees
#19.	MeSH descriptor: [Narcotics] explode all trees
#20.	(opioid* or opiate* or narcotic*):ti,ab

#21.	MeSH descriptor: [Morphine] explode all trees
#22.	(morphine or Sevredol or MST Continus or Morphgesic or MXL or Zomorph or Oramorph or Cyclimorph):ti,ab
#23.	MeSH descriptor: [Meperidine] this term only
#24.	(pethidine or meperidine) .ti,ab
#25.	MeSH descriptor: [Tramadol] this term only
#26.	(tramadol or Zydol or Zamadol or Invodol or Mabron or Maneo or Marol or Oldaram or Tilodol or Tradorec or Tramulief or Zamadol or Zeridame or Maxitram or Tramquel):ti,ab
#27.	MeSH descriptor: [Codeine] explode all trees
#28.	(codeine or methylmorphine or Galcodine or Co-codamol or Codipar or Kapake or Solpadol or Zapain or Codipar or Paracodol or Tylex):ti,ab
#29.	MeSH descriptor: [Acetaminophen] explode all trees
#30.	(paracetamol or acetaminophen or Mandanol or Panadol or Paravict or Calpol or Perfalgan or Alvedon or Tramacet):ti,ab
#31.	MeSH descriptor: [Butylscopolammonium Bromide] this term only
#32.	(Buscopan or butylscopolammonium or N-butylscopolammonium or hyoscine or scopolamine or butylscopolamine):ti,ab
#33.	(or #7-#32)
#34.	#6 and #33

B.1.2 Children

Table 25: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 21 March 2018	Exclusions Children
Embase (OVID)	1974 – 21 March 2018	Exclusions Children
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 3 of 12 CENTRAL to 2018 Issue 2 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	Children

Medline (Ovid) search terms

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/

11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	exp Analgesics/
28.	analgesic*.ti,ab.
29.	exp anti inflammatory agents, non steroidal/
30.	((non-steroid* or nonsteroid*) adj (antiinflammatory or anti-inflammatory)).ti,ab.
31.	NSAID*.ti,ab.
32.	exp Ibuprofen/
33.	(ibuprofen or brufen or calprofen or cuprofen or ibucalm or ibuderm or ibugel or ibuleve or ibuspray or nurofen).ti,ab.
34.	Diclofenac/
35.	(diclofenac or Voltarol or Voltaren or Fenactol or Dicloflex or Diclomax or Motifene or Econac).ti,ab.
36.	Naproxen/
37.	(naproxen or Arthroxen or Naprosyn or Naprosin or Stirlescent or Vimovo or Napratec).ti,ab.
38.	exp Analgesics, Opioid/
39.	exp Opiate Alkaloids/
40.	Narcotics/
41.	(opioid* or opiate* or narcotic*).ti,ab.
42.	exp Morphine/
43.	(morphine or Sevredol or MST Continus or Morphgesic or MXL or Zomorph or Oramorph or Cyclimorph).ti,ab.
44.	Meperidine/
45.	(pethidine or meperidine).ti,ab.
46.	Tramadol/
47.	(tramadol or Zydol or Zamadol or Invodol or Mabron or Maneo or Marol or Oldaram or Tilodol or Tradorec or Tramulief or Zamadol or Zeridame or Maxitram or Tramquel).ti,ab.
48.	exp Codeine/
49.	(codeine or methylmorphine or Galcodine or Co-codamol or Codipar or Kapake or Solpadol or Zapain or Codipar or Paracodol or Tylex).ti,ab.
50.	Acetaminophen/

51.	(paracetamol or acetaminophen or Mandanol or Panadol or Paravict or Calpol or Perfalgan or Alvedon or Tramacet).ti,ab.
52.	Butylscopolammonium Bromide/
53.	(Buscopan or butylscopolammonium or N-butylscopolammonium or hyoscine or scopolamine or butylscopolamine).ti,ab.
54.	or/27-53
55.	26 and 54
56.	exp child/
57.	exp Pediatrics/
58.	child*.ti,ab.
59.	exp Infant/
60.	infan*.ti,ab.
61.	(baby or babies).ti,ab.
62.	"Adolescent"/ or adolescen*.ti,ab.
63.	(pediatric*1 or paediatric*1).ti,ab.
64.	(neonat* or newborn*).ti,ab.
65.	or/56-64
66.	55 and 65

1 **Embase (Ovid) search terms**

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	exp analgesic agent/

26.	analgesic*.ti,ab.
27.	exp nonsteroid antiinflammatory agent/
28.	((non-steroid* or nonsteroid*) adj (antiinflammatory or anti-inflammatory)).ti,ab.
29.	NSAID*.ti,ab.
30.	ibuprofen/
31.	(ibuprofen or brufen or calprofen or cuprofen or ibucalm or ibuderm or ibugel or ibuleve or ibuspray or nurofen).ti,ab.
32.	diclofenac/
33.	(diclofenac or Voltarol or Voltaren or Fenactol or Dicloflex or Diclomax or Motifene or Econac).ti,ab.
34.	naproxen/
35.	(naproxen or Arthroxen or Naprosyn or Naprosin or Stirlescent or Vimovo or Napratec).ti,ab.
36.	exp narcotic analgesic agent/
37.	exp opiate/
38.	exp narcotic agent/
39.	(opioid* or opiate* or narcotic*).ti,ab.
40.	morphine/
41.	exp morphine derivate/
42.	(morphine or Sevredol or MST Continus or Morphgesic or MXL or Zomorph or Oramorph or Cyclimorph).ti,ab.
43.	pethidine/
44.	(pethidine or meperidine).ti,ab.
45.	tramadol/
46.	(tramadol or Zydol or Zamadol or Invodol or Mabron or Maneo or Marol or Oldaram or Tilodol or Tradorec or Tramulief or Zamadol or Zeridame or Maxitram or Tramquel).ti,ab.
47.	codeine/
48.	(codeine or methylmorphine or Galcodine or Co-codamol or Codipar or Kapake or Solpadol or Zapain or Codipar or Paracodol or Tylex).ti,ab.
49.	paracetamol/
50.	paracetamol plus tramadol/
51.	(paracetamol or acetaminophen or Mandanol or Panadol or Paravict or Calpol or Perfalgan or Alvedon or Tramacet).ti,ab.
52.	scopolamine butyl bromide/
53.	(Buscopan or butylscopolammonium or N-butylscopolammonium or hyoscine or scopolamine or butylscopolamine).ti,ab.
54.	or/25-53
55.	24 and 54
56.	exp child/
57.	exp pediatrics/
58.	child*.ti,ab.
59.	infan*.ti,ab.
60.	(baby or babies).ti,ab.
61.	exp adolescent/ or adolescen*.ti,ab.
62.	(pediatric*1 or paediatric*1).ti,ab.
63.	(neonat* or newborn*).ti,ab.
64.	or/56-63

65.	55 and 64

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Urolithiasis] explode all trees
#2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s):ti,ab
#3.	((renal or kidney* or urinary or ureter* or urethra*) near/3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)):ti,ab
#4.	stone disease*:ti,ab
#5.	((calculi or calculus or calcium oxalate or cystine) near/3 (crystal* or stone* or lithiasis)):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Analgesics] explode all trees
#8.	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#9.	((non-steroid* or nonsteroid*) near (antiinflammatory or anti-inflammatory)):ti,ab
#10.	NSAID*:ti,ab
#11.	MeSH descriptor: [Ibuprofen] this term only
#12.	(ibuprofen or brufen or calprofen or cuprofen or ibucalm or ibuderm or ibugel or ibuleve or ibuspray or nurofen):ti,ab
#13.	MeSH descriptor: [Diclofenac] this term only
#14.	(diclofenac or Voltarol or Voltaren or Fenactol or Dicloflex or Diclomax or Motifene or Econac):ti,ab
#15.	MeSH descriptor: [Naproxen] this term only
#16.	(naproxen or Arthroxen or Naprosyn or Naprosin or Stirlescent or Vimovo or Napratec):ti,ab
#17.	MeSH descriptor: [Analgesics, Opioid] explode all trees
#18.	MeSH descriptor: [Opiate Alkaloids] explode all trees
#19.	MeSH descriptor: [Narcotics] explode all trees
#20.	(opioid* or opiate* or narcotic*):ti,ab
#21.	MeSH descriptor: [Morphine] explode all trees
#22.	(morphine or Sevredol or MST Continus or Morphgesic or MXL or Zomorph or Oramorph or Cyclimorph):ti,ab
#23.	MeSH descriptor: [Meperidine] this term only
#24.	(pethidine or meperidine) .ti,ab
#25.	MeSH descriptor: [Tramadol] this term only
#26.	(tramadol or Zydol or Zamadol or Invodol or Mabron or Maneo or Marol or Oldaram or Tilodol or Tradorec or Tramulief or Zamadol or Zeridame or Maxitram or Tramquel):ti,ab
#27.	MeSH descriptor: [Codeine] explode all trees
#28.	(codeine or methylmorphine or Galcodine or Co-codamol or Codipar or Kapake or Solpadol or Zapain or Codipar or Paracodol or Tylex):ti,ab
#29.	MeSH descriptor: [Acetaminophen] explode all trees
#30.	(paracetamol or acetaminophen or Mandanol or Panadol or Paravict or Calpol or Perfalgan or Alvedon or Tramacet):ti,ab
#31.	MeSH descriptor: [Butylscopolammonium Bromide] this term only
#32.	(Buscopan or butylscopolammonium or N-butylscopolammonium or hyoscine or scopolamine or butylscopolamine):ti,ab
#33.	(or #7-#32)
#34.	#6 and #33
#35.	[mh child]

#36.	[mh Pediatrics]
#37.	child*:ti,ab
#38.	[mh Infant]
#39.	infan*:ti,ab
#40.	(baby or babies):ti,ab
#41.	[mh ^Adolescent] or adolescen*:ti,ab
#42.	(pediatric* or paediatric*):ti,ab
#43.	(neonat* or newborn*):ti,ab
#44.	(or #35-#43)
#45.	#34 and #44

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to renal and ureteric stones population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies.

Table 26: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 9 March 2018	Exclusions Health economics studies
Embase	2014 – 9 March 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 9 March 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.

15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

1 **Embase (Ovid) search terms**

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/

11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

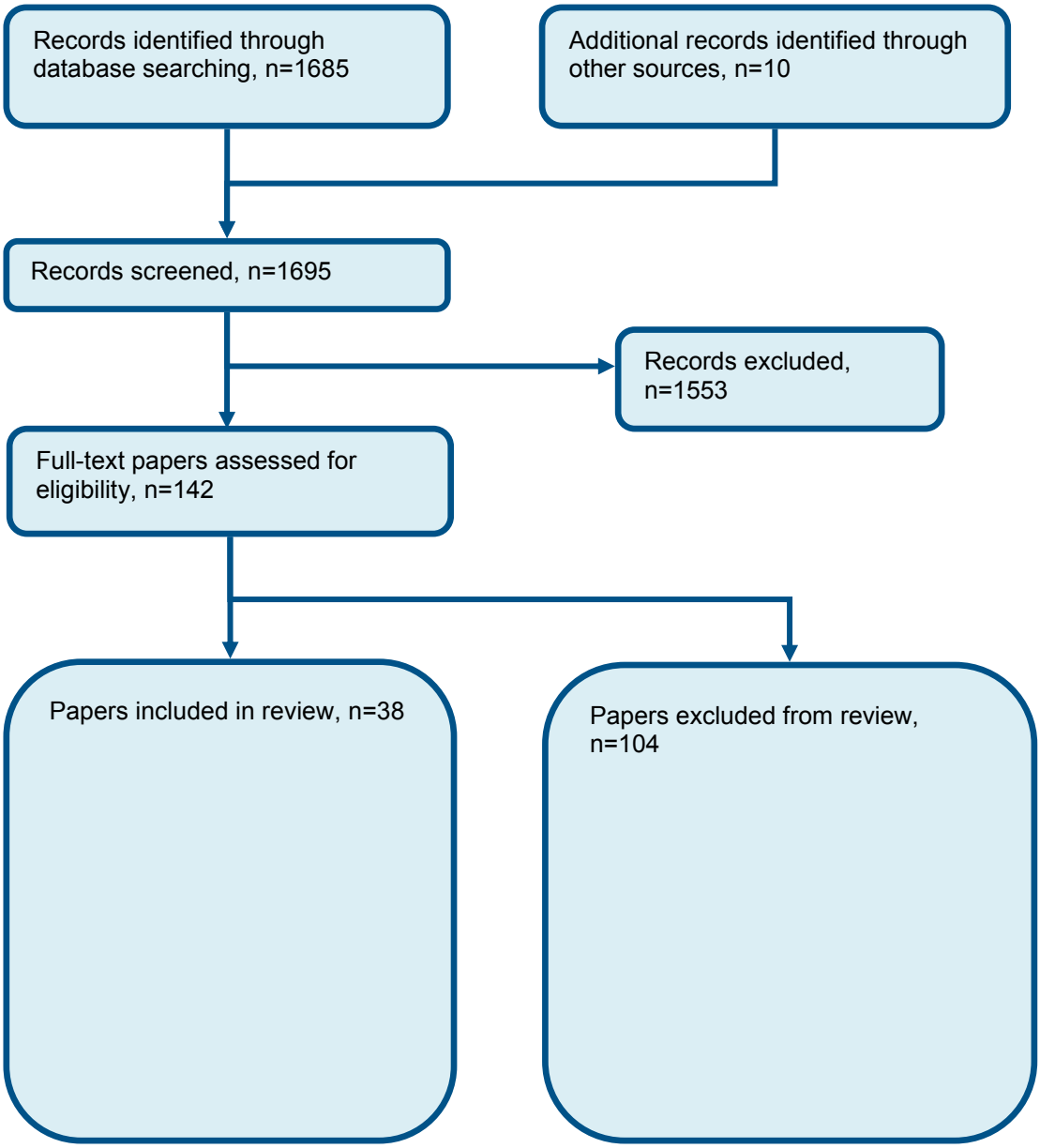
1 **NHS EED and HTA (CRD) search terms**

#46.	MeSH DESCRIPTOR urolithiasis EXPLODE ALL TREES
#47.	(((nephrolitiasis or nephrolith or urolithiasis)))
#48.	((((renal or kidney or urinary or ureteric or ureteral or ureter or urethra*) adj2 (stone* or calculi or calculus or calculosis or lithiasis or colic))))
#49.	((stone disease*))
#50.	((((calculi or calculus) adj2 (stone* or lithiasis))))
#51.	(#1 OR #2 OR #3 OR #4 OR #5)

2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of Pain management



Appendix D: Clinical evidence tables

Study	Aganovic 2012[3]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=400)
Countries and setting	Conducted in Bosnia-Herzegovina; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 minutes
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Not reported
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: NSAIDs - Diclofenac. Diclofenac 75 mg. intramuscular. Duration Single dose. Concurrent medication/care: In case the pain was not relieved, within 30 minutes an additional dose of the drug was administered or Tramal amp. 50 mg. i.v. (ITT), and if the patient did not respond to either drug, a more invasive urological treatment was applied. Indirectness: No indirectness (n=100) Intervention 2: Smooth muscle relaxant /antispasmotic - Butylscopolammonium bromide. Butylscopolamin amp. intravenously. Duration Single dose. Concurrent medication/care: In case the pain was not relieved, within 30 minutes an additional dose of the drug was administered or Tramal amp. 50 mg. i.v. (ITT), and if the patient did not respond to either drug, a more invasive urological treatment was applied. Indirectness: No indirectness (n=100) Intervention 3: Placebo. distilled water (aqua redestilata) intravenously. Duration Single dose. Concurrent medication/care: In case the pain was not relieved, within 30 minutes an additional dose of the

	drug was administered or Tramal amp. 50 mg. i.v. (ITT), and if the patient did not respond to either drug, a more invasive urological treatment was applied. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus BUTYLSCOPOLAMMONIUM BROMIDE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 30 minutes; RR; 0.263 (95%CI 0.175 to 0.395, Units:);
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PLACEBO

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 30 minutes; RR; 0.213 (95%CI 0.143 to 0.316) VAS 0-10 Top=High is poor outcome;
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUTYLSCOPOLAMMONIUM BROMIDE versus PLACEBO

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 30 minutes; RR; 0.809 (95%CI 0.717 to 0.912);
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Adverse events (unspecified) at 30 minutes; Group 1: 84/100, Group 2: 1/100
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Al 2017[6]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=300)
Countries and setting	Conducted in Turkey; Setting: Emergency department of Gaziantep University's Hospital for Research and Practice and two other state hospitals in Gaziantep, Turkey
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30-minute follow-up for pain intensity
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients suspected with renal colic during their examinations underwent thin-section non-contrast abdominal tomography for diagnosis and differential diagnosis
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with suspected renal colic before definitive diagnosis; Male and female patients aged between 16 and 65 years; Started having bilateral/unilateral flank pain within the last 12 hours; Pain was at a level of 4cm (0r 40mm) or above according to the VAS scale at the time of admission; Diagnosis of renal colic confirmed on CT
Exclusion criteria	Patients aged below 16 years and over 65 years; Side pain complaint lasting longer than 12 hours; 'History of direct blunt trauma to the CVAT within the last week'; Patients who marked the VAS at <40 mm or <4 cm at the zeroth minute in the emergency department; Patients with a history of allergy to the drugs to be used in the study; Patients with a systolic arterial blood pressure of <90 mm Hg at the time of admission to the emergency department; Patients with a history of prostate, renal and adrenal, and bladder malignancy or a history of surgery on these regions within the last six months; Patients with any history of chronic pain syndrome; Patients with a history of pain-killer, antidepressant, anticonvulsant, muscle relaxant, or steroid use for any reason within the past 12 hours; Patients with a history of substance or alcohol dependency; Pregnant women, nursing mothers, and women with pelvic inflammatory disease (PID); Patients not diagnosed with renal colic as a result of imaging and laboratory tests. Patients who had been treated with renal colic suspicion at the time of admission but whose diagnosis was not confirmed by CT as renal colic were excluded from the study
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: mean 42.2 years (no SD or range reported). Gender (M:F): 216/84 (DKT: 78/22; Paracetamol: 67/33; Fentanyl: 71/29). Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness

Interventions	(n=100) Intervention 1: NSAIDs - Dexketoprofen trometamol. 50 mg dexketoprofen trometamol (DKT) (Arveles ampoule, 50 mg/ml DKT, Menarini International, Italy) in the form of an intravenous rapid infusion in 100 ml of isotonic saline . Duration 30 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=100) Intervention 2: Paracetamol. Intravenous paracetamol, 10 mg (Parol vial, 10 mg/ml, 100 ml vial paracetamol, Atabey Kimya San, Turkey). Duration 30 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DEXKETOPROFEN TROMETAMOL versus FENTANYL

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (number of patients with pain completely gone/ complete pain relief) at discharge; Group 1: 46/100, Group 2: 31/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (number of patients with need for rescue medication) at 30 minutes; Group 1: 31/100, Group 2: 45/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (number of patients with partial pain relief) at discharge; Group 1: 54/100, Group 2: 69/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Minor adverse events - dizziness at Not reported; Group 1: 1/100, Group 2: 9/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study

criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Adults (≥16 years): Minor adverse events - vomiting at Not reported; Group 1: 1/100, Group 2: 1/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DEXKETOPROFEN TROMETAMOL versus PARACETAMOL

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (number of patients with pain completely gone/ complete pain relief) at discharge; Group 1: 46/100, Group 2: 39/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (number of patients with need for rescue medication) at 30 minutes; Group 1: 31/100, Group 2: 53/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (number of patients with partial pain relief) at discharge; Group 1: 54/100, Group 2: 61/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define

- Actual outcome for Adults (≥16 years): Minor adverse events - dizziness at Not reported; Group 1: 1/100, Group 2: 1/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Adults (≥16 years): Minor adverse events - vomiting at Not reported; Group 1: 1/100, Group 2: 1/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FENTANYL versus PARACETAMOL

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (number of patients with pain completely gone/ complete pain relief) at discharge; Group 1: 31/100, Group 2: 39/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (number of patients with need for rescue medication) at 30 minutes; Group 1: 45/100, Group 2: 53/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (number of patients with partial pain relief) at discharge; Group 1: 69/100, Group 2: 61/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Minor adverse events - dizziness at Not reported; Group 1: 9/100, Group 2: 1/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Minor adverse events - vomiting at Not reported; Group 1: 1/100, Group 2: 1/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There was no significant relationship between sex and the agents used (p=0.215)'. Study criteria say that patients over 65 years were excluded but data were included from patients >65 years in DKT and fentanyl treatment groups.; Group 1

Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	**Al-sahlawi 1996[4]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Kuwait; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention + follow up: 60 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: History, clinical examination, urinalysis and radiological examination
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 20-60 years with acute renal colic
Exclusion criteria	Patients who had recieved treatment for renal colic prior to their admission were excluded. Patients with known allergy to salicylates and other non-steroidal anti-inflammatory drugs and patients with peptic ulcer, gastritis, bronchial asthma, pregnant women and lactating mothers were also excluded
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Aged >20 years. Gender (M:F): 71:29. Ethnicity: 1
Further population details	
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Opioids/opiates - Pethidine. Pethidine 100mg, administered in a single dose by intravenous route. Duration Single dose. Concurrent medication/care: A single intravenous dose of pethidine 100mg was given 30 minutes after treatment if pain had not been relieved at all . Indirectness: No indirectness (n=50) Intervention 2: NSAIDs - Indomethacin. Indomethacin 100mg, administered in a single dose by

	intravenous route. Duration Single dose . Concurrent medication/care: A single intravenous dose of pethidine 100mg was given 30 minutes after treatment if pain had not been relieved at all . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PETHIDINE versus INDOMETHACIN

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Need for rescue medication at 30 minutes; Group 1: 0/50, Group 2: 2/50
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): No pain relief at 30 minutes; Group 1: 0/50, Group 2: 2/50
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): No pain relief at 15 minutes; Group 1: 0/50, Group 2: 10/50
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): No pain relief at 5 minutes; Group 1: 0/50, Group 2: 10/50
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Partial pain relief at 5 minutes; Group 1: 37/50, Group 2: 32/50
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Partial pain relief at 15 minutes; Group 1: 15/50, Group 2: 13/50
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Partial pain relief at 30 minutes; Group 1: 5/50, Group 2: 13/50
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Complete pain relief at 5 minutes; Group 1: 13/50, Group 2: 8/50
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Complete pain relief at 15 minutes; Group 1: 35/50, Group 2: 27/50
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Complete pain relief at 30 minutes; Group 1: 45/50, Group 2: 35/50
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Dizziness at 60 minutes; Group 1: 0/50, Group 2: 2/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Anon 1991[42]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=234)
Countries and setting	Conducted in Spain; Setting: 13 hospitals in Spain
Line of therapy	1st line
Duration of study	Intervention + follow up: 60 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients of both sexes, aged 18-65 years, who had been diagnosed as having acute renal colic on the basis of presenting symptoms at least suggestive of such a condition (colicky pain in the flank and/or radiating to homolateral hemiabdomen, with or without vegetative symptoms). Additional confirmatory criteria included more than 3 red cells per filed in the urine sediment, passage of calculus, and the presence of a radiopaque stone in a plain abdominal x-ray
Exclusion criteria	Patients with any other disorder requiring special management and those with the following conditions were subsequently excluded: known allergy to salicylates or other non-steroidal anti-inflammatory agents, peptic ulcer or gastrointestinal bleeding, mild colicky pain (graded as 0 or 1 by the observer), pregnant women and nursing mothers
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): NSAID group 40.7 years (13.9); opioid group 41.4 years (12.7). Gender (M:F): 124:110. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=116) Intervention 1: NSAIDs - Diclofenac. Diclofenac sodium 75mg. Duration Single dose. Concurrent medication/care: Rescue medication consisted of a single dose of pethidine 100mg, given 30 minutes after the treatment (n=118) Intervention 2: Opioids/opiates - Pethidine. Pethidine 100mg. Duration Single dose. Concurrent medication/care: Rescue medication consisted of a single dose of pethidine 100mg, given 30 minutes after the treatment. Indirectness: No indirectness

Funding	Academic or government funding (Partial financial support from Laboratorios Europharma, S.S., and Institut Municipal d'Investigacio Medica, Barcelona)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PETHIDINE Protocol outcome 1: Pain intensity (visual analogue scale) at Define - Actual outcome for Adults (≥16 years): Need for rescue medication at 30 minutes; Group 1: 19/116, Group 2: 23/118 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Dizziness at 60 minutes; Group 1: 5/116, Group 2: 24/118 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Nausea at 60 minutes; Group 1: 15/116, Group 2: 46/118 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Sedation at 60 minutes; Group 1: 0/116, Group 2: 1/118 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Urinary retention at 60 minutes; Group 1: 0/116, Group 2: 1/118 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Vomiting at 60 minutes; Group 1: 11/116, Group 2: 38/118 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Ay 2014[9]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Turkey; Setting: Emergency department
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Abdominal ultrasound
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients between the ages of 18 and 70 of both gender who volunteered and signed a consent and who were admitted with the diagnosis of renal colic
Exclusion criteria	Patients with NSAID allergy, analgesic drug use in the last 24 hours, a history of gastrointestinal bleeding, a diagnosed peptic ulcer, receiving anticoagulant therapy, 1 kidney, moderate to severe hydronephrosis, serum creatinine value >2mg/dL, pregnant or lactating hypersensitivity to meperidine, hepatic impairment, uptake of monoamine oxidase inhibitors (within 2-3 weeks) or agents with serotonergic activity, seizure disorder, coma, or severe respiratory depression
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: 18-70 years. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: NSAIDs - Dexketoprofen trometamol. Dexketoprofen trometamol (Arveles ampules of 50mg per 2mL). Duration Single dose. Concurrent medication/care: A 50mg additional dose of meperidine was administered to patients with ongoing pain at 30 minutes. Indirectness: No indirectness (n=26) Intervention 2: Opioids/opiates - Meperidine. Meperidine hydrochloride (Aldolan Gerot ampules of 100mg per 2mL). Duration Single dose. Concurrent medication/care: A 50mg additional dose of meperidine was administered to patients with ongoing pain at 30 minutes. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DEXKETOPROFEN TROMETAMOL versus MEPERIDINE	

Protocol outcome 1: Pain intensity (visual analogue scale) at Define - Actual outcome for Adults (≥16 years): Pain at 30 minutes; Group 1: mean 1.7 (SD 1); n=26, Group 2: mean 2.6 (SD 1.6); n=26; Numerical rating scale (NRS) 0-10 Top=High is poor outcome; Comments: Baseline scores: NSAID group 7.6 (0.9); opioid group 8.3 (0.9) Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Need for rescue medication at 30 minutes; Group 1: 3/26, Group 2: 3/26 Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Nausea and vomiting at 30 minutes; Group 1: 1/26, Group 2: 2/26 Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Azizkhani 2013[11]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=124)
Countries and setting	Conducted in Iran; Setting: Al-Zahra Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Confirmed by means of urine analysis, ultrasonography
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	People referring to the emergency ward with a renal colic pain complaint, who were aged 15-80 years and had a weight of 60-80 kg
Exclusion criteria	Those who were addicted, allergic to opioids and acetaminophen, those who had received any types of analgesic drugs within previous 6 h, cases of kidney transplantation, patients with known heart failure, liver failure, respiratory failure, renal failure, cases of blindness and physical disabilities who were not able to communicate
Recruitment/selection of patients	Convenience sampling was used
Age, gender and ethnicity	Age - Mean (SD): Morphine group 39.73 (11.62); paracetamol group 38.40 (11.60). Gender (M:F): 84:40. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=62) Intervention 1: Opioids/opiates - Morphine. The specified dosage for morphine, based on patient's weight, was 0.1 mg/kg. This was infused over 15 minutes. . Duration One dose. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=62) Intervention 2: Paracetamol - Acetaminophen. 15mg/kg intravenously over 15 minutes. Duration One dose. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (Financial support for this project has been done by the University Research Council and also the Presidential Department of Science and Technology)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MORPHINE versus ACETAMINOPHEN	

Protocol outcome 1: Pain intensity (visual analogue scale) at Define - Actual outcome for Adults (≥16 years): Pain at 30 minutes; Group 1: mean 0.75 (SD 1.31); n=62, Group 2: mean 2.41 (SD 3.29); n=62; VAS 0-10 Top=High is poor outcome; Comments: Baseline scores: morphine group 5.0 (1.04); paracetamol group 2.70 (1.78) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Dizziness at 30 minutes; Group 1: 15/62, Group 2: 0/62 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Vomiting at 30 minutes; Group 1: 1/62, Group 2: 0/62 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Arterial hypotension at 30 minutes; Group 1: 6/62, Group 2: 0/62 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Bektas 2009[15]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=165)
Countries and setting	Conducted in Turkey; Setting: Emergency department
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT, intravenous urography, radiologist performed US, plain radiography, stone recovery
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults aged 18-55 with acute flank pain, with a clinical diagnosis of suspected acute renal colic and reporting either mild or greater pain intensity on a 4-point verbal rating scale or at least 20mm on a 100mm VAS
Exclusion criteria	Known allergy or contraindication to morphine or contraindication to morphine, paracetamol or any opioid analgesic; hemodynamic instability; fever (temperature >38 degrees C); evidence of peritoneal inflammation; documented or suspected pregnancy; known or suspected aortic dissection or aneurysm; use of any analgesic within 6 hours of ED presentation; or previous study enrolment; known renal, pulmonary, cardiac or hepatic failure, as well as those with renal transplantation
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Paracetamol group 35 (10); morphine group 39 (11); placebo group 36 (10). Gender (M:F): 90:56. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: Paracetamol. Paracetamol (Perfalgan, 1g in 100ml normal saline solution). Duration Single dose. Concurrent medication/care: Those who had inadequate pain relief at 30 minutes received rescue fentanyl 0.75µg/kg intravenously. Indirectness: No indirectness (n=55) Intervention 2: Opioids/opiates - Morphine. Morphine (0.1 mg/kg in 100mL normal saline solution). Duration Single dose. Concurrent medication/care: Those who had inadequate pain relief at 30 minutes received rescue fentanyl 0.75µg/kg intravenously. Indirectness: No indirectness (n=55) Intervention 3: Placebo. Placebo (100ml normal saline solution). Duration Single dose. Concurrent medication/care: Those who had inadequate pain relief at 30 minutes received rescue fentanyl 0.75µg/kg

	intravenously. Indirectness: No indirectness
Funding	Academic or government funding (Supported by the Akdeniz University Research and Project Unit)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARACETAMOL versus MORPHINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Need for rescue medication at 30 minutes; Group 1: 21/46, Group 2: 24/49
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 9; Group 2 Number missing: 6
- Actual outcome for Adults (≥16 years): Pain at 30 minutes; MD; 2 (95%CI -13 to 16) VAS 0-100 Top=High is poor outcome;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 9; Group 2 Number missing: 6
- Actual outcome for Adults (≥16 years): Pain at 15 minutes; MD; 13 (95%CI 0.1 to 25) VAS 0-100 Top=High is poor outcome;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 9; Group 2 Number missing: 6

Protocol outcome 2: Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define
- Actual outcome for Adults (≥16 years): Respiratory depression at 30 minutes; Group 1: 0/46, Group 2: 0/49
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 9; Group 2 Number missing: 6

Protocol outcome 3: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Nausea and vomiting at 30 minutes; Group 1: 7/46, Group 2: 9/49
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 9; Group 2 Number missing: 6
- Actual outcome for Adults (≥16 years): Urinary retention at 30 minutes; Group 1: 0/46, Group 2: 1/49
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 9; Group 2 Number missing: 6

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARACETAMOL versus PLACEBO

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Need for rescue medication at 30 minutes; Group 1: 21/46, Group 2: 34/51
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 9; Group 2 Number missing: 4
- Actual outcome for Adults (≥16 years): Pain at 30 minutes; MD; 16 (95%CI 5 to 27) VAS 0-100 Top=High is poor outcome;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 9; Group 2 Number missing: 4
- Actual outcome for Adults (≥16 years): Pain at 15 minutes; MD; 26 (95%CI 15 to 38) VAS 0-100 Top=High is poor outcome;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 9; Group 2 Number missing: 4

Protocol outcome 2: Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define
- Actual outcome for Adults (≥16 years): Respiratory depression at 30 minutes; Group 1: 0/46, Group 2: 0/51
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 9; Group 2 Number missing: 4

Protocol outcome 3: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Urinary retention at 30 minutes; Group 1: 0/46, Group 2: 0/51
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 9; Group 2 Number missing: 4
- Actual outcome for Adults (≥16 years): Nausea and vomiting at 30 minutes; Group 1: 7/46, Group 2: 2/51
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 9; Group 2 Number missing: 4

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MORPHINE versus PLACEBO

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 30 minutes; MD; 14 (95%CI 0.4 to 27) VAS 0-100 Top=High is poor outcome;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing:

6; Group 2 Number missing: 4
- Actual outcome for Adults (≥16 years): Pain at 15 minutes; MD; 14 (95%CI 3 to 25) VAS 0-100 Top=High is poor outcome, Units: ;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 6; Group 2 Number missing: 4
- Actual outcome for Adults (≥16 years): Need for rescue medication at 30 minutes; Group 1: 24/49, Group 2: 34/51
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 6; Group 2 Number missing: 4

Protocol outcome 2: Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define
- Actual outcome for Adults (≥16 years): Respiratory depression at 30 minutes; Group 1: 0/49, Group 2: 0/51
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 6; Group 2 Number missing: 4

Protocol outcome 3: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Nausea and vomiting at 30 minutes; Group 1: 9/49, Group 2: 2/51
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 6; Group 2 Number missing: 4
- Actual outcome for Adults (≥16 years): Urinary retention at 30 minutes; Group 1: 1/49, Group 2: 0/51
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Morphine group had slightly higher baseline pain; Group 1 Number missing: 6; Group 2 Number missing: 4

Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Use of healthcare services at Define; Length of stay at Define

Study	**Cenker 2017[22]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200 randomised (301 assessed for eligibility))
Countries and setting	Conducted in Turkey; Setting: Emergency department (ED) of a tertiary care hospital with annual census of approximately 87,000 visits
Line of therapy	1st line
Duration of study	Intervention + follow up: 30-minute follow-up for pain intensity

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients presenting with flank pain. The ultimate diagnosis of renal colic was performed by a detailed medical history, physical examination, direct urinary system graphy, ultrasound and computerised tomography
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18-60 years, presenting with flank pain
Exclusion criteria	Patients denied to give informed consent; Use of any analgesia within 6 h of ED presentation; 'Patients with fewer or hemodynamically unstable'; Peritoneal irritation signs; Cardiac failure; History of renal and hepatic failure; Prior known allergy to paracetamol or ibuprofen; Suspected or documented pregnancy; Patients with vision problems
Recruitment/selection of patients	301 people were assessed for eligibility and 101 were excluded for the following reasons: <18 or >60 years (n=32); Denied to give consent (n=9); Received analgesic within 6 hours (n=57); Known study drug allergy (n=1); Known hepatic, renal and cardiac failure (n=2)
Age, gender and ethnicity	Age - Mean (SD): 36 (9). Gender (M:F): 129/71. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: NSAIDs - Ibuprofen. Intravenous ibuprofen (Intrafen, Gen, Turkey) 800 mg in 100 ml normal saline . Duration 30 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=100) Intervention 2: Paracetamol. Intravenous paracetamol (Perfalgan, Bristol Myers Squibb, Itxassou, France) 1 g in 100 ml normal saline. Duration 30 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (The study received no industrial funding. The expenditure of the drugs was covered by the Pamukkale University.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus PARACETAMOL

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 30 minutes; Group 1: mean 20.4 Not applicable (SD 14.4); n=97, Group 2: mean 35.2 Not applicable (SD 18.2); n=99; 100-mm visual analogue scale 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 patients withdrawn from the study after 15 minutes, one of them voluntarily and one due to allergic reaction; 1 patient withdrawn before 15 minutes voluntarily; Group 2 Number missing: 1, Reason: No data obtained

inadvertently secondary to vomiting at 30 minutes - Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 15 minutes; Group 1: mean 44 Not applicable (SD 17); n=99, Group 2: mean 51.3 Not applicable (SD 17.5); n=100; 100-mm visual analogue scale 0-100 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 patient withdrawn before 15 minutes voluntarily; Group 2 Number missing: 0 - Actual outcome for Adults (≥16 years): Pain intensity (need for rescue medication) at 30 minutes; Group 1: 2/97, Group 2: 10/99 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 patients withdrawn from the study after 15 minutes, one of them voluntarily and one due to allergic reaction; 1 patient withdrawn before 15 minutes voluntarily; Group 2 Number missing: 1, Reason: No data obtained inadvertently secondary to vomiting at 30 minutes Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Minor adverse events - vomiting at Not reported; Group 1: 2/97, Group 2: 5/99 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 patients withdrawn from the study after 15 minutes, one of them voluntarily and one due to allergic reaction; 1 patient withdrawn before 15 minutes voluntarily; Group 2 Number missing: 1, Reason: No data obtained inadvertently secondary to vomiting at 30 minutes - Actual outcome for Adults (≥16 years): Minor adverse events - allergic reaction at Not reported; Group 1: 1/97, Group 2: 0/99 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 patients withdrawn from the study after 15 minutes, one of them voluntarily and one due to allergic reaction; 1 patient withdrawn before 15 minutes voluntarily; Group 2 Number missing: 1, Reason: No data obtained inadvertently secondary to vomiting at 30 minutes - Actual outcome for Adults (≥16 years): Minor adverse events - epigastric pain at Not reported; Group 1: 1/97, Group 2: 0/99 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 patients withdrawn from the study after 15 minutes, one of them voluntarily and one due to allergic reaction; 1 patient withdrawn before 15 minutes voluntarily; Group 2 Number missing: 1, Reason: No data obtained inadvertently secondary to vomiting at 30 minutes - Actual outcome for Adults (≥16 years): Minor adverse events - vertigo at Not reported; Group 1: 0/97, Group 2: 1/99 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 patients withdrawn from the study after 15 minutes, one of them voluntarily and one due to allergic reaction; 1 patient withdrawn before 15 minutes voluntarily; Group 2 Number missing: 1, Reason: No data obtained inadvertently secondary to vomiting at 30 minutes
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Cordell 1996[27]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=106)
Countries and setting	Conducted in USA; Setting: Emergency department
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: IV pyelography or ultrasonography or on the basis of stone passage or stone recovery during surgery
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients 18 years or older with a history and physical examination findings compatible with renal colic and with pain of moderate to severe intensity on a categorical scale
Exclusion criteria	Known allergy or contraindication to any opioid or non-opioid analgesic, history of active peptic ulcer in the preceding 6 months, history of bleeding problems, anticoagulation therapy in the preceding 4 weeks, pregnancy, history of renal insufficiency, and suspicion of drug seeking behaviour. Patients who had had any analgesic in the preceding 3 hours were also excluded
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): NSAID group 38.8 (10.2); opioid group 42.0 (11.24). Gender (M:F): 58:13. Ethnicity: White 86%; black 11%; other 2%
Further population details	
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: NSAIDs - Ketorolac. Intravenous ketorolac 60mg and a placebo (normal saline solution). Duration Single dose. Concurrent medication/care: Participants with inadequate pain relief at 30 minutes were allowed supplemental IV doses of meperidine as needed, with the dose determined by the attending physician. Participants were permitted Participants were allowed one 200mg rectal dose of trimethobenazamide hydrochloride for nausea or vomiting. Indirectness: No indirectness (n=51) Intervention 2: Opioids/opiates - Meperidine. Intravenous meperidine 50mg and placebo (normal saline solution). Duration Single dose. Concurrent medication/care: Participants with inadequate pain relief at 30 minutes were allowed supplemental IV doses of meperidine as needed, with the dose determined by the attending physician. Participants were permitted Participants were allowed one 200mg rectal dose of

	trimethobenazamide hydrochloride for nausea or vomiting. Indirectness: No indirectness
Funding	Other (Supported by Roche Laboratories)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus MEPERIDINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Need for rescue medication at 30 minutes; Group 1: 23/36, Group 2: 31/35
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: No confirmed diagnosis of renal colic; Group 2 Number missing: 14, Reason: No confirmed diagnosis of renal colic
- Actual outcome for Adults (≥16 years): Pain at 30 minutes; Group 1: mean 24.7 (SD 4.6); n=36, Group 2: mean 56.6 (SD 5.2); n=35; VAS 1-100 Top=High is poor outcome; Comments: Baseline scores: NSAID group 80.3 (3.5); opioid group 77.4 (3.6)
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: No confirmed diagnosis of renal colic; Group 2 Number missing: 14, Reason: No confirmed diagnosis of renal colic

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Dizziness at 2 hours; Group 1: 4/36, Group 2: 18/35
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: No confirmed diagnosis of renal colic; Group 2 Number missing: 14, Reason: No confirmed diagnosis of renal colic
- Actual outcome for Adults (≥16 years): Sleepiness at 2 hours; Group 1: 6/36, Group 2: 4/35
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: No confirmed diagnosis of renal colic; Group 2 Number missing: 14, Reason: No confirmed diagnosis of renal colic

Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Curry 1995[28]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	Conducted in New Zealand; Setting: Emergency department
Line of therapy	1st line
Duration of study	Intervention + follow up: 120 minutes
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	People with pain consistent with renal colic
Exclusion criteria	Age below 18 or above 75, known hypersensitivities, known contraindications to NSAIDs or pethidine, and known or suspected narcotic addiction
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 40 years (18-74). Gender (M:F): 31:10. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Opioids/opiates - Pethidine. Pethidine 75mg intravenously. Duration Single dose. Concurrent medication/care: Patients had intravenous metoclopramide 10mg before treatment. Indirectness: No indirectness (n=17) Intervention 2: NSAIDs - Tenoxicam. Tenoxicam, 40mg intravenously. Duration Single dose. Concurrent medication/care: Patients had intravenous metoclopramide 10mg before treatment. Indirectness: No indirectness
Funding	Study funded by industry (Roche NZ Ltd provided funding support)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PETHIDINE versus TENOXICAM

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Need for rescue medication at 30 minutes; Group 1: 4/24, Group 2: 3/17
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Minor adverse events at 30 minutes; Group 1: 4/24, Group 2: 0/17 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	**Dawood al-waili 1998[31]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=47)
Countries and setting	Conducted in United Arab Emirates; Setting: Casualty department
Line of therapy	1st line
Duration of study	Intervention + follow up: 60 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinalysis, intravenous urography, ultrasonography and the voiding of a calculus
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	People presenting with acute renal colic, complaining of acute loin pain, nausea and vomiting and with a diagnosis of acute renal colic
Exclusion criteria	Patients who received anti-spasmodic, pethidine or any other prostaglandin synthesis inhibitors within 2 hours and those with renal or hepatic impairments, cardiovascular diseases, glaucoma, allergy to other non-steroidal anti-inflammatory drugs
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 36 years (20-45). Gender (M:F): 40:7. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: NSAIDs - Tenoxicam. Tenoxican, 20mg, intravenously . Duration Single dose. Concurrent medication/care: If there was no satisfactory response after the first hour, then 100mg was

	given. Indirectness: No indirectness (n=22) Intervention 2: Smooth muscle relaxant /antispasmotic - Buscopan. Buscopan compositum, 20g, intravenously. Duration Single dose. Concurrent medication/care: If there was no satisfactory response after the first hour, then 100mg was given. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TENOXICAM versus BUSCOPAN Protocol outcome 1: Pain intensity (visual analogue scale) at Define - Actual outcome for Adults (≥16 years): Need for rescue medication at 60 minutes; Group 1: 5/25, Group 2: 6/22 Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'No statistical difference between groups for age, sex and severity of symptoms' - not actually reported; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Minor adverse events (dry mouth/drowsiness) at 60 minutes; Group 1: 0/25, Group 2: 22/22 Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'No statistical difference between groups for age, sex and severity of symptoms' - not actually reported; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Grissa 2011[45]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Tunisia; Setting: Emergency department
Line of therapy	1st line
Duration of study	Intervention + follow up: 90 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinalysis or ultrasonography
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Consenting patients (16 years or older) presenting clinical symptoms and signs of renal colic. Diagnosis criteria were a history of unilateral colicky acute flank pain with urinalysis or ultrasonography findings consistent with the diagnosis of renal colic. Only patients displaying at least a visual analog scale (VAS) ≥30/100 were included.
Exclusion criteria	Patients could not be included if they had a history of peptic ulcer disease, asthma, bleeding disorder (including the use of oral anticoagulant), impaired renal or hepatic function, suspected hypersensivity to aspirin or NSAID or paracetamol, and if they were pregnant and breast-feeding women. Patients could not be included if they had received painkillers within 6 hours before presentation.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): NSAID group 40 (14); paracetamol group 39 (13). Gender (M:F): 41:59. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: NSAIDs - Piroxicam. Piroxicam (20 mg intramuscularly). All the patients received saline serum infusion. . Duration One dose. Concurrent medication/care: Rescue therapy was defined as the need of intravenous morphine titration if VAS at 60 minutes was more than 50% the initial VAS or if VAS was more than 50/100 at 2 successive time points. Indirectness: No indirectness (n=50) Intervention 2: Paracetamol. Paracetamol (1 g in 100mLof serum saline intravenously, 15 minutes). Duration One dose. Concurrent medication/care: Rescue therapy was defined as the need of intravenous morphine titration if VAS at 60 minutes was more than 50% the initial VAS or if VAS was more than 50/100 at 2 successive time points. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PIROXICAM versus PARACETAMOL Protocol outcome 1: Pain intensity (visual analogue scale) at Define - Actual outcome for Adults (≥16 years): Pain at 30 minutes; Group 1: mean 48 (SD 27); n=50, Group 2: mean 36 (SD 30); n=50; VAS 0-100 Top=High is poor outcome; Comments: Baseline values: NSAID group 82 (15); paracetamol group 75 (21) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Pain at 45 minutes; Group 1: mean 45 (SD 29); n=50, Group 2: mean 29 (SD 30); n=50; VAS 0-100 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Pain at 15 minutes; Group 1: mean 54 (SD 26); n=50, Group 2: mean 44 (SD 30); n=50; VAS 0-100 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Pain (a decrease of VAS of 50%) at 90 minutes; Group 1: 24/50, Group 2: 40/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Vomiting at Not reported; Group 1: 0/50, Group 2: 1/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Hosseini 2015[52]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=541 randomised (586 assessed for eligibility))
Countries and setting	Conducted in Iran; Setting: Centres in Jahrom and Shiraz cities in Iran
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: 'patients with renal colic'
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	History of allergy to NSAIDs; Hemorrhoids and anal fissures; Peptic ulcers; Coagulopathy; Inflammatory bowel disease; Pregnancy; Ischemic coronary diseases; Chronic obstructive pulmonary disease; Liver or renal failure
Recruitment/selection of patients	Recruitment between December 2009 and April 2011
Age, gender and ethnicity	Age - Other: Not reported. Gender (M:F): 351/190. Ethnicity: Not reported
Further population details	
Extra comments	Unclear if previous treatment given for renal colic
Indirectness of population	Serious indirectness: Diagnosis not confirmed/unclear
Interventions	(n=266) Intervention 1: NSAIDs - Diclofenac. A single 100 mg dosage of rectal diclofenac sodium (RDS). Duration 'more than 30 minutes'. Concurrent medication/care: Not reported. Indirectness: Serious indirectness; Indirectness comment: Diagnosis not confirmed/unclear (n=275) Intervention 2: Opioids/opiates - Pethidine. A single 50 mg dosage of intramuscular pethidine injection (IMP). Duration 'more than 30 minutes'. Concurrent medication/care: Not reported. Indirectness: Serious indirectness; Indirectness comment: Diagnosis not confirmed/unclear
Funding	Funding not stated ('more than 30 minutes follow up')
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PETHIDINE	

Protocol outcome 1: Pain intensity (visual analogue scale) at Define - Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - reduction in pain by 50% at 30 minutes; Group 1: 233/266, Group 2: 254/275; Comments: Number analysed reported as number randomised with no loss to follow-up but limitations of study highlight that patients who responded to medication were discharged and their VAS did not record up to 30 minutes Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Comments - 'whenever a patient responded to medication (e.g. 10 or 20 minutes) was discharged and his/her VAS did not record up to 30 minutes' ; Indirectness of outcome: Serious indirectness, Comments: Diagnosis not confirmed/unclear; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - reduction in pain by 50% at 20 minutes; Group 1: 191/266, Group 2: 191/275; Comments: Number analysed reported as number randomised with no loss to follow-up but limitations of study highlight that patients who responded to medication were discharged and their VAS did not record up to 30 minutes Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Comments - 'whenever a patient responded to medication (e.g. 10 or 20 minutes) was discharged and his/her VAS did not record up to 30 minutes' ; Indirectness of outcome: Serious indirectness, Comments: Diagnosis not confirmed/unclear; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - reduction in pain by 50% at 10 minutes; Group 1: 121/266, Group 2: 123/275; Comments: Number analysed reported as number randomised with no loss to follow-up but limitations of study highlight that patients who responded to medication were discharged and their VAS did not record up to 30 minutes Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Comments - 'whenever a patient responded to medication (e.g. 10 or 20 minutes) was discharged and his/her VAS did not record up to 30 minutes' ; Indirectness of outcome: Serious indirectness, Comments: Diagnosis not confirmed/unclear; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define; Use of healthcare services at Define; Length of stay at Define

Study	**Hosseininejad 2017[53]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=300 randomised (483 assessed for eligibility))
Countries and setting	Conducted in Iran; Setting: Adult emergency department of Emam Khomeini hospital, a tertiary general hospital affiliated with Mazandaran University of Medical Sciences, in Northern Iran
Line of therapy	1st line
Duration of study	Intervention + follow up: 40-minute follow-up for pain intensity
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis of acute renal colic (sudden sharp colic flank pain with or without radiation to genitalia or groin and with or without urinary symptoms)

Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	18-55 years of age; Clinical diagnosis of acute renal colic (sudden sharp colic flank pain with or without radiation to genitalia or groin and with or without urinary symptoms) who had pain score of 5 or more measured by 10-cm visual analogue scale (VAS)
Exclusion criteria	History of kidney or renal dysfunction and severe dehydration; Pregnancy; Breastfeeding; Single kidney or kidney transplantation; History of peptic ulcers and gastrointestinal bleeding; Receiving analgesics within 6 hours before presentation; History of bleeding diathesis; History of cardiovascular disease and the use of angiotensin-converting-enzyme inhibitor (ACE inhibitor) or angiotensin receptor blockers (ARB); Anticoagulant medication or coagulation disorders; History of drug dependence or current use of methadone or chronic consumption of tobacco and alcohol and peritonitis or presence of any peritoneal sign
Age, gender and ethnicity	Age - Other: 30.28 (10.3) (morphine and ketorolac); 28.81 (9.8) (morphine); 29.66 (9.7) (ketorolac). Gender (M:F): 67/33 (morphine and ketorolac); 72/28 (morphine); 69/31 (ketorolac). Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: NSAIDs - Ibuprofen. Combined therapy consisting of 30 mg intravenous injection of ketorolac (Keterolac-Combaxona, 30 mg/mL, Combino Pharmaceutical, Spain) in combination with 0.1 mg/kg intravenous morphine (Morphien Sulfate, 10 mg/ml, Daru Pakhsh, Iran). All the injections were given during a 1-min period through a cubital venous line. The drugs were prepared in same syringes which were opaque. All the drugs were prepared in laboratory of pharmacology school.. Duration 40 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness Comments: Combined therapy: ketorolac and morphine (n=100) Intervention 2: NSAIDs - Ketorolac. 30 mg intravenous injection of ketorolac (Ketorolac-Combaxona, 30 mg/mL, Combino Pharmaceutical, Spain) in combination with placebo (undefined). All the injections were given during a 1-min period through a cubital venous line. The drugs were prepared in same syringes which were opaque. All the drugs were prepared in laboratory of pharmacology school.. Duration 40 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=100) Intervention 3: Opioids/opiates - Morphine. 0.1 mg/kg intravenous morphine (Morphien Sulfate, 10 mg/mL, Daru Pakhsh, Iran) and same amount of intravenous normal saline as placebo. All the injections were given during a 1-min period through a cubital venous line. The drugs were prepared in same syringes which were opaque. All the drugs were prepared in laboratory of pharmacology school.. Duration 40 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness

Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus KETOROLAC

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale): change in pain intensity at Unclear (40 minutes); Group 1: mean 3.01 (SD 0.98); n=100, Group 2: mean 3.68 (SD 0.88); n=100; VAS 0-10 Top=High is poor outcome; Comments: 'The pain intensity was comparable between three study groups after 20-min of intervention'
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity: rescue medication (0.05 mg/kg of intravenous morphine for persistent pain - pain intensity more than 4 in VAS) at 20 minutes; Group 1: 10/100, Group 2: 11/100
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity: rescue medication (0.05 mg/kg of intravenous morphine for persistent pain - pain intensity more than 4 in VAS) at 40 minutes; Group 1: 16/100, Group 2: 24/100
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Minor adverse events (nausea) at Not reported; Group 1: 2/100, Group 2: 4/100
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Minor adverse events (vomiting) at Not reported; Group 1: 2/100, Group 2: 2/100
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Adults (≥16 years): Minor adverse events (vertigo) at Not reported; Group 1: 3/100, Group 2: 1/100
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus MORPHINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale): change in pain intensity at Unclear (40 minutes); Group 1: mean 3.01 (SD 0.98); n=100, Group 2: mean 3.66 (SD 1.02); n=100; VAS 0-10 Top=High is poor outcome; Comments: 'The pain intensity was comparable between three study groups after 20-min of intervention'
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity: rescue medication (0.05 mg/kg of intravenous morphine for persistent pain - pain intensity more than 4 in VAS) at 20 minutes; Group 1: 10/100, Group 2: 12/100
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity: rescue medication (0.05 mg/kg of intravenous morphine for persistent pain - pain intensity more than 4 in VAS) at 40 minutes; Group 1: 16/100, Group 2: 20/100
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Minor adverse events (nausea) at Not reported; Group 1: 2/100, Group 2: 4/100
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Minor adverse events (vomiting) at Not reported; Group 1: 2/100, Group 2: 4/100
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:
:
- Actual outcome for Adults (≥16 years): Minor adverse events (vertigo) at Not reported; Group 1: 3/100, Group 2: 6/100
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus MORPHINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale): change in pain intensity at 40 minutes; Group 1: mean 3.68 (SD 0.88); n=100, Group 2: mean 3.66 (SD 1.02); n=100; VAS 0-10 Top=High is poor outcome; Comments: Note: rescue analgesic was given to some patients at 20 minutes and these are not excluded from the number analysed at 40 minutes. 'The pain intensity was comparable between three study groups after 20-min of intervention'
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity: rescue medication (0.05 mg/kg of intravenous morphine for persistent pain - pain intensity more than 4 in VAS) at 20 minutes; Group 1: 11/100, Group 2: 12/100
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline

nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Pain intensity: rescue medication (0.05 mg/kg of intravenous morphine for persistent pain - pain intensity more than 4 in VAS) at 40 minutes; Group 1: 24/100, Group 2: 20/100 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Minor adverse events (nausea) at Not reported; Group 1: 4/100, Group 2: 4/100 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Minor adverse events (vomiting) at Not reported; Group 1: 2/100, Group 2: 4/100 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Minor adverse events (vertigo) at Not reported; Group 1: 1/100, Group 2: 6/100 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Rescue analgesia given to some patients at 20 minutes but they do not appear to be excluded from outcomes at 40 minutes. Baseline nephrolithiasis in 54% of ketorolac and morphine group, 31% of morphine group and 39% of ketorolac group; Indirectness of outcome: No indirectness ; Baseline details: Patients with nephrolithiasis: 54/100 (ketorolac and morphine); 31/100 (morphine); 39/100 (ketorolac) p-value 0.064; Blinding details: triple-blinded study although opioids 'associated with severe side effects'; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Hetherington 1986[48]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=58)
Countries and setting	Conducted in United Kingdom; Setting: Emergency department
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 hour
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with severe pain and thought to have acute renal colic
Exclusion criteria	Patients already taking NSAIDs; those with a history of allergies, asthma, peptic ulceration or renal insufficiency; and those who had been given strong analgesics by their GP before admission
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 46 (19-85). Gender (M:F): 41:17. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Opioids/opiates - Pethidine. 100mg. Duration One dose. Concurrent medication/care: A second injection of the same drug was offered after 30 minutes if the first had not been successful or if the pain returned. If pain persisted after 1 hour or returned thereafter, patients were given 100mg pethidine intramuscularly . Indirectness: No indirectness (n=30) Intervention 2: NSAIDs - Diclofenac. Diclofenac sodium, 75mg. Duration One dose. Concurrent medication/care: A second injection of the same drug was offered after 30 minutes if the first had not been successful or if the pain returned. If pain persisted after 1 hour or returned thereafter, patients were given 100mg pethidine intramuscularly . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PETHIDINE versus DICLOFENAC

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Need for rescue medication at 30 minutes; Group 1: 10/28, Group 2: 2/30
Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Minor adverse events at 30 minutes; Group 1: 14/28, Group 2: 5/30
Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	**Indudhara 1990[55]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=94)
Countries and setting	Conducted in India; Setting: Emergency out-patient department
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Plain x-ray KUB or ultrasound
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with renal colic, received no drug in the past 6 hours, aged between 18-60. Only those who had indisputable renal colic and rated their pain as horrible or excruciating (4 or 5 on the 1-5 ordinal scale) were included
Exclusion criteria	Patients aged below 18 or above 60 years; history of upper gastrointestinal/lower gastrointestinal bleed; history of peptic ulcer, cardiac, renal and hepatic dysfunction; history of allergy to aspirin; presence of any abnormal physical findings apart from tenderness in renal angle

Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 19-57. Gender (M:F): 68:26. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: NSAIDs - Diclofenac. Diclofenac sodium, 150mg, orally . Duration Single dose. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=31) Intervention 2: Opioids/opiates - Pethidine. Pethidine, 50mg intramuscularly . Duration Single dose. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PETHIDINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): No pain relief at 1 hour; Group 1: 3/33, Group 2: 2/31
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Only says that there was no difference for 3 parameters but does not provide data; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Minor adverse events (nausea, vomiting, epigastric discomfort) at 3 hours;
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Only says that there was no difference for 3 parameters but does not provide data; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Kaynar 2015[61]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=124)
Countries and setting	Conducted in Turkey; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention + follow up: 120 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinalysis, x-ray, ultrasonography, and computed tomography
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Consenting patients (≥18 years) who were experiencing renal colic clinical symptoms. Standardized screening forms were used to help identify eligible patients
Exclusion criteria	The presence of coronary artery disease, coagulopathy, anticoagulant therapy, peptic ulcer, renal failure, hepatic failure, pregnancy, the need for immediate surgical or other intervention, NSAID or acetaminophen hypersensitivity, fever, renal colic due to reasons other than urolithiasis, and the use of other analgesics within 6 hours of the treatment at our facility.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (range): Paracetamol group 46.3 (19-81); NSAID group 37.98 (18-72). Gender (M:F): 48:32. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: NSAIDs - Diclofenac. 75 mg of diclofenac sodium in the form of a single intramuscular injection. Duration One dose. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=40) Intervention 2: Paracetamol - Acetaminophen. 1 g/100 mL of serumsaline of IV acetaminophen (Perfalgan; Bristol Myers Squibb, Itxassou, France) for 15 minutes. Duration One dose. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus ACETAMINOPHEN

Protocol outcome 1: Pain intensity (visual analogue scale) at Define

- Actual outcome for Adults (≥16 years): Pain at 30 minutes; Mean; NSAID group 2.68; paracetamol group 3.46, Comments: SD not reported; Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Dizziness at Not reported; Group 1: 0/40, Group 2: 1/40 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Allergic reaction at Not reported; Group 1: 0/40, Group 2: 1/40 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Rash at Not reported; Group 1: 1/40, Group 2: 0/40 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	**Larkin 1999[69]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention + follow up: 90 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Intravenous pyelogram or by the passage of visible calculi
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	People diagnosed as having an acute attack of renal colic

Exclusion criteria	Age younger than 18, weight less than 50kg, known or potential pregnancy, contraindications to NSAIDs, opiates, or iodinated contrast, suspicion of substance abuse, renal dysfunction, diagnosis of ureterolithiasis was not confirmed by intravenous pyelogram or by the passage of visible calculi
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): NSAID group 45.5 (16); opioid group 40.7 (13.3). Gender (M:F): 53:17. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: NSAIDs - Ketorolac. Ketorolac, 60mg intramuscularly . Duration Single dose. Concurrent medication/care: Rescue analgesia was offered after 20 minutes if no relief was obtained, the choice of analgesia was left to the discretion of the attending EP. Indirectness: No indirectness (n=37) Intervention 2: Opioids/opiates - Meperidine. Single weight dependent dose of intramuscular meperidine: patients weighing 50-90kg received 100mg, those weighing more than 90kg received 150mg. Duration Single dose. Concurrent medication/care: Rescue analgesia was offered after 20 minutes if no relief was obtained, the choice of analgesia was left to the discretion of the attending EP. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus MEPERIDINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Need for rescue medication at 20 minutes; Group 1: 11/33, Group 2: 16/37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Nausea at 90 minutes; Group 1: 5/33, Group 2: 4/37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Lehtonen 1983[70]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=124)
Countries and setting	Conducted in Finland; Setting: Four central hospitals in Finland
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical examination including urine analysis and urography
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	People with ureteric colic
Exclusion criteria	Asthma, antiallergy to antiinflammatory analgesics, latent or active gastric or duodenal ulcer, pregnancy and medication taken or received by the patients before arriving at hospital
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): NSAID group 44.6 (16-79); opioid group 39.5 (23-75). Gender (M:F): 95:29. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=93) Intervention 1: NSAIDs - Indomethacin. Single 5ml intravenous injection of 50mg indomethacin. All injections were diluted to a volume of 5ml as needed and were administered over a period of at least 5 minutes. Duration Single dose. Concurrent medication/care: If pain relief was not obtained within 30 minutes after the injection, some other potent analgesic was administered according to the routine of the hospital. Patients were not allowed to drink any liquids. . Indirectness: No indirectness (n=31) Intervention 2: Opioids/opiates - Pethidine. A single 5ml intravenous injection of 50mg pethidine. Duration Single dose. Concurrent medication/care: If pain relief was not obtained within 30 minutes after the injection, some other potent analgesic was administered according to the routine of the hospital. Patients were not allowed to drink any liquids. . Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Indomethacin supplied A/S Dumex, Denmark)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INDOMETHACIN versus PETHIDINE	

Protocol outcome 1: Pain intensity (visual analogue scale) at Define - Actual outcome for Adults (≥16 years): No pain relief at 30 minutes; Group 1: 5/93, Group 2: 2/31 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Partial pain relief at 30 minutes; Group 1: 33/93, Group 2: 13/31 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Complete pain relief at 30 minutes; Group 1: 55/93, Group 2: 16/31 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Need for rescue medication at 30 minutes; Group 1: 20/93, Group 2: 8/31 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Vomiting at 30 minutes; Group 1: 3/93, Group 2: 3/31 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Nausea at 30 minutes; Group 1: 9/93, Group 2: 6/31 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Dizziness at 30 minutes; Group 1: 11/93, Group 2: 2/31 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Tiredness at 30 minutes; Group 1: 0/93, Group 2: 1/31 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Lundstam 1980[73]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=19)
Countries and setting	Conducted in Sweden; Setting: Emergency ward
Line of therapy	1st line
Duration of study	Intervention + follow up: 25 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Intravenous pyelogram or radiorenography and plain abdominal x-ray
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	People with attacks of ureteral colic
Exclusion criteria	Patients without verified ureteral stones
Age, gender and ethnicity	Age - Range: NSAID group 25-62; placebo group 24-69. Gender (M:F): 16:3. Ethnicity: Not reported
Further population details	
Extra comments	After the treatment, diagnosis/assessment was performed. Those without verified ureteral stones were then excluded
Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: NSAIDs - Diclofenac. 50mg diclofenac sodium, intramuscularly. Duration Single dose. Concurrent medication/care: Patients who experienced significant pain 25 minutes after the injection were treated with 50mg diclofenac sodium intramuscularly. Indirectness: No indirectness (n=10) Intervention 2: Placebo. Placebo (saline), intramuscular injection. Duration Single dose. Concurrent medication/care: Patients who experienced significant pain 25 minutes after the injection were treated with 50mg diclofenac sodium intramuscularly. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PLACEBO

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Complete pain relief at 15 minutes; Group 1: 4/9, Group 2: 0/10
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Adults (≥16 years): Partial pain relief at 15 minutes; Group 1: 5/9, Group 2: 3/10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): No pain relief at 15 minutes; Group 1: 0/9, Group 2: 7/10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): No pain relief at 25 minutes; Group 1: 0/9, Group 2: 7/10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Partial pain relief at 25 minutes; Group 1: 3/9, Group 2: 3/10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Complete pain relief at 25 minutes; Group 1: 6/9, Group 2: 0/10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Pain reduction at 25 minutes; Group 1: mean -54 (SD 27); n=9, Group 2: mean 4 (SD 12.65); n=10; VAS 0-100 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define - Actual outcome for Adults (≥16 years): Adverse events at 25 minutes; Group 1: 0/9, Group 2: 0/10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Adverse events at 25 minutes; Group 1: 0/9, Group 2: 0/10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Use of healthcare services at Define; Length of stay at Define

Study	Magrini 1984[76]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Italy; Setting: Emergency ward
Line of therapy	1st line
Duration of study	Intervention + follow up: 180 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: History and clinical examination, roentgenographic examination and urinalysis
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	People admitted to hospital emergency ward with episodes of renal colic or having such attacks whilst in hospital, with the presence of severe or very severe pain and verbal informed consent
Exclusion criteria	A history of hemorrhagic disorders or peptic ulcer; severe hepatic, renal, respiratory or cardiac insufficiency; obesity; and diabetes mellitus; severely debilitated patients; narcotics addicts; subjects with known hypersensitivity to ketoprofen or ASA, patients who had previously received analgesics, and subjects unlikely to cooperate or give reliable answers
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): NSAID group 48.5 (30-69); placebo group 42.5 (32-75). Gender (M:F): 11:9. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: NSAIDs - Ketoprofen. Ketoprofen 200mg. Duration Single dose. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=10) Intervention 2: Placebo. Placebo by IV injection. Duration Single dose. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOPROFEN versus PLACEBO

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 180 minutes; Group 1: mean 8.6 (SD 1.4863); n=10, Group 2: mean 0.8 (SD 1.5495); n=10; VAS 0-10

Top=High is good outcome Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Need for rescue medication at 180 minutes; Group 1: 1/10, Group 2: 10/10 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define - Actual outcome for Adults (≥16 years): Adverse events at 180 minutes; Group 1: 0/10, Group 2: 0/10 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Adverse events at 180 minutes; Group 1: 0/10, Group 2: 0/10 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Use of healthcare services at Define; Length of stay at Define

Study	**Marthak 1991[79]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in India; Setting: Multi-centre
Line of therapy	1st line
Duration of study	Intervention + follow up: 60 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinalysis, intravenous pyelography, abdominal x-ray examinations
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients presenting with signs or symptoms of moderate to severe renal or ureteric colic, and diagnosed as having renal or ureteric colic based on patients' history and a clinical examination supported by laboratory investigations

Exclusion criteria	People with peptic ulcer, severe cardia, hepatic or renal insufficiency or a known hypersensitivity to any of the trial drugs, asthmatics with a history of asthma, urticaria, or rhinitis precipitated by aspirin or other prostaglandin synthetase inhibiting drugs, females or reproductive age who were pregnant or not employing reliable contraceptive methods, and patients who obtained marked pain relief from strong analgesics in the 3 hours preceding trial drug administration
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): NSAID group 36.4 (22-65); opioid group 34 (24-62). Gender (M:F): 37:13. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: NSAIDs - Diclofenac. Deep intramuscular injection into the gluteal region of 3ml (75mg) diclofenac sodium. Duration Single dose. Concurrent medication/care: If no pain relief was achieved within 60 minutes, a second injection of a drug of the investigators choice was given. Indirectness: No indirectness (n=25) Intervention 2: Opioids/opiates - Pethidine. Deep intramuscular injection into the gluteal region of 3ml (75mg pethidine). Duration Single dose. Concurrent medication/care: If no pain relief was achieved within 60 minutes, a second injection of pethidine was administered. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PETHIDINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): No pain relief at 30 minutes; Group 1: 1/25, Group 2: 0/25
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Partial pain relief at 30 minutes; Group 1: 24/25, Group 2: 25/25
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Complete pain relief at 30 minutes; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): No pain relief at 60 minutes; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Adults (≥16 years): Partial pain relief at 60 minutes; Group 1: 1/25, Group 2: 5/25 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Complete pain relief at 60 minutes; Group 1: 24/25, Group 2: 20/5 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Nausea at 60 minutes; Group 1: 0/25, Group 2: 2/25 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Vomiting at 60 minutes; Group 1: 0/25, Group 2: 8/25 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Drowsiness at 60 minutes; Group 1: 0/25, Group 2: 1/25 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Total adverse events (number of patients) at 60 minutes; Group 1: 1/25, Group 2: 21/25 Risk of bias: All domain - ; Indirectness of outcome: No indirectness - Actual outcome for Adults (≥16 years): Dizziness at 60 minutes; Group 1: 0/25, Group 2: 4/25 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Masoumi 2014[81]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in Iran; Setting: Hospital emergency department
Line of therapy	1st line
Duration of study	Intervention + follow up: 60 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: kidney or urinary tract stones were confirmed by ultrasound or CT scan
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18-55 years, diagnosed with acute renal colic based on their chief complaint, history, and physical examination, and, or past medical history of renal stone
Exclusion criteria	Allergy to morphine or acetaminophen, hemodynamic instability, fever greater than 38 C, evidence of peritoneal inflammation, pregnancy or suspected pregnancy, proven or suspected aortic aneurysm or dissection, use of any analgesic drug up to 6 hours before evaluation, heart failure, renal failure, respiratory failure, liver failure, kidney transplant patients, and opioid addiction
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Paracetamol group 36.07 (9.7); opioid group 34.96 (8.94). Gender (M:F): 82:26. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: Paracetamol. Patients received intravenous acetaminophen (England, commissioned by Cobel Darou-Iran, in 1 gram vials) with a dose of 1 gram in 100mL normal saline, infused over 5-10 minutes. Duration One dose. Concurrent medication/care: If any degree of pain persisted after min 60, a second 1 µgr/kg dose of fentanyl was administered. Indirectness: No indirectness (n=55) Intervention 2: Opioids/opiates - Morphine. 0.1mg/kg morphine in 100mL normal saline was infused. Both drugs were infused during 5–10minutes. Duration One dose. Concurrent medication/care: If any degree of pain persisted after min 60, a second 1 µgr/kg dose of fentanyl was administered.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARACETAMOL versus MORPHINE

Protocol outcome 1: Length of stay at Define
- Actual outcome for Adults (≥16 years): Number discharged within one hour at 1 hour; Group 1: 49/54, Group 2: 39/54
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 2: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 15 minutes; Group 1: mean 5.87 (SD 2); n=54, Group 2: mean 7.46 (SD 2.51); n=54; VAS 0-10 Top=High is poor outcome; Comments: Baseline measures: paracetamol group 8.84 (1.37); opioid group 9.14 (1.13)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1
- Actual outcome for Adults (≥16 years): Pain at 30 minutes; Group 1: mean 4.09 (SD 2.68); n=54, Group 2: mean 6.09 (SD 2.69); n=54; VAS 0-10 Top=High is poor outcome; Comments: Baseline measures: paracetamol group 8.84 (1.37); opioid group 9.14 (1.13)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1
- Actual outcome for Adults (≥16 years): Pain at 45 minutes; Group 1: mean 2.46 (SD 2.09); n=54, Group 2: mean 4.26 (SD 2.51); n=54; VAS 0-10 Top=High is poor outcome; Comments: Baseline measures: paracetamol group 8.84 (1.37); opioid group 9.14 (1.13)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1
- Actual outcome for Adults (≥16 years): Pain at 60 minutes; Group 1: mean 2.02 (SD 2.03); n=54, Group 2: mean 3.31 (SD 2.51); n=54; VAS 0-10 Top=High is poor outcome; Comments: Baseline measures: paracetamol group 8.84 (1.37); opioid group 9.14 (1.13)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1
- Actual outcome for Adults (≥16 years): Need for rescue medication at 30 minutes; Group 1: 17/54, Group 2: 30/54
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 3: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Vomiting at Not reported; Group 1: 0/54, Group 2: 6/55
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1
- Actual outcome for Adults (≥16 years): Nausea at Not reported; Group 1: 0/54, Group 2: 8/54
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcomes not reported by the study	Quality of life at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Hospitalisation at Define

Study	**Mozafari 2017[89]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63 randomised (95 assessed for eligibility))
Countries and setting	Conducted in Iran; Setting: Emergency departments of Golestan general Hospital at Ahvaz, southwest Iran, with 73,000 annual visits from August 2015 to April 2016
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis of renal colic based on history and physical examination and pain score greater than 3, as determined by visual analogue scale (VAS)
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable:
Inclusion criteria	Patients diagnosed with renal colic; Colic flank pain associated with costo-vertebral angle tenderness and urinary tract irritation symptoms that suggest a clinical diagnosis of renal colic based on history and physical examination and pain score greater than 3, as determined by visual analogue scale (VAS)
Exclusion criteria	Age <18 years and age >55 years; Any pain killer during the previous 6 h, addiction (self-report or medical record) to opioids or NSAIDs; Systolic blood pressure <90 mmHg; Abdominal tenderness and rebound; Body temperature >38˚C; History or documents suggesting ischemic heart disease, renal failure, gastrointestinal bleeding, active peptic ulcer, seizure, metabolic disorder, pregnancy, clinical concern for aortic aneurysm or dissection, inability to speak, and any intervention beyond the study protocol because of intolerable pain or patient disagreement
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 37.38 (1.83) (buprenorphine: 39.18 (1.63); ketorolac: 35.58 (2.04) . Gender (M:F): 52/11 (buprenephrine: 25/7; ketorolac: 27/4). Ethnicity: Not reported
Further population details	
Extra comments	Acute renal colic because of renal stones was confirmed by clinical manifestations associated with urine analysis and ultrasonography or CT scanning
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Opioids/opiates - Morphine. 2 mg sublingual buprenorphine tablet (Mehr darou Pharmaceutical Company, Razi distribution company; Tehran, Iran) with 1 cc intravenous sterile water as

	placebo simultaneously. Duration 24 hour follow-up. Concurrent medication/care: Not reported. Indirectness: No indirectness Comments: Drug/Specific: Buprenorphine (n=31) Intervention 2: NSAIDs - Ketorolac. 30 mg ketorolac tromethamine (Caspian Tamin Pharmaceutical Company; Rasht, Iran; 30 mg/cc, Ampule) with a sublingual tab similar to buprenorphine (made by the college pharmacy laboratory simultaneously; Ahvaz Jundishapur University of Medical Sciences) as placebo. Duration 24-hour follow-up. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	No funding (24 hours after medication)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUPRENORPHINE versus KETOROLAC

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 20 minutes; Group 1: mean 5.9 (SD 1); n=9, Group 2: mean 5.5 (SD 1.16); n=12; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 23, Reason: Data appear to be excluded at 20 minutes for patients who later received rescue medication; Group 2 Number missing: 19, Reason: Data appear to be excluded at 20 minutes for patients who later received rescue medication
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 40 minutes; Group 1: mean 2.8 (SD 1.16); n=9, Group 2: mean 3 (SD 1.28); n=12; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 60 minutes; Group 1: mean 1.55 (SD 0.52); n=9, Group 2: mean 1.66 (SD 0.65); n=12; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - rescue medication (any patient with a pain score >5 received 1 µg/kg of intravenous fentanyl) at 40 minutes; Group 1: 23/32, Group 2: 19/31
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - rescue medication (any patient with a pain score >2 in minute of 60 min, received 1 µg/kg of intravenous fentanyl) at 60 minutes;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Minor adverse events (vomiting) at Unclear (24 hours); Group 1: 6/32, Group 2: 0/31; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 20, 40 and 60 minutes Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Minor adverse events (nausea) at Unclear (24 hours); Group 1: 6/32, Group 2: 0/31; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 20, 40 and 60 minutes Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Minor adverse events (dizziness) at Unclear (24 hours); Group 1: 7/32, Group 2: 0/31; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 20, 40 and 60 minutes Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Narci 2012[92]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75 randomised (183 assessed for eligibility))
Countries and setting	Conducted in Turkey; Setting: Emergency Department
Line of therapy	1st line
Duration of study	Intervention + follow up: 60-minute follow-up for pain intensity
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 'presenting clinical symptoms and signs of renal colic'. In addition to the history and physical examination, the clinical evaluation included urine analysis for hematuria and radiologist-performed ultrasonography to detect hydronephrosis; confirmation of the diagnosis involved CT, intravenous urography, plain radiography, and stone recovery
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	History of peptic ulcer disease; Asthma; Bleeding disorder; Impaired renal or hepatic function; Suspected hypersensitivity to aspirin or NSAID or acetaminophen; Pregnant and breast-feeding women; Received analgesics within 6 hours before presentation
Recruitment/selection of patients	Consecutive consenting patients
Age, gender and ethnicity	Age - Mean (SD): acetaminophen: 35.8 (13 years); diclofenac: 39.6 (18 years); acetominophen and diclofenac: 34 (12 years) . Gender (M:F): 42/33 (acetaminophen: 14/11; diclofenac: 13/12; acetominophen and diclofenac: 15/10). Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Paracetamol - Acetaminophen. 'Placebo (i.m. normal saline) given by the administration of 1 g of oral acetaminophen'. Duration 60 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=25) Intervention 2: NSAIDs - Diclofenac. 'Placebo tablet (starch) given by the administration of 75 mg of intramuscular diclofenac sodium'. Duration 60 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=25) Intervention 3: Paracetamol - Acetaminophen. '1000 mg of oral acetaminophen given by the administration of 75 mg of i.m. diclofenac sodium'. Duration 60 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness

	Comments: Combined acetaminophen and diclofenac
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACETAMINOPHEN versus DICLOFENAC

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 30 minutes; Group 1: mean 42.8 (SD 13.2); n=25, Group 2: mean 30.2 (SD 19.53); n=25; VAS 0-100 mm Top=High is poor outcome; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 30 minutes
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 60 minutes; Group 1: 8/25, Group 2: 8/25; Comments: Outcome measured after pain relief given
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 15 minutes; Group 1: mean 56.2 (SD 15.5); n=25, Group 2: mean 46.8 (SD 21.1); n=25; VAS 0-100 mm Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity - rescue treatment (50 mg of intramuscular meperidine) for patients whose pain was severe and failed to improve at 30 minutes; Group 1: 6/25, Group 2: 2/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity - complete pain relief at Unclear (60 minutes); Group 1: 8/25, Group 2: 8/25; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 30 minutes
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Adverse events (drug related complication or side effect) at 60 minutes; Group 1: 0/25, Group 2: 0/25; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 30 minutes
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACETAMINOPHEN versus ACETAMINOPHEN AND DICLOFENAC

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 30 minutes; Group 1: mean 42.8 (SD 13.2); n=25, Group 2: mean 13.6 (SD 22.4); n=25; VAS 0-100 mm Top=High is poor outcome; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 30 minutes
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 60 minutes; Group 1: mean 27.1 (SD 16.9); n=25, Group 2: mean 14.1 (SD 19.97); n=25; VAS 0-100 mm Top=High is poor outcome; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 30 minutes
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 15 minutes; Group 1: mean 56.2 (SD 15.5); n=25, Group 2: mean 33.8 (SD 20.87); n=25; VAS 0-100 mm Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity - rescue treatment (50 mg of intramuscular meperidine) for patients whose pain was severe and failed to improve at 30 minutes; Group 1: 6/25, Group 2: 2/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity - complete pain relief at Unclear time pointGroup 1: 8/25, Group 2: 20/25; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 30 minutes
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Adverse events (drug related complication or side effect) at 60 minutes; Group 1: 0/25, Group 2: 0/25; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 30 minutes
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus ACETAMINOPHEN AND DICLOFENAC

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 30 minutes; Group 1: mean 30.2 (SD 19.53); n=25, Group 2: mean 13.6 (SD 22.4); n=25; VAS 0-100 mm Top=High is poor outcome; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 30 minutes
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 60 minutes; Group 1: mean 14.1 (SD 19.97); n=25, Group 2: mean 5.4 (SD 12.2); n=25; VAS 0-100 mm Top=High is poor outcome; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 30 minutes Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain intensity at 15 minutes; Group 1: mean 46.8 (SD 21.1); n=25, Group 2: mean 33.8 (SD 20.87); n=25; VAS 0-100 mm Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Pain intensity - rescue treatment (50 mg of intramuscular meperidine) for patients whose pain was severe and failed to improve at 30 minutes; Group 1: 2/25, Group 2: 2/25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Pain intensity - complete pain relief at Unclear (60 minutes); Group 1: 8/25, Group 2: 20/25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Adverse events (drug related complication or side effect) at 60 minutes; Group 1: 0/25, Group 2: 0/25; Comments: Number analysed taken as number randomised but rescue treatment given to some patients at 30 minutes Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Oosterlinck 1976[97]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Belgium; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Pyelography
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	People with severe pain provoked by an ureteral or renal stone
Exclusion criteria	Children and individuals suffering from any serious disease other than the stone
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Muscle relaxant group 44.2; opioid group 44.8 (SD not reported). Gender (M:F): Define. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Smooth muscle relaxant /antispasmotic - Buscopan. A single injection of Buscopan compositum (20mg hyoscine-N-butylbromide and 2.5g sodium phenyl-dimethyl-pyrazolon-methylaminomethane sulphonate), intravenously over 5 minutes minutes . Duration Single dose. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=20) Intervention 2: Opioids/opiates - Meptazinol. A single injection of 60mg meptazinol. Duration Single dose. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUSCOPAN versus MEPTAZINOL

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Complete pain relief at Not reported; Group 1: 9/20, Group 2: 15/20

Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Dizziness at Not reported; Group 1: 4/20, Group 2: 13/20 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Nausea and vomiting at Not reported; Group 1: 5/20, Group 2: 6/20 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Number of people with adverse events at Not reported; Group 1: 6/20, Group 2: 16/20 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Oosterlinck 1990[98]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=125)
Countries and setting	Conducted in United Kingdom; Setting: Multicentre study with 5 centres
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiological evidence of s renal stone or acute renal obstruction
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were suffering from pain due to renal colic, and who described that pain as at least moderate according to a 4-point verbal rating scale. Patients were aged between 18-75 and have a weight between 45-100kg. Patients were fit and health, including women with adequate contraceptive protection
Exclusion criteria	Patients with a known history of allergy or previous adverse reaction to salicylates or nonsteroidal antiinflammatory drugs, patients known to abuse alcohol, narcotics or other drugs, and patients with a temperature above 37.5 degrees C
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): NSAID group 40.5 (21-71); opioid group 39 (18-70) years. Gender (M:F): 90:31. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=84) Intervention 1: NSAIDs - Ketorolac. Single intramuscular dose of 10mg (1ml of 1% solution) in 45 patients, and 90mg (3ml of 3% solution) in 37 patients, of ketorolac. Duration Single dose. Concurrent medication/care: If insufficient analgesia was reported following the test medication, the clinician was allowed to prescribe his usual standard analgesic, and the time of administration was recorded . Indirectness: No indirectness (n=39) Intervention 2: Opioids/opiates - Pethidine. Single intramuscular dose of 100mg (2ml of 5% solution) of pethidine. Duration Single dose. Concurrent medication/care: If insufficient analgesia was reported following the test medication, the clinician was allowed to prescribe his usual standard analgesic, and the time of administration was recorded . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus PETHIDINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 1 hour; Group 1: mean 59.2 (SD 23.23); n=74, Group 2: mean 57 (SD 26); n=37; VAS 0-100 Top=High is poor outcome; Comments: Baseline scores: NSAID 80.95 (16.4); Opioid 80 (13)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 2
- Actual outcome for Adults (≥16 years): Need for rescue medication at 10 hour; Group 1: 23/71, Group 2: 18/34
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13, Reason: ; Group 2 Number missing: 5
- Actual outcome for Adults (≥16 years): Pain relief at 1 hour; Group 1: 28/74, Group 2: 11/37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 2

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Sleepiness at 12 hours; Group 1: 10/84, Group 2: 7/39
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Vomiting at 12 hours; Group 1: 4/84, Group 2: 7/39
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Nausea at 12 hours; Group 1: 1/84, Group 2: 0/39
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Injection site pain at 12 hours; Group 1: 3/84, Group 2: 0/39
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Pathan 2016[101]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1645)
Countries and setting	Conducted in Qatar; Setting: Hamad General Hospital Emergency Department, Hamad Medical Corporation, Qatar
Line of therapy	1st line
Duration of study	Intervention + follow up: 90 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: It was expected that all participants would be investigated with a CT scan or ultrasonography examination to confirm their diagnosis.
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18 years or older and younger than 65 years who presented with renal colic of intensity on a Numerical pain Rating Scale (NRS 0 to 10) of 4 or more
Exclusion criteria	Exclusion criteria were known allergy to any of the study drugs, a history of asthma, known renal or liver failure or impairment, previous enrolment in the study, pregnancy, pain caused by a traumatic mechanism (in the setting of injury, for example motor vehicle crash, fall, or assault), or previous use of analgesia within 6 h of emergency department presentation. Renal or liver failure or impairment were reported by patients if they were diagnosed earlier or based on the diagnosis available in the medical records on presentation to the emergency department. Patients with chronic pain disorder or cancer were not specifically excluded. However, data for medical history were collected and reported.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Median (IQR): NSAID group 35.1 (29.2-42.6); opioid group 34.7 (28.8-41.7); paracetamol group 34.4 (28.6-41.5). Gender (M:F): 1362:283. Ethnicity: Indian 24%; Egyptian 21%; Nepalese 12%; Pakistani 9%; Bangladeshi 8%; Sri Lankan 7%; other 20%
Further population details	
Indirectness of population	No indirectness
Interventions	(n=548) Intervention 1: NSAIDs - Diclofenac. Participants in the diclofenac group received a 75 mg/3 mL intramuscular injection as the active drug. Participants also received two placebo intravenous injections . Duration Single dose. Concurrent medication/care: If the participant's expectation for reduction of pain was not met after 30 min, rescue analgesia was administered as morphine 3 mg intravenously every 5 min until either their pain score dropped to less than or equal to 2 on the NRS or the participant refused further analgesia..

	Indirectness: No indirectness (n=548) Intervention 2: Paracetamol. Participants in the paracetamol group received 1 g/100 mL paracetamol administered intravenously over 3–5 minutes, plus one intramuscular placebo injection and one intravenous placebo injection. Duration Single dose. Concurrent medication/care: No additional analgesia was administered for 30 min after administration of the trial drug. If the participant's expectation for reduction of pain was not met after 30 min, rescue analgesia was administered as morphine 3 mg intravenously every 5 min until either their pain score dropped to less than or equal to 2 on the NRS or the participant refused further analgesia.. Indirectness: No indirectness (n=549) Intervention 3: Opioids/opiates - Morphine. Participants in the morphine group received 0·1 mg/kg intravenous morphine over 2–5 minutes, plus one intramuscular placebo injection and one intravenous placebo injection. Duration Single dose. Concurrent medication/care: No additional analgesia was administered for 30 min after administration of the trial drug. If the participant's expectation for reduction of pain was not met after 30 min, rescue analgesia was administered as morphine 3 mg intravenously every 5 min until either their pain score dropped to less than or equal to 2 on the NRS or the participant refused further analgesia.. Indirectness: No indirectness
Funding	Study funded by industry (The trial was funded by Hamad Medical Corporation Medical Research Center, Doha, Qatar)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PARACETAMOL

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 30 minutes; Group 1: mean 3.3 (SD 2.3); n=547, Group 2: mean 3.3 (SD 2.4); n=548; NRS 0-10 Top=High is poor outcome; Comments: Baseline pain (median IQR): diclofenac 8 (7-10); paracetamol 8 (7-10)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome for Adults (≥16 years): Need for rescue analgesia at 30 minutes; Group 1: 63/547, Group 2: 111/548
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Adults (≥16 years): Reduction in initial pain by ≥50% at 30 minutes; Group 1: 371/547, Group 2: 364/548
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Adults (≥16 years): Reduction pain by NRS score ≥3 at 30 minutes; Group 1: 448/547, Group 2: 448/548
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Adults (≥16 years): Persistent pain at 60 minutes; Group 1: 131/547, Group 2: 162/548

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Acute adverse events (unspecified) at 14 days; Group 1: 7/547, Group 2: 7/548
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus MORPHINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 30 minutes; Group 1: mean 3.3 (SD 2.3); n=547, Group 2: mean 3.8 (SD 2.6); n=549; NRS 0-10 Top=High is poor outcome; Comments: Baseline pain (median, IQR): diclofenac 8 (7-10); morphine 8 (7-10)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome for Adults (≥16 years): Need for rescue analgesia at 30 minutes; Group 1: 63/547, Group 2: 126/549
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Adults (≥16 years): Reduction in initial pain by ≥50% at 30 minutes; Group 1: 371/547, Group 2: 335/549
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome for Adults (≥16 years): Reduction pain by NRS score ≥3 at 30 minutes; Group 1: 448/547, Group 2: 429/549
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Adults (≥16 years): Persistent pain at 60 minutes; Group 1: 131/547, Group 2: 207/549
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Acute adverse events (unspecified) at 14 days; Group 1: 7/547, Group 2: 19/549
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARACETAMOL versus MORPHINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define

- Actual outcome for Adults (≥16 years): Pain at 30 minutes; Group 1: mean 3.3 (SD 2.4); n=548, Group 2: mean 3.8 (SD 2.6); n=549; NRS 0-10 Top=High is poor outcome; Comments: Baseline pain (median IQR): paracetamol 8 (7-10); morphine 8 (7-10) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults (≥16 years): Need for rescue analgesia at 30 minutes; Group 1: 111/548, Group 2: 126/549 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults (≥16 years): Reduction in initial pain by ≥50% at 30 minutes; Group 1: 364/548, Group 2: 335/549 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults (≥16 years): Reduction pain by NRS score ≥3 at 30 minutes; Group 1: 448/548, Group 2: 429/549 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults (≥16 years): Persistent pain at 60 minutes; Group 1: 162/548, Group 2: 207/549 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Acute adverse events (unspecified) at 14 days; Group 1: 7/548, Group 2: 19/549 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Safdar 2006[112]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=130)
Countries and setting	Conducted in USA; Setting: Emergency department
Line of therapy	1st line
Duration of study	Intervention + follow up: 40 minutes
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Objective criteria
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 18-55 years, clinical diagnosis of acute renal colic, and patient pain rating of 5 or more on 10-cm visual analogue scale or at least 'moderate' pain on a 4 category verbal pain scale (non, mild/little/some, moderate, severe)
Exclusion criteria	Documented or suspected pregnancy, breastfeeding, contraindication to nonsteroidal antiinflammatory drugs or opiates, known renal dysfunction, received analgesics within 6 hours before presentation, history of bleeding diathesis, confirmed history of peptic ulcer disease, current use of warfarin, history of drug dependence or current use of methadone, peritonitis or presence of any peritoneal sign, non-english speaking, previously enrolled in the study, age over 55
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): NSAID group 39.3 (9.9); opioid group 37.3 (10). Gender (M:F): 58:28. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: NSAIDs - Ketorolac. Ketorolac 15mg. Participants received two injections (a medication and placebo, or two medications if in the combination group). Duration Single dose. Concurrent medication/care: Rescue analgesia was defined as 5mg of IV morphine, administered for persistent pain at 40 minutes and was titrated at the discretion of the attending physician. Indirectness: No indirectness (n=43) Intervention 2: Opioids/opiates - Morphine. Morphine 5mg. . Duration Single dose. Concurrent medication/care: Rescue analgesia was defined as 5mg of IV morphine, administered for persistent pain at 40 minutes and was titrated at the discretion of the attending physician. Indirectness: No indirectness

Funding	Academic or government funding (Partial funding was provided by the Connecticut Chapter of American College of Emergency Physicians)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus MORPHINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 40 minutes; MD; 0.4 (95%CI -1.1 to 2) VAS 0-10 Top=High is poor outcome, Comments: Mean pain score at 40 minutes: NSAID group 4.1; opioid group 3.7;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Need for rescue medication at 40 minutes; Group 1: 14/43, Group 2: 18/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Nausea at Time-point not reported; Group 1: 1/43, Group 2: 7/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Vomiting at Time-point not reported; Group 1: 0/43, Group 2: 2/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Dizziness at Time-point not reported; Group 1: 0/43, Group 2: 4/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Salameh 2011[114]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100 randomised)
Countries and setting	Conducted in Israel; Setting: University general hospital with 60,000 admissions a year to the ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 30-minute follow-up for pain intensity
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: clinical diagnosis of renal colic
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 18 years of age (and less than 65 years); Ability to provide written informed consent; Confirmed diagnosis of ureteral calculus; Only patients with moderate to severe pain (VAS score greater or equal to 4) were included
Exclusion criteria	Allergy to the study drugs; Peptic ulcer disease; Renal failure; Diabetes; Hypertension; Pregnant and breast feeding women; Patients who got analgesics up to six hours before admission
Recruitment/selection of patients	From June 2007 until January 2009
Age, gender and ethnicity	Age - Other: Mean 37 (10); diclofenac mean 37 (10); tramadol mean 37 (11). Gender (M:F): 3/1 (diclofenac: 5/2; tramadol: 3/1). Ethnicity: Not reported
Further population details	
Extra comments	The diclofenac group included 17% with bladder stones; the tramadol group included 12% with bladder stones
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: NSAIDs - Diclofenac. IM diclofenac 75 mg. Duration 30 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=49) Intervention 2: Opioids/opiates - Tramadol. IM tramadol 100 mg. Duration 30 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus TRAMADOL	

Protocol outcome 1: Pain intensity (visual analogue scale) at Define - Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) - change in pain based on 1-10 VAS scale at 30 minutes; Group 1: mean 4.2 (SD 2.6); n=48, Group 2: mean 5.6 (SD 2.9); n=49; VAS 1-10 cm Top=High is poor outcome; Comments: Note: VAS lower end of range is usually zero Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 'lack of accurate pain estimation'; Group 2 Number missing: 1, Reason: 'lack of accurate pain estimation' - Actual outcome for Adults (≥16 years): Pain intensity - rescue medication (intravenous morphine 0.1 mg/kg) when pain control was not achieved (less than 50% reduction in VAS score) at 30 minutes; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 'lack of accurate pain estimation'; Group 2 Number missing: 1, Reason: 'lack of accurate pain estimation' Protocol outcome 2: Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define - Actual outcome for Adults (≥16 years): Major adverse events - significant side effects at Not reported; Group 1: 0/48, Group 2: 0/49 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 'lack of accurate pain estimation'; Group 2 Number missing: 1, Reason: 'lack of accurate pain estimation'	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Sandhu 1994[118]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=154)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with moderate to severe pain in the lumbar region due to suspected renal colic, with or without radiation down the ureter, which had onset within the previous 24 hours
Exclusion criteria	Patients known to have received an analgesic or spasmolytic agent within 2 hours prior to study entry were excluded, as were pregnant women, nursing mothers, and patients with a relevant medical history of gastro-intestinal, renal or hepatic disease, asthma, haemorrhagic diathesis and drug abuse
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): NSAID group 45.2 (14.6); opioid group 42.1 (14.6). Gender (M:F): 117:37. Ethnicity: Not reported
Further population details	
Indirectness of population	Serious indirectness: Renal colic was confirmed in 60/76 patients in the ketorolac group and 51/78 in the pethidine group
Interventions	(n=76) Intervention 1: NSAIDs - Ketorolac. Ketorolac 30mg intramuscularly. Duration Single dose. Concurrent medication/care: Rescue medication was the drug of choice for each centre, provided that it wasn't an NSAID. Concomitant medication was noted. Indirectness: No indirectness (n=78) Intervention 2: Opioids/opiates - Pethidine. Pethidine 100mg intramuscularly . Duration Single dose. Concurrent medication/care: Rescue medication was the drug of choice for each centre, provided that it wasn't an NSAID. Concomitant medication was noted. Indirectness: No indirectness
Funding	Study funded by industry (Drug supply and financial support provided by Syntex Development Research)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus PETHIDINE	

Protocol outcome 1: Pain intensity (visual analogue scale) at Define - Actual outcome for Adults (≥16 years): Need for rescue medication at 24 hours; Group 1: 38/68, Group 2: 53/72 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 6 Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Number of people with adverse events at 24 hours; Group 1: 21/76, Group 2: 40/78 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults (≥16 years): Nausea and vomiting at 24 hours; Group 1: 15/76, Group 2: 28/78 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults (≥16 years): Dizziness at 24 hours; Group 1: 1/76, Group 2: 13/78 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults (≥16 years): Sleepiness at 24 hours; Group 1: 1/76, Group 2: 10/78 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	**Serinken 2012[120]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Turkey; Setting: Tertiary care hospital emergency department
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The ultimate diagnosis of renal colic was confirmed using ultrasonography or CT
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable

Inclusion criteria	Patients aged 18-55 years with flank pain were potentially eligible for the study. Individuals were enrolled if they had a clinical diagnosis of acute renal colic and complained of moderate to severe pain according to the 4-point verbal scale
Exclusion criteria	Patients were excluded if they refused to give informed consent; used any analgesics within 6 h of their ED visit; presented with fever or were haemodynamically unstable; had signs of peritoneal irritation or cardiac failure; had a history of renal failure, hepatic failure or a prior known allergy to paracetamol or morphine; were pregnant or suspected of being pregnant; and had known vision problems. Patients thought to have renal colic but ultimately diagnosed with a renal abscess, renal infarction or renal vein thrombosis were also excluded from the study.
Recruitment/selection of patients	Consecutively 24 h a day, 7 days a week
Age, gender and ethnicity	Age - Mean (SD): Paracetamol group 29.1 (8.2); morphine group 31.3 (9.0). Gender (M:F): 51:29. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Paracetamol. a single intravenous dose of either paracetamol (Perfalgan, Bristol Myers Squibb, Itxassou, France; 1 g in 100 ml normal saline), given as a bolus infusion within 2-4 min. Duration Single dose . Concurrent medication/care: Subjects who required rescue analgesia due to inadequate pain relief received fentanyl 1 mg/kg intravenously.. Indirectness: No indirectness (n=40) Intervention 2: Opioids/opiates - Morphine. Morphine (0.1 mg/kg in 100 ml normal saline), given as a bolus infusion within 2-4 min. Duration Single dose. Concurrent medication/care: Subjects who required rescue analgesia due to inadequate pain relief received fentanyl 1 mg/kg intravenously. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARACETAMOL versus MORPHINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain score at 30 minutes; Group 1: mean 63.7 (SD 21.7); n=40, Group 2: mean 56.6 (SD 24.4); n=40; VAS 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Over both groups, three with intractable pain, one with persistent vomiting, two with failure to detect a stone and one diagnosed with renal vein thrombosis; Group 2 Number missing: 5, Reason: Over both groups, three with intractable pain, one with persistent vomiting, two with failure to detect a stone and one diagnosed with renal vein thrombosis
- Actual outcome for Adults (≥16 years): Need for rescue medication at Not reported; Group 1: 6/38, Group 2: 7/35

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Over both groups, three with intractable pain, one with persistent vomiting, two with failure to detect a stone and one diagnosed with renal vein thrombosis; Group 2 Number missing: 5, Reason: Over both groups, three with intractable pain, one with persistent vomiting, two with failure to detect a stone and one diagnosed with renal vein thrombosis Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Nausea and vomiting at Not reported; Group 1: 2/38, Group 2: 1/35 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Over both groups, three with intractable pain, one with persistent vomiting, two with failure to detect a stone and one diagnosed with renal vein thrombosis; Group 2 Number missing: 5, Reason: Over both groups, three with intractable pain, one with persistent vomiting, two with failure to detect a stone and one diagnosed with renal vein thrombosis - Actual outcome for Adults (≥16 years): Dizziness at Not reported; Group 1: 0/38, Group 2: 3/35 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Over both groups, three with intractable pain, one with persistent vomiting, two with failure to detect a stone and one diagnosed with renal vein thrombosis; Group 2 Number missing: 5, Reason: Over both groups, three with intractable pain, one with persistent vomiting, two with failure to detect a stone and one diagnosed with renal vein thrombosis - Actual outcome for Adults (≥16 years): Respiratory depression at Not reported; Group 1: 0/38, Group 2: 0/35 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Over both groups, three with intractable pain, one with persistent vomiting, two with failure to detect a stone and one diagnosed with renal vein thrombosis; Group 2 Number missing: 5, Reason: Over both groups, three with intractable pain, one with persistent vomiting, two with failure to detect a stone and one diagnosed with renal vein thrombosis	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Shirazi 2015[121]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Iran; Setting: Emergency room of Shahid Faghihi hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Conformed by ultrasonography
Stratum	Adults (≥16 years):
Subgroup analysis within study	Not applicable
Inclusion criteria	People with renal colic caused by urolithiasis without any previous treatment. All patients with acute renal colic secondary to urolithiasis conformed by ultrasonography without previous treatment who presented to the center were included within the study period.
Exclusion criteria	Patients with hypertension, ischemic heart disease, rhinitis, influenza, those on anticoagulation therapy, peptic ulcer and those with renal or liver failure were excluded. Pregnant women were also excluded from the study. Those who had hypersensitivity to NSAIDs were not included in the study. Use of analgesics within 4 hours and Alpha blockers before admission, history of addiction, surgery on the kidney or ureter, and fluids therapy immediately before admission were among the exclusion criteria. During the study, if a patient could not bear the pain and did not want to continue, he/she was excluded.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): opioid group 39.1 (8.9); NSAID group 36.7 (9.2). Gender (M:F): 45:35. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Opioids/opiates - Tramadol. Tramadol (Mikasa Pharmaceutical, Tokyo, Japan) 50 mg intramuscularly. Duration Single dose. Concurrent medication/care: Patients who had no satisfactory pain relief within 30 minutes, a second treatment were administrated. Indirectness: No indirectness (n=40) Intervention 2: NSAIDs - Indomethacin. Indomethacin 100mg rectally (Arya Pharmaceutical, Karaj, Iran). Duration Single dose. Concurrent medication/care: Patients who had no satisfactory pain relief within

	30 minutes, a second treatment were administrated. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRAMADOL versus INDOMETHACIN Protocol outcome 1: Pain intensity (visual analogue scale) at Define - Actual outcome for Adults (≥16 years): Pain at 30 minutes; Group 1: mean 3.6 (SD 0.6); n=40, Group 2: mean 4.7 (SD 0.4); n=40; VAS 0-10 Top=High is poor outcome; Comments: Baseline score (mean, SD): opioid group 8.3 (1.2); NSAID group 8.3 (0.9) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Complete pain relief at 30 minutes; Group 1: 30/40, Group 2: 19/40 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Need for rescue medication at 30 minutes; Group 1: 10/40, Group 2: 21/40 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define; Use of healthcare services at Define; Length of stay at Define

Study	**Snir 2008[124]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=59)
Countries and setting	Conducted in Israel; Setting: Two centres
Line of therapy	1st line
Duration of study	Intervention + follow up: 40 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinalysis and/or imaging findings
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable

Inclusion criteria	Patients referred to the emergency department who had a clear clinical presentation of renal colic supported by urinalysis and/or imaging findings
Exclusion criteria	Patients with complete arteriovenous block, peptic ulcer disease, asthma, or known allergy to papaverine hydrochloride or sodium diclofenac, children, breast feeding women and patients who had received analgesic medication within 4 hours before hospital admission
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Muscle relaxant group 46.2; NSAID group 44.1 (SD not reported). Gender (M:F): 48:11. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Smooth muscle relaxant /antispasmotic - Papaverine hydrochloride. 120g intravenous papverine hydrochloride, administered in 100 cc 0.9% saline infusion during a minimum of 3 minutes. Duration Single dose. Concurrent medication/care: Patients requiring further analgesia after 40 minutes were given 1mg/kg of intramuscular meperidine. Indirectness: No indirectness (n=30) Intervention 2: NSAIDs - Diclofenac. 75mg intramuscular sodium diclofenac. Duration Single dose. Concurrent medication/care: Patients requiring further analgesia after 40 minutes were given 1mg/kg of intramuscular meperidine. Indirectness: No indirectness (n=30) Intervention 3: Smooth muscle relaxant /antispasmotic - Papaverine hydrochloride. Combination therapy: 120g intravenous papaverine hydrochloride, administered in 100 cc 0.9% saline infusion during a minimum of 3 minutes; 75mg intramuscular sodium diclofenac. Duration Single dose. Concurrent medication/care: Patients requiring further analgesia after 40 minutes were given 1mg/kg of intramuscular meperidine. Indirectness: No indirectness Comments: Combined smooth muscle relaxant (papaverine hydrochloride) and NSAID (diclofenac)
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PAPAVERINE HYDROCHLORIDE versus DICLOFENAC

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 20 minutes; Group 1: mean 4.93 (SD 2.78); n=29, Group 2: mean 3.6 (SD 2.55); n=30; VAS 0-10 Top=High is poor outcome; Comments: Baseline scores: papaverine group 8.55 (1.74); diclofenac 7.8 (2.22)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome for Adults (≥16 years): Pain at 40 minutes; Group 1: mean 3.65 (SD 2.74); n=29, Group 2: mean 2.46 (SD 2.43); n=30; VAS 0-10

Top=High is poor outcome; Comments: Baseline scores: papaverine group 8.55 (1.74); diclofenac 7.8 (2.22)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome for Adults (≥16 years): Need for rescue medication at 40 minutes; Group 1: 13/29, Group 2: 2/30
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Dizziness at 40 minutes; Group 1: 3/29, Group 2: 0/30
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome for Adults (≥16 years): Sleepiness at 40 minutes; Group 1: 1/29, Group 2: 0/30
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PAPAVERINE HYDROCHLORIDE + DICLOFENAC versus PAPAVERINE HYDROCHLORIDE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 20 minutes; Group 1: mean 4.7 (SD 2.96); n=27, Group 2: mean 4.93 (SD 2.78); n=29; VAS 0-10
Top=High is poor outcome; Comments: Baseline scores: papaverine + diclofenac group 8.59 (1.74); papaverine group 8.55 (1.74)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported
- Actual outcome for Adults (≥16 years): Pain at 40 minutes; Group 1: mean 2.96 (SD 3.06); n=27, Group 2: mean 3.65 (SD 2.74); n=29; VAS 0-10
Top=High is poor outcome; Comments: Baseline scores: papaverine + diclofenac group 8.59 (1.74); papaverine group 8.55 (1.74)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported
- Actual outcome for Adults (≥16 years): Need for rescue medication at 40 minutes; Group 1: 7/27, Group 2: 13/29
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Dizziness at 40 minutes; Group 1: 0/27, Group 2: 3/29

Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported - Actual outcome for Adults (≥16 years): Sleepiness at 40 minutes; Group 1: 0/27, Group 2: 1/29 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PAPAVERINE HYDROCHLORIDE + DICLOFENAC versus DICLOFENAC Protocol outcome 1: Pain intensity (visual analogue scale) at Define - Actual outcome for Adults (≥16 years): Pain at 20 minutes; Group 1: mean 3.6 (SD 2.55); n=27, Group 2: mean 4.7 (SD 2.96); n=30; VAS 0-10 Top=High is poor outcome; Comments: Baseline scores: papaverine + diclofenac group 8.59 (1.74); diclofenac 7.8 (2.22) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not reported; Group 2 Number missing: 0 - Actual outcome for Adults (≥16 years): Pain at 40 minutes; Group 1: mean 2.96 (SD 3.06); n=27, Group 2: mean 2.46 (SD 2.43); n=30; VAS 0-10 Top=High is poor outcome; Comments: Baseline scores: papaverine + diclofenac group 8.59 (1.74); diclofenac 7.8 (2.22) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not reported; Group 2 Number missing: 0 - Actual outcome for Adults (≥16 years): Need for rescue medication at 40 minutes; Group 1: 7/27, Group 2: 2/30 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not reported; Group 2 Number missing: 0 Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Dizziness at 40 minutes; Group 1: 0/27, Group 2: 0/30 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not reported; Group 2 Number missing: 0 - Actual outcome for Adults (≥16 years): Sleepiness at 40 minutes; Group 1: 0/27, Group 2: 0/30 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not reported; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

	124

Study	Song 2012[127]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=89 randomised; 115 assessed for eligibility)
Countries and setting	Conducted in South Korea; Setting: Adult ED of a tertiary care, urban academic hospital in Bundang, Korea, with 67,000 annual visits from 1 November 2007 to 30 December 2008
Line of therapy	Unclear
Duration of study	Intervention + follow up: 40 minute follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients with a clinical presentation of 'typical renal colic' rather than 'confirmed urinary stone by CT scan'; patients presenting with flank pain

Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were at least 18 years of age and whose flank pain was consistent with an abrupt onset of severe paroxysmal unilateral location. Suspicion of renal colic was confirmed by the attending physician after triage by a clinical research nurse.
Exclusion criteria	Patients were excluded from the study if they met any of the following criteria: patient pain rating less than five on a 10cm visual analogue scale (VAS); confirmed or suspected pregnancy; breastfeeding; contraindication to NSAIDs, opioids or butylscopolammonium bromides; history of peptic ulcer or renal disease; use of analgesics within 6h of presentation; current use of anticoagulants; history of bleeding tendency; suspicious surgical condition; hemodynamic instability, defined as pulse >110/min and systolic blood pressure <100mmHg; or previous participation in the study
Recruitment/selection of patients	During the 13 months between November 2007 and December 2008, 115 adult patients suspected of having acute renal colic were assessed for eligibility
Age, gender and ethnicity	Age - Mean (SD): Butylscopolammonium bromide + morphine + ketorolac: 38.8 (9.8); morphine + ketorolac + normal saline: 41.9 (9.6). Gender (M:F): 72/17. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: Smooth muscle relaxant /antispasmotic - Butylscopolammonium bromide. 20mg butylscopolammonium bromide intravenously, which was diluted with 50mL of normal saline by the treating nurse so that the study drug appeared identical to the placebo . Duration 40 minutes. Concurrent medication/care: All patients received 1L of normal saline hydration at 240mL per hour, 30mg ketorolac intravenously, and 5mg morphine intravenously over 5 minutes at time zero. Indirectness: No indirectness Comments: Combination therapy: butylscopolammonium bromide + morphine + ketorolac (n=43) Intervention 2: Opioids/opiates - Morphine. 50mL of normal saline solution at time zero. Duration 40 minutes. Concurrent medication/care: All patients received 1L of normal saline hydration at 240mL per hour, 30mg ketorolac intravenously, and 5mg morphine intravenously over 5 minutes at time zero. Indirectness: No indirectness Comments: Combination therapy: morphine + ketorolac
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUTYLSCOPOLAMMONIUM BROMIDE + MORPHINE + KETOROLAC versus MORPHINE + KETOROLAC

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) at 20 minutes; Group 1: mean 2.6 (SD 2.4); n=46, Group 2: mean 3.1 (SD 2.4); n=43; VAS 0-10 Top=High is good outcome; Comments: Baseline pain intensity (VAS): butylscopolammonium bromide + morphine + ketoralac 8.4 (1.4); morphine + ketoralac 8.4 (1.4)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (visual analogue scale) at 40 minutes; Group 1: mean 1.3 (SD 1.9); n=46, Group 2: mean 2.5 (SD 2.6); n=43; VAS 0-10 Top=High is good outcome; Comments: Baseline pain intensity (VAS): butylscopolammonium bromide + morphine + ketoralac 8.4 (1.4); morphine + ketoralac 8.4 (1.4)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Comments - Total number of participants analysed is reported as total randomised but rescue medication was administered at either 20 minutes or 40 minutes ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (need for rescue medication) at 40 minutes; Group 1: 7/46, Group 2: 14/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define
- Actual outcome for Adults (≥16 years): Major adverse events - respiratory depression at 40 minutes; Group 1: 0/46, Group 2: 0/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Comments - Total number of participants analysed is reported as total randomised but rescue medication was administered at either 20 minutes or 40 minutes ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Minor adverse events - nausea at 40 minutes; Group 1: 0/46, Group 2: 1/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Comments - Total number of participants analysed is reported as total randomised but rescue medication was administered at either 20 minutes or 40 minutes ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Minor adverse events - vomiting at 40 minutes; Group 1: 0/46, Group 2: 1/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Comments - Total number of participants analysed is reported as total randomised but rescue medication was administered at either 20 minutes or 40 minutes ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Minor adverse events - dizziness at 40 minutes; Group 1: 2/46, Group 2: 1/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Comments - Total number of participants analysed is reported as total randomised but rescue medication was administered at either 20 minutes or 40 minutes ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Minor adverse events - sleepiness at 40 minutes; Group 1: 1/46, Group 2: 0/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Comments - Total number of participants analysed is reported as total randomised but rescue medication was administered at either 20 minutes or 40 minutes ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Use of healthcare services at Define; Length of stay at Define

Study	**Stankov 1994[128]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=104)
Countries and setting	Conducted in Germany; Setting: Investigational centres
Line of therapy	1st line
Duration of study	Intervention + follow up: 120 minutes
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults 18 years and older, informed consent obtained, acute colicky pain judged as grade 3 (severe) or 4 (excruciating) on a 5 point scale
Exclusion criteria	Pretreatment with analgesics or spasmolytics during the last 24 hours; intolerance to the study drugs, analgesics, food stabilizers, alcohol, furs, hair colourants; preexisting diseases such as hepatic porphyria, deficiency of glucose-6-phosphate dehydrogenase, narrow angle glaucoma, prostatic adenoma, stenosis of the gastrointestinal tract, megacolon, acute pulmonary edema, bronchial asthma, analgesic-inducible asthma, chronic respiratory tract infection, tachyarrhythmia, circulatory instability, RR systolic less than 100mm Hg, damaged hematopoiesis, intoxication with alcohol or other drugs; pregnant or nursing women; impaired compliance
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 46.4 (16.2). Gender (M:F): 71:33. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Opioids/opiates - Tramadol. 100mg tramadol (1 ampoule, 1ml) given i.v. as a slow injection . Duration Single dose. Concurrent medication/care: If no adequate pain relief had been achieved after 20 minutes, a second i.v. injection was given (patients receiving tramadol intially, received

	butylscopolamine, 20mg). Indirectness: No indirectness (n=33) Intervention 2: Smooth muscle relaxant /antispasmotic - Butylscopolammonium bromide. Butylscopolamine, 20mg (Buscopan; 1 ampoule; 1ml) as i.v. injection. Duration Single dose. Concurrent medication/care: If no adequate pain relief had been achieved after 20 minutes, a second i.v. injection was given (patients receiving butylscopolamine initially, received tramadol, 100mg). Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRAMADOL versus BUTYLSCOPOLAMINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity difference at 20 minutes; Group 1: mean 35.6 (SD 33.6); n=35, Group 2: mean 37.8 (SD 38.6); n=33; VAS 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Need for rescue medication at 20 minutes; Group 1: 13/35, Group 2: 11/33
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define
- Actual outcome for Adults (≥16 years): Dizziness at 120 minutes; Group 1: 2/35, Group 2: 1/33
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Nausea/vomiting at 120 minutes; Group 1: 1/35, Group 2: 0/33
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Blurred vision at 120 minutes; Group 1: 1/35, Group 2: 0/33
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Thompson 1989[131]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=58)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	1st line
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The diagnosis was confirmed by the presence of a calculus on urography or by passage of or removal of a calculus
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a presumed diagnosis of renal colic
Exclusion criteria	patients with asthma, hypersensitivity to aspirin, impaired renal function (serum creatinine concentration >150 [tmol/l) or hepatic function, or inflammatory bowel disease; those who had received strong analgesics within four hours of admission; and those who were pregnant or lactating.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=29) Intervention 1: NSAIDs - Diclofenac. Diclofenac 100mg rectally. Duration Single dose. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=29) Intervention 2: Opioids/opiates - Pethidine. Pethidine, 100mg given by injection. Plus prochlorperazine 12.5mg. Duration Single dose. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PETHIDINE

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain free at 1 hour; Group 1: 21/25, Group 2: 15/25
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Incorrect initial diagnosis; Group 2 Number missing: 4, Reason: Incorrect initial diagnosis - Actual outcome for Adults (≥16 years): Need for rescue analgesia at Not reported; Group 1: 1/25, Group 2: 12/25 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Incorrect initial diagnosis; Group 2 Number missing: 4, Reason: Incorrect initial diagnosis Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Nausea at Not reported; Group 1: 0/25, Group 2: 8/25 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Incorrect initial diagnosis; Group 2 Number missing: 4, Reason: Incorrect initial diagnosis - Actual outcome for Adults (≥16 years): Dizziness at Not reported; Group 1: 0/25, Group 2: 4/25 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Incorrect initial diagnosis; Group 2 Number missing: 4, Reason: Incorrect initial diagnosis - Actual outcome for Adults (≥16 years): Vomiting at Not reported; Group 1: 0/25, Group 2: 3/25 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Incorrect initial diagnosis; Group 2 Number missing: 4, Reason: Incorrect initial diagnosis	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

Study	Vignoni 1983[134]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=131)
Countries and setting	Conducted in Italy; Setting: Medical Emergency Ward
Line of therapy	1st line
Duration of study	Intervention + follow up: 55 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients in whom the diagnosis of renal colic was not confirmed by urine analysis, intravenous urography or voiding of a calculus were excluded from the analysis
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients in whom ureteral colic was diagnosed on the basis of signs and symptoms
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): NSAID group 39.2 (14.74); placebo group 37.6 (11.69). Gender (M:F): NSAID group 3.53:1, placebo group 3.42:1. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=63) Intervention 1: NSAIDs - Diclofenac. Intramuscular injection of sodium diclofenac (Voltaren 75mg/3ml). Duration Single dose. Concurrent medication/care: Patients who still experienced significant pain 25 minutes after the first injection were treated with 75mg diclofenac sodium intramuscularly. Indirectness: No indirectness (n=68) Intervention 2: Placebo. Intramuscular injection of placebo (3ml saline in identical ampoules). Duration Single dose. Concurrent medication/care: Patients who still experienced significant pain 25 minutes after the first injection were treated with 75mg diclofenac sodium intramuscularly. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PLACEBO

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain at 25 minutes; Group 1: mean 20.55 (SD 26.25); n=62, Group 2: mean 41.3 (SD 35.5); n=68; VAS 0-100

Top=High is poor outcome; Comments: Baseline scores: NSAID group 66.1 (17.17); placebo 71.6 (17.38) Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Initial pain was higher in the placebo group: NSAID 66.17 (17.17); placebo group 71.67 (17.38); Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Need for rescue medication at 25 minutes; Group 1: 17/63, Group 2: 40/68 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Initial pain was higher in the placebo group: NSAID 66.17 (17.17); placebo group 71.67 (17.38); Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Complete pain relief at 25 minutes; Group 1: 37/63, Group 2: 20/68 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Initial pain was higher in the placebo group: NSAID 66.17 (17.17); placebo group 71.67 (17.38); Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define; Use of healthcare services at Define; Length of stay at Define

Study	**Zamanian 2016[142]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=158 randomised)
Countries and setting	Conducted in Iran; Setting: Emergency department of Imam Hospital and Shariati hospital, two tertiary care university affiliated teaching hospitals
Line of therapy	1st line
Duration of study	Intervention + follow up: 90-minute follow-up for pain intensity
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of renal colic primarily made by triage nurse and then confirmed by the emergency medicine resident and attending physician
Stratum	Adults (≥16 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Confirmed diagnosis of renal colic; Aged between 18 and 75 years
Exclusion criteria	Unwillingness to participate in the study or to receive suppository analgesics; Pregnancy; Breastfeeding; History of current or past drug abuse; analgesic intake during up to 4 hours prior to admission; Long-term use of NSAIDs; Drug history of hypnotic drugs or phenothiazines; History of drug hypersensitivity reaction

	due to morphine or NSAIDs; Diarrhea; Peritonitis; History of chronic diseases including liver disorders, renal disorders, respiratory problems, gastrointestinal problems, and endocrine problems
Recruitment/selection of patients	Between March 2011 and March 2013
Age, gender and ethnicity	Age - Mean (SD): 37.4 911.1) (indomethiacin: 37.2 (10.6); morphine: 37.3 (11.5)). Gender (M:F): 102/56 (indomethiacin: 1.75; morphine: 1.88). Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=79) Intervention 1: Opioids/opiates - Morphine. 10 mg morphine suppository. Duration 90 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=79) Intervention 2: NSAIDs - Indomethacin. 100 mg indomethiacin suppository. Duration 90 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (This study was funded and supported by Tehran University of Medical Sciences)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MORPHINE versus INDOMETHACIN

Protocol outcome 1: Pain intensity (visual analogue scale) at Define
- Actual outcome for Adults (≥16 years): Pain intensity (numerical rating scale) - change in pain intensity at 20 minutes; Group 1: mean 5.46 (SD 1.34); n=79, Group 2: mean 4.37 (SD 1.63); n=79; Numerical Rating Scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (numerical rating scale) - change in pain intensity at 40 minutes; Group 1: mean 6.26 (SD 1.62); n=79, Group 2: mean 6.04 (SD 1.59); n=79; Numerical Rating Scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (numerical rating scale) - change in pain intensity at 60 minutes; Group 1: mean 6.27 (SD 1.79); n=79, Group 2: mean 6.11 (SD 1.66); n=79; Numerical Rating Scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥16 years): Pain intensity (numerical rating scale) - change in pain intensity at 90 minutes; Group 1: mean 6.28 (SD 1.75); n=79, Group 2: mean 6.07 (SD 1.67); n=79; Numerical Rating Scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Minor adverse events (GI disturbance without bleeding, vomiting and nausea, constipation, diarrhoea, pain, dizziness, sleepiness, urinary retention) at Define - Actual outcome for Adults (≥16 years): Minor adverse events (nausea) at Not reported; Group 1: 42/79, Group 2: 37/79; Comments: Events reported as % only Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Minor adverse events (vomiting) at Not reported; Group 1: 34/79, Group 2: 40/79; Comments: Events reported as % only Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Minor adverse events (dizziness) at Not reported; Group 1: 34/79, Group 2: 45/79; Comments: Events reported as % only Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥16 years): Minor adverse events (drowsiness) at Not reported; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Major adverse events (GI haemorrhage, acute kidney injury, respiratory depression, mortality, cardiac event) at Define; Use of healthcare services at Define; Length of stay at Define

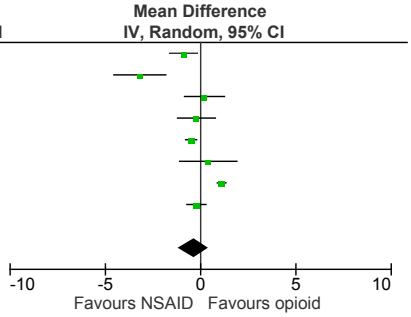
Appendix E: Forest plots

E.1 NSAID versus opioid/opiate

Figure 2: Pain (VAS & NRS; 0-10; final and change scores)

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Opioid Mean	Opioid SD	Opioid Total	Weight	Mean Difference IV, Random, 95% CI
Ay 2014	1.7	1	26	2.6	1.6	26	13.2%	-0.90 [-1.63, -0.17]
Cordell 1996	2.47	2.76	36	5.66	3.076	35	10.3%	-3.19 [-4.55, -1.83]
Mozafari 2017	3	1.28	12	2.8	1.16	9	11.7%	0.20 [-0.85, 1.25]
Oosterlinck 1990	-5.92	2.323	74	-5.7	2.6	37	12.0%	-0.22 [-1.21, 0.77]
Pathan 2016	3.3	2.3	547	3.8	2.6	549	14.5%	-0.50 [-0.79, -0.21]
Safdar 2006	4.1	3.5486	43	3.7	3.5486	43	9.6%	0.40 [-1.10, 1.90]
Shirazi 2015	4.7	0.4	40	3.6	0.6	40	14.6%	1.10 [0.88, 1.32]
Zamanian 2016	6.04	1.59	79	6.26	1.62	79	14.0%	-0.22 [-0.72, 0.28]
Total (95% CI)			**857**			**818**	**100.0%**	**-0.35 [-1.14, 0.43]**

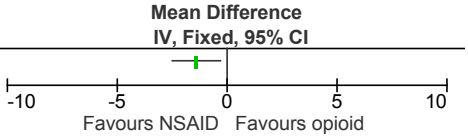
Heterogeneity: Tau² = 1.09; Chi² = 119.38, df = 7 (P < 0.00001); I² = 94%
Test for overall effect: Z = 0.88 (P = 0.38)



Route of administration (NSAID, opioid): Ay 2014: IV, IV; Cordell 1996: IV, IV; Mozafari 2017: IV, sublingual tab; Oosterlinck 1990: IM, IM; Pathan 2016: IM, IM; Safdar 2006: IV, IV; Shirazi 2015: rectal, IM; Zamanian 2016: rectal, rectal

Figure 3: Pain (VAS 1-10)

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Opioid Mean	Opioid SD	Opioid Total	Mean Difference IV, Fixed, 95% CI
Salameh 2011	4.2	2.6	48	5.6	2.9	49	-1.40 [-2.50, -0.30]

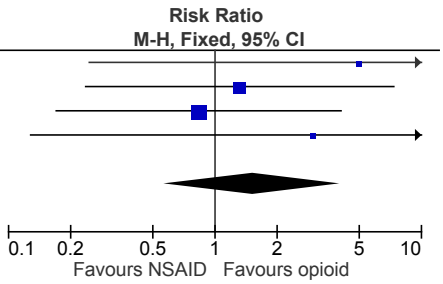


Route of administration (NSAID, opioid): IM, IM

Figure 4: Pain (no pain relief)

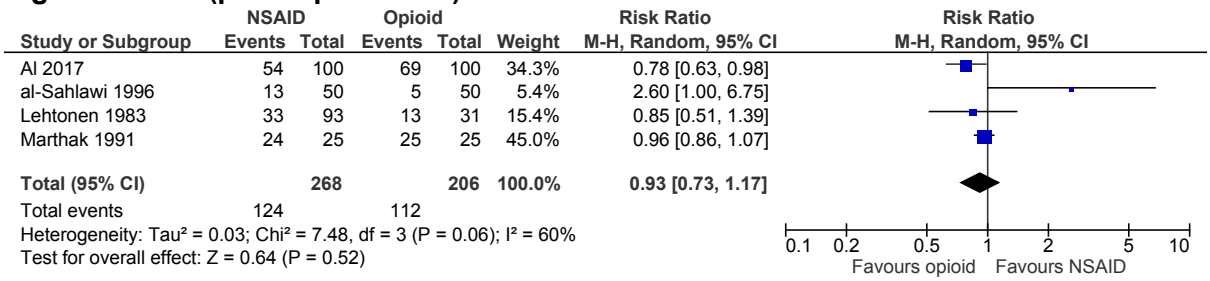
Study or Subgroup	NSAID Events	NSAID Total	Opioid Events	Opioid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
al-Sahlawi 1996	2	50	0	50	8.2%	5.00 [0.25, 101.58]
Indudhara 1990	3	33	2	29	34.7%	1.32 [0.24, 7.35]
Lehtonen 1983	5	93	2	31	48.9%	0.83 [0.17, 4.08]
Marthak 1991	1	25	0	25	8.2%	3.00 [0.13, 70.30]
Total (95% CI)		**201**		**135**	**100.0%**	**1.52 [0.57, 4.07]**
Total events	11		4			

Heterogeneity: Chi² = 1.35, df = 3 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)



Route of administration (NSAID, opioid): al-Sahlawi 1996: IV, IV; Indudhara 1990: oral, IM; Lehtonen 1993: IV, IV; Marthak 1991: IM, IM

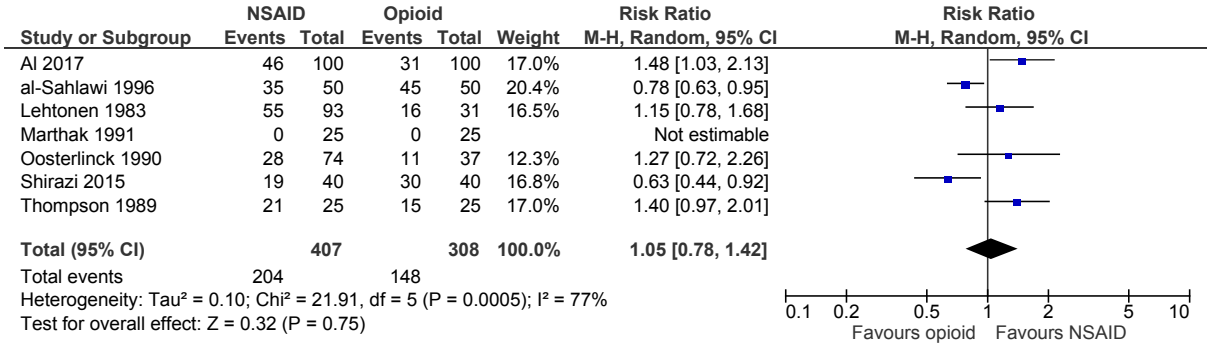
Figure 5: Pain (partial pain relief)



Route of administration (NSAID, opioid): Al 2017: IV, IV: al-Sahlawi 1996: IV, IV; Lehtonen 1993: IV, IV; Marthak 1991: IM, IM

1

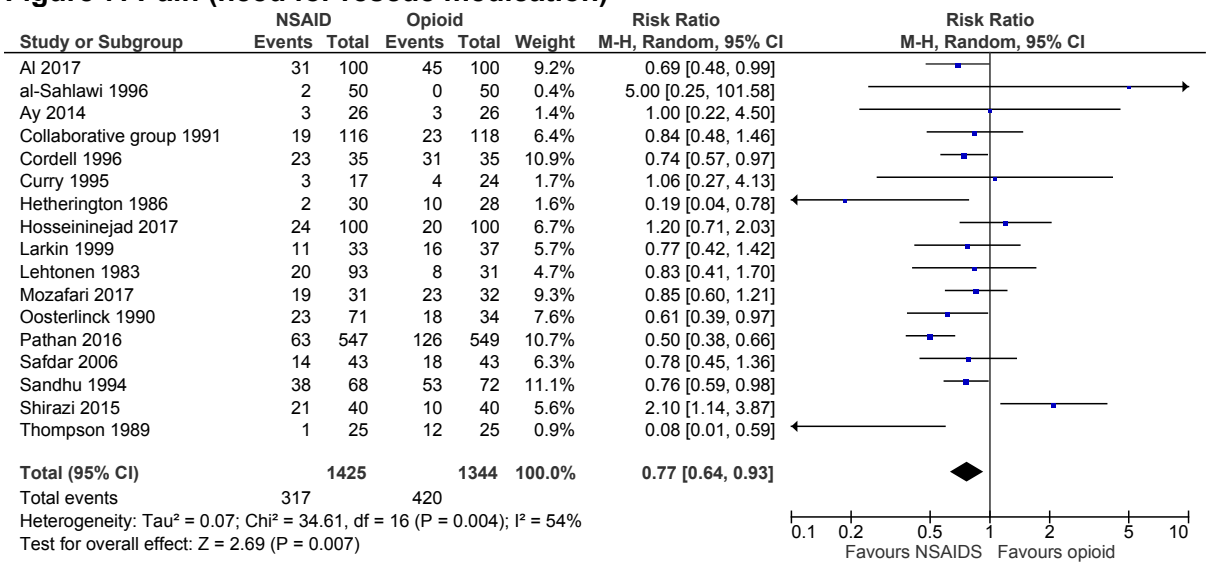
Figure 6: Pain (complete pain relief)



Route of administration (NSAID, opioid): Al 2017: IV, IV: al-Sahlawi 1996: IV, IV; Lehtonen 1993: IV, IV; Marthak 1991: IM, IM: Oosterlinck 1990: IM, IM; Shirazi 2015: rectal, IM; Thompson 1989: rectal, 'injection'

2

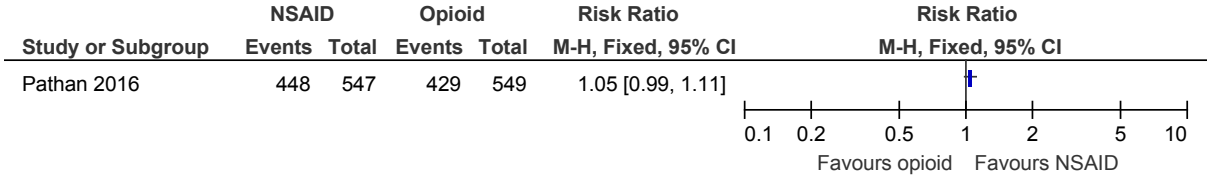
Figure 7: Pain (need for rescue medication)



Route of administration (NSAID, opioid): Al 2017: IV, IV: al-Sahlawi 1996: IV, IV; Collaborative group 1991: IM, IM; Cordell 1996: IV, IV: Curry 1995: IV, IV: Hetherington 1986: IM, IM; Hosseininejad 2017: IV, IV: Larkin 1999: IM, IM: Lehtonen 1993: IV, IV; Mozafari 2017: IV, sublingual tab: Oosterlinck 1990: IM, IM; Pathan 2016: IM, IV: Safdar 2006: IV, IV: Shirazi 2015: rectal, IM; Thompson 1989: rectal, 'injection'

3

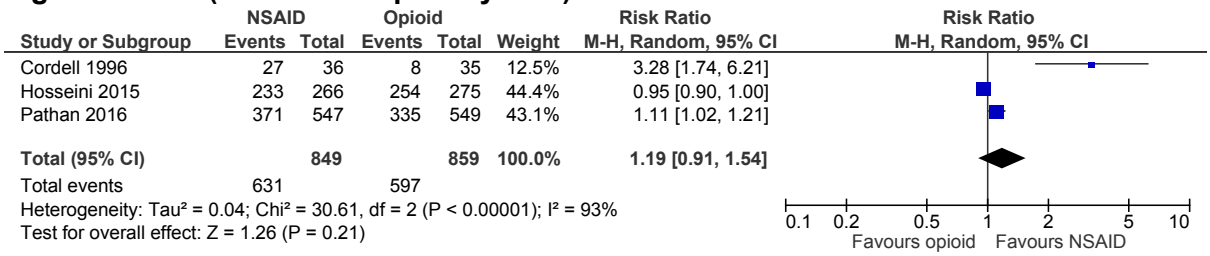
Figure 8: Pain (reduction in pain NRS score of >3)



Route of administration (NSAID, opioid): IM, IV

1

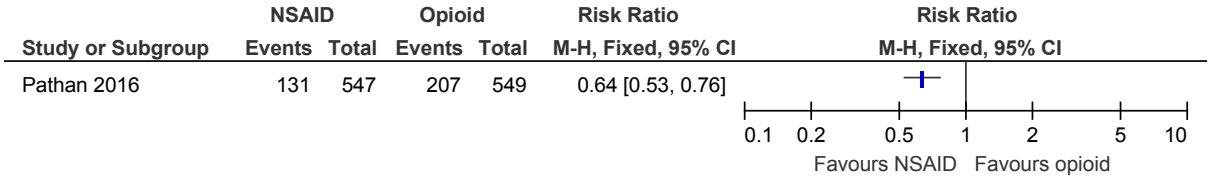
Figure 9: Pain (reduction in pain by 50%)



Route of administration (NSAID, opioid): Cordell 1996: IV, IV: Hosseininejad 2017: IV, IV: Pathan 2016: IM, IV

2

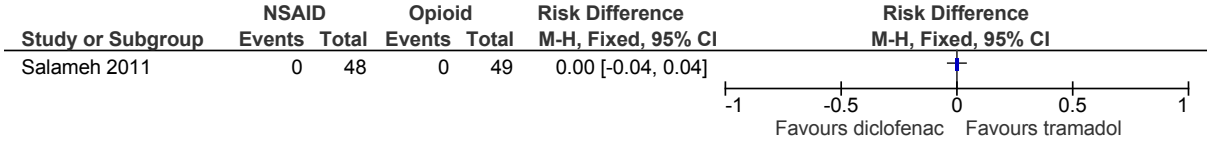
Figure 10: Pain (persistent pain at 60 minutes)



Route of administration (NSAID, opioid): IM, IV

3

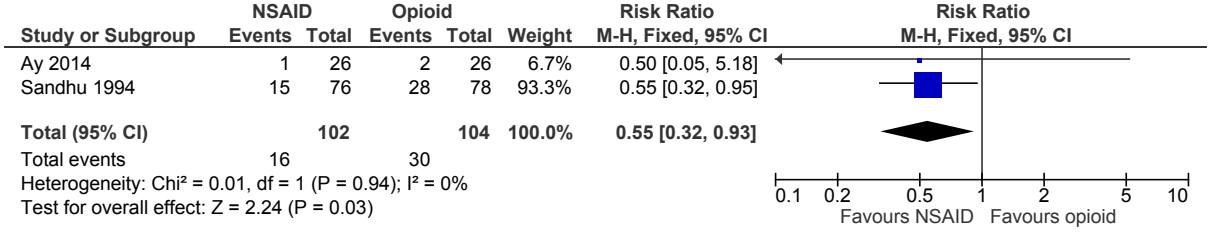
Figure 11: Major adverse events (significant side effects - unspecified)



Route of administration (NSAID, opioid): IM, IM

4

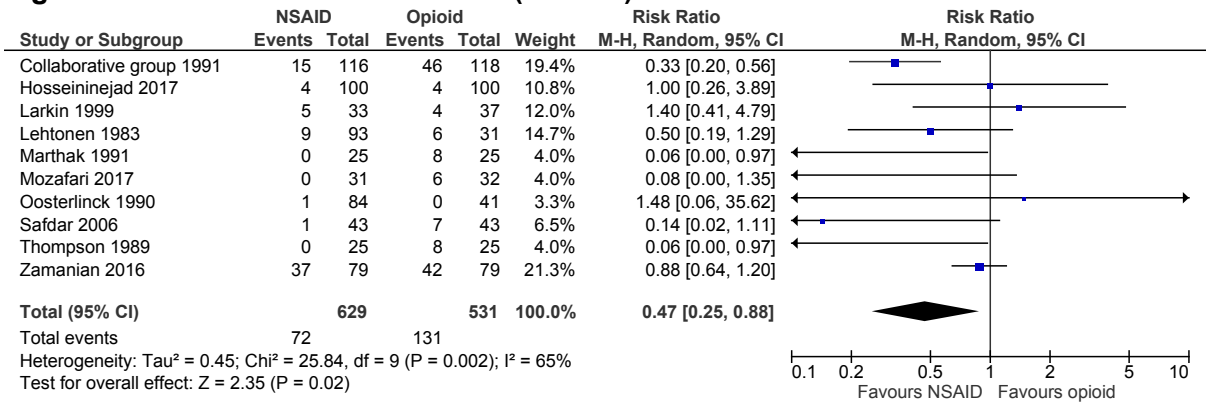
Figure 12: Minor adverse events (nausea and vomiting)



Route of administration (NSAID, opioid): Ay 2014: IV, IV; Sandhu 1994: IM, IM

5

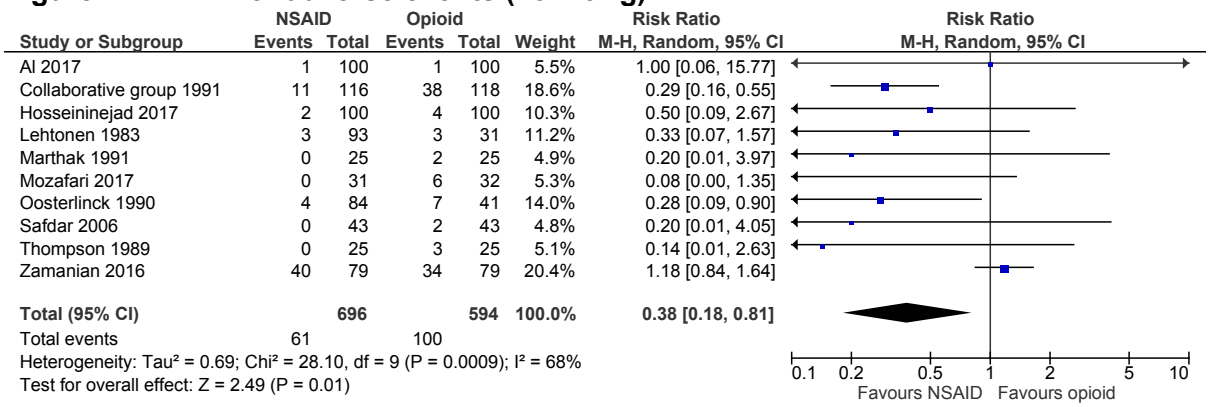
Figure 13: Minor adverse events (nausea)



Route of administration (NSAID, opioid): Collaborative group 1991: IM, IM; Hosseininejad 2017: IV, IV: Larkin 1999: IM, IM; Lehtonen 1993: IV, IV; Marthak 1991: IM, IM; Mozafari 2017: IV, sublingual tab; Oosterlinck 1990: IM, IM; Safdar 2006: IV, IV; Thompson 1989: rectal, 'injection': Zamanian 2016: rectal, rectal

1

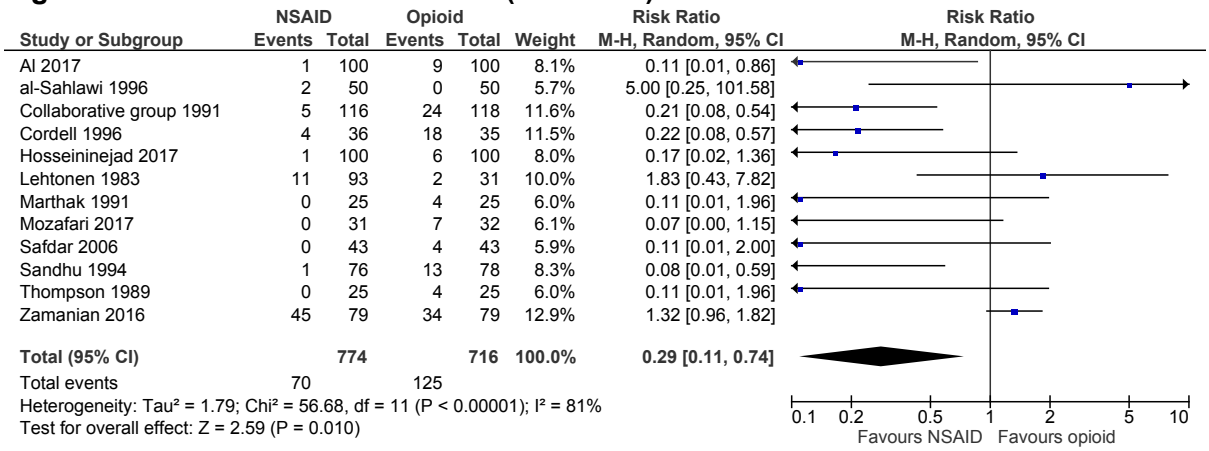
Figure 14: Minor adverse events (vomiting)



Route of administration (NSAID, opioid): AI 2017: IV, IV; Collaborative group 1991: IM, IM; Hosseininejad 2017: IV, IV; Lehtonen 1993: IV, IV; Marthak 1991: IM, IM; Mozafari 2017: IV, sublingual tab; Oosterlinck 1990: IM, IM; Safdar 2006: IV, IV; Thompson 1989: rectal, 'injection': Zamanian 2016: rectal, rectal

2

Figure 15: Minor adverse events (dizziness)

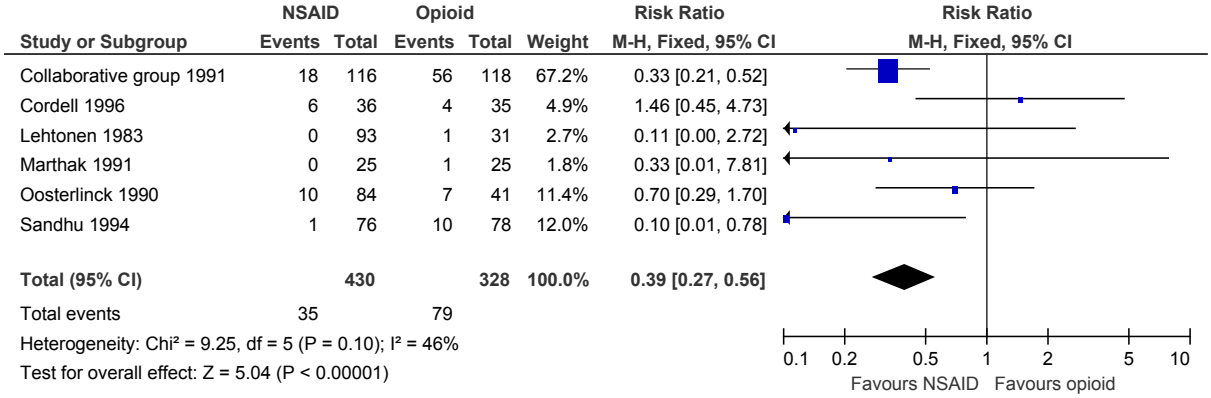


Route of administration (NSAID, opioid): AI 2017: IV, IV; al-Sahlawi 1996: IV, IV; Collaborative group 1991: IM, IM; Cordell 1996: IV, IV; Hosseininejad 2017: IV, IV; Lehtonen 1993: IV, IV; Marthak 1991: IM, IM; Mozafari

2017: IV, sublingual tab; Safdar 2006: IV, IV; Sandhu 1994: IM, IM; Thompson 1989: rectal, 'injection': Zamanian 2016: rectal, rectal

1

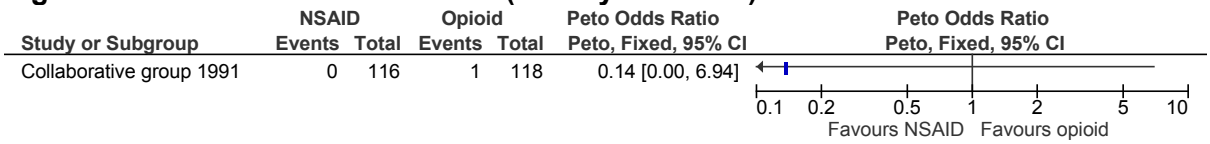
Figure 16: Minor adverse events (sleepiness)



Route of administration (NSAID, opioid): Collaborative group 1991: IM, IM; Cordell 1996: IV, IV; Lehtonen 1993: IV, IV; Marthak 1991: IM, IM; Oosterlinck 1990: IM, IM; Sandhu 1994: IM, IM

2

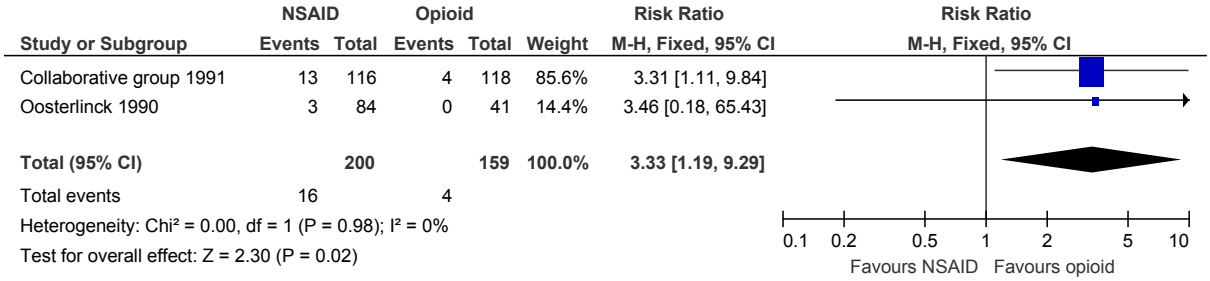
Figure 17: Minor adverse events (urinary retention)



Route of administration (NSAID, opioid): IM, IM

3

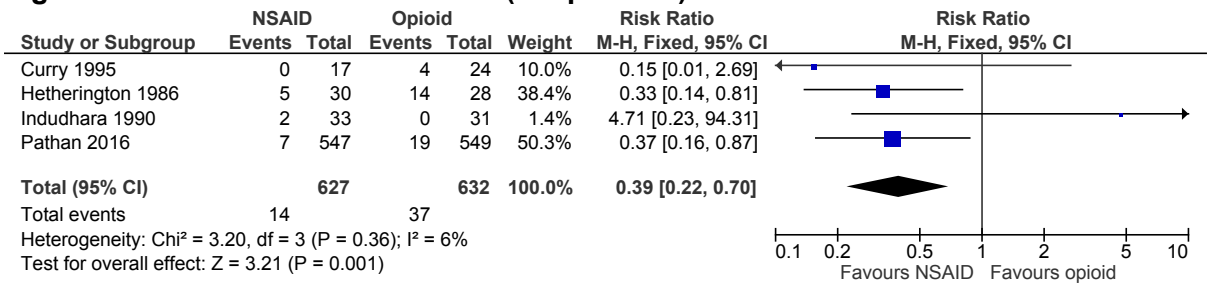
Figure 18: Minor adverse events (pain - injection site/local)



Route of administration (NSAID, opioid): Collaborative group 1991: IM, IM; Oosterlinck 1990: IM, IM

4

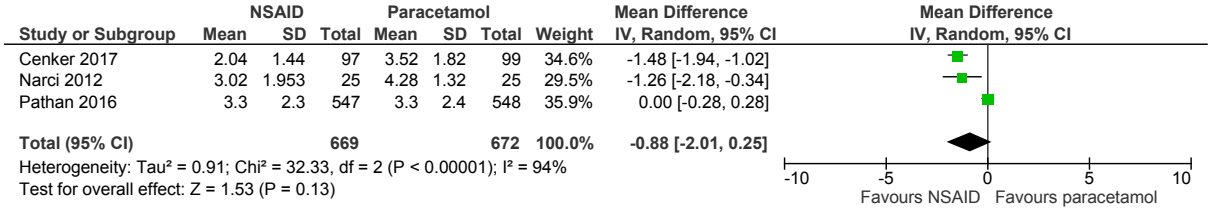
Figure 19: Minor adverse events (unspecified)



Route of administration (NSAID, opioid): Curry 1995: IV, IV: Hetherington 1986: IM, IM; Indudhara 1990: oral, IM; Pathan 2016: IM, IV

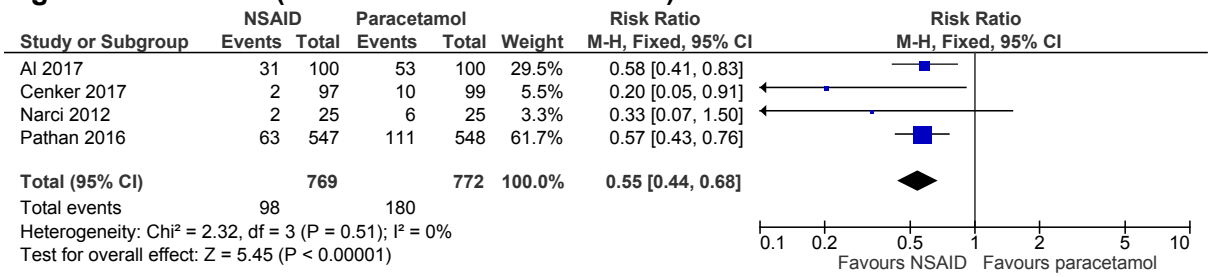
E.2 NSAID versus paracetamol

Figure 20: Pain (NRS or VAS; 0-10)



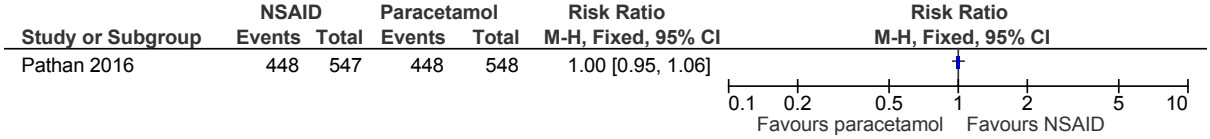
Route of administration (NSAID, paracetamol): Cenker 2017: IV, IV; Narci 2012: IM, oral; Pathan 2016: IM, IV

Figure 21: Pain (need for rescue medication)



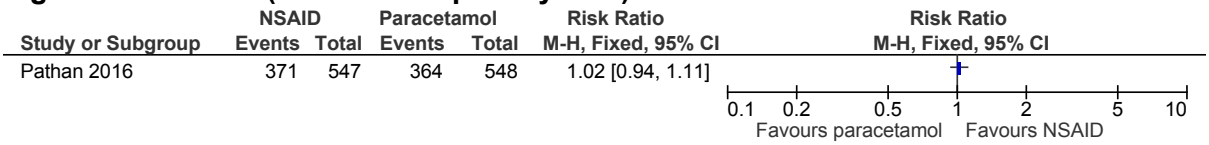
Route of administration (NSAID, paracetamol):AI 2017: IV, IV; Cenker 2017: IV, IV Narci 2012: IM, oral; Pathan 2016: IM, IV

Figure 22: Pain (reduction in NRS pain score by >3)



Route of administration (NSAID, paracetamol): IM, IV

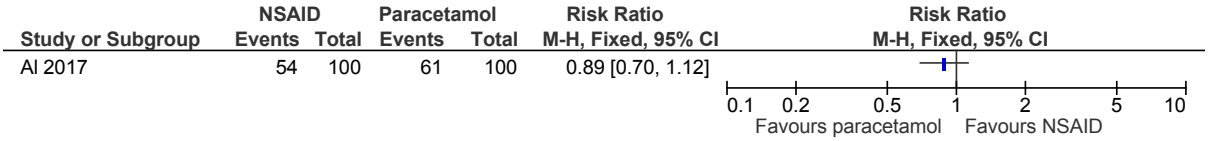
Figure 23: Pain (reduction in pain by 50%)



Route of administration (NSAID, paracetamol): IM, IV

1

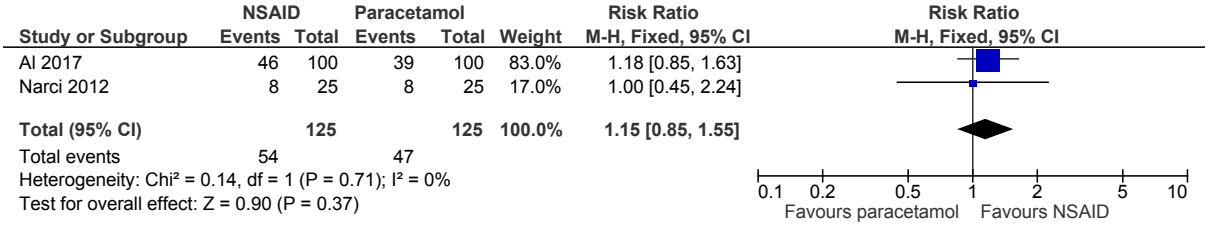
Figure 24: Partial pain relief



Route of administration (NSAID, paracetamol): AI 2017: IV, IV

2

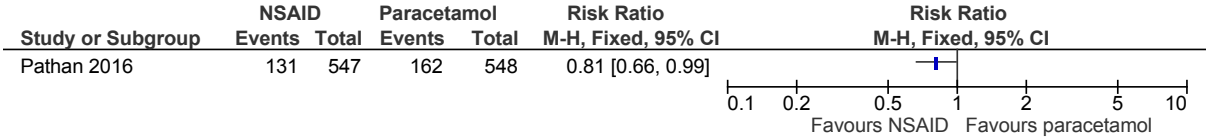
Figure 25: Complete pain relief



Route of administration (NSAID, paracetamol): AI, 2017: IV, IV;; Narci 2012: IM, oral)

3

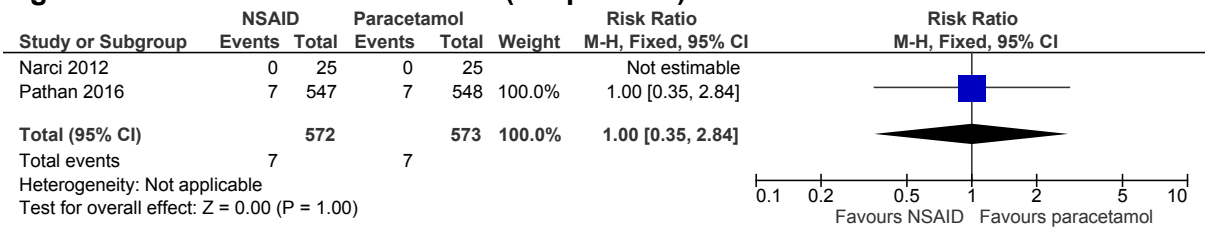
Figure 26: Pain (persistent pain at 60 minutes)



Route of administration (NSAID, paracetamol): IM, IV

4

Figure 27: Minor adverse events (unspecified)



Route of administration (NSAID, paracetamol): Narci 2012: IM, oral; Pathan 2016: IM, IV

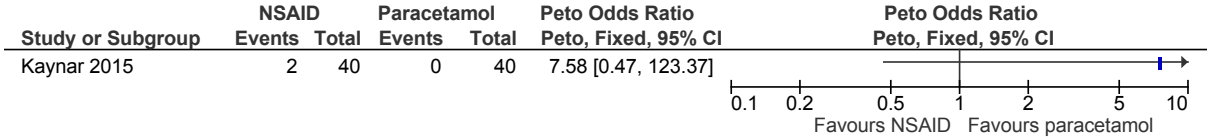
5

Figure 28: Minor adverse events (vomiting)

Route of administration (NSAID, paracetamol): Al 2017: IV, IV; Cenker 2017: IV, IV; Kaynar 2015: IM, IV

1

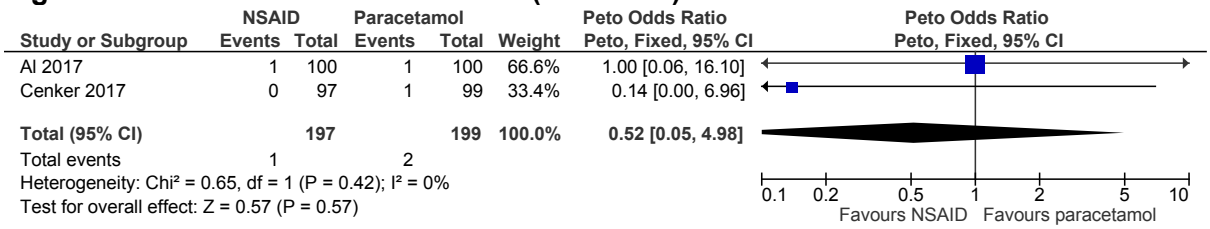
Figure 29: Minor adverse events (pain - abdominal)



Route of administration (NSAID, paracetamol): IM, IV

2

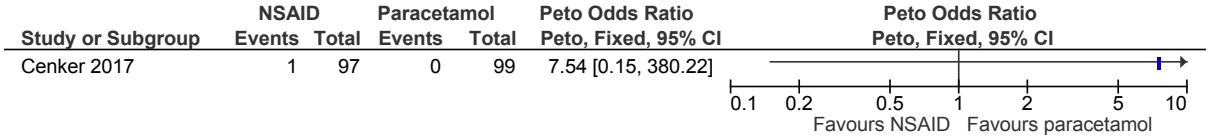
Figure 30: Minor adverse advents (dizziness)



Route of administration (NSAID, paracetamol): Al 2017: IV, IV; Cenker 2017: IV, IV

3

Figure 31: Minor adverse events (epigastric pain)

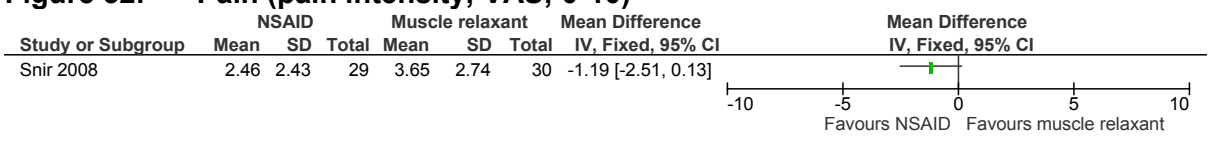


Route of administration (NSAID, paracetamol): Cenker 2017: IV, IV

4

E.3 NSAID versus muscle relaxant/antispasmodic

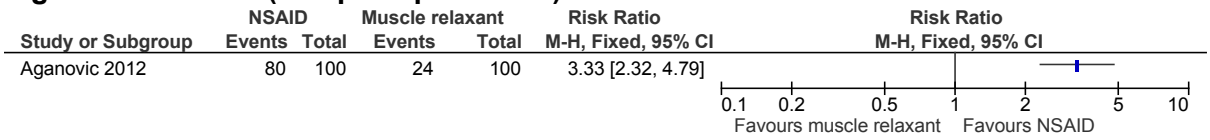
Figure 32: Pain (pain intensity; VAS; 0-10)



Route of administration (NSAID, muscle relaxant): IM, IV

5

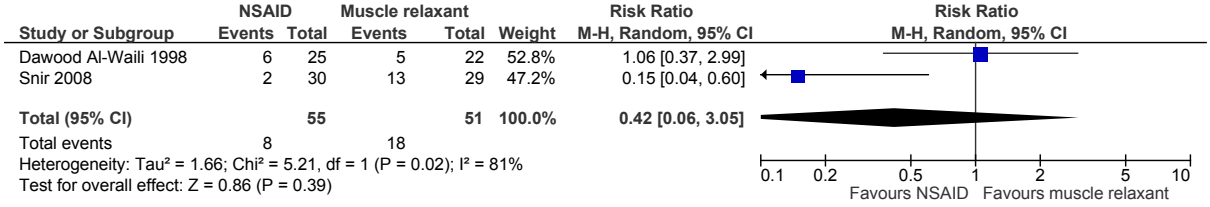
Figure 33: Pain (complete pain relief)



Route of administration (NSAID, muscle relaxant): IM, IV
Reported as number of 'cured' and 'non cured' participants, not defined by study

1

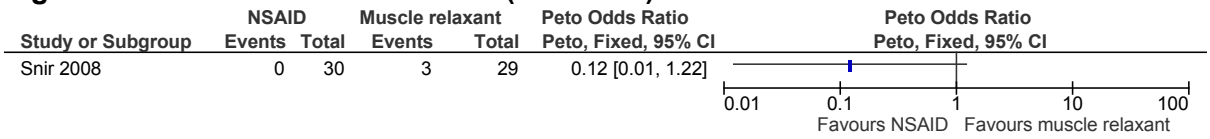
Figure 34: Pain (need for rescue medication)



Route of administration (NSAID, muscle relaxant): Dawood Al-Waili 1998: IV, IV; Snir 2008: IM, IV

2

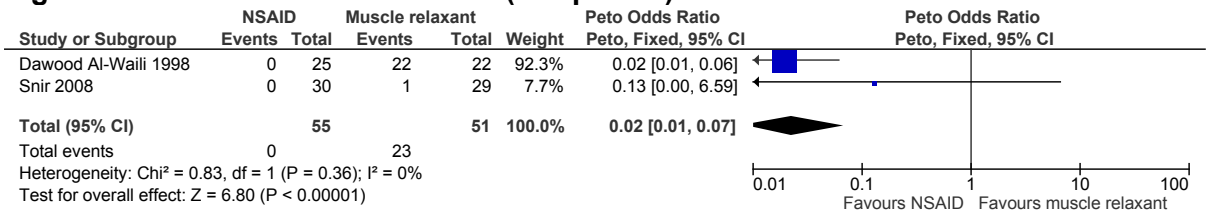
Figure 35: Minor adverse events (dizziness)



Route of administration (NSAID, muscle relaxant): IM, IV

3

Figure 36: Minor adverse events (sleepiness)

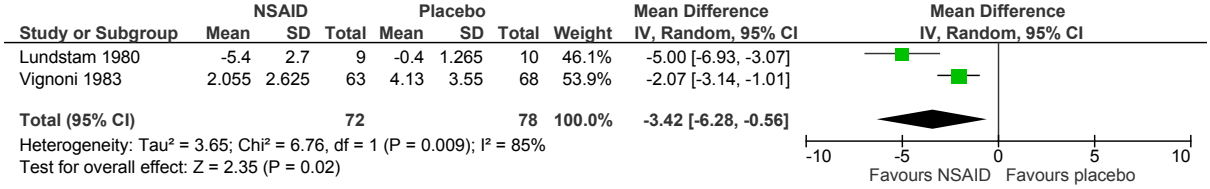


Route of administration (NSAID, muscle relaxant): Dawood Al-Waili 1998: IV, IV; Snir 2008: IM, IV

4

E.4 NSAID versus placebo

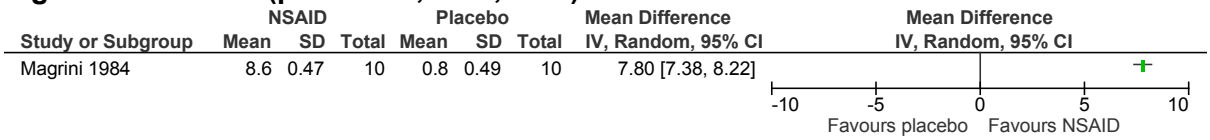
Figure 37: Pain (pain intensity; VAS; 0-10; change & final scores)



Route of administration (NSAID, placebo): Lundstam 1980: IM, IM; Vignoni 1983: IM, IM

5

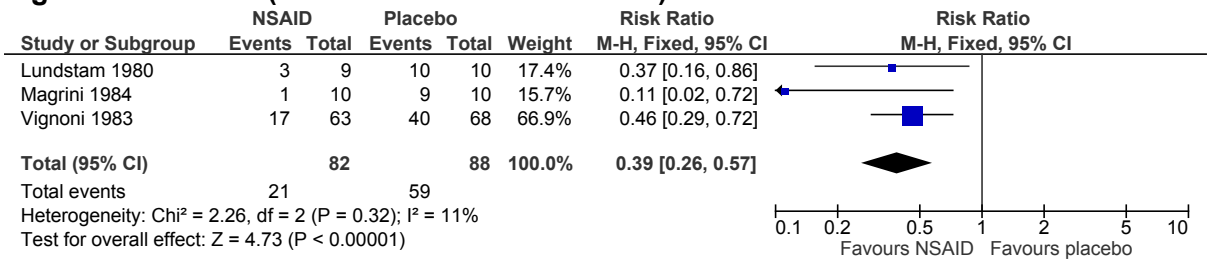
Figure 38: Pain (pain relief; VAS; 0-10)



Route of administration (NSAID, placebo): IV, IV

1

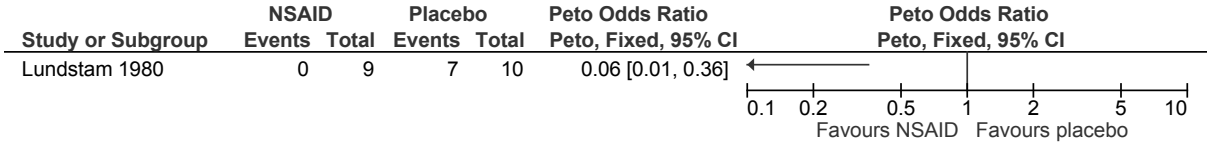
Figure 39: Pain (need for rescue medication)



Route of administration (NSAID, placebo): Lundstam 1980: IM, IM; Magrini 1984: IV, IV; Vignoni 1983: IM, IM

2

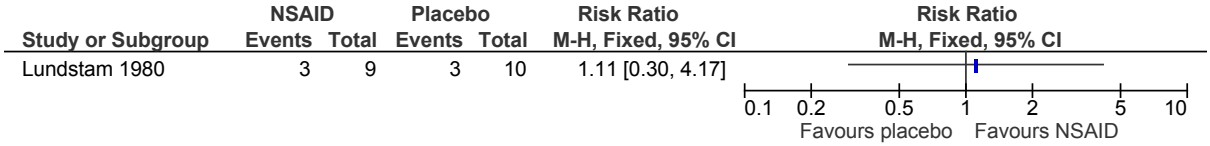
Figure 40: Pain (no pain relief)



Route of administration (NSAID, placebo): IM, IM

3

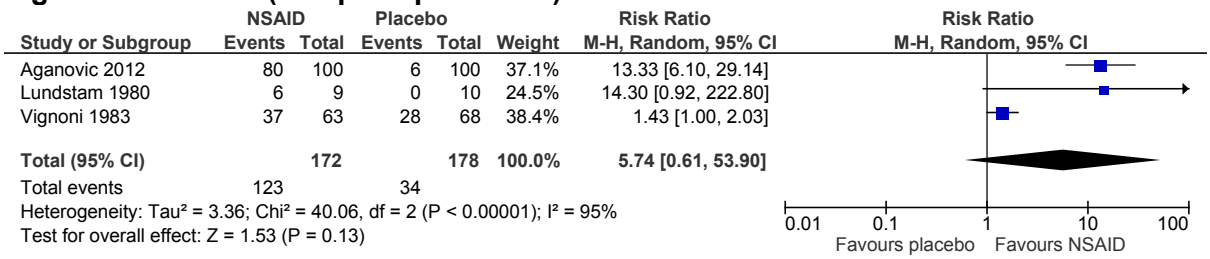
Figure 41: Pain (partial pain relief)



Route of administration (NSAID, placebo): IM, IM

4

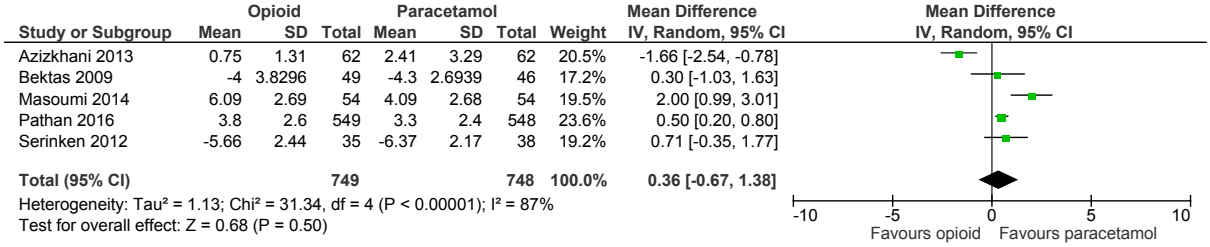
Figure 42: Pain (complete pain relief)



Route of administration (NSAID, placebo*): Aganovic 2012: IM, IV; Lundstam 1980: IM, IM; Vignoni 1983: IM, IM*
Aganovic 2012 reports number of 'cured' and 'non cured' participants, not defined by study

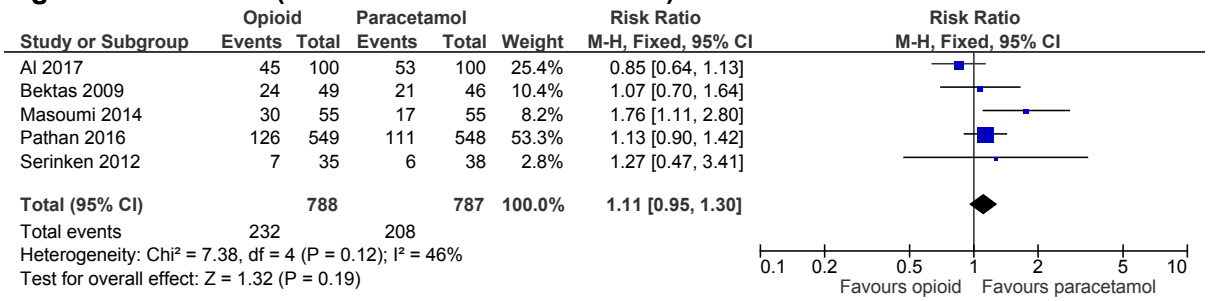
E.5 Opioid/opiate versus paracetamol

Figure 43: Pain (pain intensity; VAS & NRS; 0-10; final and change scores)



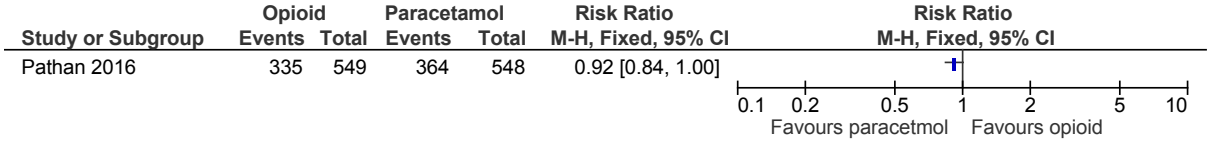
Route of administration (opioid, paracetamol): Azizkhani 2013: IV, IV; Berkas 2009: IV, IV: Masoumi 2014: IV, IV; Pathan 2016: IV, IV; Serinken 2012: IV, IV

Figure 44: Pain (need for rescue medication)



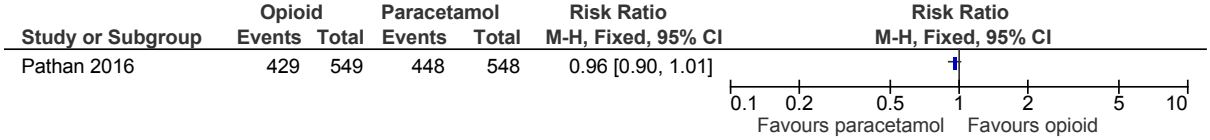
Route of administration (opioid, paracetamol): AI 2017: IV, IV; Berkas 2009: IV, IV: Masoumi 2014: IV, IV; Pathan 2016: IV, IV; Serinken 2012: IV, IV

Figure 45: Pain (reduction in pain by 50%)



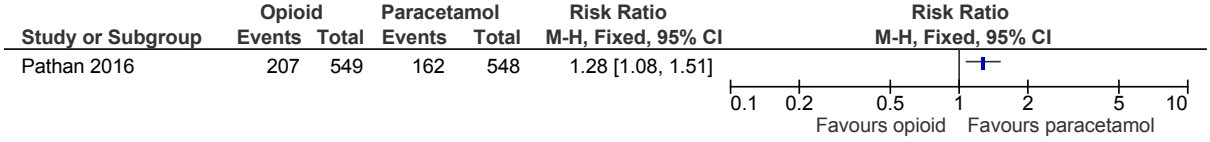
Route of administration (opioid, paracetamol): IV, IV

Figure 46: Pain (reduction in pain NRS score by >3)



Route of administration (opioid, paracetamol): IV, IV

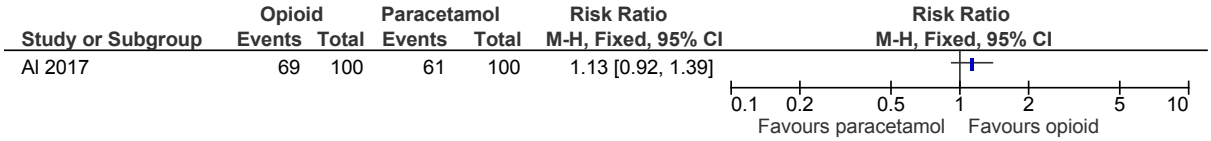
Figure 47: Pain (persistent pain at 60 minutes)



Route of administration (opioid, paracetamol): IV, IV

1

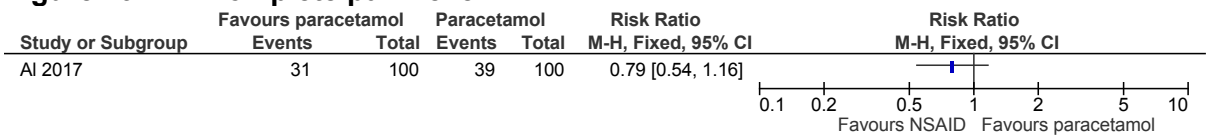
Figure 48: Partial pain relief



Route of administration (opioid, paracetamol): IV, IV

2

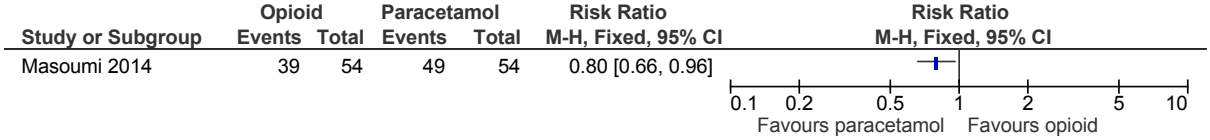
Figure 49: Complete pain relief



Route of administration (opioid, paracetamol): IV, IV

3

Figure 50: Use of healthcare services (length of stay - discharged within 1 hour)



Route of administration (opioid, paracetamol): IV, IV

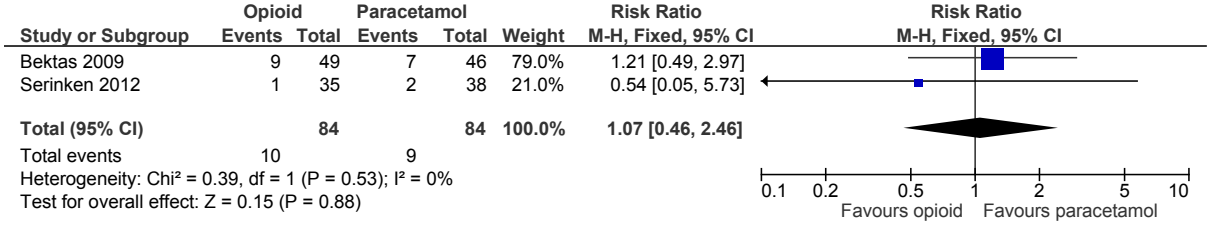
4

Figure 51: Major adverse events (respiratory depression)

Route of administration (opioid, paracetamol): Berkas 2009: IV, IV: Serinken 2012: IV, IV

5

Figure 52: Minor adverse events (nausea and vomiting)

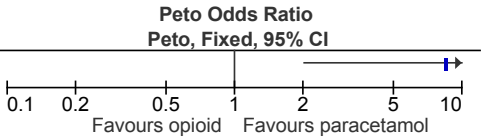


Route of administration (opioid, paracetamol): Berkas 2009: IV, IV: Serinken 2012: IV, IV

6

Figure 53: Minor adverse events (nausea)

Study or Subgroup	Opioid Events	Opioid Total	Paracetamol Events	Paracetamol Total	Peto Odds Ratio Peto, Fixed, 95% CI
Masoumi 2014	8	54	0	54	8.50 [2.03, 35.64]



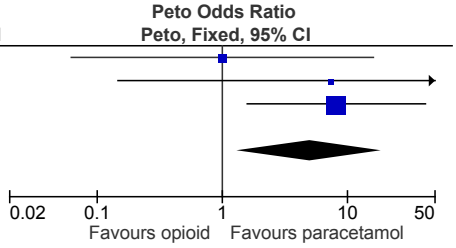
Route of administration (opioid, paracetamol): IV, IV

1

Figure 54: Minor adverse events (vomiting)

Study or Subgroup	Opioid Events	Opioid Total	Paracetamol Events	Paracetamol Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Al 2017	1	100	1	100	22.8%	1.00 [0.06, 16.10]
Azizkhani 2013	1	62	0	62	11.5%	7.39 [0.15, 372.38]
Masoumi 2014	6	54	0	54	65.7%	8.15 [1.58, 41.98]
Total (95% CI)		**216**		**216**	**100.0%**	**4.99 [1.32, 18.83]**
Total events	8		1			

Heterogeneity: Chi² = 1.67, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 2.37 (P = 0.02)



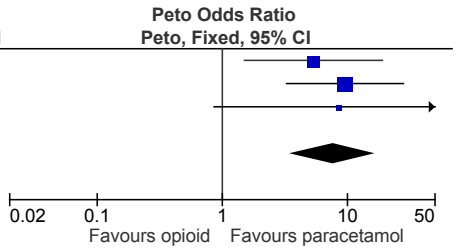
Route of administration (opioid, paracetamol): Al 2017: IV, IV; Azizkhani 2013: IV, IV; Masoumi 2014: IV, IV

2

Figure 55: Minor adverse events (dizziness)

Study or Subgroup	Opioid Events	Opioid Total	Paracetamol Events	Paracetamol Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Al 2017	9	100	1	100	37.1%	5.34 [1.50, 19.00]
Azizkhani 2013	15	62	0	62	51.6%	9.55 [3.26, 28.00]
Serinken 2012	3	35	0	38	11.3%	8.54 [0.86, 84.99]
Total (95% CI)		**197**		**200**	**100.0%**	**7.61 [3.51, 16.47]**
Total events	27		1			

Heterogeneity: Chi² = 0.48, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 5.15 (P < 0.00001)

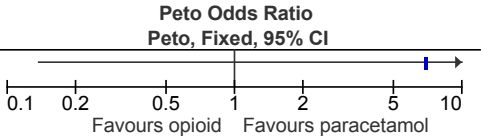


Route of administration (opioid, paracetamol): Al 2017: IV, IV; Azizkhani 2013: IV, IV; Serinken 2012: IV, IV

3

Figure 56: Minor adverse events (urinary retention)

Study or Subgroup	Opioid Events	Opioid Total	Paracetamol Events	Paracetamol Total	Peto Odds Ratio Peto, Fixed, 95% CI
Bektas 2009	1	49	0	46	6.95 [0.14, 350.96]

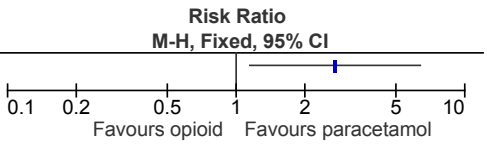


Route of administration (opioid, paracetamol): IV, IV

4

Figure 57: Minor adverse events (unspecified)

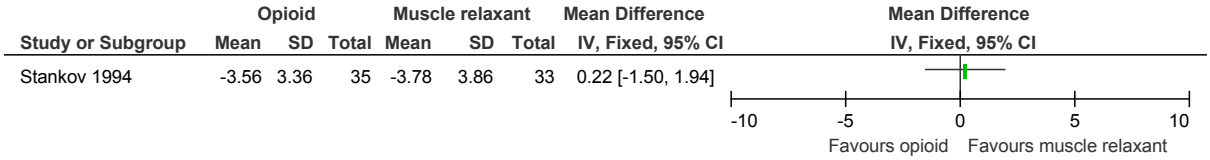
Study or Subgroup	Opioid Events	Opioid Total	Paracetamol Events	Paracetamol Total	Risk Ratio M-H, Fixed, 95% CI
Pathan 2016	19	549	7	548	2.71 [1.15, 6.39]



Route of administration (opioid, paracetamol): IV, IV

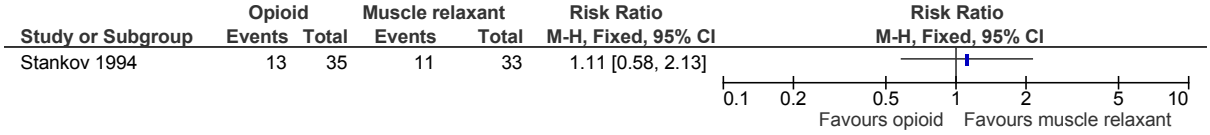
E.6 Opioid/opiate versus muscle relaxant/antispasmodic

Figure 58: Pain (pain intensity; VAS; 0-10; change score)



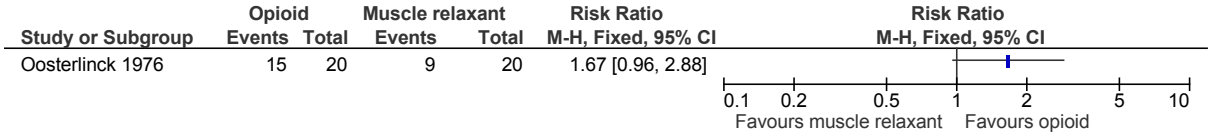
Route of administration (opioid, muscle relaxant): IV, IV

Figure 59: Pain (need for rescue medication)



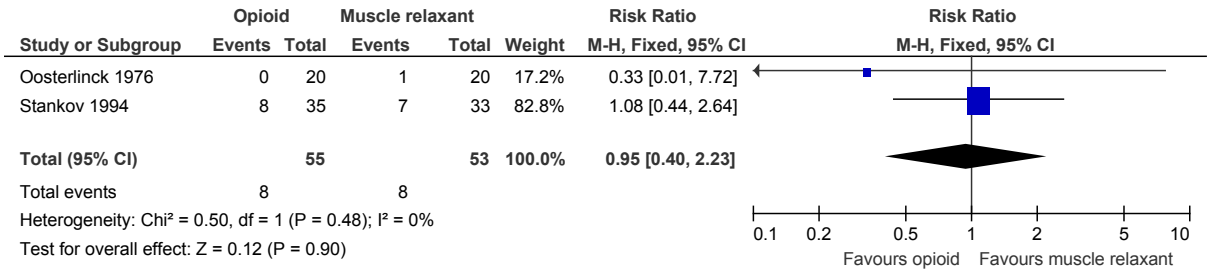
Route of administration (opioid, muscle relaxant): IV, IV

Figure 60: Pain (complete pain relief)



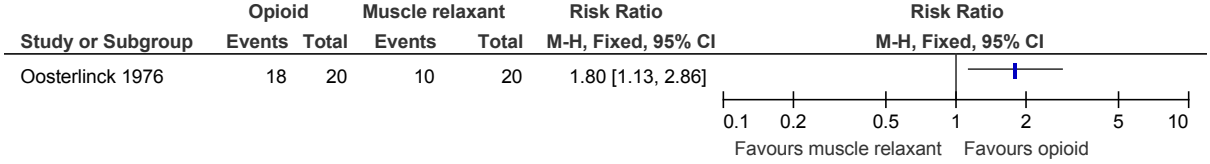
Route of administration (opioid, muscle relaxant): IV, IV

Figure 61: Pain (no pain relief)



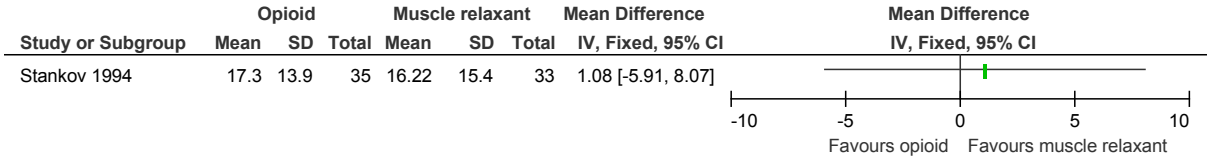
Route of administration (opioid, muscle relaxant): Oosterlinck 1976: IV, IV; Stankov 1994: IV, IV

Figure 62: Pain (time to pain relief within 5 minutes)



Route of administration (opioid, muscle relaxant): IV, IV

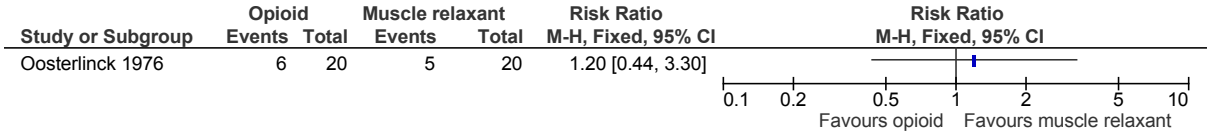
Figure 63: Pain (time to pain relief)



Route of administration (opioid, muscle relaxant): IV, IV

1

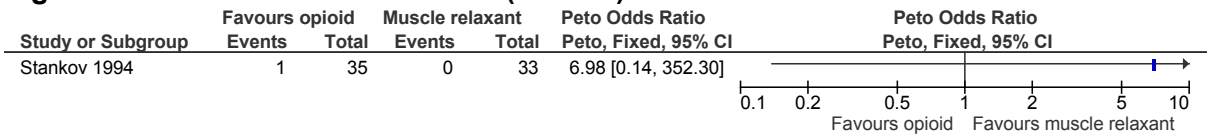
Figure 64: Minor adverse events (nausea and vomiting)



Route of administration (opioid, muscle relaxant): IV, IV

2

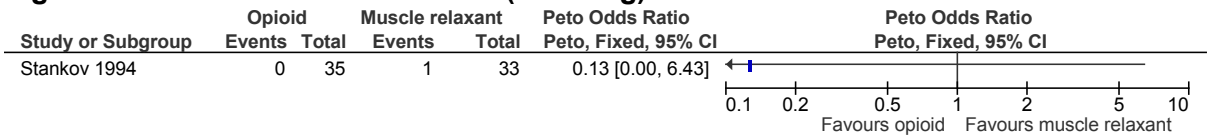
Figure 65: Minor adverse events (nausea)



Route of administration (opioid, muscle relaxant): IV, IV

3

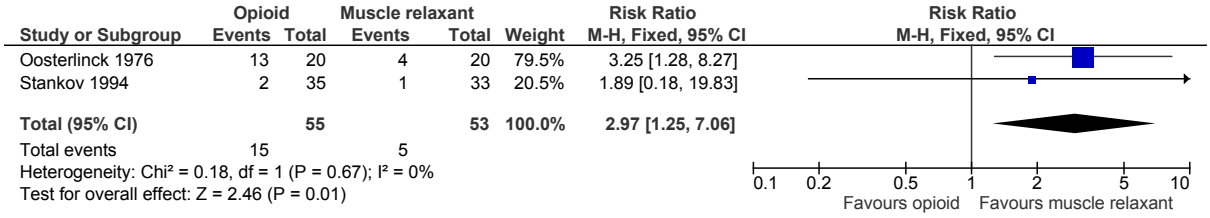
Figure 66: Minor adverse events (vomiting)



Route of administration (opioid, muscle relaxant): IV, IV

4

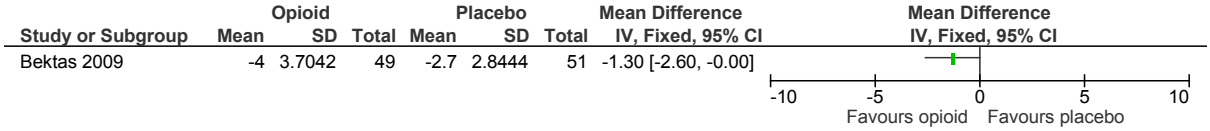
Figure 67: Minor adverse events (dizziness)



Route of administration (opioid, muscle relaxant): Oosterlinck 1976: IV, IV; Stankov 1994: IV, IV

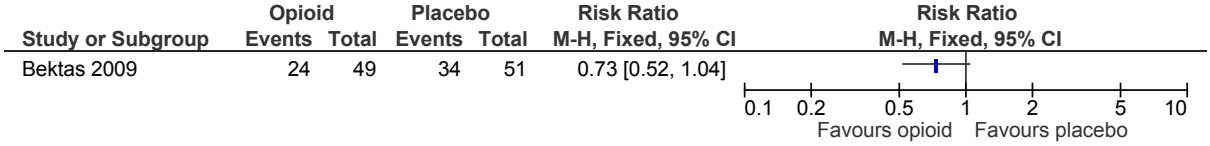
E.7 Opioid/opiate versus placebo

Figure 68: Pain (pain intensity; VAS; 0-10; change score)



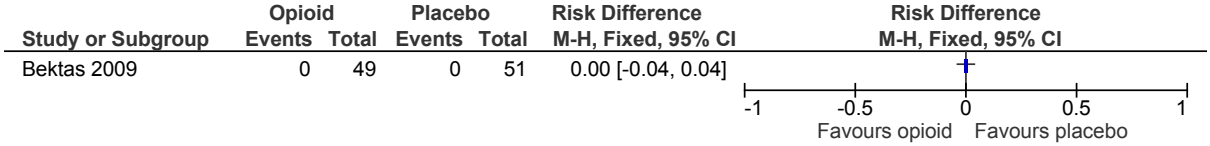
Route of administration (opioid, placebo): IV, IV

Figure 69: Pain (need for rescue medication)



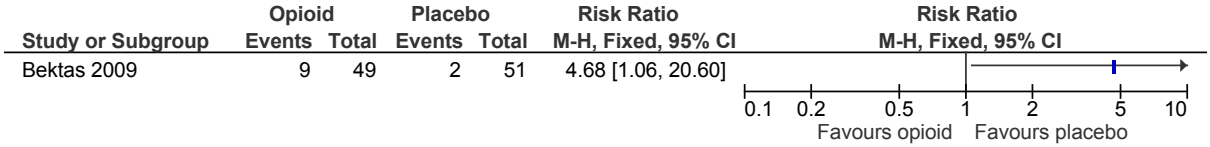
Route of administration (opioid, placebo): IV, IV

Figure 70: Major adverse events (respiratory depression)



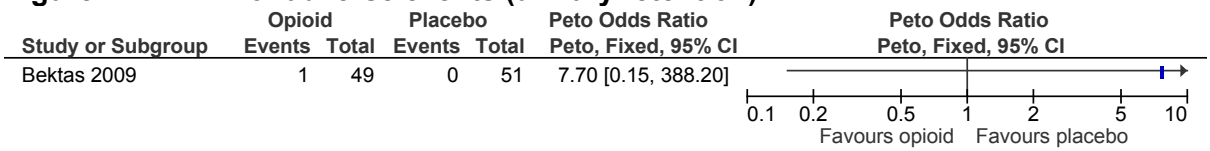
Route of administration (opioid, placebo): IV, IV

Figure 71: Minor adverse events (nausea and vomiting)



Route of administration (opioid, placebo): IV, IV

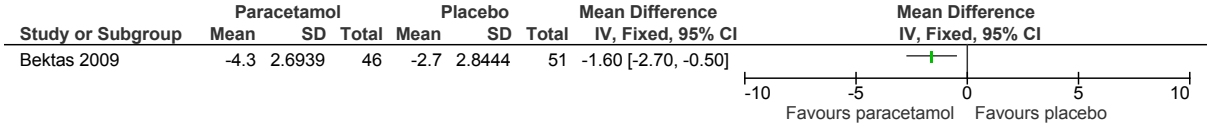
Figure 72: Minor adverse events (urinary retention)



Route of administration (opioid, placebo): IV, IV

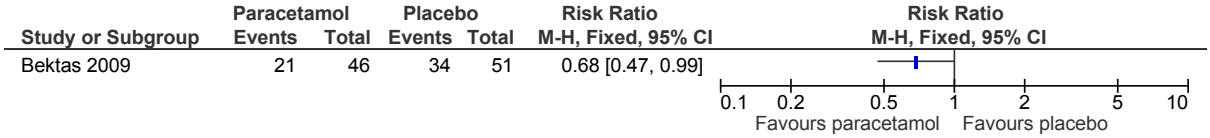
E.8 Paracetamol versus placebo

Figure 73: Pain (pain intensity; VAS; 0-10; change score)



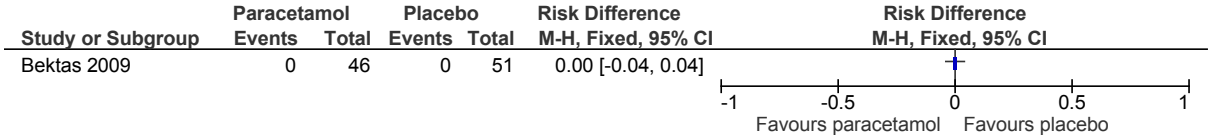
Route of administration (paracetamol, placebo): IV, IV

Figure 74: Pain (need for rescue medication)



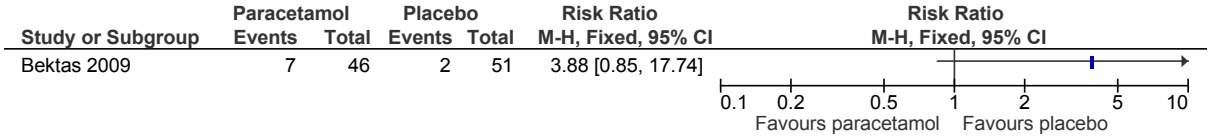
Route of administration (paracetamol, placebo): IV, IV

Figure 75: Major adverse events (respiratory depression)



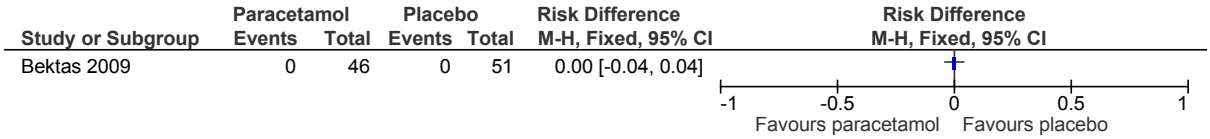
Route of administration (paracetamol, placebo): IV, IV

Figure 76: Minor adverse events (nausea and vomiting)



Route of administration (paracetamol, placebo): IV, IV

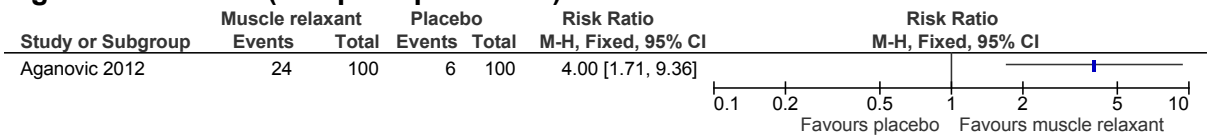
Figure 77: Minor adverse events (urinary retention)



Route of administration (opioid, placebo): IV, IV

E.9 Muscle relaxant/antispasmodic versus placebo

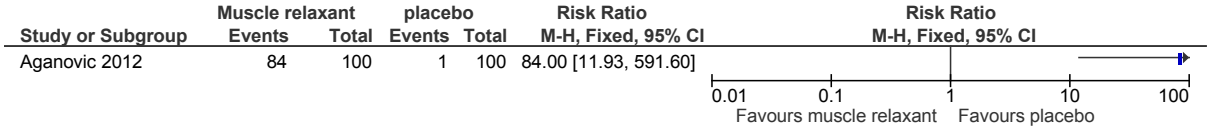
Figure 78: Pain (complete pain relief)



Route of administration (muscle relaxant, placebo): IV, IV
Reported as number of 'cured' and 'non cured' participants, not defined by study

1

Figure 79: Minor adverse events (unspecified)

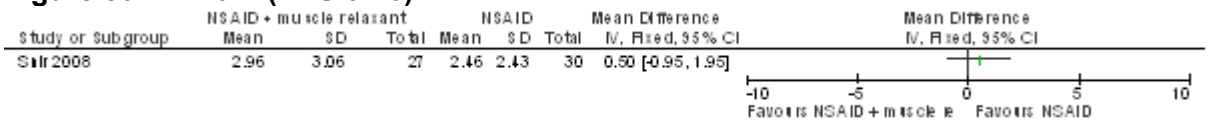


Route of administration (muscle relaxant, placebo): IV, IV

2 E.10 Combinations

3 E.10.1 NSAID + muscle relaxant versus NSAID

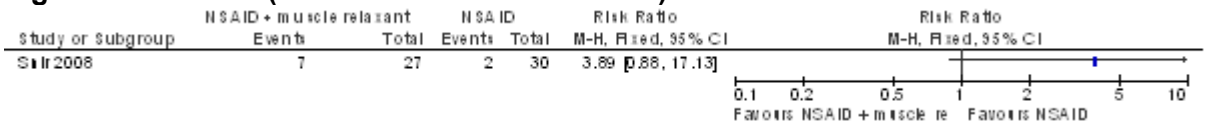
Figure 80: Pain (VAS 0-10)



Route of administration (combination, NSAID): IM + IV, IM

4

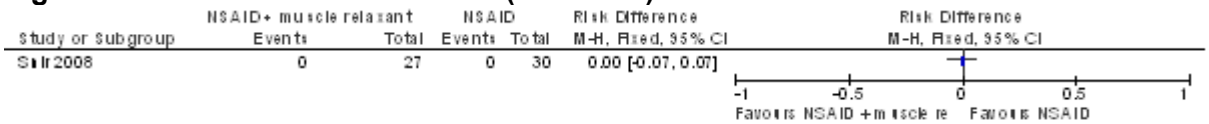
Figure 81: Pain (need for rescue medication)



Route of administration (combination, NSAID): IM + IV, IM

5

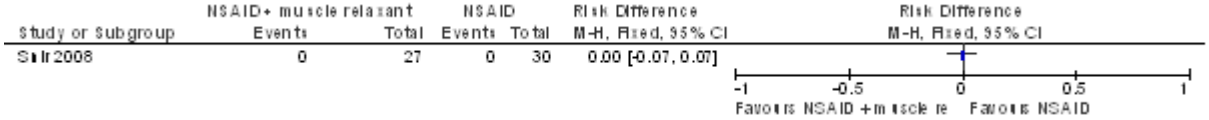
Figure 82: Minor adverse events (dizziness)



Route of administration (combination, NSAID): IM + IV, IM

6

Figure 83: Minor adverse events (sleepiness)

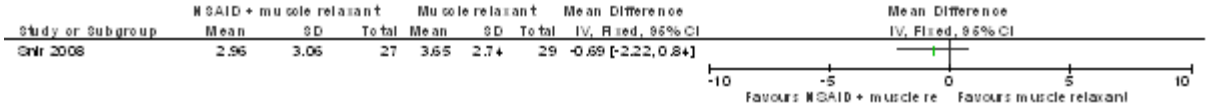


Route of administration (combination, NSAID): IM + IV, IM

7 E.10.2 NSAID + muscle relaxant versus muscle relaxant

8

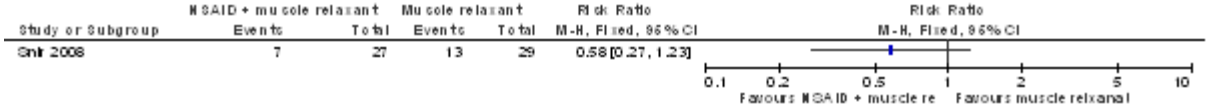
Figure 84: Pain (VAS 0-10)



Route of administration (combination, muscle relaxant): IM + IV, IV

1

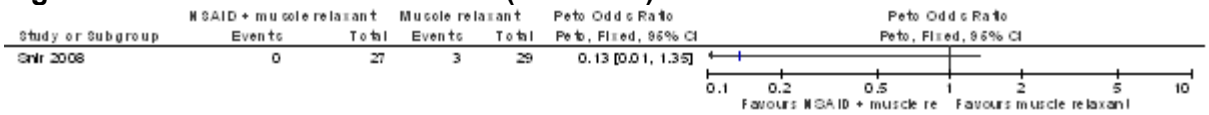
Figure 85: Pain (need for rescue medication)



Route of administration (combination, muscle relaxant): IM + IV, IV

2

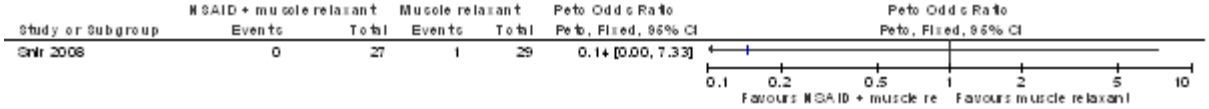
Figure 86: Minor adverse events (dizziness)



Route of administration (combination, muscle relaxant): IM + IV, IV

3

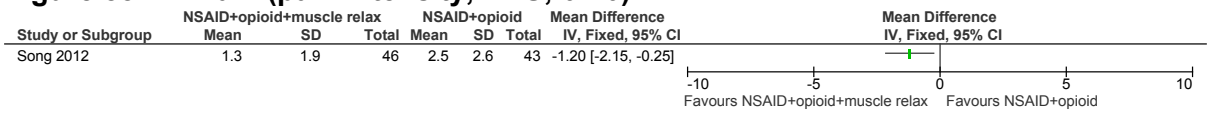
Figure 87: Minor adverse events (sleepiness)



Route of administration (combination, muscle relaxant): IM + IV, IV

4 E.10.3 NSAID + opioid + muscle relaxant versus NSAID + opioid

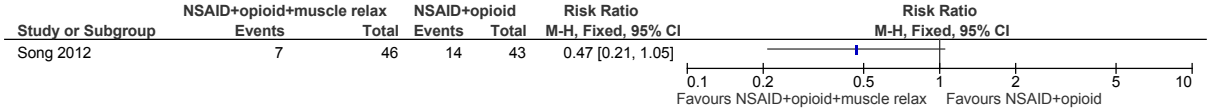
Figure 88: Pain (pain intensity; VAS; 0-10)



Route of administration (NSAID + opioid + muscle relaxant, NSAID + opioid): IV + IV + IV, IV + IV

5

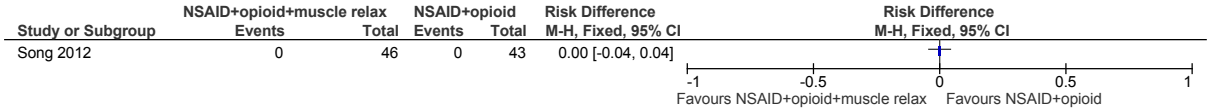
Figure 89: Pain (need for rescue medication)



Route of administration (NSAID + opioid + muscle relaxant, NSAID + opioid): IV + IV + IV, IV + IV

6

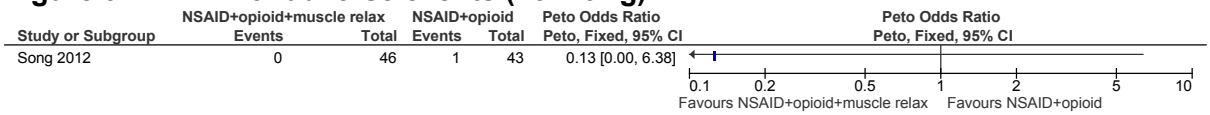
Figure 90: Major adverse events (respiratory depression)



Route of administration (NSAID + opioid + muscle relaxant, NSAID + opioid): IV + IV + IV, IV + IV

1

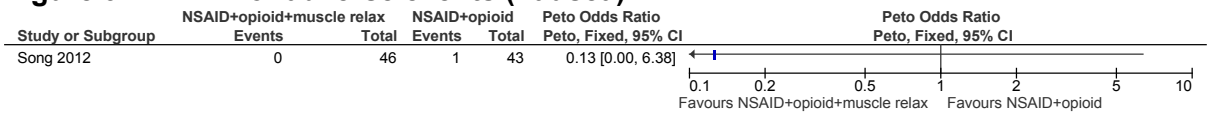
Figure 91: Minor adverse events (vomiting)



Route of administration (NSAID + opioid + muscle relaxant, NSAID + opioid): IV + IV + IV, IV + IV

2

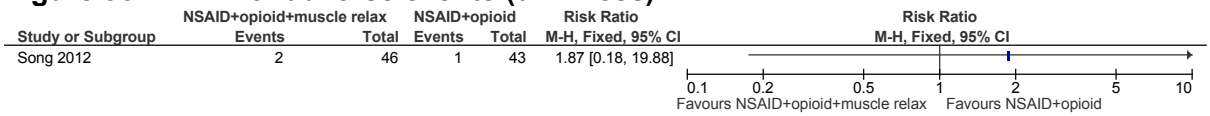
Figure 92: Minor adverse events (nausea)



Route of administration (NSAID + opioid + muscle relaxant, NSAID + opioid): IV + IV + IV, IV + IV

3

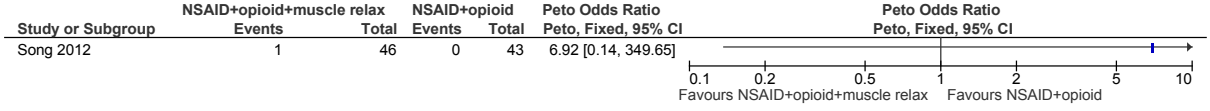
Figure 93: Minor adverse events (dizziness)



Route of administration (NSAID + opioid + muscle relaxant, NSAID + opioid): IV + IV + IV, IV + IV

4

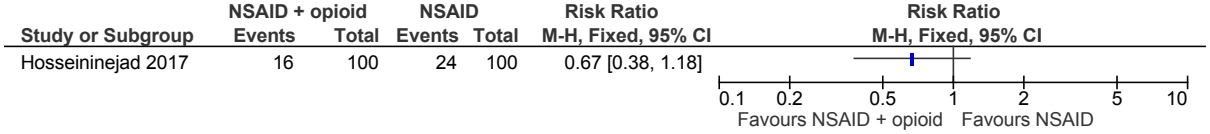
Figure 94: Minor adverse events (sleepiness)



Route of administration (NSAID + opioid + muscle relaxant, NSAID + opioid): IV + IV + IV, IV + IV

5 **E.10.4 NSAID + opioid versus NSAID**

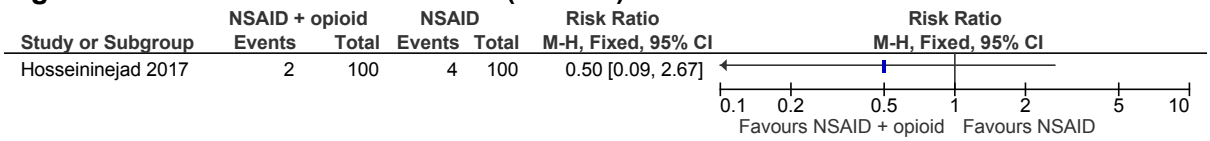
Figure 95: Pain (need for rescue medication)



Route of administration (NSAID + opioid, NSAID): IV + IV, IV

6

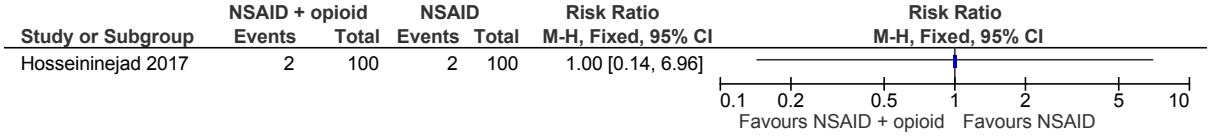
Figure 96: Minor adverse events (nausea)



Route of administration (NSAID + opioid, NSAID): IV + IV, IV

1

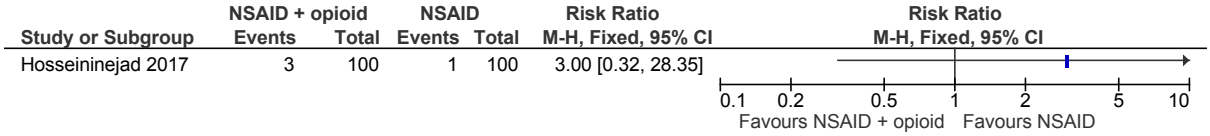
Figure 97: Minor adverse events (vomiting)



Route of administration (NSAID + opioid, NSAID): IV + IV, IV

2

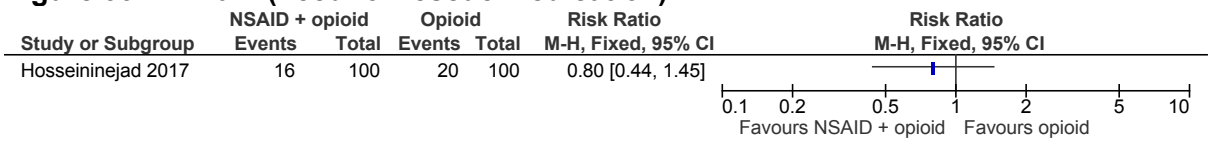
Figure 98: Minor adverse events (dizziness - vertigo)



Route of administration (NSAID + opioid, NSAID): IV + IV, IV

3 ## E.10.5 NSAID + opioid versus opioid

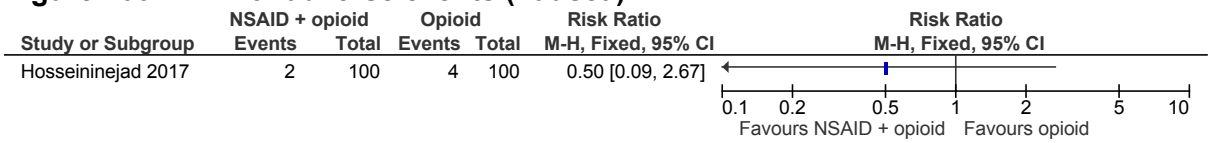
Figure 99: Pain (need for rescue medication)



Route of administration (NSAID + opioid, NSAID): IV + IV, IV

4

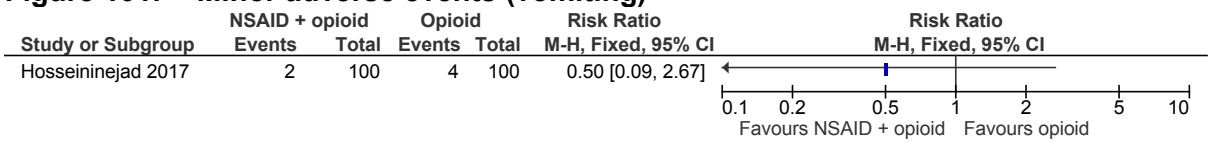
Figure 100: Minor adverse events (nausea)



Route of administration (NSAID + opioid, NSAID): IV + IV, IV

5

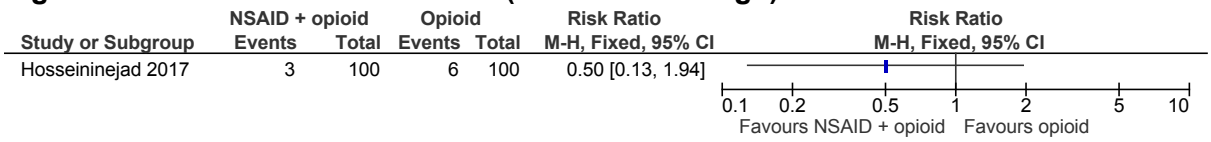
Figure 101: Minor adverse events (vomiting)



Route of administration (NSAID + opioid, NSAID): IV + IV, IV

1

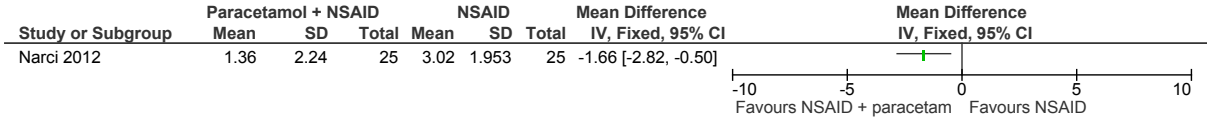
Figure 102: Minor adverse events (dizziness - vertigo)



Route of administration (NSAID + opioid, NSAID): IV + IV, IV

2 ## E.10.6 NSAID + paracetamol versus NSAID

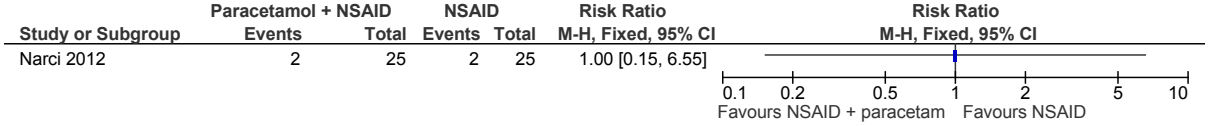
Figure 103: Pain (VAS 0-10)



Route of administration (NSAID + paracetamol, NSAID): IM + oral, IM

3

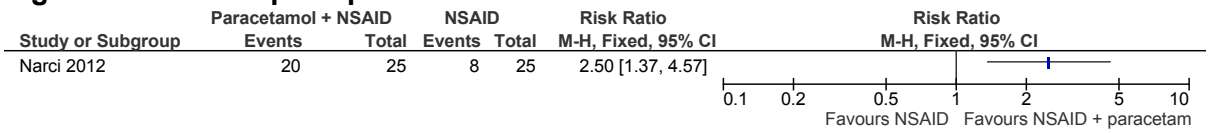
Figure 104: Pain (need for rescue medication)



Route of administration (NSAID + paracetamol, NSAID): IM + oral, IM

4

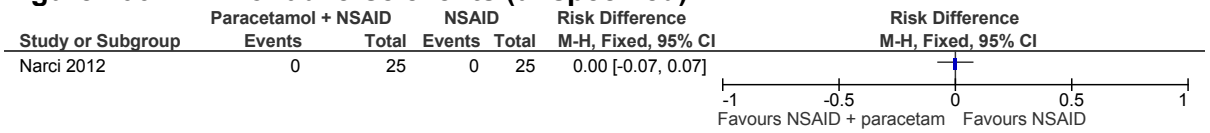
Figure 105: Complete pain relief



Route of administration (NSAID + paracetamol, NSAID): IM + oral, IM

5

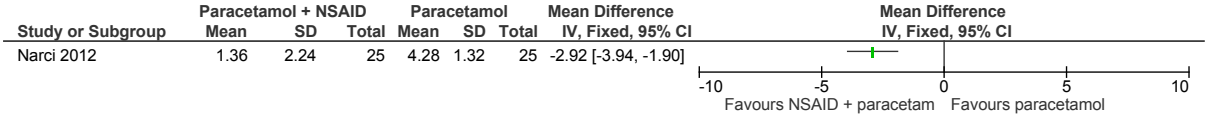
Figure 106: Minor adverse events (unspecified)



Route of administration (NSAID + paracetamol, NSAID): IM + oral, IM

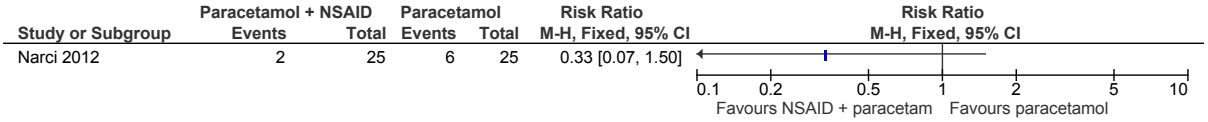
E.10.7 NSAID + paracetamol versus paracetamol

Figure 107: Pain (VAS 0-10)



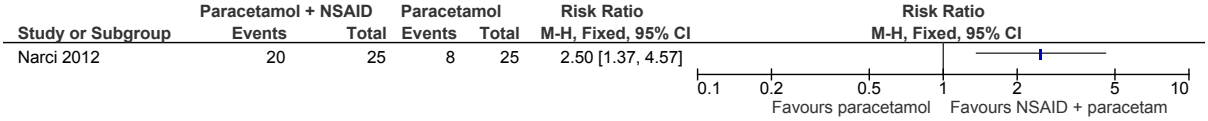
Route of administration (NSAID + paracetamol, paracetamol): IM + oral, oral

Figure 108: Pain (need for rescue medication)



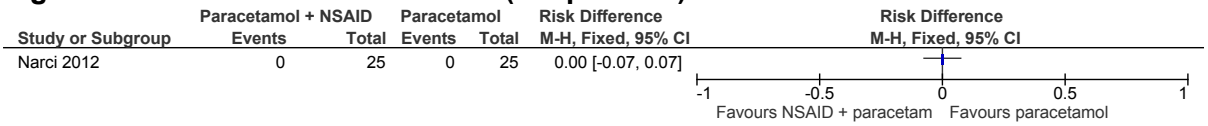
Route of administration (NSAID + paracetamol, paracetamol): IM + oral, oral

Figure 109: Complete pain relief



Route of administration (NSAID + paracetamol, paracetamol): IM + oral, oral

Figure 110: Minor adverse events (unspecified)



Route of administration (NSAID + paracetamol, paracetamol): IM + oral, oral

Appendix F: GRADE tables

Table 27: Clinical evidence profile: NSAID versus opioid/opiate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAID	Opioid	Relative (95% CI)	Absolute		
Pain (VAS & NRS) [final and change scores] (follow-up 30-60 minutes; range of scores: 0-10; Better indicated by lower values)												
8	randomised trials	serious[1]	very serious[2]	no serious indirectness	no serious imprecision	none	857	818	-	MD 0.35 lower (1.14 lower to 0.43 higher)	⊕OOO VERY LOW	CRITICAL
Pain (VAS 1-10) (follow-up 30 minutes; range of scores: 1-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	48	49	-	MD 1.4 lower (2.5 to 0.3 lower)	⊕OOO VERY LOW	CRITICAL
Need for rescue medication (follow-up 30-40 minutes)												
17	randomised trials	serious[1]	serious[4]	no serious indirectness	serious[3]	none	317/1425 (22.2%)	35.7%	RR 0.77 (0.64 to 0.93)	82 fewer per 1000 (from 25 fewer to 129 fewer)	⊕OOO VERY LOW	CRITICAL
No pain relief (follow-up 30-60 minutes)												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/201 (5.5%)	3%	RR 1.52 (0.57 to 4.07)	17 more per 1000 (from 14 fewer to 98 more)	⊕OOO VERY LOW	CRITICAL
Partial pain relief (follow-up 30 minutes/ at discharge)												
4	randomised trials	very serious[1]	serious[5]	no serious indirectness	serious[3]	none	124/268 (46.3%)	55.5%	RR 0.93 (0.73 to 1.17)	39 fewer per 1000 (from 150 fewer to 94 more)	⊕OOO VERY LOW	CRITICAL
Complete pain relief (follow-up 30-60 minutes/ at discharge)												

7	randomised trials	serious[1]	very serious[6]	no serious indirectness	very serious[3]	none	204/407 (50.1%)	51.6%	RR 1.05 (0.78 to 1.42)	26 more per 1000 (from 114 fewer to 217 more)	⊕OOO VERY LOW	CRITICAL
Persistent pain (follow-up 60 minutes)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	131/547 (23.9%)	37.7%	RR 0.64 (0.53 to 0.76)	136 fewer per 1000 (from 90 fewer to 177 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Reduction in pain NRS score >3 (follow-up 30 minutes)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	448/547 (81.9%)	78.1%	RR 1.05 (0.99 to 1.11)	39 more per 1000 (from 8 fewer to 86 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Reduction in pain by 50% (follow-up 30 minutes)												
3	randomised trials	serious[1]	very serious[7]	no serious indirectness	very serious[3]	none	631/849 (74.3%)	61%	RR 1.19 (0.91 to 1.54)	116 more per 1000 (from 55 fewer to 329 more)	⊕OOO VERY LOW	CRITICAL
Major adverse events (significant side effects) (follow-up not reported)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/48 (0%)	0%	See comment	0 fewer per 1000 (from 39 fewer to 39 more)[12]	⊕⊕OO LOW	CRITICAL
Minor adverse events (unspecified) (follow-up 14 days)												
4	randomised trials	serious[1]	no serious inconsistency	serious[8]	no serious imprecision	none	14/627 (2.2%)	10.1%	RR 0.39 (0.22 to 0.7)	62 fewer per 1000 (from 30 fewer to 79 fewer)	⊕⊕OO LOW	CRITICAL
Minor adverse events (urinary retention (follow-up 60 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/116 (0%)	0.85%	Peto OR 0.14 (0 to 6.94)	8 fewer per 1000 (from 9 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (nausea and vomiting) (follow-up 30 minutes - 24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	16/102 (15.7%)	28.8%	RR 0.55 (0.32 to 0.93)	98 fewer per 1000 (from 15 fewer to 148 fewer)	⊕⊕OO LOW	CRITICAL

Minor adverse events (vomiting) (follow-up unclear time point											
10	randomised trials	serious[1]	serious[9]	no serious indirectness	serious[3]	none	61/696 (8.8%)	10.8%	RR 0.38 (0.18 to 0.81)	67 fewer per 1000 (from 21 fewer to 89 fewer)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (nausea) (follow-up unclear time point											
10	randomised trials	serious[1]	serious[10]	no serious indirectness	serious[3]	none	72/629 (11.4%)	19.1%	RR 0.47 (0.25 to 0.88)	101 fewer per 1000 (from 23 fewer to 143 fewer)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (dizziness) (follow-up not reported)											
12	randomised trials	serious[1]	serious[11]	no serious indirectness	serious[3]	none	70/774 (9%)	16%	RR 0.29 (0.11 to 0.74)	114 fewer per 1000 (from 42 fewer to 142 fewer)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (sleepiness) (follow-up 1-24 hours or not reported)											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	35/430 (8.1%)	24.1%	RR 0.39 (0.27 to 0.56)	74 fewer per 1000 (from 53 fewer to 88 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Minor adverse events (pain) (follow-up 12 hours)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	16/200 (8%)	2.5%	RR 3.33 (1.19 to 9.29)	40 more per 1000 (from 3 more to 141 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 or 2 increments because heterogeneity, I2= 94%, p= > 0.1, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Downgraded by 1 or 2 increments because heterogeneity, I2= 54%, p= > 0.1, unexplained by subgroup analysis
[5] Downgraded by 1 or 2 increments because heterogeneity, I2= 60%, p= > 0.1, unexplained by subgroup analysis
[6] Downgraded by 1 or 2 increments because heterogeneity, I2= 77%, p= > 0.1, unexplained by subgroup analysis
[7] Downgraded by 1 or 2 increments because heterogeneity, I2= 93%, p= > 0.1, unexplained by subgroup analysis
[8] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[9] Downgraded by 1 or 2 increments because heterogeneity, I2= 68%, p= > 0.1, unexplained by subgroup analysis
[10] Downgraded by 1 or 2 increments because heterogeneity, I2= 65%, p= > 0.1, unexplained by subgroup analysis
[11] Downgraded by 1 or 2 increments because heterogeneity, I2= 81%, p= > 0.1, unexplained by subgroup analysis
[12] Risk difference calculated in Review Manager

Table 28: Clinical evidence profile: NSAID versus paracetamol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAID versus paracetamol	Control	Relative (95% CI)	Absolute		
Pain (NRS or VAS; 0-10) (follow-up 30 minutes; range of scores: 0-10; Better indicated by lower values)												
3	randomised trials	serious[1]	very serious[2]	no serious indirectness	very serious[3]	none	669	672	-	MD 0.88 lower (2.01 lower to 0.25 higher)	⊕OOO VERY LOW	CRITICAL
Reduction in pain by 50% (follow-up 30 minutes)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	371/547 (67.8%)	66.4%	RR 1.02 (0.94 to 1.11)	13 more per 1000 (from 40 fewer to 73 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Reduction in NRS pain score by >3 (follow-up 30 minutes)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	448/547 (81.9%)	81.8%	RR 1 (0.95 to 1.06)	0 fewer per 1000 (from 41 fewer to 49 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Persistent pain (follow-up 60 minutes)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	131/547 (23.9%)	29.6%	RR 0.81 (0.66 to 0.99)	56 fewer per 1000 (from 3 fewer to 101 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Partial pain relief (follow-up at discharge)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	54/100 (54%)	61%	RR 0.89 (0.7 to 1.12)	67 fewer per 1000 (from 183 fewer to 73 more)	⊕⊕OO LOW	CRITICAL

Complete pain relief (follow-up at discharge/unclear (60 minutes))												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	54/125 (43.2%)	35.5%	RR 1.15 (0.85 to 1.55)	53 more per 1000 (from 53 fewer to 195 more)	⊕OOO VERY LOW	CRITICAL
Need for rescue medication (follow-up 30 minutes)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	98/769 (12.7%)	22.1%	RR 0.55 (0.44 to 0.68)	99 fewer per 1000 (from 71 fewer to 124 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Minor adverse events (unspecified) (follow-up 60 minutes/14 days)												
2	randomised trials	serious[1]	no serious inconsistency	serious[5]	very serious[3]	none	7/572 (1.2%)	0.6%	RR 1 (0.35 to 2.84)	0 fewer per 1000 (from 4 fewer to 11 more)[4]	⊕OOO VERY LOW	CRITICAL
Minor adverse events (vomiting) (follow-up 90 minutes/not reported)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/237 (1.3%)	2.5%	RR 0.47 (0.13 to 1.66)	13 fewer per 1000 (from 22 fewer to 16 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (abdominal pain) (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/40 (5%)	0%	Peto OR 7.58 (0.47 to 123.37)	50 more per 1000 (from 31 fewer to 131 more)[4]	⊕OOO VERY LOW	CRITICAL
Minor adverse events (dizziness) (follow-up not reported)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/197 (0.51%)	1%	Peto OR 0.52 (0.05 to 4.98)	5 fewer per 1000 (from 9 fewer to 38 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (epigastric pain) (follow-up not reported)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/97 (1%)	0%	Peto OR7.54 (0.15 to 380.22)	10 more per 1000 (from 18 fewer to 38 more)[4]	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 or 2 increments because heterogeneity, I2= 94%, p= > 0.1, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Risk difference calculated in Review Manager
[5] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 29: Clinical evidence profile: NSAID versus muscle relaxant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NSAID**	**muscle relaxant/antispasmodic**	**Relative (95% CI)**	**Absolute**		
Pain (VAS, 0-10) (follow-up 40 minutes; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	30	-	MD 1.19 lower (2.51 lower to 0.13 higher)	⊕⊕OO LOW	CRITICAL
Need for rescue medication (follow-up 40-60 minutes)												
2	randomised trials	serious[1]	very serious[3]	no serious indirectness	very serious[2]	none	8/55 (14.5%)	35.3%	RR 0.42 (0.06 to 3.05)	196 fewer per 1000 (from 318 fewer to 693 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (sleepiness)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/55 (0%)	45.1%	Peto OR 0.02 (0.01 to 0.07)	496 fewer per 1000 (from 447 fewer to 506 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Minor adverse events (dizziness)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/30 (0%)	10.3%	Peto OR 0.12 (0.01 to 1.22)	89 fewer per 1000 (from 102 fewer to 20 more)	⊕⊕OO LOW	CRITICAL
Complete pain relief (follow-up 30 minutes)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[4]	no serious imprecision	none	80/100 (80%)	24%	RR 3.33 (2.32 to 4.79)	559 more per 1000 (from 317 more to 910 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 or 2 increments because heterogeneity, I2= 81%, p= > 0.1, unexplained by subgroup analysis
[4] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 30: Clinical evidence profile: NSAID versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NSAID**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Pain (VAS; 0-10) [change & final scores] (follow-up 25 minutes - 10 days; range of scores: 0-10; Better indicated by lower values)												
2	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	none	72	78	-	MD 3.42 lower (6.28 to 0.56 lower)	⊕OOO VERY LOW	CRITICAL
Pain relief (VAS; 0-10) (follow-up 180 minutes; range of scores: 0-10; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 7.8 higher (7.38 to 8.22 higher)	⊕⊕⊕O MODERATE	CRITICAL
Need for rescue medication (follow-up 25 minutes)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/82 (25.6%)	67%	RR 0.39 (0.26 to 0.57)	549 fewer per 1000 (from 387 fewer to 666 fewer)	⊕⊕OO LOW	CRITICAL
No pain relief (follow-up 25 minutes)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/9 (0%)	70%	Peto OR 0.06 (0.01 to 0.36)	577 fewer per 1000 (from 243 fewer to 677 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Partial pain relief (follow-up 25 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/9 (33.3%)	30%	RR 1.11 (0.3 to 4.17)	33 more per 1000 (from 210 fewer to 951 more)	⊕OOO VERY LOW	CRITICAL
Complete pain relief (follow-up 25-30 minutes)												
3	randomised trials	serious[1]	very serious[4]	no serious indirectness	very serious[3]	none	43/72 (59.7%)	35.9%	RR 5.74 (0.61 to 53.9)	284more per 1000 (from 23 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 or 2 increments because heterogeneity, I2= 85%, p= > 0.1, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Downgraded by 1 or 2 increments because heterogeneity, I2= 95%, p= > 0.1, unexplained by subgroup analysis

Table 31: Clinical evidence profile: opioid/opiate versus paracetamol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Opioid**	**Paracetamol**	**Relative (95% CI)**	**Absolute**		
Pain (VAS & NRS, 0-10) [final and change scores] (follow-up 30 minutes; range of scores: 0-10; Better indicated by lower values)												
5	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	none	749	748	-	MD 0.36 higher (0.67 lower to 1.38 higher)	⊕OOO VERY LOW	CRITICAL
Reduction in pain by 50% (follow-up 30 minutes)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	335/549 (61%)	66.4%	RR 0.92 (0.84 to 1)	53 fewer per 1000 (from 106 fewer to 0 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Need for rescue medication (follow-up 30 minutes)												

5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	232/788 (29.4%)	30.9%	RR 1.11 (0.95 to 1.3)	34 more per 1000 (from 15 fewer to 93 more)	⊕OOO VERY LOW	CRITICAL
Reduction in pain NRS score >3 (follow-up 30 minutes)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	429/549 (78.1%)	81.8%	RR 0.96 (0.9 to 1.01)	33 fewer per 1000 (from 82 fewer to 8 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Persistent pain (follow-up 60 minutes)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	207/549 (37.7%)	29.6%	RR 1.28 (1.08 to 1.51)	83 more per 1000 (from 24 more to 151 more)	⊕⊕⊕O MODERATE	CRITICAL
Partial pain relief (follow-up at discharge)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	69/100 (69%)	61%	RR 1.13 (0.92 to 1.39)	79 more per 1000 (from 49 fewer to 238 more)	⊕OOO VERY LOW	CRITICAL
Complete pain relief (follow-up at discharge)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	31/100 (31%)	39%	RR 0.79 (0.54 to 1.16)	82 fewer per 1000 (from 179 fewer to 62 more)	⊕⊕OO LOW	CRITICAL
Minor adverse events (nausea and vomiting) (follow-up time-point not reported)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/84 (11.9%)	10.7%	RR 1.07 (0.46 to 2.46)	7 more per 1000 (from 55 fewer to 149 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (nausea) (follow-up time-point not reported)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/54 (14.8%)	0%	Peto OR 8.5 (2.03 to 35.64)	148 more per 1000 (from 49 more to 245 more)[4]	⊕⊕⊕O MODERATE	CRITICAL
Minor adverse events (vomiting) (follow-up time-point not reported)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/216 (3.7%)	0%	Peto OR 4.99 (1.32 to 18.83)	111 more per 1000 (from 22 more to 200 more)[4]	⊕OOO VERY LOW	CRITICAL
Minor adverse events (unspecified) (follow-up 14 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[5]	serious[3]	none	19/549 (3.5%)	1.3%	RR 2.71 (1.15 to 6.39)	22 more per 1000 (from 2 more to 69 more)	⊕⊕OO LOW	CRITICAL
Minor adverse events (dizziness) (follow-up not reported)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	27/197 (13.7%)	0%	Peto OR 7.61 (3.51 to 16.47)	132 more per 1000 (from 83 more to 181 more)[4]	⊕OOO VERY LOW	CRITICAL
Minor adverse events (urinary retention) (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/49 (2%)	0%	Peto OR 6.95 (0.14 to 350.96)	20 more per 1000 (from 35 fewer to 76 more)[4]	⊕OOO VERY LOW	CRITICAL
Major adverse events (respiratory depression) (follow-up time-point not reported)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/84 (0%)	0/84 (0%)	See comment	0 fewer per 1000 (from 40 fewer to 40 more)[4]	⊕OOO VERY LOW	CRITICAL
Length of stay (discharged within 1 hour) (follow-up 1 hour)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	39/54 (72.2%)	49/54 (90.7%)	RR 0.8 (0.66 to 0.96)	181 fewer per 1000 (from 36 fewer to 309 fewer)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 or 2 increments because heterogeneity, I2= 87%, p= > 0.1, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Risk difference calculated in Review Manager
[5] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

Table 32: Clinical evidence profile: Opioid/opiate versus muscle relaxant/antispasmodic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opioid/opiate	muscle relaxant/antispasmodic	Relative (95% CI)	Absolute		
Pain (VAS, 0-10) (follow-up 20 minutes; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35	33	-	MD 0.22 higher (1.5 lower to 1.94 higher)	⊕OOO VERY LOW	CRITICAL
Pain (complete pain relief) (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/20 (75%)	45%	RR 1.67 (0.96 to 2.88)	301 more per 1000 (from 18 fewer to 846 more)	⊕⊕OO LOW	CRITICAL
Pain (no pain relief) (follow-up not reported)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/55 (14.5%)	15.1%	RR 0.95 (0.40 to 2.23)	7 fewer per 1000 (from 79 fewer to 161 more)	⊕OOO VERY LOW	CRITICAL
Pain (need for rescue medication) (follow-up 20 minutes)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/35 (37.1%)	33.3%	RR 1.11 (0.58 to 2.13)	37 more per 1000 (from 140 fewer to 376 more)	⊕OOO VERY LOW	CRITICAL
Pain (time to pain relief within 5 minutes) (follow-up not reported)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/20 (90%)	50%	RR 1.80 (1.13 to 2.86)	400 more per 1000 (from 65 more to 930 more)	⊕⊕OO LOW	CRITICAL
Pain (time to pain relief) (follow-up not reported; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35	33	-	MD 1.08 higher (5.91 lower to 8.07 higher)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (nausea and vomiting) (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/20 (30%)	25%	RR 1.2 (0.44 to 3.3)	50 more per 1000 (from 140 fewer to 575 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (nausea) (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/35 (2.9%)	0%	Peto OR 6.98 (0.14 to 352.3)	29 more per 1000 (from 48 fewer to 105 more)[3]	⊕OOO VERY LOW	CRITICAL
Minor adverse events (vomiting) (follow-up time-point not reported)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/35 (0%)	3%	Peto OR 0.13 (0 to 6.43)	26 fewer per 1000 (from 30 fewer to 136 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (dizziness) (follow-up 12 hours or not reported)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/55 (27.3%)	9.4%	RR 2.97 (1.25 to 7.06)	227 more per 1000 (from 29 more to 697 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Risk difference calculated in Review Manager

Table 33: Clinical evidence profile: opioid/opiate versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opioid/opiate	placebo	Relative (95% CI)	Absolute		
Pain (30 minutes; VAS 0-10) [change score] (follow-up 30 minutes; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46	51	-	MD 1.3 lower (2.60 lower to 0.00 higher)	⊕⊕OO LOW	CRITICAL
Need for rescue medication (follow-up 30 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24/49 (49%)	66.7%	RR 0.73 (0.52 to 1.04)	180 fewer per 1000 (from 320 fewer to 27 more)	⊕⊕OO LOW	CRITICAL
Major adverse events (respiratory depression) (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/49 (0%)	0%	See comment	0 fewer per 1000 (from 39 fewer to 39 more)[3]	⊕OOO VERY LOW	CRITICAL
Minor adverse events (nausea and vomiting) (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/49 (18.4%)	3.9%	RR 4.68 (1.06 to 20.6)	144 more per 1000 (from 2 more to 764 more)	⊕⊕OO LOW	CRITICAL

Minor adverse events (urinary retention) (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/49 (2%)	0%	Peto OR 7.7 (0.15 to 388.2)	20 more per 1000 (from 34 fewer to 75 more)[3]	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Risk difference calculated in Review Manager

Table 34: Clinical evidence profile: paracetamol versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Paracetamol**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Pain (VAS, 0-10) [change score] (follow-up 30 minutes; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46	51	-	MD 1.6 lower (2.7 to 0.5 lower)	⊕⊕OO LOW	CRITICAL
Need for rescue analgesia (follow-up 30 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/46 (45.7%)	66.7%	RR 0.68 (0.47 to 0.99)	213 fewer per 1000 (from 7 fewer to 354 fewer)	⊕⊕OO LOW	CRITICAL
Major adverse events (respiratory depression) (follow-up time-point not reported)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/46 (0%)	0%	See comment	0 fewer per 1000 (from 40 fewer to 40 more)[3]	⊕OOO VERY LOW	CRITICAL
Minor adverse events (nausea and vomiting) (follow-up 30 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/46 (15.2%)	3.9%	RR 3.88 (0.85 to 17.74)	112 more per 1000 (from 6 fewer to 653 more)	⊕⊕OO LOW	CRITICAL
Minor adverse events (urinary retention) (follow-up time-point not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/46 (0%)	0%	See comment	0 fewer per 1000 (from 40 fewer to 40 more)[3]	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Risk difference calculated in Review Manager

Table 35: Clinical evidence profile: muscle relaxant/antispasmodic versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Muscle relaxant/antispasmodic**	**placebo**	**Relative (95% CI)**	**Absolute**		
Complete pain relief (follow-up 30 minutes)												

1	randomised trials	serious[2]	no serious inconsistency	very serious[1]	no serious imprecision	none	24/100 (24%)	6/100 (6%)	RR 4 (1.71 to 9.36)	180 more per 1000 (from 43 more to 502 fewer)	⊕OOO VERY LOW	CRITICAL
Adverse events (unspecified) (follow-up 30 minutes)												
1	randomised trials	serious[2]	no serious inconsistency	very serious[1]	no serious imprecision	none	84/100 (84%)	1/100 (1%)	RR 84 (11.93 to 591.6)	830 more per 1000 (from 109 more to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 36: Clinical evidence profile: NSAID + muscle relaxant/antispasmodic versus NSAID

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination: NSAID + muscle relaxant versus NSAID**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain intensity (VAS) (follow-up 40 minutes; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	27	30	-	MD 0.5 higher (0.95 lower to 1.95 higher)	⊕OOO VERY LOW	CRITICAL
Need for rescue medication (follow-up 40 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/27 (25.9%)	6.7%	RR 3.89 (0.88 to 17.13)	194 more per 1000 (from 8 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Minor adverse events (dizziness) (follow-up 40 minutes)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/27 (0%)	0%	See comment	0 fewer per 1000 (from 66 fewer to 66 more)[3]	⊕⊕⊕O MODERATE	CRITICAL
Minor adverse events (sleepiness) (follow-up 40 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/27 (0%)	0%	See comment	0 fewer per 1000 (from 66 fewer to 66 more)[3]	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Risk difference calculated in Review Manager

Table 37: Clinical evidence profile: NSAID + muscle relaxant/antispasmodic versus muscle relaxant/antispasmodic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination: NSAID + muscle relaxant versus muscle relaxant**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain intensity (VAS) (follow-up 40 minutes; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27	29	-	MD 0.69 lower (2.22 lower to 0.84 higher)	⊕⊕OO LOW	CRITICAL
Need for rescue medication (follow-up 40 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/27 (25.9%)	44.8%	RR 0.58 (0.27 to 1.23)	188 fewer per 1000 (from 327 fewer to 103 more)	⊕⊕⊕O MODERATE	CRITICAL
Minor adverse events (dizziness) (follow-up 40 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/27 (0%)	10.3%	Peto OR 0.13 (0.01 to 1.35)	90 fewer per 1000 (from 102 fewer to 36 more)	⊕⊕OO LOW	CRITICAL
Minor adverse events (sleepiness) (follow-up 40 minutes)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/27 (0%)	3.5%	Peto OR 0.14 (0 to 7.33)	30 fewer per 1000 (from 35 fewer to 222 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 38: Clinical evidence profile: NSAID + opioid/opiate + muscle relaxant/antispasmodic versus NSAID + opioid/opiate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination: NSAID + opioid + muscle relaxant versus NSAID + opioid	Control	Relative (95% CI)	Absolute		
Pain intensity (VAS) (follow-up 40 minutes; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46	43	-	MD 1.2 lower (2.15 to 0.25 lower)	⊕⊕OO LOW	CRITICAL
Need for rescue medication (follow-up 40 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/46 (15.2%)	32.6%	RR 0.47 (0.21 to 1.05)	173 fewer per 1000 (from 258 fewer to 16 more)	⊕⊕OO LOW	CRITICAL
Minor adverse events (vomiting) (follow-up 40 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/46 (0%)	2.3%	Peto OR 0.13 (0 to 6.38)	20 fewer per 1000 (from 23 fewer to 108 more)	⊕⊕⊕O MODERATE	CRITICAL
Minor adverse events (nausea) (follow-up 40 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/46 (0%)	2.3%	Peto OR 0.13 (0 to 6.38)	20 fewer per 1000 (from 23 fewer to 108 more)	⊕OOO VERY LOW	CRITICAL

Minor adverse events (dizziness) (follow-up 40 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/46 (4.3%)	2.3%	RR 1.87 (0.18 to 19.88)	20 more per 1000 (from 19 fewer to 434 more)	⊕OOO VERY LOW	CRITICAL
Major adverse events (respirator depression) (follow-up 40 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/46 (0%)	0%	See comment	0 fewer per 1000 (from 43 fewer to 43 more)[3]	⊕OOO VERY LOW	CRITICAL
Minor adverse events (sleepiness) (follow-up 40 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/46 (2.2%)	0%	Peto OR 6.92 (0.14 to 349.65)	22more per 1000 (from 38 fewer to 81 more)[3]	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Risk difference calculated in Review Manager

Table 39: Clinical evidence profile: NSAID + opioid/opiate versus NSAID

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination: NSAID + opioid versus NSAID**	**Control**	**Relative (95% CI)**	**Absolute**		
Need for rescue medication (follow-up 40 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/100 (16%)	24%	RR 0.67 (0.38 to 1.18)	79 fewer per 1000 (from 149 fewer to 43 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (nausea) (follow-up not reported)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/100 (2%)	4%	RR 0.5 (0.09 to 2.67)	20 fewer per 1000 (from 36 fewer to 67 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (vomiting) (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/100 (2%)	2%	RR 1 (0.14 to 6.96)	0 fewer per 1000 (from 17 fewer to 119 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (dizziness) (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/100 (3%)	1%	RR 3 (0.32 to 28.35)	20 more per 1000 (from 7 fewer to 273 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 40: Clinical evidence profile: NSAID + opioid/opiate versus opioid/opiate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination: NSAID + opioid versus opioid**	**Control**	**Relative (95% CI)**	**Absolute**		
Need for rescue medication (follow-up 40 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/100 (16%)	20%	RR 0.8 (0.44 to 1.45)	40 fewer per 1000 (from 112 fewer to 90 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (nausea) (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/100 (2%)	4%	RR 0.5 (0.09 to 2.67)	20 fewer per 1000 (from 36 fewer to 67 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (vomiting) (follow-up not reported)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/100 (2%)	4%	RR 0.5 (0.09 to 2.67)	20 fewer per 1000 (from 36 fewer to 67 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (dizziness) (follow-up not reported)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious	none	3/100 (3%)	6%	RR 0.5 (0.13 to 1.94)	30 fewer per 1000 (from 52 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 41: Clinical evidence profile: NSAID + paracetamol versus NSAID

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination NSAID + paracetamol versus NSAID**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain (VAS 0-10) (follow-up 30 minutes; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	25	25	-	MD 1.66 lower (2.82 to 0.5 lower)	⊕OOO VERY LOW	CRITICAL
Need for rescue medication (follow-up 30 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/25 (8%)	8%	RR 1 (0.15 to 6.55)	0 fewer per 1000 (from 68 fewer to 444 more)	⊕OOO VERY LOW	CRITICAL
Complete pain relief (follow-up Unclear (60 minutes))												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20/25 (80%)	32%	RR 2.5 (1.37 to 4.57)	480 more per 1000 (from 118 more to 1000 more)	⊕OOO VERY LOW	CRITICAL

Minor adverse events (unspecified) (follow-up 60 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/25 (0%)	0%	See comment	0 fewer per 1000 (from 75 fewer to 75 more)[3]	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Risk difference calculated in Review Manager

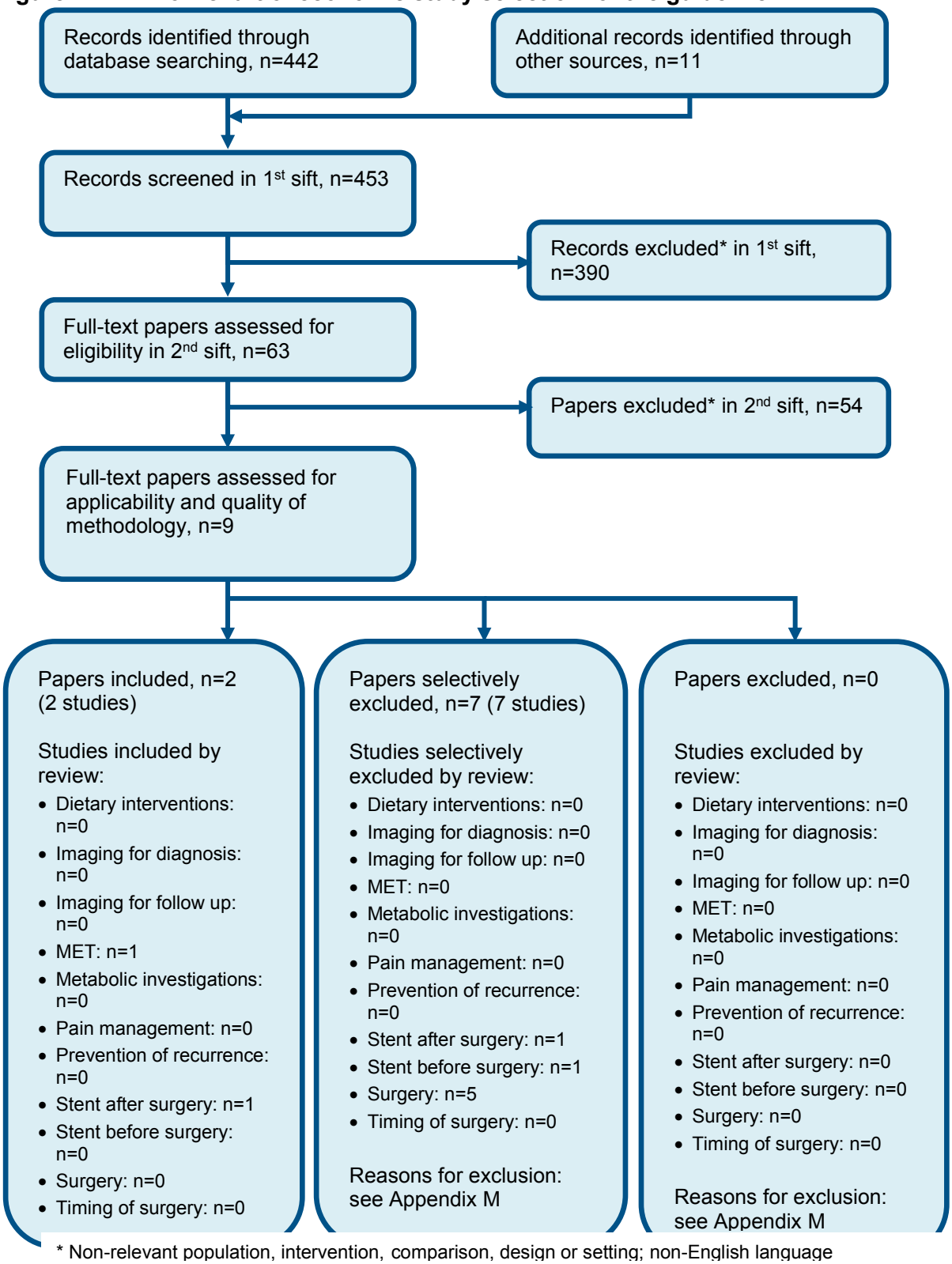
Table 42: Clinical evidence profile: NSAID + paracetamol versus paracetamol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination NSAID + paracetamol versus paracetamol**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain (VAS 0-10) (follow-up 30 minutes; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	25	25	-	MD 2.92 lower (3.94 to 1.9 lower)	⊕OOO VERY LOW	CRITICAL
Need for rescue medication (follow-up 30 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/25 (8%)	24%	RR 0.33 (0.07 to 1.5)	161 fewer per 1000 (from 223 fewer to 120 more)	⊕OOO VERY LOW	CRITICAL
Complete pain relief (follow-up Unclear time time point												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20/25 (80%)	32%	RR 2.5 (1.37 to 4.57)	480 more per 1000 (from 118 more to 1000 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (unspecified) (follow-up 60 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/25 (0%)	0%	See comment	0 fewer per 1000 (from 75 fewer to 75 more)[3]	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Risk difference calculated in Review Manager

Appendix G: Health economic evidence selection

Figure 111: Flow chart of economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 10: Studies excluded from the clinical review

Study	Exclusion reason
Abbasi 2018[1]	Incorrect comparison
Afshar 2015[2]	Review checked for references
Al-Waili 1999[5]	Inappropriate comparison
Anonymous 2009[7]	Incorrect study design
Asgari 2012[8]	Incorrect interventions
Aydogdu 2009[10]	Incorrect interventions
Bahn zobbe 1986[12]	Incorrect interventions
Barry 2016[13]	Abstract only
Basar 1991[14]	Incorrect interventions
Benyajati 1986[16]	Incorrect interventions
Bergus 1996[17]	Abstract only
Boubaker 2010[18]	Incorrect interventions. Inappropriate comparison
Bultitude 2012[19]	Review
Burrows 2017[20]	Incorrect study design
Caravati 1989[21]	Crossover study
Chaudhary 1999[23]	Incorrect interventions
Cohen 1998[24]	Inappropriate comparison
Cordell 1994[26]	Crossover study
Daljord 1983[29]	Not in English
Dash 2012[30]	Incorrect interventions
Dolatabadi 2017[89]	Incorrect comparison
Ebell 2004[32]	Abstract only
Elliott 1979[34]	Inappropriate comparison
El-sherif 1990[33]	Incorrect interventions
Engeler 2005[35]	No relevant outcomes
Erden 2007[36]	Incorrect interventions
Ergene 2001 [37]	Incorrect interventions
Faridaalaee 2016[38]	Incorrect population
Firouzian 2016[39]	Incorrect intervention
Fraga 2003[40]	Incorrect interventions
Galassi 1983[41]	Not in English
Glina 2011[43]	Inappropriate comparison
Gonzalez Ramallo[44]	Not in English
Grissa 2011[45]	Incorrect intervention

Study	Exclusion reason
Hatipoglu 2018[46]	Incorrect population
Hazhir 2010[47]	Incorrect interventions
Holdgate 2004[50]	Systematic review checked for references
Holdgate 2005[49]	Systematic review checked for references
Holmlund 1978[51]	Incorrect study design
Iguchi 2002[54]	Incorrect interventions
Ioannidis 2014[56]	Incorrect interventions
Jones 1998[57]	Incorrect interventions
Jones 2001[58]	Incorrect interventions
Jonsson 1987[59]	Incorrect interventions
Kandaswamy 2015[60]	Incorrect interventions
Kekec 2000[62]	Incorrect interventions
Khalifa 1986[63]	Unclear population including bilharzial ureteral stricture
Kheirollahi 2010[64]	Incorrect interventions
Kromann-Andersen 1987[65]	Not in English
Kumar 2011[66]	Incorrect interventions
Laerum 1995[68]	Incorrect population
Laerum 1996[67]	Inappropriate comparison
Lloret 1987[71]	Incorrect interventions
Lund 1986[72]	Not in English
Lundstam 1982[74]	Incorrect interventions
Lupi 1986[75]	Incorrect interventions. Inappropriate comparison
Maldonado-Avila 2018[77]	Incorrect population
Mankongsrisuk 2017[78]	Incorrect population
Martin Carrasco 1993[80]	Not in English
Miano 1986[82]	Incorrect interventions
Miralles 1987[83]	Incorrect interventions
Montiel-Jarquín Á[84]	Not in English
Mora Durban 1995[85]	Not in English
Mortelmans 2006[86]	No outcomes
Morteza-Bagi 2015[87]	Incorrect interventions
Moustafa 2013[88]	Incorrect population
Muriel 1993[91]	Incorrect interventions
Muriel-Villoria 1995[90]	Incorrect interventions
Nicolas Torralba 1999[94]	Not in English
O'Connor 2000[95]	Inappropriate comparison
Oliveira 2018[96]	Systematic review checked for references
Pathan 2016[99]	Incorrect study design
Pathan 2017[100]	Systematic review checked for references
Pavlik 2004[102]	Incorrect interventions
Payandemehr 2014[103]	Inappropriate comparison
Pellegrino 1999[104]	Not in English
Persson 1985[105]	Incorrect interventions
Phillips 2009[106]	Incorrect interventions
Porena 2004[107]	Review checked for references

Study	Exclusion reason
Porwal 2012[108]	Incorrect interventions
Quilez 1984[109]	Not in English
Roberts 2017[110]	Incorrect population
Romics 2003[111]	Incorrect interventions
Sakr 2017[113]	Incorrect interventions
Sanahuja 1990[115]	Incorrect interventions
Sanchez-Carpena 2003[117]	Incorrect interventions
Sanchez-Carpena 2007[116]	Incorrect interventions
Sen 2017[119]	Incorrect interventions
Sjodin 1983[122]	No relevant outcomes
Slade 1967[123]	Incorrect interventions. Inappropriate comparison
Soleimanpour 2012[125]	Incorrect interventions
Sommer 1989[126]	No extractable outcomes
Stein 1996[129]	Inappropriate comparison
Supervia 1998[130]	Inappropriate comparison
Torchi 1983[132]	Incorrect interventions
Uden 1983[133]	Incorrect interventions
Walden 1993[135]	Inappropriate comparison
Warren 1985[136]	Incorrect interventions
Wolfson 1991[137]	Incorrect study design
Wood 2000[138]	Incorrect interventions
Xue 2013[139]	Incorrect interventions
Yakoot 2014[140]	Incorrect interventions
Yencilek [141]	Incorrect population
Ziapor 2017[143]	Incorrect comparison

I.2 Excluded health economic studies

None

Appendix J: Research recommendations

J.1 Non-steroidal anti-inflammatory drug route of administration

Research question: What is the most clinically and cost effective route of administration for NSAID in the management of acute pain thought to be due to renal or ureteric stones?

Why this is important:

People with renal and ureteric stones may suffer repeated episodes of severe acute pain. A review of the literature has demonstrated that Non-Steroidal Anti Inflammatory Drugs (

NSAID) are effective at treating this pain however existing evidence is mixed and uses agents, formulations and methods of administration not used in the UK.

People with renal colic present to A and E departments and receive a wide range of treatments which may not be evidence based and may result in additional use of opiate agents.

If a NSAID was demonstrated to be effective which could be given in primary care or by the patient themselves this would improve pain management and reduce unplanned hospital admissions and A and E attendances.

Criteria for selecting high-priority research recommendations:

PICO question	**Population**: Adults presenting to hospital with acute pain suspected to be related to renal or ureteric stones **Intervention**: • NSAID agent given orally, rectally, intramuscularly or intravenously in recommended doses for acute pain **Comparisons**: • compared with each other **Outcomes**: • Effectiveness of pain control • Use of additional agents • Duration of time to pain control • Use of hospital and primary care services, time in A and E and hospital admissions • Cost effectiveness
Importance to patients or the population	This would enable patients to receive the most effective treatment given in the most efficient way. In the long term this may enable better treatment to be given in the community and reduce the need for hospital and primary care attendance
Relevance to NICE guidance	This study would develop a strong evidence base for the most effective treatment of the condition and improve the strength of the recommendations given in a new guideline.
Relevance to the NHS	This may reduce the need for the use of hospital and primary care services. If the treatment is shown to be effective it may also reduce the long term risk of opiate analgesia in those with repeated episodes of pain.
National priorities	None.
Current evidence base	The current evidence base includes a majority of studies which are not based in the UK, they use agents which are not used in the NHS and include only small numbers of patients
Equality	None.
Study design	A randomised controlled trial comparing the effects of a single agent given at recommended doses for acute pain and given either orally, rectally, intravenously, or intramuscularly. The gold standard trial would be double blind with each patient receiving 1 active agent and 3 placebos. This would eliminate the high placebo effect of having a more invasive treatment such as an injection or suppository rather than oral treatment. This may not be practical and a more real world study would be patients randomised to active treatment only. This would accept the fact some of

	the benefits of the invasive treatments is related to the mode of administration.
Feasibility	This research could be effectively run in centres with large A and E Units with urological units with an interest in the management of ureteric stones
Other comments	None.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline. This research would determine future pathways for the management of people with renal and ureteric stones

1