National Institute for Health and Care Excellence

Final

Intrapartum care

[E] Evidence reviews for programmed intermittent epidural bolus

NICE guideline NG235

Evidence reviews underpinning recommendation 1.6.41 in the NICE guideline

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Final

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Programmed intermittent epidural bolus

Review question

What is the effectiveness of programmed intermittent epidural bolus compared to other methods of maintaining epidural analgesia?

Introduction

Use of epidural injections (containing a mixture of local anaesthetic and an opioid) are commonly used during labour to provide pain relief. After an epidural is sited, analgesia is maintained using a continuous epidural infusion (CEI) through a pump, or via intermittent boluses given by a healthcare professional. Some pumps have the facility for patient administered epidural analgesia, either alone, or more commonly in combination with CEI. This is known as patient controlled epidural analgesia (PCEA). More recently, epidural pumps have been manufactured that are able to deliver a programmed intermittent epidural bolus (PIEB). PIEB may either be used alone, with CEI or PCEA, or in combination with both CEI and PCEA.

The aim of this review was to determine if PIEB provides safe and effective maintenance of epidural analgesia in women in labour.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	• Women in labour who are pregnant with a single baby, who go into labour at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk birth • Women who are having their labour induced • Women who have had a previous caesarean birth • Women in labour whose baby has not been identified before labour to be at high risk of adverse outcomes • Singleton babies born at term (37 to 42 weeks of pregnancy) with no previously identified problems (for example congenital malformations, genetic anomalies, intrauterine growth restriction, placental problems) • Women who have received epidural or combined spinal–epidural analgesia to establish regional analgesia in labour
Intervention	The following interventions in combination with bupivacaine plus opioid: • Programmed intermittent epidural bolus • Programmed intermittent epidural bolus in combination with PCEA • Programmed intermittent epidural bolus with continuous background infusion

Comparison	• Continuous epidural infusion • Intermittent epidural bolus (given by healthcare professional) • PCEA only • PCEA with continuous background infusion
Outcome	**Critical** • Anaesthetist re-attendance for breakthrough pain • Motor block • General labour pain **Important** • Duration of labour • Mode of birth (spontaneous vaginal, instrumental vaginal, caesarean birth) • Neonatal admission (includes NICU and SCBU) • Women's experience of labour and birth

NICU: neonatal intensive care unit; PCEA: patient controlled epidural analgesia; SCBU: special care baby unit

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Fifteen studies were included for this review. Fourteen were randomised controlled trials (RCTs) (Bourges 2021, Capogna 2011, Chalekar 2022, Diez-Picazo 2019, Ferrer 2017, Fidkowski 2019, Haidl 2020, Meena 2022, Morau 2019, Nunes 2016, Rodriguez-Campoo 2019, Roofthooft 2020, Song 2021 and Wong 2006) and 1 was a systematic review (SR) (Huang 2021). The SR had 9 RCTs included (Chua 2004, Fan 2019, Fettes 2006, Leo 2010, Lim 2010, Lin 2016, Ojo 2020, Sia 2007 and Sia 2013).

Three studies (Bourges 2021, Meena 2022 and Roofthooft 2020) compared PIEB in combination with PCEA to PCEA alone. Eleven studies (Capogna 2011, Fan 2019, Haidl 2020, Leo 2010, Lin 2016, Morau 2019, Ojo 2020, Sia 2007, Sia 2013, Song 2021 and Wong 2006) compared PIEB in combination with PCEA to CEI in combination with PCEA. Six studies (Chalekar 2022, Chua 2004, Fetter 2006, Ferrer 2017, Fidowksi 2019 and Lim 2010) compared PIEB to CEI. Two studies (Diez-Picazo 2019 and Rodriguez-Campoo 2019) compared PIEB in combination with PCEA and CEI to PCEA in combination with CEI. One study (Nunes 2016) compared PIEB to CEI in combination PCEA.

The studies were from Belgium, China, Colombia, France, Italy, India, Norway, Portugal, Scotland, Singapore, Spain and the United States.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes
Bourges 2021 Randomised controlled trial France	N=457 women Nulliparous BMI – mean (SD): Intervention: 24 (5) Comparison: 24 (6)	PIEB + PCEA Epidural maintenance solution: 0.0625% levobupivacaine anaesthetic with sufentanil PIEB pump programmed to deliver 8ml bolus epidural solution every 60 minutes. PCEA boluses of 8ml also available, without a lockout period of 8 minutes.	PCEA Epidural maintenance solution: 0.0625% levobupivacaine anaesthetic with sufentanil PCEA boluses of 8ml epidural solution with a lockout period of 8 minutes.	• Anaesthetist re-attendance for breakthrough pain • Motor block • Duration of labour • Mode of birth: Instrumental birth; caesarean birth • Women's experience of labour and birth
Capogna 2011 Randomised controlled trial Italy	N=150 women Nulliparous BMI not reported	PIEB + PCEA Epidural maintenance solution: 0.0625% levobupivacaine with sufentanil. PIEB pump programmed to deliver 10ml bolus epidural solution every 60minutes. PCEA boluses also available to deliver 5ml of 0.125% levobupivacine with a lockout	CEI + PCEA Epidural maintenance solution: 0.0625% levobupivacaine with sufentanil. CEI pump programmed to deliver epidural solution at a rate of 10ml/hour. PCEA boluses also available to deliver 5ml of 0.125% levobupivacine with a lockout period of 10 minutes	• Anaesthetist re-attendance for breakthrough pain • Motor block • Duration of labour • Mode of birth: instrumental birth; caesarean birth

Study	Population	Intervention	Comparison	Outcomes
		period of 10 minutes.		
Chalekar 2022 Randomised controlled trial India	N=60 women Parity not reported BMI healthy weight range – means not reported	PIEB Epidural maintenance solution: 0.15% ropivacaine with fentanyl. PIEB pump programmed to deliver 8ml bolus every hour.	CEI Epidural maintenance solution: 0.15% ropivacaine with fentanyl. CEI pump administered epidural infusion at a rate of 8 ml/hour.	• Anaesthetist re-attendance for breakthrough pain • Motor block • General labour pain • Duration of labour • Mode of birth: spontaneous vaginal birth; instrumental birth; caesarean birth • Women's experience of labour and birth
Diez-Picazo 2019 Randomised controlled trial Spain	N=120 women Nulliparous women BMI – mean (SD): Intervention: 28 (5) Comparison: 28 (4)	PIEB + PCEA + CEI Epidural maintenance solution: 0.125% levobupivacaine with fentanyl. PIEB pump programmed to deliver 10ml bolus epidural solution every 60 minutes. CEI pump administered a background epidural infusion at a rate of 5ml/hour. PCEA boluses of 10ml epidural solution were also available. A 20 minute lockout period was configured between PIEB/PCEA boluses.	PCEA + CEI Epidural maintenance solution: 0.125% levobupivacaine with fentanyl. CEI pump administered a background epidural infusion at a rate of 5ml/hour. PCEA boluses of 10ml epidural solution were also available. A 20 minute lockout period was configured between PCEA boluses.	• Anaesthetist re-attendance for breakthrough pain • Motor block • General labour pain • Duration of labour • Mode of birth: spontaneous vaginal birth; instrumental birth; caesarean birth • Women's experience of labour and birth
Ferrer 2017 Randomised controlled trial Colombia	N= 132 women Mixed parity BMI – mean (SD) Intervention: 31.6 (5.1)	PIEB Epidural maintenance solution: 0.1% bupivacaine with fentanyl.	CEI Epidural maintenance solution: 0.1% bupivacaine with fentanyl.	• Anaesthetist re-attendance for breakthrough pain • Motor block • General labour pain

Study	Population	Intervention	Comparison	Outcomes
	Comparison: 32.3 (3.8)	PIEB pump programmed to deliver 10ml bolus of epidural solution every 60minutes.	CEI pump programmed to deliver epidural solution at rate of 10ml/hour.	• Duration of labour • Mode of birth: spontaneous vaginal birth; instrumental birth; caesarean birth • Women's experience of labour and birth
Fidkowski 2019 Randomised controlled trial United States	N=150 women Mixed parity BMI – mean (SD): Intervention: 36 (7.6) Comparison: 36 (10)	<u>PIEB</u> Epidural maintenance solution: 0.125% bupivacaine with fentanyl. PIEB pump programmed to deliver 5ml bolus of epidural solution every 30 minutes, or 10ml bolus every 60minutes. 3-arm study with 2 PIEB intervention arms: 5ml/30mins or 10ml/60mins. PIEB arms were combined.	<u>CEI</u> Epidural maintenance solution: 0.125% bupivacaine with fentanyl. CEI pump programmed to deliver epidural solution at a rate of 10ml/hour.	• Anaesthetist re-attendance for breakthrough pain • Motor block • General labour pain • Duration of labour • Mode of birth: spontaneous vaginal birth; caesarean birth • Women's experience of labour and birth
Haidl 2020 Randomised controlled trial Norway	N=151 women Mixed parity BMI not reported	<u>PIEB + PCEA</u> Epidural maintenance solution: 0.1% bupivacaine with fentanyl. PIEB pump was programmed to deliver 5ml bolus of epidural solution every 60 minutes. Option for PCEA bolus of epidural solution at 5ml with a lockout time of 20 minutes.	<u>CEI + PCEA</u> Epidural maintenance solution: 0.1% bupivacaine with fentanyl. CEI pump programmed to deliver epidural solution at a rate of 5ml/hour. Option for PCEA bolus of epidural solution at 5ml with a lockout time of 20 minutes.	• Anaesthetist re-attendance for breakthrough pain • Motor block • General labour pain • Duration of labour • Mode of birth: spontaneous vaginal birth; instrumental birth; caesarean birth • Women's experience of labour and birth

Study	Population	Intervention	Comparison	Outcomes
Huang 2021 Cochrane systematic review China, Scotland, Singapore, United States	K=9 (Chua 2004, Fan 2019, Fettes 2006, Leo 2010, Lim 2010, Lin 2016, Ojo 2020, Sia 2007, Sia 2013) N=3532 Mixed parity BMI: Not reported for PIEB versus CEI. Fan 2019 Intervention: 26 (2.6) Comparison: 25.9 (2.8) Leo 2019 Intervention: 26.6 (3.1) Comparison: 27.4 (4.2) Lin 2016 Intervention: 28.35 (1.42) Comparison: 28.54 (1.51) Ojo 2020 Intervention: 32.9 (7.0) Comparison: 32.6 (7.2) Sia 2013 Intervention: 27.3 (3.9) Comparison: 28.2 (4.9)	PIEB (Chua 2004, Fettes 2006, Lim 2010) Epidural maintenance solution: • 0.1% ropivacaine and fentanyl • 0.2% ropivacaine and fentanyl Programme: • 5ml bolus every 60 minutes • 10 ml bolus every 60 minutes • 2.5ml bolus every 60 minutes	CEI (Chua 2004, Fettes 2006, Lim 2010) Epidural maintenance solution: • 0.1% ropivacaine and fentanyl • 0.2% ropivacaine and fentanyl Programme: Epidural solution administered at a rate of: • 5ml/hour • 10ml/hour	• Anaesthetist re-attendance for breakthrough pain • Motor block • General labour pain • Duration of labour • Mode of birth: spontaneous vaginal birth; instrumental birth; caesarean birth • Women's experience with labour and birth
		PIEB + PCEA (Fan 2019, Leo 2010, Lin 2016, Ojo 2020, Sia 2007, Sia 2013) Epidural maintenance solution: • 0.1% ropivacaine and fentanyl/sufentanil • 0.8% ropivacaine and fentanyl Programme: • 5ml bolus every hour, with an option for PCEA 5ml bolus with 10/20 minute lockout • 6ml bolus every 45 minutes with option for	CEI + PCEA (Fan 2019, Leo 2010, Lin 2016, Ojo 2020, Sia 2007, Sia 2013) Epidural maintenance solution: • 0.1% ropivacaine and fentanyl/sufentanil • 0.8% ropivacaine and fentanyl Programme: Epidural solution infused at a rate of: • 5ml/hour, option for PCEA 5ml bolus with 10/20 minute lockout • 8ml/hour, option for PCEA 8ml bolus with 10 minute lockout	• Anaesthetist re-attendance for breakthrough pain • Motor block • General labour pain • Duration of labour • Mode of birth: spontaneous vaginal birth; instrumental birth; caesarean birth • Women's experience with labour and birth

Study	Population	Intervention	Comparison	Outcomes
		PCEA 8ml bolus with 10 minute lockout • 10ml bolus every hour with option for PCEA 5ml bolus with 30minute lockout	• 10ml/hour, option for PCEA 5ml bolus with 30 minute lockout	
Meena 2022 Randomised controlled trial India	N=50 Primigravid BMI overweight range	<u>PIEB + PCEA</u> Epidural maintenance solution: 0.1% levobupivacaine with fentanyl PIEB pump was programmed to deliver 5ml bolus of epidural solution every 60 minutes. PCEA bolus of 5ml was available.	<u>PCEA</u> Epidural maintenance solution: 0.1% levobupivacaine with fentanyl PCEA bolus of 5ml was available with 15 minutes lockout.	• Duration of labour • Mode of birth: spontaneous vaginal birth; instrumental vaginal birth • Women's experience with labour and birth
Morau 2019 Randomised controlled trial France	N=298 women Nulliparous BMI not reported	<u>PIEB + PCEA</u> Epidural maintenance solution: 0.1% levobupivacaine with sufentanil. PIEB pump was programmed to deliver 8ml bolus of epidural solution every 60 minutes. PCEA boluses of 8ml available, with a minute refractory period and a maximum hourly dose of 24ml. 10 minute refractory period	<u>CEI + PCEA</u> Epidural maintenance solution: 0.1% levobupivacaine with sufentanil. CEI pump programmed to deliver epidural solution at a rate of 8ml/hour. PCEA boluses of 8ml available, with a minute refractory period and a maximum hourly dose of 24ml.	• Anaesthetist re-attendance for breakthrough pain • Motor block • General labour pain • Duration of labour • Mode of birth: spontaneous vaginal birth; instrumental birth • Women's experience with labour and birth

Study	Population	Intervention	Comparison	Outcomes
		also programmed between PIEB and PCEA boluses.		
Nunes 2016 Randomised controlled trial Portugal	N=166 women Mixed parity BMI not reported Twin pregnancy - number: PIEB 0.1%: 0 PIEB 0.15%: 3 CEI: 1	<u>PIEB</u> Epidural maintenance solution: 0.1% or 0.15% ropivacaine with sufentanil. PIEB pump programmed to deliver 10ml bolus of epidural solution every 60minutes. 3-arm study with 2 intervention arms. Concentration of anaesthetic in each PIEB arm differed.	<u>CEI + PCEA</u> Epidural maintenance solution: 0.15% ropivacaine with sufentanil. CEI pump programmed to deliver epidural solution at a rate of 5ml/hour. PCEA bolus available at 5ml epidural solution with a lockout period of 20 minutes.	• Motor block • Mode of birth: spontaneous vaginal birth; instrumental birth; caesarean birth • Women's experience of labour and birth
Rodriguez-Campoo 2019 Randomised controlled trial Spain	N=200 women Primiparous BMI not reported	<u>PIEB + PCEA + CEI</u> Epidural maintenance solution: 0.0625% levobupivacaine with fentanyl. PIEB pump programmed to deliver 7ml bolus epidural solution every 30 minutes. CEI pump programmed to deliver epidural solution at a rate of 2ml/hour. PCEA bolus of 6ml epidural solution also available every 20 minutes. PIEB dose delated if PCEA was administered.	<u>CEI + PCEA</u> Epidural maintenance solution: 0.0625% levobupivacaine with fentanyl. CEI pump programmed to deliver epidural solution at a rate of 5ml/hour. PCEA bolus of 6ml epidural solution also available every 20 minutes.	• General labour pain • Instrumental birth • Women's experience of labour and birth

Study	Population	Intervention	Comparison	Outcomes
Roofthooft 2020 Randomised controlled trial Belgium	N=130 women Nulliparous BMI not reported	PIEB + PCEA Epidural maintenance solution: ropivacaine 0.12% with sufentanil. PIEB pump was programmed to deliver 10ml bolus epidural solution every 60 minutes. 5ml PCEA bolus of epidural solution also available with a 20 minutes lockout period.	PCEA Epidural maintenance solution: ropivacaine 0.12% with sufentanil. 5ml PCEA bolus of epidural solution with 12 minute lockout period.	• Anaesthetist re-attendance for breakthrough pain • Motor block • General labour pain • Duration of labour • Mode of birth: instrumental vaginal birth, caesarean birth • Women's experience of labour and birth
Song 2021 Randomised controlled trial China	N=120 Nulliparous BMI: Intervention: 25.7 (3.00) Comparison: 26.3 (3.12)	PIEB + PCEA Epidural maintenance solution: 0.1% ropivacaine with sufentanil. PIEB pump programmed to deliver 8 ml bolus of epidural solution every 60 minutes. 5ml PCEA bolus of epidural solution also available with 20 minutes lockout period.	CEI + PCEA Epidural maintenance solution: 0.1% ropivacaine with sufentanil. CEI pump programmed to administer epidural solution at a rate of 8ml/hour. 5ml PCEA bolus of epidural solution also available with 20 minutes lockout period 3-arm study with 2 comparison arms combined. CEI in both arms but different epidural techniques (dural puncture epidural or conventional epidural).	• Anaesthetist re-attendance for breakthrough pain • Motor block • General labour pain • Duration of labour • Mode of birth: spontaneous vaginal birth, instrumental birth, caesarean birth. • Women's experience with labour and birth
Wong 2006 Randomised controlled trial	N=158 women Mixed parity BMI not reported	PIEB + PCEA Epidural maintenance solution:	CEI + PCEA Epidural maintenance solution: 0.0625%	• Anaesthetist re-attendance for breakthrough pain • Motor block

Study	Population	Intervention	Comparison	Outcomes
United States		0.0625% bupivacaine with fentanyl. PIEB pump programmed to deliver 6ml bolus of epidural solution every 30minutes. 5ml PCEA bolus available with a lockout period of 10 minutes.	bupivacaine with fentanyl. CEI pump programmed to deliver epidural solution at a rate of 12ml/hour. 5ml PCEA bolus available with a lockout period of 10 minutes.	• General labour pain • Duration of labour • Mode of birth: spontaneous vaginal birth, instrumental birth, caesarean birth • Women's experience with labour and birth

BMI: body mass index; CEI: continuous epidural infusion; PCEA: patient controlled epidural analgesia; PIEB: programmed intermittent epidural bolus; SD: standard deviation

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

Across all the comparisons identified, there were generally no important differences, or no evidence of an important difference, between the interventions for general labour pain, duration of labour or mode of birth, although this varied depending on the concentration of the anaesthetic and the type of opioid used. There were some benefits of PIEB combined with PCEA, compared to PCEA alone and for PIEB compared to CEI, in terms of anaesthetist re-attendance for breakthrough pain, or motor block.

PIEB + PCEA versus PCEA

PIEB in combination with PCEA showed an important benefit over PCEA alone in terms of anaesthetist re-attendance for breakthrough pain, and motor block. However, the benefit varied depending on the concentration of anaesthetic. Data for general labour pain was reported as median data. There were generally no important differences between groups, although some of the data showed higher pain in the PCEA only group. There were no important differences between groups in terms of duration of labour. There was no evidence of an important difference between groups on mode of birth, and no important differences between groups in terms of women's experience with labour and birth. Most of the evidence was very low quality due to concerns around indirectness due to the anaesthetic used, and imprecision. Some of the evidence was also downgraded for risk of bias with concerns around non-blinded subjective reporting of outcomes. Only some of the evidence was rated low and moderate quality.

PIEB + PCEA versus CEI + PCEA

Some of the evidence showed an important benefit for PIEB in combination with PCEA over CEI in combination with PCEA, in terms of anaesthetic re-attendance for breakthrough pain and motor block. The evidence varied depending on the concentration of anaesthetic, and the body mass index (BMI) range, however a clear pattern could not be established.

Most of the evidence for this comparison showed no important differences, or no evidence of an important difference in terms of general labour pain using a range of different anaesthetic concentrations, and at different BMI ranges. Some of the evidence at the later stages of labour showed a benefit favouring PIEB in combination with PCEA. Most of the evidence also showed no important difference or no evidence of an important difference in terms of duration of labour for this comparison. However some of the evidence showed an important

benefit for PIEB in combination with PCEA for the duration of the second stage, when compared to CEI in combination with PCEA.

In terms of mode of birth, most of the evidence showed no important difference or no evidence of an important difference between groups, however there was some evidence showing a benefit for PIEB in combination with PCEA in terms of instrumental births.

Most of the evidence on women's experience of labour and birth was reported as median data. Most of the evidence showed no important difference between groups, with some of the evidence showing no evidence of an important difference. There was some evidence showing a benefit for PIEB in combination with PCEA in terms of women's experience of labour and birth.

The quality of the evidence ranged from very low to high, with the majority of the evidence of very low to low quality. The main concerns were around imprecision, and indirectness due to the anaesthetic used.

PIEB versus CEI

PIEB alone was compared to CEI alone. The evidence was mixed in terms of anaesthetist reattendance for breakthrough pain and motor block, with some of the evidence showing an important benefit for PIEB, and some showing no evidence of an important difference between groups. The evidence varied by anaesthetic concentration and BMI range, however there was not a clear trend.

Some of the evidence on general labour pain showed an important benefit for PIEB over CEI, however most of the evidence showed no important differences between groups, or no evidence of an important difference. The evidence did not show a clear trend by anaesthetic concentration, or BMI range, however the benefits were mainly seen towards the end of labour.

Some of the evidence showed an important benefit for PIEB in terms of duration of labour, however most of the evidence showed no important differences or no evidence of an important between groups for this outcome.

Most of the evidence for mode of birth showed no evidence of an important difference, with some of the evidence showing no important differences between groups. Most of the evidence for women's experience with labour and birth showed no important differences between groups, or no evidence of an important difference, but there was some evidence showing an important benefit for PIEB over CEI.

The quality of the evidence ranged for very low to high, with most of the evidence of very low to low quality. The main concerns were around imprecision and indirectness due to the anaesthetic used. There were some concerns around the risk of bias for some outcomes.

PIEB + PCEA + CEI versus PCEA + CEI

PIEB in combination with PCEA and CEI was compared to PCEA in combination with CEI. The evidence showed no important differences or no evidence of an important difference between groups for anaesthetist re-attendance for breakthrough pain, motor block, general labour pain, duration of labour or women's experience with labour and birth.

Most of the evidence showed no evidence of an important difference between groups for modes of birth. There was an exception for instrumental births, where some of the evidence showed a possible important harm for PIEB in combination with PCEA and CEI over PCEA and CEI alone.

The evidence was mostly very low to low quality, with some evidence at moderate quality. All of the evidence was downgraded for indirectness due to anaesthetic used, and most of the

evidence was downgraded due to concerns around imprecision. Some of the evidence was also downgraded for bias due to unexplained missing data.

PIEB versus CEI + PCEA

PIEB was compared to CEI in combination with PCEA. There was no evidence of an important difference between groups in terms of motor block or women's experience of labour and birth.

In terms of mode of birth, there was no evidence of an important difference between groups for spontaneous vaginal births. The evidence showed a harm for PIEB alone in terms of instrumental births, but a possible important benefit in terms of caesarean births. All of the evidence was very low quality with concerns around indirectness due to the type of anaesthetic used, and also risk of bias due to not blinding participants. There were also concerns around imprecision.

There was no evidence identified for neonatal admission for any of the comparisons.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Economic model

This review was initially prioritised for economic modelling but ultimately no economic modelling was undertaken for this review. The clinical evidence gave mixed results and could not be readily synthesised. Furthermore, the committee noted that modern pumps are adaptable to any method of maintaining epidural analgesia and therefore it was decided that recommendations were unlikely to have a significant resource impact.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee agreed that anaesthetist re-attendance for breakthrough pain was a critical outcome for this review, as it would be an indicator of the effectiveness of the analgesia at maintaining pain relief without additional intervention from the anaesthetist. They also agreed that motor block was a critical outcome, as this is an important side-effect of epidural analgesia which can impair a woman's ability to move around during labour and push during the second stage of labour. They agreed that it would be useful to find out which method of maintaining analgesia provided effective pain relief, without leading to excessive motor block. The committee also prioritised general labour pain as a critical outcome as it directly provides information on the effectiveness of the method of maintaining analgesia for pain relief.

The committee also chose important outcomes for the review. They agreed duration of labour was an important outcome as epidural analgesia may increase the length of labour and they wanted to identify if this was more or less of a problem with PIEB compared to other methods of administration. They also chose mode of birth as an important outcome to find out whether a different method of maintaining epidural analgesia led to an increase in the number of women requiring a caesarean birth or vaginal birth with forceps or ventouse. The committee also wanted to find out whether there was any impact on the neonate and chose neonatal admission to identify this. The committee also wanted to explore women's

experience during labour and whether the method of maintaining epidural analgesia had an impact on this. The committee recognised the great importance of women's experience, but they were aware that data on this outcome was likely to be sparse and unlikely to inform decision-making in a meaningful way, so they prioritised other outcomes as critical.

The quality of the evidence

The quality of the evidence ranged from high to very low, with most of the evidence of moderate to very low quality, and only 4 outcomes rated as high quality. The evidence was mainly downgraded for indirectness, as levobupivacaine or ropivacaine were used rather than bupivacaine, and also mainly downgraded for imprecision around the estimate of effect. There were also concerns around risk of bias due to unexplained missing data for some of the evidence, and also concerns around not blinding in some of the evidence.

Some of the studies were funded by industry, or pumps were provided by industry. This is unlikely to have an impact on the outcomes specified in protocol, and there are no concerns around bias. For more detail please see the evidence tables in appendix D.

Benefits and harms

The committee discussed that the quality of most of the evidence was rated as low to very low, with most of the concerns around imprecision, and also indirectness due to the use of anaesthetics other than bupivacaine. The committee agreed that although bupivacaine, the anaesthetic specified in the protocol, and is most commonly used in UK practice, they could still use the evidence on other anaesthetics to guide recommendations for the best method of maintaining epidural analgesia, as levobupivacaine and ropivacaine were used in some units. The committee discussed that the studies had used fentanyl and sufentanil – fentanyl was used in the UK as sufentanil is not available (it does not have a marketing authorisation in the UK), but the drugs were closely related and again the committee agreed that the evidence on sufentanil could still be used in their overall evaluation of the evidence. The committee agreed that it was the mode of birth which was more important than the actual drugs used in terms of the review goals of what was safe and effective.

The committee discussed that in practice PIEB can be used alone, or in combination with a PCEA or a CEI, and that these combinations were well represented in the evidence. They agreed that in practice PIEB would most commonly be used in combination with PCEA, wherever it was available.

The committee discussed that there was evidence of benefit for PIEB as a method of maintaining epidural analgesia for some outcomes. However, they also noted that for those same outcomes there was additional evidence from different studies that showed no differences between intervention and comparison groups. The committee looked to the subgroup analyses for any trends or patterns to explain this variation, however, the analyses by concentration of anaesthetic, type of opioid or BMI range of the women did not provide an explanation for the differences in effect across the different studies included for the same comparison. There was also insufficient information in the evidence to inform the subgroup analysis for age of woman, ethnicity, disability, deprived socioeconomic group, country income status. The committee did however agree that as the benefit of PIEB across some of the studies and comparisons was not limited to a particular BMI range, PIEB could be beneficial for women across any BMI range.

The committee discussed that most of the benefits of PIEB across the evidence were in terms of a reduced need for anaesthetist re-attendance for breakthrough pain and reduced motor block. They discussed the benefits of fewer re-attendances in terms of hospital resources and staff workload, which may also reduce the possibility of women waiting in pain for re-attendance. They also discussed that less motor block would be related to a better experience for women in labour, and would allow greater mobility. However, the committee

acknowledged that not all of the evidence showed benefit for these outcomes. The committee discussed that the different regimes of PIEB, and the use of a PCEA in some comparisons, may explain the variation in the evidence. They considered that the volume of anaesthetic delivered could vary between studies due to the different PIEB regimes, and that the number of PCEA boluses may be different because of varying pain thresholds among women. Therefore, some of the benefits seen in the evidence could be a result of a higher volume of anaesthetic delivered, however the committee warned that, according to their clinical experience, this could be associated with a higher degree of motor block and extended labour. The committee discussed that this factor would have been very difficult to control for especially since the option of PCEA is widely available in current practice.

The committee discussed that most of the evidence showed no difference between PIEB (alone or in combination) compared to other methods of maintaining epidural analgesia in terms of general labour pain and duration of labour. There was the exception with some of the evidence showing a benefit in terms of pain at the later stages in labour, but this was not consistent throughout the evidence. The committee again discussed varying pain thresholds among women, the option of a PCEA, and the different regimens of PIEB, and as such agreed that they could not make a clear conclusion regarding PIEB and the effects on general labour pain and duration of labour.

The committee discussed modes of birth and noted that most of the evidence showed no differences between PIEB (alone or in combination) compared to other methods of maintaining epidural analgesia. However, they acknowledged that some of the evidence showed that PIEB was associated with a harm in terms of more births with forceps or ventouse, but also a benefit of fewer caesarean births. They discussed that this was not consistent across all the comparisons including PIEB. Finally, the committee noted that there was some evidence in favour of PIEB in terms of women's experience of labour and birth.

The committee agreed it was important to consider the possible harms associated with PIEB, compared to the benefits seen in the evidence in terms of anaesthetist reattendance for breakthrough pain and motor block. Overall, the committee agreed that PIEB should be offered as an additional option to women alongside the existing recommendation on methods of maintaining epidural analgesia. Taking into consideration that there was some harm in terms of increased number of births with forceps or ventouse with PIEB, the committee agreed that PIEB was not more favourable than other methods of maintaining epidural analgesia and included PIEB as an option but did not recommend that PIEB should be used over methods already recommended for maintaining epidural analgesia.

Cost effectiveness and resource use

Whilst there was some evidence of benefit for PIEB this was not found in all studies. However, the committee noted that PIEB would not require new pumps as modern pumps could deliver all methods of maintaining epidural analgesia and therefore, they did not consider there would be a significant resource impact from a recommendation to support the use of PIEB. Based on the available evidence it was not possible for the committee to determine whether PIEB was more or less cost effective than alternative methods and therefore concluded that it was reasonable for PIEB to be added to the methods that could be recommended.

Recommendations supported by this evidence review

This evidence review supports recommendation 1.6.41.

References – included studies

Effectiveness

Bourges 2021

Bourges, Jennifer, Gakuba, Clement, Plass, Felipe et al. (2021) Effect of patient-controlled epidural analgesia with and without automatic intermittent bolus on levobupivacaine consumption during labour: A single centre prospective double-blinded randomised controlled study. Anaesthesia, critical care & pain medicine: 100936

Capogna 2011

Capogna, Giorgio, Camorcia, Michela, Stirparo, Silvia et al. (2011) Programmed intermittent epidural bolus versus continuous epidural infusion for labor analgesia: the effects on maternal motor function and labor outcome. A randomized double-blind study in nulliparous women. Anesthesia and analgesia 113(4): 826-31

Chalekar 2021

Chalekar, R.; Patil, B.; Kagalkar, N.; Reddy, N.K.; Comparision of intermittent bolus versus continuous infusion of epidural labour analgesia by 0.15% ropivacaine and fentanyl: A randomised clinical study; Tropical Journal of Pharmaceutical Research; 2021; vol. 15 (no. 22); uc05-uc09

Chua 2004

Chua, Sebastian M. H. and Sia, Alex T. H. (2004) Automated intermittent epidural boluses improve analgesia induced by intrathecal fentanyl during labour. Canadian journal of anaesthesia = Journal canadien d'anesthesie 51(6): 581-5

Diez-Picazo 2019

Diez-Picazo, Luis D., Guasch, Emilia, Brogly, Nicolas et al. (2019) Is breakthrough pain better managed by adding programmed intermittent epidural bolus to a background infusion during labor epidural analgesia? A randomized controlled trial. Minerva anestesiologica 85(10): 1097-1104

Fan 2019

Fan, Yuru, Hou, Wenwen, Feng, Shi et al. (2019) Programmed intermittent epidural bolus decreases the incidence of intra-partum fever for labor analgesia in primiparous women: a randomized controlled study. Archives of gynecology and obstetrics 300(6): 1551-1557

Ferrer 2017

Ferrer, Leopoldo E., Romero, David J., Vasquez, Oscar I. et al. (2017) Effect of programmed intermittent epidural boluses and continuous epidural infusion on labor analgesia and obstetric outcomes: a randomized controlled trial. Archives of gynecology and obstetrics 296(5): 915-922

Fettes 2006

Fettes PD, Moore CS, Whiteside JB et al. (2006) Intermittent vs continuous administration of epidural ropivacaine with fentanyl for analgesia during labour. British journal of anaesthesia 97(3): 359-364

Fidkowski 2019

Fidkowski, Christina W.; Shah, Sonalee; Alsaden, Mohamed-Rida (2019) Programmed intermittent epidural bolus as compared to continuous epidural infusion for the maintenance of labor analgesia: a prospective randomized single-blinded controlled trial. Korean journal of anesthesiology 72(5): 472-478

Haidl 2020

Haidl, Felix, Arne Rosseland, Leiv, Rorvik, Anne-Marte et al. (2020) Programmed intermittent boluses vs continuous epidural infusion in labor using an adrenaline containing solution: A randomized trial. Acta anaesthesiologica Scandinavica 64(10): 1505-1512

Huang 2021

Huang, Rui, Zhu, Jiang, Zhao, Zizuo et al. (2021) The effect of programmed intermittent epidural bolus compared with continuous epidural infusion in labor analgesia with ropivacaine: a meta-analysis of randomized controlled trials. Annals of palliative medicine 10(3): 2408-2420

Leo 2010

Leo, S., Ocampo, C. E., Lim, Y. et al. (2010) A randomized comparison of automated intermittent mandatory boluses with a basal infusion in combination with patient-controlled epidural analgesia for labor and delivery. International journal of obstetric anesthesia 19(4): 357-64

Lim 2010

Lim, Y., Chakravarty, S., Ocampo, C. E. et al. (2010) Comparison of automated intermittent low volume bolus with continuous infusion for labour epidural analgesia. Anaesthesia and intensive care 38(5): 894-9

Lin 2016

Lin, Y., Li, Q., Liu, J. et al. (2016) Comparison of continuous epidural infusion and programmed intermittent epidural bolus in labor analgesia. Therapeutics and clinical risk management 12: 1107-1112

Meena 2022

Meena, Anuradha; Mitra, Sukanya; Singh, Jasveer; Saroa, Richa; Takker, Navneet; Analgesic efficacy of programmed intermittent epidural bolus vs patient-controlled epidural analgesia in laboring parturients.; Journal of anaesthesiology, clinical pharmacology; 2022; vol. 38 (no. 2); 178-183

Morau 2019

Morau, Estelle, Jaillet, Malaury, Storme, Brigitte et al. (2019) Does programmed intermittent epidural bolus improve childbirth conditions of nulliparous women compared with patient-controlled epidural analgesia?: A multicentre, randomised, controlled, triple-blind study. European journal of anaesthesiology 36(10): 755-762

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Nunes, Joana, Nunes, Sara, Veiga, Mariano et al. (2016) A prospective, randomized, blinded-endpoint, controlled study - continuous epidural infusion versus programmed intermittent epidural bolus in labor analgesia. Brazilian journal of anesthesiology (Elsevier) 66(5): 439-44

Ojo 2020

Ojo, Oluremi A., Mehdiratta, Jennifer E., Gamez, Brock H. et al. (2020) Comparison of Programmed Intermittent Epidural Boluses With Continuous Epidural Infusion for the Maintenance of Labor Analgesia: A Randomized, Controlled, Double-Blind Study. Anesthesia and analgesia 130(2): 426-435

Rodriguez-Campoo 2019

Rodriguez-Campoo, Maria Belen, Curto, Antonio, Gonzalez, Manuel et al. (2019) Patient intermittent epidural boluses (PIEB) plus very low continuous epidural infusion (CEI) versus patient-controlled epidural analgesia (PCEA) plus continuous epidural infusion (CEI) in primiparous labour: a randomized trial. Journal of clinical monitoring and computing 33(5): 879-885

Roofthooft 2020

Roofthooft, E., Barbe, A., Schildermans, J. et al. (2020) Programmed intermittent epidural bolus vs. patient-controlled epidural analgesia for maintenance of labour analgesia: a two-centre, double-blind, randomised study. Anaesthesia 75(12): 1635-1642

Sia 2007

Sia AT; Lim Y; Ocampo C (2007) A comparison of a basal infusion with automated mandatory boluses in parturient-controlled epidural analgesia during labor. Anesthesia and analgesia 104(3): 673-678

Sia 2013

Sia AT; Leo S; Ocampo CE (2013) A randomised comparison of variable-frequency automated mandatory boluses with a basal infusion for patient-controlled epidural analgesia during labour and delivery. Anaesthesia 68(3): 267-275

Song 2021

Song, Yujie, Du, Weijia, Zhou, Shuangqiong et al. (2021) Effect of Dural Puncture Epidural Technique Combined With Programmed Intermittent Epidural Bolus on Labor Analgesia Onset and Maintenance: A Randomized Controlled Trial. Anesthesia and analgesia 132(4): 971-978

Wong 2006

Wong, Cynthia A., Ratliff, John T., Sullivan, John T. et al. (2006) A randomized comparison of programmed intermittent epidural bolus with continuous epidural infusion for labor analgesia. Anesthesia and analgesia 102(3): 904-9

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021277555
Review title	What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?
Review question	What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?
Objective	To update the recommendations in CG190 (2014). Stakeholders have identified new literature for the use of Programmed intermittent epidural bolus for maintaining epidural analgesia and would welcome an update of the recommendation 1.9.19.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • International Health Technology Assessment database Searches will be restricted by: • No date limitations • English language only

Field	Content
	• Human studies only Other searches: • Inclusion lists of systematic reviews The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Labour and birth
Population	• Women in labour who are pregnant with a single baby, who go into labour at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk birth • Women who are having their labour induced • Women who have had a previous caesarean birth • Women in labour whose baby has not been identified before labour to be at high risk of adverse outcomes • Singleton babies born at term (37 to 42 weeks of pregnancy) with no previously identified problems (for example congenital malformations, genetic anomalies, intrauterine growth restriction, placental problems) • Women who have received epidural or combined spinal–epidural analgesia to establish regional analgesia in labour
Intervention	The following interventions in combination with bupivacaine plus opioid: • Programmed intermittent epidural bolus • Programmed intermittent epidural bolus in combination with patient controlled epidural analgesia (PCEA) • Programmed intermittent epidural bolus with continuous background infusion

Field	Content
Comparator	• Continuous epidural infusion • Intermittent epidural bolus (given by healthcare professional) • Patient controlled epidural analgesia (PCEA) only • Patient controlled epidural analgesia (PCEA) with continuous background infusion
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs (individual or cluster) Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
Other exclusion criteria	Population: • Women in labour who are identified before labour to be at high risk, or whose baby is at high risk, of complications or adverse outcomes • Women with non-cephalic presentation • Women in preterm labour • Women with an intrauterine fetal death • Women with multi-fetal pregnancies *If any study or systematic review includes <1/3 of women with the above characteristics, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness.*
Context	The population of this guideline may overlap with the population of women included in other NICE guidelines (such as caesarean birth or induction of labour)
Primary outcomes (critical outcomes)	• Anaesthetist re-attendance for breakthrough pain

Field	Content
	• Motor block • General labour pain
Secondary outcomes (important outcomes)	• Duration of labour • Mode of birth (spontaneous vaginal, instrumental vaginal, caesarean birth) • Neonatal admission (includes neonatal intensive care unit [NICU] and special care baby unit [SCBU]) • Women's experience of labour and birth
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster-randomized trials The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies

Field	Content
	will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be 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/ Minimally important differences: • Validated scales/continuous outcomes: published MIDs where available • All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes ; +/- 0.5x control group SD for continuous outcomes
Analysis of subgroups	Evidence will be stratified by: • BMI thresholds on booking: ○ Underweight range: <18.5 kg/m^2 ○ Healthy weight range: 18.5 to 24.9 kg/m^2 ○ Overweight range: 25 to 29.99 kg/m^2 ○ Obesity range 1: 30 to 34.99 kg/m^2 ○ Obesity range 2: 35 to 39.99 kg/m^2 • Concentration of bupivacaine • Type of opioid Stratifications will be dealt with in a hierarchy (this is, first by BMI thresholds, then by concentration of bupivacaine and then by type of opioid) Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Age of woman (<35 vs >/= 35) • Ethnicity

Field	Content	
	○ White ○ Asian/Asian British ○ Black/African/Caribbean/Black British ○ Mixed/Multiple ethnic groups ○ Other ethnic group • Women with disability vs not • Deprived socioeconomic group vs not • Country where the study was conducted: high income countries versus low and middle income countries (as defined by the OECD) Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date	15/09/2021	

Field	Content
Anticipated completion date	22/03/2023
Named contact	5a. Named contact Guideline Development Team National Guideline Alliance (NGA) 5b. Named contact e-mail IPCupdate@nice.org.uk 5c. Organisational affiliation of the review Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)
Review team members	From the Guideline Development Team NGA • Senior Systematic Reviewer • Systematic Reviewer
Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team NGA, Centre for Guidelines, which is part of the National Institute for Health and Care Excellence (NICE).
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/cg190
Other registration details	None
URL for published	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=277555

Field	Content
protocol	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	
Details of existing review of same topic by same authors	Not applicable
Additional information	None
Details of final publication	www.nice.org.uk

BMI: body mass index; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; NICU: neonatal intensive care unit; OECD: Organisation for Economic Co-operation and Development; PCEA: patient-controlled epidural analgesia; PRESS: peer review of electronic search strategies; RCT: randomised controlled trial; RoB(IS): risk of bias (in systematic reviews); SCBU: special care baby unit; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?

Database: Medline – OVID interface

Date of last search: 06/12/2022

#	Searches
1	PREGNANCY/
2	PARTURITION/
3	exp LABOR, OBSTETRIC/
4	exp DELIVERY, OBSTETRIC/
5	OBSTETRIC LABOR, PREMATURE/
6	(pregnan$ or labo?r? or childbirth$ or partu$ or intra?part$ or peri?part$).ab,ti.
7	((during or giving or give) adj5 (birth$ or deliver$)).ti,ab.
8	or/1-7
9	((program* or automat*) adj5 intermittent* adj5 bolus*).ti,ab.
10	PIEB.ti,ab.
11	or/9-10
12	8 and 11
13	limit 12 to english language
14	LETTER/
15	EDITORIAL/
16	NEWS/
17	exp HISTORICAL ARTICLE/
18	ANECDOTES AS TOPIC/
19	COMMENT/
20	CASE REPORT/
21	(letter or comment*).ti.
22	or/14-21
23	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
24	22 not 23
25	ANIMALS/ not HUMANS/
26	exp ANIMALS, LABORATORY/
27	exp ANIMAL EXPERIMENTATION/
28	exp MODELS, ANIMAL/
29	exp RODENTIA/
30	(rat or rats or mouse or mice).ti.
31	or/24-30
32	13 not 31
33	META-ANALYSIS/
34	META-ANALYSIS AS TOPIC/
35	(meta analy* or metanaly* or metaanaly*).ti,ab.
36	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
37	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
38	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
39	(search* adj4 literature).ab.
40	(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.
41	cochrane.jw.
42	or/33-41
43	randomized controlled trial.pt.
44	controlled clinical trial.pt.
45	pragmatic clinical trial.pt.
46	randomi#ed.ab.
47	placebo.ab.
48	randomly.ab.
49	CLINICAL TRIALS AS TOPIC/
50	trial.ti.
51	or/43-50
52	32 and 42
53	32 and 51
54	or/52-53

Database: Embase – OVID interface

Date of last search: 06/12/2022

#	Searches
1	*PREGNANCY/
2	*PERINATAL PERIOD/
3	exp *BIRTH/
4	exp *LABOR/
5	*PREMATURE LABOR/
6	*INTRAPARTUM CARE/
7	(pregnan$ or labo?r? or childbirth$ or partu$ or intra?part$ or peri?part$).ab,ti.
8	((during or giving or give) adj5 (birth$ or deliver$)).ti,ab.
9	or/1-8
10	((program* or automat*) adj5 intermittent* adj5 bolus*).ti,ab.
11	PIEB.ti,ab.
12	or/10-11
13	9 and 12
14	limit 13 to english language
15	letter.pt. or LETTER/
16	note.pt.
17	editorial.pt.
18	CASE REPORT/ or CASE STUDY/
19	(letter or comment*).ti.
20	or/15-19
21	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
22	20 not 21
23	ANIMAL/ not HUMAN/
24	NONHUMAN/
25	exp ANIMAL EXPERIMENT/
26	exp EXPERIMENTAL ANIMAL/
27	ANIMAL MODEL/
28	exp RODENT/
29	(rat or rats or mouse or mice).ti.
30	or/22-29
31	14 not 30
32	SYSTEMATIC REVIEW/
33	META-ANALYSIS/
34	(meta analy* or metanaly* or metaanaly*).ti,ab.
35	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
36	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
37	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
38	(search* adj4 literature).ab.
39	(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.
40	((pool* or combined) adj2 (data or trials or studies or results)).ab.
41	cochrane.jw.
42	or/32-41
43	random*.ti,ab.
44	factorial*.ti,ab.
45	(crossover* or cross over*).ti,ab.
46	((doubl* or singl*) adj blind*).ti,ab.
47	(assign* or allocat* or volunteer* or placebo*).ti,ab.
48	CROSSOVER PROCEDURE/
49	SINGLE BLIND PROCEDURE/
50	RANDOMIZED CONTROLLED TRIAL/
51	DOUBLE BLIND PROCEDURE/
52	or/43-51
53	31 and 42
54	31 and 52
55	or/53-54

Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews – Wiley interface

Date of last search: 06/12/2022

#	Searches
#1	MeSH descriptor: [Pregnancy] this term only
#2	MeSH descriptor: [Parturition] this term only
#3	MeSH descriptor: [Labor, Obstetric] explode all trees
#4	MeSH descriptor: [Delivery, Obstetric] explode all trees
#5	MeSH descriptor: [Obstetric Labor, Premature] this term only
#6	(pregnan* or labor* or labour* or childbirth* or partu* or intrapart* or intra-part* or peripart* or peri-part*):ti,ab
#7	((during or giving or give) near/5 (birth* or deliver*)):ti,ab
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7
#9	((program* or automat*) near/5 intermittent* near/5 bolus*):ti,ab
#10	PIEB:ti,ab
#11	#9 or #10
#12	#8 and #11

Database: International Health Technology Assessment

Date of last search: 06/12/2022

#	Searches
	All: (bolus or boluses)
	AND All: (intermittent or intermittently)

Health Economics search strategies

Database: Medline – OVID interface

Date of last search: 06/12/2022

#	Searches
1	PREGNANCY/
2	PARTURITION/
3	exp LABOR, OBSTETRIC/
4	exp DELIVERY, OBSTETRIC/
5	OBSTETRIC LABOR, PREMATURE/
6	(pregnan$ or labo?r? or childbirth$ or partu$ or intra?part$ or peri?part$).ab,ti.
7	((during or giving or give) adj5 (birth$ or deliver$)).ti,ab.
8	or/1-7
9	((program* or automat*) adj5 intermittent* adj5 bolus*).ti,ab.
10	PIEB.ti,ab.
11	or/9-10
12	8 and 11
13	limit 12 to english language
14	LETTER/
15	EDITORIAL/
16	NEWS/
17	exp HISTORICAL ARTICLE/
18	ANECDOTES AS TOPIC/
19	COMMENT/
20	CASE REPORT/
21	(letter or comment*).ti.
22	or/14-21
23	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
24	22 not 23
25	ANIMALS/ not HUMANS/
26	exp ANIMALS, LABORATORY/
27	exp ANIMAL EXPERIMENTATION/
28	exp MODELS, ANIMAL/
29	exp RODENTIA/
30	(rat or rats or mouse or mice).ti.
31	or/24-30
32	13 not 31
33	ECONOMICS/
34	VALUE OF LIFE/
35	exp "COSTS AND COST ANALYSIS"/

#	Searches
36	exp ECONOMICS, HOSPITAL/
37	exp ECONOMICS, MEDICAL/
38	exp RESOURCE ALLOCATION/
39	ECONOMICS, NURSING/
40	ECONOMICS, PHARMACEUTICAL/
41	exp "FEES AND CHARGES"/
42	exp BUDGETS/
43	budget*.ti,ab.
44	cost*.ti,ab.
45	(economic* or pharmaco?economic*).ti,ab.
46	(price* or pricing*).ti,ab.
47	(financ* or fee or fees or expenditure* or saving*).ti,ab.
48	(value adj2 (money or monetary)).ti,ab.
49	resourc* allocat*.ti,ab.
50	(fund or funds or funding* or funded).ti,ab.
51	(ration or rations or rationing* or rationed).ti,ab.
52	ec.fs.
53	or/33-52
54	32 and 53

Database: Embase – OVID interface

Date of last search: 06/12/2022

#	Searches
1	*PREGNANCY/
2	*PERINATAL PERIOD/
3	exp *BIRTH/
4	exp *LABOR/
5	*PREMATURE LABOR/
6	*INTRAPARTUM CARE/
7	(pregnan$ or labo?r? or childbirth$ or partu$ or intra?part$ or peri?part$).ab,ti.
8	((during or giving or give) adj5 (birth$ or deliver$)).ti,ab.
9	or/1-8
10	((program* or automat*) adj5 intermittent* adj5 bolus*).ti,ab.
11	PIEB.ti,ab.
12	or/10-11
13	9 and 12
14	limit 13 to english language
15	letter.pt. or LETTER/
16	note.pt.
17	editorial.pt.
18	CASE REPORT/ or CASE STUDY/
19	(letter or comment*).ti.
20	or/15-19
21	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
22	20 not 21
23	ANIMAL/ not HUMAN/
24	NONHUMAN/
25	exp ANIMAL EXPERIMENT/
26	exp EXPERIMENTAL ANIMAL/
27	ANIMAL MODEL/
28	exp RODENT/
29	(rat or rats or mouse or mice).ti.
30	or/22-29
31	14 not 30
32	HEALTH ECONOMICS/
33	exp ECONOMIC EVALUATION/
34	exp HEALTH CARE COST/
35	exp FEE/
36	BUDGET/
37	FUNDING/
38	RESOURCE ALLOCATION/
39	budget*.ti,ab.
40	cost*.ti,ab.
41	(economic* or pharmaco?economic*).ti,ab.
42	(price* or pricing*).ti,ab.
43	(financ* or fee or fees or expenditure* or saving*).ti,ab.
44	(value adj2 (money or monetary)).ti,ab.

#	Searches
45	resourc* allocat*.ti,ab.
46	(fund or funds or funding* or funded).ti,ab.
47	(ration or rations or rationing* or rationed).ti,ab.
48	or/32-47
49	31 and 48

Databases: Cochrane Central Register of Controlled Trials – Wiley interface

Date of last search: 06/12/2022

#	Searches
#1	MeSH descriptor: [Pregnancy] this term only
#2	MeSH descriptor: [Parturition] this term only
#3	MeSH descriptor: [Labor, Obstetric] explode all trees
#4	MeSH descriptor: [Delivery, Obstetric] explode all trees
#5	MeSH descriptor: [Obstetric Labor, Premature] this term only
#6	(pregnan* or labor* or labour* or childbirth* or partu* or intrapart* or intra-part* or peripart* or peri-part*):ti,ab
#7	((during or giving or give) near/5 (birth* or deliver*)):ti,ab
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7
#9	((program* or automat*) near/5 intermittent* near/5 bolus*):ti,ab
#10	PIEB:ti,ab
#11	#9 or #10
#12	#8 and #11
#13	MeSH descriptor: [Economics] this term only
#14	MeSH descriptor: [Value of Life] this term only
#15	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#16	MeSH descriptor: [Economics, Hospital] explode all trees
#17	MeSH descriptor: [Economics, Medical] explode all trees
#18	MeSH descriptor: [Resource Allocation] explode all trees
#19	MeSH descriptor: [Economics, Nursing] this term only
#20	MeSH descriptor: [Economics, Pharmaceutical] this term only
#21	MeSH descriptor: [Fees and Charges] explode all trees
#22	MeSH descriptor: [Budgets] explode all trees
#23	budget*:ti,ab
#24	cost*:ti,ab
#25	(economic* or pharmaco?economic*):ti,ab
#26	(price* or pricing*):ti,ab
#27	(financ* or fee or fees or expenditure* or saving*):ti,ab
#28	(value near/2 (money or monetary)):ti,ab
#29	resourc* allocat*:ti,ab
#30	(fund or funds or funding* or funded):ti,ab
#31	(ration or rations or rationing* or rationed):ti,ab
#32	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31
#33	#12 and #32

Database: International Health Technology Assessment

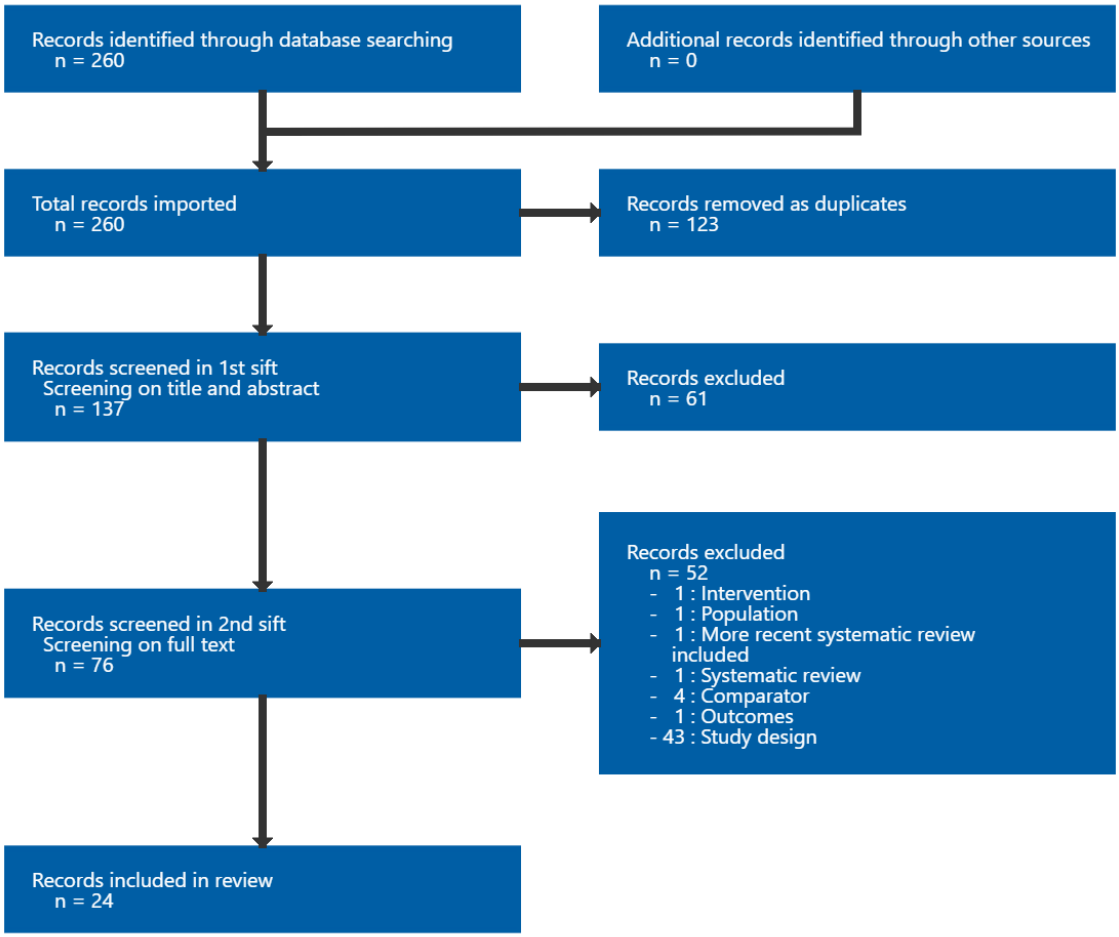
Date of last search: 06/12/2022

#	Searches
	All: (bolus or boluses)
	AND All: (intermittent or intermittently)

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?

Figure 1: Study selection flow chart[a]



[a] 15 studies were included in this review. However, as 1 of the studies is a systematic review with 9 additional studies, these individual studies appear in the included records section of the PRISMA diagram.

Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?

Bourges, 2021

Bibliographic Reference Bourges, Jennifer; Gakuba, Clement; Plass, Felipe; Gerard, Jean-Louis; Simone, Therese; Hanouz, Jean-Luc; Effect of patient-controlled epidural analgesia with and without automatic intermittent bolus on levobupivacaine consumption during labour: A single centre prospective double-blinded randomised controlled study; Anaesthesia, critical care & pain medicine; 2021; 100936

Study details

Country/ies where study was carried out	France
Study type	Randomised controlled trial (RCT)
Study dates	November 2016 - November 2017
Inclusion criteria	• Nulliparous women • >18 years • ASA physical status 2 • singleton vertex uncomplicated pregnancy • admitted for labour • >35 weeks gestation
Exclusion criteria	Pre randomisation • refused consent • contraindication to epidural analgesia • allergy/hypersensitivity to local anaesthetics or sufentanil • in utero foetal death • opioid misuse and addiction • language barriers

	• incomplete understanding of the self-management of local anaesthetic administration Post randomisation • unintentional dural puncture during epidural space identification • planned caesarean birth according to the attending obstetrician decision • unable to obtain primary outcome data because of pump failure or pump turned off before data was recorded
Patient characteristics	Maternal age, years - mean ± SD PCEA +PIEB group: 27±5 PCEA group: 28±5 BMI - mean ± SD PCEA + PIEB group: 24±5 PCEA group: 24±6 Gestational age, weeks - mean ± SD PCEA + PIEB group: 40±1 PCEA group: 40±1 Balance between groups for women's characteristics was assessed using absolute standardised difference (defined as the between group difference in means, mean rankings, or proportions, as appropriate, divided by a pooled estimate of standard deviation). A standardised difference > 0.20 suggests imbalance between groups.
Intervention(s)/control	Epidural analgesia initiation: Epidural catheter inserted at L3 or L4 lumbar interspace in both group. 3 mL test dose of lidocaine 20 mg/ml without epinephrine was administered to exclude an intrathecal placement. 10 ml bolus of solution with 0.625 mg/ml (0.0625%) levobupivacaine, and 5ug of sufentanil. If there was no change in pain in 60 minutes, the participant was withdrawn and block assumed failed.

	Epidural analgesia maintenance: Programmed intermittent epidural bolus (PIEB) + Patient controlled epidural analgesia (PCEA) • PIEB pump programmed to deliver 8ml of epidural solution (levobupivacaine 0.625mg/ml, sufentanil 50ug/200ml, clonidine 75ug/200ml) every 60 min with a lockout period of 8 min. • First bolus administered 60 minutes after initial 10ml loading dose. • patient activated boluses of 8ml, with a refractory period of 8 min also available. PCEA group • patient-activated boluses of 8ml, with a lockout period of 8 min. In both groups, a volume of 120 mL of local anaesthetic solution (i.e., 75 mg of levobupivacaine) within 4 h stopped the electronic pump and the senior anaesthesiologist was requested. Additional bolus of 5-10ml of levobupivacaine (0.625ml/ml) or lidocaine (20mg/ml) could be administered in case of insufficient analgesia at the discretion of the anaesthesiologist.
Duration of follow-up	not specified
Sources of funding	Not industry funded
Sample size	N = 457 women randomised (130 were excluded from analysis, 317 analysed) PCEA + PIEB group n = 155 randomised PCEA group n = 162 randomised

Other information	

Outcomes

Outcome	PCEA + PIEB, , N = 155	PCEA, , N = 162
Women requiring additional bolus (anaesthetist administered) No of events	n = 22	n = 15
Motor block No of events	n = 25	n = 19
Duration of labour (Minutes) Duration of labour defined as the time from the onset of the active labour phase (cervical dilation >3 cm with more than 3 uterine contractions within 10 min) to delivery (if labour started at home, duration was recorded from the time of admission). Mean (SD)	751 (311)	764 (287)
Instrumental vaginal birth No of events	n = 25	n = 31
Caesarean birth Lower values are better No of events	n = 18	n = 29
Women's satisfaction for epidural analgesia Excellent or good No of events	n = 138	n = 143

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Computer generated randomisation, and allocation concealed. No baseline imbalances to suggest any issues.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, midwife, 1 of 2 anaesthesiologists and obstetrician were blind to the intervention. Analysis was by intention to treat.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Around 10% of data is missing as the pump was switched off and data could not be collected for the primary outcome of the study. There is no information provided on why the pump was turned off, but it could be because of reasons related to the outcomes. However, missing outcome data is balanced.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was not inappropriate, and outcome assessors were blind to the intervention for subjective outcomes.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Data reported as specified in the trial protocol)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation in bias across outcomes.

Capogna, 2011

Bibliographic Capogna, Giorgio; Camorcia, Michela; Stirparo, Silvia; Farcomeni, Alessio; Programmed intermittent epidural bolus versus

Reference continuous epidural infusion for labor analgesia: the effects on maternal motor function and labor outcome. A randomized double-blind study in nulliparous women; Anesthesia and analgesia; 2011; vol. 113 (no. 4); 826-31

Study details

Country/ies where study was carried out	Italy
Study type	Randomised controlled trial (RCT)
Study dates	April 2009 - July 2010
Inclusion criteria	• >37 weeks gestation • nulliparous • singleton pregnancy • vertex pregnancies in spontaneous labor • <4 cm cervical dilation
Exclusion criteria	• Women with any disorder of pregnancy • breech presentation • multiple gestation • who had received parenteral opioids • required oxytocin before epidural analgesia • who were unable to perform motor block evaluation tests
Patient characteristics	Maternal age, years - mean ± SD PIEB + PCEA Group: 29±5 CEI + PCEA Group: 27±5 Gestational age, weeks - mean ± SD PIEB + PCEA Group: 38.9±0.7 CEI + PCEA Group: 38.7±0.7

	Women in the PIEB + PCEA Group were slightly older: p <0.01
Intervention(s)/control	Epidural analgesia was initiated with 20ml of epidural solution of levobupivacaine 0.0625% with sufentanil 0.5 ug/ml. Women with a failed blocked (VAPS 10mm or less or requesting a PCEA bolus within 30 minutes) were deemed as having a failed block and excluded from the study. No test dose was administered Epidural analgesia maintenance: <u>Programmed intermittent epidural bolus (PIEB) + Patient controlled epidural analgesia (PCEA)</u> • PIEB pump delivered a 10 ml bolus of epidural solution every hour beginning 60 minutes after the initial dose. • Option for a PCEA. The PCEA pump was programmed to deliver 5ml patient activated bolus of levobupivacaine of 0.125% with a lockout interval of 10 minutes and a per hour maximum volume of 15ml. • PCEA pump was available immediately after the loading dose. <u>Continuous epidural infusion (CEI) + PCEA</u> • CEI pump delivered epidural solution administered at a rate of 10 ml/h, beginning immediately after the initial dose. • Option for a PCEA. The PCEA pump was programmed to deliver 5ml patient activated bolus of levobupivacaine of 0.125% with a lockout interval of 10 minutes and a per hour maximum volume of 15ml. • PCEA pump was available immediately after the loading dose. If the woman still felt pain after 2 PCEA boluses in a 20-minute period, an anaesthesiologist administered 5ml of levobupivacaine 0.125% until the VAPS score was <10 mm. Epidural analgesia maintenance was continued until birth of the fetus.
Duration of follow-up	not specified
Sources of funding	Not industry funded
Sample size	N= 150 women randomised (5 lost to follow up in CEI. 4 due to a reported VAPS <10 mm 30mins after the epidural injection and 1 due to unintentional epidural catheter dislodgement during labour)

	PIEB + PCEA Group n= 75 randomised (75 included in analysis) CEI + PCEA Group n= 75 randomised (70 included in analysis)

Outcomes

Outcome	**PIEB + PCEA Group, , N = 75**	**CEI + PCEA Group, , N = 70**
Anaesthetist re-attendance for breakthrough pain No of events	n = 0	n = 0
Motor block No of events	n = 2	n = 26
Duration of labour (Minutes) Duration of labour analgesia from initiation to birth Median (IQR)	335 (326 to 358)	332 (318 to 380)
Instrumental vaginal birth No of events	n = 5	n = 14
Caesarean birth No of events	n = 13	n = 15

Critical appraisal

Section	**Question**	**Answer**
Domain 1: Bias arising from the	Risk of bias judgement for the	Low

Section	Question	Answer
randomisation process	randomisation process	*(Women in the programmed intermittent epidural bolus arm were slightly older (p<0.01) but no other characteristics were different, and no concerns as allocation sequence was random and concealed.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Assumed per protocol analysis. Participants and personnel were unaware of intervention. Participants could have been excluded post-randomisation if there was a failed block. Only 4 participants were excluded, therefore no concerns regarding non-adherence.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data was available for nearly all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring outcomes was not inappropriate and observations and assessments were made by a researcher blinded to the intervention)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No information available on pre-specified outcomes as unable to locate protocol.)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes

Chalekar, 2021

Bibliographic Reference Chalekar, R.; Patil, B.; Kagalkar, N.; Reddy, N.K.; Comparision of intermittent bolus versus continuous infusion of epidural labour analgesia by 0.15% ropivacaine and fentanyl: A randomised clinical study; Tropical Journal of Pharmaceutical Research; 2021; vol. 15 (no. 22); uc05-uc09

Study details	
Country/ies where study was carried out	India
Study type	Randomised controlled trial (RCT)
Study dates	June 2014 to June 2015
Inclusion criteria	• American Social of Anaesthesiologists (ASA) II pregnant women • 18-35 years old • term pregnancy with singleton • cephalic presentation • in active first stage of labour wanted epidural analgesia • cervical dilation more than 3 and less than 5 • over 145cm in height; BMI between 18-25.
Exclusion criteria	• Medical disorders and pregnancy associated disorders • spine abnormalities • local skin infections • coagulopathies • non reassuring non stress test • preterm labour or false labour pains • inadequate epidural analgesia even after 45 minutes of initial block • blood tap from epidural • accidental dural puncture.
Patient characteristics	**Maternal age, year - mean (SD):** Intervention (PIEB): 27.93 (1.14) Control (CEI): 27.87 (1.28) **Gestational age, weeks - mean (SD):** Intervention (PIEB): 39.32 (1.4) Control (CEI): 39.02 (1.3)

	Cervical dilatation, cm - mean (SD): Intervention (PIEB): 3.56 (0.62) Control (CEI): 3.58 (0.64) **Baseline visual analog scale (VAS) score:** Intervention (PIEB): 6.80 (1.32) Control (CEI): 7.06 (1.24)
Intervention(s)/control	Epidural analgesia initiation: Epidural analgesia initiated during first stage of labour. Epidural inserted at L3-L4 interspinous space with 18G Tuohy's epidural needle. Test dose of 3ml of 2% lignocaine with adrenaline. Then 12ml of 0.15% ropivacaine with fentanyl 50 micrograms given over 10 minutes. If target sensory level of T10 was not achieved within 30 minutes, additional 5ml of ropivacaine 0.15% with fentanyl 2microgram/ml given. Intervention - programmed intermittent epidural bolus (PIEB): • 1 hour after initial bolus dose PIEB group received 8ml of 0.15% ropivacaine with fentanyl 2 microgram/ml every hour Control - continuous epidural infusion (CEI) • CEI group received 8ml of 0.15% ropivacaine with fentanyl 2 microgram/ml as a continuous infusion immediately Breakthrough pain was treated with 8ml of 0.15% ropivacaine with fentanyl 2 microgram/ml in both groups. The attending anaesthesiologist was informed when pain recurred (VAS ≥4) and additional top-ups given.
Sources of funding	Not reported

Sample size	N=60 randomised Intervention (PIEB): n=30 Control (CEI): n=30

Outcomes

Outcome	**Intervention (PIEB), , N = 30**	**Control (CEI), , N = 30**
Anaesthetist re-attendance for breakthrough pain No of events	n = 21	n = 22
Motor block No of events	n = 0	n = 2
Pain at 5 minutes (Visual analogue scale) Mean (SD)	6.8 (1.19)	6.8 (1.19)
Pain at 10 minutes (Visual analogue scale) Mean (SD)	3.9 (0.76)	3.9 (0.76)
Pain at 15 minutes (Visual analogue scale) Mean (SD)	1.63 (0.49)	1.6 (0.45)
Pain at 30 minutes (Visual analogue scale) Mean (SD)	0 (0)	0 (0)
Pain at 1 hour (Visual analogue scale) Mean (SD)	0 (0)	0 (0)
Pain at 2 hours (Visual analogue scale)	1.4 (2.02)	3.03 (1.88)

Outcome	Intervention (PIEB), , N = 30	Control (CEI), , N = 30
Mean (SD)		
Pain at 3 hours (Visual analogue scale) Mean (SD)	1.8 (2.04)	2.1 (2.09)
Duration of labour - second stage - 40 minutes or less No of events	n = 25	n = 12
Duration of labour - second stage - over 40 minutes No of events	n = 0	n = 11
Spontaneous vaginal birth No of events	n = 22	n = 17
Instrumental vaginal birth No of events	n = 3	n = 1
Caesarean birth No of events	n = 5	n = 7
Women's experience - maternal satisfaction rated as good or excellent No of events	n = 30	n = 29

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the	Risk of bias judgement for the	Low

Section	Question	Answer
randomisation process	randomisation process	*(Allocation was random and sealed using sealed envelopes. No baseline imbalances to suggest any issues with randomisation.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(The study does not clearly mention if there were any deviations from intended interventions although it might be assumed there were none using the flow chart. There was also no mention of analysis. Participants were not blinded nor were those delivering the intervention therefore there is possibility for deviations therefore some concerns.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data was available for all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcomes assessors were blinded to the intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No protocol available)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation

Diez-Picazo, 2019

Bibliographic Reference Diez-Picazo, Luis D.; Guasch, Emilia; Brogly, Nicolas; Gilsanz, Fernando; Is breakthrough pain better managed by adding programmed intermittent epidural bolus to a background infusion during labor epidural analgesia? A randomized controlled trial; Minerva anestesiologica; 2019; vol. 85 (no. 10); 1097-1104

Study details

Country/ies where study was carried out	Spain
Study type	Randomised controlled trial (RCT)
Study dates	June 2016 to August 2017
Inclusion criteria	• Healthy nulliparous women • 18-40 years old • singleton pregnancy • gestational age 37 to 41 weeks • cervical dilation of ≤4cm • requesting epidural analgesia • signed an informed consent.
Exclusion criteria	• Contraindications for epidural analgesia • systemic disease affecting labour of epidural analgesia • inability to understand the woman.
Patient characteristics	Age, years - mean (±SD) PIEB + PCEA + BEI: 31 (6) PCEA + BEI: 32 (5) BMI, kg/m2 - mean (±SD) PIEB + PCEA + BEI: 28 (5) PCEA + BEI: 28 (4) Gestational age, weeks - mean (±SD) PIEB + PCEA + BEI: 40 (1.4) PCEA + BEI: 39 (1.5) VRS pain score at block request - median (range) PIEB + PCEA + BEI: 7 (6 to 10)

	PCEA + BEI: 8 (6 to 10) No significant differences at baseline between groups.
Intervention(s)/control	• Epidural block was performed with an 18-G Tuohy needle. • An epidural catheter was inserted (B-Braun) and a 3ml test dose of bupivacaine 0.25% plus adrenaline 1:200,000 was administered. • Epidural block was considered successful when VRS <4 after 60 minutes. If block failed, participant was excluded from analysis. • Epidural analgesia was maintained with a solution of levobupivacaine 0.125% plus fentanyl 1.45 ug/ml infused by an epidural pump. <u>Intervention: Programmed Intermittent Epidural Bolus (PIEB) + Patient Controlled Epidural Analgesia (PCEA) + Background Epidural Infusion (BEI)</u> • An initial 10ml bolus was administered and a background epidural infusion of 5ml/h was started. • The programmed 10ml boluses were set at 1 hour intervals. • The programmed boluses started 60 minutes after the initial bolus. • PCEA 10ml bolus delivered by pump when required. • A 20 minute lockout interval was configured between PCEA or PIEB/PCEA boluses. • 10ml boluses were dispensed by the infusion pump at rate 200ml/h. <u>Comparison: PCEA + BEI</u> • An initial 10ml bolus was administered and a background epidural infusion of 5ml/h was started. • PCEA 10ml bolus delivered by pump when required. • A 20 minute lockout interval was configured between PCEA boluses. • 10ml boluses were dispensed by the infusion pump at rate 200ml/h. Epidural pump was stopped if sensory block reached a level above T10, or if motor block was <4 on a modified Bromage scale.
Sources of funding	Smiths Medical paid for trial insurance and provided the pumps.
Sample size	N=120 women randomised

	PIEB + PCEA + BEI, n=58 (53 included for analysis. n=5 lost due to failed technique or analgesia) PCEA + BEI, n=62 (53 included for analysis. n=9 lost due to failed technique of analgesia)
Other information	Study uses the term background epidural infusion; however this is the same as continuous epidural infusion. It will be referred to as continuous epidural infusion in other sections of the review for consistency.

Outcomes

Outcome	**PIEB + PCEA + CEI, , N = 53**	**PCEA + CEI, , N = 53**
Anaesthetist re-attendance for breakthrough pain Number of clinician administered bolus No of events	n = 0	n = 0
Motor block Modified Bromage score <4 (weakness of hips and knees) No of events	n = 1	n = 0
General labour pain pain at birth No of events	n = 1	n = 1
Duration of labour (Minutes) Time from epidural block to birth Mean (SD)	404 (164)	407 (161)
Duration of labour (Minutes) First stage of labour Mean (SD)	310 (149)	293 (122)

Outcome	PIEB + PCEA + CEI, , N = 53	PCEA + CEI, , N = 53
Duration of labour (Minutes) Second stage of labour Mean (SD)	92 (49)	89 (50)
Spontaneous vaginal birth No of events	n = 34	n = 31
Instrumental birth No of events	n = 8	n = 7
Caesarean birth No of events	n = 11	n = 15
Maternal satisfaction - score 8 to 10 0 to 10 scale, 0 being the worst No of events	n = 48	n = 49

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was computer generated and concealed. No baseline imbalances.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Assumed per protocol analysis. Participants and anaesthesiologists monitoring participant were blinded to the intervention. Participants could have been excluded post-randomisation is there was a failed block. The number of exclusions at this stage were small therefore no concerns regarding*

Section	Question	Answer
		non-adherence.)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(14 participants excluded from analysis and no information on reasons why. Likely missingness depended on true value, and exclusions are not balanced between groups (9 vs 5). Possible that women were excluded from analysis for reasons that influence outcome true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome assessors were blinded to intervention)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Outcome reporting is as specified in the trial protocol.)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes

Ferrer, 2017

Bibliographic Reference Ferrer, Leopoldo E.; Romero, David J.; Vasquez, Oscar I.; Matute, Ednna C.; Van de Velde, Marc; Effect of programmed intermittent epidural boluses and continuous epidural infusion on labor analgesia and obstetric outcomes: a randomized controlled trial; Archives of gynecology and obstetrics; 2017; vol. 296 (no. 5); 915-922

Study details

Country/ies where study was carried out	Colombia

Study type	Randomised controlled trial (RCT)
Study dates	June 2015- May 2016
Inclusion criteria	• Women aged 18-45 requiring epidural analgesia
Exclusion criteria	• Women with American Society of Anesthesiologist physical status III or more (for example pre-eclampsia with severe features, gestational diabetes with complications) • allergic to local anaesthetics • Haemodynamic instability • chronic use of analgesics • mental disease • pregnancy related disease or high obstetric risk • any neuraxial contraindication.
Patient characteristics	Maternal age, years - mean ± SD PIEB: 31.6 ± 5.1 CEI: 32.3 ± 3.8 Parity - number (%) **Nulliparous** PIEB: 42 (65.6) CEI: 38 (59.4) **Multiparous** PIEB: 22 (34.4) CEI: 26 (40.6) Gestational age, weeks - mean ± SD PIEB: 38.2 ± 1.6 CEI: 38.6 ± 0.7 BMI - mean ± SD PIEB: 31.6 ± 5.1

	CEI: 32.3 ± 3.8 Baseline pain before epidural - mean ± SD PIEB: 7.9 ± 2.05 CEI: 7.6 ± 1.9 No significant differences between groups at baseline
Intervention(s)/control	Each participant received an initial loading dose of 10ml of 0.1% bupivacaine (2ml of 0.5% bupivacaine plus 50ug/ml of fentanyl in 7ml of 0.9% normal saline). Epidural maintenance solution: 0.1% bupivacaine plus 2ug/ml of fentanyl in 0.9% normal saline PIEB group • Hourly dose of a 10ml bolus of epidural solution. • First PIEB bolus was given 1 hour after the initial loading dose. • The pump was set to administer bolus at an infusion speed of 125ml/h. • 10 ml rescue bolus of the same mixture were available as needed by the participants and programmed in the pump by the obstetric nurse. CEI group • Continuous infusion of 10ml/hour of epidural solution. • Given immediately after initial loading dose. • 10 ml rescue bolus of the same mixture were available as needed by the participants and programmed in the pump by the obstetric nurse. Obstetric nurse had access to the pump using a security access code that meant bolus application by the patient of any other health personnel was avoided. Rescue boluses were programmed by the obstetric nurse. There was no limited for the number of rescue bolus administered.
Duration of follow-up	4 hours
Sources of funding	Not industry funded

Sample size	N= 132 women randomised, 4 lost to incomplete data (2 per arm) PIEB n= 66 randomised CEI n= 66 randomised

Outcomes

Outcome	**PIEB, , N = 64**	**CEI , , N = 64**
Anaesthetist re-attendance for breakthrough pain (obstetric nurse administered) At least one rescue bolus No of events	n = 12	n = 25
Motor block at 15 minutes Modified Bromage scale No of events	n = 5	n = 12
Motor block at 60 minutes Modified Bromage scale No of events	n = 7	n = 16
Motor block at 120 minutes Modified Bromage scale No of events	n = 9	n = 16
Motor block at 180 minutes Modified Bromage scale No of events	n = 9	n = 14
General labour pain at 15 minutes	2.2 (2.7)	2.5 (2.3)

Outcome	PIEB, , N = 64	CEI , , N = 64
VAS score - lower values better Mean (SD)		
General labour pain at 60 minutes VAS score - lower values better Mean (SD)	2.2 (2.8)	2.9 (2.8)
General labour pain at 120 minutes VAS score - lower values better Mean (SD)	2.5 (3.3)	3.6 (3.1)
General labour pain at 180 minutes VAS score - lower values better Mean (SD)	2.6 (3.1)	2.9 (2.7)
General labour pain at 240 minutes VAS score - lower values better Mean (SD)	2 (2.6)	3.3 (3.2)
Duration of labour (Minutes) Outcome labelled as 'duration of labour analgesia' but assumed same as duration of labour from study text Mean (SD)	219.7 (134.2)	186.3 (93.4)
Spontaneous vaginal birth No of events	n = 50	n = 51
Instrumental vaginal birth No of events	n = 5	n = 2

Outcome	PIEB, , N = 64	CEI , , N = 64
Caesarean birth No of events	n = 9	n = 11
Satisfaction at 15 minutes VRS score 7 or more (satisfied) No of events	n = 62	n = 59
Satisfaction at 60 minutes VRS score 7 or more (satisfied) No of events	n = 59	n = 55
Satisfaction at 120 minutes VRS score 7 or more (satisfied) No of events	n = 38	n = 43
Satisfaction at 180 minutes VRS score 7 or more (satisfied) No of events	n = 28	n = 29

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was computer generated and concealed. No baseline imbalances to suggest problems with randomisation.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(No information on any deviations from intended intervention, but participants and anaesthesiologists not aware of assignment. Intention*

Section	Question	Answer
intervention)		*to treat analysis assumed as no information on any exclusions post-randomisation.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data available for most participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of outcome measurement was not inappropriate, and outcome assessors were blinded to the intervention.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Study reported the primary outcome as specified in the trial protocol.)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation between outcomes.

Fidkowski, 2019

Bibliographic Reference	Fidkowski, Christina W.; Shah, Sonalee; Alsaden, Mohamed-Rida; Programmed intermittent epidural bolus as compared to continuous epidural infusion for the maintenance of labor analgesia: a prospective randomized single-blinded controlled trial; Korean journal of anesthesiology; 2019; vol. 72 (no. 5); 472-478

Study details

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)

Study dates	May 2015 - July 2017
Inclusion criteria	• English speaking • term gestation • desiring epidural analgesia • scheduled for induction of labour.
Exclusion criteria	• Less than 18 years old • gestational age below <37 weeks • spontaneous labour on admission • spontaneous rupture of membranes • breech position or other fetal malposition • multiple gestation • any severe pregnancy related disorder.
Patient characteristics	Maternal age, years - mean (±SD) PIEB 5ml/30min: 26.4 (5.6) PIEB 10ml/60min: 24.9 (4.5) Combined PIEB (not reported by study, manually calculated): 25.7 (5.1) CEI: 27.2 (5.5) BMI - mean (±SD) PIEB 5ml/30min: 38.6 (8.2) PIEB 10ml/60min: 33.3 (6.9) Combined PIEB (not reported by study, manually calculated): 36 (7.6) CEI: 36.0 (10.0) Gestational age, weeks - mean (±SD) PIEB 5ml/30min: 39.8 (1.5) PIEB 10ml/60min: 39.6 (1.4) Combined PIEB (not reported by study, manually calculated): 39.7 (1.5) CEI: 39.5 (1.4) Parity, number (%)

	PIEB 5ml/30min • Nulliparous: 18 (43.9) • Primiparous: 10 (24.4) • Multiparous: 10 (24.4) • Grand multiparous (p≥5): 3 (7.3) PIEB 10ml/60min • Nulliparous: 22 (51.2) • Primiparous: 13 (30.2) • Multiparous: 8 (18.6) • Grand multiparous (p≥5): 0 (0) CEI • Nulliparous: 12 (35.3) • Primiparous: 9 (26.5) • Multiparous: 11 (32.4) • Grand multiparous (p≥5): 2 (5.9)
Intervention(s)/control	• Participants were randomised to each group at the time of epidural analgesia request. • An experienced anaesthesia provider placed a lumbar epidural catheter with a 17 gauge tuohy needle. A 19 gauge spring-wound closed-tip catheter (B Braun) was threaded 4-6 cm into the epidural space. • All participants received a test dose of 3-5ml of 1.5% lidocaine with 1:200,000 epinephrine, following by an initial loading dose of 5ml of the standard epidural solution - 0.125% bupivacaine with 2 µg/ml fentanyl. • All participants received the standard epidural solution. • The epidural pump used is capable of PIEB or PCEA, with or without a background continuous infusion. • If epidural analgesia was appropriately established as demonstrated by a sensory level to ice, the participant continued with the study in the group determined at randomisation stage. <u>PIEB</u> • Pump set to administer bolus of 5ml of standard epidural solution every 30 minutes, or 10ml every 60 minutes

	• First PIEB dose administered immediately when pump was connected. CEI • Pump administered a continuous epidural infusion at 10 ml/hour of standard epidural solution. (All groups received an equal hourly rate of bupivacaine of 12.5 mg/h) Breakthrough pain was managed with a physician-administered epidural bolus. Local anaesthetic, concentration, and volume was left to the discretion of the anaesthesia provider.
Sources of funding	Not specified
Sample size	N = 150 women randomised PIEB 5ml/30min, n=50 (n=41 included in analysis) PIEB 10ml/60min, n=50 (n=43 included in analysis) CEI, n=50 (n=34 included in analysis) Excluded from analysis: PIEB 5ml/30min, n=3 delivered within 30 minutes, n=6 failed epidural PIEB 10ml/60min, n=4 delivered within 30 minutes, n=5 failed epidural CEI, n=2 delivered within 30 minutes, n=4 failed epidural, n= 3 did not receive treatment, n=7 fetal intolerance; chorioamnionitis; spontaneous rupture of membrane on admission; preterm gestation 2 participants allocated to CEI received PIEB 10ml/60min and were analysed in the PIEB 10ml/60min group.

Other information	3-arm study, but 2 PIEB arms have been combined to give 2-arms. Mean and standard deviations have been combined using Guideline Development Team NGA methods.

Outcomes

Outcome	**PIEB, , N = 84**	**CEI, , N = 34**
Physician administered epidural bolus No of events	n = 40	n = 21
Motor block Bromage scale No of events	n = 23	n = 9
General labour pain Average pain score (total pain normalised to the duration of epidural anaesthesia) - lower values better Mean (SD)	2.85 (2.35)	3.01 (2.6)
Duration of labour (hours) time from epidural analgesia to birth of the neonate Mean (SD)	8.37 (5.67)	8.6 (6.4)
Duration of labour (hours) duration of stage 2 of labour - time of complete cervical dilation to birth of neonate (only those with vaginal birth) Mean (SD)	1.35 (1.41)	0.88 (1.11)
Vaginal birth No of events	n = 66	n = 23
Instrumental birth No of events	n = 3 ; % = 3.6	n = 2 ; % = 5.9%

Outcome	PIEB, , N = 84	CEI, , N = 34
Caesarean birth No of events	n = 18	n = 11
Patient satisfaction Satisfied (1 or 2 on Likert scale) No of events	n = 82	n = 32

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was by opaque envelopes and sequence was concealed.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Some concerns due to 2 participants analysed 'as treated' as they were grouped according to the intervention they received, not randomised to, but unlikely to impact significantly on results as small percentage.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Participants were excluded post randomisation, however this was for reasons that do not depend on the true value of the outcome, and was balanced between groups.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(It is implied that obstetric staff were outcome assessors, and they were blinded to the intervention.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No protocol available to compare pre-specified outcomes, however unlikely to have been selected from multiple outcome measurements or analyses.)*

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes

Haidl, 2020

Bibliographic Reference Haidl, Felix; Arne Rosseland, Leiv; Rorvik, Anne-Marte; Dahl, Vegard; Programmed intermittent boluses vs continuous epidural infusion in labor using an adrenaline containing solution: A randomized trial; Acta anaesthesiologica Scandinavica; 2020; vol. 64 (no. 10); 1505-1512

Study details

Country/ies where study was carried out	Norway
Study type	Randomised controlled trial (RCT)
Study dates	March 2017 to September 2018
Inclusion criteria	• Women over 18 years • American Society of Anesthesiolgists class <3 (no severe systemic disease) • Singleton pregnancy • Gestational age over 37 weeks • Maximum of 1 previous birth.
Exclusion criteria	• Poor communication skills in Norwegian or English • Body height below 150cm • Pre-eclampsia

	• Any contraindication to epidural analgesia, including any of the medications used.
Patient characteristics	Baseline characteristics for both groups were similar. No differences between groups for age, pre-delivery weight, height, gestational age or parity. Age, mean (SD) PIEB + PCEA: 30.4 (4.1) CEI + PCEA: 29.8 (4.25) Pre-delivery weight in kg, mean (SD) PIEB + PCEA: 80.8 (12.2) CEI + PCEA: 82.3 (14.8) Gestational age - weeks + days, mean (SD in days) PIEB + PCEA: 40 + 0 (9) CEI + PCEA: 40 + 0 (8) Parity, number (%) **Nulliparous** PIEB + PCEA: 48 (64) CEI + PCEA: 48 (64) **Multiparous** PIEB + PCEA: 27 (36) CEI + PCEA: 27 (36)
Intervention(s)/control	Both groups received the same epidural analgesia for initiation: • Catheter placed 5cm in the epidural space. • 5ml of the epidural analgesia solution given for initiation. 1mg/ml (0.1%) bupivacaine, 2 microgram/ml fentanyl, and 2microgram/ml adrenaline. • If no signs of intrathecal injection were detected an additional 5ml was injected. • 15minutes after the second bolus, an infusion pump was started.

	Intervention: Programmed intermittent epidural bolus (PIEB) + patient controlled epidural analgesia (PCEA) • The pump was initiated by giving a 5ml bolus. • Then the pump gave a 5ml bolus every hour after initiation. • Option for PCEA of 5ml with a lockout time of 20minutes, if participants felt they had inadequate analgesia. • Additional lockout time of 20 minutes from the delivery of a programmed bolus by machine default. • A PIEB bolus would be delayed by the PCEA lockout interval. Control: Continuous epidural infusion (CEI) +PCEA • Pump was started with an infusion rate of 5ml/hour. • Option for PCEA of 5ml with a lockout time of 20minutes, if participants felt they had inadequate analgesia. Midwives were instructed to contact the anaesthetist if analgesia was inadequate despite the use of PCEA.
Sources of funding	Not industry funded.
Sample size	N=151 randomised Intervention: n=75 randomised and analysed Control: n=76 randomised, 75 analysed 1 participants withdrew consent and was excluded.

Outcomes

Outcome	**PIEB + PCEA, , N = 75**	**CEI + PCEA, , N = 75**
Number of physician administered manual boluses of the study epidural solution No of events	n = 9	n = 5

Outcome	PIEB + PCEA, , N = 75	CEI + PCEA, , N = 75
Motor block at 60 minutes No of events	n = 14	n = 9
Motor block at birth No of events	n = 23	n = 28
General labour pain (Numerical rating scale) Median (IQR)	8 (3 to 10)	8 (2.5 to 9.5)
Duration of labour - time from epidural placement to birth (Minutes) Median (IQR)	455 (68 to 2209)	443 (67 to 1725)
Vaginal birth No of events	n = 47	n = 43
Instrumental birth No of events	n = 18	n = 19
Caesarean birth No of events	n = 10	n = 13
Satisfaction with treatment (numeric rating scale 0-10) No information on polarity - assumed higher scores are better Median (IQR)	10 (9 to 10)	10 (9 to 10)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was computer generated and concealed. No baseline imbalances.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and study personnel blinded. Intention to treat not specified but assumed - all participants received their allocated intervention and were analysed according to their group.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for nearly all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome assessors were blind to intervention assigned)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Data reported as set out in pre-specified protocol.)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes

Huang, 2021

Bibliographic Reference Huang, Rui; Zhu, Jiang; Zhao, Zizuo; Wang, Bin; The effect of programmed intermittent epidural bolus compared with continuous epidural infusion in labor analgesia with ropivacaine: a meta-analysis of randomized controlled trials; Annals of palliative medicine; 2021; vol. 10 (no. 3); 2408-2420

Study details

Country/ies where study was carried out	Chua 2004 *Singapore Fan 2019 *China Fettes 2006 *Scotland Leo 2010 *Singapore Lim 2010 *Singapore Lin 2016 *China Ojo 2020 *United States Sia 2007 *Singapore Sia 2013 *Singapore
Study type	Systematic review of randomised controlled trials
Study dates	Chua 2004 Not reported Fan 2019

	*October 2012 - December 2017 Fettes 2006 Not reported Leo 2010 Not reported Lim 2010 *February and March 2007 Lin 2016 Not reported Ojo 2020 *November 2016 to November 2017 Sia 2007 Not reported Sia 2013 Not reported
Inclusion criteria	*Inclusion criteria extracted from individual RCT for all studies Chua 2004 • ASA physical status I • Nulliparous • early spontaneous labour with at least 1 contraction in 5 minutes • requested neuraxial block Fan 2019 • Singleton pregnancy • spontaneous labour

- requesting epidural analgesia
- maternal age between 20 and 45 years
- gestational age at term (37 to 41 weeks)
- nulliparous women
- cervical dilation 1-3cm.

Fettes 2006

- ASA status I-II
- Primigravid
- uncomplicated pregnancy at term 37 or more weeks

Leo 2010

- Healthy, ASA status I nulliparous women
- Gestational age over 36 weeks
- singleton
- vertex presentation
- early labour (cervical dilation <5 cm
- requesting epidural analgesia

Lim 2010

- Healthy, nulliparous pregnant women
- cephalic presentation
- 36 weeks or more gestational age
- early spontaneous labour
- cervical dilation ≤ 5cm

Lin 2016

- Healthy, nulliparous pregnant women
- ASA physical status I or II
- 37 weeks or more gestational age
- early spontaneous labour

	• having at least 1 uterine contraction every 5 minutes • requested neuraxial block • cervical dilation between 2-4cm (examined by midwife) Ojo 2020 • over 18 years old pregnant women • ASA status II or III • Gestational age >36 weeks • singleton pregnancy • vertex presentation • in labour, with a cervical dilation between 2-7cm and requesting epidural analgesia • VAS pain more than 5. Sia 2007 • Healthy, nulliparous pregnant women • ASA physical status I • cephalic presentation • 36 weeks or more gestational age • early spontaneous labour • cervical dilation ≤ 5cm • requested neuraxial blocks for analgesia Sia 2013 • Healthy nulliparous pregnant women • ASA status I • Over 36 weeks gestational age • singleton fetus • early labour, defined as cervical dilation <5 cm • women who had requested labour epidural
Exclusion criteria	*Exclusion criteria extracted from individual RCT for all studies

Chua 2004

- multiparous
- pain score less 30 on a 0 to 100 visual analogue scale (higher score worse)
- cervical dilation more than 5cm
- gestational age less than 36
- suspected macrosomia
- non-cephalic presentation
- pre-eclampsia
- gestational diabetes mellitus
- contraindications to neuraxial block (such as sepsis, haemorrhage, coagulopathy)

Fan 2019

- scheduled induction of labour
- multiple pregnancy
- American Society of Anaesthesiologists (ASA) physical status of 3 or higher
- height less than 150cm or more than 170cm
- BMI more than 35
- Contraindications for epidural analgesia
- baseline temperature ≥37.5 degrees C
- allergic to opioids and/or local anaesthetics
- epidural catheterisation failed
- organic dysfunction
- women not willing to, or not able to finish the whole study
- unable to perform analgesia evaluation
- using or used monoamine oxidase inhibitors in the past 14 days
- alcohol or narcotic dependency
- non-vertex presentation
- high risk pregnancy (gestational diabetes, gestational hypertension, placenta previa, placental abruption, pre-eclampsia).

Fettes 2006

- Received parenteral opioid analgesia with 2 hours
- weight more than 110 kg

- height less than 150cm
- cervical dilation greater than 5cm

Leo 2010

- Multiple pregnancy
- non-cephalic presentation
- obstetric complications (pre-eclampsia, premature rupture of membranes)
- contraindications to neuraxial blockade
- received parenteral opioids within the last 2 hours

Lim 2010

- Contraindication to neuraxial block
- multiple pregnancy
- obstetric complications (such as pre-eclampsia, gestational diabetes, or premature rupture of amniotic membranes)
- parenteral opioid administration within the previous four hours

Lin 2016

- Presence of systemic disease, such as diabetes, hypertension or pre-eclampsia
- chronic analgesic use
- multiple pregnancies
- preterm labour

Ojo 2020

- BMI >50kg/m2
- history of IV drug use or opioid abuse
- allergies to local anaesthetics
- conditions requiring assisted second stage of labour

Sia 2007

	• Women who had received parenteral opioids in the last 4hours • those who had contraindications to neuraxial blocks (such as coagulopathy) • multiple pregnancy • non-cephalic presentation • premature labour • obstetric complications (such as pre-eclampsia, gestational diabetes, premature rupture of amniotic membranes) Sia 2013 • multiple pregnancy • non-cephalic presentation • obstetric complications (such as pre-eclampsia, premature rupture of membranes) • contraindications to neuraxial blockade • received parenteral opioids within the last 2 hours.
Patient characteristics	Chua 2004 No baseline differences between groups for maternal height and weight, baseline pain score or cervical dilation. Maternal age or gestational age not reported. Fan 2019 No baseline differences between groups for maternal age, BMI, gestational age or cervical dilation. **Age, years - mean (SD)** Intervention: 29 (4) Comparator: 29 (4) **BMI, kg/m2 - mean (SD)** Intervention: 26 (2.6) Comparator: 25.9 (2.8) **Gestational age, weeks - mean (SD)** Intervention: 39.6 (0.9) Comparator: 39.5 (0.9) Fettes 2006 No baseline differences between groups for maternal age, maternal height and weight, gestational age, cervical dilation,

number of women induced.

Age, years - mean (SD)
Intervention: 25.8 (6.3) Comparator: 27.1 (4.5)

Gestational age, weeks - mean (SD)
Intervention: 40.3 (1.3) Comparator: 40.8 (1.3)

Number of women induced - number
Intervention: 14 Comparator: 12

Leo 2010

No baseline differences between groups for BMI or cervical dilation. Maternal age or gestational age not reported.

BMI, kg/m2 - mean (SD)
Intervention: 26.6 (3.1) Comparator: 27.4 (4.2)

Cervical dilation, cm - mean (SD)
Intervention: 2.9 (0.5) Comparator: 3.2 (0.69)

Lim 2010
No baseline differences between groups for maternal height and weight, baseline pain score or cervical dilation. Maternal age or gestational age not reported.

Baseline pain score – mean (SD)
Intervention: 6.6 (1.7) Comparator: 6.9 (2.3)

Cervical dilation, cm - median (range) (study labelled as mean and SD, but assumed median and range)
Intervention: 3 (1 to 4) Comparator: 3 (2 to 5)

Lin 2016

No baseline differences between groups for maternal age, gestational age, BMI, baseline pain score, cervical dilation.

	Maternal age, years - mean (±SEM) Intervention: 27.45 (4.61) Comparator: 28.16 (4.679) **Gestational age, weeks - mean (±SEM)** Intervention: 39.12 (0.81) Comparator: 38.84 (0.76) **BMI, kg/m2 - mean (±SEM)** Intervention: 28.35 (1.42) Comparator: 28.54 (1.51) **Cervical dilation, cm - mean (±SEM)** Intervention: 2.93 (0.21) Comparator: 3.02 (0.3) <u>Ojo 2020</u> No baseline differences between groups for maternal age, BMI, gestational age, parity, induction of labour, cervical dilation. **Maternal age, years - mean (SD)** Intervention: 29 (5) Comparator: 30 (5) **BMI kg/m2 - mean (SD)** Intervention: 32.9 (7.0) Comparator: 32.6 (7.2) **Gestational age, weeks - mean (SD)** Intervention: 39 (1) Comparator: 39 (1) **Nulliparous, number (%)** Intervention: 41 (67.2) Comparator: 45 (76.3) **Induction of labour, number (%)** Intervention: 46 (75.4) Comparator: 44 (74.6) **Cervical dilation, cm - mean (SD)** Intervention: 4 (1) Comparator: 4 (2)

	Sia 2007 No baseline differences between groups for maternal height or weight, cervical dilation or baseline pain score. Maternal age or gestational age not reported. **Cervical dilation, cm - median (range)** Intervention: 3 (2 to 5) Comparator: 3 (1 to 5) Sia 2013 No baseline differences between groups for BMI, cervical dilation, baseline pain score. Maternal age or gestational age not reported. **BMI, kg/m2 - mean (SD)** Intervention: 27.3 (3.9) Comparator: 28.2 (4.9) **Cervical dilation, cm - mean (SD)** Intervention: 3.2 (0.7) Comparator: 3.2 (0.9)
Intervention(s)/control	Chua 2004 Analgesia initiation: Combined spinal-epidural (CSE) 25ug fentanyl. (*Test dose of 3ml of 1.5% lidocaine). Epidural analgesia maintenance solution: Ropivacaine 0.1% and fentanyl 2ug/ml. **Intervention Programmed Intermittent Epidural Bolus (PIEB):** 5ml bolus of epidural solution every hour. *Initial bolus administered 30minutes after time 0). **Comparator Continuous Epidural Infusion (CEI):** Epidural solution infused at rate 5ml/h. *If VAS was more than 10, 20 minutes after time 0 the participant was excluded as the block was considered ineffective. Fan 2019 Analgesia initiation: Epidural analgesia 10ml 0.125% ropivacaine; 0.4ug/ml sufentanil. (*Testing dose of 3ml 1.5% lidocaine with 1:200000 epinephrine). Epidural analgesia maintenance solution: Ropivacaine 0.8% and fentanyl 0.4ug/ml. **PIEB + Patient controlled epidural analgesia (PCEA):** 10ml bolus of epidural solution every hour. Option for PCEA 5 ml

bolus, 30 minute lockout. *Initial PIEB bolus given 75minutes post loading dose.
CEI + PCEA: Epidural solution infused at rate 10 ml/h. Option for PCEA 5 ml bolus, 30 minute lockout.
*If pain was higher than 3 on VAS 15 minutes after initial loading dose, participant was excluded.
*If pain score was above 3 on VAS, after 2 doses for PCEA in a 60 minute period, an additional manual incremental bolus of 5ml of 0.15% ropivacaine was administered.
*Epidural infusion pumps discontinued 2 hours after birth.

Fettes 2006

Analgesia initiation: Epidural analgesia ropivacaine 2mg/ml, 10ml. (*Testing dose of 5ml ropivacaine 2mg/ml, and 5 minutes later a further 10ml administered. Additional 5ml given if still in pain 30minutes later).
Epidural analgesia maintenance solution: Ropivacaine 0.2% and fentanyl 2 ug/mL.
PIEB: 10ml bolus of epidural solution every hour. *Initial PIEB dose started 30 minutes after time 0.
CEI: Epidural solution infused at rate 10ml/h.
*If no bilateral block to T10, 45minutes after testing dose, participant was excluded.

Leo 2010

Analgesia initiation: Combined spinal-epidural. Ropivacaine 2 mg; fentanyl 15 ug. (*Testing dose of 3ml of 1.5% lidocaine).
Epidural analgesia maintenance solution: Ropivacaine 0.1%, fentanyl 2 ug/mL.
PIEB + PCEA: 5ml bolus of epidural solution every hour. Option for PCEA 5 mL bolus, 10 minutes lockout. *First PIEB dose delivered 30 minutes from time 0).
CEI + PCEA: Epidural solution infused at rate 5ml/h. Option for PCEA 5 mL bolus, 10 minutes lockout.
*If motor block (inability to flex either knee) developed within 15minutes of testing dose, participant was withdrawn.
*If VAS was equal or above 3 while on PCEA, anaesthesiologist adminstered 0.2% ropivacaine in 5ml aliquots every 10 min (max 20ml) until VAS was less than 3. Fentanyl 50ug added if after 10ml epidural VAS still not below 3.
*If analgesia failed after top-up by clinician, (VAS 3 or more) participant withdrawn.

Lim 2010

Analgesia initiation: Combined spinal-epidural. Ropivacaine 2 mg; fentanyl 15 ug. (*Testing dose 3ml of 1.5% lignocaine).
Epidural analgesia maintenance solution: Ropivacaine 0.1%, fentanyl 2 ug/mL.

PIEB: 2.5ml bolus of epidural solution every 15 min.

CEI: Epidural solution infused at rate 10ml/h.
*If pain was more than 3, 20 minutes after test, the block was considered failed and the participant withdrawn.

Lin 2016

Analgesia initiation: Epidural analgesia. Ropivacaine, 0.15%; 10 ml. (*Administered 5 minutes after testing dose with 4ml 0.1% lidocaine).
Epidural analgesia maintenance solution: Ropivacaine 0.1%, sufentanil 0.3ug/ml.
PIEB + PCEA: 5 ml bolus of epidural solution every hour. Option for PCEA 5ml bolus, 20 minutes lockout.
CEI + PCEA: Epidural solution infused at rate 5ml/h. Option for PCEA 5ml bolus, 20 minutes lockout.
*If VAS score was not at least 1 or lower than the baseline within 30minutes after epidural injection, or if requested a PCEA bolus within 30 minutes, the participant was withdrawn.

Ojo 2020

Analgesia initiation: Epidural analgesia. Ropivacaine, 0.1%; *20 ml.
Epidural analgesia maintenance solution: Ropivacaine 0.1%; fentanyl, 2 ug/mL.
PIEB + PCEA: 6 ml bolus of epidural solution every 45 minutes. Option for PCEA 8ml bolus, 10 minutes lockout. *First bolus administered 30 minutes after epidural initiation.
CEI + PCEA: Epidural infused at rate 8ml/h. Option for PCEA 8ml bolus, 10 minutes lockout. *CEI began immediately after the loading dose.
*If participants had pain above 4 at 30 minutes, they were withdrawn from the study.
*If the participant has inadequate analgesia despite 2 PCEA boluses in the last 20minutes, a clinician administered a bolus using 5l of ropivacaine 0.2% every 10 minutes. If after 10ml, analgesia was not adequate and they had bilateral sensort levels they were withdrawn.

Sia 2007

Analgesia initiation: Combined spinal-epidural. Ropivacaine, 2mg; fentanyl 15ug.
Epidural analgesia maintenance solution: Ropivacaine, 0.1%; fentanyl 2ug/ml.
PIEB + PCEA: 5 ml bolus of epidural solution every hour. Option for PCEA 5ml bolus, 10 minutes lockout.
CEI + PCEA: Epidural solution infused at rate 5ml/h. Option for PCEA 5ml bolus, 10 minutes lockout.
*Onset of motor block (inability to flex either knee), or hypotension (reduced systolic pressure of more than 25%), within the next 10 mins of time 0 was considered misplacement of catheter and participant excluded.
*If participant felt pain was inadequate, the anaesthesiologist administered additional pain relief (5ml of 0.2% ropivacaine

	every 10 minutes (max 20ml) followed by epidural fentanyl 50ug if needed after 10ml ropivacaine until pain was relieved. Sia 2013 Analgesia initiation: Combined spinal-epidural. Ropivacaine, 2mg; fentanyl 15ug. Epidural analgesia maintenance solution: Ropivacaine 0.1%, fentanyl 2ug/ml. **PIEB + PCEA:** 5 ml bolus of epidural solution every hour. Option for PCEA 5ml bolus, 10 minutes lockout. *First bolus delivered 60minutes from time 0. **CEI + PCEA:** Epidural solution infused at rate 5ml/h. Option for PCEA 5ml bolus, 10 minutes lockout. *If participant had pain of 3 or more on VAS, 15 minutes after analgesia initiation the block was deemed ineffective and the participant was withdrawn. *If participant had pain of 3 or more on VAS, during PCEA, additional pain relief was administered by anaesthetist (5ml of 0.2% ropivacaine every 10 min (max 20 ml) until VAS decreased to below 3 cm. Fentanyl 50 ug was added if the VAS was 3 or more after 10ml ropivacaine.
Duration of follow-up	
Sample size	Chua 2004 N=42 Intervention, n=21 Comparator, n=21 Fan 2019 N=2865 Intervention. n=1454 Comparator, n=1411 Fettes 2006 N=40 Intervention. n=20 Comparator, n=20 Leo 2010 N=62 Intervention. n=31 Comparator, n=31

	Lim 2010 N=62 Intervention. n=31 Comparator, n=31 Lin 2016 N=197 Intervention. n=98 Comparator, n=99 Ojo 2020 N=120 Intervention. n=61 Comparator, n=59 Sia 2007 N=42 Intervention. n=21 Comparator, n=21 Sia 2013 N=102 Intervention. n=51 Comparator, n=51

Outcomes

Chua 2004

Outcome	**PIEB, , N = 21**	**CEI, , N = 21**
Rescue analgesia Anaesthetist administered analgesia for breakthrough pain No of events	n = 17	n = 16
Motor block	n = 1	n = 1

Outcome	PIEB, , N = 21	CEI, , N = 21
*1 or less Bromage score No of events		

Fan 2019

Outcome	PIEB + PCEA, , N = 1454	CEI + PCEA, , N = 1411
Motor block *0 Bromage score (no motor block) No of events	n = 1454	n = 1411
General labour pain - 1 hour *visual analogue scale (0-10, lower values better) Median (IQR)	1 (1 to 2)	1 (1 to 2)
General labour pain - 2 hours *visual analogue scale (0-10, lower values better) Median (IQR)	1 (1 to 2)	2 (1 to 2)
General labour pain - 3 hours *visual analogue scale (0-10, lower values better) Median (IQR)	2 (1 to 2)	2 (1 to 3)
General labour pains - 4 hours *visual analogue scale (0-10, lower values better) Median (IQR)	2 (2 to 3)	3 (2 to 4)
General labour pains - 5 hours *visual analogue scale (0-10, lower values better) Median (IQR)	2 (2 to 3)	3 (2 to 4)

Outcome	PIEB + PCEA, , N = 1454	CEI + PCEA, , N = 1411
General labour pains - at birth *visual analogue scale (0-10, lower values better) Median (IQR)	3 (2 to 4)	4 (3 to 4)
Duration of labour - first stage (Minutes) * Mean (SD)	539 (107)	547 (121)
Duration of labour - second stage (Minutes) Mean (SD)	51 (12)	52 (12)
Instrumental birth No of events	n = 86	n = 92
Women's experience - satisfaction score * taken after birth (0 to 10, higher values better) Median (IQR)	9 (9 to 10)	7 (6 to 7)

Fettes 2006

Outcome	PIEB, , N = 20	CEI, , N = 20
Rescue anaesthesia (assumed delivered by anaesthetist from discussion in the study) No of events	n = 4	n = 12
General labour pain *Visual analogue scale - area under curve Median (IQR)	592 (107 to 1547)	1121 (0 to 2963)
Duration of labour - first stage (Minutes)	467.1 (273.3)	587.1 (267.1)

Outcome	PIEB, , N = 20	CEI, , N = 20
* Mean (SD)		
Duration of labour - second stage (Minutes) Mean (SD)	99.2 (66.2)	102.8 (62.6)
Instrumental birth No of events	n = 10	n = 10
Caesarean birth No of events	n = 3	n = 5

Leo 2010

Outcome	PIEB + PCEA, , N = 31	CEI + PCEA, , N = 31
Rescue analgesia (breakthrough pain requiring epidural top-up by anaesthesiologist) No of events	n = 4	n = 6
General labour pain - 4 hours *VAS (0 to 10, higher scores worse) Mean (SD)	0.16 (0.8)	1.11 (1.8)
Duration of labour - total labour time (Minutes) Mean (SD)	443.3 (221.3)	422.7 (200.7)
Duration of labour - second stage (Minutes) Mean (SD)	62.2 (37.4)	76.2 (58.2)
Spontaneous vaginal birth	n = 21	n = 16

Outcome	PIEB + PCEA, , N = 31	CEI + PCEA, , N = 31
* No of events		
Instrumental birth No of events	n = 2	n = 6
Caesarean birth No of events	n = 8	n = 9
Women's experience overall labour analgesia experience (*verbal scale 0 to 100, higher scores beter) Mean (SD)	93.9 (7)	85.8 (7.2)

Lim 2010

Outcome	PIEB, , N = 25	CEI, , N = 25
Rescue analgesia (anaesthetist provided epidural analgesia for breakthrough pain) No of events	n = 9	n = 8
General labour pain - 15 minutes *VAS (0 to 10, higher scores worse) Mean (SD)	0.2 (0.7)	0.4 (1.8)
General labour pain - 30 minutes *VAS (0 to 10, higher scores worse) Mean (SD)	0 (0.2)	0.1 (0.4)
General labour pain - 2 hours	0.5 (1.4)	0 (0.2)

Outcome	PIEB, , N = 25	CEI, , N = 25
*VAS (0 to 10, higher scores worse) Mean (SD)		
General labour pain - 4 hours *VAS (0 to 10, higher scores worse) Mean (SD)	0.3 (0.7)	1.1 (2.2)
General labour pain - 8 hours *VAS (0 to 10, higher scores worse) Mean (SD)	1.2 (2.3)	0.6 (1.1)
Duration of labour - total labour (Minutes) Mean (SD)	369 (63)	441 (21)
Duration of labour - second stage (Minutes) Mean (SD)	76 (63)	98 (70)
Spontaneous vaginal birth * No of events	n = 19	n = 15
Instrumental birth No of events	n = 3	n = 6
Caesarean birth No of events	n = 3	n = 4
Satisfaction * 0 to 100, higher score better	100 (8.75)	90 (5)

Outcome	PIEB, , N = 25	CEI, , N = 25
Mean (SD)		

Lin 2016

Outcome	PIEB + PCEA, , N = 102	CEI + PCEA, , N = 99
Duration of labour - second stage (Minutes) Mean (SD)	55.31 (9.71)	58.53 (8.19)
Instrumental birth No of events	n = 10	n = 9
Caesarean birth No of events	n = 8	n = 10

Ojo 2020

Outcome	PIEB + PCEA, , N = 61	CEI + PCEA, , N = 59
Rescue analgesia (clinician administered) No of events	n = 13	n = 14
Motor block Bromage score <5 (1= complete block, 5=no weakness able to raise extended leg) No of events	n = 14	n = 26
General labour pain Maximum pain score VAS (higher scores worse) Median (IQR)	3 (0 to 6)	2 (0 to 4)
Duration of labour - second stage (Minutes)	44 (26)	63 (25.8)

Outcome	PIEB + PCEA, , N = 61	CEI + PCEA, , N = 59
only those with spontaneous vaginal birth Mean (SD)		
Spontaneous vaginal birth No of events	n = 41	n = 37
Instrumental birth No of events	n = 5	n = 5
Caesarean birth No of events	n = 15	n = 17
Maternal satisfaction - very satisfied or satisfied * No of events	n = 44	n = 42

Sia 2007

Outcome	PIEB + PCEA, , N = 21	CEI + PCEA, , N = 21
Rescue analgesia (*breakthrough pain required an anaesthesiologists intervention) No of events	n = 5	n = 3
Motor block Bromage score >0 No of events	n = 1	n = 0
Duration of labour - total duration (Minutes) Mean (SD)	375 (155.3)	313 (219)

Outcome	PIEB + PCEA, , N = 21	CEI + PCEA, , N = 21
Duration of labour - second stage (Minutes) Mean (SD)	72 (36)	80 (36)
Spontaneous vaginal birth No of events	n = 13	n = 16
Instrumental birth No of events	n = 1	n = 2
Caesarean birth No of events	n = 7	n = 3
Maternal satisfaction VAS 0-100, higher score better Mean (SD)	95 (8.75)	90 (10)

Sia 2013

Outcome	PIEB + PCEA, , N = 51	CEI+ PCEA, , N = 51
Rescue analgesia (*breakthrough pain requiring supplementation by an anaesthetist) No of events	n = 3	n = 12
Motor block No of events	n = 0	n = 0
Duration of labour - total duration (Minutes) Mean (SD)	389.4 (202.9)	414.2 (181.3)

Outcome	PIEB + PCEA, , N = 51	CEI+ PCEA, , N = 51
Duration of labour - second stage (Minutes) Mean (SD)	69.8 (48.9)	84.9 (57.9)
Spontaneous vaginal birth * No of events	n = 33	n = 32
Instrumental birth No of events	n = 5	n = 8
Caesarean birth No of events	n = 13	n = 11
Maternal satisfaction VAS 0 to 100, higher scores are better Mean (SD)	96.5 (5)	89.2 (9.4)

Critical appraisal - NGA Critical appraisal - ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Unclear *(Not enough study characteristics were extracted.)*

Section	Question	Answer
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Fully applicable

Limitations for each of the included studies assessed with the Cochrane Risk of Bias Tool v1, based on the Cochrane review assessments

Study	Answer
Chua 2004	Random sequence generation: Some concerns Allocation concealment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk Blinding of participants and personnel: Low risk Blinding of outcome assessment: Low risk
Fan 2019	Random sequence generation: Low risk Allocation concealment: Some concerns Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk Blinding of participants and personnel: Low risk Blinding of outcome assessment: Low risk
Fettes 2006	Random sequence generation: Low risk Allocation concealment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk

Study	Answer
	Blinding of participants and personnel: Low risk Blinding of outcome assessment: Low risk
Leo 2010	Random sequence generation: High risk Allocation concealment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk Blinding of participants and personnel: Low risk Blinding of outcome assessment: Low risk
Lim 2010	Random sequence generation: Low risk Allocation concealment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk Blinding of participants and Low risk
Lin 2016	Random sequence generation: Low risk Allocation concealment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk Blinding of participants and personnel: Low risk Blinding of outcome assessment: Low risk
Ojo 2019	Random sequence generation: Low risk Allocation concealment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk Blinding of participants and personnel: Low risk Blinding of outcome assessment: Low risk

Study	Answer
Sia 2007	Random sequence generation: Low risk Allocation concealment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk Blinding of participants and personnel: Low risk Blinding of outcome assessment: Low risk
Sia 2013	Random sequence generation: Low risk Allocation concealment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk Blinding of participants and personnel: Low risk Blinding of outcome assessment: Low risk

Meena, 2022

Bibliographic Reference Meena, Anuradha; Mitra, Sukanya; Singh, Jasveer; Saroa, Richa; Takker, Navneet; Analgesic efficacy of programmed intermittent epidural bolus vs patient-controlled epidural analgesia in laboring parturients.; Journal of anaesthesiology, clinical pharmacology; 2022; vol. 38 (no. 2); 178-183

Study details

Study type	Randomised controlled trial (RCT)
Inclusion criteria	• American Society of Anesthesiologists (ASA) grade I and II parturient • over 18 years old • requesting epidural for analgesia in labour • able to use a PCEA pump • baseline pain score more than 30 on a visual analogue scale 0-100 • with age >18 years, requesting for epidural • primigravid

	• spontaneous onset of labour at 36 weeks or more • cervical dilation 5 cm or less • cephalic presentation.
Exclusion criteria	• Refusal by participant • if they have received parenteral opioids in the last 4 hours • systemic or local sepsis • deranged coagulation profile • multiple pregnancy • premature labour • obstetric complications including: premature rupture of amniotic membranes; chorioamnionitis; HELLP syndrome; non-cephalic presentations; allergy to levobupivacaine or fentanyl.
Patient characteristics	**Age, mean (SD):** PCEA: 26.72 (2.6) PIEB + PCEA: 26.76 (3.57) **BMI, mean (SD):** PCEA: 28.39 (5.01) PIEB + PCEA: 28.55 (4.26)
Intervention(s)/control	PCEA: • Participants were given a hand-held device and self-administered PCEA bolus (5 ml of 0.1% levobupivacaine + 2mcg/ml fentanyl) by pressing a button on the device. • Lockout interval was 15 minutes. • First PCEA bolus administered when the participant felt pain after spinal anaesthesia. • If pain-relief was inadequate (VAS more than 30) then rescue analgesia by physician was available (5ml of same

	drug) PIEB + PCEA: • Participants received physician-controlled programmed intermittent boluses (5ml of 0.1% levobupivacaine + 2mcg/ml fentanyl). • First PIEB dose given when participant felt pain after the subarachnoid block. • PIEB doses were administered hourly. • If pain-relief was inadequate (VAS more than 30) then rescue analgesia by PCEA was available (5ml of same drug).
Sources of funding	Not industry funded
Sample size	N=50 randomised PCEA: n=25 PIEB + PCEA: n=25

Outcomes

Outcome	**PIEB + PCEA, , N = 25**	**PCEA , , N = 25**
Duration of labour, minutes Median (IQR)	244 (163 to 382)	273 (156 to 539)
Mode of delivery - Vaginal birth No of events	n = 21	n = 21
Mode of delivery - instrumental birth No of events	n = 4	n = 4
Maternal satisfaction, VAS 0-100 Mean (SD)	98.4 (3.78)	99.2 (2.38)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Computer generated randomisation, and allocation concealed. No baseline imbalances to suggest any issues.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No mention of blinding. There could have been deviations from the intended interventions but unlikely to have affected the outcome. Assumed intention to treat.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all participants randomised.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome assessors were not blinded, but duration of labour and mode of birth outcomes were objective therefore not subject to bias. Some concerns for maternal satisfaction as this outcome is subjective and could have been influenced by knowing the intervention*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Outcomes were reported in accordance with the pre-specified protocol.)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Some concerns for duration of labour and mode of birth. High for maternal satisfaction.

Morau, 2019

Bibliographic Morau, Estelle; Jaillet, Malaury; Storme, Brigitte; Nogue, Erika; Bonnin, Martine; Chassard, Dominique; Benhamou, Dan;

Reference Nagot, Nicolas; Dadure, Christophe; Does programmed intermittent epidural bolus improve childbirth conditions of nulliparous women compared with patient-controlled epidural analgesia?: A multicentre, randomised, controlled, triple-blind study; European journal of anaesthesiology; 2019; vol. 36 (no. 10); 755-762

Study details

Country/ies where study was carried out	France
Study type	Randomised controlled trial (RCT)
Study dates	January 2014 to June 2016
Inclusion criteria	• Nulliparous women • term pregnancy (≥37 weeks gestation) • healthy singleton pregnancy • vertex position • spontaneous labour • cervical dilation of 4cm or less • pain score more than 4 on a 0-10 verbal numeric pain scale (VNS) at the time of epidural request • written consent.
Exclusion criteria	• Contraindication to epidural analgesia • contraindication to maternal pushing efforts • administration of opioids within 4 hours before the epidural request • abnormal fetal heart rate • maternal neuromuscular disease • unknown uterine malformations • patient refusal • does not speak French • no health insurance.

Patient characteristics	No baseline differences between the groups for age, height weight, gestational age or ASA physical status score Age, years - mean (±SD) PIEB+PCEA: 28.4 (4.5) PCEA+CEI: 28.6 (4.7) Weight before pregnancy, kg - mean (±SD) PIEB+PCEA: 61.7 (12.8) PCEA+CEI: 61.7 (11.4) Height, cm - mean (±SD) PIEB+PCEA: 164.4 (6.2) PCEA+CEI: 165.0 (7.0) Gestational age (weeks) PIEB+PCEA: 39.9 (1.05) PCEA+CEI: 40.0 (0.97)
Intervention(s)/control	Epidural analgesia was initiated in both groups. An epidural catheter was inserted 3 to 4 cm into the epidural space. No test dose was given. Following a negative aspiration rest, analgesia was initiated with levobupivacaine 15 mg (15ml or 0.1% Chirocaine) and 10ug of sufentanil. 30 minutes after the epidural loading dose, patients with suspected nonfunctioning epidural catheter (a VNS score more than 1) or significant motor blockade (Bromage <3) were excluded. Programmed Intermittent Epidural Bolus (PIEB) + Patient Controlled Epidural Analgesia (PCEA) • Analgesia was maintained using 0.1% levobupivacaine with 0.36ug/ml sufentanil. • 8ml bolus administered via a pump every 60 minutes. • First dose given 60 minutes after the initial dose. • The pump was also programmed to administer PCEA boluses of 8ml with a minute refractory period, and a maximum hourly dose of 24ml. • 10 minute refractory period also programmed between PIEB and PCEA boluses.

	PCEA + Continuous Epidural Infusion (CEI) • Analgesia was maintained using 0.1% levobupivacaine with 0.36ug/ml sufentanil. • A continuous infusion rate of 8ml/60 minutes began immediately. • The pump was also programmed to administer PCEA boluses of 8ml with a minute refractory period, and a maximum hourly dose of 24ml. If pain persisted after 2 consecutive PCEA boluses, the anaesthetic team could administer an additional 5ml bolus of the solution combined with 50ug of clonidine. This was available to both groups. The pump was switched off after birth.
Duration of follow-up	• 30 minutes after initial epidural loading dose • at 6-8 cm dilation • at full cervical dilation • at birth.
Sources of funding	Study funded by Smiths Medical France
Sample size	N=298 randomised PIEB+PCEA: n=149 (124 analysed) PCEA + CEI: n=149 (125 analysed)
Other information	Participants were included from 4 maternity units. No adjusted have been made to the sample size as study reports randomisation was stratified by centre, therefore assumed appropriate randomisation.

Outcomes

Outcome	**PIEB + PCEA , , N = 124**	**PCEA + CEI, , N = 125**
Anaesthetist re-attendance for breakthrough pain Median (IQR)	0 (0 to 10)	0 (0 to 10)
Motor block Bromage score No of events	n = 36	n = 47

Outcome	PIEB + PCEA , , N = 124	PCEA + CEI, , N = 125
Pain at 6-8cm dilation verbal numerical score <3 No of events	n = 95	n = 87
Pain when fully dilated verbal numerical score <3 No of events	n = 98	n = 85
Duration of labour (hours) Analgesia duration Median (IQR)	7.4 (5.6 to 9.7)	7.3 (5.7 to 9.1)
Spontaneous vaginal birth No of events	n = 94	n = 83
Instrumental birth No of events	n = 32	n = 45
Maternal satisfaction with analgesia 0 to 10 scale (high values better) Median (IQR)	9 (9 to 10)	9 (9 to 10)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was random and no baseline differences to suggest problems.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, obstetricians and anaesthesiologists were blinded to the intervention. Analysis was by intention to treat.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data was not available for all participants, but missing data could not have influenced true value of outcomes and was balanced between groups.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring outcome could not have differed between groups, and outcome assessors were blinded.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Outcomes reported as in the pre-specified protocol. Results not likely to have been selected from multiple measurements or analyses.)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation

Nunes, 2016

Bibliographic Reference Nunes, Joana; Nunes, Sara; Veiga, Mariano; Cortez, Mara; Seifert, Isabel; A prospective, randomized, blinded-endpoint, controlled study - continuous epidural infusion versus programmed intermittent epidural bolus in labor analgesia; Brazilian journal of anesthesiology (Elsevier); 2016; vol. 66 (no. 5); 439-44

Study details

Country/ies where study was carried out	Portugal
Study type	Randomised controlled trial (RCT)
Study dates	April to June 2013
Inclusion criteria	• Viable pregnancy • requesting epidural analgesia • cervical dilation >3 and <5cm • baseline pain score (at the peak of contraction) from 5 to 10 in a verbal numerical scale (VNS).
Exclusion criteria	• Women who had received parenteral opioids • women who did not speak the language • unable to perform motor block evaluation tests.
Patient characteristics	No baseline differences between groups for maternal age, weight or height, or gestational age. <u>Maternal age, years - mean (±SD)</u> PIEB 0.1%: 29.4 (6.3) PIEB 0.15%: 28.1 (6.7) CEI: 29.2 (6.1) <u>Weight, kg - mean (±SD)</u> PIEB 0.1%: 79.9 (15.1) PIEB 0.15%: 78.2 (12.6) CEI: 76.6 (11.8) <u>Height, cm - mean (±SD)</u> PIEB 0.1%: 161.7 (6.4) PIEB 0.15%: 161.9 (6.4)

	CEI: 161.8 (4.9) Gestational age, weeks - mean (±SD) PIEB 0.1%: 39.5 (1.2) PIEB 0.15%: 39.5 (1.3) CEI: 39.3 (1.5) Induced labour - number: PIEB 0.1%: 12 PIEB 0.15%: 14 CEI: 22 Multiparous - number: PIEB 0.1%: 11 PIEB 0.15%: 13 CEI: 19 Twin pregnancy - number: PIEB 0.1%: 0 PIEB 0.15%: 3 CEI: 1 Twin pregnancies similar between groups.
Intervention(s)/control	Epidural analgesia was initiated using a Tuohy epidural needle 3-4cm into the epidural space. Participants did not receive a test dose. Initial epidural loading dose was 10ml of 0.15% ropivacaine plus sufentanil 10ug. Women were excluded is assumed to have a failed blocked: if VNS was >3, or if women requested an epidural bolus less than 30 minutes after the initial dose. Programmed Intermittent Epidural Bolus (PIEB) 0.1% or 0.15% • The PIEB pump was programmed to deliver the epidural solution of 10ml of either 0.1% or 0.15% ropivacaine plus sufentanil 0.2ug/ml solution every hour. • The first dose was delivered 60 minutes after the initial epidural loading dose.

	• Participants could also push a button for an anesthesiologist to administer an additional bolus. <u>Continuous Epidural Infusion (CEI) + Patient Controlled Epidural Analgesia (PCEA)</u> • The pump for CEI was programmed to deliver epidural solution of ropivacaine 0.15% plus sufentanil 0.2 ug/ml, at a rate of 5ml per hour. • Participants could an additional PCEA bolus of 5ml with a lockout interval of 20 minutes, and a maximum volume of 15ml per hour. • Participants could also push a button for an anaesthesiologist to administer an additional bolus.
Sources of funding	Not reported
Sample size	N=166 randomised (130 analysed) PIEB 0.1%, n=41 randomised (n=33 analysed. 1 did not receive allocated intervention. 5 excluded with no reason provided. 2 excluded because no data on maternal satisfaction). PIEB 0.15%, n=47 randomised (n=37 analysed. 7 excluded with no reason provided. 2 excluded because no data on maternal satisfaction). CEI, n=78 randomised (n=60 analysed. 3 did not receive allocation intervention. 13 excluded with no reason provided. 2 excluded because no data on maternal satisfaction).

Outcomes

Outcome	**PIEB 0.1%, , N = 33**	**PIEB 0.15% , , N = 37**	**CEI 0.15% + PCEA, , N = 60**
Motor block No of events	n = 0	n = 1	n = 4
Spontaneous vaginal birth No of events	n = 20	n = 18	n = 39

Outcome	PIEB 0.1%, , N = 33	PIEB 0.15% , , N = 37	CEI 0.15% + PCEA, , N = 60
Instrumental birth No of events	n = 11	n = 11	n = 8
Caesarean birth No of events	n = 2	n = 8	n = 13
Maternal satisfaction VNS scale (assumed 0 to 10, higher score worse, not described in study). Median 95% CI Median (IQR)	8.6 (7.9 to 9.3)	8.6 (7.7 to 9.4)	8.8 (8.3 to 9.3)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Participant record numbers used for allocation sequence. Odd/even numbers at the end of clinical file number used therefore sequence was predictable and unlikely to have been concealed. However no baseline imbalances to suggest a problem.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(Participants were aware of intervention. There is only mention of blinded nurse at the endpoint. The two interventions were different in that one group had PCEA and one did not and therefore it was not possible to blind the two. No mention of a placebo type of PCEA for the other arm, therefore no blinding of participants. Likely personnel caring for participants also unblinded. There were deviations from the intervention as not all participants received their allocated intervention. These were unbalanced between groups, and although the number of deviations were small there was no information regarding appropriate analysis.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(For maternal satisfaction outcome - an equal proportion were excluded from the analysis because of missing maternal satisfaction data. This could have been due to the true value of the outcome, but it is a small number so not a high concern. For other outcomes - there are other missing outcome data but this is due to reasons that are unlikely to influence the true value of the outcome (excluded due to failed block).)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(High risk of bias for maternal satisfaction. Maternal satisfaction was assessed by a blinded nurse, but the rating is assumed to have been given by the woman herself who was not blinded, therefore this outcome is subjective and could be influenced by knowledge of the intervention. Other outcomes are not subjective and not affected by knowledge of the intervention received. Low risk of bias for other outcomes.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No pre-specified protocol available to appropriately address bias, but unlikely results could have been selected from multiple measurements or analyses.)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable
Overall bias and Directness	Risk of bias variation across outcomes	High risk of bias for maternal satisfaction (randomisation concerns and subjective reporting for this when intervention was known). Some concerns for other outcomes (randomisation concerns).

Rodriguez-Campoo, 2019

Bibliographic Reference Rodriguez-Campoo, Maria Belen; Curto, Antonio; Gonzalez, Manuel; Aldecoa, Cesar; Patient intermittent epidural boluses (PIEB) plus very low continuous epidural infusion (CEI) versus patient-controlled epidural analgesia (PCEA) plus continuous epidural infusion (CEI) in primiparous labour: a randomized trial; Journal of clinical monitoring and computing; 2019; vol. 33 (no. 5); 879-885

Study details

Country/ies where study was carried out	Spain
Study type	Randomised controlled trial (RCT)
Study dates	September 2015 and July 2017
Inclusion criteria	• Primiparous women • age 20 to 40 • no pregnancy risk illness • term pregnancy • no drug allergies • vertex presentation • normal initial onset of epidural • understand the procedure and sign the informed consent.
Exclusion criteria	• Women with illnesses that involved a pregnancy risk • epidural contraindications • levobupivacaine allergy • multiparous • epidural catheter replacement due to initial incomplete onset of block • did not sign informed consent • did not understand procedure.
Patient characteristics	All primiparous women. No other details reported.
Intervention(s)/control	At the time of epidural request, epidural analgesia was initiated using an epidural catheter. A 10ml levobupivacaine 0.125% bolus was administered with a 2mcg/ml fentanyl. The catheter was attached, and a nurse (not participating in the birth) set up the epidural pump. Levobupivacaine 0.0625% + fentanyl was then administered.

	<u>Programmed Intermittent Epidural Bolus (PIEB) + Continuous Epidural Infusion (CEI) + Patient administered Epidural Analgesia (PCEA):</u> • Participants received a 2ml/hour continuous infusion with a 7ml/30min PIEB bolus. • Participants could administer a PCEA if required at 6ml/20min. • Next PIEB bolus was delayed if a PCEA was administered. <u>CEI + PCEA</u> • Participants received a 5ml/hour continuous infusion. • Participants could administer a PCEA if required at 6ml/20min. Patients were shown how to press the PCEA button. Epidural administration was calculated so that both groups theoretically received the same dose per hour, provided that all PCEA doses were requested in an hour.
Sources of funding	Not reported
Sample size	N=200 patients randomised PIEB+CEI+PCEA, n=103 (100 analysed) CEI+PCEA, n=97 (95 analysed)

Outcomes

Outcome	**PIEB+CEI+PCEA , , N = 103**	**CEI+PCEA, , N = 97**
General labour pain - 15 minutes after epidural (0-10 higher values are worse) (Visual analogue scale) Mean (SD)	2.33 (2.23)	2.2 (2.15)
General labour pain - 3 hours 15minutes after epidural	1.94 (2.06)	1.75 (1.99)

Outcome	PIEB+CEI+PCEA , , N = 103	CEI+PCEA, , N = 97
Mean (SD)		
General labour pain - 6 hours 15 minutes after epidural Mean (SD)	1.93 (1.85)	2.01 (1.81)
General labour pain - 9 hours 15 minutes after epidural Mean (SD)	2.11 (1.82)	2.52 (2.13)
Instrumental birth No of events	n = 22	n = 11
Satisfaction score 1 or 2 (satisfied) Likert Scale (1-5, lower values are better) No of events	n = 93	n = 89

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(No information on baseline characteristics, but allocation was random and concealed in opaque envelopes.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and caring personnel were blinded to the intervention. Intention to treat analysis assumed. Trial participants were not excluded post-randomisation.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data available for nearly all participants)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome assessors were blind to the intervention and measurement of the outcome was not inappropriate.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Motor block was not reported on, but no bias concerns as it was selected from other measurements. Other outcomes reported as specified in the study protocol. Not likely to have been selected from multiple outcome measurements of analyses.)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes.

Roofthooft, 2020

Bibliographic Reference Roofthooft, E.; Barbe, A.; Schildermans, J.; Cromheecke, S.; Devroe, S.; Fieuws, S.; Rex, S.; Wong, C. A.; Van de Velde, M.; Programmed intermittent epidural bolus vs. patient-controlled epidural analgesia for maintenance of labour analgesia: a two-centre, double-blind, randomised study; Anaesthesia; 2020; vol. 75 (no. 12); 1635-1642

Study details

Country/ies where study was carried out	Belgium
Study type	Randomised controlled trial (RCT)
Study dates	February 2016 - February 2017
Inclusion criteria	• ASA physical status-2

	• Nulliparous women • ≥ 18 years of age • In active labour • Cervical dilation < 7 cm.
Exclusion criteria	• Preterm birth • Multiple gestation • Allergy to the study drugs • Contraindication to regional analgesia • Did not understand Dutch
Patient characteristics	No noticeable differences in baseline for maternal age, weight, height, gestational age or cervical dilation. Statistical significance not reported no obvious differences. Maternal age, years - mean ± SD PIEB: 28.4± 3.6 PCEA: 27.9 ± 4.3 Gestational age, weeks median (IQR [range]). PIEB: 39(39-40[31-41]) PCEA: 39 (38–40 [36–41])
Intervention(s)/control	Labour analgesia initiated using a combined spinal epidural technique at L3/4 or L4/5. Spinal analgesia provided with 4.8mg or ropivacaine and 3ug of sufentanil in 4ml, and epidural catheter inserted into epidural space. Women were excluded if the VAS score of 20mm or less had not been achieved 45 minutes after spinal injection. Epidural analgesia was maintained using epidural solution of ropivacaine 0.12% and sufentanil 0.75 µg/ml for both groups. Epidural analgesia maintenance:

	<u>Programmed epidural intermittent bolus (PIEB) + Patient controlled epidural analgesia (PCEA)</u> • PIEB pump started 15 minutes after spinal injection. • First 10ml bolus of epidural solution administered 30 minutes after starting the pump. • 10 ml boluses of epidural solution administered every hour. • 5 ml PCEA boluses of epidural solution with a 20 min lockout interval were available. <u>PCEA</u> • Analgesia was maintained using 5 ml PCEA boluses of epidural solution with a 12 min lockout interval. The maximum epidural volume per hour was 25 ml in both groups. Breakthrough pain was defined as a VAS score > 30 mm with a request for additional analgesia after at least one PCEA bolus had been administered. 8ml top-up of epidural solution administered if there was breakthrough pain. If VAS remained >30mmm after 20minutes, another top-up was given. If VAS >30mm after second top-up, block was deemed to have failed and woman was excluded. Breakthrough pain was treated by anaesthetist, as described in the discussion section of the study.
Duration of follow-up	not specified
Sources of funding	Not industry funded. • MVdV has received financial support for lectures and consultancy from Smiths Medical (producer of the PIEB pumps) and has received financial compensation for lectures and consultancy from CSL Behring, Sintetica,Grunenthal, Ferrer, Nordic Pharma, MSD, HeronTx, Halyard, Flatmedical, Aquettant, Viforpharma and Medtronic.
Sample size	N= 130 women randomised (125 included in analysis) <u>PIEB + PCEA</u> n= 65 (excluded n=1 [epidural catheter failure]) n= 64 analysed

	PCEA n= 65 (excluded n= 4 [1 epidural catheter failure; 1 failed spinal block; 2 incomplete data sets]) n= 61 analysed
Other information	2 centres were included but randomisation was at participant level.

Outcomes

Outcome	**PIEB + PCEA, , N = 64**	**PCEA, , N = 61**
Anaesthetist re-attendance for breakthrough pain Breakthrough pain defines as a VAS score >30mm. Lower values are better No of events	n = 7	n = 38
Motor block No of events	n = 1	n = 8
VAS pain score 15 mins after spinal injection (0-100) Lower values are better Median (IQR)	0 (0 to 20)	0 (0 to 20)
VAS pain score 30 mins after spinal injection (0-100) Lower values are better Median (IQR)	0 (0 to 10)	0 (0 to 10)
VAS pain score 45 mins after spinal injection (0-100) Lower values are better Median (IQR)	0 (0 to 10)	0 (0 to 10)
VAS pain score 60 mins after spinal injection (0-100) Lower values are better	0 (0 to 0)	0 (0 to 0)

Outcome	PIEB + PCEA, , N = 64	PCEA, , N = 61
Median (IQR)		
VAS pain score 120 mins after spinal injection (0-100) Lower values are better Median (IQR)	0 (0 to 5)	5 (0 to 30)
VAS pain score 180 mins after spinal injection (0-100) Lower values are better Median (IQR)	0 (0 to 10)	10 (0 to 40)
VAS pain score 240 mins after spinal injection (0-100) Lower values are better Median (IQR)	0 (0 to 10)	3 (0 to 20)
VAS pain score 300 mins after spinal injection (0-100) Lower values are better Median (IQR)	0 (0 to 10)	0 (0 to 30)
VAS pain score 360 mins after spinal injection (0-100) Lower values are better Median (IQR)	0 (0 to 10)	30 (0 to 60)
VAS pain score 420 mins after spinal injection (0-100) Lower values are better Median (IQR)	10 (0 to 10)	10 (0 to 40)
Duration of labour (mins) (Minutes) Lower values are better. No information on whether this was 1st or 2nd stage Median (IQR)	304 (225 to 417)	312 (192 to 411)
Operative vaginal birth	n = 15	n = 14

Outcome	PIEB + PCEA, , N = 64	PCEA, , N = 61
Lower values are better No of events		
Caesarean birth Lower values are better No of events	n = 16	n = 11
Maternal satisfaction at 1 hour post birth (VAS 0-100) Higher values are better Median (IQR)	100 (100 to 100)	100 (98 to 100)
Maternal satisfaction at 24 hours post birth (VAS 0-100) Higher values are better Median (IQR)	100 (90 to 100)	100 (90 to 100)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was computer generated and concealed. No differences in baseline to suggest problems)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Per protocol analysis. Participants and personnel not aware of intervention and there were no failures to implement, or non-adherence.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data available for nearly all women.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of assessing outcomes was not inappropriate. Outcome assessors were blind to the intervention.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Outcome unlikely to have been selected for multiple measures or analyses. Not enough information on pre-specified outcomes and protocol not available.)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes.

Song, 2021

Bibliographic Reference Song, Yujie; Du, Weijia; Zhou, Shuangqiong; Zhou, Yao; Yu, Yibing; Xu, Zhendong; Liu, Zhiqiang; Effect of Dural Puncture Epidural Technique Combined With Programmed Intermittent Epidural Bolus on Labor Analgesia Onset and Maintenance: A Randomized Controlled Trial; Anesthesia and analgesia; 2021; vol. 132 (no. 4); 971-978

Study details

Country/ies where study was carried out	China
Study type	Randomised controlled trial (RCT)
Study dates	December 2017
Inclusion criteria	• Nulliparous women • Classified as American Society of Anesthesiologists class II • Singleton pregnancy

	• Vertex presentation • 37–42 weeks' gestation • In active labour with a cervical dilation <5 cm • Baseline pain score >50 mm on a 100- mm visual analogue scale (VAS) at the time of request for epidural analgesia
Exclusion criteria	• Age <20 or >40 years • Morbid obesity • Pregnancy-related diseases (i.e. gestational diabetes, gestational hypertension, and preeclampsia) • History of drug abuse • Contraindications to neuraxial blocks, • Conditions that increase the risk of a caesarean birth (i.e. placenta praevia, history of uterine anomaly, or surgery) • Known fetal abnormalities • Inadvertent dural puncture using the epidural needle • When cerebrospinal fluid (CSF) could not be confirmed with the spinal needle while performing the dural puncture • If a birth occurred within 1 hour after epidural catheter placement.
Patient characteristics	No specific information on whether statistically significant difference but no obvious differences baseline for maternal age, BMI, gestational age, induction of labour or cervical dilation. <u>Maternal age, years - mean (±SD)</u> PIEB + PCEA: 29.1 (3.06) CEI (EP) + PCEA: 28.8 (3.17) CEI (DPE) + PCEA: 29.9 (2.89) Combined CEI + PCEA: (not reported by study, manually calculated): 29.4 (3.03) <u>BMI - mean (±SD)</u> PIEB + PCEA: 25.7 (3.00) CEI (EP) + PCEA: 26.4 (2.91) CEI (DPE) + PCEA: 26.2 (3.33) Combined CEI + PCEA: (not reported by study, manually calculated): 26.3 (3.12)

	Gestational age, days - mean (±SD) PIEB + PCEA: 276 (6.3) CEI (EP) + PCEA: 279 (6.5) CEI (DPE) + PCEA: 278 (7.9) Combined CEI + PCEA: (not reported by study, manually calculated): 278.5 (7.2) Induction of labour, n (%) PIEB + PCEA: 9 (23.7) CEI (EP): 9 (23.7) CEI (DPE): 10 (25) Combined CEI + PCEA: (not reported by study, manually calculated): 19 (23.8)
Intervention(s)/control	Dural puncture epidural (DPE) technique was used for programmed intermittent epidural bolus (PIEB) arm, and either DEP or conventional epidural (EP) technique was used for the comparator arms. A test dose of 3ml of 1.5% lidocaine, with epinephrine 15ug was administered. Epidural analgesia was then initiated with 10ml of 0.1% ropivacaine with 0.3 ug/ml of sufentanil. PIEB + PCEA • Epidural analgesia was maintained with epidural solution 0.1% ropivacaine with 0.3ug/ml sufentanil. • 8ml bolus of epidural solution administered every hour, with the first dose 1 hour after initiation. • Patient controlled epidural analgesia (PCEA) was available, with a 5ml bolus of epidural solution and a 20 minutes lockout period. CEI + PCEA • Epidural analgesia was maintained with epidural solution 0.1% ropivacaine with 0.3ug/ml sufentanil. • Epidural infusion of 8ml epidural solution administered every hour. • Patient controlled epidural analgesia (PCEA) was available, with a 5ml bolus of epidural solution and a 20 minutes lockout period. If breakthrough pain was not resolved by PCEA, a provider bolus of 5ml of 0.125% ropivacaine was administered.
Duration of follow-up	24 hours
Sources of funding	Not industry funded

Sample size	N = 120 women randomised CEI (EP) + PCEA n = 40 randomised (n = 38 analysed, n=2 excluded [1 blood aspiration; 1 birth within 1 hour]) CEI (DPE) + PCEA n = 40 randomised and analysed DPE + PIEB group n = 40 (n=38 analysed, n=2 excluded [1 unable to puncture dural; 1 birth within 1 hour])
Other information	3-arm trial. 2 comparator arms used different epidural techniques and have been combined.

Outcomes

Outcome	**PIEB + PCEA, , N = 38**	**CEI + PCEA, , N = 78**
Number of provider given boluses Lower values are better No of events	n = 4	n = 27
Motor block Modified Bromage score No of events	n = 0	n = 1
Labour pain at 10 minutes VAS score 0-100. Lower values are better Mean (SD)	18 (18.4)	21.55 (21.08)

Outcome	PIEB + PCEA, , N = 38	CEI + PCEA, , N = 78
Labour pain at 20 minutes VAS score 0-100. Lower values are better Mean (SD)	11.7 (12.4)	16.31 (16.71)
Labour pain at 30 minutes VAS score 0-100. Lower values are better Mean (SD)	15.7 (15)	17.41 (16.04)
Labour pain at 2 hours VAS score 0-100. Lower values are better Mean (SD)	24.2 (17.9)	29.91 (18.05)
Labour pain at 3.5 hours VAS score 0-100. Lower values are better Mean (SD)	31.2 (17.5)	38.16 (18.04)
Labour pain at 5 hours VAS score 0-100. Lower values are better Mean (SD)	30.3 (18.3)	44.25 (16.5)
Duration of first stage of labour minutes. lower values are better Mean (SD)	504 (205)	593 (228.46)
Duration of second stage of labour minutes. Lower values are better Mean (SD)	37 (23.6)	44.77 (30.87)
Spontaneous vaginal birth	n = 32 ; % = 91.4	n = 61 ; % = 78.2

Outcome	PIEB + PCEA, , N = 38	CEI + PCEA, , N = 78	
higher values are better No of events			
Instrumental vaginal birth lower values are better No of events	n = 3	n = 6	
Caesarean birth lower values are better No of events	n = 3	n = 11	
Satisfaction with analgesia higher values are better Median (IQR)	97.5 (90 to 100)	90 (87.5 to 100) *(CEI + EP)*	92.55 (80 to 100) *(CEI + DPE)*

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was computer generated and concealed. No baseline imbalances.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Analysis assumed per protocol. 4 participants were excluded post randomisation due to failed block or delivery, but unlikely to have an impact on results.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data available for nearly all women)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome assessment not inappropriate. Outcome assessors were blinded.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Outcomes reported as in the specified protocol. Unlikely to have been selected.)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes.

Wong, 2006

Bibliographic Reference	Wong, Cynthia A.; Ratliff, John T.; Sullivan, John T.; Scavone, Barbara M.; Toledo, Paloma; McCarthy, Robert J.; A randomized comparison of programmed intermittent epidural bolus with continuous epidural infusion for labor analgesia; Anesthesia and analgesia; 2006; vol. 102 (no. 3); 904-9

Study details

Country/ies where study was carried out	Unites States
Study type	Randomised controlled trial (RCT)
Study dates	June 2003 to April 2005
Inclusion criteria	• Healthy, parous (at least 1 previous vaginal birth) • term pregnancy • singleton pregnancy • vertex presentation

	• scheduled for an induction of labour.
Exclusion criteria	• Presence of systemic disease for example, diabetes mellitus, hypertension, preeclampsia • chronic analgesic use • birth within 90 min of intrathecal injection (epidural initiation) - 90 minutes was the expected duration of intrathecal analgesia, and any epidural anaesthetic given within 90 minutes would have had limit impact of the analgesia felt.
Patient characteristics	No differences between groups for gestational age, parity, height, weight, baseline visual analogue scale for pain. <u>Gestational age in weeks - mean (range):</u> PIEB + PCEA: 39 (37 to 41) CEI + PCEA: 39 (37 to 41) <u>Parity - mean (range):</u> PIEB + PCEA: 1 (1 to 4) CEI + PCEA: 1 (1 to 3) <u>Height cm - mean (±SD):</u> PIEB + PCEA: 165 (6) CEI + PCEA: 167 (7) <u>Weight kg - mean (±SD):</u> PIEB + PCEA: 76 (10) CEI + PCEA: 81 (13) <u>Baseline visual analog scale for pain (0-100mm) - mean (±SD):</u> PIEB + PCEA: 59 (18) CEI + PCEA: 57 (16)
Intervention(s)/control	For both groups combined spinal-epidural analgesia was initiated - 1.25mg bupivacaine and 15 microgram of fentanyl

	injected intrathecal. A test dose of lidocaine 1.5% with epinephrine 1:200,000 was administered. Participants continued with the study if their VAS was <100 10 minutes after the intrathecal injection. Epidural solution for maintenance of analgesia was 0.625mg/ml (0.0625%) bupivacaine and fentanyl 2ug/ml. <u>Intervention: Programmed intermittent epidural bolus (PIEB) + patient controlled epidural analgesia (PCEA)</u> • PIEB pump delivered 6ml bolus at a rate of 400ml/h every 30 minutes - beginning 45 minutes after administration of the intrathecal dose. • PCEA pump was programmed to deliver 5ml patient-activated boluses with a lockout interval of 10 mins and a per hour maximum of 15ml. <u>Control: Continuous epidural infusion (CEI) + PCEA</u> • CEI pump delivered a continuous infusion at 12ml/h - beginning 15 minutes after administration of the intrathecal dose. • PCEA pump programmed as with PIEB group. Participants could push the button for PCEA whenever they felt uncomfortable. If participants felt they had inadequate analgesia after activating PCEA bolus two times in a 20 minutes period, the anaesthesiologist administered manual boluses of bupivacaine (1.25mg/ml 5 to 15ml) until VAS was <10mm.
Sources of funding	Not reported.
Sample size	N=158 women randomised PIEB n=63 analysed (84 randomised)

	CEI n=63 analysed (72 randomised) 20 participants excluded because they delivered within 90 minutes of intrathecal analgesia (PIEB=11; CEI=9). 10 participants in the PIEB groups were excluded because they did not receive programmed boluses (pump occlusion limits were exceeded). 2 participants had VAS >10mm at 10 minutes after intrathecal injection - no information regarding their allocated group.

Outcomes

Outcome	**PIEB + PCEA, , N = 63**	**CEI + PCEA, , N = 63**
Manual rescue bolus No of events	n = 20	n = 34
Motor block No of events	n = 1	n = 1
General labour pain VAS score x time curve from start of epidural infusion to birth Median (IQR)	6.7 (0 to 42.3)	10.3 (0 to 57.6)
Duration of labour Time from analgesia initiation to birth (minutes) Median (IQR)	188 (92 to 498)	184 (96 to 614)
Spontaneous vaginal birth No of events	n = 59	n = 59
Instrumental birth No of events	n = 3	n = 4

Outcome	PIEB + PCEA, , N = 63	CEI + PCEA, , N = 63
Caesarean birth No of events	n = 1	n = 0
Satisfaction with labour analgesia VAS scale 0-100 mm. Higher values are better Median (IQR)	92 (89 to 95)	85 (77 to 90)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was computer generated and concealed. No baseline differences suggesting an imbalance.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Per protocol analysis. Participants and other personnel were blinded to the intervention. Intervention was implemented for most participants. Intervention was set up at the start so no concerns regarding adherence.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for most participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring outcome was not inappropriate. Outcome assessors were unaware of intervention received.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Outcome data unlikely to have been selected from multiple measurements or analyses. Not enough information on whether there were deviations from the protocol as protocol unavailable.)*

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes.

ASA: American Society of Anesthesiologists; BEI: background epidural infusion; BMI: body mass index; CEI: continuous epidural infusion; CI: confidence interval; CSE: combined spinal-epidural; DPE: dural puncture epidural; EP: conventional epidural; IQR: interquartile range; NGA: National Guideline Alliance; PCEA: patient controlled epidural analgesia; PIEB: programmed intermittent epidural bolus; RCT: randomised controlled trial; SD: standard deviation; SEM: standard error of the mean; VAPS: visual analogue pain scale; VAS: visual analogue scale; VRS: verbal rating scale; VNS: visual numerical scale

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Comparison 2: PIEB + PCEA versus CEI + PCEA

Figure 2: Anaesthetist re-attendance for breakthrough pain – BMI n.r (0.1%; fentanyl)

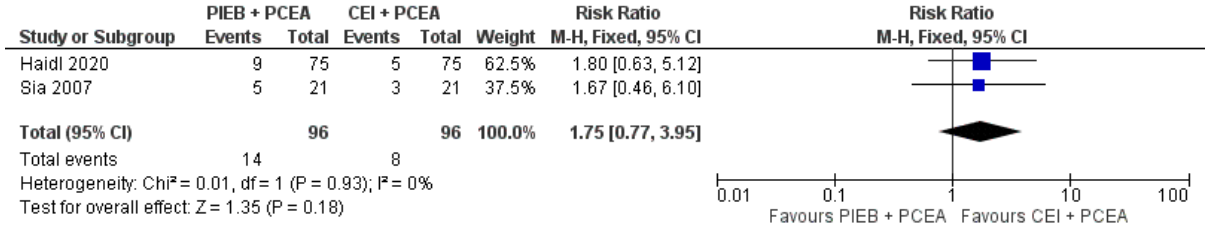


Figure 3: Anaesthetist re-attendance for breakthrough pain – BMI overweight range (0.1%; fentanyl)

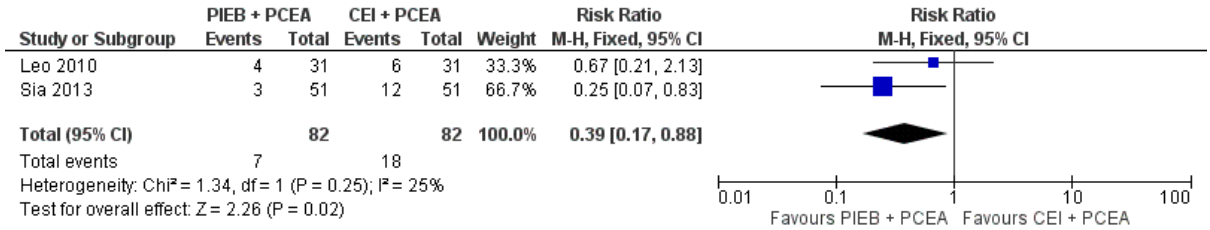


Figure 4: Motor block – BMI n.r (0.1%; fentanyl)

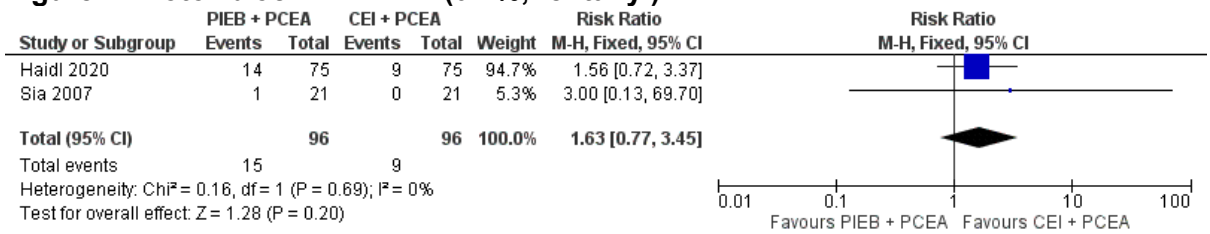


Figure 5: Duration of labour – 2nd stage – BMI overweight range (0.1%; fentanyl)

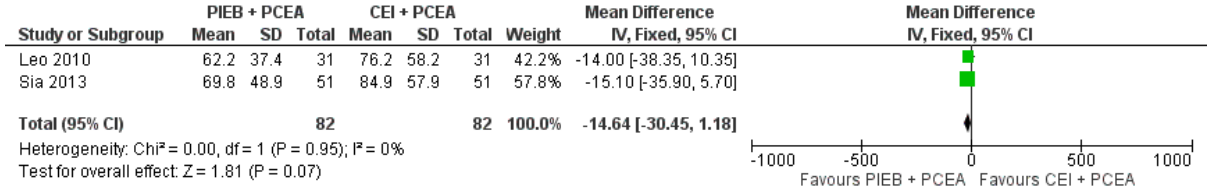


Figure 6: Duration of labour – total – BMI overweight range (0.1%; fentanyl)

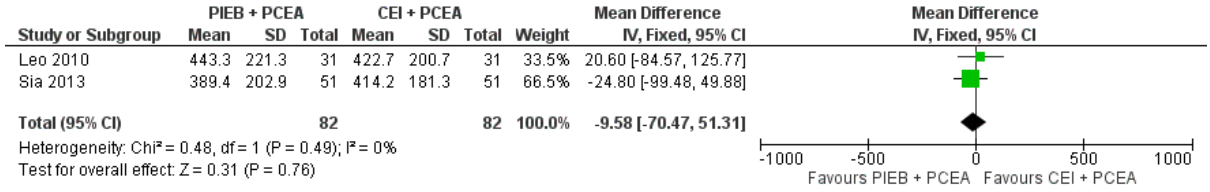


Figure 7: Duration of labour – total – BMI overweight range (0.1%; sufentanil)

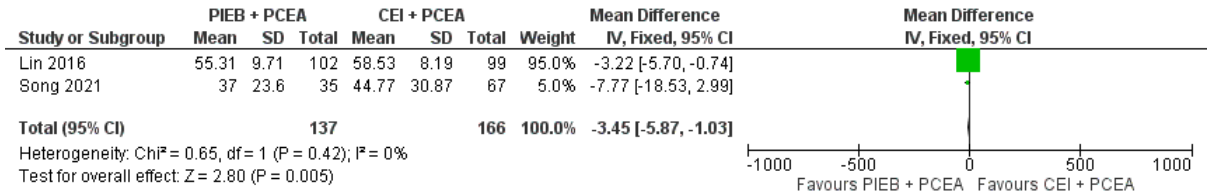


Figure 8: Spontaneous vaginal birth – BMI n.r (0.1%; fentanyl)

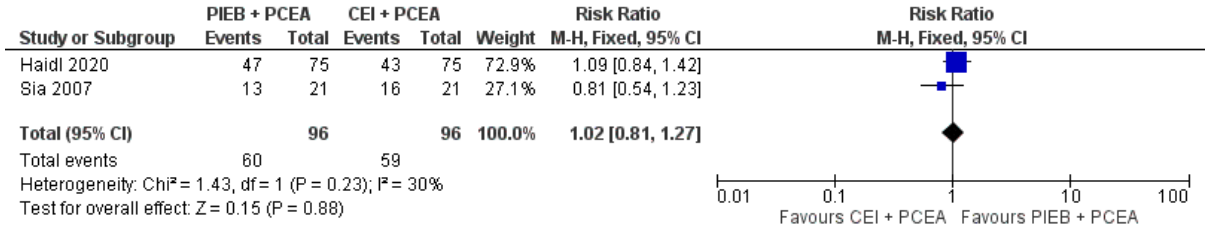


Figure 9: Spontaneous vaginal birth – BMI overweight range (0.1%; fentanyl)

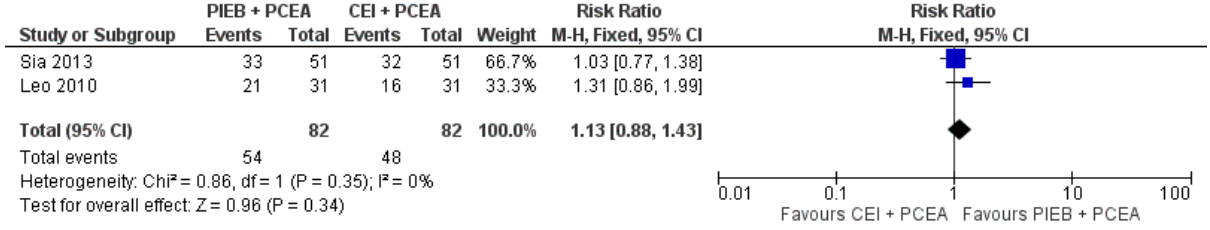


Figure 10: Instrumental birth – BMI n.r (0.1%; fentanyl)

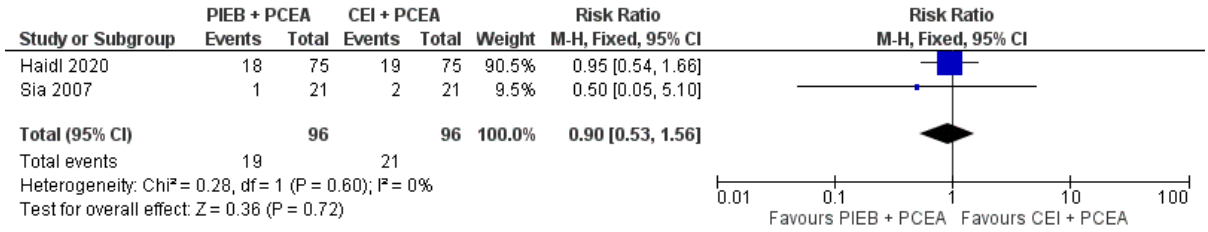


Figure 11: Instrumental birth – BMI overweight range (0.1%; fentanyl)

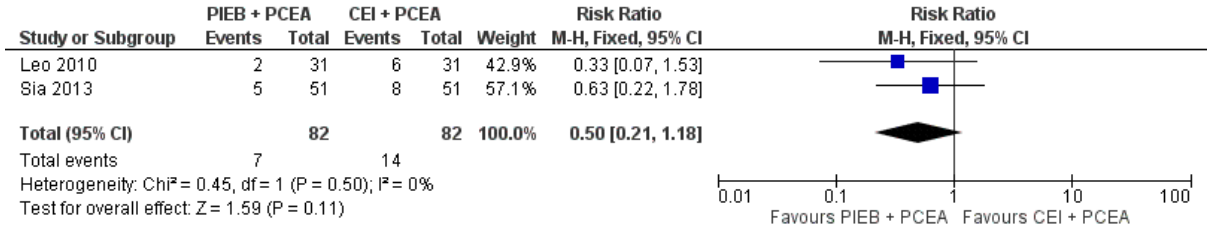


Figure 12: Instrumental birth – BMI overweight range (0.1%; sufentanil)

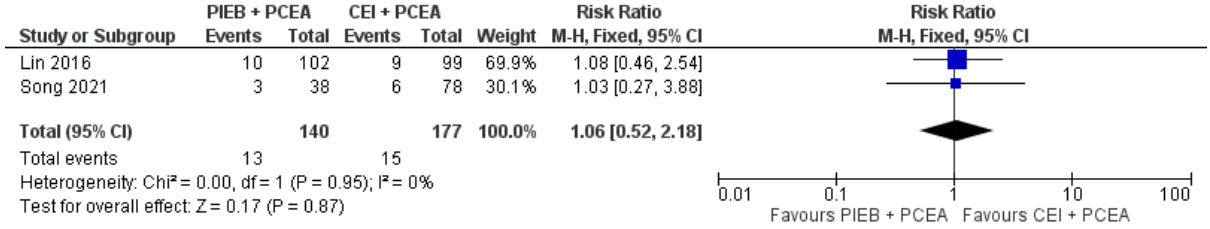


Figure 13: Caesarean birth – BMI n.r (0.1% fentanyl)

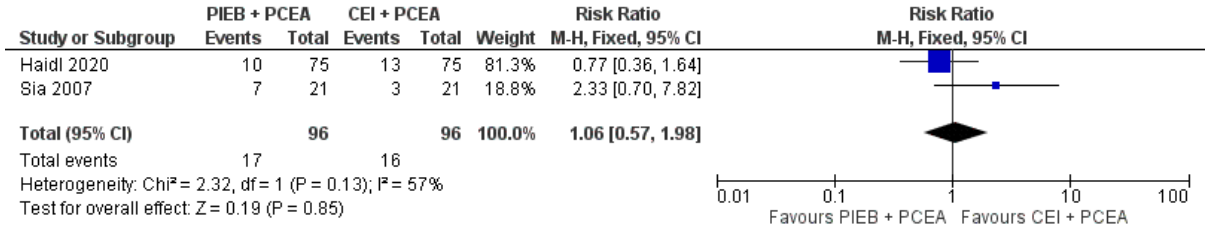


Figure 14: Caesarean birth – BMI overweight range (0.1%; fentanyl)

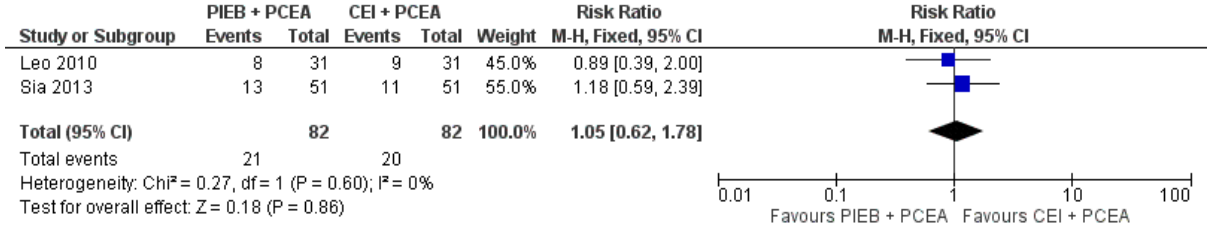


Figure 15: Caesarean birth – BMI overweight range (0.1%; sufentanil)

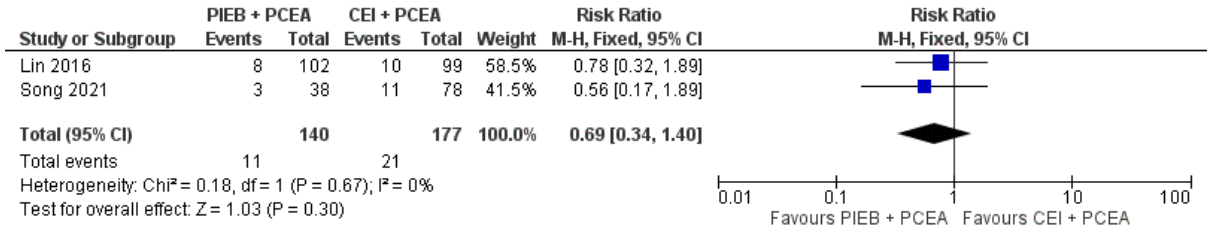
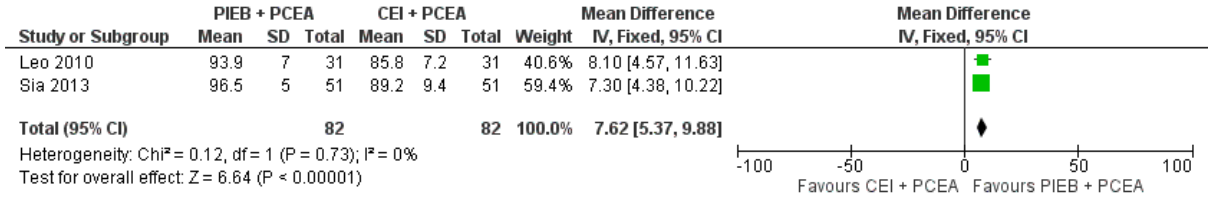
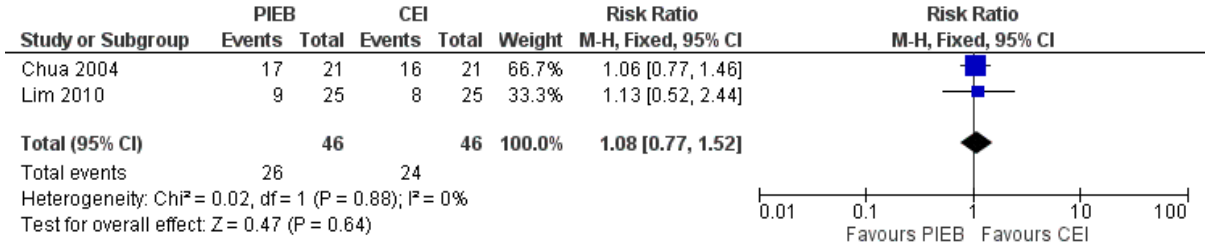


Figure 16: Women's experience of labour and birth – satisfaction – BMI overweight range (0.1%; fentanyl)



Comparison 3: PIEB versus CEI

Figure 17: Anaesthetist re-attendance for breakthrough pain – BMI n.r (0.1%; fentanyl)



Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?

Table 4: Evidence profile for comparison 1: PIEB + PCEA versus PCEA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	PCEA	Relative (95% CI)	Absolute		
Anaesthetist re-attendance for breakthrough pain – BMI healthy weight range (0.0625%; sufentanil)												
1 (Bourges 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	22/155 (14.2%)	15/162 (9.3%)	RR 1.53 (0.83 to 2.84)	49 more per 1000 (from 16 fewer to 170 more)	LOW .	CRITICAL
Anaesthetist re-attendance for breakthrough pain – BMI n.r (0.12%; sufentanil)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	7/64 (10.9%)	38/61 (62.3%)	RR 0.18 (0.08 to 0.36)	511 fewer per 1000 (from 399 fewer to 573 fewer)	MODERATE	CRITICAL
Motor block – BMI healthy weight range (0.0625%; sufentanil) (assessed with: Bromage scale)												
1 (Bourges 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[4]	none	25/155 (16.1%)	19/162 (11.7%)	RR 1.38 (0.79 to 2.39)	45 more per 1000 (from 25 fewer to 163 more)	VERY LOW .	CRITICAL
Motor block – BMI n.r (0.12%; sufentanil) (assessed with: Bromage scale)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[2]	none	1/64 (1.6%)	8/61 (13.1%)	RR 0.12 (0.02 to 0.92)	115 fewer per 1000 (from 10 fewer to 129 fewer)	LOW	CRITICAL
General labour pain at 15 minutes – BMI n.r (0.12%; sufentanil) (measured with: VAS ; range of scores: 0-100; Better indicated by lower values)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 0 (range 0 to 20), Median in PCEA: 0 (range 0 to 20)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	PCEA	Relative (95% CI)	Absolute		
General labour pain at 30 minutes – BMI n.r (0.12%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 0 (range 0 to 10), Median in PCEA: 0 (range 0 to 10)	VERY LOW	CRITICAL
General labour pain at 45 minutes – BMI n.r (0.12%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 0 (range 0 to 10), Median in PCEA: 0 (range 0 to 10)	VERY LOW	CRITICAL
General labour pain at 60 minutes – BMI n.r (0.12%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 0 (range 0 to 0), Median in PCEA: 0 (range 0 to 0)	VERY LOW	CRITICAL
General labour pain at 120 minutes – BMI n.r (0.12%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 0 (range 0 to 5), Median in PCEA: 5 (range 0 to 30)	VERY LOW	CRITICAL
General labour pain at 180 minutes – BMI n.r (0.12%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 0 (range 0 to 10), Median in PCEA: 10 (range 0 to 40)	VERY LOW	CRITICAL
General labour pain at 240 minutes – BMI n.r (0.12%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 0 (range 0 to 10), Median in PCEA: 3 (range 0 to 20)	VERY LOW	CRITICAL
General labour pain at 300 minutes – BMI n.r (0.12%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Roofthooft	randomised	no serious	no serious	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 0 (range	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	PCEA	Relative (95% CI)	Absolute		
2020)	trials	risk of bias	inconsistency							0 to 10), Median in PCEA: 0 (range 0 to 30)		
General labour pain at 360 minutes – BMI n.r (0.12%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 0 (range 0 to 10), Median in PCEA: 30 (range 0 to 60)	VERY LOW	CRITICAL
General labour pain at 420 minutes – BMI n.r (0.12%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 10 (range 0 to 10), Median in PCEA: 10 (range 0 to 40)	VERY LOW	CRITICAL
Duration of labour - total – BMI healthy weight range (0.0625%; sufentanil) (measured with: minutes; Better indicated by lower values)												
1 (Bourges 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	155	162	-	MD 13 lower (78.96 lower to 52.96 higher)	MODERATE	IMPORTANT
Duration of labour - BMI overweight range (0.1%; fentanyl) (measured with: minutes; Better indicated by lower values)												
1 (Meena 2022)	randomised trials	serious[6]	no serious inconsistency	serious[1]	very serious[5]	none	25	25	-	Median in PIEB + PCEA: 244 (range 163 to 382), Median in PCEA: 273 (range 156 to 539)	VERY LOW	IMPORTANT
Duration of labour - total – BMI n.r (0.12%; sufentanil) (measured with: minutes; Better indicated by lower values)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 304 (range 225 to 417), Median in PCEA: 312 (range 192 to 411)	VERY LOW	CRITICAL
Spontaneous vaginal birth - BMI overweight range (0.1%; fentanyl)												
1 (Meena 2022)	randomised trials	serious[6]	no serious inconsistency	serious[1]	very serious[4]	none	21/25 (84%)	21/25 (84%)	RR 1 (0.79 to 1.27)	0 fewer per 1000 (from 176 fewer to 227 more)	VERY LOW	IMPORTANT
Instrumental vaginal birth – BMI healthy weight range (0.0625%; sufentanil)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	PCEA	Relative (95% CI)	Absolute		
1 (Bourges 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[4]	none	25/155 (16.1%)	31/162 (19.1%)	RR 0.84 (0.52 to 1.36)	31 fewer per 1000 (from 92 fewer to 69 more)	VERY LOW	IMPORTANT
Instrumental vaginal birth - BMI overweight range (0.1%; fentanyl)												
1 (Meena 2022)	randomised trials	serious[6]	no serious inconsistency	serious[1]	very serious[4]	none	4/25 (16%)	4/25 (16%)	RR 1 (0.28 to 3.56)	0 fewer per 1000 (from 115 fewer to 410 more)	VERY LOW	IMPORTANT
Instrumental vaginal birth – BMI n.r (0.12%; sufentanil)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[4]	none	15/64 (23.4%)	14/61 (23%)	RR 1.02 (0.54 to 1.93)	5 more per 1000 (from 106 fewer to 213 more)	VERY LOW	IMPORTANT
Caesarean birth – BMI healthy weight range (0.0625%; sufentanil)												
1 (Bourges 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	18/155 (11.6%)	29/162 (17.9%)	RR 0.65 (0.38 to 1.12)	63 fewer per 1000 (from 111 fewer to 21 more)	LOW	IMPORTANT
Caesarean birth – BMI n.r (0.12%; sufentanil)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[4]	none	16/64 (25%)	11/61 (18%)	RR 1.39 (0.7 to 2.74)	70 more per 1000 (from 54 fewer to 314 more)	VERY LOW	IMPORTANT
Women's experience with labour and birth - satisfaction – BMI healthy weight range (0.0625%; sufentanil)												
1 (Bourges 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	138/155 (89%)	143/162 (88.3%)	RR 1.01 (0.93 to 1.09)	9 more per 1000 (from 62 fewer to 79 more)	MODERATE	IMPORTANT
Women's experience with labour and birth - satisfaction 1 hour post birth – BMI n.r (0.12%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by higher values)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 100 (range 100 to 100), Median in PCEA: 100 (range 98 to 100)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	PCEA	Relative (95% CI)	Absolute		
Women's experience with labour and birth - satisfaction 24 hours post birth – BMI n.r (0.12%; sufentanil) (measured with: VAS ; range of scores: 0-100; Better indicated by higher values)												
1 (Roofthooft 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	64	61	-	Median in PIEB + PCEA: 100 (range 90 to 100), Median in PCEA: 100 (range 90 to 100)	VERY LOW	IMPORTANT
Women's experience with labour and birth - satisfaction – BMI overweight range (0.1%; fentanyl) (measured with: VAS; range of scores: 0-100; Better indicated by higher values)												
1 (Meena 2022)	randomised trials	very serious[7]	no serious inconsistency	serious[1]	serious[8]	none	25	25	-	MD 0.8 lower (2.55 lower to 0.95 higher)	VERY LOW	IMPORTANT

BMI: body mass index; CI: confidence interval; MD: mean difference; n.r: not reported; RR: risk ratio; PCEA: patient controlled epidural analgesia; PIEB: programmed intermittent epidural bolus; VAS: visual analogue scale
1 Intervention is indirect due to anaesthetic used is levobupivacaine
2 95% CI crosses 1 MID
3 Intervention is indirect due to anaesthetic used is ropivacaine
4 95% CI crosses 2 MIDs
5 Sample size <200
6 Serious risk of bias in the evidence contributing to outcomes as per RoB 2
7 Very serious risk of bias in the evidence contributing to outcomes as per RoB 2
8 95% CI crosses 1 MID (0.5x control group SD, for satisfaction = 1.19)

Table 5: Evidence profile for comparison 2: PIEB + PCEA versus CEI + PCEA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
Anaesthetic re-attendance for breakthrough pain - BMI n.r (0.0625%; sufentanil)												
1 (Capogna	randomised trials	no serious	no serious inconsistency	serious[1]	very serious[2]	none	0/75 (0%)	0/70 (0%)	RD 0 (-0.03 to 0.03)	0 fewer per 1000 (from 30 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
2011)		risk of bias								to 30 more)		
Anaesthetic re-attendance for breakthrough pain - BMI n.r (0.0625%; fentanyl)												
1 (Wong 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	20/63 (31.7 %)	34/63 (54%)	RR 0.59 (0.38 to 0.90)	221 fewer per 1000 (from 54 fewer to 335 fewer)	LOW	CRITICAL
Anaesthetic re-attendance for breakthrough pain - BMI n.r (0.1% fentanyl)												
2 (Haidl 2020, Sia 2007)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	14/96 (14.6 %)	8/96 (8.3%)	RR 1.75 (0.77 to 3.95)	62 more per 1000 (from 19 fewer to 246 more)	VERY LOW	CRITICAL
Anaesthetic re-attendance for breakthrough pain - BMI n.r (0.1%; sufentanil)												
1 (Morau 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[6]	none	124	125	-	Median PIEB + PCEA 0 (range 0 to 10), Median CEI + PCEA 0 (range 0 to 10)	LOW	CRITICAL
Anaesthetic re-attendance for breakthrough pain - BMI overweight range (0.1% fentanyl)												
2 (Leo 2010, Sia 2013	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	7/82 (8.5%)	18/82 (22%)	RR 0.39 (0.17 to 0.88)	134 fewer per 1000 (from 26 fewer to 182 fewer)	LOW	CRITICAL
Anaesthetic re-attendance for breakthrough pain - BMI overweight range (0.1% sufentanil)												
1 (Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	4/38 (10.5 %)	27/78 (34.6%)	RR 0.3 (0.11 to 0.81)	242 fewer per 1000 (from 66 fewer to 308 fewer)	LOW	CRITICAL
Anaesthetic re-attendance for breakthrough pain - BMI obesity range 1 (0.1% fentanyl)												
1 (Ojo 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	13/61 (21.3 %)	14/59 (23.7%)	RR 0.90 (0.46 to 1.75)	24 fewer per 1000 (from 128 fewer to 178 more)	VERY LOW	CRITICAL
Motor block - BMI n.r (0.0625%; sufentanil) (assessed with: Bromage scale)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
1 (Capogna 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	2/75 (2.7%)	26/70 (37.1%)	RR 0.07 (0.02 to 0.29)	345 fewer per 1000 (from 264 fewer to 364 fewer)	MODERATE	CRITICAL
Motor block - BMI n.r (0.0625%; fentanyl) (assessed with: Bromage scale)												
1 (Wong 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	1/63 (1.6%)	1/63 (1.6%)	RR 1 (0.06 to 15.64)	0 fewer per 1000 (from 15 fewer to 232 more)	LOW	CRITICAL
Motor block - BMI n.r (0.1%; fentanyl) (assessed with: Bromage scale)												
2 (Haidl 2020, Sia 2007)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	15/96 (15.6 %)	9/96 (9.4%)	RR 1.63 (0.77 to 3.45)	59 more per 1000 (from 22 fewer to 230 more)	VERY LOW	CRITICAL
Motor block - BMI n.r (0.1%; sufentanil) (assessed with: Bromage scale)												
1 (Morau 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	36/124 (29%)	47/125 (37.6%)	RR 0.77 (0.54 to 1.1)	86 fewer per 1000 (from 173 fewer to 38 more)	LOW	CRITICAL
Motor block - BMI overweight range (0.08%; sufentanil) (assessed with: Bromage scale)												
1 (Fan 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	0/1454 (0%)	0/1411 (0%)	RD 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 more)	MODERATE	CRITICAL
Motor block - BMI overweight range (0.1%; fentanyl) (assessed with: Bromage scale)												
1 (Sia 2013)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	0/51 (0%)	0/51 (0%)	RD 0 (-0.04 to 0.04)	0 fewer per 1000 (from 40 fewer to 40 more)	VERY LOW	CRITICAL
Motor block - BMI overweight range (0.1%; sufentanil) (assessed with: Bromage scale)												
1 (Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	0/38 (0%)	1/78 (1.3%)	RD 0 (-0.06 to 0.03)	13 fewer per 1000 (from 12 fewer to 14 fewer)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
Motor block - BMI obesity range 1 (0.1%; fentanyl) (assessed with: Bromage scale)												
1 (Ojo 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	14/61 (23%)	26/59 (44.1%)	RR 0.52 (0.3 to 0.9)	212 fewer per 1000 (from 44 fewer to 308 fewer)	LOW	CRITICAL
General labour pain - BMI n.r (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Haidl 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	75	75	-	Median PIEB + PCEA 8 (range 3 to 10), Median CEI + PCEA 8 (range 2.5 to 9.5)	VERY LOW	CRITICAL
General labour pain at 6-8cm dilation - BMI n.r (0.1%; sufentanil) (assessed with: VNS less than 3)												
1 (Morau 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	95/124 (76.6 %)	87/125 (69.6%)	RR 1.1 (0.95 to 1.28)	70 more per 1000 (from 35 fewer to 195 more)	LOW	CRITICAL
General labour pain at full dilation - BMI n.r (0.1%; sufentanil) (assessed with: VNS less than 3)												
1 (Morau 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	98/124 (79%)	85/125 (68%)	RR 1.16 (1 to 1.35)	109 more per 1000 (from 0 more to 238 more)	LOW	CRITICAL
General labour pain at 1 hour - BMI overweight range (0.08%; sufentanil) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Fan 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	1454	1411	-	Median PIEB + PCEA 1 (range 1 to 2), Median CEI + PCEA 1 (range 1 to 2)	MODERATE	CRITICAL
General labour pain at 2 hours - BMI overweight range (0.08%; sufentanil) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Fan 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	1454	1411	-	Median PIEB + PCEA 1 (range 1 to 2), Median CEI + PCEA 2 (range 1 to 2)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
General labour pain at 3 hours - BMI overweight range (0.08%; sufentanil) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Fan 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	1454	1411	-	Median PIEB + PCEA 2 (range 1 to 2), Median CEI + PCEA 2 (range 1 to 3)	MODERATE	CRITICAL
General labour pain at 4 hours - BMI overweight range (0.08%; sufentanil) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Fan 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	1454	1411	-	Median PIEB + PCEA 2 (range 2 to 3), Median CEI + PCEA 3 (range 2 to 4)	MODERATE	CRITICAL
General labour pain at 5 hours - BMI overweight range (0.08%; sufentanil) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Fan 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	1454	1411	-	Median PIEB + PCEA 2 (range 2 to 3), Median CEI + PCEA 3 (range 2 to 4)	MODERATE	CRITICAL
General labour pain at delivery - BMI overweight range (0.08%; sufentanil) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Fan 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	1454	1411	-	Median PIEB + PCEA 3 (range 2 to 4), Median CEI + PCEA 4 (range 3 to 4)	MODERATE	CRITICAL
General labour pain at 4 hours - BMI overweight range (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Leo 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	31	31	-	MD 1 lower (1.69 to 0.31 lower)	LOW	CRITICAL
General labour pain at 10 minutes - BMI overweight range (0.1%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	38	78	-	MD 3.55 lower (11.04 lower to 3.94 higher)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
General labour pain at 20 minutes - BMI overweight range (0.1%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	38	78	-	MD 4.61 lower (10.02 lower to 0.8 higher)	LOW	CRITICAL
General labour pain at 30 minutes - BMI overweight range (0.1%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	38	78	-	MD 1.71 lower (7.66 lower to 4.24 higher)	LOW	CRITICAL
General labour pain at 2hours - BMI overweight range (0.1%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	36	76	-	MD 5.71 lower (12.83 lower to 1.41 higher)	LOW	CRITICAL
General labour pain at 3.5hours - BMI overweight range (0.1%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	26	68	-	MD 6.96 lower (14.94 lower to 1.02 higher)	LOW	CRITICAL
General labour pain at 5hours - BMI overweight range (0.1%; sufentanil) (measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1 (Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	19	46	-	MD 13.95 lower (23.46 to 4.44 lower)	LOW	CRITICAL
General labour pain - BMI obesity range 1 (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Ojo 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	61	59	-	Median PIEB + PCEA 3 (range 0 to 6), Median CEI + PCEA 2 (range 0 to 4)	VERY LOW	CRITICAL
Duration of labour - 1st stage - BMI overweight range (0.08%, sufentanil) (measured with: minutes; Better indicated by lower values)												
1 (Fan 2019)	randomised trials	no serious	no serious inconsistency	serious[3]	no serious imprecisio	none	1454	1411	-	MD 8 lower (16.37 lower to	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
		risk of bias			n					0.37 higher)		
Duration of labour - 1st stage - BMI overweight range (0.1%; sufentanil) (measured with: minutes; Better indicated by lower values)												
1 (Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	35	67	-	MD 89 lower (176.21 to 1.79 lower)	LOW	IMPORTANT
Duration of labour - 2nd stage - BMI n.r (0.1%; fentanyl) (measured with: minutes; Better indicated by lower values)												
1 (Sia 2007)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	21	21	-	MD 8 lower (29.77 lower to 13.77 higher)	LOW	IMPORTANT
Duration of labour - 2nd stage - BMI overweight range (0.08%, sufentanil) (measured with: minutes; Better indicated by lower values)												
1 (Fan 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	1454	1411	-	MD 1 lower (1.88 to 0.12 lower)	MODERATE	IMPORTANT
Duration of labour - 2nd stage - BMI overweight range (0.1%; fentanyl) (measured with: minutes; Better indicated by lower values)												
2 (Leo 2010, Sia 2013,)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	82	82	-	MD 14.64 lower (30.45 lower to 1.18 higher)	LOW	IMPORTANT
Duration of labour - 2nd stage - BMI overweight range (0.1%; sufentanil) (measured with: minutes; Better indicated by lower values)												
2 (Lin 2016; Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	137	166	-	MD 3.45 lower (5.87 to 1.03 lower)	MODERATE	IMPORTANT
Duration of labour - 2nd stage - BMI obesity range 1 (0.1%; fentanyl) (measured with: minutes; Better indicated by lower values)												
1 (Ojo 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	61	59	-	MD 19 lower (28.27 to 9.73 lower)	LOW	IMPORTANT
Duration of labour - total - BMI n.r (0.0625%; sufentanil) (measured with: minutes; Better indicated by lower values)												
1	randomise	no	no serious	serious[1]	very	none	75	70	-	Median PIEB +		IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
(Capogna 2011)	d trials	serious risk of bias	inconsistency		serious[2]					PCEA 335 (range 326 to 358), Median CEI + PCEA 332 (range 318 to 380)	VERY LOW	
Duration of labour - total - BMI n.r (0.0625%; sufentanil) (measured with: minutes; Better indicated by lower values)												
1 (Wong 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	63	63	-	Median for PIEB + PCEA 188 (range 92 to 498, Median for CEI + PCEA 184 (range 96 to 614)	LOW	IMPORTANT
Duration of labour - total - BMI n.r (0.1%; fentanyl) (measured with: minutes; Better indicated by lower values)												
1 (Haidl 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	75	75	-	Median PIEB + PCEA 455 (range 68 to 2209), Median CEI + PCEA 443 (range 67 to 1725)	LOW	IMPORTANT
Duration of labour - total - BMI n.r (0.1%; fentanyl) (measured with: minutes; Better indicated by lower values)												
1 (Sia 2007)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	21	21	-	MD 62 higher (52.83 lower to 176.83 higher)	LOW	IMPORTANT
Duration of labour - total - BMI n.r (0.1%; sufentanil) (measured with: hours; Better indicated by lower values)												
1 (Morau 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[6]	none	124	125	-	Median for PIEB + PCEA 7.4 (range 5.6 to 9.7), Median for CEI + PCEA 7.3 (range 5.7 to 9.1)	LOW	IMPORTANT
Duration of labour - total - BMI overweight range (0.1%; fentanyl) (measured with: minutes; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
2 (Leo 2010; Sia 2013)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	82	82	-	MD 9.58 lower (70.47 lower to 51.31 higher)	MODERATE	IMPORTANT
Spontaneous vaginal birth - BMI n.r (0.0625%; sufentanil)												
1 (Wong 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/63 (93.7 %)	59/63 (93.7%)	RR 1 (0.91 to 1.1)	0 fewer per 1000 (from 84 fewer to 94 more)	HIGH	IMPORTANT
Spontaneous vaginal birth - BMI n.r (0.1%; fentanyl)												
2 (Haidl 2020; Sia 2007)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	60/96 (62.5 %)	59/96 (61.5%)	RR 1.02 (0.81 to 1.27)	12 more per 1000 (from 117 fewer to 166 more)	LOW	IMPORTANT
Spontaneous vaginal birth - BMI n.r (0.1%; sufentanil)												
1 (Morau 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	94/124 (75.8 %)	83/125 (66.4%)	RR 1.14 (0.97 to 1.34)	93 more per 1000 (from 20 fewer to 226 more)	LOW	IMPORTANT
Spontaneous vaginal birth - BMI overweight range (0.1%; fentanyl)												
2 (Leo 2010; Sia 2013;	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	54/82 (65.9 %)	48/82 (58.5%)	RR 1.13 (0.88 to 1.43)	76 more per 1000 (from 70 fewer to 252 more)	LOW	IMPORTANT
Spontaneous vaginal birth - BMI overweight range (0.1%; sufentanil)												
1 (Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	32/38 (84.2 %)	61/78 (78.2%)	RR 1.08 (0.9 to 1.29)	63 more per 1000 (from 78 fewer to 227 more)	LOW	IMPORTANT
Spontaneous vaginal birth - BMI obesity range 1 (0.1%; fentanyl)												
1 (Ojo 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	41/61 (67.2 %)	37/59 (62.7%)	RR 1.07 (0.82 to 1.39)	44 more per 1000 (from 113 fewer to 245 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
Instrumental birth - BMI n.r (0.0625%; sufentanil)												
1 (Capogna 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	5/75 (6.7%)	14/70 (20%)	RR 0.33 (0.13 to 0.88)	134 fewer per 1000 (from 24 fewer to 174 fewer)	LOW	IMPORTANT
Instrumental birth - BMI n.r (0.0625%; fentanyl)												
1 (Wong 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	3/63 (4.8%)	4/63 (6.3%)	RR 0.75 (0.17 to 3.22)	16 fewer per 1000 (from 53 fewer to 141 more)	LOW	IMPORTANT
Instrumental birth - BMI n.r (0.1%; fentanyl)												
2 (Haidl 2020; Sia 2007)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	19/96 (19.8 %)	21/96 (21.9%)	RR 0.9 (0.53 to 1.56)	22 fewer per 1000 (from 103 fewer to 122 more)	VERY LOW	IMPORTANT
Instrumental birth - BMI n.r (0.1%; sufentanil)												
1 (Morau 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	32/124 (25.8 %)	45/125 (36%)	RR 0.72 (0.49 to 1.05)	101 fewer per 1000 (from 184 fewer to 18 more)	LOW	IMPORTANT
Instrumental birth - BMI overweight range (0.08%; sufentanil)												
1 (Fan 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	86/1454 (5.9%)	92/1411 (6.5%)	RR 0.91 (0.68 to 1.21)	6 fewer per 1000 (from 21 fewer to 14 more)	LOW	IMPORTANT
Instrumental birth - BMI overweight range (0.1%; fentanyl)												
2 (Leo 2010; Sia 2013)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	7/82 (8.5%)	14/82 (17.1%)	RR 0.5 (0.21 to 1.18)	85 fewer per 1000 (from 130 fewer to 3 more)	LOW	IMPORTANT
Instrumental birth - BMI overweight range (0.1%; sufentanil)												
2 (Lin 2016; Song	randomised trials	no serious risk of	no serious inconsistency	serious[3]	very serious[5]	none	13/140 (9.3%)	15/177 (8.5%)	RR 1.06 (0.52 to 2.18)	5 more per 1000 (from 41 fewer to 100 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
2021)		bias										
Instrumental birth - BMI obesity range 1 (0.1%; fentanyl)												
1 (Ojo 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	5/61 (8.2%)	5/59 (8.5%)	RR 0.97 (0.3 to 3.17)	3 fewer per 1000 (from 59 fewer to 184 more)	VERY LOW	IMPORTANT
Caesarean birth - BMI n.r (0.0625%; sufentanil)												
1 (Capogna 2011)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[5]	none	13/75 (17.3 %)	15/70 (21.4%)	RR 0.81 (0.41 to 1.58)	41 fewer per 1000 (from 126 fewer to 124 more)	VERY LOW	IMPORTANT
Caesarean birth - BMI n.r (0.0625%; fentanyl)												
1 (Wong 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/63 (1.6%)	0/63 (0%)	POR 7.39 (0.15 to 372.38)	20 more per 1000 (from 30 fewer to 60 more)	LOW	IMPORTANT
Caesarean birth - BMI n.r (0.1%; fentanyl)												
2 (Haidl 2020; Sia 2007)	randomised trials	no serious risk of bias	serious[8]	serious[3]	very serious[5]	none	17/96 (17.7 %)	16/96 (16.7%)	RR 1.06 (0.57 to 1.98)	10 more per 1000 (from 72 fewer to 163 more)	VERY LOW	IMPORTANT
Caesarean birth - BMI overweight range (0.1%; fentanyl)												
2 (Leo 2010; Sia 2013)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	21/82 (25.6 %)	20/82 (24.4%)	RR 1.05 (0.62 to 1.78)	12 more per 1000 (from 93 fewer to 190 more)	VERY LOW	IMPORTANT
Caesarean birth - BMI overweight range (0.1%; sufentanil)												
2 (Lin 2016; Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[5]	none	11/140 (7.9%)	21/177 (11.9%)	RR 0.69 (0.34 to 1.40)	37 fewer per 1000 (from 78 fewer to 47 more)	VERY LOW	IMPORTANT
Caesarean birth - BMI obesity range 1 (0.1%; fentanyl)												
1 (Ojo	randomise	no	no serious	serious[3]	very	none	15/61	17/59	RR 0.85	43 fewer per		IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
2020)	d trials	serious risk of bias	inconsistency		serious[5]		(24.6 %)	(28.8%)	(0.47 to 1.55)	1000 (from 153 fewer to 158 more)	VERY LOW	
Women's experience of labour and birth - satisfaction - BMI n.r (0.0625%; fentanyl) (range of scores: 0-100; Better indicated by higher values)												
1 (Wong 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	63	63	-	Median PIEB + PCEA 92 (range 89 to 95), Median CEI + PCEA 85 (range 77 to 90)	VERY LOW	IMPORTANT
Women's experience of labour and birth - satisfaction - BMI n.r (0.1% fentanyl) (range of scores: 0-10; Better indicated by higher values)												
1 (Haidl 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	75	75	-	Median PIEB + PCEA 10 (range 9 to 10), Median CEI + PCEA 10 (range 9 to 10)	LOW	IMPORTANT
Women's experience of labour and birth - satisfaction - BMI n.r (0.1%; fentanyl) (range of scores: 0-100; Better indicated by higher values)												
1 (Sia 2007)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[7]	none	21	21	-	MD 5 higher (0.68 lower to 10.68 higher)	LOW	IMPORTANT
Women's experience of labour and birth - satisfaction - BMI n.r (0.1%; sufentanil) (range of scores: 0-10; Better indicated by higher values)												
1 (Morau 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[6]	none	124	125	-	Median for PIEB + PCEA 9 (range 9 to 10), Median for CEI + PCEA 9 (range 9 to 10)	LOW	IMPORTANT
Women's experience of labour and birth - satisfaction - BMI overweight range (0.08%; sufentanil) (range of scores: 0-10; Better indicated by higher values)												
1 (Fan 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	1454	1411	-	Median PIEB + PCEA 9 (range 9 to 10), Median CEI + PCEA 7 (range 6 to 7)	MODERATE	IMPORTANT
Women's experience of labour and birth - satisfaction - BMI overweight range (0.1%; fentanyl) (range of scores: 0-100; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA	CEI + PCEA	Relative (95% CI)	Absolute		
2 (Leo 2010; Sia 2013)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	82	82	-	MD 7.62 higher (5.37 to 9.88 higher)	MODERATE	IMPORTANT
Women's experience of labour and birth - satisfaction - BMI obesity range 1 (0.1%; fentanyl)												
1 (Ojo 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	44/61 (72.1 %)	42/59 (71.2%)	RR 1.01 (0.81 to 1.27)	7 more per 1000 (from 135 fewer to 192 more)	LOW	IMPORTANT
Women's experience of labour and birth – satisfaction - BMI overweight range (0.1%; sufentanil) (range of scores: 0-100; Better indicated by higher values)												
1 (Song 2021)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	38	78		Median PIEB + PCEA 97.5 (range 90 to 100), Median CEI (EP) + PCEA 90 (range 87.5 to 100), Median CEI (DPE) + PCEA 92.55 (range 80 to 100)	VERY LOW	IMPORTANT

BMI: body mass index; CI: confidence interval; MD: mean difference; n.r: not reported; RD: risk difference; RR: risk ratio; PCEA: patient controlled epidural analgesia; PIEB: programmed intermittent epidural bolus; VAS: visual analogue scale
1 Intervention is indirect due to levobupivacaine anaesthetic used
2 Sample size <200
3 Intervention is indirect due to ropivacaine anaesthetic used
4 95% CI crosses 1 MID
5 95% CI crosses 2 MIDs
6 Sample size 200 - 400
7 95% CI crosses 1 MID (0.5x control group SD, for 'General labour pain, overweight range, 0.1%' at 10min, 20min, 30min, 2hours, 3.5hours, 5hours = 5.95'; General labour pain, overweight range, 0.1% at 4hours' = 1; 'Duration of labour 1st stage, overweight range, sufentanil' = 114.23; 'Duration of labour 2nd stage, obesity range 1 = 12.9; 'Duration of labour 2nd stage, BMI n.r' = 18; 'Duration of labour 2nd stage, overweight range, fentanyl' = 29.03; 'Duration of labour - total - BMI n.r' = 109.5; 'Women's experience, BMI n.r, fentanyl' = 5)
8 Serious heterogeneity unexplained by subgroup analysis

Table 6: Evidence profile comparison 3: PIEB versus CEI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB	CEI	Relative (95% CI)	Absolute		
Anaesthetist re-attendance for breakthrough pain – BMI n.r (0.1%; fentanyl)												
2 (Chua 2004; Lim 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	26/46 (56.5%)	24/46 (52.2%)	RR 1.08 (0.77 to 1.52)	42 more per 1000 (from 120 fewer to 271 more)	VERY LOW	CRITICAL
Anaesthetist re-attendance for breakthrough pain – BMI n.r (0.2%; fentanyl)												
1 (Fettes 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	4/20 (20%)	12/20 (60%)	RR 0.33 (0.13 to 0.86)	402 fewer per 1000 (from 84 fewer to 522 fewer)	LOW	CRITICAL
Anaesthetist re-attendance for breakthrough pain - BMI healthy (0.15%; fentanyl)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	21/30 (70%)	22/30 (73.3%)	RR 0.95 (0.69 to 1.31)	37 fewer per 1000 (from 227 fewer to 227 more)	VERY LOW	CRITICAL
Anaesthetist re-attendance for breakthrough pain – BMI obesity range 1 (0.1%; fentanyl)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	12/64 (18.8%)	25/64 (39.1%)	RR 0.48 (0.26 to 0.87)	203 fewer per 1000 (from 51 fewer to 289 fewer)	MODERATE	CRITICAL
Anaesthetist re-attendance for breakthrough pain – BMI obesity range 2 (0.125%; fentanyl)												
1 (Fidkowski 2019)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	40/84 (47.6%)	21/34 (61.8%)	RR 0.77 (0.55 to 1.09)	142 fewer per 1000 (from 278 fewer to 56 more)	LOW	CRITICAL
Motor block – BMI n.r (0.1%; fentanyl) (assessed with: Bromage scale)												
1 (Chua 2004)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	1/21 (4.8%)	1/21 (4.8%)	RR 1 (0.07 to 14.95)	0 fewer per 1000 (from 44 fewer to 664 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB	CEI	Relative (95% CI)	Absolute		
Motor block - BMI healthy (0.15%; fentanyl)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/30 (0%)	2/30 (6.7%)	RR 0.2 (0.01 to 4.00)	53 fewer per 1000 (from 66 fewer to 200 more)	VERY LOW	CRITICAL
Motor block at 15 minutes – BMI obesity range 1 (0.1%; fentanyl) (assessed with: Bromage scale)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	5/64 (7.8%)	12/64 (18.8%)	RR 0.42 (0.16 to 1.11)	109 fewer per 1000 (from 157 fewer to 21 more)	MODERATE	CRITICAL
Motor block at 60 minutes – BMI obesity range 1 (0.1%; fentanyl) (assessed with: Bromage scale)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	7/62 (11.3%)	16/62 (25.8%)	RR 0.44 (0.19 to 0.99)	145 fewer per 1000 (from 3 fewer to 209 fewer)	MODERATE	CRITICAL
Motor block at 120 minutes – BMI obesity range 1 (0.1%; fentanyl) (assessed with: Bromage scale)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	9/44 (20.5%)	16/45 (35.6%)	RR 0.58 (0.28 to 1.16)	149 fewer per 1000 (from 256 fewer to 57 more)	MODERATE	CRITICAL
Motor block at 180 minutes – BMI obesity range 1 (0.1%; fentanyl) (assessed with: Bromage scale)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	9/30 (30%)	14/30 (46.7%)	RR 0.64 (0.33 to 1.25)	168 fewer per 1000 (from 313 fewer to 117 more)	MODERATE	CRITICAL
Motor block – BMI obesity range 2 (0.125%; fentanyl) (assessed with: Bromage scale)												
1 (Fidkowski 2019)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	23/84 (27.4%)	9/34 (26.5%)	RR 1.03 (0.53 to 2)	8 more per 1000 (from 124 fewer to 265 more)	VERY LOW	CRITICAL
General labour pain at 5 minutes - BMI healthy (0.15%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 0 higher (0.6 lower to 0.6 higher)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB	CEI	Relative (95% CI)	Absolute		
General labour pain at 10 minutes - BMI healthy (0.15%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 0 higher (0.38 lower to 0.38 higher)	MODERATE	CRITICAL
General labour pain at 15 minutes - BMI healthy (0.15%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 0.03 higher (0.21 lower to 0.27 higher)	MODERATE	CRITICAL
General labour pain at 15 minutes – BMI obesity range 1 (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	64	64	-	MD 0.3 lower (1.17 lower to 0.57 higher)	MODERATE	CRITICAL
General labour pain at 15 minutes – BMI n.r (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Lim 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	25	25	-	MD 0.2 lower (0.96 lower to 0.56 higher)	MODERATE	CRITICAL
General labour pain at 30 minutes - BMI n.r (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Lim 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	25	25	-	MD 0.1 lower (0.28 lower to 0.08 higher)	MODERATE	CRITICAL
General labour pain at 30 minutes - BMI healthy (0.15%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 0 higher (0 to 0 higher)	MODERATE	CRITICAL
General labour pain at 60 minutes - BMI healthy (0.15%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB	CEI	Relative (95% CI)	Absolute		
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 0 higher (0 to 0 higher)	MODERATE	CRITICAL
General labour pain at 60 minutes – BMI obesity range 1 (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	64	64		MD 0.7 lower (1.67 lower to 0.27 higher)	MODERATE	CRITICAL
General labour pain at 120 minutes - BMI healthy (0.15%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 1.63 lower (2.62 to 0.64 lower)	MODERATE	CRITICAL
General labour pain at 120 minutes – BMI obesity range 1 (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	64	64		MD 1.1 lower (2.21 lower to 0.01 higher)	MODERATE	CRITICAL
General labour pain at 120 minutes – BMI n.r (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Lim 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	25	25		MD 0.5 higher (0.05 lower to 1.05 higher)	MODERATE	CRITICAL
General labour pain at 180 minutes - BMI healthy (0.15%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[6]	none	30	30	-	MD 0.3 lower (1.35 lower to 0.75 higher)	VERY LOW	CRITICAL
General labour pain at 180 minutes – BMI obesity range 1 (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	64	64	-	MD 0.3 lower (1.31 lower to 0.71 higher)	MODERATE	CRITICAL
General labour pain at 240 minutes – BMI obesity range 1 (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB	CEI	Relative (95% CI)	Absolute		
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	64	64	-	MD 1.3 lower (2.31 to 0.29 lower)	MODERATE	CRITICAL
General labour pain at 240 minutes – BMI n.r (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Lim 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[5]	none	25	25	-	MD 0.8 lower (1.7 lower to 0.1 higher)	LOW	
General labour pain at 8 hours - BMI n.r (0.1%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Lim 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[5]	none	25	25		MD 0.6 higher (0.4 lower to 1.6 higher)	LOW	CRITICAL
General labour pain - BMI obesity range 2 (0.125%; fentanyl) (range of scores: 0-10; Better indicated by lower values)												
1 (Fidkowski 2019)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	84	34		MD 0.16 lower (1.17 lower to 0.85 higher)	MODERATE	CRITICAL
General labour pain - BMI n.r (0.2%; fentanyl) (measured with: VAS – area under curve; Better indicated by lower values)												
1 (Fettes 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[7]	none	20	20		Median in PIEB: 592 (range 107 to 1547) , Median in CEI: 1121 (range 0 to 2963)	VERY LOW	CRITICAL
Duration of labour – total - BMI obesity range 1 (0.1%; fentanyl) (measured with: minutes; Better indicated by lower values)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	64	64		MD 33.4 higher (6.66 lower to 73.46 higher)	MODERATE	IMPORTANT
Duration of labour – total - BMI obesity range 2 (0.125%; fentanyl) (measured with: hours; Better indicated by lower values)												
1 (Fidkowski 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	84	34		MD 0.21 lower (2.68 lower to 2.26 higher)	HIGH	IMPORTANT
Duration of labour - total - BMI n.r (0.1%; fentanyl) (measured with: minutes; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB	CEI	Relative (95% CI)	Absolute		
1 (Lim 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	25	25		MD 72 lower (98.03 to 45.97 lower)	MODERATE	IMPORTANT
Duration of labour - 1st stage - BMI n.r (0.2%; fentanyl) (measured with: minutes ; Better indicated by lower values)												
1 (Fettes 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[5]	none	20	20		MD 120 lower (287.48 lower to 47.48 higher)	LOW	IMPORTANT
Duration of labour - 2nd stage - BMI n.r (0.1%; fentanyl) (measured with: minutes; Better indicated by lower values)												
1 (Lim 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[5]	none	25	25		MD 22 lower (58.92 lower to 14.92 higher)	LOW	IMPORTANT
Duration of labour - 2nd stage - BMI obesity range 2 (0.125%; fentanyl) (measured with: hours; Better indicated by lower values)												
1 (Fidkowski 2019)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	54[8]	20[8]		MD 0.47 higher (0.14 lower to 1.08 higher)	LOW	IMPORTANT
Duration of labour - 2nd stage - BMI n.r (0.2%; fentanyl) (measured with: minutes; Better indicated by lower values)												
1 (Fettes 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[6]	none	20	20		MD 3.6 lower (43.53 lower to 36.33 higher)	VERY LOW	IMPORTANT
Duration of labour - 2nd stage - 40 minutes or less - BMI healthy (0.15%; fentanyl)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/30 (83.3%)	12/30 (40%)	RR 2.08 (1.31 to 3.32)	432 more per 1000 (from 124 more to 928 more)	MODERATE	IMPORTANT
Spontaneous vaginal birth - BMI healthy (0.15%; fentanyl)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	22/30 (73.3%)	17/30 (56.7%)	RR 1.29 (0.88 to 1.89)	164 more per 1000 (from 68 fewer to 504 more)	LOW	IMPORTANT
Spontaneous vaginal birth – BMI obesity range 1 (0.1%; fentanyl)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB	CEI	Relative (95% CI)	Absolute		
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50/64 (78.1%)	51/64 (79.7%)	RR 0.98 (0.82 to 1.17)	16 fewer per 1000 (from 143 fewer to 135 more)	HIGH	IMPORTANT
Spontaneous vaginal birth – BMI obesity range 2 (0.125%; fentanyl)												
1 (Fidkowski 2019)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	66/84 (78.6%)	23/34 (67.6%)	RR 1.16 (0.9 to 1.5)	108 more per 1000 (from 68 fewer to 338 more)	LOW	IMPORTANT
Spontaneous vaginal birth – BMI n.r (0.1%; fentanyl)												
1 (Lim 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	19/25 (76%)	15/25 (60%)	RR 1.27 (0.86 to 1.87)	162 more per 1000 from 84 fewer to 522 more)	LOW	IMPORTANT
Instrumental vaginal birth - BMI healthy (0.15%; fentanyl)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/30 (10%)	1/30 (3.3%)	RR 3 (0.33 to 27.23)	67 more per 1000 (from 22 fewer to 874 more)	VERY LOW	IMPORTANT
Instrumental vaginal birth – BMI – obesity range 1 (0.1%; fentanyl)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/64 (7.8%)	2/64 (3.1%)	RR 2.5 (0.5 to 12.42)	47 more per 1000 (from 16 fewer to 357 more)	LOW	IMPORTANT
Instrumental vaginal birth – BMI obesity range 2 (0.125%; fentanyl)												
1 (Fidkowski 2019)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/84 (3.6%)	2/34 (5.9%)	RR 0.61 (0.11 to 3.47)	23 fewer per 1000 (from 52 fewer to 145 more)	VERY LOW	IMPORTANT
Instrumental vaginal birth – BMI n.r (0.1%; fentanyl)												
1 (Lim 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	3/25 (12%)	6/25 (24%)	RR 0.5 (0.14 to 1.78)	120 fewer per 1000 (from 206 fewer to 187 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB	CEI	Relative (95% CI)	Absolute		
Instrumental vaginal birth – BMI n.r (0.2%; fentanyl)												
1 (Fettes 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	10/20 (50%)	10/20 (50%)	RR 1 (0.54 to 1.86)	0 fewer per 1000 (from 230 fewer to 430 more)	VERY LOW	IMPORTANT
Caesarean birth - BMI healthy (0.15%; fentanyl)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/30 (16.7%)	7/30 (23.3%)	RR 0.71 (0.25 to 2)	68 fewer per 1000 (from 175 fewer to 233 more)	VERY LOW	IMPORTANT
Caesarean birth – BMI obesity range 1 (0.1%; fentanyl)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/64 (14.1%)	11/64 (17.2%)	RR 0.82 (0.36 to 1.84)	31 fewer per 1000 (from 110 fewer to 144 more)	LOW	IMPORTANT
Caesarean birth – BMI obesity range 2 (0.125%; fentanyl)												
1 (Fidkowski 2019)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	18/84 (21.4%)	11/34 (32.4%)	RR 0.66 (0.35 to 1.25)	110 fewer per 1000 (from 210 fewer to 81 more)	LOW	IMPORTANT
Caesarean birth – BMI n.r (0.1%; fentanyl)												
1 (Lim 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	3/25 (12%)	4/25 (16%)	RR 0.75 (0.19 to 3.01)	40 fewer per 1000 (from 130 fewer to 322 more)	VERY LOW	IMPORTANT
Caesarean birth – BMI n.r (0.2%; fentanyl)												
1 (Fettes 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	3/20 (15%)	5/20 (25%)	RR 0.6 (0.17 to 2.18)	100 fewer per 1000 (from 207 fewer to 295 more)	VERY LOW	IMPORTANT
Women's experience of labour and birth - satisfied at 15 minutes – BMI obesity range 1 (0.1%; fentanyl) (assessed with: VRS)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	62/64 (96.9%)	59/64 (92.2%)	RR 1.05 (0.97 to	46 more per 1000 (from 28 fewer to 129 more)	HIGH	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB	CEI	Relative (95% CI)	Absolute		
									1.14)			
Women's experience of labour and birth - satisfied at 60 minutes – BMI obesity range 1 (0.1%; fentanyl) (assessed with: VRS)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/64 (92.2%)	55/64 (85.9%)	RR 1.07 (0.95 to 1.21)	60 more per 1000 (from 43 fewer to 180 more)	HIGH	IMPORTANT
Women's experience of labour and birth - satisfied at 120 minutes – BMI obesity range 1 (0.1%; fentanyl) (assessed with: VRS)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	38/64 (59.4%)	43/64 (67.2%)	RR 0.88 (0.68 to 1.15)	81 fewer per 1000 (from 215 fewer to 101 more)	MODERATE	IMPORTANT
Women's experience of labour and birth - satisfied at 180 minutes – BMI obesity range 1 (0.1%; fentanyl) (assessed with: VRS)												
1 (Ferrer 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	28/64 (43.8%)	29/64 (45.3%)	RR 0.97 (0.66 to 1.42)	14 fewer per 1000 (from 154 fewer to 190 more)	LOW	IMPORTANT
Women's experience of labour and birth – satisfied – BMI obesity range 2 (0.125%; fentanyl) (assessed with: Likert scale)												
1 (Fidkowski 2019)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/84 (97.6%)	32/34 (94.1%)	RR 1.04 (0.95 to 1.14)	38 more per 1000 (from 47 fewer to 132 more)	MODERATE	IMPORTANT
Women's experience of labour and birth - satisfied – BMI n.r (0.1%; fentanyl) (Better indicated by lower values)												
1 (Lim 2010)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	25	25		MD 10 higher (6.05 to 13.95 higher)	MODERATE	IMPORTANT
Women's experience of labour and birth - BMI healthy (0.15%; fentanyl) (assessed with: maternal satisfaction rated good or excellent)												
1 (Chalekar 2021)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/30 (100%)	29/30 (96.7%)	RR 1.03 (0.94 to 1.13)	29 more per 1000 (from 58 fewer to 126 more)	MODERATE	IMPORTANT

BMI: body mass index; CEI: continuous epidural infusion; CI: confidence interval; MD: mean difference; n.r: not reported; RR: risk ratio; PIEB: programmed intermittent epidural bolus; VAS: visual analogue scale

1 Intervention is indirect due to anaesthetic used is ropivacaine
2 95% CI crosses 2 MIDs
3 95% CI crosses 1 MID
4 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
5 95% CI crosses 1 MID (0.5x control group SD, for 'General labour pain, obesity range 1, at 15 mins, 60 mins, 120mins, 180mins, 240mins' = 0.95; 'General labour pain, BMI n.r at 240mins, at 8 hours = 1.15', 'Duration of labour - total, obesity range 1, 0.1% = 46.7; 'Duration of labour – 1st stage 0.2%' = 133.5; 'Duration of labour – 2nd stage 0.1% = 35; 'Duration of labour – 2nd stage 0.125% = 0.56)
6 95% CI crosses 2 MID (0.5x control group SD, for pain at 3 hours = 0.62; for 'Duration of labour – 2nd stage 0.2% = 31.3)
7 Sample size <200
8 Only women who had a vaginal birth

Table 7: Evidence profile for comparison 4: PIEB + PCEA + CEI versus PCEA + CEI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA + CEI	PCEA + CEI	Relative (95% CI)	Absolute		
Anaesthetist re-attendance for breakthrough pain – BMI overweight range (0.125%; fentanyl)												
1 (Diez-Picazo 2019)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/53 (0%)	0/53 (0%)	RD 0 (-0.04 to 0.04)	0 fewer per 1000 (from 40 fewer to 40 more)	VERY LOW	CRITICAL
Motor block – BMI overweight range (0.125%; fentanyl) (assessed with: Bromage scale)												
1 (Diez-Picazo 2019)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	1/53 (1.9%)	0/53 (0%)	POR 7.39 (0.15 to 372.38)	20 more per 1000 (from 30 fewer to 70 more)	VERY LOW	CRITICAL
General labour pain at 15 minutes – BMI n.r (0.0625%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Rodriguez-Campoo 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[5]	none	103	96	-	MD 0.13 higher (0.48 lower to 0.74 higher)	LOW	CRITICAL
General labour pain at 3.25 hrs – BMI n.r (0.0625%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Rodriguez-Campoo 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[5]	none	103	95	-	MD 0.19 higher (0.37 lower to 0.75 higher)	LOW	CRITICAL
General labour pain at 6.25 hrs – BMI n.r (0.0625%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA + CEI	PCEA + CEI	Relative (95% CI)	Absolute		
1 (Rodriguez-Campoo 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	103	95	-	MD 0.08 lower (0.59 lower to 0.43 higher)	MODERATE	CRITICAL
General labour pain at 9.25 hrs – BMI n.r (0.0625%; fentanyl) (measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1 (Rodriguez-Campoo 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[5]	none	103	95	-	MD 0.41 lower (0.96 lower to 0.14 higher)	LOW	CRITICAL
General labour pain - pain at birth – BMI overweight range (0.125%; fentanyl)												
1 (Diez-Picazo 2019)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	1/53 (1.9%)	1/53 (1.9%)	RR 1 (0.06 to 15.57)	0 fewer per 1000 (from 18 fewer to 275 more)	VERY LOW	CRITICAL
Duration of labour - 1st stage – BMI overweight range (0.125%; fentanyl) (measured with: minutes; Better indicated by lower values)												
1 (Diez-Picazo 2019)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[5]	none	53	53	-	MD 17 higher (34.85 lower to 68.85 higher)	VERY LOW	IMPORTANT
Duration of labour - 2nd stage – BMI overweight range (0.125%; fentanyl) (measured with: minutes; Better indicated by lower values)												
1 (Diez-Picazo 2019)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	53	53	-	MD 3 higher (15.85 lower to 21.85 higher)	LOW	IMPORTANT
Spontaneous vaginal birth – BMI overweight range (0.125%; fentanyl)												
1 (Diez-Picazo 2019)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[6]	none	34/53 (64.2%)	31/53 (58.5%)	RR 1.1 (0.81 to 1.49)	58 more per 1000 (from 111 fewer to 287 more)	VERY LOW	IMPORTANT
Instrumental birth – BMI overweight range (0.125%; fentanyl)												
1 (Diez-Picazo 2019)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	8/53 (15.1%)	7/53 (13.2%)	RR 1.14 (0.45 to 2.93)	18 more per 1000 (from 73 fewer to 255 more)	VERY LOW	IMPORTANT
Instrumental birth – BMI n.r (0.0625%; fentanyl)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB + PCEA + CEI	PCEA + CEI	Relative (95% CI)	Absolute		
1 (Rodriguez-Campoo 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[6]	none	22/103 (21.4%)	11/97 (11.3%)	RR 1.88 (0.97 to 3.68)	100 more per 1000 (from 3 fewer to 304 more)	LOW	IMPORTANT
Caesarean birth – BMI overweight range (0.125%; fentanyl)												
1 (Diez-Picazo 2019)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	11/53 (20.8%)	15/53 (28.3%)	RR 0.73 (0.37 to 1.45)	76 fewer per 1000 (from 178 fewer to 127 more)	VERY LOW	IMPORTANT
Women's experience of labour and birth – satisfaction – BMI overweight range (0.125%; fentanyl) (assessed with: scores 8 to 10 on 0 - 10 scale)												
1 (Diez-Picazo 2019)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	48/53 (90.6%)	49/53 (92.5%)	RR 0.98 (0.87 to 1.1)	18 fewer per 1000 (from 120 fewer to 92 more)	LOW	IMPORTANT
Women's experience of labour and birth – satisfaction – BMI n.r (0.0625%; fentanyl) (assessed with: 1 or 2 Likert scale)												
1 (Rodriguez-Campoo 2019)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	93/103 (90.3%)	89/97 (91.8%)	RR 0.98 (0.9 to 1.07)	18 fewer per 1000 (from 92 fewer to 64 more)	MODERATE	IMPORTANT

BMI: body mass index; CEI: continuous epidural infusion; CI: confidence interval; MD: mean difference; n.r: not reported; POR: Peto odds ratio; RD: risk difference; RR: risk ratio; PCEA: patient controlled epidural analgesia; PIEB: programmed intermittent epidural bolus; VAS: visual analogue scale
1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 Intervention is indirect due to levobupivacaine anaesthetic used
3 Sample size <200
4 95% CI crosses 2 MIDs
5 95% CI crosses 1 MID (0.5x control group SD, for 'General labour pain at 15minutes; at 3.25 hours; at 9.25 hours' = 0.618; 'Duration of labour 1st stage = 61)
6 95% CI crosses 1 MID

Table 8: Evidence profile from comparison 5: PIEB versus CEI + PCEA

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB	CEI + PCEA	Relative (95% CI)	Absolute		
Motor block – BMI n.r (0.1%; sufentanil) (assessed with: Bromage scale)												
1 (Nunes 2016)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/33 (0%)	4/60 (6.7%)	POR 0.2 (0.03 to 1.62)	53 fewer per 1000 (from 65 fewer to 41 more)	VERY LOW	CRITICAL
Motor block – BMI n.r (0.15%; sufentanil) (assessed with: Bromage scale)												
1 (Nunes 2016)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/37 (2.7%)	4/60 (6.7%)	RR 0.41 (0.05 to 3.49)	39 fewer per 1000 (from 63 fewer to 166 more)	VERY LOW	CRITICAL
Spontaneous vaginal birth – BMI n.r (0.1%; sufentanil)												
1 (Nunes 2016)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20/33 (60.6%)	39/60 (65%)	RR 0.93 (0.67 to 1.3)	45 fewer per 1000 (from 214 fewer to 195 more)	VERY LOW	IMPORTANT
Spontaneous vaginal birth – BMI n.r (0.15%; sufentanil)												
1 (Nunes 2016)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	18/37 (48.6%)	39/60 (65%)	RR 0.75 (0.51 to 1.09)	162 fewer per 1000 (from 318 fewer to 59 more)	VERY LOW	IMPORTANT
Instrumental birth – BMI n.r (0.1%; sufentanil)												
1 (Nunes 2016)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	11/33 (33.3%)	8/60 (13.3%)	RR 2.5 (1.12 to 5.6)	200 more per 1000 (from 16 more to 613 more)	VERY LOW	IMPORTANT
Instrumental birth – BMI n.r (0.15%; sufentanil)												
1 (Nunes 2016)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	11/37 (29.7%)	8/60 (13.3%)	RR 2.23 (0.99 to 5.03)	164 more per 1000 (from 1 fewer to 537 more)	VERY LOW	IMPORTANT
Caesarean birth – BMI n.r (0.1%; sufentanil)												
1 (Nunes 2016)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	2/33 (6.1%)	13/60 (21.7%)	RR 0.28 (0.07 to 1.17)	156 fewer per 1000 (from 202 fewer to 37 more)	VERY LOW	IMPORTANT
Caesarean birth – BMI n.r (0.15%; sufentanil)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB	CEI + PCEA	Relative (95% CI)	Absolute		
1 (Nunes 2016)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	8/37 (21.6%)	13/60 (21.7%)	RR 1 (0.46 to 2.18)	0 fewer per 1000 (from 117 fewer to 256 more)	VERY LOW	IMPORTANT
Women's experience of labour and birth – satisfaction – BMI n.r (0.1%; sufentanil) (measured with: VNS ; range of scores: 0-10; Better indicated by higher values)												
1 (Nunes 2016)	randomised trials	very serious[5]	no serious inconsistency	serious[2]	very serious[6]	none	33	60	-	Median for PIEB 8.6 (range 7.9 to 9.3), Median for CEI + PCEA 8.8 (range 8.3 to 9.3)	VERY LOW	IMPORTANT
Women's experience of labour and birth – satisfaction – BMI n.r (0.15%; sufentanil) (measured with: VNS ; range of scores: 0-10; Better indicated by higher values)												
1 (Nunes 2016)	randomised trials	very serious[5]	no serious inconsistency	serious[2]	very serious[6]	none	37	60	-	Median for PIEB 8.6 (range 7.7 to 9.4), Median for CEI + PCEA 8.8 (range 8.3 to 9.3)	VERY LOW	IMPORTANT

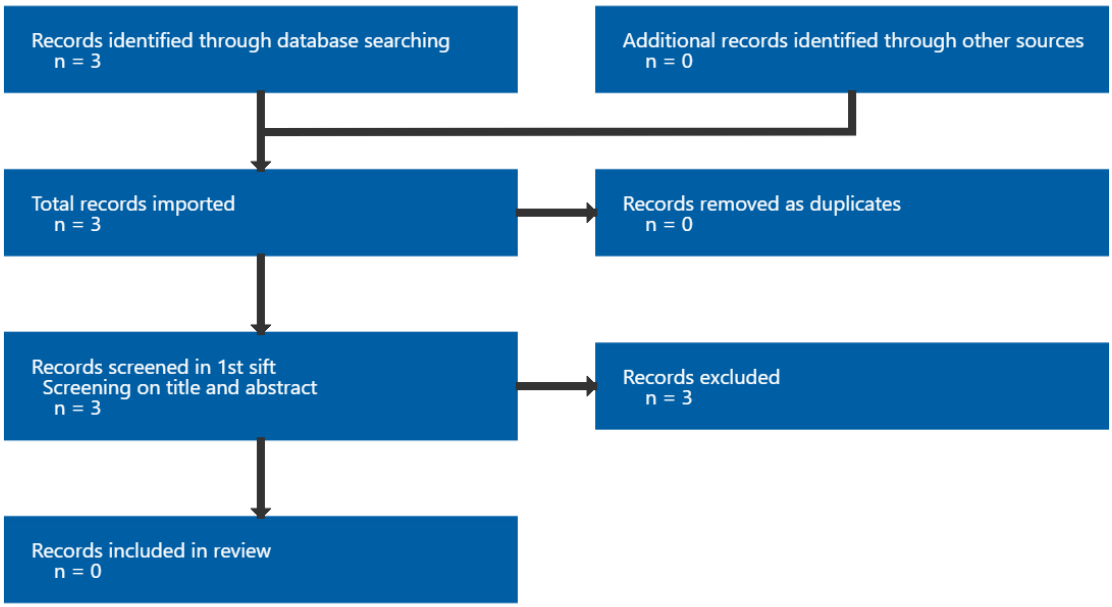
BMI: body mass index; CEI: continuous epidural infusion; CI: confidence interval; n.r: not reported; POR: Peto odds ratio; RR: risk ratio; PCEA: patient controlled epidural analgesia; PIEB: programmed intermittent epidural bolus; VNS: verbal numerical scale
1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 Intervention is indirect due to ropivacaine anaesthetic used.
3 95% CI crosses 2 MIDs
4 95% CI crosses 1 MID
5 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
6 Sample size <200

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?

No economic evidence was identified which was applicable to this review question.

Figure 18: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?

Excluded effectiveness studies

Table 9: Excluded studies and reasons for their exclusion

Study	Reason
Barbe, A., Schildermans, J., Devroe, S. et al. (2017) Breakthrough pain during labor: Conventional patient controlled epidural analgesiawithout background infusion vs programmed intermittent epidural boluses: A randomized, double blind study in nulliparous women. Regional Anesthesia and Pain Medicine 42(5supplement1): e53	- Study design Conference abstract only
Chakravarty, S., Lim, Y., Teoh, W. H. L. et al. (2006) Automated intermittent boluses for labor epidural analgesia - comparison with continuous infusion. Anesthesiology 105: a14	- Study design
Chi, Ctr Ior (2017) Effects of programmed intermittent epidural bolus and continuous epidural infusion for labor analgesia on maternal and infant temperature and inflammatory factors. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-IOR-17013016	- Study design Clinical trial entry. Unable to locate published results
ChiCtr (2018) Effect of programmed intermittent epidural bolus at different maintenance bolus dose for labor analgesia on maternal fever. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1800019250	- Study design Clinical trial entry. Published results not located
ChiCtr (2018) Effect of programmed intermittent epidural bolus at different maintenance bolus dose for labor analgesia on maternal fever. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1800020446	- Study design Clinical trial entry. Published results not located
ChiCtr (2019) The Efficacy of Programmed Intermittent Epidural Bolus Compared with Continuous Epidural Infusions for Postcesarean Delivery Analgesia: a randomized controlled trial. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1900021499	- Study design Clinical trial entry. Published results not located
ChiCtr (2019) Research for maternal inflammatory status and epidural-related maternal fever: a randomized controlled trial. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1900023966	- Study design Clinical trial entry. Published results not located
ChiCtr (2019) The Clinical Efficacy of Different Approaches in The Programmed Intermittent Epidural Bolus (PIEB) for Labor Analgesia in Parturients and Influence on the stages of labor. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1900020889	- Study design Clinical trial entry. Published results not located
ChiCtr (2019) Clinical efficacy of programmed intermittent epidural bolus and patient-controlled epidural infusion for labor analgesia. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1900021142	- Study design Clinical trial entry. Published results not located
ChiCtr (2019) A randomized controlled trial for optimum volume of	- Study design

Study	Reason
Programmed Intermittent Epidural Bolus for Labor Analgesia During First Stage of Labor. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1900028196	Clinical trial entry. Published results not located.
ChiCtr (2020) Comparison of programmed intermittent epidural boluses with continuous epidural infusion for the relief of uterine contraction pain after cesarean section: a randomized, controlled, double-blind, superiority trial. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000032645	- Study design Clinical trial entry. Full results are in preprint but have not been published yet
ChiCtr (2020) Effect of programmed intermittent epidural bolus at different dosage regimens for labor analgesia: a clinical multicenter, randomized controlled trial. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000040450	- Study design Clinical trial entry only. Full results not located
ChiCtr (2020) Patient-controlled intermittent epidural bolus versus programmed intermittent epidural bolus for labor analgesia: a prospective double-blind randomized trial. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000032791	- Study design Clinical trial entry only. Unable to locate published results
Ctri (2018) A study for comparing two techniques to control pain during labour. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2018/03/012384	- Study design Clinical trial entry only. Results not yet published
Ctri (2020) Comparison of the two techniques of nerve blockade for painless labour in pregnant women. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2020/02/023369	- Study design Clinical trial entry only. Results not yet published
Ctri (2021) Effect of painless delivery with epidural analgesia on occurrence postpartum depression. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2021/04/033031	- Study design Clinical trial entry only. Results not yet published
Euctr, B. E. (2015) Conventional patient controlled epidural analgesia (PCEA) versus programmed intermittent epidural boluses (PIEB) for labor analgesia: a randomized, double blind study in nulliparous women. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2015-004600-30-BE	- Study design Clinical trial entry only. Full results assessed under Roofthooft 2020
Euctr, E. S. (2015) COMPARATION BETWEEN TWO SCHEMES OF ANALGESIA IN PREGNANT WOMEN. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2014-004696-24-ES	- Study design Clinical trial entry only. Full results assessed under Diez-Picazo 2019
Ferreira E Veiga, M., Freitas, J., Nunes, S. et al. (2014) Labor analgesia: Analyzing outcomes. A randomized controlled trial. Regional Anesthesia and Pain Medicine 39(5suppl1): e196	- Study design Conference abstract only
Freitas, J., Veiga, M., Zenha, S. et al. (2014) Continuous epidural infusion versus programmed intermittent epidural bolus for labor analgesia: Effects on maternal motor function and satisfaction. Regional Anesthesia and Pain Medicine 39(5suppl1): e187	- Study design Conference abstract only
Karadjova, Dafina, Shosholcheva, Mirjana, Ivanov, Emilija et al. (2019) Side Effects of Intravenous Patient-Controlled Analgesia with Remifentanil Compared with Intermittent Epidural Bolus for Labour Analgesia - A Randomized Controlled Trial. Prilozi (Makedonska akademija na naukite i umetnostite. Oddelenie za medicinski nauki) 40(3): 99-108	- Comparator Women in the comparison arm did not receive epidural analgesia to establish regional analgesia. They received intravenous remifentanil

Study	Reason
Kct (2019) Comparison of the effects of epidural injection for labor analgesia: a randomized controlled trial. http://www.who.int/trialsearch/Trial2.aspx?TrialID=KCT0004389	- Study design Clinical trial entry - unable to locate published results
Leo, S., Ocampo, C. E., Lim, Y. et al. (2009) A comparison of automated intermittent mandatory boluses with a basal infusion in patient-controlled epidural analgesia for labour and delivery. International Journal of Obstetric Anesthesia 18(suppl1): 8	- Study design Conference abstract only
Liu, Jie, Xu, Jiqian, Xiao, Hairong et al. (2019) A Systematic Review and Meta-Analysis Comparing Programmed Intermittent Bolus and Continuous Infusion as the Background Infusion for Parturient-Controlled Epidural Analgesia. Scientific reports 9(1): 2583	- Study design Systematic review. Included studies have been checked and relevant ones included in the review
Nct (2016) PIEB vs PCEA With Epidural or CSE Technique. A Randomized Double Blind Clinical Trial. https://clinicaltrials.gov/show/NCT02768272	- Study design Clinical trial entry only. Published results assessed under Diez-Picazo 2019
Nct (2013) PIEB-PCEA Versus CEI-PCEA for Labor Analgesia in Nulliparous. https://clinicaltrials.gov/show/NCT01856166	- Study design Clinical trial entry only. Published results assessed under Morau 2019
Nct (2016) Comparison of PIEB vs CEI for Labor Analgesia. https://clinicaltrials.gov/show/NCT02949271	- Study design Clinical trial entry only. Published results assessed under Ojo 2020
Nct (2015) A Comparison of Epidural Analgesia: continuous Infusion Versus Programmed Intermittent Boluses. https://clinicaltrials.gov/show/NCT02510287	- Study design Clinical trial entry only. Published results assessed under Ferrer 2017
Nct (2015) Programmed Intermittent Epidural Bolus for Labor Analgesia During First Stage of Labor. https://clinicaltrials.gov/show/NCT02550262	- Study design Clinical trial entry only. Published results not located
Nct (2015) PIEB vs CEI for Labor Analgesia: an MLAC Study. https://clinicaltrials.gov/show/NCT02573597	- Study design Clinical trial entry. Results not yet published
Nct (2016) Programmed Intermittent Epidural Bolus for Labor Analgesia During First Stage of Labor-3. https://clinicaltrials.gov/show/NCT02887222	- Study design Clinical trial entry only. Comparator does not fit the protocol criteria - only comparing two different volumes so full text not accessed
Nct (2016) Programmed Intermittent Epidural Bolus for Labor Analgesia During First Stage of Labor 2. https://clinicaltrials.gov/show/NCT02758405	- Comparator No comparator of interest. Study looking at different time intervals between PIEB boluses
Nct (2017) Combined Implementation of Dural Puncture Epidural and Programmed Intermittent Epidural Bolus for Labor Analgesia. https://clinicaltrials.gov/show/NCT03366935	- Study design Clinical trial entry only. Published results

Study	Reason
	assessed under Song 2021
Nct (2017) The Programmed Intermittent Epidural Bolus Adrenaline Study. https://clinicaltrials.gov/show/NCT03043781	- Study design Clinical trial entry only. Results not yet published
Nct (2018) Programmed Intermittent Epidural Bolus Versus Continuous Infusion in Labour Analgesia. https://clinicaltrials.gov/show/NCT03730753	- Study design Clinical trial entry only. Unable to locate any published results
Nct (2016) Comparison of Programmed Intermittent Epidural Bolus With Continuous Epidural Infusion for Labor Epidural Analgesia. https://clinicaltrials.gov/show/NCT02873091	- Study design Clinical trial entry only - unable to locate any published results
Nct (2016) Comparison of Two Methods of Administration of the Epidural, by Programmed Intermittent Bolus or Continuous Perfusion, on the Incidence of Cesarean Sections and Instrumented Deliveries in Primiparous Women. https://clinicaltrials.gov/show/NCT02705872	- Study design Clinical trial entry only - not completed status withdrawn
Nunes, J., Nunes, S., Veiga, M. et al. (2014) Programmed intermittent boluses: Are we improving epidural labour analgesia?. European Journal of Anaesthesiology 31(suppl52): 182-183	- Study design Conference abstract
Ocampo, C. E. T.; Leo, S.; Sia, A. (2009) Automated intermittent mandatory boluses vs basal continuous infusion in patient controlled epidural analgesia for labor and delivery. Canadian Journal of Anesthesia 56(suppl1): 60	- Study design Conference abstract
Riazanova, Oksana V., Alexandrovich, Yuri S., Guseva, Yana V. et al. (2019) A randomized comparison of low dose ropivacaine programmed intermittent epidural bolus with continuous epidural infusion for labour analgesia. Romanian Journal of Anaesthesia and Intensive Care 26(1): 25-30	- Intervention Epidural analgesia solution does not contain opioid (only ropivacaine)
Satomi, Shiho, Kakuta, Nami, Murakami, Chiaki et al. (2018) The Efficacy of Programmed Intermittent Epidural Bolus for Postoperative Analgesia after Open Gynecological Surgery: A Randomized Double-Blinded Study. BioMed research international 2018: 6297247	- Population Study population not pregnant women (women undergoing surgery for other reasons)
Schildermans, J., Roofthooft, E., Barbe, A. et al. (2018) Programmed intermittent epidural boluses versus patient controlled epidural analgesia without background infusion for labour analgesia: effects on local anaesthetic consumption and maternal motor function: a randomised, double-blind study in nulliparous women. International journal of obstetric anesthesia 35: S10	- Study design Conference abstract details only. Published results assessed under Roofthooft 2020
Sehlapelo, Mathabe, Perrie, Helen, Scribante, Juan et al. (2021) Comparison between two epidural analgesia maintenance techniques at a regional hospital. Anesthesia and Analgesia 133(3suppl2): 1121	- Study design Conference abstract only
Sng, B. L. (2014) Maintaining labour analgesia: Old and new solutions. Regional Anesthesia and Pain Medicine 39(5suppl1): e88-e89	- Study design Conference abstract
Sng, B. L., Zeng, Y., de Souza, N. N. A. et al. (2018) Automated mandatory bolus versus basal infusion for maintenance of epidural analgesia in labour. Cochrane Database of Systematic Reviews	- More recent systematic review included References checked and all relevant to the protocol have already been included
Soued, M., Bouattour, K., Rosa, A. et al. (2017) Modern neuraxial labour analgesia. Regional Anesthesia and Pain Medicine 42(5supplement1): e49-e50	- Study design Conference abstract only

Study	Reason
Stirparo, S., Camorcia, M., Farcomeni, A. et al. (2011) Maternal motor block during the second stage of labor and labor outcome: A comparison between programmed intermittent epidural bolus (PIEB) and continuous epidural infusion (CEI) analgesia. European Journal of Anaesthesiology 28(suppl48): 3	- Study design Conference abstract only
Van Houwe, M., Roofthooft, E., Rex, S. et al. (2022) High-volume PCEAversus PIEB for labour analgesia - the effects on local anaesthetic consumption and obstetric outcome: a randomised study. International Journal of Obstetric Anesthesia 50(supplement1): 4	- Study design Conference abstract only
Wang, Jing, Zhang, Longxin, Xiao, Peihan et al. (2021) A randomized trial of the dural puncture epidural technique combined with programmed intermittent epidural boluses for labor analgesia. Annals of palliative medicine 10(1): 404-414	- Comparator Study comparing two different techniques (dural puncture epidural to continuous epidural infusion) in combination with programmed intermittent epidural bolus, so the comparator does not meet those specified in the protocol
Wang, Luyang, Wu, Zhanhuai, Hu, Lijuan et al. (2022) Programmed intermittent epidural bolus for post-cesarean delivery analgesia: a randomized controlled double-blind trial. Journal of anesthesia 36(1): 32-37	- Outcomes No outcomes matching the protocol. Pain outcomes are post-birth and not pain during labour
Wang, Xian-Xue, Zhang, Xiao-Lan, Zhang, Zhao-Xia et al. (2022) Programmed intermittent epidural bolus in parturients: A meta-analysis of randomized controlled trials. Medicine 101(5): e28742	- Comparator Most of the included studies already included in the review. Other included studies not relevant due to either comparator not matching PICO or non-English language articles
Zuo, R H, Dang, J J, Zhuang, J W et al. (2022) The incidence of breakthrough pain associated with programmed intermittent bolus volumes for labor epidural analgesia: a randomized controlled trial. International journal of obstetric anesthesia: 103571	- Comparator Comparisons are different PIEB volumes therefore do not match the protocol

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of Programmed Intermittent Epidural Bolus compared to other methods of maintaining epidural analgesia?

No research recommendations were made for this review question.