CHARACTERISTICS OF INCLUDED STUDIES

Fasting

Study	*Participants*	*Interventions*
Kupietzky 2008 (Ref ID: 15936) non-randomised controlled study Randomisation unit: Patient. Trial held in Israel. Setting: primary care dental practice. Funding :unclear/ not stated	Inclusion criteria: Healthy children selected consecutively as they presented for 2 or more separate restorative dentistry appointments; required NOA inhalation for uncooperative or anxious behaviour. Exclusion criteria: None noted. Study comments: Controlled crossover study Fasting: Study of fasting. Medical reason: dental treatment. Procedure type: Painful; dental - restorations. First procedure?: mixed. ASA details: I-II. Learning disabilities: none mentioned. Age: mixed; Ages 24 to 160 months with mean age of 74 months. Gender: 64 males and 49 females. Weight: all patients weighed more than 5 kg; Mean weight 23 kg. Planned sedation level: mild. Purpose: mixed. Sedationist: dental practitioner. Procedure carried out by: dental practitioner. Sedation monitoring by: another person - no details.	1) No solids for 6 hours prior to sedation and no clear liquids for 2 hours prior to sedation; volume: Nitrous oxide 50%; (n=113). 2) No fasting required; volume: Nitrous oxide 50%; (n= 113). Other interventions: None. Intervention concurrent medications: Random assignment to fasting or non fasting groups in a cross over design. Control concurrent medications: Random assignment to fasting or non fasting groups in a cross over design. Intervention - achieved sedation: titrated. Control - achieved sedation: titrated. Other analgesics therapy: Not stated. Monitoring for intervention: Parents and office staff. Monitoring for control: Parents and office staff.

METHODOLOGICAL QUALITY OF STUDIES

Fasting

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Kupietzky 2008 (Ref ID: 15936)	Unclear / not stated; Convenience sample randomly assigned to fast vs no fast in crossover trial.	Not stated.	Patient: no - crossover trial. Outcome assessor: No.	ITT: Unclear/not stated. Power calculation: Not stated.	Yes, all completed intervention.	Yes - cross over trial.

CHARACTERISTICS OF INCLUDED STUDIES

Psychological preparation

Study	*Participants*	*Interventions*
Mahajan 1998 (Ref ID: 645) RCT Randomisation unit: Patient. Trial held in USA. Setting: gastroenterology. Funding :unclear/ not stated	Inclusion criteria: Children undergoing gastrointestinal endoscopy. Exclusion criteria: Children who were neurologically impaired or unable to complete the questionnaires were excluded. Fasting: put if patients were fasted, time of fasting, i.e. before intervention and duration of fasting. Medical reason: gastrointestinal. Procedure type: Painful; upper endoscopy. First procedure?: not known / unclear. ASA details: Not stated. Learning disabilities: Children who were neurologically impaired or unable to complete the questionnaires were excluded. Age: mixed; ages 6-19 years. Gender: 22 males; 38 females. Weight: all patients weighed more than 5 kg. Planned sedation level: not stated / unknown. Purpose: decrease anxiety. . Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: .	1) Sedation plus usual explanation and demonstration using a doll model, or a book with photographs; volume: n/a; (n=30). 2) Sedation plus usual explanation; volume: n/a; (n=30). Other interventions: None. Intervention concurrent medications: Not stated. Control concurrent medications: Not stated. Intervention - achieved sedation: titrated. Control - achieved sedation: titrated. Other analgesics therapy: when general or unespecified analgesics given to patients not as part of the intervention. Monitoring for intervention: Not stated. Monitoring for control: Not stated.

Psychological preparation

Study	*Participants*	*Interventions*
Olumide 2009 (Ref ID: 15940) RCT Randomisation unit: Patient. Trial held in UK. Setting: primary care dental practice. Funding :unclear/ not stated	Inclusion criteria: Dental clinic patients between ages 8-12 years whose parents gave consent. Exclusion criteria: Children who refused or whose understand of and spoken level of English was insufficient for participation or children who were visually disabled. Study comments: This study assessed an intervention leaflet with preparatory information vs. a leaflet about healthy eating Fasting: NA. Medical reason: dental treatment. Procedure type: -------; not stated / unknown. First procedure?: not known / unclear. ASA details: I-II. Learning disabilities: Not stated. Age: 5 to 12 years of age. Gender: 24 boys and 26 girls. Weight: all patients weighed more than 5 kg. Planned sedation level: not stated / unknown. Purpose: decrease anxiety. . Procedure carried out by: . Sedation monitoring by: .	1) preparatory leaflet; volume: n/a; (n=25). 2) control leaflet on healthy eating; volume: n/a; (n= 25). Other interventions: None. Intervention concurrent medications: . Control concurrent medications: . Intervention - achieved sedation: ----------. Control - achieved sedation: . Other analgesics therapy: . Monitoring for intervention: Facial Image Scale used to assess anxiety before and after reading the leaflet. Monitoring for control: Facial Image Scale used to assess anxiety before and after reading the leaflet.

METHODOLOGICAL QUALITY OF STUDIES

Psychological preparation

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Mahajan 1998 (Ref ID: 645)	Unclear / not stated.	Not stated.	Patient: no single blind trial. Outcome assessor: Yes.	ITT: Yes, all followed. Power calculation: Not stated; Details on what outcome study powered for, at what level and power, and n patients.	Yes, all completed intervention.	Yes mainly; No significant differneces between groups in age, sex, race, type of endoscipic procedure or prior endoscopic experience.
Olumide 2009 (Ref ID: 15940)	Adequate- computer or calculator generated sequence.	Adequate- sequentially numbered, opaque, sealed envelopes.	Patient: yes double blind trial. Outcome assessor: Yes.	ITT: Yes, all followed. Power calculation: Yes; Adequately powered for outcome of anxiety.	Yes, all completed intervention.	Yes mainly; Comparable on age, sex and parental support.

CHARACTERISTICS OF INCLUDED STUDIES

Midazolam

Study	*Participants*	*Interventions*
Al-zahrani 2009 (Ref ID: 15922) RCT - crossover Randomisation unit: Patient. Trial held in Saudi Arabia. Setting: dental hospital. Funding :university study	Inclusion criteria: aged between 4-6 years, ASA-I, child's weight within normal range, no previous dental treatment, behaviour category Frankl scale #2, i.e.negative, reluctant to accept treatment with evidence of negative attitude, not profound, (see study commments). Exclusion criteria: those needing pulp therapy or extractions, who had recently used medications (e.g. erythromycin, anticonvulsants) that may interfere with pharmacokinetics or midazolam, with any conditions that predispose to airway obstruction or difficulties. Study comments: continued from inclusion criteria: children who needed bilateral restorative treatment in lower arch and with no cognitive impairment) Fasting: emphasis on nothing per mouth at least 6 hours before the appointment were given as part of the preoperative written instructions (with verbal reinforcement). Medical reason: dental treatment. Procedure type: Painful; dental - restorations. First procedure?: first procedure. ASA details: I. Learning disabilities: none stated. Age: mixed; range 4 to 6 years or 48 to 72 months; mean age 55.07 months (SD9.29). Gender: overall: 56.7%(17/30) male and 43.3% (13/30) female. Weight: all patients weighed more than 5 kg; range 13 to 24 Kg; mean weight 17.45 Kg (SD3.46). Planned sedation level: conscious sedation. Purpose: increase cooperation. Sedationist: dental practitioner. Procedure carried out by: dental practitioner. Sedation monitoring by: experienced observer.	1) oral midazolam [0.6 mg/kg, preparation of intravenous midazolam with a flavoured diluent] + topical anaesthesia [benzocaine 20%] + local anaesthesia [lidocaine 2%, max 4.4mg/kg]; volume: weight dependant; (n=30). 2) oral midazolam [0.6 mg/kg, same as intervention] + titrated inhalation nitrous oxide/oxygen [analgesia unit, up to 30-50%] + topical anaesthesia [benzocaine 20%] + local anaesthesia [lidocaine 2%, max 4.4mg/kg]; volume: dependant on weight and titration of N2O and O2; (n=30). Other interventions: none. Intervention concurrent medications: patients received mouth prop before topical anaesthesia and were inmobilised with papoose board; one parent remained present in sedation room and was instructed to be passive; rubber dam was applied. Control concurrent medications: same as intervention. Washout period: one week. Intervention - achieved sedation: bolus. Control - achieved sedation: mixed. Other analgesics therapy: not stated. Monitoring for intervention: sedation onset signs that were recorded every 5 mins included glazed look, delayed eye movement, lack of muscle coordination, slurred speech, sleep; haemodynamic parameters continuously monitored from beginning throughout end of procedure & recovery. Monitoring for control: same as intervention.

CHARACTERISTICS OF INCLUDED STUDIES

Midazolam

Study	*Participants*	*Interventions*
Antmen 2005 (Ref ID: 426) RCT Randomisation unit: Patient. Trial held in Turkey. Setting: haematology - outpatients. Funding :university study	Inclusion criteria: children undergoing diagnostic bone marrow aspiration. Exclusion criteria: not stated. Fasting: no food or fluids for at least 4hr before the procedure. Medical reason: blood disorders: diagnosis, cancer, infection, etc. Procedure type: Painful; bone marrow aspiration. First procedure?: not known / unclear. ASA details: not stated. Learning disabilities: none stated. Age: mixed; overall mean age 9.2 years (SD3) and overall range: 5 to 16 years. Gender: not stated. Weight: not known / unclear. Planned sedation level: conscious sedation. Purpose: decrease anxiety. Sedationist: not stated / unknown. Procedure carried out by: not stated / unknown. Sedation monitoring by: not stated / unknown.	1) i.v. midazolam 0.05 mg/kg + i.v. alfentanil 20 mg/kg (infusion over 1 min); volume: weight dependant; (n=20). 2) i.v. alfentanil 20 mg/kg (infusion over 1 min); volume: weight dependant; (n=20). Other interventions: i.v. midazolam 0.05 mg/kg + i.v. ramifentanil 0.5 mg/kg (infusion over 1 min), (n=20); i.v. ramifentanil 1 mg/kg (infusion over 1 min), (n=20). Intervention concurrent medications: none stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: mixed. Control - achieved sedation: infusion. Other analgesics therapy: not stated. Monitoring for intervention: AAP guidelines: monitoring/management during & after sedation for diagnostic & therapeutic procedures; continuous monitoring of heart & respiratory rate, O2 saturation & intermittent BP; vital signs recorded b4, during & 5 & 15 min after procedure. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Connors 1994 (Ref ID: 1286) RCT Randomisation unit: Patient. Trial held in USA. Setting: accidents & emergencies. Funding :unclear/ not stated	Inclusion criteria: haemodynamically & neurologically stable children without an intravenous line present, with single laceration 0.5 to 6 cm long, judged to be anxious by the attending physicians on A&E presentation. Exclusion criteria: not stated. Fasting: not stated. Medical reason: laceration repair. Procedure type: Painful; suturing. First procedure?: not known / unclear. ASA details: not stated. Learning disabilities: none stated. Age: mixed; overall age range: 2 to 10 years; mean age: oral midazolam 4.4 years (SD2.5), intranasal midazolam 3.5 years (SD2). Gender: % male per group (after 4 excluded, 2 in each group): oral 62% (16/26), nasal 39% (11/28) grou. Weight: all patients weighed more than 5 kg; mean: oral midazolam 18 kg (SD5), intranasal midazolam 16kg (SD4). Planned sedation level: not stated / unknown. Purpose: decrease anxiety. Sedationist: nurse. Procedure carried out by: physician. Sedation monitoring by: not stated / unknown.	1) oral midazolam 0.5 mg/kg [max 8 mg; mean 7.5mg(SD0.9); total 0.1ml/kg; anxious children:single repeat dose after 30min if adequate sedation not achieved] + intranasal placebo (inactive oral solution -sterile water-); volume: weight dependant; (n=28). 2) intranasal midazolam 0.25 mg/kg [max 8 mg;mean 4mg(SD1); total 0.05 ml/kg; anxious children:single repeat dose after 30min if adequate sedation not achieved] + oral placebo [inactive oral sterile water; half in each nostril over 30-60 secs]; volume: weight dependant; (n=30). Other interventions: none. Intervention concurrent medications: papoose use (in standard form) to restrain children for laceration repair; parents who were not overly anxious encouraged to sit at the bedside during procedures & maintain physical contact with their child. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: titrated. Other analgesics therapy: topical solution, 3 mL of tetracaine (0.05%), epinephrine (1:1000) and cocaine (11.8%) (TAC); or 1% lidocaine; administered carefully by slow infiltration in a stardard A&E manner; administered 2 to 5 mins before intervention administration. Monitoring for intervention: continuous monitoring: heart rate, pulse oximetry at baseline & from times of intervention administration until each chil met discharge criteria; BP, repiratory rate recorded at baseline & just before discharge from A&E. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Dilli 2008 (Ref ID: 2659) RCT Randomisation unit: Patient. Trial held in Turkey. Setting: accidents & emergencies. Funding :unclear/ not stated	Inclusion criteria: children requiring lumbar puncture for suspected meningitis admitted between January 2004 and December 2006; haemodinamically and neurologically stable. Exclusion criteria: children with history of AE reaction to midazolam or ketamine, psychiatric or behavioural disorder, risk of raised intracranial or intraocular pressure, thyroid disorder, porphyria, blocked nose or who have been sedated within 4 hrs of presentation. Fasting: fasting time notes as the last time to time of first dose of medication: midazolam+ketamine 3.9(SD2.9), ketamine 3.5 (SD2.8). Medical reason: suspected meningitis. Procedure type: Painful; lumbar puncture. First procedure?: not known / unclear. ASA details: not stated. Learning disabilities: none stated. Age: mixed; overall age range 2 to 14 years; per group: midazolam+ketamine 7.1 years (SD3.9), ketamine 6.0 years (SD3.5). Gender: overall 60% were boys; per group: midazolam+ketamine 56%(27/48), ketamine 63% (32/51). Weight: not known / unclear. Planned sedation level: conscious sedation. Purpose: decrease anxiety. Sedationist: not stated / unknown. Procedure carried out by: physician. Sedation monitoring by: not stated / unknown.	1) iv midazolam 0.1 mg/kg [over 1-2 min] + iv ketamine 1mg/kg + atropine 0.01 mg/kg [ketamine would be added (0.5 mg/kg) if conscious sedation not achieved within 5 minutes but no patient needed additional ketamine]; volume: weight dependant; (n=48). 2) iv ketamine 1mg/kg [administered over 1min; ketamine added 0.5 mg/kg, if conscious sedation not achieved within 5 minutes -administered twice to 5 patients] + atropine 0.01 mg/kg; volume: weight dependant; (n=51). Other interventions: none. Intervention concurrent medications: not stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: titrated. Other analgesics therapy: not stated. Monitoring for intervention: monitoring of respiratory and heart rates, oxygen saturation via pulse oximeter and recorded at 5 minute intervals beginning before drug injection and ending after proceudre when patient fully awake. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Disma 2005 (Ref ID: 334) RCT Randomisation unit: Patient. Trial held in Italy. Setting: gastroenterology. Funding :university study	Inclusion criteria: children schedualed for diagnostic endoscopic procedures of the upper gastrointestinal tract; enrolled during the period between January 2001 and May 2004. Exclusion criteria: not stated. Fasting: in children aged 1 to 3 years old nothing by mouth at least 6 hrs before the procedure; in children older than 3 years nothing by mouth for at least 8 hrs before the procedure. Medical reason: gastrointestinal. Procedure type: Painful; mixed. First procedure?: not known / unclear. ASA details: I-II. Learning disabilities: none stated. Age: mixed; overall age range: 1 to 12 years; mean age per group: midazolam 7.1 years (SD3.1), usual care 6.7 years (2.9), Fentanyl 6.8 years (SD2.8). Gender: overall 51% (123/240) were mal; midazolam 49% (38/78), usual care 57% (46/80), fentanyl 48% (39/82). Weight: all patients weighed more than 5 kg; mean weight per group: midazolam 27.5 kg (SD16.2), usual care 22.7 kg (SD10.8), fentanyl 25.6 kg (SD9). Planned sedation level: deep. Purpose: mixed. Sedationist: anaesthetist. Procedure carried out by: specialist of the area - paediatric gastroenterologist. Sedation monitoring by: sedationist for both groups.	1) TA (EMLA venipucture sites; Lidocaine -larynx) + iv midazolam 0.1 mg/kg [2min before procedure; max 7.5 mg] + iv propofol 3 mg/kg [in 3 doses of 1 mg/kg over 1 min; suppl propofol as required] + O2 (3Lmin); volume: weight dependant; (n=78). 2) TA(EMLAcream -venipucture; Lido -larynx) + iv pro 3mg/kg [3doses 1mg/kg over 1min; suppl pro as required] + O2 (3Lmin); volume: weight dependant; (n=80). Other interventions: TA (as above) + iv fenta (1mg/kg) + iv propofol (as above) + O2 (as above), n=82. Intervention concurrent medications: all patients received intravenous propofol 3mg/kg divided into 3 doses of 1 mg/kg each given over 1 min; also, all patients received standard premedication oral midazolam 0.5mg/kg/max 7.5mg/kg 20 min before procedure to establish iv line before sedation. Control concurrent medications: same as intervention and continued: all patients were given supplemental oxygen via a nasal cannula and allowed to breathe spontaneously without tracheal intubation. Intervention - achieved sedation: bolus plus maintenance. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: heart rate, blood pressure, etc were recorded and defined as baseline values; heart rate, mean arterial pressure, respiratory rate & oxygen saturation (pulse oximeter) were recorded at 1 min intervals during procedure and every 5 min during recovery. Monitoring for control: same as intervention.

CHARACTERISTICS OF INCLUDED STUDIES

Midazolam

Study	*Participants*	*Interventions*
Everitt 2002 (Ref ID: 3302) RCT Randomisation unit: Patient. Trial held in Australia. Setting: accidents & emergencies. Funding :unclear/ not stated	Inclusion criteria: children with uncomplicated lacerations that required two or more sutures. Exclusion criteria: children with significant head injury, cognitive delay, on medication with sedative activity, any contraindication to the study drugs. Fasting: not stated. Medical reason: laceration repair. Procedure type: Painful; suturing. First procedure?: some patients had prior procedure. ASA details: not stated. Learning disabilities: none stated. Age: 1 to 5 years of age. Gender: details not reported. Weight: not known / unclear. Planned sedation level: conscious sedation. Purpose: decrease anxiety. Sedationist: nurse. Procedure carried out by: main investigator. Sedation monitoring by: anaesthetist.	1) oral midazolam 1 mg/kg [max 15 mg; administered with small amount of juice] + topical anaesthesia 1ml/10 kg (amethicaine/lignocaine/adrenaline); volume: weight dependant; (n=45). 2) intranasal midazolam 0.5 mg/kg [max 10 mg; alternating nostrils by slow droplet installation] + topical anaesthesia 1ml/10 kg (amethicaine/lignocaine/adrenaline); volume: weight dependant; (n=42). Other interventions: oral diazepam syrup 0.5 mg/kg (max 10 mg), (n=42); mean time to sedation 31 min (SD9). Intervention concurrent medications: if deeemed necessary by treating doctor during procedure children were wrapped in a sheet to prevent movement; parents present all time to provide additional comfort. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: titrated. Other analgesics therapy: not stated. Monitoring for intervention: heart rate, and recovery scores every 15 min with a score of 0 to 2 for motor activity assessment, conscious state; children required a minimum score of 9 to be discharged. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Fatovich 1995 (Ref ID: 2763) RCT Randomisation unit: Patient. Trial held in Australia. Setting: accidents & emergencies. Funding :unclear/ not stated	Inclusion criteria: children younger than 10 years who presented to the A&E with a laceration. Exclusion criteria: children who had received medication with sedative effectt in the preceding 24 hr, had: a laceration that required plastic surgery; a known allergy to lidocaine or midazolam; history of cardiac; respiratory or neurologic disorder; or consent not obtained. Study comments: mean length of lacerations 2cm (SD1.6) (range 0.5-10.5); 2% of children had multiple lacerations Fasting: not stated. Medical reason: laceration repair. Procedure type: Painful; suturing. First procedure?: not known / unclear. ASA details: not stated. Learning disabilities: none stated. Age: mixed; overall mean age 4.8 years (SD3) (range 0.8 to 10). Gender: overall 63% were male. Weight: not known / unclear. Planned sedation level: not stated / unknown. Purpose: decrease anxiety. Sedationist: not stated / unknown. Procedure carried out by: not stated / unknown. Sedation monitoring by: not stated / unknown.	1) oral midazolam 0.3 mg/kg [flavoured with fruit concentrate and water] + 1% of plain lidocaine (given 30-45 min after administration of intervention); volume: weight dependant; (n=32). 2) oral placebo [similar in taste to intervention; mix flavoured with fruit concentrate and water] + 1% of plain lidocaine (given 30-45 min after administration of intervention); volume: as intervention; (n=23). Other interventions: oral midazolam 0.3 mg/kg (flavoured with fruit concentrate and water) + buffered lidocaine 1% buffered with sodium bicarbonate, n=25; oral placebo 0.3 mg/kg + buffered lidocaine 1% buffered with sodium bicarbonate, n=27. Intervention concurrent medications: none stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: children's heart and respiratory rates before, during and after procedure. Monitoring for control: same as intervention.

CHARACTERISTICS OF INCLUDED STUDIES

Midazolam

Study	*Participants*	*Interventions*
Fishbein 1997 (Ref ID: 1089) RCT Randomisation unit: Patient. Trial held in USA. Setting: gastroenterology. Funding :university study	Inclusion criteria: children undergoing their first esophagogastroduodenoscopy. Exclusion criteria: children with chronic respiratory ailments, cerebral palsy, seizure disorder, or severe developmental delay. Fasting: not stated. Medical reason: gastrointestinal. Procedure type: Painful; esophagogastroduodenoscopy. First procedure?: first procedure. ASA details: not stated. Learning disabilities: none stated. Age: mixed; overall age range: 2 to 12 years. Gender: details not reported. Weight: not known / unclear. Planned sedation level: conscious sedation. Purpose: decrease anxiety. Sedationist: nurse. Procedure carried out by: not stated / unknown. Sedation monitoring by: not stated / unknown.	1) VENIPUNCTURE intranasal midazolam 0.2 mg/k [max 5 mg] + ENDOSCOPY intravenous placebo 0.04 ml/kg [0.9% NaC] + intravenous meperidine 1 mg/kg; volume: midazolam: titrated over a 30 secs intervals administering half dose in each nostril; (n=20). 2) VENIPUNCTURE intranasal placebo 0.04 ml/kg [0.9% NaCl] + ENDOSCOPY intravenous midazolam 0.05 mg/kg + intravenous meperidine 1 mg/kg; volume: midazolam: titrated over a 30 secs intervals administering half dose in each nostril; (n=20). Other interventions: none. Intervention concurrent medications: all received intravenous meperidine 1 mg/kg; parents stayed with children until 5 min before procedure or until the drug reached the maximum effect (~10 min) after which parents were asked to leave the endoscopy suite; routine care after procedure. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: mixed. Other analgesics therapy: not stated. Monitoring for intervention: blood pressure and oxygen saturation readings were recorded every 90 seconds; a 24-hour follow-up was obtained to determine any subsequent adverse events. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Fuks 1994 (Ref ID: 1297) RCT - crossover Randomisation unit: Patient. Trial held in Israel. Setting: dental hospital. Funding :university study	Inclusion criteria: children displaying uncooperative behaviour with ratings 1 to 2 on the Frankl scale considered if they were healthy (ASAI) with no previous dental experience, needing at least 2 restorative visits. Exclusion criteria: not stated. Fasting: NPO? For 4hr before the appointment. Medical reason: dental treatment. Procedure type: Painful; dental - restorations. First procedure?: first procedure. ASA details: I; described as medically health with ASA I. Learning disabilities: none stated. Age: 1 to 5 years of age; mean age 2.7 years (range: 1.7 to 3.5 years). Gender: details not reported. Weight: not known / unclear. Planned sedation level: not stated / unknown. Purpose: increase cooperation. Sedationist: dental practitioner. Procedure carried out by: main investigator. Sedation monitoring by: not stated / unknown.	1) intranasal midazolam 0.3 mg/kg + 50% of nitrous oxide / oxygen analgesia (administered at the first appointment); volume: varied with weight and N2O administration; (n=30). 2) intranasal midazolam 0.2 mg/kg + 50% of nitrous oxide / oxygen analgesia (administered at the second appointment); volume: varied with weight and N2O administration; (n=30). Other interventions: none. Intervention concurrent medications: patients sitting reclined on parents' lap; restrained in a papoose board with a head holder; parent remained in the room through procedure; place of a mouth prop and rubber dam. Control concurrent medications: same as intervention. Intervention - achieved sedation: mixed. Control - achieved sedation: mixed. Other analgesics therapy: not stated. Monitoring for intervention: vital signs monitored with precordial stethoscope & pulse oximeter probe; pulse & oxygen saturation recorded at beginning of each session & every 5 min thereafter until end of procedure. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Fukuta 1994 (Ref ID: 1282) RCT Randomisation unit: Patient. Trial held in Japan. Setting: dental hospital. Funding :grant- other	Inclusion criteria: ASA I-II mentally handicapped 5-20 years old presenting for tx at a paediatric dentistry clinic who had previously exhibited combative behaviour sufficiently violent as to rule out dental tx using routine behaviour mgmt techniques incl N2O/O2. Exclusion criteria: upper respiratory, ear infection within 10 days preceding physical examination. Study comments: physical examination not more than 48hrs before procedure (scheduled for early morning appts); all pts kept without solid foods for a min of 6hrs prior to sedation & only light liquids permitted up to 4 hrs before sedation; pts were age stratified Fasting: for at least 6hrs prior to sedation; light liquids permitted up to 4 hrs before procedure. Medical reason: dental treatment. Procedure type: Painful; dental - restorations. First procedure?: prior procedures. ASA details: I-II; described as mentally handicapped patients. Learning disabilities: mentally handicapped. Age: mixed; range 5 to 20 years; average: intranasal midazolam 0.3 - 11.6 years; intranasal midazolam 0.2 - 13.6 years. Gender: overall 51% Male; for 0.2 midazolam 50%(11/22) male and 0.3 midazolam 52%(11/21) male. Weight: all patients weighed more than 5 kg; mean weight for 0.2 midazolam 38.6(SD15.6) kg and mean for 0.3 midazolam 42.2(SD12.6) kg. Planned sedation level: not stated / unknown. Purpose: increase cooperation. Sedationist: not stated / unknown. Procedure carried out by: not stated / unknown. Sedation monitoring by: not stated / unknown.	1) intranasal midazolam 0.3 mg/kg + continuous nitrous oxide 30% / oxygen 70%; volume: varied with weight and N2O administration; (n=22). 2) intranasal midazolam 0.2 mg/kg+ continuous nitrous oxide 30% / oxygen 70%; volume: varied with weight and N2O administration; (n=21). Other interventions: none. Intervention concurrent medications: continuing administration of 30% N20 plus 70% oxygen via nasal mask. Control concurrent medications: same as intervention. Intervention - achieved sedation: mixed. Control - achieved sedation: mixed. Other analgesics therapy: not stated. Monitoring for intervention: CPR equipment ready at all times; for AE: ECG, BP, heart rate, respiratory rate and oxygen saturation monitored at 5 min intervals; AE vomiting, respiratory depresssion, depressed vital signs monitored durig rest period, dental tx and post tx. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Hartgraves 1994 (Ref ID: 1303) RCT Randomisation unit: Patient. Trial held in USA. Setting: dental hospital. Funding :university study	Inclusion criteria: children between 1.5 to 6 years of age, healthy (ASA I) and judged before the sedation as precooperative or definitely negative according to the Frankl behaviour rating scale. Exclusion criteria: not stated. Study comments: procedures completed under rubber dam isolatio & followed established sedation techniques Fasting: not stated. Medical reason: dental treatment. Procedure type: Painful; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: not known / unclear. ASA details: I. Learning disabilities: none stated. Age: mixed; mean: oral midazolam 3.3 years (range 1.5 to 5.9), intranasal midazolam 3.1 years (range 1.5 to 5.8). Gender: overall 50% Male: 50% Female; midazolam intranasal 52%(26/50) female and midazolam oral 48%(24/50). Weight: all patients weighed more than 5 kg; mean weight 14.3kg (range 9 to 21kg);mean midazolam intranasal 14.3 kg and midazolam oral 14.2 kg. Planned sedation level: not stated / unknown. Purpose: increase cooperation. Sedationist: not stated / unknown. Procedure carried out by: not stated / unknown. Sedation monitoring by: not stated / unknown.	1) oral midazolam 0.5 mg/kg [mean 6.8 mg] + continuous nitrous oxide 40% / oxygen 60% + analgesia (2% lidocaine with 1:100,000 epinephrine; max recommended dose 4.4 mg/kg); volume: varied with weight and N2O administration; (n=50). 2) intranasal midazolam 0.2 mg/kg [mean 2.8 mg] + continuous nitrous oxide 40% / oxygen 60% + analgesia (2% lidocaine with 1:100,000 epinephrine; max recommended dose 4.4 mg/kg); volume: varied with weight and N2O administration; (n=50). Other interventions: none. Intervention concurrent medications: nitrous oxide USP in 40% with oxygen in 60% was administered via nasal hood to all patients. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: all patients continuously monitored with a pulse oximeter and a pretracheal stethoscope. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Havel 1999 (Ref ID: 903) RCT Randomisation unit: Patient. Trial held in USA. Setting: accidents & emergencies. Funding :grant- other	Inclusion criteria: children presenting to A&E of a tertirary care children's hospital with isolated extremity injury necessitating procedural sedation for closed reduction. Exclusion criteria: history of cardiac disease, haemodynamic compromise, allergy to any study medication, eggs, or soybeans and inability to obtain consent from a parent or guardian. Study comments: complications defined as: hypoxemia, hypoperfusion, dimished peripheral pulses, cool and pale distal extremities, or delayed capillary refill, agitation, vomiting, pain with medication administration, procedure recall Fasting: sedation was performed in all patients considered to have 'full stomachs' with close attention to the level of sedation induced. Medical reason: close reduction. Procedure type: Painful; mixed. First procedure?: not known / unclear. ASA details: I-III; ASA I: midazolam 83% (38/46), propofol 84% (36/43); ASA II: midazolam 15% (7/46), propofol 16% (7/43); ASA III: midazolam 2% (1/46), propofol 0%. Learning disabilities: none stated. Age: mixed; overall age range 2 to 18; mean years (SD): midazolam 8.6 years (SD4.2), propofol 9 years (SD3.8). Gender: male % (n): midazolam 76% (35/46), propofol 58% (25/43);. Weight: all patients weighed more than 5 kg; mean kg (SD): midazolam 37.2 kg (SD21.6), propofol 37.4 kg (SD19.1). Planned sedation level: not stated / unknown. Purpose: mixed. Sedationist: investigator. Procedure carried out by: specialist of the area - paediatric gastroenterologist. Sedation monitoring by: nurse.	1) intravenous midazolam initial dose 0.1 mg/kg over 1-2 mins [max single dose 5 mg] + intravenous morphine (analgesic) 0.05-0.1 mg/kg [max single dose 5 mg/kg] + placebo bolus and infusions; volume: varied with weigh, titration and infusion; (n=49). 2) intravenous bolus infusion propofol 1 mg/kg [initially 0.1 mg/kg over 1-2 mins; max single dose 5 mg] + intravenous morphine (analgesic) 0.05-0.1 mg/kg [max single dose 5 mg/kg] + intravenous lidocaine 2% preservative free, 0.5 mg/kg + intravenous placebo; volume: varied with weigh, titration and infusion; (n=43). Other interventions: . Intervention concurrent medications: paediatric nurse accompanied patients at all times throughout procedural sedation. Control concurrent medications: same as intervention. Intervention - achieved sedation: mixed. Control - achieved sedation: mixed. Other analgesics therapy: not stated. Monitoring for intervention: sedation levels, pulse oximetry every 5 min; blood pressure, heart rate, respiratory rate, recorded every 5 min. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Kanegaye 2003 (Ref ID: 601) RCT Randomisation unit: Patient. Trial held in USA. Setting: accidents & emergencies. Funding :unclear/ not stated	Inclusion criteria: children requiring sedation for potentially painful procedures enrolled as a convenience sample when both investigator & adequate monitor bed space available; with lesion & procedure isolated to skin & amenable to treatment under local anaesthesia. Exclusion criteria: GOS score<15, fasting<2hrs, history of AE to LA/midazolam, narcotic analgesia sedation within 4hr of presentation, inhability to comply w/aftercare instructions, IV catheter in place/required pre-enrollment, injury-related lab test, organ system injury. Fasting: per group:mean hours (SD): higher dose: 4.4(SD2.4) and lower dose: 4.2 (SD1.9). Medical reason: laceration repair. Procedure type: Painful; suturing. First procedure?: not known / unclear. ASA details: I-II. Learning disabilities: none stated. Age: mixed; overall range 0.5 to 4 years; mean years (SD): higher dose: 2.5(SD1) and lower dose: 2.13(SD0.9). Gender: overall 62% (40/65) were male;% male per group: higher dose: 61%(20/33) and 69%(20/32). Weight: all patients weighed more than 5 kg; mean kg (SD): higher dose: 14.4 (SD2.8) and lower dose: 12.8 (SD02.2). Planned sedation level: conscious sedation. Purpose: decrease anxiety. Sedationist: nurse. Procedure carried out by: physician. Sedation monitoring by: not stated / unknown.	1) rectal midazolam 2 mg/kg [identical in appearance to comparison drug] + analgesia [suitable wounds: tetracaine-adrenaline-cocaine; wounds not suitable/incomplete: 1% lidocaine for local infiltration/nerve block]; volume: weight dependant; (n=33). 2) rectal midazolam 1 mg/kg [identical appearance to intervention drug]; volume: weight dependant; (n=32). Other interventions: none. Intervention concurrent medications: some patients -whose parents were blinded to dose- received midazolam without tapping buttocks after administration; use of physical restrain or additional sedative agents proceeded at physician's discretion; continued in control concurrent…. Control concurrent medications: continued from control: LA could occur concurrently w/drug administration or following topical anaesthetic postmedication sedation score; same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: continuous nursing and electronic monitoring; pts monitored from time of medication administration until adequate recovery occurred in accordance with AE protocol following sedation guidelines AAP. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Kapur 2004 (Ref ID: 455) RCT Randomisation unit: Patient. Trial held in India. Setting: dental hospital. Funding :university study	Inclusion criteria: children having at least one carious deciduous mandibular molar requiring a class I amalgam restoration, with no previous dental experience amongst children attending paediatric and preventive dentistry unit. Exclusion criteria: not stated. Fasting: patients were fasted for solids overnight and 3 hours for clear liquids. Medical reason: dental treatment. Procedure type: Painful; dental - restorations. First procedure?: first procedure. ASA details: I. Learning disabilities: none stated. Age: mixed; less than 4 years of age. Gender: details not reported. Weight: not known / unclear. Planned sedation level: conscious sedation. Purpose: increase cooperation. Sedationist: investigator. Procedure carried out by: main investigator. Sedation monitoring by: same person who performed procedure.	1) oral midazolam 0.5 mg/kg [for parental administration, diluted in strawberry syrup] + routine behaviour management [Love care, Tell show do technique, physical restrain]; volume: varied with weight and increments; (n=20). 2) oral placebo saline water 0.5 mg/kg, diluted in strawberry syrup (with equal quantity and consistency as intervention) + routine behaviour management (Love care, Tell show do technique, physical restrain); volume: same as intervention; (n=20). Other interventions: none. Intervention concurrent medications: pts with parents - quiet preoperative room & to encouraged them to sleep;pts with investigator/anaesthetist in operative room; restorative procedure: use of rubber dam application; behaviour management therapy & physical restrain during procedure. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: pulse rate, respiratory rate, blood pressure, oxygen saturation monitored throughout the procedure. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Layangool 2008 (Ref ID: 4388) RCT Randomisation unit: Patient. Trial held in Thailand. Setting: cardiology - outpatients. Funding :unclear/ not stated	Inclusion criteria: children aged between 6 months and 5 years who were not well adapted for an echocardiogram. Exclusion criteria: children with upper airway obstruction, on-going respiratory tract infection, significant hepatic, renal or brain disease, history of hypertensive to either sedative drug, had problems which a physician determines would not be a good candidate for study. Fasting: children were nil orally for at least four hours before medication started. Medical reason: echocardiographic evaluation. Procedure type: Non-Painful; echocardiogram (ECHO). First procedure?: not known / unclear. ASA details: not stated. Learning disabilities: none stated. Age: mixed; age range: 6 months to 5 years; mean age: chloral hydrate 20.6 months (SD12.9), midazolam 19.3 months (SD11.6). Gender: male vs female: overall: 53%(139/264) vs 47%(125/264); chloral hydrate: 58%(77/132) vs 42%(55/132), midazolam:47%(62/132) vs 53%(70/132). Weight: all patients weighed more than 5 kg; mean weight: chloral hydrate 9.4 Kg (SD2.8), midazolam 9.3 Kg (SD2.8). Planned sedation level: conscious sedation. Purpose: mixed. Sedationist: nurse. Procedure carried out by: specialist of the area - paediatric cardiologist. Sedation monitoring by: same person who performed procedure.	1) sublingual midazolam (from iv preparation) 0.3 mg/kg initially [max <5mg; additional half doses applied if children not sufficiently sedated within 30 mins postmedication]; volume: varied with weigh and depth of sedation; (n=132). 2) oral chloral hydrate 50 mg/kg initially [max <1gm; additional half doses applied if children not sufficiently sedated within 30 mins postmedication]; volume: varied with weigh and depth of sedation; (n=132). Other interventions: none. Intervention concurrent medications: none stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: by second nurse: vital signs oxygen saturation and conscious level were monitored until children's status showed full recovery. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Lee-Kim 2004 (Ref ID: 454) RCT Randomisation unit: Patient. Trial held in USA. Setting: dental hospital. Funding :university study	Inclusion criteria: children with Early Childhood Caries, medically healthy (ASAI) or with controlled systemic disease (ASAII); needing 1or more dental visits for comprehensive dental care;with definitely or slightly negative behaviour. Exclusion criteria: without fever, runny nose, cough preceding & immediately prior to sedation. Study comments: ethnicity: oral midazolam 40% African-American, 15% Caucasian, 45% Hispanic; intranasal midazolam 35% African-American, 20% Caucasian, 45% Hispanic Fasting: no food or liquids for at least 4 to 6 hrs prior to sedation appointment and with no signs or symptoms of fever, runny nose, cough preceding & immediately prior to sedation. Medical reason: dental treatment. Procedure type: Painful; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: not known / unclear. ASA details: I-II; medically healthy: ASA I; or with controlled systemic disease: ASA II. Learning disabilities: none stated. Age: mixed; age range: 2 to 6 years; oral midazolam mean age 3.4 years (SD11); intranasal midazolam 3.2 years (10). Gender: overall 53%(21/40) male: 55%(11/20) male in the oral midazolam, 50%(10/20) male in the intranasal midazolam groups. Weight: all patients weighed more than 5 kg; oral midazolam mean weight 17 kg (SD4); intranasal midazolam mean weight 16 kg (SD4). Planned sedation level: conscious sedation. Purpose: mixed. Sedationist: dental practitioner or parents. Procedure carried out by: main investigator.	1) oral midazolam 0.7 mg/kg + nitrous oxide 45% (midazolam diluted in cherry flavoured syrup) + analgesia (0.9 to 3.6 ml of 2% lidocaine with 1:100,000 epinephrine during sedation); volume: varied with weight and N2O administration; (n=20). 2) intranasal midazolam 0.3 mg/kg + nitrous oxide 45% + analgesia (0.9 to 3.6 ml of 2% lidocaine with 1:100,000 epinephrine during sedation); volume: varied with weight and N2O administration; (n=20). Other interventions: none. Intervention concurrent medications: patients restrained in a papoose board (used as standard of care restraint device in paediatric dentistry clinic for all patients under sedation) without a head todler. Control concurrent medications: same as intervention. Intervention - achieved sedation: mixed. Control - achieved sedation: mixed. Other analgesics therapy: not stated. Monitoring for intervention: by dental assistant; procedure videotaped, vital signs including respiratory rate, heart rate, oxygen saturation and blood pressure were recorded every 15 min by trained dental assistant who also recorded time of onset and duration of procedure. Monitoring for control: same as intervention.

Midazolam

Study	Participants	Interventions
Liacouras 1998 (Ref ID: 1029) RCT Randomisation unit: Patient. Trial held in USA. Setting: gastroenterology. Funding :university study	Inclusion criteria: all patients older than 1 year of afe undergoing either upper or lower endoscopy. Exclusion criteria: children excluded if they had previosu complications related to conscious sedation, allergy to intervention drug, respiratory distress, history of cardial or renal abnormalities, developmental delay or neurologic impairment. Study comments: Other additional comments Fasting: not stated. Medical reason: gastrointestinal. Procedure type: Painful; upper and lower endoscopy. First procedure?: not known / unclear. ASA details: not stated. Learning disabilities: none stated. Age: mixed; mean age: oral midazolam 7.7 years (SD4.4), placebo 7.9 years (SD4.4). Gender: overall 56% were male (69/123): male in each group: oral midazolam 54% (33/62), placebo 58% (36/61). Weight: all patients weighed more than 5 kg; mean weight: oral midazolam 29 kg (SD17), placebo 32 kg (SD19). Planned sedation level: conscious sedation. Purpose: mixed. Sedationist: endoscopist. Procedure carried out by: endoscopist. Sedation monitoring by: physician and nurse.	1) before iv placement: oral midazolam 0.5 mg/kg [injectable midazolam 5 mg/mL diluted (1:1) with flavoured syrup (to give before iv insertion)]; volume: weight dependant; (n=62); inconsistency in the number of randomised patients reported for each group at baseline (midazolam, n=61; placebo, n=62) and in the results (midazolam, n=62; placebo, n=61); so we took those from the results. 2) before intravenous placement: oral placebo, flavoured syrup diluted (1:1) with water 0.5 mg/kg (assumed dose)(labeled and packaged in identical manner to give before intravenous insertion); volume: same as intervention; (n=61); inconsistency in the number of randomised patients reported for each group at baseline (midazolam, n=61; placebo, n=62) and in the results (midazolam, n=62; placebo, n=61); so we took those from the results. Other interventions: before endoscopy: oral midazolam 0.5 mg/kg (max 20 mg) + intravenous midazolam; oral placebo 0.5 mg/kg (assumed dose) + intravenous midazolam; [groups had either intravenous meperidine or intravenous fentanil but doses not stated]. Intervention concurrent medications: before endoscopy all patients were given intravenous midazolam and either mepedidine or fentanil intravenously; all doses were titrated by endoscopist to achieve adequate conscious sedation. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: monitoring of heart and respiratory rate, blood pressure before introduction into study, at time of intravenous placement & every 5 min during the procedure -endoscopy-, and during recovery period; pulse

Midazolam

Study	*Participants*	*Interventions*
Ljungman 2000 (Ref ID: 902) RCT - crossover Randomisation unit: Patient. Trial held in Sweden. Setting: oncology. Funding :grant- other	Inclusion criteria: older than 0.5 years needing needling insertion 3 times during study period but were not terrified by procedure that sedative had been given regularly previously. Exclusion criteria: not stated. Study comments: interventions: 1st midazolam-placebo-placebo or placebo-midazolam-midazolam; 2nd step child was own control; 3rd step without crossover, compared with step 2 conducted for psychological carry-over effect; midazolam compared to placebo in the 1st two steps Fasting: no food or fluids were allowed 30 mins before the procedure. Medical reason: paediatric oncology. Procedure type: Painful; insertion of a needle in a subcutaneously implanted central venous port. First procedure?: prior procedures. ASA details: not stated. Learning disabilities: none stated. Age: mixed; crossover trial; mean age: midazolam 5 years (range: 0.8 to 18). Gender: 45%(17/38) boys for fist intervention=midazolam; 44%(16/36) for second intervention=placeb; two children dropped out in the placebo. Weight: all patients weighed more than 5 kg; mean weight: midazolam 28kg (range: 9-79), placebo 29kg (range:9-84). Planned sedation level: conscious sedation. Purpose: decrease anxiety. Sedationist: not stated / unknown. Procedure carried out by: not stated / unknown. Sedation monitoring by: not stated / unknown.	1) intranasal midazolam 0.2 mg/kg [0.1mL per puff; max 5mg=10 puffs] + analgesia (EMLA patch with 25 mg lidocaine/25mg prilocaine; needle inserted 60-120 mins after patch application); volume: midazolam: children receiving 2 puffs received 2 puffs in each nostril initially followed by another dose after 1 min;no extra dose given; (n=38). 2) intranasal placebo, saline water with citric acid + analgesia (EMLA patch with 25 mg lidocaine/25mg prilocaine; needle inserted 60-120 mins after patch application); volume: same as intervention; (n=36). Other interventions: none. Intervention concurrent medications: drug administered when child was calm and sitting in lap of parent for administration of intervention. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: pulse oximeter used if children became so sedated with difficulties responding to questions; monitoring of effects & side effects were documented on a chart for conscious sedation at the ward; all were observed for at least 1hr after sedation. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Luhmann 2001 (Ref ID: 824) RCT Randomisation unit: Patient. Trial held in USA. Setting: accidents & emergencies. Funding :university study	Inclusion criteria: children presenting to A&E for repair of facial lacerations. Exclusion criteria: previous laceration repairs; solid/liquid oral intake within 2hr of evaluation; abnormalities: airway, cardiac, hepatic, renal, CNS; bowel obstruction; otitis media; AE history to study drugs; lacerations that would inhibit mask use for N2O administration. Study comments: ethnicity: overall: 34% (69/204) White, 66% (135/204) Black; % White per group: midazolam plus SC 14%(27/51), SC 30%(15/50), midazolam plus SC plus N2O 44%(23/52), N2O 37%(17/51) Fasting: solid or liquid oral intake up to 2hr before evaluation. Medical reason: laceration repair. Procedure type: Painful; suturing. First procedure?: first procedure. ASA details: I-II. Learning disabilities: none stated. Age: mixed; overall mean age 4.1 years (range: 2 to 6); per group: midazolam 4.2 years (SD1.4), SC 4 years (SD1.4), midazolam plus SC plus N2O 4 years (SD1.4), N2O 4.2 years (SD1.4). Gender: overall % male: 66%(135/204); % male per group: midazolam plus SC 65%(33/51), SC 66%(33/50), midazolam plus SC plus N2O 65%(34/52), N2O 69%(35/51). Weight: not known / unclear. Planned sedation level: not stated / unknown. Purpose: decrease anxiety. Sedationist: physician. Procedure carried out by: physician. Sedation monitoring by: sedationist for both groups.	1) oral midazolam 0.5 mg/kg + standard care [comforting techniques] + topical anaesthetics; volume: weight dependant; (n=52). 2) standard care alone [included: age appropriate comforting techniques (video watching, book reading by parents/emergency staff) + topical anesthetic combination (lidocaine/epinephrine/tetracaine) supplemented after 20 min by injected buffered lidocaine]; volume: same as intervention; (n=50). Other interventions: oral midazolam 0.5 mg/kg (max 20 mg), (n=20) + standard care + nitrous oxide 50%, (n=52); nitrous oxide 50% / oxygen 50% through nasal mask + standard care (given just before wound preparation), (n=51). Intervention concurrent medications: nurses remained with subjectes throughout procedure and recovery periods; comforting techniques included watching videotapes, reading books and were delivered by parents or emergency staff; use of papoose board if needed at discretion of suturer. Control concurrent medications: same as intervention. Intervention - achieved sedation: mixed. Control - achieved sedation: mixed. Other analgesics therapy: not stated. Monitoring for intervention: room equipped for monitoring, resuscitation, audiovisual recording; before & throughout sedation, consciousness levels, heart/respiratory rates, BP & O2 saturation monitored continuously in all pts; end-tidal N2O levels at 5/10 min intervals by nurse. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Mortazavi 2009 (Ref ID: 2777) RCT Randomisation unit: Patient. Trial held in Iran. Setting: hospital - outpatients. Funding :university study	Inclusion criteria: children aged 3-5 years attending posgraduate paediatric clinic who could not cooperate sufficiently to permit the required & identical treatment for their D/E teeth, pulpotomy & restoration (continuation on this section on study comments). Exclusion criteria: not stated. Study comments: all rated 1 or 2 on Frankl Behavioural Rating Scale as negative (75% of 40) or definitely negative (25% of 40); had no respiratory distress or remarkable adenoidhypertrophy; had no neurological impairment or contraindication to midazolam Fasting: no solid food or milk at least 4-6 hrs before sedation but children could drink a glass or clear liquid at least 2hrs before starting of procedure. Medical reason: dental treatment. Procedure type: ; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: not known / unclear. ASA details: I; described as healthy children with ASA I. Learning disabilities: none stated. Age: mixed; age range3-5 year;mean age 3.99 years (SD 0.38). Gender: not stated. Weight: not known / unclear. Planned sedation level: conscious sedation. Purpose: increase cooperation. Sedationist: operator - no more details. Procedure carried out by: unclear. Sedation monitoring by: not stated / unknown.	1) oral midazolam 0.25 mg/kg [of a 15mg/3ml of iv midazolam mixed in black cherry syrup]; volume: weight dependant; (n=20). 2) syrup alone (with no active medication); volume: same as intervention; (n=20). Other interventions: none. Intervention concurrent medications: children not restrained with a papoose board. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: children continuously observed and monitored with pulse oximetry sensor, pericordial stethoscope to listen breath sounds; vital signs monitored before and after sedation every 10 minutes. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Paspatis 2006 (Ref ID: 239) RCT Randomisation unit: Patient. Trial held in Grece. Setting: gastroenterology. Funding :unclear/ not stated	Inclusion criteria: children who underwent upper gastrointetinal endoscopy. Exclusion criteria: children <3 years, with:significant neurological disability, history of allergies to intervention drugs or their components, metabolic, cardiac or renal disease, previous complications to intravenous sedation, respiratory distress & ASA >II. Study comments: two nurses were in attendance, one was assigned to observe the patient and secure endoscope and the other recorded vital signs and assisted with biopsies Fasting: not stated. Medical reason: gastrointestinal. Procedure type: Painful; upper endoscopy. First procedure?: not known / unclear. ASA details: I-II; excluded patients with ASA>II. Learning disabilities: none stated. Age: mixed; mean age: midazolam plus propofol 8 years (SD3), propofol 9 years (SD3). Gender: overall 48%(26/54) male: oral midazolam plus propofol 50% male (13/26), propofol 46% male (13/28). Weight: all patients weighed more than 5 kg; mean weight: oral midazolam plus propofol 32 kg (SD11), propofol 35 kg (SD13). Planned sedation level: deep. Purpose: mixed. Sedationist: anaesthetist. Procedure carried out by: endoscopist. Sedation monitoring by: not stated / unknown.	1) oral midazolam 0.5 mg/kg [max 20 mg] + intravenous propofol 0.5 mg/kg [titrated in repeated doses; no maximum dose; mean dose 1.8 mg/kg (SD0.7)] + analgesia (2% lidocaine mixed 1ml in every 20 mL of 1% propofol); volume: variable dependant on weight and titration; (n=26). 2) intravenous propofol 0.5 mg/kg [no max dose; mean 2.9 mg/kg (SD0.9)] + analgesia (2% lidocaine mixed 1ml in every 20 mL of 1% propofol); volume: variable dependant on weight and titration; (n=28). Other interventions: none. Intervention concurrent medications: all patients given supplemental oxygen intranasally. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: continuous monitoring for heart rate (20% below or above baseline = significant), oxygen saturation (saturation <92% for more than 10 seconds = significant), & mean arterial blood pressure (>10mmHg from baseline = significant). Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Shashikran 2006 (Ref ID: 275) RCT Randomisation unit: Patient. Trial held in India. Setting: dental hospital. Funding :university study	Inclusion criteria: children designated to have negative or definitely negative behaviour according to Frankl's rating scale (assessed by senior paediatric dentist -prof supervising study) and whose procedure necessitated the administration of a local analgesic injection. Exclusion criteria: not stated. Fasting: parents wer instructed to give the children a glass of mil or sogt dring and one sandwich or small piece of cake at least 2hr before commencement of procedure under sedation. Medical reason: dental treatment. Procedure type: Painful; not stated / unknown. First procedure?: not known / unclear. ASA details: not stated; reported that pre-anaesthetic assessment carried out & paediatric physician's fitness certificate obtained to ascertain child's physiologic status for sedation. Learning disabilities: none stated. Age: 1 to 5 years of age; overall age range: 2 to 5 years; mean age: intranasal midazolam 3.5 years (SD0.7) (range 2.5-5), intramuscular midazolam 3.4 years (SD 0.6) (range 2-4.5). Gender: overall 48% male (19/40): intranasal midazolam 55% male (11/20), intramuscularl midazolam 40% male (8/20). Weight: all patients weighed more than 5 kg; mean weight: intranasal midazolam 12.6 kg (SD1.4) (range 10-15), intramuscular midazolam 12.2 kg (SD1.2) (range 10-14). Planned sedation level: conscious sedation. Purpose: increase cooperation. Sedationist: not stated / unknown. Procedure carried out by: not stated / unknown. Sedation monitoring by: not stated / unknown.	1) intranasal midazolam 0.2 mg/kg + analgesia (administered when child permitted or offered little or no resistance); volume: weight dependant; (n=20). 2) intramuscular midazolam 0.2 mg/kg + analgesia; volume: weight dependant; (n=20). Other interventions: none. Intervention concurrent medications: none stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: heart rate and respiratory rate monitored. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Sherwin 2000 (Ref ID: 897) RCT Randomisation unit: Patient. Trial held in USA. Setting: accidents & emergencies. Funding :university study	Inclusion criteria: children for ketamine sedation requiring short procedures specially in which immbolization was required or examinations likely to produce emotional distress; attempted to enroll consecutive children treated by 6 physicians from AE. Exclusion criteria: used standard ketamine exclusion criteria. Fasting: not stated. Medical reason: intravenous line placement. Procedure type: Painful; intravenous catheter insertion. First procedure?: not known / unclear. ASA details: I-II; ASA I: midazolam group 89% and placebo group 88%; ASA II: midazolam group 11% and placebo group 12%. Learning disabilities: none stated. Age: mixed; age range 1 to 15 years; midazolam mean age 7 years (IQR 4-11), placebo mean age 6 years (IQR 2-11). Gender: overall 67% (70/104) male; midazolam 75%(40/53), placebo 59%(30/51). Weight: all patients weighed more than 5 kg; midazolam mean weight 25kg (IQR 17-37), placebo mean weight 20 (IQR 14-42). Planned sedation level: not stated / unknown. Purpose: decrease distress. Sedationist: practitioner. Procedure carried out by: main investigator. Sedation monitoring by: not stated / unknown.	1) intravenous midazolam 0.05 mg/kg [max 2mg] + intravenous ketamine 1.5 mg/kg [max=0.5] + atropine [0.01 mg/kg, 0.1 mg minimum and 0.5 mg maximum]; volume: varied with weight and titration; (n=53). 2) intravenous ketamine 1.5 mg/kg + intravenous placebo saline solution 0.05 mg/kg (assumed dose) + atropine 0.01 mg/kg; volume: same as intervention; (n=51). Other interventions: none. Intervention concurrent medications: if treating physicians noted recovery agitation during recovery, at discretion, patients could be treated with nonblinded midazolam at their choosing doses; no specific criteria for this was stipulated. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: patients monitored with continuous pulse oximetry and cardiac monitoring throughout sedation. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Singh 2002 (Ref ID: 752) RCT Randomisation unit: Patient. Trial held in India. Setting: dental hospital. Funding :unclear/ not stated	Inclusion criteria: children requiring short dental procedures like extractions, restorations and endodontic treatment with or without local anaesthesia. Exclusion criteria: not stated. Fasting: not stated. Medical reason: dental treatment. Procedure type: Painful; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: not known / unclear. ASA details: I. Learning disabilities: none stated. Age: mixed; overall age range 3 to 9 years. Gender: not stated. Weight: not known / unclear. Planned sedation level: conscious sedation. Purpose: decrease anxiety. Sedationist: not stated / unknown. Procedure carried out by: not stated / unknown. Sedation monitoring by: not stated / unknown.	1) oral midazolam 0.5 mg/kg mixed in juice to mask taste and distiction; volume: weight dependant; (n=30). 2) oral triclofos sodium 70 mg/kg mixed in juice to maintain uniformity with midazolam and to mask distinction; volume: same as intervention; (n=30). Other interventions: oral promethazine 1.2 mg/kg, n=30; mixed in juice to maintain uniformity with midazolam and to mask distinction. Intervention concurrent medications: not stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: arterial BP, pulse rate and respiratory rate recorded before administration of drugs and at definite intervals during procedure; patients continuously observed by operator. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Theroux 1993 (Ref ID: 1393) RCT Randomisation unit: Patient. Trial held in USA. Setting: accidents & emergencies. Funding :unclear/ not stated	Inclusion criteria: children who had not reached their 5th birthday who went to the emergency department with a simple laceration that required suturing. Exclusion criteria: children who had a laceration complicated by serious injury such as bone fracture or closed head injury associated with GCS of <3; children with cognitive and motor delay or a seizure disorder for which they were currently taking anticonvulsant tx. Study comments: all emergency department physicians and registered nurses participated in the study; simple laceration=if emergency department physician felt comfortable with the repair; papoose board used in most of suturing procedures Fasting: not stated. Medical reason: laceration repair. Procedure type: Painful; suturing. First procedure?: not known / unclear. ASA details: not stated. Learning disabilities: none stated. Age: mixed; median 2.5 years (ranged between 0.75 and 4.9 years); mean: midazolam 2.85 years, placebo 2.5 years, control 2.8 years. Gender: details not reported. Weight: not known / unclear. Planned sedation level: not stated / unknown. Purpose: mixed. Sedationist: not stated / unknown. Procedure carried out by: practitioner. Sedation monitoring by: same person who performed procedure.	1) intranasal midazolam 0.4 mg/kg (mix from parental form) + local anaesthesia with lidocaine before suturing; volume: varied with weight and titration; (n=27). 2) intranasal placebo sterile normal saline 0.4 mg/kg (as single dose); volume: same as intervention; (n=17). Other interventions: control, no drug given and suturing procedure was performed in a routine manner, (n=15). Intervention concurrent medications: none stated. Control concurrent medications: none stated. Intervention - achieved sedation: titrated. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: heart/respiratory rate, BP, oxygen saturation monitored every 5 mins from prior to suturing and during procedure; cry, movement and struggle monitored at 5 min interval. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Wathen 2000 (Ref ID: 845) RCT Randomisation unit: Patient. Trial held in USA. Setting: hospital - outpatients. Funding :university study	Inclusion criteria: children who presented to paediatric A&E receiving paediatric A&E procedures where the attending physician chose ketamine for sedation. Exclusion criteria: age<4 months, HBP, glaucoma, globe injury, increased intracranial pressure/CNS mass lesion, active upper/lower respiratory infection, pharynx/larynx/trachea proc, congenital/anatomic airway abnormalities, majopsychiatric disorder, porphyria, ketamin AE hx. Fasting: median (interquartile range) per group hours since last oral intake: M+K 5.4 hours (3.6-7.1), K 5.9 hours (4.2-8.5). Medical reason: likely to be mixed. Procedure type: Painful; mixed. First procedure?: not known / unclear. ASA details: I-II. Learning disabilities: none stated. Age: mixed; overall age range: 0.3 to 18 years; median age (interquarile range) per group: Midazolam+Ketamine 5.6 years (3.4-9.6), Ketamine 6.8 years (4.4-10.3). Gender: overall 56% (139/266) were male; % male per group: Midazolam+Ketamine 55.5% (76/137), Ketamine 56.6% (73/129). Weight: not known / unclear. Planned sedation level: not stated / unknown. Purpose: decrease distress. Sedationist: nurse. Procedure carried out by: physician. Sedation monitoring by: not stated / unknown.	1) intravenous midazolam 0.1 mg/kg [over 1-2 mins] + intravenous ketamine 1mg/kg + intravenous glycopyrrolate 5 mg/kg [max 250 mg]; volume: varied with weight and titration; (n=130). 2) intravenous ketamine 1mg/kg + intravenous glycopyrrolate 5 mg/kg; volume: same as intervention; (n= 137). Other interventions: none. Intervention concurrent medications: pain medications administered before ketamine and time since last oral intake for either liquids or solids. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: continuous pulse oximetry, cardiorespiratory monitoring for the duration of sedation, BP every 15 mins, resuscitation equipment available at bedside for all pts. Monitoring for control: same as intervention.

Midazolam

Study	*Participants*	*Interventions*
Zier 2008 (Ref ID: 4328) RCT Randomisation unit: Patient. Trial held in USA. Setting: gastroenterology. Funding :university study	Inclusion criteria: children and adolescents scheduled to receive botulium toxin A (BoNT-A) injections for management of spasticity. Exclusion criteria: children who had specific contraindications to nitrous oxide. Fasting: not stated. Medical reason: cerebral palsy. Procedure type: Painful; botulium toxin A (BoNT-A) injections. First procedure?: prior procedures. ASA details: not stated. Learning disabilities: cerebral palsy. Age: mixed; midazolam group 8:7 years (SD4:9), nitrous oxide group 8:6 (3:8). Gender: % male: midazolam group 60%(15/25); nitrous oxide goup 56%(14/25). Weight: not known / unclear. Planned sedation level: not stated / unknown. Purpose: mixed. Sedationist: other study personnel. Procedure carried out by: physician. Sedation monitoring by: nurse.	1) rectal midazolam 0.35-0.5 mg/kg [max of 10 mg/kg] + topical anaesthesia (applied at least 30 min before injections) + placebo (fo N2O) + distraction (storytelling, soothing discourse); volume: varied with weight; (n=25). 2) nitrous oxide 70% + topical anaesthesia (applied at least 30 min before injections) + placebo (for midazolam) + distraction (storytelling, soothing discourse); volume: varied with weight and N2O administration; (n= 25). Other interventions: none. Intervention concurrent medications: none stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: titrated. Other analgesics therapy: not stated. Monitoring for intervention: monitored with continuous gas oximentry and direct nursing observation. Monitoring for control: same as intervention.

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Al-zahrani 2009 (Ref ID: 15922)	Inadequate- for e.g. allocation by alteratoin, birthdate, day of week; patients randomly selected through screening of sedation waiting list of dental patients in the dentristry clinics of university dentistry college.	Unclear; pharmacy from the university dental college prepared the midazolam mixture but unclear who allocated these to patients or what the pharmacy knew.	Patient: no, crossover trial. Outcome assessor: Unclear; dental treatment provided by same operator during the two visits; and an experience observer assessed and recorded all behavioural and haemodyanamic parameters but not clear what he knew about patients.	ITT: Yes, all followed; all randomised patients appeared to be included in analyses as assigned to original group. Power calculation: Not stated.	Yes, all completed; no patients appeared to have dropped out of the study at any time.	Yes - cross over trial.
Antmen 2005 (Ref ID: 426)	Partial- random permuted blocks; computer generated randomised scheme; permuted block randomisation by Zelen.	Not stated.	Patient: not stated. Outcome assessor: Unclear; sedation and pain scores assessed by the same anaesthetist but unclear if this applied sedative regimen or what he/she knew about treatment.	ITT: Yes, all followed; all randomised patients appeared to be included in analyses as assigned to original groups. Power calculation: Yes; based on 80% power to detect differences in mean values of intervention groups with two-sided overall significant level alpha=0.05; the number required per group was 20 patients.	Yes, all completed; study stated that no patients withdrew from the study.	Yes; groups were not significantly different in terms of age and weight, blood pressure, heart and respiratory rate; 6 pts had baseline hypertension, 6 had baseline tachycardia but did not require intervention; after sedation/analgesia these were normal.

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Connors 1994 (Ref ID: 1286)	Unclear / not stated.	Not stated.	Patient: yes, double blind trial. Outcome assessor: Yes; outcome independently assessed by nursing and attending physician using a 5-point validated scale.	ITT: ITT not performed, per protocol analysis instead; analyses of patients excluding randomised patients with protocol violations and incomplete data. Power calculation: Not stated.	No (≤ 20% did not complete intervention); 7% (4/58): 2 children excluded from each group because of protocol violations or incomplete data collection.	Yes; groups were not significantly different in terms of age, weight, laceration location & length, heart & respiratory rate, BP, O2 saturation & initial anxiety score; although not significant; there were more boys in the oral (17/28) than nasal (12/30) group.
Dilli 2008 (Ref ID: 2659)	Adequate- computer or calculator generated sequence; computer generated randomised allocations.	Adequate- sequentially numbered, opaque, sealed envelopes; sealed opaque envelopes.	Patient: not stated. Outcome assessor: Yes; all patients evaluated by the same physician were not present during drug administration and were unaware of each patient's allocation.	ITT: ITT not performed, per protocol analysis instead; 104 randomised but 99 analysed: midazolam+ketamine=48, ketamine=51. Power calculation: Not stated.	No (≤ 20% did not complete intervention); midazolam+ketamine group: 4%(2/50) one patient did not received allocated intervention and one was lost to follow-up; 6%(3/54) one patient did not received allocated intervention and two were lost to follow-up.	Yes; patients between groups were not significantly different in terms of age, sex, level of consciousness, severity of illness, final diagnosis, fasting time, sedation time, recovery time.

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Disma 2005 (Ref ID: 334)	Unclear / not stated.	Not stated.	Patient: not stated. Outcome assessor: Unclear; anaesthetist administered sedation drugs, carried out physical examination and clinical assessments and obtained medical history but not clear if blinded to drug treatment.	ITT: Yes, all followed; all enrolled patients appeared to have been randomised and all analysed as assigned to their original group. Power calculation: Not stated.	Yes, all completed; no withdrawals reported.	Yes mainly; patients in both groups were statistically comparable in terms of age, weight, gender and they were no statistical different in terms duration of endoscopy, recovery time or endoscopist's rating.
Everitt 2002 (Ref ID: 3302)	Partial- random permuted blocks; stated as block randomised single blind trial.	Unclear; a nurse not involved in patients' care administered drug but unclear what he/she knew about sedative drugs.	Patient: no, single blind trial. Outcome assessor: Partial; distress (VAS) assessed independently by assessed by parents who knew about drug and route and by sututing doctor, investigator and nurse assisting with suturing who were unaware of sedative drugs allocation; anxiety (WILTON) by investigator.	ITT: Unclear/not stated; not clear if reported analyses include all randomised patients who completed the trial regardless of loss of follow up. Power calculation: Yes; based on the dichotomous endpoint of whether patients could be discharged 90 min after sedation: to have an 80% probability of confidence interval excluding the value of 20%, the required sample sizes were 47 and 26.	Unclear or Not stated; unclear dropouts and unclear inclusion of these in analyses.	Yes; groups were similar in terms of age, heart & respiratory rate, BP, oxygen saturation, previous laceration & sedation, anxiety score and laceration characteristics; no patients had change in vital signs or respiratory depression before or during procedure.

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Fatovich 1995 (Ref ID: 2763)	Unclear / not stated; stated as prospective randomised double blind placebo controlled trial.	Adequate- independent third party: allocates interventions & retains schedule/code; pharmacist prepared solutions and placed them weekly in A&E; containers of local anaesthesia also replaced simultaneously.	Patient: yes, double blind trial. Outcome assessor: Yes.	ITT: Unclear/not stated; not clear if reported analyses include all randomised patients who completed the trial regardless of loss of follow up. Power calculation: Yes; a power of 0.90 at 0.5 significant level would require 24 cases in each group.	Unclear or Not stated; unclear dropouts and unclear inclusion of these in analyses.	Yes, but limited data; groups were not significantly different in terms of age, gender and location and length of laceration.
Fishbein 1997 (Ref ID: 1089)	Partial- random numbers, randomisation table; computer generated table with random numbers with equal chance to being assigned to either gorup.	Not stated.	Patient: yes, double blind trial. Outcome assessor: Yes; independent blinded observer evaluated negative behaviours from time of patients' arrival in endoscopy suite until completion of procedure.	ITT: No, available case analysis; data case analysis for patients with major negative behaviours during venipuncture. Power calculation: Yes; 20 patients were required in each group to enale detectgion of a 25% difference in major negative behaviours exhibited during venipuncture; power analysis assumed a SD of 30% and desired power of 80%; statistical significance a priori at $p<0.05$.	No (≤ 20% did not complete intervention); one patient in each group receiving venipuncture were missing from analyses of major negative behaviour and the reasons were not reported.	Yes mainly; patients between groups did not differ in terms of age, percentage of minor negative behaviours.

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Fuks 1994 (Ref ID: 1297)	Unclear / not stated.	Unclear; drug treatment administered by operator dentist who was blind to midazolam doses but unclear allocation method.	Patient: not stated. Outcome assessor: Yes; assessment of alertness, movement, crying (during procedure) and overall behaviour (end of procedure), by one of two senior investigators blinded to doses; reliability of ratings assessed separately by 2 investigators from videotapes of procedures.	ITT: Yes, all followed; all randomised patients appeared to be included in analyses as assigned to original groups. Power calculation: Not stated.	Yes, all completed; no withdrawals reported.	Yes - cross over trial.
Fukuta 1994 (Ref ID: 1282)	Unclear / not stated.	Not stated.	Patient: yes, double blind trial. Outcome assessor: Yes; isolated dental treatment room for each patient; observations performed by two dentists calibrated for conformity and blinded as to dose of medication; neither was the clinical operator.	ITT: Yes, all followed; all randomised patients appeared to have completed the trial and included in analyses. Power calculation: Not stated.	Yes, all completed; no withdrawals reported.	Yes; treatment did not differ from each group with respect to age, weight, sex, obesity, ASA physical status, length of treatment time and number of previous attempts at dental procedures.

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Hartgraves 1994 (Ref ID: 1303)	Unclear / not stated.	Not stated.	Patient: not blinded. Outcome assessor: Unclear; nature of interventions: different routes; sedative effect assessed by the 'operator' but not clear if blind to interventions.	ITT: Unclear/not stated; not clear if reported analyses include all randomised patients who completed the trial regardless of loss of follow up. Power calculation: Not stated.	Unclear or Not stated; unclear dropouts and unclear inclusion of these in analyses.	Yes; no significant difference between the two groups in terms of age, sex or weight and mean number of procedures (mean 3.2 in both groups); however, no comparable in no. of extractions, restorations and pulpotomies.
Havel 1999 (Ref ID: 903)	Partial- random permuted blocks; randomised blocks of ten.	Inadequate - sedationist knew medications, infusion tubing, intravenous site.	Patient: yes, double blind trial. Outcome assessor: Yes.	ITT: ITT not performed, per protocol analysis instead; 91 randomised but 89 analysed: midazolam=46, propofol=43. Power calculation: Yes; expected propofol patients to recover from sedation in 1/4 the time of that for midazolam patients, using alpha of 0.05 and beta of 0.2, a total of 32 patients would be required.	No (≤ 20% did not complete intervention); two patients in the propofol group had technical problems with the intravenous tubing during sedation and were therefore excluded from further data collection and analysis.	Yes mainly; groups were not significantly different in terms of age, weight, gender, race or ASA class; 84% (75/89) underwent isolated forearm fractures; not statistically significant differences between groups with respect to type of injury sustained.

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Kanegaye 2003 (Ref ID: 601)	Partial- random permuted blocks; stated as randomised double blind; computer generated permutted blocks randomisation.	Adequate- independent third party: allocates interventions & retains schedule/code; randomisation table kept in the hospital pharmacy and only the terms 'drug A' and 'drug B' appeared on randomisation table and on medication vials.	Patient: some patients. Outcome assessor: Yes; investigators were unaware of assigned dose until after the completion of data analysis; only pharmacy investigator knew concentrations contained in each vial and did not have patient contact or involvement.	ITT: Yes, all followed; if sedation failed, the achieved levels recorded & included for analysis on an ITT; if patients failed to retain entire doses, doses were repeated as originally assigned to groups; delays (>20min) before/during procedures resulted in elimination. Power calculation: Yes; n=144 to detect 20% point absolute difference in children successfully sedated; 90% and 70% for the more and less successful dose at the best level of sedation; $p<0.05$ for efficacy variable.	Yes, all completed; no dropouts due to interruptions in procedures/protocol violations; 4 patients expulsed the drug but mean sedation scores changed minimally in analysis with and without these thus no further analysis was performed; 2 failed to retain drug.	Yes mainly; groups were not significantly different in terms of age, gender, wound age, fasting duration, injury location, procedure type, levels of physician experience, type of local anaesthetic; patients in the higher dose group were heavier ($p=0.01$).
Kapur 2004 (Ref ID: 455)	Unclear / not stated.	Unclear; co-investigator prepared test solution interventions and handed them over to chief investigator who administered them, performed procedure and recorded various parameters but not clear allocation process.	Patient: yes, double blind trial. Outcome assessor: Yes; stated double blind.	ITT: Unclear/not stated; not clear if reported analyses include all randomised patients who completed the trial regardless of loss of follow up. Power calculation: Not stated.	Unclear or Not stated; unclear dropouts and unclear inclusion of these in analyses.	Yes; groups were not significantly different in terms of age, gender, body weight and type of tooth or cavity (meio-occlusal/disto-occlusal).

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Layangool 2008 (Ref ID: 4388)	Partial- random permuted blocks; randomised (by a study nurse) to chloral hydrate or midazolam in blocks of four.	Inadequate -; nurse who randomised and enrolled patients also gave sedation drugs to children.	Patient: yes, double blind trial. Outcome assessor: Yes; pediatric cardiologist who performed echocardiogram and second nurse who monitored vital signs, O2 saturation and conscious levels were blinded to randomisation; ability to complete procedure and sedation levels determined by pediatric cardiologist.	ITT: No, available case analysis; analyses reported for children who completed the procedure plus those who completed procedure partially. Power calculation: Not stated.	No (≤ 20% did not complete intervention); two patients, one in each group, were unable to complete procedure - reasons not stated- and thus excluded from analyses; children who completed procedure partially were included in analyses.	Yes mainly; groups were not statistically significant comparable in terms of age, sex, body weight, baseline oxygen saturation, functional heart classification before sedation; the underlying diseases in both groups were not different -not clear if statistically sig-.
Lee-Kim 2004 (Ref ID: 454)	Unclear / not stated; patients received drug treatment randomnly based on a random assigment to regimen.	Unclear.	Patient: not blinded - nature of intervention: different routes of administration. Outcome assessor: Yes; videotapes evaluated and scored by blinded and calibrated evaluator using Houpt's behaviour rating scale.	ITT: Yes, all followed; all randomised patients appeared to have completed the trial and included in analyses. Power calculation: Not stated.	Yes, all completed; no withdrawals were reported.	Yes mainly; patients between groups did not differ in gender, sex, ethnicity & weight; significatively differed in onset time (16min (SD5) for oral, 6min (SD2) for intranasal; p=.000) & procedure duration (38min (SD6) for oral, 29min (SD12) for intranasal; p=0.007).

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	Sequence Generation	Allocation Concealment	Blinding	ITT and Power Calculation	Attrition details	Baseline Comparable
Liacouras 1998 (Ref ID: 1029)	Unclear / not stated.	Adequate- sequentially numbered, opaque, sealed envelopes; doses of placebo and midazolam both labeled with appropriate identification number to match randomisation lots and placed in a brown opaque plastic bag.	Patient: yes, double blind trial. Outcome assessor: Yes; stated to be blinded to patient, parent, and assessors (nurse and physician).	ITT: Unclear/not stated; not clear if reported analyses included all randomised patients who completed the trial regardless of loss of follow up; there is available case analysis for secondary outcome - patients' satisfaction. Power calculation: Not stated.	Unclear or Not stated; unclear for the outcome of completion of procedure; available case for the outcome of patients' satisfaction: 26% (32/123) of patients, 23% (14/62) in intervention and 30% (18/61) in the control group,could not be contacted.	Yes mainly; groups were not significantly different in terms of age and gender; patients presedated with oral midazolam were more frequently judged to be adequately sedated for intravenous placement ($p<0.0001$) and for the procedure ($p<0.001$).
Ljungman 2000 (Ref ID: 902)	Unclear / not stated.	Unclear; batches with blinded ampules prepared by pharmacies but not clear allocation method and who administered drug interventions.	Patient: yes, double blind trial. Outcome assessor: Yes; children, parents and nurses; research nurse who did not attend procedure, helped children who did not understand the questions for evaluation of sedation and procedure.	ITT: Unclear/not stated; pain: pts M 50%(14/38), P 47%(17/36); parents M 0, P 6%(2/36); distress (discomfort): pts M 34%(13/38), P 47%(17/36); parents M 0, P 6%(2/36). Power calculation: Yes; sample size calculated to reach a power of 80% with alpha<0.05 for the 1ry outcome which was child's experience of procedure using intranasal spray; stated that difference between midazolam & placebo was greater than expected & power almost reached 100%.	No (>20% did not complete intervention; greater in 1 group); satisfaction: pts M 29%(11/38), P 39%(14/36); parents M 60%(23/38), P 72%(26/36); distress (discomfort): pts 50% in each gps; parents M 0, P 6%(2/36);.	Yes - cross over trial.

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Luhmann 2001 (Ref ID: 824)	Partial- random permuted blocks; blocks of 20 randomisation sequences predetermined by random number generator.	Partial- not met all requirements: sealed/numbered/opaque envelopes; sequences mantained in sealed envelops until consent obtained; for pts safety and because study medication delivery is easily distinguishable, physicians performing sedation were not blinded to study regimens.	Patient: not blinded - nature of intervention: standard care vs drug(s); parents and sedators not blinded to drug treatment. Outcome assessor: Yes; one of 2 observers blinded to study purpose and design scored viedotapes; scorers were not health professionals and were instructed that various equipment and monitoring were being evaluated.	ITT: No, available case analysis; 1 of 205 randomised patients had protocol violation and received IV midazolam and was excluded from analyses. Power calculation: Yes; assuming population mean observational scale of behavioural distress revised (OSBDR)=1.75 (SD1.85), 80% power & alpha=0.5, 50 children in each group were needed to detect change in mean of 1.05 OSBD.	No (≤ 20% did not complete intervention); 1/205 randomised patients had protocol violation and excluded from analyses; treatment failed in 3/204 patients who completed trial: 2 from midazolam and 1 from standard care groups; for 14% (28/204) patients, AE questionnaires were not completed.	Yes; study states that patients between groups were no different in terms of age, sex, race, ASA class, laceration length or no. of sutures but does not say whether this differences are significant or not.
Mortazavi 2009 (Ref ID: 2777)	Unclear / not stated.	Partial- independent part but unclear treatment allocation; intervention & placebo kept in refrigerator in dark&closed bottle; dental nurse gave medication in plastic cup but unclear what she knew about intervention and children's status; operator blind to drug administered medication.	Patient: yes, double blind trial. Outcome assessor: Unclear.	ITT: Unclear/not stated; data for completion of procedure only and unclear whether further analyses -if any- included all patients. Power calculation: Not stated; Details on what outcome study powered for, at what level and power, and n patients.	No (>20% overall did not complete intervention); completion of procedure could not be rendered in 45% (11/20) in the placebo groups as compared to 0% in the intervention group.	Not stated; overall and per group children rated 1or 2 on Frankl Behavioural Rating Scale as negative (75% of 40) or definitely negative (25% of 40); no more details.

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Paspatis 2006 (Ref ID: 239)	Partial- random numbers, randomisation table; table of random numbers.	Unclear; study not blind for either the endoscopist -who performed procedure- and for anaesthesiologist -who administered sedatives- because the sedatives were clearly visible; study was blind for paediatritian.	Patient: not stated. Outcome assessor: Unclear; stated: study blind for paediatrician; and a paediatrician participanted in the procedure also assessed ease of line placement, separation from parents, pain and obtained patient's evaluation of procedure but unclear if study refered to the same person.	ITT: Yes, all followed; all randomised patients appeared to have completed the trial and included in analyses. Power calculation: Not stated.	Yes, all completed; no withdrawals reported; study broke randomisation by age stratifying (cutoff: 6 years or older) pain (not validated scale) & patients' evaluation of the procedure (discomfort: not relevant outcome).	Yes; groups were not significantly different in terms of age, gender, weight, duration of procedure and ASA grade I and II.
Shashikran 2006 (Ref ID: 275)	Unclear / not stated.	Not stated.	Patient: not blinded - nature of intervention: different routes of administration. Outcome assessor: Unclear.	ITT: Yes, all followed; all randomised patients appeared to have completed the trial and included in analyses. Power calculation: Not stated.	Yes, all completed; no withdrawals reported.	Yes mainly; groups were not significantly different in terms of age, gender and weight.

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Sherwin 2000 (Ref ID: 897)	Adequate- computer or calculator generated sequence; stated as double blind clinical trial; computer generated randomisation scheme with nonrepeating blocks of 10 treatments with 5 active and 5 placebo treatments randomly allocated within each block.	Adequate- independent third party: allocates interventions & retains schedule/code; effective randomisation achieved by using vials in numeric order; pharmacy had the only copy of code broken at completion of study.	Patient: yes, double blind trial. Outcome assessor: Yes; ketamine administered in doses to achieve ketamine's dissociation state, personnel could not identify whether children had received midazolam; physicians/nurses-VAS recovery period, crying, AE(nightmares, hallucinations), external stimulation.	ITT: Yes, all followed; all randomised patients appeared to have completed the trial and included in analyses. Power calculation: Yes; not possible at study onset; there had not been studies measuring magnitude of recovery agitation with VAS; sample calculation based on SD (17mm) of 1st 50 pts; data not normally distrib, so 96 pts necessary to detect a 10 mm difference in VAS between gps.	Yes, all completed; no withdrawals reported.	Yes, but limited data; not reported to be significant: patients were similar in age, gender, weight, type & no. of procedures, ASA I-II class, preprocedure agitation median, no. of ketamine doses administered, median of external estimulation from physician & nurse assessment.
Singh 2002 (Ref ID: 752)	Unclear / not stated.	Not stated.	Patient: yes, double blind trial. Outcome assessor: Yes.	ITT: Unclear/not stated. Power calculation: Not stated.	Unclear or Not stated; Missing data in each group.	Yes mainly; does not say whether the following differences are significant or not between groups but patients were similar with respect to patients number, age, sex, weight and health status.

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	Sequence Generation	Allocation Concealment	Blinding	ITT and Power Calculation	Attrition details	Baseline Comparable
Theroux 1993 (Ref ID: 1393)	Unclear / not stated.	Partial - third party: retained codes and contents but unclear what third party knew; used lettered bottles with content which changed regularly and a third party mantained list of codes and contents but unclear what third party knew and who and how randomisation was performed.	Patient: partial - some patients and/or parents. Outcome assessor: Partial; crying and motion assessed by physicians who left bedside for a short interval before procedure even if no drops were given; struggle assessed by assistant but not known what he/she knew about interventions and whether he/she left bedside before procedure.	ITT: No, available case analysis; for the outcome of parents' satisfaction, the reported analyses included only those parents in whom telephone interviews could be performed. Power calculation: Not stated.	No (≤ 20% did not complete intervention); in 17% (10/59) of the parents, five in each group, telephone interviews were not performed for the outcome of parents' satisfaction.	Yes, but limited data; not well described; stated that groups did not differ significantly on age, wound length, more than one layer (%) of suturing, site of laceration (chin, face, scalp), or use of a papoose board.
Wathen 2000 (Ref ID: 845)	Partial- random numbers, randomisation table.	Adequate- independent third party: allocates interventions & retains schedule/code; independent nurse who used random numbers to assign patients to each group & prepare medications and another nurse administered drugs; combination of midazolam and ketamine infusion to be compatible in colour.	Patient: yes, double blind trial. Outcome assessor: Yes; nurse blinded to drug type administered drugs, assessed AE, length of sedation, sedation efficacy & physician/parental satisfaction; separate blinded nurse rated videotape & additional emergence phaenomena; physician-procedure own satisfaction.	ITT: ITT not performed, per protocol analysis instead; randomised patients with protocol violations were excluded from analyses. Power calculation: Yes; 242 patients (12 per group) were required to obtain 80% power at the 5% significance level to detect a decrese from 15% in the midazolam plus ketamine group to 30% in the ketamine group; thought to represent a clinically significant difference.	No (≤ 20% did not complete intervention); 1% (3/299) of randomised patients had protocol violation: 2 patients in the M+K and 1 patient in the K received intramuscular instead of intravenous medications; age and ketamine dose subgroup analysis for oxygen desaturation and vomiting were reported.	Yes mainly; of the 266 study stated that both groups were similar in terms of age, gender, hrs of fasting, prior narcotics, sedation time (total time, procedure time, net time), type of procedure, physician satisfaction, parental satisfaction.

METHODOLOGICAL QUALITY OF STUDIES

Midazolam

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Zier 2008 (Ref ID: 4328)	Adequate- computer or calculator generated sequence; random number list.	Adequate- different parties administered sedation drug and were unaware of sedation randomisation; N2O or O2 administered by personnel not directly involved with the procedure or with data collection for the study; children, parents, physician, staff adminsitering injections, nursing staff, trained observer were all blinded to sedation randomisation.	Patient: yes, double blind trial. Outcome assessor: Yes.	ITT: Yes, all followed; all patients included in analyses. Power calculation: Not stated.	Yes, all completed.	Yes, but limited data; groups were not different in terms of age, sex, prior BoNTA injections and midazolam sedation, no. of injections per visit, injection sites, cerebral palsy type and gross motor classification system (GMFCS) but does not mention whether significant or not.

CHARACTERISTICS OF INCLUDED STUDIES

Ketamine

Study	*Participants*	*Interventions*
Acworth 2001 (Ref ID: 815) RCT Randomisation unit: Patient. Trial held in Australia. Setting: accidents & emergencies. Funding :grant- other	Inclusion criteria: ages 6 months to 12 years; haemodynamically and neurologically stable and in need of a procedure likely to cause distress. The procedure had to either be non-painful or one in which the pain could be removed with local anaesthetic.. Exclusion criteria: history of adverse reaction to midzolam or ketamine, psychiatric or behavioural disorder, risk of raised intracranial or intraocular pressure, thyroid disorder, porphyria, blocked nose or sedation within four hours of presentation. Fasting: children were fasted while in emergency deparment awaiting the procedure but no minimum duration of starvation was required before drug administration. Medical reason: likely to be mixed. Procedure type: Non-Painful; mixed. First procedure?: first procedure. ASA details: Not stated. Learning disabilities: none mentioned. Age: mixed; 6 months to 12 years. Gender: 54% male in intravenous midazolam ketamine group and 58% male in intranasal midazolam. Weight: all patients weighed more than 5 kg. Planned sedation level: not stated / unknown. Purpose: mixed. Sedationist: not stated / unknown. Procedure carried out by: physician. Sedation monitoring by: another trained person different from whom performed procedure.	1) iv ketamine 1mg plus iv midazolam 0.1 mg/kg (max 5 mg) + local anaesthesia (1% lidocaine for all lacerations); volume: weight dependant; (n=27). 2) intranasal midazolam + local anaesthesia (1% lidocaine for all lacerations); volume: weight dependant; (n=26). Other interventions: none. Intervention concurrent medications: not stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: Sedation score and physiiological variables were recorded before drug administration, at five minute intervals until the procedure ended then at 10 minute intervals until discharge by the nurse observer.. Monitoring for control: same as intervention.

Ketamine

Study	*Participants*	*Interventions*
Erden 2009 (Ref ID: 4356) RCT Randomisation unit: Patient. Trial held in Turkey. Setting: imaging. Funding :unclear/ not stated	Inclusion criteria: Children undergoing interventional radiology. Exclusion criteria: ASA IV or more and allergy to study meds or eggs. If taking sedative or analgesic drugs patients were also excluded.. Study comments: No premedication Fasting: 2-4-6 rule. Medical reason: not stated. Procedure type: Painful; elective procedures. First procedure?: not known / unclear. ASA details: I-III. Learning disabilities: none mentioned. Age: mixed; Group 1 mean age 8.93 years +/- 4.0; group 2 6.97 years +/- 3.8. Range 1-16 years. Gender: Group 1 - 63% male,37% female; group 2 57% male and 43% female-. Weight: all patients weighed more than 5 kg. Planned sedation level: not stated / unknown. Purpose: not stated / unknown. Sedationist: anaesthetist. Procedure carried out by: practitioner. Sedation monitoring by: anaesthetist.	1) propofol 0.5 mg/kg + fentanyl 1 microgram/kg + ketamine 0.5 mg/kg; volume: ; (n=30). 2) propofol 0.5 mg/kg + fentanyl 1 microgram/kg + NaCl placebo; volume: ; (n=30). Other interventions: None. Intervention concurrent medications: None. Control concurrent medications: . Intervention - achieved sedation: bolus. Control - achieved sedation: bolus. Other analgesics therapy: prilocaine after sedation. Monitoring for intervention: Patients monitored for adverse events particularly respiratory depression, oxygen saturation less than 90%.. Monitoring for control: Patients monitored for adverse events particularly respiratory depression, oxygen saturation less than 90%..

Ketamine

Study	*Participants*	*Interventions*
Godambe 2003 (Ref ID: 630) RCT Randomisation unit: Patient. Trial held in USA. Setting: accidents & emergencies. Funding :grant- other	Inclusion criteria: children aged 3 years to 18 years who required sedation for emergency orthopedic procedures. Exclusion criteria: ASA class III or greater, fractures >24 hours old, and known allergy to any of the study medications or eggs. Study comments: a convenience sample was recruited by one of the investigators Fasting: At least 4 hours before procedure. Medical reason: orthopaedic. Procedure type: Painful; orthopedic. First procedure?: not known / unclear. ASA details: I-II. Learning disabilities: none mentioned. Age: mixed; 3 years to 18 years. Gender: overall 78%(88/113) were male; no significant difference between groups. Weight: all patients weighed more than 5 kg. Planned sedation level: deep. Purpose: mixed. Sedationist: sedation nurse. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: same person who performed procedure.	1) iv midazolam (0.05 mg/kg to a max of 2mg) was given slowly over 1-2 minutes. After 3 minutes this was followed by IV ketamine (1-2 mg/kg) given slowly over 1-2 minutes.; volume: weight dependant; (n=54). 2) iv fentanyl (1-2 micrograms/kg) was given slowly over 1-2 minutes and titrated to provide adequate analgesia. After 5 minutes a slow bolus of 1mg/kg IV propofol was followed by subsequent administration of smaller aliquots based on patient response.; volume: weight dependant; (n=59). Other interventions: none. Intervention concurrent medications: 44/54 (81%) received opiod premedication. Control concurrent medications: 50/59 (85%) received opiod premedication. Intervention - achieved sedation: titrated. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: Sedation nurse recorded sedation times and adverse events. Monitoring for control: same as intervention.

Ketamine

Study	*Participants*	*Interventions*
Kennedy 1998 (Ref ID: 1014) RCT Randomisation unit: Patient. Trial held in USA. Setting: accidents & emergencies. Funding :grant- other	Inclusion criteria: patients between 5 and 15 years requiring fracture or joint reduction and meeting ASA class I or II criteria. Exclusion criteria: abnormalities of airway, cardiorespiratory, hepatic, renal or central nervous systems; history of psychoses, ethanol, psychotropic or nonprescribed narcotic drug use within 6 hours of the procedure and adverse reaction to the study drugs, opiates or benzo. Fasting: mean hours fasted: 5.2 in FM group and 4.8 in KM group. Medical reason: orthopaedic. Procedure type: Painful; ----. First procedure?: first procedure. ASA details: I-II; ASA class I 83% in FM group and 78% in KM group. Learning disabilities: none mentioned. Age: mixed; age 5-15. Gender: 72% male (n=94) in FM group and 68% male (n=88) in KM group. Weight: all patients weighed more than 5 kg. Planned sedation level: deep. Purpose: mixed. Sedationist: physician. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: physician and nurse.	1) glycopyrrolate 5 micrograms/kg (max 250 micrograms) given; 1 minutes after midazolam ketamine less than or equal to 0.5mg/kg given every 3 minutes until a decreased response to verbal or painful stimuli or a max first reduction dose of 2 mg/kg given; volume: varied according to weight; (n=130). 2) 1 minute after midazolam fentanyl less than or equal to 0.5 micrograms/kg given every 3 minutes until decreased response to verbal or painful stimuli occurred or a max first reduction dose of 2 micrograms/kg (max, 100 micrograms) had been administered; volume: varied according to weight; (n=130). Other interventions: none. Intervention concurrent medications: 46 patients had presedation medications, primarily parenteral opiates (morphine, meperidine or fentanyl). Control concurrent medications: 38 patients had presedation medications, primarily parenteral opiates (morphine, meperidine or fentanyl). Intervention - achieved sedation: titrated. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: sedators observed subjects directly throughout sedation and reduction periods and vital signs were documented by nurse at 5 minute intervals or 3 minutes after each medication bolus. Monitoring for control: same as intervention.

CHARACTERISTICS OF INCLUDED STUDIES

Ketamine

Study	*Participants*	*Interventions*
Kriwanek 2006 (Ref ID: 206) RCT Randomisation unit: Patient. Trial held in USA. Setting: accidents & emergencies. Funding :unclear/ not stated	Inclusion criteria: patients aged 8 years or older with obvious isolated forearm deformities what would require manipulation. Exclusion criteria: hypersensitivity to lidocaine, morphine, ketamine or midazolam; neurovalcular abnormality in the fractured extremity; open fracture; forearm fracture as part of polytrauma; infection in the skin overlying the axilla; known bleeding diathesis; seizures. Study comments: recovery times were not reported. Units or method of analysis of CHEOPS and Faces scales not reported. Allocation concealment and blinding not possible. There were 11 incomplete and 2 failed ABRA procedures. Fasting: in this setting when midazolam is administered for anxiolysis strict adherence to the NPO guidelines was not required. Medical reason: orthopaedic. Procedure type: Painful; ----. First procedure?: not known / unclear. ASA details: Not stated. Learning disabilities: none mentioned. Age: mixed; 8 years or older. Gender: Overall 76% male (31/41). Weight: not known / unclear. Planned sedation level: deep. Purpose: decrease distress. Sedationist: physician. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: nurse.	1) iv midazolam (0.1 mg/kg up to a max of 2 mg) and ketamine 1 mg/kg followed by additional doses titrated to patient comfort.; volume: weight dependant; (n=21). 2) patients were given an 'anxiolytic dose' of intramuscular midazolam (max 5 mg) before ABRA. Axillary (brachial plexus) block using 0.7 ml/kg up (to a max of 40 ml) of 1% lidocaine, with epinephrine into the axillary sheath with a 25 gauge, 5 cm needle.; volume: weight dependant; (n=20). Other interventions: none. Intervention concurrent medications: all patients received parenteral morphine sulfate of 0.1 mg/kg (max of 10 mg) before randomization. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: during reduction a pediatric nurse evaluated pain and distress using the CHEOPS score and if the score was 12 or higher supplemental fentanyl was given.. Monitoring for control: same as intervention.

Ketamine

Study	*Participants*	*Interventions*
Lucas Da Silva 2007 (Ref ID: 153) RCT Randomisation unit: Patient. Trial held in Brazil. Setting: hospital - inpatients. Funding :unclear/ not stated	Inclusion criteria: non intubated children in PICU requiring CVC from ages 3 months to 14 years. Exclusion criteria: abnormalities in the airways; serious impairment of the central nervous system; intracranial hypertension; glaucoma; hyperthyroidism; severe respiratory disease; history of psychosis; sensitivity ot study drugs; recent alcohol or psychotropic drugs. Fasting: not stated. Medical reason: intravenous line placement. Procedure type: Painful; insertion of a needle in a subcutaneously implanted central venous port. First procedure?: first procedure. ASA details: Mixed; 8 (14%) ASA II, 37 (65%) ASA III and 12 (21%) ASA IV. Learning disabilities: none mentioned. Age: mixed; 3 months to 14 years. Gender: Not reported. Weight: all patients weighed more than 5 kg. Planned sedation level: moderate. Purpose: not stated / unknown. Sedationist: nurse. Procedure carried out by: not stated / unknown. Sedation monitoring by: another trained person different from whom performed procedure.	1) iv midazolam (0.15mg/kg with max dose 0.5mg/kg) then, after a 1 minute interval ketamine (0.5 mg/kg); volume: variable as additional bolus given prn; (n=29). 2) iv mdazolam (0.15mg/kg with max dose 0.5mg/kg) then, after a 1 minute interval fentanyl (1 microgram /kg, max 100 microgram dose); volume: variable as additional bolus given prn; (n=28). Other interventions: none. Intervention concurrent medications: oxygen supplementatin via nasal cannula or by blow-by throughout the procedure. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: standard cardiopulmonary parameters and oxygen saturation wee monitored continuously before and during sedtion functions and blood pressure recorded eery 5 minutes.. Monitoring for control: same as intervention.

Ketamine

Study	*Participants*	*Interventions*
Luhmann 2006 (Ref ID: 220) RCT Randomisation unit: Patient. Trial held in USA. Setting: accidents & emergencies. Funding :unclear/ not stated	Inclusion criteria: children 5-17 years requiring reduction of middle to distal forearm fractures. Exclusion criteria: open fracture; history of previous fracture reduction or adverse effect associated with previous ketamine, midazolam, nitrous oxide or lidocain; diagnosis of acute OM or psychiatric disease. Study comments: distress was assessed by Procedure Behavior Checklist (PBCL), a validated observational measure for children 4 years and older; respiratory depression was measured as oxygen saturation of <93% and therefore not included in results; Fasting: 2 hour minimum. Medical reason: orthopaedic. Procedure type: Painful; orthopedic. First procedure?: first procedure. ASA details: I-II. Learning disabilities: none mentioned. Age: mixed; 5-17 years. Gender: 58% in K/M group; 62% in nitrous oxide group. Weight: all patients weighed more than 5 kg. Planned sedation level: deep. Purpose: mixed. Sedationist: physician. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: nurse.	1) iv midazolam [0.1 mg/kg with max of 2 mg] + glycopyrrolate [5 micro grams/kg with a max of 200 micrograms given 2 minutes before reductio] + iv ketamine [1 mg/kg administered 1 minute before reduction]; volume: weight dependant; (n=55). 2) mixture of 50% NO + 50% oxygen through a scented face mask for about 3 minutes before placement of HB; HB injection was 2.5 mg/kg of 1% buffered lidocain with max dose of 150 mg (15 ml) into fracture hematoma; volume: weight dependant; (n=47). Other interventions: none. Intervention concurrent medications: All patients received oral oxycodone 0.2 mg/kg (max 15 mg) at triage before obtaining radiographs or study enrollment.. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: titrated. Other analgesics therapy: Lidocaine injected for IV placement. Monitoring for intervention: Data were recorded every 5 minutes by emergency nurse during the procedure and then during recovery until a level of moderate sedation occurred; thereafter data were recorded every 15 minutes until full recovery .. Monitoring for control: same as intervention.

Ketamine

Study	*Participants*	*Interventions*
Roback 2006 (Ref ID: 212) RCT Randomisation unit: Patient. Trial held in USA. Setting: accidents & emergencies. Funding :grant- other	Inclusion criteria: patients 4 months to 18 years presenting with an orthopedic injury and receiving procedural sedation and analgesia for orthopedic reduction. Exclusion criteria: contraindications for receiving ketamine such as previous adverse reaction, hypertension, glaucoma or acute globe injury,increased intracranial pressure or central nervous system mass lesion, major psychiatric disorder, porphyria or refusal of consent.. Study comments: the study was terminated prematurely at nursing request, given that perceived differences in the duration of recovery and rates of emesis between groups markedly hindered enrollement/ Fasting: not stated. Medical reason: orthopaedic. Procedure type: Painful; orthopedic. First procedure?: not known / unclear. ASA details: I-II; either a normally healthy patient or a patient with a mild systemic disease. Learning disabilities: none mentioned. Age: mixed; 1.2 years-15.8 years. Gender: 65% (n=71) IV group; 63.6% (n=63.6) IM group. Weight: all patients weighed more than 5 kg. Planned sedation level: not stated / unknown. Purpose: not stated / unknown. Sedationist: physician. Procedure carried out by: physician. Sedation monitoring by: physician and nurse.	1) iv ketamine [1 mg/kg, maximum dose 200 micrograms] + glycopyrrolate [5 micrograms/kg; maximum dose 250 micrograms]; volume: 1 mg/kg IV with maximum dose 200 micrograms and glycopyrrolate 5 micrograms/kg (maximum dose 250 micrograms); (n=109). 2) intramuscular ketamine [4 mg/kg, maximum dose 200 mg] + glycopyrrolate [5 micrograms/kg; maximum dose 250 micrograms]; volume: 4 mg/kg IM, maximum dose 200 mg and glycopyrrolate 5 micrograms/kg (maximum dose 250 micrograms); (n=99). Other interventions: none. Intervention concurrent medications: not stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: vital signs and pulse oximetry at baseline, during procedure every 5 minutes and postprocedure. Monitoring for control: same as intervention.

Ketamine

Study	*Participants*	*Interventions*
Tosun 2007 (Ref ID: 97) RCT Randomisation unit: Patient. Trial held in Turkey. Setting: gastroenterology. Funding :unclear/ not stated	Inclusion criteria: patients aged 1-16 years. Exclusion criteria: neurologically impaired children. Study comments: parental informed consent obtained Fasting: not sated. Medical reason: gastrointestinal. Procedure type: Painful; upper and lower endoscopy. First procedure?: not known / unclear. ASA details: I-II. Learning disabilities: none mentioned. Age: mixed; ages 1-16 years; no significant difference between groups. Gender: Overall 51% male and 49% female;NS difference between groups. Weight: all patients weighed more than 5 kg. Planned sedation level: deep. Purpose: mixed. Sedationist: anaesthetist. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: anaesthetist.	1) drugs were prepared as follows: ketamin 10 mg/ml (2 ml ketamine, 8 ml NaCl 0.9%) and fentanyl 10 micrograms/ml (2 ml fentanyl, 8 ml NaCl 0.9%). Groups received either 1 ml/10 kg ketamine or fentanyl and 1.2 mg/kg propofol bolus for sedation induction.; volume: 1 ml/10kg; (n=46). 2) drugs were prepared as follows: ketamin 10 mg/ml (2 ml ketamine, 8 ml NaCl 0.9%) and fentanyl 10 micrograms/ml (2 ml fentanyl, 8 ml NaCl 0.9%). Groups received either 1 ml/10 kg ketamine or fentanyl and 1.2 mg/kg propofol bolus for sedation induction.; volume: 1 ml/10 kg; (n=44). Other interventions: none. Intervention concurrent medications: additional propofol (0.5-1 mg/kg) was administered when a patient showed discomfort in both groups. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: same as intervention. Other analgesics therapy: A spray of lidocaine 10% to the posterior pharynx given to diminish discomfort (gag reflex) during the endoscopy. Monitoring for intervention: heart rate, systolic arterial pressure, oxygen saturation, respiratory rate and Ramsey sedation scores were recorded at baseline, after induction and every 5 minutes thereafter during the procedure by the anesthesiologist. Monitoring for control: same as intervention.

METHODOLOGICAL QUALITY OF STUDIES

Ketamine

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Acworth 2001 (Ref ID: 815)	Adequate- computer or calculator generated sequence.	; Drug route precluded double blinding but the doctor and nurse responsible for scoring sedation level were not present during drug dministration and were blinded to allocation by use of dummy armboard applied to children receiving the intranasal medication.	Patient: no single blind trial. Outcome assessor: Yes.	ITT: Yes, all followed. Power calculation: Yes; A total of 50 patients (25 in each group) was initially identified as required to give 90% power to detect a mean difference in the Sedation Scores between groups of 1.0 (SD=1.0) at 5% significance level.	Yes, all completed intervention.	Yes; There were no significant differences found between treatment groups with regard to sex, age, weight, procdure type, length or site of laceration, duration of procedure.
Erden 2009 (Ref ID: 4356)	Adequate- computer or calculator generated sequence.	Adequate- Third party cluster: third party had no knowledge.	Patient: yes double blind trial. Outcome assessor: Yes.	ITT: Yes, all followed. Power calculation: Not stated; Power calculation not described ; sample size 113.	Yes, all completed intervention.	Yes mainly.

METHODOLOGICAL QUALITY OF STUDIES

Ketamine

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Godambe 2003 (Ref ID: 630)	Inadequate; odd or even day assignment.	Inadequate- schedule known in advance, birthdate, case recore.	Patient: yes double blind trial. Outcome assessor: Yes; patient, parent and assessor were blinded.	ITT: Yes, all included in analysis, no details; all patients included in analyses. Power calculation: Not stated.	Yes, all completed intervention.	Yes mainly; patients in each group did nto differ in age, sex, rac, weight NPO time, use of opioid premedication and type of injury.
Kennedy 1998 (Ref ID: 1014)	Partial- random permuted blocks; subjects were stratified acording to initial parental choice to remain in the room or not during reduction. Subjects were randomly assigned in blocks of 20 within strata to receive fentanyl or ketamine. A random number generator used.	Adequate- Third party cluster: third party had no knowledge; two trained independent observers.	Patient: not stated. Outcome assessor: Partial; two trained observers were blinded to study purpose and design reviewed the videotape of each study. Unable to blind sedators.	ITT: Yes, all followed. Power calculation: Yes; calculations based on OSBD. A sample of 40 required to detect a change in the mean of 1.05.	Yes, all completed intervention.	Yes mainly; FM and KM groups did not differ in mean age, weight, gender, race, ASA class time from last oral intake, fracture location or presedation medications.

METHODOLOGICAL QUALITY OF STUDIES

Ketamine

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Kriwanek 2006 (Ref ID: 206)	Adequate- computer or calculator generated sequence; computer generated randomization table in balanced blocks of 10.	Not stated.	Patient: no not blinded. Outcome assessor: No; interventions differed in delivery method and blinding not possible.	ITT: Yes, all followed; all were followed for procedural outcomes and CHEOPS. Power calculation: Yes; a sample size of 4=34 patients was required to detect a 2 point difference in the CHEOPS scale between the 2 groups, accepting a type I error of 0.05 and a power of 80%.	Yes, all completed intervention; satisfaction scores are not reported as 2 patients in the ABRA group were lost to follow up and 1 parent could not be contacted. Therefore sample size fell below 20.	Yes mainly; the 2 groups were similar with respect to age, sex, types of fracture, narcotic analgesia received and anxiolytic dose of midazolam administered.
Lucas Da Silva 2007 (Ref ID: 153)	Adequate- random numbers table or satistical table; random number generator.	Adequate- sequentially numbered, opaque, sealed envelopes; maintained in sealed opaque envelopes.	Patient: no not blinded. Outcome assessor: No; double blinding was deemed impractical because of different dosing algorithms of the drugs used and because medications ued present clincially distinuishable effects.	ITT: Yes, all included in analysis, no details. Power calculation: No.	Yes, all completed intervention.	Yes mainly; there were no differences between the groups regarding age, weight, risk classification (ASA) and final sedation score.

METHODOLOGICAL QUALITY OF STUDIES

Ketamine

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Luhmann 2006 (Ref ID: 220)	Adequate- computer or calculator generated sequence.	Adequate- independent third party: allocates interventions & retains schedule/code.	Patient: no not blinded - nature of intervention: different routes of administration. Outcome assessor: Yes.	ITT: Yes, all followed; 6 protocol failures: one subject in the NO group was inadequately sedated and then received IV ketamine. Five subjects randomly assigned to receive K/M required more than the study dose of 1mg/kg; these were analyzed according to ITT methodology. Power calculation: Yes; to achieve statistical power of 0.80 and a significance level of 0.05, a sample size of 50 per group or a total of 100 patients was needed.	Yes, all completed intervention.	Yes mainly; the two groups were similar with regard to age, gender, race, ASA class, fracture location and baseline Procedure Behavior Checklist (PBCL).
Roback 2006 (Ref ID: 212)	Adequate- computer or calculator generated sequence.	Partial- third party cluster: unclear what third party knew; sham IV was placed in patients receiving IM ketamine.	Patient: no single blind trial. Outcome assessor: Yes.	ITT: Yes, all followed; 5 protocol violations (randomised to IM but received IV. Analyzed in IM group). Power calculation: Not stated.	Unclear or Not stated.	Not stated.

METHODOLOGICAL QUALITY OF STUDIES

Ketamine

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Tosun 2007 (Ref ID: 97)	Unclear / not stated.	Patial- not met all requirements:serially numbered/identical/allocated sequentially; only 'sealed envelopes' described.	Patient: yes double blind trial. Outcome assessor: Yes.	ITT: Yes, all followed. Power calculation: Not stated.	Yes, all completed intervention.	Yes; there were no statistically significant differences between groups with respect to age, weight, sex.

CHARACTERISTICS OF INCLUDED STUDIES

Chloral hydrate

Study	*Participants*	*Interventions*
Dallman 2001 (Ref ID: 772) RCT - crossover Randomisation unit: Patient. Trial held in USA. Setting: primary care dental practice. Funding :no funding	Inclusion criteria: history of uncooperative, obstructive or otherwise negative behaviour at initial examination.. Exclusion criteria: failure to keep both sedation appointments. Fasting: dietary precautions consistent with AAPD guidelines. Medical reason: dental treatment. Procedure type: Painful; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: not known / unclear. ASA details: Not stated. Learning disabilities: none mentioned. Age: 1 to 5 years of age; 24 to 54 months. Gender: 23 males and 8 females; 74% male, 26% female. Weight: all patients weighed more than 5 kg. Planned sedation level: conscious sedation. Purpose: mixed. Sedationist: not stated / unknown. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: another trained person different from whom performed procedure.	1) chloral hydrate [62.5 mg/kg]; volume: weight dependant; (n=31). 2) intranasal midazoalm [0.2 mg/kg]; volume: weight dependant; (n=31). Other interventions: nitrous oxide. Intervention concurrent medications: promethazine 12.5 mg and nitrous oxide and oxygen from 25-50%. Control concurrent medications: nitrous oxide and oxygen from 25-50%. Washout period: time between appointments. Intervention - achieved sedation: bolus. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: independent observer. Monitoring for control: same as intervention.

Chloral hydrate

Study	*Participants*	*Interventions*
Houpt 1985 (Ref ID: 3625) RCT - crossover Randomisation unit: Patient. Trial held in USA. Setting: primary care dental practice. Funding :unclear/ not stated	Inclusion criteria: children requiring treatment with sedation at two different appointments. Exclusion criteria: not stated. Study comments: the requirement of some food was made to reduce the possible gastric irritation effect of chloral hydrate. There were three incidence of vomitting incidences of vomiting in the sample, all after eating a large meal. Fasting: milk and cereal two hours before procedure. Medical reason: dental treatment. Procedure type: Painful; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: first procedure. ASA details: Not stated. Learning disabilities: none mentioned. Age: 1 to 5 years of age. Gender: 10 male and 7 female. Weight: all patients weighed more than 5 kg. Planned sedation level: not stated / unknown. Purpose: mixed. Sedationist: dental practitioner. Procedure carried out by: dental practitioner. Sedation monitoring by: same person who performed procedure.	1) oral chloral hydrate high dose [mean dose of 1062 mg]; volume: mean dose of 1062 mg; (n=17). 2) oral chloral hydrate low dose [mean dose of 708 mg]; volume: mean dose of 708 mg; (n=17). Other interventions: none. Intervention concurrent medications: parents remained with child; a concentration of 40% nitrous oxide was administered to all patients and raised to 50% in all low dose patients and in 3 of 17 high dose patients. Control concurrent medications: same as intervention. Washout period: time between two different appointments. Intervention - achieved sedation: bolus. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: monitored by dentist. Monitoring for control: same as intervention.

Chloral hydrate

Study	*Participants*	*Interventions*
Houpt 1989 (Ref ID: 1564) RCT - crossover Randomisation unit: Patient. Trial held in USA. Setting: primary care dental practice. Funding :unclear/ not stated	Inclusion criteria: child in good health and requiring 2 restorative dentistry appointments with the use of sedation. Exclusion criteria: not stated. Study comments: unvalidated scales used for crying and movement; chloral hydrate was more effective than placebo for these paramenters but not uniformly so. It appears that nitrous oxide and chloral hydrate will sedate most children most of the time but not all. Fasting: NPO for 6 hours. Medical reason: dental treatment. Procedure type: Painful; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: not known / unclear. ASA details: Not stated. Learning disabilities: none mentioned. Age: 1 to 5 years of age; 19-41 months. Gender: not stated. Weight: not known / unclear. Planned sedation level: not stated / unknown. Purpose: mixed. Sedationist: not stated / unknown. Procedure carried out by: dental practitioner. Sedation monitoring by: not stated / unknown.	1) oral chloral hydrate; volume: 525 mg to 955 mg with a mean of 701 mg; 50 mg/kg; (n=19). 2) usual care; volume: n/a; (n=19). Other interventions: none. Intervention concurrent medications: parents present; all patients also received 50% nitrous oxide/oxygen. Control concurrent medications: same as intervention. Washout period: between dental appointments. Intervention - achieved sedation: bolus. Control - achieved sedation: n/a. Other analgesics therapy: not stated. Monitoring for intervention: monitoring in the operatory of pulse, oxygen saturtion and respiration. Monitoring for control: same as intervention.

Chloral hydrate

Study	*Participants*	*Interventions*
Loewy 2005 (Ref ID: 3050) quasi RCT Randomisation unit: Patient. Trial held in USA. Setting: hospital - inpatients. Funding :unclear/ not stated	Inclusion criteria: paediatric inpatients ages 1 month to 5 years requiring EEG. Exclusion criteria: not stated. Study comments: this study is a comparison between chloral hydrate and music therapy Fasting: NPO from midnight except babies who were NPO for 6 hours before EEG. Medical reason: likely to be mixed. Procedure type: Non-Painful; electroencephalogram. First procedure?: not known / unclear. ASA details: Mixed. Learning disabilities: none mentioned. Age: mixed; ages 1 month to 5 years. Gender: 26 female and 32 male. Weight: not known / unclear. Planned sedation level: not stated / unknown. Purpose: mixed. Sedationist: not stated / unknown. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: another person - no details.	1) oral chloral hydrate [60 mg.kg with a maximum of 1.5 g]; volume: weight dependant; (n=24). 2) music therapy; volume: live music chosen for particular subject; (n=34). Other interventions: none. Intervention concurrent medications: if upon receiving music therapy or chloral hydrate the child was not sleeping in a relaxed state within 30 minutes of therapy initiation,the alternative therapy was administered. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: n/a. Other analgesics therapy: not stated. Monitoring for intervention: several research interns maintained a record of the medication and comparator, music therapy. Monitoring for control: same as intervention.

Chloral hydrate

Study	*Participants*	*Interventions*
Marti-Bonmati 1995 (Ref ID: 1204) RCT Randomisation unit: Patient. Trial held in Spain. Setting: imaging. Funding :unclear/ not stated	Inclusion criteria: children over 1 month of age receiving sedation for MRI. Exclusion criteria: children less than 1 month of age, with severe respiratory, hepatic or renal disease, with severe central nervous system depression or able to cooperate were not sedated. Fasting: Permitted oral fluids before examination. Medical reason: likely to be mixed. Procedure type: Non-Painful; magnetic resonance imaging (MRI). First procedure?: not known / unclear. ASA details: Not stated. Learning disabilities: none mentioned. Age: mixed; for babies enter age since birth when procedure was carried out. Gender: 50 girls and 47 boys. Weight: all patients weighed more than 5 kg; range 3.7 - 36 kg. Planned sedation level: not stated / unknown. Purpose: increase cooperation. Sedationist: nurse. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: physician and nurse.	1) oral chloral hydrate high dose; volume: mean total dose 96+/- 2 mg/kg; (n=50). 2) oral chloral hydrate low dose; volume: mean total dose 70+/- 2 mg/kg; (n=47). Other interventions: none. Intervention concurrent medications: recorded in medical record. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: observed by a nurse throughout stay in the imaging unit, never less than 4 hours. Monitoring for control: same as intervention.

Chloral hydrate

Study	*Participants*	*Interventions*
Reeves 1996 (Ref ID: 1182) RCT Randomisation unit: Patient. Trial held in USA. Setting: primary care dental practice. Funding :unclear/ not stated	Inclusion criteria: children who exhibited definitely negative behaviour per the Frankl scale. Exclusion criteria: not stated. Study comments: patients were rated by the primary operator and one observer Fasting: NPO for 6 hours. Medical reason: dental treatment. Procedure type: Painful; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: not known / unclear. ASA details: Not stated. Learning disabilities: none mentioned. Age: mixed; 27 to 73 months. Gender: 19 girls and 21 boys. Weight: all patients weighed more than 5 kg. Planned sedation level: not stated / unknown. Purpose: mixed. Sedationist: dental practitioner. Procedure carried out by: dental practitioner. Sedation monitoring by: another trained person different from whom performed procedure.	1) oral chloral hydrate [50 mg/kg not to exceed 1 gm] + hydroxyzine [25 mg] + local anaesthesia (lidocaine); volume: based on weight; (n=20). 2) oral midazolam [0.5 mg/kg with acetaminophen elixir 10 mg/kg] + local anaesthesia (lidocaine); volume: based on weight; (n=20). Other interventions: none. Intervention concurrent medications: not stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: primary operator and one observer. Monitoring for control: same as intervention.

Chloral hydrate

Study	*Participants*	*Interventions*
Thompson 1982 (Ref ID: 1739) RCT Randomisation unit: Patient. Trial held in USA. Setting: imaging. Funding :unclear/ not stated	Inclusion criteria: aspect of study reviewed here includes inpatient children requiring CT examination of the head. Exclusion criteria: sensitivity ot the sedative, suspected central respiration depression, COPD or impairment of gag; patients who were comatose or immobile. Study comments: this study compared CH to GA and also to AMPS (atropine, meperidine, promethazine and secobarbital). AMPS data was not extraced as it is not a comparison of interest. Fasting: Chloral hydrate - restrict oral intake to clear liquids; GA - appropriate fasting interval. Medical reason: likely to be mixed. Procedure type: Non-Painful; computed tomography (CT). First procedure?: not known / unclear. ASA details: Not stated. Learning disabilities: none mentioned. Age: mixed; from birth to 9 years of age. Gender: not stated. Weight: not known / unclear. Planned sedation level: not stated / unknown. Purpose: increase cooperation. Sedationist: not stated / unknown. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: not stated / unknown.	1) oral chloral hydrate [80 mg/kg, 2 gm maximum]; volume: weight dependant; (n=101). 2) general anesthesia; volume: weight dependant; (n=101). Other interventions: AMPS information not extraced.. Intervention concurrent medications: not stated. Control concurrent medications: not stated. Intervention - achieved sedation: bolus. Control - achieved sedation: n/a. Other analgesics therapy: not stated. Monitoring for intervention: not stated. Monitoring for control: anesthetist.

METHODOLOGICAL QUALITY OF STUDIES

Chloral hydrate

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Dallman 2001 (Ref ID: 772)	Unclear / not stated.	Not stated.	Patient: no single blind trial. Outcome assessor: Yes.	ITT: Yes, all followed. Power calculation: Not stated.	No (≤ 20% did not complete intervention).	Yes - cross over trial.
Houpt 1985 (Ref ID: 3625)	Unclear / not stated.	Not stated.	Patient: yes double blind trial. Outcome assessor: Yes; two independent raters who were blinded to drug dose evaluated crying and body movements throughout the procedure.	ITT: Yes, all followed. Power calculation: Not stated.	No (>20% did not complete intervention; greater in 1 group).	Yes - cross over trial.

METHODOLOGICAL QUALITY OF STUDIES

Chloral hydrate

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Houpt 1989 (Ref ID: 1564)	Unclear / not stated.	Not stated.	Patient: yes double blind trial. Outcome assessor: Yes.	ITT: Yes, all followed. Power calculation: Not stated.	Yes, all completed intervention; none.	Yes - cross over trial.
Loewy 2005 (Ref ID: 3050)	Inadequate- for e.g. allocation by alteratoin, birthdate, day of week.	Inadequate- schedule known in advance, birthdate, case recore.	Patient: no not blinded. Outcome assessor: No.	ITT: Yes, all followed. Power calculation: Not stated.	Yes, all completed intervention.	Some comparable; 26 female and 32 maile from ages 1 month through 5 years.

METHODOLOGICAL QUALITY OF STUDIES

Chloral hydrate

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Marti-Bonmati 1995 (Ref ID: 1204)	Unclear / not stated.	Not stated.	Patient: yes double blind trial. Outcome assessor: Yes.	ITT: Yes, all followed. Power calculation: Not stated.	Yes, all completed intervention.	Yes mainly; the two groups were not significantly different in sex, weight, age, diagnosis or ambulatory medication.
Reeves 1996 (Ref ID: 1182)	Unclear / not stated.	Not stated.	Patient: yes double blind trial. Outcome assessor: Yes.	ITT: Yes, all followed. Power calculation: Not stated.	Yes, all completed intervention; none.	Yes mainly; no significant differences between the two groups.

METHODOLOGICAL QUALITY OF STUDIES

Chloral hydrate

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Thompson 1982 (Ref ID: 1739)	Inadequate- for e.g. allocation by alteratoin, birthdate, day of week.	Inadequate- schedule known in advance, birthdate, case recore.	Patient: no not blinded. Outcome assessor: No.	ITT: Yes, all followed. Power calculation: Not stated.	No (≤ 20% did not complete intervention).	Not stated; distribution of ages not equal: 203 infants 0-1month, 82 children ages 1-2 years and remaining equally divided between years 2-0 years.

CHARACTERISTICS OF INCLUDED STUDIES

Triclofos sodium

Study	*Participants*	*Interventions*
Singh 2002 (Ref ID: 752) RCT Randomisation unit: Patient. Trial held in India. Setting: dental hospital. Funding :unclear/ not stated	Inclusion criteria: children requiring short dental procedures like extractions, restorations and endodontic treatment with or without local anaesthesia. Exclusion criteria: not stated. Fasting: not stated. Medical reason: dental treatment. Procedure type: Painful; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: not known / unclear. ASA details: I. Learning disabilities: none mentioned. Age: mixed; overall age range 3 to 9 years. Gender: not stated. Weight: not known / unclear. Planned sedation level: 'conscious sedation' - title. Purpose: decrease anxiety. Sedationist: not stated / unknown. Procedure carried out by: not stated / unknown. Sedation monitoring by: not stated / unknown.	1) oral triclofos sodium 70 mg/kg mixed in juice to maintain uniformity with midazolam and to mask distinction; volume: weight dependant; (n=30). 2) oral midazolam 0.5 mg/kg mixed in juice to mask taste and distiction; volume: weight dependant; (n=30). Other interventions: oral promethazine 1.2 mg/kg, n=30; mixed in juice to maintain uniformity with midazolam and to mask distinction. Intervention concurrent medications: not stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: same as intervention. Other analgesics therapy: none stated. Monitoring for intervention: arterial BP, pulse rate and respiratory rate recorded before administration of drugs and at definite intervals during procedure; patients continuously observed by operator. Monitoring for control: same as intervention.

METHODOLOGICAL QUALITY OF STUDIES

Triclofos sodium

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Singh 2002 (Ref ID: 752)	Unclear / not stated.	Not stated.	Patient: yes, double blind trial. Outcome assessor: Yes.	ITT: Unclear/not stated. Power calculation: Not stated.	Unclear or Not stated; Missing data in each group.	Yes mainly; does not say whether the following differences are significant or not between groups but patients were similar with respect to patients number, age, sex, weight and health status.

CHARACTERISTICS OF INCLUDED STUDIES

Nitrous oxide

Study	*Participants*	*Interventions*
Averley 2004 (Ref ID: 486) RCT Randomisation unit: Patient. Trial held in UK. Setting: primary care dental practice. Funding :donation of drugs/equipment	Inclusion criteria: children between ages 6-14 years referred for dental treatment using anxiety management;adequate comprehension of treatment; accept EMLA and nasal hood. Exclusion criteria: history of hypersensitivity to benzodiazqpines, sevoflurane, nitrous oxide or local anesthetics. Fasting: not stated. Medical reason: dental treatment. Procedure type: Painful; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: prior procedures. ASA details: I-II. Learning disabilities: none mentioned. Age: mixed; ages 6-14 years. Gender: 45% (311) male; 55% (386) female. Weight: all patients weighed more than 5 kg. Planned sedation level: conscious sedation. Purpose: mixed. Sedationist: anaesthetist. Procedure carried out by: dental practitioner. Sedation monitoring by: anaesthetist.	1) 40% nitrous oxide/oxygen +iv midazolam 0.5 mg/min + topical anaesthesia + local anaesthesia [lidocaine injection]; volume: nitrous oxide continuous;midazolam titrated to level 3 on consciousness scale; (n=256). 2) iv midazolam + inhaled medical air + topical anaesthesia + local anaesthesia [lidocaine injection]; volume: medical air continuous; midazolam titrated to level 3 on consciousness scale; (n=174). Other interventions: inhaled combination of 0.3% sevoflurane and 40% nitrous oxide in oxygen + IV midazolam 0.5 mg/min until level 3 on consciousness scale reached. Intervention concurrent medications: Local anesthetic only. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: titrated. Other analgesics therapy: not stated. Monitoring for intervention: sedation monitored by anaesthetist during the procedure and by a nurse during recovery. Monitoring for control: same as intervention.

Nitrous oxide

Study	*Participants*	*Interventions*
Ekbom 2005 (Ref ID: 15942) RCT Randomisation unit: Patient. Trial held in Sweden. Setting: hospital - outpatients. Funding :unclear/ not stated	Inclusion criteria: ASA I. Exclusion criteria: . Study comments: use of N2O for venous cannulation Fasting: no solid food or liquid after midnight for glucose tolerance test. Medical reason: intravenous line placement. Procedure type: Painful; intravenous catheter insertion. First procedure?: prior procedures. ASA details: I. Learning disabilities: none mentioned. Age: mixed; ages 6-18 years. Gender: 27 male and 23 female. Weight: all patients weighed more than 5 kg. Planned sedation level: mild. Purpose: increase comfort. Sedationist: nurse. Procedure carried out by: nurse. Sedation monitoring by: nurse.	1) nitrous oxide [gradual stages starting with 2 l N2O /6 l O2 increasing to 4 l N2O] + topical anaesthesia [EMLA cream]; volume: gradual increase; (n=25). 2) usual care + topical anaesthesia [EMLA cream] only; volume: n/a; (n=25). Other interventions: none. Intervention concurrent medications: not stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: n/a. Other analgesics therapy: not stated. Monitoring for intervention: not stated. Monitoring for control: same as intervention.

Nitrous oxide

Study	*Participants*	*Interventions*
Fauroux 2004 (Ref ID: 546) RCT Randomisation unit: Patient. Trial held in France. Setting: tertiary referral teaching hospital. Funding :unclear/ not stated	Inclusion criteria: eEligible if undergoing diagnostic or therapeutic FB. Exclusion criteria: severe respiratory distress, hemodynamic instability, impaired consciousness, vit. B12 deficiency, intracranial hypertension, pneumothorax or fractures of facial bones.. Fasting: fasting variable depending on patient age. Medical reason: elective thoracic. Procedure type: Painful; bronchoscopy. First procedure?: not known / unclear. ASA details: Not stated. Learning disabilities: none mentioned. Age: mixed; 1 month to 18 years. Gender: 25.5% male (48.5) male. Weight: not known / unclear; weight range of children not given. Planned sedation level: not stated / unknown. Purpose: mixed. Sedationist: not stated / unknown. Procedure carried out by: endoscopist. Sedation monitoring by: physician and nurse.	1) 50% nitrous oxide + local anesthesia (lidocaine spray); volume: Continuous inhalation; (n=53). 2) 50% nitrogen/oxygen + local anesthesia (lidocaine spray); volume: continuous inhalation; (n=52). Other interventions: none. Intervention concurrent medications: none stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: titrated. Other analgesics therapy: not stated. Monitoring for intervention: continuous monitoring via nurse and endoscopist, including puls oximetery, and videotape recorder. Monitoring for control: same as intervention.

Nitrous oxide

Study	*Participants*	*Interventions*
McCann 1996 (Ref ID: 1195) RCT - crossover Randomisation unit: Patient. Trial held in USA. Setting: primary care dental practice. Funding :unclear/ not stated	Inclusion criteria: children requiring more than one sedation visit for completion of operative dentistry and who had exhibited uncooperative behaviours in previous procedures. Exclusion criteria: not stated. Study comments: there was not statistically significant difference in any physiologic or behavioral parameter as a function of inhalation agent. Significant differneces fore found only as a function of procedural events. Fasting: not stated. Medical reason: dental treatment. Procedure type: Painful; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: prior procedures. ASA details: I-II. Learning disabilities: none mentioned. Age: 1 to 5 years of age; ages 36-60 months. Gender: 26 males and 14 females. Weight: all patients weighed more than 5 kg. Planned sedation level: conscious sedation. Purpose: mixed. Sedationist: operator - no more details. Procedure carried out by: dental practitioner. Sedation monitoring by: sedationist for both groups.	1) 50% nitrous oxide/50% oxygen + topical anaesthesia + local anesthesia; volume: continuous flow; (n=20). 2) 100% oxygen + topical anaesthesia + local anesthesia; volume: continuous flow; (n=20). Other interventions: none. Intervention concurrent medications: all children received chloral hydrate, 40 mg/kg and hydroxyzine, 2mg/kg po 45 minutes before treatment. Topical and local anesthetics were used during each procedure. Control concurrent medications: same as intervention. Washout period: time between treatments. Intervention - achieved sedation: titrated. Control - achieved sedation: titrated. Other analgesics therapy: not stated. Monitoring for intervention: physiological parameters were recorded by automated monitor recorders and by an assistant.The automated counting system computer software program was used to quntify behavioral categories by a rater throughout the procedure. Monitoring for control: same as intervention.

Nitrous oxide

Study	*Participants*	*Interventions*
Primosch 1999 (Ref ID: 965) RCT - crossover Randomisation unit: Patient. Trial held in USA. Setting: primary care dental practice. Funding :unclear/ not stated	Inclusion criteria: children 5-9 years old ASA I not taking any medications and without contraindications to nitrous oxidewho exhibited cooperative but anxious behaviour during previous dental treatment. At least two appointments of restorative dentristry with similar compl. Exclusion criteria: not stated. Fasting: not stated. Medical reason: dental treatment. Procedure type: Painful; dental - restorations. First procedure?: prior procedures. ASA details: I-II. Learning disabilities: none mentioned. Age: 5 to 12 years of age. Gender: 10 males and 12 females. Weight: not known / unclear. Planned sedation level: mild. Purpose: mixed. Sedationist: dental practitioner. Procedure carried out by: dental practitioner. Sedation monitoring by: another person - no details.	1) 40% nitrous oxide/60% oxygen inhalation; volume: continuous administration; (n=22). 2) 100% oxygen; volume: continuous administration; (n=22). Other interventions: none. Intervention concurrent medications: none stated. Control concurrent medications: same as intervention. Washout period: time to second appointment. Intervention - achieved sedation: titrated. Control - achieved sedation: titrated. Other analgesics therapy: not stated. Monitoring for intervention: all patients were monitored continuously for RR, HR, and Oxygen saturation. The Ohio State University Behavior Rating Scale (OS)was performed each minute. Monitoring for control: same as intervention.

Nitrous oxide

Study	*Participants*	*Interventions*
Veerkamp 1993 (Ref ID: 1367) RCT Randomisation unit: Patient. Trial held in The Netherlands. Setting: primary care dental practice. Funding :unclear/ not stated	Inclusion criteria: highly fearful children who had been referred to dental fear clinic. Ages 6-11 yers in normal primary school. Exclusion criteria: none stated. Study comments: behaviour was observed a using Veham anxiety scale for first and last session and average scores were was calculated. There was significantly lower anxiety in nitrous oxide group maintained throughout treatment Fasting: not stated. Medical reason: dental treatment. Procedure type: Painful; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: prior procedures. ASA details: Not stated. Learning disabilities: none mentioned. Age: mixed; ages 6-11 years. Gender: matched on age and gender. Weight: all patients weighed more than 5 kg. Planned sedation level: not stated / unknown. Purpose: decrease fear. Sedationist: not stated / unknown. Procedure carried out by: dental practitioner. Sedation monitoring by: not stated / unknown.	1) nitrous oxide; volume: continuous flow; (n=27). 2) behaviour management at dental fear clinic; volume: n/a; (n=25). Other interventions: none. Intervention concurrent medications: none stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: n/a. Other analgesics therapy: not stated but is usual dental practice. Monitoring for intervention: all dental sessions were videotaped. Monitoring for control: same as intervention.

Nitrous oxide

Study	*Participants*	*Interventions*
Veerkamp 1995 (Ref ID: 1245) RCT Randomisation unit: Patient. Trial held in The Netherlands. Setting: primary care dental practice. Funding :no funding	Inclusion criteria: native Dutch speakers in normal primary education who had jproved untreatable due to fear. Exclusion criteria: no siblings. Study comments: behavioural observations measured by Venham scale which has been validated in this age group. Anxiety scores were significantly less in nitrous oxide group than Behavior Modification Group and decreased anxiety appeared to continue over time. Fasting: not stated. Medical reason: dental treatment. Procedure type: Painful; dental - mixed - e.g. extractions, restorations, pulpotomies, brief. First procedure?: prior procedures. ASA details: Not stated. Learning disabilities: none mentioned. Age: mixed; ages 6-11 years. Gender: Groups were matched by sex and age. Weight: all patients weighed more than 5 kg. Planned sedation level: not stated / unknown. Purpose: decrease anxiety. Sedationist: dental practitioner. Procedure carried out by: dental practitioner. Sedation monitoring by: not stated / unknown.	1) nitrous oxide; volume: continuous; (n= 23). 2) behavioural management; volume: n/a; (n=26). Other interventions: none. Intervention concurrent medications: None stated. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: n/a. Other analgesics therapy: not stated. Monitoring for intervention: All sessions were recorded by video camera. Monitoring for control: same as intervention.

Nitrous oxide

Study	Participants	Interventions
Wilson 2002 (Ref ID: 711) RCT - crossover Randomisation unit: Patient. Trial held in United Kingdom. Setting: dental hospital. Funding :unclear/ not stated	Inclusion criteria: patients referred to the sedation department at Newcastle Dental Hospital for orthodontic extraction of at least four teeth -premolars or canines- under local anaesthetic and sedation. Exclusion criteria: not stated. Study comments: behaviour was assessed using the Houpt Scale. Behaviour categories include excellent, very good, good and treatment aborted. There was no significant difference between groups Fasting: not stated. Medical reason: dental treatment. Procedure type: Painful; dental - extraction of teeth. First procedure?: not known / unclear. ASA details: I. Learning disabilities: none mentioned. Age: mixed; mean 12.5 years (range 10 to 16 years). Gender: 16 male and 30 female. Weight: not known / unclear. Planned sedation level: mild. Purpose: mixed. Sedationist: specialised sedationist. Procedure carried out by: dental practitioner. Sedation monitoring by: sedationist for both groups.	1) nitrous oxide/70% oxygen [MDM quantified inhalation sedation unit] + distraction/reasurance + topical anaesthesia [gingivae for 2 mins] + local anaesthesia [2% lidocaine, 1:80,000 epinephrine]; volume: increments of 10% to a max of 30%; (n=26). 2) oral midazolam + topical anaesthesia [gingivae for 2 mins] + local anaesthesia [2% lidocaine, 1:80,000 epinephrine]; volume: 0.5 mg/kg; (n=26). Other interventions: none. Intervention concurrent medications: on completion of treatment N2O flow was switched off and 100% oxygen administered for 2 mins before nasal mask removed. Control concurrent medications: on completion of treatment pt transferred to recovery for at least 20 mins supervised by a parent and a sedation nurse; patient's fitness for discharge assessed and full writted and verbal postoperative sedation and surgical instructions provided. Washout period: not stated. Intervention - achieved sedation: titrated. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: same as control plus the clinician made sure that once 30% NO2 level was reached, this was mantained throughout subsequent dental treatment. Monitoring for control: dental sedationist monitored patient's clinical status throughout each session assisted by a trained nurse; patient also monitored in recovery area under supervision of a parent and sedation nurse; monitoring clinically and by pulse oximetry.

Nitrous oxide

Study	*Participants*	*Interventions*
Wilson 2002 (Ref ID: 729) RCT - crossover Randomisation unit: Patient. Trial held in UK. Setting: primary care dental practice. Funding :unclear/ not stated	Inclusion criteria: children ages 10-16 years requiring bilateral identical extractions on opposite sides of the mouth. Exclusion criteria: non stated. Study comments: may be subgroup of Wilson 2002 with 46 patients. Behaviour was assessed using the Houpt Scale. Behaviour categories include excellent, very good, good and treatment aborted. There was not significant difference between groups, p>0.05 Fasting: 'starve' two hours prior to appointment. Medical reason: dental treatment. Procedure type: Painful; dental - restorations. First procedure?: prior procedures. ASA details: I-II. Learning disabilities: none mentioned. Age: mixed; ages 10 - 16 years. Gender: 12 male and 14 female. Weight: not known / unclear. Planned sedation level: conscious sedation. Purpose: mixed. Sedationist: experienced sedationist. Procedure carried out by: dental practitioner. Sedation monitoring by: sedationist for both groups.	1) nitrous oxide 30%/70% oxygen + local anaesthesia [20% benzocaine, lidocaine 2% with 1:80,000 epinephrine]; volume: titrated to treatment level of 30% nitrous oxide and then continuous; (n=22). 2) oral midazolam [0.5 mg/kg] + local anaesthesia [20% benzocaine, lidocaine 2% with 1:80,000 epinephrine]; volume: dose weight dependant; (n=26). Other interventions: none. Intervention concurrent medications: none. Control concurrent medications: same as intervention. Washout period: time to second appointment. Intervention - achieved sedation: titrated. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: the dental sedationist monitored the patient's clinical status throughout each session assisted by a trained dental sedation nurse. Monitoring for control: same as intervention.

Nitrous oxide

Study	*Participants*	*Interventions*
Wilson 2003 (Ref ID: 589) RCT - crossover Randomisation unit: Patient. Trial held in UK. Setting: primary care dental practice. Funding :unclear/ not stated	Inclusion criteria: patients who required bilateral, identical extractions (upper or lower) on opposite sides of the mouth. Exclusion criteria: not stated. Study comments: the Houpt Behaviour Rating scale was used and patients were assessed as having excellen, very good, fair or poor behaviour. Only two patients in each group scored fair or poor Fasting: 2 hours before treatment. Medical reason: dental treatment. Procedure type: Painful; dental - extraction of teeth. First procedure?: prior procedures. ASA details: I-II. Learning disabilities: none mentioned. Age: older than 12 years; ages 12-16 years. Gender: 10 male and 30 female. Weight: all patients weighed more than 5 kg. Planned sedation level: conscious sedation. Purpose: mixed. Sedationist: experienced sedationist. Procedure carried out by: dental practitioner. Sedation monitoring by: sedationist for both groups.	1) 30% nitrous oxide/70% oxygen + local anaesthesia [20% benzocaine, lidocaine 2% with 1:80,000 epinephrine]; volume: continuous flow; (n=40). 2) iv midazolam [0.5 mg per minute to a maximum of 5 mg] + local anaesthesia [20% benzocaine, lidocaine 2% with 1:80,000 epinephrine]; volume: dose titrated up to 5 mg; (n=40). Other interventions: none. Intervention concurrent medications: none. Control concurrent medications: same as intervention. Washout period: time between appointments. Intervention - achieved sedation: titrated. Control - achieved sedation: titrated. Other analgesics therapy: not stated. Monitoring for intervention: monitoring every two minutes by sedationist and dental nurse. Monitoring for control: same as intervention.

Nitrous oxide

Study	*Participants*	*Interventions*
Wilson 2006 (Ref ID: 204) RCT - crossover Randomisation unit: Patient. Trial held in United Kingdom. Setting: primary care dental practice. Funding :unclear/ not stated	Inclusion criteria: ASA I-II pts referred to sedation department for extraction of 4 primary teeth, 1in each of 4 quadrants in mouth. After assessed for need and fitness of sedation, only recruited those who failed to have dental treatment carried out under local anaesthesia. Exclusion criteria: not stated. Study comments: behaviour during treatment was graded using Houpt Behaviour scale sections 1-3 No 'disruptive' behavour seen in nitrous oxide group but 8/35 children in the Midazolam group had some disruptive behaviour. Differences were not statistically significant Fasting: fast from solids and liquids for 2 hours before treatment visit. Medical reason: dental treatment. Procedure type: Painful; dental - extraction of teeth. First procedure?: prior procedures. ASA details: I-II; all but one were ASA physical status I. Learning disabilities: none mentioned. Age: 5 to 12 years of age; mean: 7.4 years of age (range 5 to 10 years). Gender: overall 54% (9/35) were male. Weight: all patients weighed more than 5 kg; mean range 29.5 kg (range 17 to 55 kg). Planned sedation level: mild. Purpose: not stated / unknown. Sedationist: trained dental sedation nurse. Procedure carried out by: dental practitioner. Sedation monitoring by: not stated / unknown.	1) nitrous oxide/oxygen [MDM quantified inhalation sedation unit] + distraction/reasurance [during procedure] + topical anaesthesia [bezocaine 20% for 2 min] + local anaesthesia [lidocaine2%, 1:80000 adrenaline]; volume: increments of 10% to a max of 30%; (n=42). 2) oral midazolam [standard iv preparation] + topical anaesthesia [bezocaine 20% for 2 min] + local anaesthesia [lidocaine2%, 1:80000 adrenaline]; volume: minimum of 0.3 mg/kg [mean dose:8.6 mg (range 3.3-16.5mg)]; 1child did not manage to swallow full prescribed dose accounting for the minimum of 3.3 mg; mean range dose administered 8.6 (range 3.3 to 16.5) mg; (n=42). Other interventions: none. Intervention concurrent medications: on completion of sedation, 100% oxygen administered for 3 mins before nasal mask removed; pt transferred to recovery with a parent & supervised by sedation nurse & remained in recovery for at least 20 min after treatment. Control concurrent medications: on completion of treatment pt transferred to recovery with a parent & supervised by sedation nurse & remained in recovery for at least 60 min after treatment. Washout period: 2hr before treatment visit. Intervention - achieved sedation: titrated. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: clinician made sure the 30% NO2 level of sedation was mantained throughout dental procedure; monitoring same as control. Monitoring for control: sedation-trained nurse monitored pts throughout int effect (20-30min); BP, pulse, O2 saturation, respiration, colour/responsiveness monitored & recorded every 2min for first 20 min & every 5 min thereafter using Brietkopf & Buttner emotional status.

Nitrous oxide

Study	*Participants*	*Interventions*
Wilson 2007 (Ref ID: 111) RCT - crossover Randomisation unit: Patient. Trial held in UK. Setting: primary care dental practice. Funding :unclear/ not stated	Inclusion criteria: children aged 10-16 years, ASA I & II who had been referred for orthodontic extractions of four premolar teeth under sedation and local analgesia. Exclusion criteria: children considered to be mouth breathers, those on central nervous system depressants and those sensitive to benzodiazepines were excluded. Study comments: study is underpowered as only 36 of the required 40 patients completed the study. 45 patients were recruited but nine withdrew. Spielberger Scal was used to assess anxiety for all subjects but a comparison between the two drug interventions was not made Fasting: 2 hours prior to treatment. Medical reason: dental treatment. Procedure type: Painful; dental - extraction of teeth. First procedure?: first procedure. ASA details: I-II. Learning disabilities: none mentioned. Age: mixed; ages 10-16. Gender: 10 male and 26 female. Weight: all patients weighed more than 5 kg. Planned sedation level: mild. Purpose: mixed. Sedationist: experienced sedationist. Procedure carried out by: dental practitioner. Sedation monitoring by: sedationist for both groups.	1) 30% Nitrous oxide/70% oxygen + local anaesthesia [20% benzocaine, lidocaine 2% with 1:80,000 epinephrine]; volume: continuous administration; (n=36). 2) transmucosal midazolam syrup [10 mg/ml supplied with a 1 ml syringe] + local anaesthesia [20% benzocaine, lidocaine 2% with 1:80,000 epinephrine]; volume: 0.2 mg/kg; (n=36). Other interventions: none. Intervention concurrent medications: none. Control concurrent medications: same as intervention. Washout period: time between appointments. Intervention - achieved sedation: titrated. Control - achieved sedation: bolus. Other analgesics therapy: not stated. Monitoring for intervention: continuous monitoring during procedure of blood pressure, pulse, oxygen saturation and respiration. Monitoring for control: same as intervention.

METHODOLOGICAL QUALITY OF STUDIES

Nitrous oxide

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Averley 2004 (Ref ID: 486)	Unclear / not stated.	Adequate- different parties: no knowledge of patients and retains schedule/code; Nnurse not connected with the study randomised patients and placed allocation group in patient record in sealed envelope.	Patient: yes double blind trial. Outcome assessor: Yes; dentist performing the procedure was blinded to type of gas received.	ITT: Yes, all followed. Power calculation: Not stated; 697 patients included.	No (>20% did not complete intervention; greater in 1 group); sn interim analysis of data showed that there was a high failure rate in Group 1 and therefore this arm of the studed was discontinued.	Yes mainly; NS differences in age, assessment of cooperation and invasiveness of procedure between groups. There was an imbalance with respect to gender between groups (fewer males in group 3 - sevoflurane) and in baseline anxiety (less in group 1 - air only).
Ekbom 2005 (Ref ID: 15942)	Unclear / not stated; patients were randomised by 'envelope' technique.	Not stated.	Patient: no not blinded - nature of intervention: different routes of administration. Outcome assessor: No.	ITT: Yes, all followed. Power calculation: Not stated.	Yes, all completed intervention.	Yes mainly; gender and diagnosis similar; ages 6-18.

METHODOLOGICAL QUALITY OF STUDIES

Nitrous oxide

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Fauroux 2004 (Ref ID: 546)	Unclear / not stated.	Not stated.	Patient: yes double blind trial. Outcome assessor: Yes.	ITT: Yes, all followed. Power calculation: Yes; 56 patients per treatment group were needed in order to reach a 90% statistical power.	Unclear or Not stated; it appears that all children were followed although greater than 20% failed with the first inhalation mixture.	Yes mainly; there was not statistically significant differences between groups re gender, age, weight.
McCann 1996 (Ref ID: 1195)	Unclear / not stated.	Not stated.	Patient: yes double blind trial. Outcome assessor: Yes.	ITT: Yes, all followed. Power calculation: Not stated.	Yes, all completed intervention.	Yes - cross over trial; 26 males and 14 females; ages 36 to 55 months (mean = 45 months). Weight ranged from 13.0 to 20.5 kg.

METHODOLOGICAL QUALITY OF STUDIES

Nitrous oxide

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Primosch 1999 (Ref ID: 965)	Unclear / not stated; Subjects were randomly assigned to received 100% oxygen or %40 nitrous oxide/60% oxygen at first appointment and the alternative treatment at the second appointment.	Not stated.	Patient: yes double blind trial. Outcome assessor: Yes.	ITT: No, available case analysis. Power calculation: Not stated.	No (≤ 20% did not complete intervention); 18% did not complete the study.	Yes - cross over trial; Mean age 7.3 years (range - 60-116 months); populatin 10 males and 12 females.
Veerkamp 1993 (Ref ID: 1367)	Unclear / not stated.	Not stated.	Patient: no not blinded. Outcome assessor: Partial; dentist and psychologist assessing the videotapes could observe the intervention but were blinded to the aim of the study.	ITT: Yes, all followed. Power calculation: Not stated.	Yes, all completed intervention.	Yes mainly; sample was matched on age and gender.

METHODOLOGICAL QUALITY OF STUDIES

Nitrous oxide

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Veerkamp 1995 (Ref ID: 1245)	Unclear / not stated; random groups were matched by sex and age.	Not stated.	Patient: no not blinded. Outcome assessor: Partial; outcome assessor was blind to purpose of study. Unable to blind dentist or patient due to different delivery methods of interventions.	ITT: Yes, all followed. Power calculation: Not stated; no power calculations.	Yes, all completed intervention.	Yes mainly; samples matched on sex and age.
Wilson 2002 (Ref ID: 711)	Partial- random numbers, randomisation table; computer generated random numbers - even numbers received oral midazolam and odd numbers nitrous oxide at their first appointment. Each group received the alternative treatment at second appointment.	Not stated.	Patient: no - crossover trial. Outcome assessor: No.	ITT: No, available case analysis. Power calculation: Not stated.	No (≤ 20% did not complete intervention); 2 patients did not complete the study.	Yes - cross over trial; patients were their own control.

METHODOLOGICAL QUALITY OF STUDIES

Nitrous oxide

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Wilson 2002 (Ref ID: 729)	Unclear / not stated; patients randomly allocated to receive either oral midazolam or nitrous oxide at their first appointment and the alternative technique for the second appointment.	Not stated.	Patient: no not blinded. Outcome assessor: No.	ITT: Yes, all followed. Power calculation: Not stated.	Yes, all completed intervention; None.	Yes - cross over trial; mean age 12.5 years (range 10-16 years); 12 male and 14 female and all ASA I.
Wilson 2003 (Ref ID: 589)	Adequate- computer or calculator generated sequence.	Adequate- different parties: no knowledge of patients and retains schedule/code.	Patient: no not blinded. Outcome assessor: No.	ITT: No, available case analysis. Power calculation: Not stated; 40 subjects required for 80% power to detect a difference in other similar studies by the same author.	No (≤ 20% did not complete intervention); two of the original 42 recruited patients withdrew.	Yes - cross over trial; 10 male and 30 female; 13.2 years was the mean age of subjects. 37 were ASA I and 2 were ASA II.

METHODOLOGICAL QUALITY OF STUDIES

Nitrous oxide

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Wilson 2006 (Ref ID: 204)	Adequate- computer or calculator generated sequence.	Adequate- independent third party: allocates interventions & retains schedule/code.	Patient: no - crossover trial. Outcome assessor: Unclear.	ITT: No, available case analysis. Power calculation: Yes; based on results from previous studies using Houpt scale to evaluate behaviour; 80% to detect difference between both groups a sample size of 40 pts was required. Therefore the study was underpowered.	No (≤ 20% did not complete intervention); 5%(2/42): 1 requested inhalation sedation for both visits; NO2: 2 unable to tolerate nasal mask; 1 failed to attend second visit.	Yes - cross over trial; patients are their own control.
Wilson 2007 (Ref ID: 111)	Adequate- computer or calculator generated sequence.	Adequate- different parties: no knowledge of patients and retains schedule/code.	Patient: no single blind trial. Outcome assessor: No.	ITT: No, available case analysis; Only the 36 who completed the study were analysed. Power calculation: Yes; 40 subjects required for 80% power.	No (≤ 20% did not complete intervention).	Yes - cross over trial; The mean age (range) was 12.9 years (10-15 years) with 10 male and 26 female patients.

CHARACTERISTICS OF INCLUDED STUDIES

Sevoflurane

Study	*Participants*	*Interventions*
Averley 2004 (Ref ID: 486) RCT Randomisation unit: Patient. Trial held in United Kingdom. Setting: dental hospital. Funding :grant- other	Inclusion criteria: child's self-expressed anxiety level was 4 or more (VAS); dentists's assessment of child's cooperation scored 3 or more (Venham scale); invasiveness of dental procedure scored 10 or more; children had to understand treatment; accept nasal hood and EMLA. Exclusion criteria: hypersensitivity to benzodiazapines, sevoflurane, NO2, local anaesthetics. Study comments: allocation to the air + iv midazolam group was terminated by DMC because of high procedural failure rate in this arm Fasting: not stated. Medical reason: dental treatment. Procedure type: Painful; not stated / unknown. First procedure?: not known / unclear. ASA details: I-II; 95% ASA 1 and 5% ASA II. Learning disabilities: none mentioned. Age: mixed; 6-14 years. Gender: 47% male Group 1(air + iv midazolam) ; 50% male Group 2 (NO2 + iv midazolam); 39% male Group 3 (sevoflurane + NO2 +iv midazolam). Weight: all patients weighed more than 5 kg. Planned sedation level: conscious sedation. Purpose: decrease anxiety. Sedationist: anaesthetist. Procedure carried out by: dental practitioner. Sedation monitoring by: anaesthetist.	1) inhaled sevoflurane [0.3%] + nitrous oxide [40% for 2 minutes] + iv midazolam [0.5 mg/min until level 3 on consciousness scale] + topical anaethesia [on gum] + local anaesthesia [lidocaine injection]; volume: titrated to reach desired level of consciousness; (n=267). 2) nitrous oxide [40% for 2 minutes] + iv midazolam [0.5 mg/min until Level 3 on consciousness scale] + topical anaethesia [on gum] + local anaesthesia [lidocaine injection]; volume: titrated to reach desired level of consciousness; (n=256). Other interventions: air + iv midazolam vs Sevoflurane + NO2 + iv midazolam. Intervention concurrent medications: dentist used calming chat during procedure. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: titrated. Other analgesics therapy: not stated. Monitoring for intervention: anaethetist delivered sedatives and monitored patient every 5 min during and after procedure until patient could walk across recovery room unaided. Monitoring for control: same as intervention.

Sevoflurane

Study	*Participants*	*Interventions*
Lahoud 2002 (Ref ID: 739) RCT Randomisation unit: Patient. Trial held in uk. Setting: dental hospital. Funding :unclear/ not stated	Inclusion criteria: age 3-10; English speaking without learning difficulties; able to sit in denatl chair, tolerrate an exam, accept nasal hood; unobstructed nasal airways; not better served with iv sedation. Exclusion criteria: hypersensitivity to sevoflurane or local anaesthetics; malignant hyperthermia; body weight outside 10th and 90th centile; history of psychoatric illness; mentally/physically handicapped. Study comments: trial terminated early due to high procedural failure rate in N20 group Fasting: not stated. Medical reason: dental treatment. Procedure type: Painful; not stated / unknown. First procedure?: first procedure. ASA details: Not stated. Learning disabilities: excluded. Age: mixed; 3-10 years. Gender: 45% female overall; 44% female in N20 and 46% female in sevoflurane. Weight: all patients weighed more than 5 kg. Planned sedation level: conscious sedation. Purpose: decrease anxiety. Sedationist: anaesthetist. Procedure carried out by: dental practitioner. Sedation monitoring by: anaesthetist.	1) inhaled sevoflurane [0.1-0.3%] + nitrous oxide [40%] + topical anaethesia [on gum] + local anaesthesia [lidocaine injection]; volume: to achieve desired level of consciousness; (n=241). 2) nitrous oxide [40%] + topical anaethesia [on gum] + local anaesthesia [lidocaine injection]; volume: to achieve desired level of consciousness; (n=170). Other interventions: none. Intervention concurrent medications: dentist used calming chat and imagery to relax/distract patient during procedure. Control concurrent medications: same as intervention. Intervention - achieved sedation: titrated. Control - achieved sedation: titrated. Other analgesics therapy: not stated. Monitoring for intervention: anaethetist delivered sedatives and monitored patient every 5 min during and after procedure until patient could walk across recovery room unaided. Monitoring for control: same as intervention.

METHODOLOGICAL QUALITY OF STUDIES

Sevoflurane

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Averley 2004 (Ref ID: 486)	Adequate- computer or calculator generated sequence.	Adequate- sequentially numbered, opaque, sealed envelopes; nurse not connected to study did central randomisation ; sealed envelopes used.	Patient: yes double blind trial. Outcome assessor: Yes.	ITT: ITT not performed, per protocol analysis instead; only ITT for the primary outcome (completion of procedure). Power calculation: Not stated; Details on what outcome study powered for, at what level and power, and n patients.	No (>20% did not complete intervention; greater in 1 group); 46% failed to complete in air + mid; 20% in N20 + mid; 7% in sevoflurane + N20 = mid.	Some comparable; slight imbalance with respect to baseline anxiety score and gender.
Lahoud 2002 (Ref ID: 739)	Unclear / not stated.	Partial- not met all requirements: sealed/numbered/opaque envelopes; sealed envelopes.	Patient: no single blind trial. Outcome assessor: Unclear.	ITT: ITT not performed, per protocol analysis instead; only ITT for primary outcome (completion of procedure). Power calculation: Not stated.	No (>20% did not complete intervention; greater in 1 group); 48% failed to complete treatment in N20 versus 11% in sevoflurane + N20.	Yes mainly; no discussion of baseline characteristics, but they appear to be similar in the table; uneven distribution of people in each group.

CHARACTERISTICS OF INCLUDED STUDIES

Propofol

Study	*Participants*	*Interventions*
Vardi 2002 (Ref ID: 724) RCT Randomisation unit: Patient. Trial held in Israel. Setting: paediatric critical care department. Funding :university study	Inclusion criteria: inpatient or ambulatory patients. Exclusion criteria: not stated. Fasting: for all patients before anaesthesia solid food including milk withheld for at least 8hrs in children over 3 yrs of age, for 6 hrs in children between 0.5-3 yrs of age, for 4 hrs in younger children; clear liquids allowed up to 3 hrs before procedure. Medical reason: likely to be mixed. Procedure type: Painful; mixed. First procedure?: not known / unclear. ASA details: Mixed; of 98 patients with 105 procedures, ASA class II: 98% (96/98) and ASA class III: 2.1% (2/98). Learning disabilities: none mentioned. Age: mixed; overall mean 7.25 years (SD5.73); overall age range 1 month to 28 years; of 105 procedures performed in 98 patients: P/LA: mean age 7.5 yrs (SD5.67); MKF: mean age 6.93 yrs (SD5.84). Gender: of 105 procedures performed in 98 patients: P/LA: 52% male (30/58); MKF: 49% (23/47). Weight: not known / unclear. Planned sedation level: prolonged sedation. Purpose: decrease anxiety. Sedationist: paediatric intensivist. Procedure carried out by: physician. Sedation monitoring by: nurse.	1) iv propofol initial dose 2.5 mg/kg in children & 3 mg/kg in infants [bolus injection] + propofol maintenance 200 mcg/kg/min + Local anaesthesia (Lidocaine 0.1 mL=1mg); volume: variable as propofol maintenance and additional boluses applied; 2.5 mg/kg in children & 3 mg/kg in infants; (n=58). 2) iv midazolam 0.1 mg/kg [bolus injection] + iv ketamine 2 mg/kg + iv fentanyl 2 mcg/kg; volume: variable as ketamine additional boluses required; (n=47). Other interventions: none. Intervention concurrent medications: supplemental O2 by face mask or blow-by before initiation and throughout procedure and initiated immediately after sedation took effect. Control concurrent medications: same as intervention. Intervention - achieved sedation: induction plus maintenance. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: vital signs at 5 min intervals started before the initiation of sedation and included electrocardiography, respiratory rate, continuous visual/auditory pulse oxymetry, noninvasive BP. Monitoring for control: same as intervention.

METHODOLOGICAL QUALITY OF STUDIES

Propofol

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Vardi 2002 (Ref ID: 724)	Inadequate; randomisation according to date of admission; procedures performed during odd-numbered months employed the ketamine/midazolam/fentanyl; procedures performed during even-numbered months employed the propofol/lidocaine.	Not stated.	Patient: not stated. Outcome assessor: Unclear; healthcare providers were not blinded to drugs but does not mention if these were the outcome assessors.	ITT: Unclear/not stated. Power calculation: Not stated.	Unclear or Not stated; not stated.	Not stated.

Opioids

Study	Participants	Interventions
Disma 2005 (Ref ID: 334) RCT Randomisation unit: Patient. Trial held in Italy. Setting: gastroenterology. Funding :university study	Inclusion criteria: children schedualed for diagnostic endoscopic procedures of the upper gastrointestinal tract; enrolled during the period between January 2001 and May 2004. Exclusion criteria: none stated. Fasting: in children aged 1 to 3 years old nothing by mouth at least 6 hrs before the procedure; in children older than 3 years nothing by mouth for at least 8 hrs before the procedure. Medical reason: gastrointestinal. Procedure type: Painful; mixed. First procedure?: not known / unclear. ASA details: I-II. Learning disabilities: none mentioned. Age: mixed; PM 7.1 years (SD3.1), P 6.7 years (2.9), PF 6.8 years (SD2.8). Gender: overall 51% (123/240) were mal; midazolam 49% (38/78), usual care 57% (46/80), fentanyl 48% (39/82). Weight: all patients weighed more than 5 kg; mean weight per group: PM 27.5 kg (SD16.2), P 22.7 kg (SD10.8), PF 25.6 kg (SD9). Planned sedation level: deep. Purpose: mixed. Sedationist: anaesthetist. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: sedationist for both groups.	1) topical anaesthesia [EMLAvenipucture sites; Lidocaine pharynx/larynx] + iv fentanyl 1mg/kg + iv propofol 3 mg/kg [in 3 doses of 1 mg/kg over 1 min; and suppl propofol as required] + O2 (3Lmin); volume: variable as supplemental propofol may have been required; (n=82). 2) topical anaesthesia [EMLAvenipucture sites; Lidocaine pharynx/larynx] + iv propofol 3 mg/kg [in 3 doses of 1 mg/kg over 1 min; and suppl propofol as required] + O2 (3Lmin); volume: variable as supplemental propofol may have been required; (n=80). Other interventions: topical anaesthesia (EMLA cream for venipucture sites and Lidocaine for larynx) + iv midazolam (0.1 mg/kg; 2 min before procedure) + iv propofol (3 mg/kg in 3 doses of 1 mg/kg over 1 min; and suppl propofol as required) + O2 (3Lmin), n=78. Intervention concurrent medications: premedication oral midazolam 0.5mg/kg (max 7.5 mg/kg 20 min before procedure to establish iv line before sedation); supplemental O2 at 3L/min via nasal cannula with spontaneous breathing and no tracheal intubation. Control concurrent medications: section continues from intervention: all patients were given supplemental oxygen via a nasal cannula and allowed to breathe spontaneously without tracheal intubation. Intervention - achieved sedation: bolus plus maintenance. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: heart rate, blood pressure, etc were recorded and defined as baseline values; heart rate, mean arterial pressure, respiratory rate & oxygen saturation (pulse oximeter) were recorded at 1 min intervals during procedure and every 5 min during recovery. Monitoring for control: same as intervention.

Opioids

Study	*Participants*	*Interventions*
Hollman 2008; Cechvala 2008 (Ref ID: 8315; 48) RCT - crossover Randomisation unit: Patient. Trial held in USA. Setting: hospital - inpatients. Funding :grant- other	Inclusion criteria: children with diagnosis of acute leukemia or lymphoma undergoing sedation for lumbar puncture; acute haematologic malignancy compromises the majority of paediatric oncology patients; enrolled after induction of chemotherapy. Exclusion criteria: ASA <=II with cardiorespiratory instability, allergy to propofol or its components, age<2 years, patients receiving concomitant sedatives and analgesics and patients with oxygen requirement. Fasting: not stated. Medical reason: acute leukemia or lymphoma. Procedure type: Painful; lumbar puncture. First procedure?: not known / unclear. ASA details: II. Learning disabilities: none mentioned. Age: mixed; overall age range 2 to 18 years; median age 5 years (range: 2.2 to 17.2). Gender: overall 64%(14/22) were male. Weight: not known / unclear. Planned sedation level: conscious sedation. Purpose: mixed. Sedationist: sedation nurse and physician. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: study investigators.	1) iv propofol 1-2mg/kg/min + iv fentanyl 1mg/kg + TA (Lido subcutaneous at 1%) + PRO maintenance of score of <=7 in CHEOPS; volume: variable as PRO maintenance applied; (n=22). 2) iv propofol 1-2mg/kg/min + placebo [normal saline] + O2 + TA (Lido subcutaneous at 1%) + PRO maintenance of score of <=7 in CHEOPS; volume: same as intervention; (n=22). Other interventions: none. Intervention concurrent medications: O2 supplementation by blow-by facemask throughout the procedure. Control concurrent medications: same as intervention. Washout period: study periods of 4 weeks betweeneach other in 11 patients and within 12 weeks in 19 patients. Intervention - achieved sedation: induction plus maintenance. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: heart and respiratory rates, BP, O2 saturation, score on modified Yale Preoperative Anxiety Scale, recorded by study investigator, stridor score to assess aiway patency. Monitoring for control: same as intervention.

Opioids

Study	*Participants*	*Interventions*
Kennedy 1998 (Ref ID: 1014) quasi RCT Randomisation unit: Patient. Trial held in USA. Setting: accidents & emergencies. Funding :grant- other	Inclusion criteria: patients between 5 and 15 years requiring fracture or joint reduction and meeting ASA class I or II criteria. Exclusion criteria: abnormalities of airway, cardiorespiratory, hepatic, renal or central nervous systems; history of psychoses, ethanol, psychotropic or nonprescribed narcotic drug use within 6 hours of the procedure and adverse reaction to the study drugs, opiates or benzo. Study comments: quasi randomised; subjects stratified acording to initial parental choice to remain in the room or not during reduction and were then randomly assigned in blocks of 20 within strata to receive fentanyl or ketamine Fasting: mean hours fasted: 5.2 in FM group and 4.8 in KM group. Medical reason: orthopaedic. Procedure type: Painful; orthopedic. First procedure?: first procedure. ASA details: I-II; ASA class I 83% in FM group and 78% in KM group. Learning disabilities: none mentioned. Age: mixed; age 5-15. Gender: 72% male (n=94) in FM group and 68% male (n=88) in KM group. Weight: all patients weighed more than 5 kg. Planned sedation level: deep. Purpose: mixed. Sedationist: physician. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: physician and nurse.	1) iv midazolam ≤0.1mg/kg [max2.5mg, every 3min until speech, slurred/glassy eyes or max1st dose reduction 0.3mg/kg-max7.5mg] + iv fentanyl ≤0.05mg/kg [every 3min until response to verbal/painful stimuli or max1st dose reduction 0.2mg/kg, max10mg/kg]; volume: varied according to weight; (n=130). 2) iv midazolam [same dose/form as intervention] + iv ketamine ≤0.5mg/kg [every 3min until response to verbal/painful stimuli or max1st dose reduction 2mg/kg] + glycopylorrate 5mcg/kg; volume: varied according to weight; (n=130). Other interventions: none. Intervention concurrent medications: 38 patients had presedation medications, primarily parenteral opiates (morphine, meperidine or fentanyl). Control concurrent medications: 46 patients had presedation medications, primarily parenteral opiates (morphine, meperidine or fentanyl); glycopyrrolate (5 mcg/kg, max 250 mcg;given 1 min after midazolam) given to this group only. Intervention - achieved sedation: titrated. Control - achieved sedation: titrated. Other analgesics therapy: not stated. Monitoring for intervention: sedators observed subjects directly throughout sedation and reduction periods and vital signs were documented by nurse at 5 minute intervals or 3 minutes after each medication bolus. Monitoring for control: same as intervention.

Opioids

Study	*Participants*	*Interventions*
Lucas Da Silva 2007 (Ref ID: 153) RCT Randomisation unit: Patient. Trial held in Brazil. Setting: hospital - inpatients. Funding :unclear/ not stated	Inclusion criteria: non intubated children in PICU requiring CVC from ages 3 months to 14 years. Exclusion criteria: abnormalities in the airways; serious impairment of the central nervous system; intracranial hypertension; glaucoma; hyperthyroidism; severe respiratory disease; history of psychosis; sensitivity ot study drugs; recent alcohol or psychotropic drugs. Fasting: not stated. Medical reason: intravenous line placement. Procedure type: Painful; insertion of a needle in a subcutaneously implanted central venous port. First procedure?: first procedure. ASA details: Mixed; 8 (14%) ASA II, 37 (65%) ASA III and 12 (21%) ASA IV. Learning disabilities: none mentioned. Age: mixed; 3 months to 14 years. Gender: not reported. Weight: all patients weighed more than 5 kg. Planned sedation level: moderate. Purpose: not stated / unknown. Sedationist: nurse. Procedure carried out by: not stated / unknown. Sedation monitoring by: another trained person different from whom performed procedure.	1) iv midazolam 0.15 mg/kg [max:0.5 mg/kg] + iv fentanyl 1 mcg/kg [max 100 mg dose]; volume: variable as additional bolus given when necessary; (n=28). 2) iv midazolam 0.15 mg/k [max: 0.5 mg/kg] + iv ketamine 0.5 mg/kg; volume: variable as additional bolus given when necessary; (n=29). Other interventions: none. Intervention concurrent medications: O2 supplementation via nasal cannula or by blow-by throughout the procedure. Control concurrent medications: same as intervention. Intervention - achieved sedation: bolus. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: standard cardiopulmonary parameters and oxygen saturation wee monitored continuously before and during sedtion functions and blood pressure recorded eery 5 minutes. Monitoring for control: same as intervention.

Opioids

Study	*Participants*	*Interventions*
Tosun 2007 (Ref ID: 97) RCT Randomisation unit: Patient. Trial held in Turkey. Setting: gastroenterology. Funding :unclear/ not stated	Inclusion criteria: patients aged 1-16 years. Exclusion criteria: neurologically impaired children. Study comments: parental informed consent obtained Fasting: not stated. Medical reason: gastrointestinal. Procedure type: Painful; upper and lower endoscopy. First procedure?: not known / unclear. ASA details: I-II. Learning disabilities: none mentioned. Age: mixed; ages 1-16 years; no significant difference between groups. Gender: overall 51% male and 49% female; ns difference between groups. Weight: all patients weighed more than 5 kg. Planned sedation level: deep. Purpose: mixed. Sedationist: anaesthetist. Procedure carried out by: specialist of the area, e.g. paediatric gastroenterologist. Sedation monitoring by: anaesthetist.	1) iv fentanyl 1 mcg/kg + propofol 1.2 mg/kg [additional doses (0.5-1 mg/kg) administered if patient had discomfort] + TA (Lidocaine 10% to the posterior pharynx to diminish discomfort -gag reflex); volume: variable as additional doses of propofol may be needed; (n=44). 2) iv propofol 1.2 mg/kg [additional doses (0.5-1 mg/kg) administered if patient had discomfort] + ketamine 1 mg/kg +TA (Lidocaine 10%); volume: variable as additional doses of propofol may be needed; (n=46). Other interventions: none. Intervention concurrent medications: supplemental O2 at 2-4 min (-1) via nasal cannula during procedure for all patients. Control concurrent medications: additional propofol (0.5-1 mg/kg) was administered when a patient showed discomfort in both groups. Intervention - achieved sedation: bolus. Control - achieved sedation: same as intervention. Other analgesics therapy: not stated. Monitoring for intervention: heart rate, systolic arterial pressure, oxygen saturation, respiratory rate and Ramsey sedation scores were recorded at baseline, after induction and every 5 minutes thereafter during the procedure by the anesthesiologist. Monitoring for control: same as intervention.

METHODOLOGICAL QUALITY OF STUDIES

Opioids

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Disma 2005 (Ref ID: 334)	Unclear / not stated.	Not stated.	Patient: not stated. Outcome assessor: Unclear; anaesthetist administered sedation drugs, carried out physical examination and clinical assessments and obtained medical history but not clear if blinded to drug treatment.	ITT: Yes, all followed; all enrolled patients appeared to have been randomised and all analysed as assigned to their original group. Power calculation: Not stated.	Yes, all completed; no withdrawals reported.	Yes mainly; patients in both groups were statistically comparable in terms of age, weight, gender and they were no statistical different in terms duration of endoscopy, recovery time or endoscopist's rating.
Hollman 2008; Cechvala 2008 (Ref ID: 8315; 48)	Partial- random permuted blocks; block size of 4; randomisation list generated using a random number generator.	Adequate- sequentially numbered, opaque, sealed envelopes; assigned by a third party (pharmacy) ; however nurse and physician administering sedation knew of the study drug.	Patient: yes, double blind trial. Outcome assessor: Yes; study investigators and oncologist performing lumbar puncturewere blinded to fentanyl and placebo administration.	ITT: No, available case analysis; 31 elegible were randomised but 9 patients declined participation after randomisation. Power calculation: Yes; n=40 proposed to detect a difference of 3% in O2 desat between groups with a 90% power and two-sided significance level of 5%; total accrual was n=44 to account for patient exclusion; Pocock stopping rule to stop early because of efficacy for futility.	No (>20% overall did not complete intervention); 29% (9/31) declined participation after randomisation due to satisfaction with the current sedation drug regimen and reluctance to consider other options.	Yes - cross over trial; and study stated that groups were not statistically significant different in the score on modified Yale Preoperative Anxiety Scale, recorded by study investigator, stridor score to assess aiway patency.

METHODOLOGICAL QUALITY OF STUDIES

Opioids

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Kennedy 1998 (Ref ID: 1014)	Partial- random permuted blocks; Subjects were stratified acording to initial parental choice to remain in the room or not during reduction. Subjects were randomly assigned in blocks of 20 within strata to receive fentanyl or ketamine. A random number generator used..	Adequate- Third party cluster: third party had no knowledge; Two trained independent observers.	Patient: not stated. Outcome assessor: Partial; Two trained observers were blinded to study purpose and design reviewed the videotape of each study; unable to blind sedators.	ITT: Yes, all followed. Power calculation: Yes; Calculations based on OSBD. A sample of 40 required to detect a change in the mean of 1.05.	Yes, all completed.	Yes mainly; FM and KM groups did not differ in mean age, weight, gender, race, ASA class time from last oral intake, fracture location or presedation medications.
Lucas Da Silva 2007 (Ref ID: 153)	Adequate- random numbers table or satistical table; Random number generator.	Adequate- sequentially numbered, opaque, sealed envelopes; Maintained in sealed opaque envelopes.	Patient: not blinded. Outcome assessor: No; Double blinding was deemed impractical because of different dosing algorithms of the drugs used and because medications ued present clincially distinuishable effects.	ITT: Yes, all included in analysis, no details. Power calculation: No; Not provided.	Yes, all completed.	Yes mainly; there were no differences between the groups regarding age, weight, risk classification (ASA) and final sedation score.

METHODOLOGICAL QUALITY OF STUDIES

Opioids

Study	*Sequence Generation*	*Allocation Concealment*	*Blinding*	*ITT and Power Calculation*	*Attrition details*	*Baseline Comparable*
Tosun 2007 (Ref ID: 97)	Unclear / not stated.	Patial- not met all requirements:serially numbered/identical/allocated sequentially; Only 'sealed envelopes' described.	Patient: yes, double blind trial. Outcome assessor: Yes.	ITT: Yes, all followed. Power calculation: Not stated.	Yes, all completed.	Yes; there were no statistically significant differences between groups with respect to age, weight, sex.