

Opioids for neonates receiving mechanical ventilation (Review)

Bellù R, de Waal KA, Zanini R



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ABSTRACT

Background

Mechanical ventilation is a potentially painful intervention widely used in neonatal intensive care units. Since newborn babies (neonates) demonstrate increased sensitivity to pain, which may affect clinical and neurodevelopmental outcomes, the use of drugs which reduce pain might be very important.

Objectives

To determine the effect of opioid analgesics (pain-killing drugs derived from opium e.g. morphine), compared to placebo, no drug, or other non-opioid analgesics or sedatives, on pain, duration of mechanical ventilation, mortality, growth and neurodevelopmental outcomes in newborn infants on mechanical ventilation.

Search strategy

Electronic searches included: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 3, 2004); MEDLINE (1966 to June 2004); EMBASE (1974 to June 2004); and CINAHL (1982 to 2003). Previous reviews and lists of relevant articles were cross-referenced.

Selection criteria

Randomised controlled trials or quasi-randomised controlled trials comparing opioids to a control, or to other analgesics or sedatives in newborn infants on mechanical ventilation.

Data collection and analysis

Data were extracted by two reviewers independently. Categorical outcomes were analysed using relative risk and risk difference; and continuous outcomes with weighted mean difference or standardised mean difference. A fixed effect model was used for meta-analysis except where heterogeneity existed, when a random effects model was used.

Main results

Thirteen studies on 1505 infants were included. Infants given opioids showed reduced premature infant pain profile (PIPP) scores compared to the control group (weighted mean difference -1.71; 95% confidence interval -3.18 to -0.24). Differences in execution and reporting of trials mean that this meta-analysis should be interpreted with caution. Heterogeneity was significantly high in all analyses of pain, even when lower quality studies were excluded and analysis limited to very preterm newborns. Meta-analyses of mortality, duration of mechanical ventilation, and long and short term neurodevelopmental outcomes showed no statistically significant differences. Very preterm infants given morphine took significantly longer to reach full enteral feeding than those in control groups (weighted mean difference 2.10 days; 95% confidence interval 0.35 to 3.85). One study compared morphine with a sedative: the treatments showed similar pain scores, but morphine had fewer adverse effects.

Authors' conclusions

There is insufficient evidence to recommend routine use of opioids in mechanically ventilated newborns. Opioids should be used selectively, when indicated by clinical judgment and evaluation of pain indicators. If sedation is required, morphine is safer than midazolam. Further research is needed.

PLAIN LANGUAGE SUMMARY

Insufficient evidence to recommend routine use of opioids (e.g. morphine) to reduce pain in newborn babies (full-term or preterm) with breathing difficulties on breathing machines.

Breathing machines, which are widely used for newborn full-term and preterm babies with breathing problems, may cause babies pain. Since newborn babies are very sensitive to pain - which may have a bad effect on future development - pain-reduction with drugs (including opioids such as morphine) might be very important. This review found no evidence from trials for routine use of opioids for newborns on breathing machines. Although relief of pain was variable, opioids were no better or worse for babies (in terms of death, strokes, future development, duration of ventilation or hospital stay) than other drugs or placebo. Further research is needed.

BACKGROUND

Mechanical ventilation is used in neonatal intensive care units for treating pulmonary insufficiency both in term and preterm newborns. A large proportion of preterm newborns undergo mechanical ventilation: newborns delivered at <28 weeks gestational age are virtually all ventilated (Wilson 2000), and about 27 % of all infants admitted to neonatal intensive care units undergo mechanical ventilation (Johnston 1997).

Mechanical ventilation is a potentially painful or uncomfortable intervention (Barker 1996). Pain is a stressful experience that may have consequences on both the course of the acute illness, and on development of the newborn. Pain and stress can interact negatively with mechanical ventilation, leading to unsynchronised breathing and suboptimal ventilation. Moreover, pain can lead to clinical instability with changes in heart rate, respiratory rate, blood pressure, intracranial pressure and oxygen saturation (of the blood), and the development of complications such as intraventricular haemorrhage (Anand 1998). There is also evidence of an endocrine stress response that leads to increased secretion of steroids, catecholamines, glucagon and an increased rate of catabolism (Anand 1987). Metabolic and immune changes have also been reported (Anand 1990). Neonates demonstrate a heightened sensitivity to repetitive noxious stimuli (Fitzgerald 1989), that leads to chronic pain and discomfort. These responses may affect long term clinical and neurodevelopmental outcomes (Anand 1993).

Reduction of pain in mechanically ventilated newborns has been considered a critical part of supportive therapy (Anand 2001; Larson 1999; Menon 1998) not only because it is important per se, but also because it is possibly associated with better outcomes. Sedation is routinely administered in intubated adults and children but there is considerable variability in the approach to sedation of neonates (Kahn 1998). Historically, the belief that newborns could not feel pain may have accounted, in part, for the low usage of analgesics. There are data reporting that neonatologists are still reluctant to use opioid analgesics in newborns (Johnston 1997), and that opioids are under utilized in neonatal intensive care units (Anand 1998; Franck 1998; Franck 2002). This is mainly because

of underestimation of pain (Purcell-Jones 1988), although more recent data are showing increased awareness of pain (de Lima 1996; Porter 1997), but fear of systemic, respiratory and cardiovascular effects, and of making the baby dependent upon the drug (de Lima 1996). A non-systematic review (Franck 1998) underlined the paucity of scientific data to define optimal drug regimens and their adverse effects, but concluded that the latter are generally overestimated. Moreover, the relative efficacy and safety of different types of analgesics (such as non-opioid analgesics) and sedatives (e.g. benzodiazepines) in the neonate is not completely clear.

Potential adverse effects of opioids include the slowing of gastric and intestinal motility, feeding intolerance, dependence and tolerance (reduction of the normal response to a drug, requiring increased doses to achieve the desired effect), and adverse neurological effects (Taddio 2002). Concern also exists about the potential inhibition of the respiratory drive, leading to difficulties in weaning from mechanical ventilation.

Recently, recommendations have been issued to promote a more aggressive approach to treatment and prevention of pain in the neonate (CPS, AAP 2000), but uncertainty remains about long term effects of opioid use in the neonate, and about which opioid is most effective and safe. Morphine and fentanyl are the most commonly used opioids, but other drugs are available for neonatal use. The benefits and risks of the use of opioids in the ventilated neonate have not yet been systematically reviewed.

The question addressed by this review is: what is the evidence, from random and quasi-random controlled trials, that an opioid is better than a placebo, a non-pharmacological treatment, a sedative, or a non-opioid analgesic for reducing pain in mechanically ventilated newborns? Does opioid treatment reduce the incidence of neonatal mortality and abnormal neurodevelopment? What is the evidence that the goal of treatment can be accomplished without hampering cardiorespiratory functions, feeding and weight gain?

OBJECTIVES

To determine the effects of opioid analgesics in neonates (term or preterm) receiving mechanical ventilation for any respiratory

disease, compared to placebo or no drug, or to other analgesics or sedatives, on the following outcomes: pain, duration of mechanical ventilation, mortality, growth and neurodevelopment.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials or quasi-randomised controlled trials.

Types of participants

Term (37 or more weeks gestational age) and preterm (less than 37 weeks gestational age) newborn infants on mechanical ventilation for any respiratory disease.

Types of intervention

Any opioid analgesics (e.g. morphine, diamorphine, fentanyl, alfentanil, sufentanil, pethidine, meperidine, codeine) administered at any dosage, either continuously or as bolus, compared to control (placebo or no intervention), or compared to other analgesics (e.g. acetaminophen) and sedatives (e.g. midazolam and other benzodiazepine). Any duration of drug treatment was considered. Studies were included if outcomes other than pain were assessed after the drug therapy was administered for at least one day; however, studies assessing pain after as little as a single dose of drug were eligible.

Types of outcome measures

Primary outcome measures include any of the following:

- (1) Pain assessed with validated methods during the administration of selected drugs;
- (2) Duration of mechanical ventilation (days);
- (3) Neonatal mortality (death within 28 days of birth) and mortality to discharge;
- (4) Neurodevelopmental outcome and quality of life (measured by validated scales) at short (≤ 1 year), medium (1-3 years) and long term (> 3 years).

Secondary outcome measures were:

- (1) Respiratory outcomes: need for oxygen at 28 days of life or oxygen at 36 weeks adjusted age;
- (2) Feeding behaviour during hospital stay: days to reach full enteral feeding; breast versus bottle feeding at discharge;
- (3) Growth parameters: (weight, length, head circumference) at term or near term (36-40 weeks adjusted age);
- (4) Length of stay in hospital;
- (5) Incidence of gastrointestinal complications (specifically necrotising enterocolitis (NEC) and focal gastrointestinal perforation);
- (6) Incidence of intraventricular haemorrhage (IVH) and periventricular leucomalacia (PVL).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Trials were searched for using the Cochrane Neonatal Review Group search strategy. Randomised and quasi-randomised controlled trials of opioid use in neonates were identified by electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 3, 2004); MEDLINE (from 1966 to June 2004); EMBASE (from 1974 to June 2004); and CINAHL (from 1982 to 2003). Expert informants in the areas of anaesthesia, paediatric surgery and neonatology were contacted, and previous reviews and lists of relevant articles cross-referenced in the search for relevant trials. Abstracts from the Society for Pediatric Research and the European Society for Pediatric Research from 1995 until 2003 were handsearched.

Because of the nature of the questions, the search strategy was focused on patients and intervention and involved the following text words and/or MeSH subject headings: infan*, neonat*, newborn*, morphine, diamorphine, fentanyl, alfentanil, sufentanil, pethidine, meperidine, codeine, methadone, narcotics, sedation, analgesia.

No language restriction was used. No attempts were made to identify unpublished studies.

METHODS OF THE REVIEW

Selection of trials

All trials identified by the above search strategy were screened (title and abstract) by the reviewers. The full text of the report of each potentially relevant study was evaluated by all reviewers, and the decision to include or exclude each study was made by consensus of the reviewers. Any trials that were not truly randomised or quasi-randomised were excluded. After the randomised controlled trials were identified, we obtained additional data directly from the authors.

Data extraction

Data on the relevant outcomes were extracted from the papers independently by two reviewers and analysed according to methods recommended in the Cochrane Reviewers' Handbook (Clarke 2002). Further information on outcomes was requested from the principal authors of the studies included in the review.

Assessment scales

The following scales, developed to assess pain, were found to fulfil validity and reliability criteria for newborn infants (term and preterm on mechanical ventilation for any respiratory disease) when critically reviewed (Abu-Saad 1998): the Neonatal Facial Coding System (NFCS) (Grunau 1987), the Neonatal Infant Pain

Scale (NIPS) (Lawrence 1993), and the Premature Infant Pain Profile (PIPP) (Stevens 1996).

In addition, the following quality of life measurements were found to fulfil basic psychometric criteria when critically reviewed (Eiser 2001): CHQ-CF87 (Landgraf 1997), PedsQL (Varni 1999), and the Health Utility Index (Feeny 1998).

Statistical analysis

Outcomes were analysed using numbers of events occurring rather than in terms of percentages. For each comparison, we planned subgroup analyses according to gestational age (term, preterm (32-36 weeks), or very preterm (<32 weeks)), according to whether the infants receiving mechanical ventilation were unselected or were selected for complications of mechanical ventilation including: extrapulmonary air leaks, pneumothorax, chronic lung disease and bronchopulmonary dysplasia; and according to dosing schedule (continuous drug administration, or "as needed" based on signs of pain, discomfort or stress).

The standard methods of the Cochrane Neonatal Review Group were used to analyse and synthesise the data. Treatment effects were analysed using relative risk (RR), risk difference (RD) and number needed to treat (NNT), each with 95% confidence intervals (95% CI), for categorical variables; and weighted mean difference (WMD) for continuous variables. If different scales were used to measure pain, standardised mean difference (SMD) was used to pool data (data are, therefore, expressed as units of standard deviation). Data from cross-over trials were extracted and analysed as parallel groups. A fixed effect model for meta-analysis was used if heterogeneity allowed ($P > 0.10$ on chi-squared or ANOVA test). Heterogeneity between trial results was examined using a chi-squared test for dichotomous outcomes and ANOVA for continuous outcomes.

A variety of scales were found in studies, so subgroup analysis was performed pooling these measurements. Pain assessments six or more hours after starting continuous infusion or repeated bolus qualified for inclusion. For trials that measured pain after a single administration of a drug, a measurement made within the period of the drug's duration of action qualified for inclusion (Taddio 2002).

Quality assessment of trials

The criteria and standard methods of the Cochrane Neonatal Review Group were used to assess the methodological quality of the included trials. Quality of the included trials was evaluated independently by two reviewers (RB, KW) in terms of allocation concealment, blinding of carers and assessors to intervention, completeness of assessment in all randomised individuals, and blinding of assessors to outcome measurement. Additional information was requested from the authors of each trial as necessary. After resolving discrepancies in quality evaluation by consensus, subgroup analysis was performed according to the methodological quality of the studies ('high quality study' if allocation concealment was adequate).

DESCRIPTION OF STUDIES

A total of 16 studies were considered for this review. Three were excluded because they compared one opioid to another (Barker 1995; Saarenmaa 1999; Wood 1998). The 13 included studies were described in 16 separate reports. Preliminary data for Anand 2004 were reported in NEOPAIN 2002 and Boyle 2003. Late outcomes in the Quinn 1992 and Quinn 1993 studies were provided in the follow up report of MacGregor 1998. For the purpose of this systematic review, all randomised infants in that report are referred to as Quinn 1992 and Quinn 1993. Details of the included studies are provided in the Table "Characteristics of Included Studies".

There were differences in methods, participants, and interventions among the 13 included studies. Three studies included both term and preterm infants (Pokela 1994; Saarenmaa 1996; Simons 2003). All other studies included only preterm infants, with three studies including only very preterm infants (less than 32 weeks gestation) (Anand 1999; Anand 2004; Guinsburg 1998).

Several different analgesia and sedation scores were used in the included studies, and some studies used modified scores. Each score is described in the individual study description.

A variety of opiates were used as interventions. One study used meperidine (Pokela 1994), another alfentanil (Saarenmaa 1996), four studies used fentanyl (Guinsburg 1998; Lago 1998; Lago 1999; Orsini 1996) and seven studies used morphine (Anand 1999; Anand 2004; Dyke 1995; Quinn 1992; Quinn 1993; Simons 2003; Siwiec 1999). Additional neuromuscular blockers were allowed, or used, in five studies (Anand 1999; Anand 2004; Dyke 1995; Quinn 1992; Quinn 1993) and an additional open-label opioid was permitted in four studies (Anand 1999; Anand 2004; Quinn 1992; Simons 2003). Seven studies used a loading dose of opioid followed by continuous infusion (Anand 1999; Anand 2004; Dyke 1995; Orsini 1996; Quinn 1993; Simons 2003; Siwiec 1999). Three studies used only continuous infusion (Lago 1998; Lago 1999; Quinn 1992) and three studies used only one dose of opioid (Guinsburg 1998; Pokela 1994; Saarenmaa 1996). The loading dose (first dose) of morphine in the different studies was 100 $\mu\text{g}/\text{kg}$ (Anand 1999; Anand 2004; Dyke 1995; Simons 2003; Siwiec 1999) or 200 $\mu\text{g}/\text{kg}$ (Quinn 1993). Continuous infusion of morphine was started after the loading dose at a dose of 10 $\mu\text{g}/\text{kg}/\text{h}$ (Dyke 1995; Simons 2003), 20 $\mu\text{g}/\text{kg}/\text{h}$ (Siwiec 1999), 25 $\mu\text{g}/\text{kg}/\text{h}$ (Quinn 1993), 10-30 $\mu\text{g}/\text{kg}/\text{h}$, depending on gestational age (Anand 1999; Anand 2004), up to 50-100 $\mu\text{g}/\text{kg}/\text{h}$ (Quinn 1992).

The loading dose of fentanyl varied between 3 $\mu\text{g}/\text{kg}$ (Guinsburg 1998) and 5 $\mu\text{g}/\text{kg}$ (Orsini 1996) with a following continuous infusion of fentanyl of 2 $\mu\text{g}/\text{kg}/\text{h}$ or less (Lago 1999; Orsini 1996). Lago 1998 used a continuous dose of fentanyl that was adjusted to render the baby sedated but arousable.

Quinn 1992

Quinn studied 95 premature newborns, with a gestational age of 34 weeks or less, who had hyaline membrane disease and were struggling against the ventilator. Newborns were excluded if prior maternal or neonatal treatment with narcotic analgesics or neuromuscular blocking agents had taken place. The eligible newborns were randomised to one of three treatment groups: morphine (group M, n = 29), pancuronium (group P, n = 28) or morphine with pancuronium (group M+P, n = 38). The dose of morphine was 50 µg/kg/h, but was increased to 100 µg/kg/h in group M infants if they continued to struggle. The dosage of pancuronium was 100 µg/kg given as required to inhibit spontaneous respiration. Babies in the M group were allowed to receive pancuronium if still fighting the ventilator (7/29), and babies in the P group were given morphine for painful procedures (4/28). Drug therapy continued until fractional inspired oxygen concentration fell below 0.45. Plasma catecholamine levels were measured on entry and at 24 hours. Clinical outcome measures were intraventricular haemorrhage, air leak (defined as pneumothorax or pulmonary interstitial emphysema), patent ductus arteriosus, duration of mechanical ventilation and mortality. These clinical outcomes were reported in 85/95 infants. Blood pressure, heart rate and ventilator settings were reported on entry and at six hours in 69 of the 95 infants. Two of the three groups in this trial (M+P and P) were eligible for inclusion in this review. The clinical outcomes are reported on 28 infants in the P group and 28 infants in the M+P group.

Quinn 1993

The second study by Quinn investigated the use of morphine to provide analgesia and sedation for ventilated preterm babies in a randomised, double-blind, placebo-controlled trial. Forty-one mechanically ventilated babies, with a gestational age of 34 weeks or less, who had been treated with surfactant for hyaline membrane disease were randomly assigned to morphine in 5% dextrose (100 µg/kg/h for two hours followed by 25 µg/kg/h continuous infusion) or placebo (5% dextrose). Newborns were excluded if no arterial line was *in situ* or if the attending physician felt the baby was experiencing pain. Muscle relaxants were allowed before or during the study period (2/21 in morphine group, 5/20 in placebo group). Plasma catecholamine concentrations were measured one hour after the first dose of surfactant and 24 hours later. Blood pressure, heart rate, peak inspiratory pressure and oxygen concentration were measured at study entry and after six hours and reported in 38/41 randomised neonates. Pain scores were assigned to 36 babies. This score, a four-item behavioural measurement of distress in the paediatric postoperative setting (Sury 1990), includes assessment of the level of consciousness, crying, posture and facial expression with scores ranging from 4 (adequate analgesia) to 20 (inadequate analgesia). The incidence of intraventricular and periventricular haemorrhage, patent ductus arteriosus, and pneumothorax, the number of ventilator days and the numbers of deaths were reported in all randomised newborns.

MacGregor 1998

MacGregor assessed the outcome at five to six years in preterm infants recruited in the neonatal period to two sequential controlled studies by Quinn (Quinn 1992; Quinn 1993). A total of 136 babies were recruited, of which 95 survived. Blinded assessments were made on 87 children at 5-6 years and blood samples for thyroid stimulating hormone measurement were obtained from children whose parents gave consent. Each child was seen by a single paediatrician and assessed using the WPPSI-R, Movement ABC, and the Child Behaviour Checklist. Primary outcomes (death and/or disability) were given for infants exposed to morphine (n = 62) and compared with outcomes of those in the non-morphine group (n = 33). The article did not state in which specific study the children had participated.

Pokela 1994

Pokela determined whether the use of an opioid (meperidine) could reduce the hypoxaemia and haemodynamic instability associated with routine intensive care procedures in term and preterm neonates with respiratory distress. Eligible newborns had to be less than one week of age and to have suffered a documented period of hypoxaemia (transcutaneous partial pressure of O₂ less than 6.6 kPa and/or arterial blood oxygen saturation less than 80%) during previous nursing care, and needed analgesia or sedation. Eighty-four mechanically ventilated distressed neonates were randomised into groups receiving 1 mg/kg meperidine or 0.9% saline 15 minutes before tracheal suction or routine nursing care. The primary outcome was the duration of hypoxaemia during treatment procedures. Heart rate, blood pressure, tcPO₂ and SaO₂ were measured from 10 minutes before until two hours after the procedure. Pain during the two hour study period was scored by a blinded researcher and reported for all infants. This novel score, a four-item behavioural measurement of distress, included assessment of facial expression, movements, response to handling and rigidity of the limbs and body with scores ranging from 0 (adequate analgesia) to 12 (inadequate analgesia). Plasma beta-endorphin, cortisol, and glucose were measured before and at one and two hours after the procedure. There was no loss to follow up.

Dyke 1995

Dyke examined the short-term cardiorespiratory effects of intravenous morphine infusion in ventilated preterm infants. Twenty-six preterm infants (29-36 weeks gestation) with hyaline membrane disease requiring ventilatory assistance on the first day after birth were randomised to morphine (100 µg/kg over 30 minutes followed by 10 µg/kg/h) or placebo (5% dextrose) for a maximum of 48 hours. Neuromuscular blockade was allowed if infants could not be stabilized (2/12 morphine, 3/14 placebo). Primary outcomes were heart rate, blood pressure, respiratory rate and interaction of spontaneous respiration with mechanical ventilation as scored according to Greenough (Greenough 1988). In this score respiratory effort is categorized by clinical observation into three groups; synchronous, asynchronous and active expiration. The two adverse respiratory patterns (asynchronous and active expiration) were categorized as one. Secondary outcomes were durations

of oxygen therapy, ventilator therapy and hospitalisation as well as incidence of bronchopulmonary dysplasia, periventricular haemorrhage and pneumothorax. There was no loss to follow up.

Saarenmaa 1996

Saarenmaa assessed the suitability of alfentanil for pain relief during tracheal suction, which is used in assisted ventilation in newborn infants. In a randomised, controlled, double blind, crossover trial, infants with a gestational age of 24 weeks or more that were mechanically ventilated were allocated to two different doses of alfentanil (10 µg/kg and 20 µg/kg) or placebo (saline) in random order two minutes before three separate endotracheal suctions, at least six hours apart. A behavioural pain score was performed before, during and after suction by a blinded researcher. This score, a five-item behavioural and physiological measurement of distress, included assessment of facial expression, crying, movements, rigidity of the limbs and body and breathing patterns with scores ranging from 0 (adequate analgesia) to eight (inadequate analgesia). This pain scale is developed from the Children's Hospital of Eastern Ontario Pain scale (McGrath 1985) and Neonatal Infant Pain Scale (Lawrence 1993). Heart rate, arterial blood pressure and oxygen saturation were measured before and after suction. Plasma adrenaline, nor-adrenalin and beta-endorphin were measured before and 30 minutes after the procedure. Reports were given for all 10 randomised newborns in a figure only. Crossover occurred after a period longer than the duration of action of the given drug, so data will be handled as if this were a single intervention study.

Orsini 1996

Orsini randomised 20 premature infants, gestational age 26 to 36 weeks, undergoing mechanical ventilation for respiratory distress syndrome to receive fentanyl at 5 µg/kg in 20 minutes followed by 2 µg/kg/h for 72 hours, or 1 µg/kg/h for 24 hours followed by 0.5 µg/kg/h for 24 hours, or a volume-matched placebo infusion (5% dextrose). The primary outcome was assessed using physiologic indexes of pain and stress. Heart rate, blood pressure, ventilatory settings and a behavioural state score were assessed by a blinded nurse every two hours for the duration of the study period. The behavioural score included assessment of sleep state, eye movements, breathing patterns and movement of extremities with scores ranging from zero to four. A lower score indicated a more sedated infant (Brueck 1962). Cortisol and 11-deoxycortisol levels were measured at baseline and then daily. Urinary 3-methyl histidine/creatinine molar ratio was collected on the fourth day and the fractional excretion of urea was measured to assess catabolic state. Long term outcomes included the incidence of intraventricular haemorrhage, patent ductus arteriosus, bronchopulmonary dysplasia and sepsis. Outcomes were presented for all infants. Data on pain, incidence of chronic lung disease (CLD) and IVH were obtained by personal communication with the author.

Guinsburg 1998

Guinsburg studied the responses of 22 ventilated preterm neonates, gestational age 32 weeks or less, to a single dose of fen-

tanyl in a randomised, double-blind, controlled trial. The babies were observed before medication and at 30 and 60 minutes after administration of fentanyl (3 µg/kg) or placebo (saline). Heart rate, blood pressure, arterial blood gases, ventilator settings, and behavioural measures were recorded during each period. Blood cortisol, growth hormone, glucose, and lactate were measured before and at 60 minutes after analgesia. A modified postoperative COMFORT score was used (Attia 1987) in assessments; this is an eight-item behavioural score that includes assessment of sleep status, facial expression, sucking, hyperreactivity, agitation, hyper-tonicity, flexion of toes and fingers and consolability with scores ranging from 0 (adequate analgesia) to 20 (inadequate analgesia). A modified Neonatal Facial Coding System was also used (Grunau 1987); this included eight items with overall scores ranging from 0 (adequate analgesia) to 8 (inadequate analgesia). Behavioural measures were assessed at the bedside (22/22) and from video films recorded during each observation period (17/22).

Lago 1998

Lago evaluated the effects of low dose fentanyl infusion analgesia on behavioural and neuroendocrine stress responses and short term outcomes in premature infants ventilated for hyaline membrane disease. Fifty-three ventilated preterm infants, gestational age between 24 and 34 weeks, were randomly assigned to receive a continuous infusion of fentanyl (0.5-2.0 µg/kg/h) or nothing. The fentanyl dose was adjusted to render the neonate sedated but arousable according to a behavioural sedation score assigned every two hours. The behavioural score used was a six-item measurement of distress in the paediatric intensive care setting (Hartwig 1991) and included assessment of the behavioural state, muscular tone, motor response, facial expression, breathing pattern and reaction to aspiration with scores ranging from 0 (deep sedation) to 18 (inadequate sedation). Secondary outcome measures included durations of oxygen treatment, ventilator therapy and hospitalisation as well as incidence of bronchopulmonary dysplasia (supplemental oxygen at 28 days), air leak (pulmonary emphysema and pneumothorax), intraventricular haemorrhage, periventricular leucomalacia, days to reach full enteral feeding and growth. Two patients died (one from each group) and were excluded from the statistical analysis.

Anand 1999

This was a pilot trial investigating the incidence of clinical outcomes in a study population using analgesia and sedation. Neonates from nine centres (24 to 32 weeks gestation) were eligible if they had been intubated and had required ventilatory support for less than eight hours, and were enrolled within 72 hours after birth. Sixty-seven neonates were randomised to receive continuous infusions of morphine sulphate, midazolam hydrochloride, or placebo (10% dextrose) for as long as sedation was considered necessary up to a maximum of 14 days. Midazolam was administered at 200 µg/kg loading dose followed by an infusion of 20, 40, or 60 µg/kg/hr for infants of gestational ages 24-26, 27-29, or 30-33 weeks, respectively. Morphine was administered

at 100 µg/kg loading dose followed by an infusion of 10, 20 or 30 µg/kg/hr for infants of gestational ages 24-26, 27-29, or 30-33 weeks, respectively. Additional sedation, if necessary, was provided by boluses of morphine, and the frequency and amount given were documented as a measure of inadequate sedation. The primary outcome was the incidence of adverse neurological events (defined as neonatal death, grade III or IV intraventricular haemorrhage, or periventricular leucomalacia). Adequacy of sedation was measured by the COMFORT score, an eight-item behavioural and physiologic measurement of distress in the paediatric intensive care unit (Marx 1994). The score includes assessment of alertness, calmness/agitation, respiratory response, physical movement, mean arterial blood pressure, heart rate, muscle tone, and facial tension, with scores ranging from eight (sedated) to 40 (not adequately sedated). Adequacy of analgesia was measured by the Premature Infant Pain Profile (PIPP) (Stevens 1996) in response to tracheal suctioning. This includes assessment of gestational age, behavioural state, heart rate, oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow, with scores ranging from 0 (adequate analgesia) to 21 (inadequate analgesia). COMFORT scores and PIPP scores were measured before, during and 12 hours after discontinuation of infusion. Other secondary outcomes included number of days of mechanical ventilation, continuous positive airway pressure, supplemental oxygen use, incidence of pneumothorax, duration of stay in neonatal intensive care unit (NICU) and hospital stay, days to full enteral feeds, daily weight gain, and neurodevelopmental outcome at 36 weeks corrected age using the Neurobehavioral Assessment of the Premature Infant examination cluster scores (Korner 1991). Outcomes were reported on all 67 infants.

Lago 1999

This study was available only as an abstract. Lago assessed the respiratory dynamics in preterm infants ventilated for respiratory distress syndrome under continuous infusion of fentanyl. Thirty-one preterm infants (gestational age 28 to 36 weeks) were randomised in a double blinded fashion to fentanyl, 1.5 µg/kg/h, scaled down by 0.5 µg/kg/h every 24 hours, or placebo (5% dextrose). The primary outcomes were ventilation parameters recorded at baseline and every 24 hours during the 72 hour study period. An unknown sedation score was obtained every four hours. Data, methods and details were obtained by personal communication with the author.

Siwiec 1999

Siwiec studied the effect of morphine on sedation scores in ventilated neonates who were ill. Twenty ventilated premature neonates (gestational age 26 to 35 weeks) were randomised to morphine, 100 µg/kg over 30 minutes followed by 20 µg/kg/h, or no treatment. All infants were assessed for pain profile at baseline and at 6, 12 and 24 hours using the PIPP and COMFORT scores (Marx 1994; Stevens 1996) as described in the Anand study (Anand 1999). Secondary outcome measures were heart rate, blood pressure and ventilatory parameters. Baseline differences were not presented in this abstract. Data were reported on all infants. Data on

pain scores were obtained by personal communication with the author.

Simons 2003

Simons evaluated the effects of continuous intravenous morphine infusion on pain responses, the incidence of intraventricular haemorrhage (IVH), and poor neurological outcome (severe IVH, periventricular leucomalacia, or death). One hundred and fifty ventilated newborns, with a postnatal age of less than three days and ventilation for less than eight hours, were randomised in a double blinded fashion to morphine (100 µg/kg followed by 10 µg/kg/h) or placebo (5% dextrose) for a maximum period of seven days. Newborns with severe asphyxia, severe IVH at start of the study, major congenital malformations and administration of neuromuscular blockers were excluded. Additional morphine (50 µg/kg followed by 5-10 µg/kg/h) was allowed upon the decision of the attending physician. The analgesic effect was measured at baseline, before and 30 minutes after the loading dose and twice a day at a standardised time point before, during and after endotracheal suctioning. At each time point the infants were videotaped and simultaneously the care giving nurse applied the visual analogue scale (VAS). The videotapes were analysed by two blinded researchers using the Neonatal Infant Pain Scale (NIPS) (Lawrence 1993) and the VAS during all moments and the PIPP (Stevens 1996) during suctioning. The NIPS is a six-item behavioural and physiologic measurement of distress and includes assessment of facial expression, crying, breathing patterns, movement of extremities and state of arousal with scores ranging from 0 (adequate analgesia) to 7 (inadequate analgesia). The VAS score is a visual score and ranges from 0 to 10 on a horizontal continuous line with 'no pain' on the left and 'extreme pain' on the right. (The PIPP score is described in the Anand 1999 study.) Secondary outcome measures were poor neurologic outcome (defined as neonatal death, grade III or IV intraventricular haemorrhage, or periventricular leucomalacia) and incidence of all grades of IVH. Clinical outcomes such as duration of ventilation, length of NICU stay and incidence of co-morbidity were noted. There was no loss to follow up.

Anand 2004

The NEOPAIN Multicenter Group conducted the largest study included in this systematic review. They investigated whether preemptive morphine analgesia protects against severe neurologic injury and/or neonatal death in ventilated preterm neonates. A total of 898 preterm neonates (gestational age 23 to 32 weeks) from 16 NICUs were randomised to receive morphine or placebo. Morphine was administered at 100 µg/kg loading dose followed by an infusion of 10, 20 or 30 µg/kg/h for infants of gestational ages 23-26, 27-29, or 30-32 weeks, respectively. Open label morphine was allowed according to predefined criteria. Central assessment of cranial ultrasonography was done at four to seven days of age and at 14-35 days. Responses to tracheal suctioning were assessed by means of the Premature Infant Pain Profile (PIPP), as described in the Anand 1999 study (Stevens 1996). The primary

outcome was the incidence of adverse neurological events (defined as neonatal death, grade III or IV intraventricular haemorrhage, or periventricular leucomalacia). Secondary outcomes were response to pain, duration of ventilation and oxygen provision, incidence of hypotension during infusion of the study drug, days till full enteral feeding, and need for intravenous nutrition. Seventy-three of the surviving infants at 28 days did not have a complete set of data. Data on PIPP scores, duration of ventilation, and days to reach full enteral feeding were obtained by personal communication with the author.

METHODOLOGICAL QUALITY

The overall quality of the studies was fair to good. Details of methodological quality of each study are described in the Characteristics of Included Studies Table.

Randomisation

Randomisation and allocation concealment were judged to be adequate in seven studies (Anand 1999; Anand 2004; Dyke 1995; Orsini 1996; Pokela 1994; Quinn 1993; Simons 2003; these were termed 'high quality studies').

Four studies (Guinsburg 1998; Lago 1998; Quinn 1992; Saarenmaa 1996); stated that randomisation was performed and the allocated treatment was obtained by drawing sealed envelopes. No details were given about how the randomisation list was generated, or allocation concealment ensured. Siwiec 1999 and Lago 1999 are abstract papers and do not give details on randomisation and allocation concealment.

Blinding for intervention

Blinding of carers to intervention was stated for all studies except Siwiec 1999 and Lago 1999. A note of caution is deserved as in most studies the carers could be more aware of the effects of pain control than stated.

Blinding for outcome measurements

Blinding of assessors to intervention was stated for all studies but Siwiec 1999 and Lago 1999. In the Siwiec study blinding was not obtained (personal communication).

Completeness of follow up

Follow up was almost complete for all studies. In the large NEOPAIN study (Anand 2004) 30/391 of the surviving infants at 28 days in the morphine group and 43/402 in the placebo group did not undergo cranial ultrasonography at four to seven or 28 to 35 days. In the report (MacGregor 1998) with long-term follow up 8.4% of the surviving patients were lost at five to six years.

RESULTS

01 OPIOID VERSUS PLACEBO OR NO TREATMENT

01.01 Pain - Premature Infant Pain Profile (PIPP)

Of the five studies that used validated multidimensional behavioural pain measures, three studies (Anand 1999; Anand 2004; Siwiec 1999) found significant results in favour of the opioid (morphine). This significant difference was not present at every time point. The Anand 2004 study found a significant difference in the Premature Infant Pain Profile (PIPP) at 24 hours after starting the study-drug, but not at 72 hours. Simons (Simons 2003) used two validated pain scores, PIPP and the Neonatal Infant Pain Score (NIPS), but found no significant difference in pain score at any time point measured.

Four studies used PIPP to evaluate pain (Anand 1999; Anand 2004; Simons 2003; Siwiec 1999). Meta-analysis showed that PIPP scores were reduced in infants who were given the opioid compared to the control group, (weighted mean difference (random effects model) -1.71; 95% confidence interval -3.18 to -0.24). When PIPP scores were pooled across these studies, considerable and significant heterogeneity was found. When only high quality studies were considered (Anand 1999; Anand 2004; Simons 2003) heterogeneity persisted, but the pain score reduction in favour of the opioid group was no longer significant (weighted mean difference (random effects model) -1.51; 95% confidence interval -3.17 to 0.14). In the meta-analysis of the results of the two studies which considered only very preterm infants (Anand 1999; Anand 2004) no significant effect was found (weighted mean difference (random effects model) -2.68; 95% confidence interval -6.62 to 1.27).

01.02 Pain - Neonatal Facial Coding System (NFCS)

One study used the Neonatal Facial Coding System (NFCS). Pain scores (NFCS and modified COMFORT) in the study by Guinsburg (Guinsburg 1998) were significantly lower only when assessed by video, not when assessed at bedside. There was no significant difference between bedside NFCS scores for the opioid group and the control (weighted mean difference 0.19; 95% confidence interval -1.15 to 1.53).

1.03 Pain - Neonatal Infant Pain Scale (NIPS)

One study (Simons 2003) reported using this scale (as well as PIPP) and found no significant effect (mean difference 0.19; 95% confidence interval -0.72 to 0.34).

01.04 Pain - other scales

Nine different non-validated pain scores were used in 10 studies. Three studies found a significant difference in pain scores in favour of the opioid group (Lago 1998; Orsini 1996; Pokela 1994) and one study found a significant difference in pain scores at the highest dose used in favour of the opioid group (Saarenmaa 1996). In the abstract by Lago (Lago 1999) it was stated that the fentanyl group showed better sedation scores than the placebo group, but no data were presented. Quinn (Quinn 1993) presented the data on pain scores of 36 infants as a median with range. There were

no significant differences at 24 hours between the two groups, (median (inter-quartile range) 5 (4 to 11) in the morphine group versus 5 (4 to 11) in the placebo group). Saarenmaa (Saarenmaa 1996) presented the data as change in pain scores in a figure only. A significant lowering of the pain score was found with 20 µg/kg alfentanil, but not with 10 µg/kg alfentanil, when compared with placebo. Guinsburg's (Guinsburg 1998) bedside assessment of the modified COMFORT scale showed no significant differences between the fentanyl and placebo groups. Careful analysis of video recordings did show a significant difference in pain score in favour of the fentanyl group, (mean standard deviation 12.55 (2.98) in the fentanyl group versus 14.27 (3.74) in the placebo group). Orsini (Orsini 1996) found a significantly lower pain score in the fentanyl group after 16, 24 and 48 hours of study drug infusion, but not at eight hours or three, four and five days of treatment. Lago (Lago 1998) found a significant difference in the sedation scores between the fentanyl and the no treatment group at 24, 48 and 72 hours using a fentanyl dose regime that kept the infant sedated but arousable (according to the behavioural sedation score assigned every two hours). The COMFORT scales used in the studies by Anand and Siwiec (Anand 1999; Siwiec 1999) and the VAS scale used by Simons (Simons 2003) were not significantly altered by treatment with morphine when compared to placebo or to no treatment. Data from Pokela's study (Pokela 1994) could not be entered in the analysis because standard deviations were missing.

The meta-analysis should be interpreted with caution because of inconsistencies in the opioids and doses of opioids used, outcome measures recorded, and differences in the statistical reporting of results. When all the different scores were combined, a significant effect was found in favour of the treatment group (standardised mean difference (random effects model) -0.89; 95% confidence interval -1.46 to -0.31, i.e. a pooled difference of 0.89 units of standard deviation was found). When only high quality studies were considered, a standardised pain score reduction of -0.75 in favour of opioids was found (standardised mean difference (random effects model) -0.73, 95% confidence interval -1.40 to -0.06); though significant heterogeneity persisted. In the meta-analysis of the results of the two studies which considered only very preterm infants (Anand 1999; Guinsburg 1998) a significant effect in favour of opioids was found (standardised mean difference (random effects model) -0.66; 95% confidence interval -1.15 to -0.16)

01.05 Duration of ventilation (days)

Ten studies reported on this outcome. Only one study (Anand 2004) found a significant difference in time spent on the ventilator between the opioid group and the control. The data on this outcome were presented in a figure with a p value, ($p = 0.0338$). The data used for meta-analysis were obtained by personal communication. Results on duration of ventilation could not be combined by meta-analysis for the studies of Quinn and Dyke (Quinn 1992; Quinn 1993; Dyke 1995), because they presented this out-

come as a median and range. Orsini 1996 described in his article that no significant differences were found in duration of ventilator use between the two groups, but no actual data were available for analysis. Meta-analysis of the results of the remaining six studies showed no significant effect (weighted mean difference 1.24 days; 95% confidence interval -0.29 to 2.77). With the meta-analysis there was minor evidence of heterogeneity. When only high quality studies were considered (Anand 1999; Anand 2004; Dyke 1995; Quinn 1993; Simons 2003) pooled results were possible for three studies. No significant effect was found (weighted mean difference 1.49 days; 95% confidence interval -0.29 to 3.27); heterogeneity increased. Meta-analysis of the results of the two studies that considered only very preterm infants (Anand 1999; Anand 2004) did not show any statistically significant effect (weighted mean difference 1.95 days; 95% confidence interval -0.50 to 4.39).

01.06 Neonatal mortality

Seven studies reported effect on mortality. None of these studies found any significant difference in mortality between the opioid group and placebo, or no treatment, group. The meta-analysis of the five trials that reported on neonatal mortality (Anand 1999; Anand 2004; Lago 1998; Quinn 1993; Simons 2003) showed no significant effect: relative risk of mortality was 1.12 (relative risk 1.12; 95% confidence interval 0.80 to 1.55). When only very preterm infants were analysed (Anand 1999; Anand 2004), the meta-analysis showed a relative risk of 1.18 (relative risk 1.18; 95% confidence interval 0.82 to 1.68).

01.07 Mortality to discharge

The meta-analysis of the four trials which reported on mortality to discharge (Dyke 1995; Lago 1998; Quinn 1992; Quinn 1993) showed no significant effect: relative risk of mortality was 0.99 (RR 0.99, 95% confidence interval 0.52 to 1.88).

01.08 Neurodevelopmental outcome (short term)

Anand (Anand 1999) assessed the neurodevelopmental outcome at 36 weeks corrected age using the Neurobehavioral Assessment of the Premature Infant (NAPI) examination cluster scores. Outcomes were reported on all infants. No significant differences occurred in NAPI scores after adjusting for differences in Neonatal Medical Index and gestational age between the morphine and placebo group, (Mean (standard deviation) NAPI score 58.8 (20.0) in the morphine group versus 55.7 (22.4) in the placebo group).

01.09 Neurodevelopmental outcome (long term)

McGregor assessed neurodevelopment at between five to six years in a cohort of preterm infants that had been recruited in the neonatal period to two sequential controlled studies by Quinn (Quinn 1992; Quinn 1993). A total of 95 of the 136 recruited infants survived, and 87 of these survivors were assessed using the WPPSI-R, Movement ABC, and the Child Behaviour Checklist. There was no significant difference at five to six years of age between the morphine and non-morphine groups for disability (relative risk

1.46; 95% confidence interval 0.51 to 4.24). There was no significant difference in combined death and disability rates between the morphine and non-morphine groups for the 136 children in the original cohorts. No significant effect was found for intelligence (point estimate 2.0; 95% confidence interval -6.0 to 11.0), motor impairment (point estimate -2.0; 95% confidence interval -5.5 to 2.0), or behavioural problems between the two groups (point estimate -3.0; 95% confidence interval -12 to 3). Calculations that assumed that outcomes on the missing newborns favoured the morphine or non morphine groups did not alter the conclusion of no significant effect on death or disability.

01.10 Incidence of bronchopulmonary dysplasia (BPD; oxygen need at 28 days of life)

The incidence of BPD or chronic lung disease (CLD) was reported in seven studies, and no significant differences in incidence of either were reported. Four studies reported on the incidence of BPD, defined as requiring oxygen at 28 days; no significant effect was found (relative risk 1.19; 95% confidence interval 0.73 to 1.92). In the meta-analysis of high quality studies (Dyke 1995; Simons 2003) no significant effect was found (relative risk 0.55; 95% confidence interval 0.55 to 1.68).

01.11 Incidence of chronic lung disease (CLD; oxygen need at 36 weeks postconceptional age)

Three studies reported on the incidence of CLD, defined as oxygen at 36 weeks postconceptional age; no significant effect was found (relative risk 0.95; 95% confidence interval 0.73 to 1.22). When analysis was restricted to high quality studies (Anand 2004; Orsini 1996) very similar results were achieved. Only one study (Anand 2004) reported on very preterm infants; no significant effect was found (relative risk 1.01; 95% confidence interval 0.78 to 1.32).

01.12 Days to reach full enteral feeding

Four studies reported on this outcome. Lago's studies (Lago 1998; Lago 1999) and Anand's first study (Anand 1999) found no significant difference in mean number of days required to achieve full enteral feeding between the opioid group and the placebo or no treatment groups. Neonates in the morphine group of the NEOPAIN study (Anand 2004) took longer than neonates of the placebo group to tolerate full volume nasogastric feeds. The data for this significant difference were presented in a figure with a p-value only, ($p = 0.0446$). Data obtained by personal communication were used. Meta-analysis showed a borderline significant effect (weighted mean difference 1.43 days; 95% confidence interval -0.01 to 2.87, $p = .05$). In the meta-analysis of two high quality studies, dealing with very preterm infants (Anand 1999; Anand 2004), a significant effect was found (weighted mean difference 2.10 days; 95% confidence interval 0.35 to 3.85). In Anand 2004, there was no significant difference in mean number of days required to achieve full volume bottle feedings between the two groups, ($p = 0.6987$).

01.13 Weight gain at term

One study (Anand 1999) reported no significant effect on weight gain at 36 to 40 weeks postconceptional age, but the data were not available for analysis.

Two studies reported on other parameters of weight gain (Anand 1999; Lago 1998). Lago could find no significant differences between the fentanyl group and the no treatment group in the mean number of days needed for growth to birthweight (Mean (standard deviation) 12 (7) days in the fentanyl group versus 15 (5) days in the no treatment group). In Anand's study (Anand 1999) the daily weight gain was adjusted for birthweight in an analysis of covariance model. The only significant difference in daily weight gain between the morphine group and the placebo group was noted 28 days after birth (Mean (standard deviation) daily weight gain normalized by birthweight 1.26 (0.152) gram/kg/day in the morphine group versus 1.15 (0.146) in the placebo group, $p = 0.04$), but not at hospital discharge (Mean (standard deviation) daily weight gain normalized by birthweight 1.78 (0.716) gram/kg/day in the morphine group versus 1.96 (0.837) in the placebo group).

01.14 Length of stay in hospital (days)

Four studies reported on length of stay (Anand 1999; Dyke 1995; Lago 1998; Lago 1999) but the results from Dyke could not be combined in the meta-analysis because he presented this outcome as median and range. No study found a significant difference between the opioid group and the control group in hospital stay. In the meta-analysis of three trials, no significant effect was found (weighted mean difference 1.80 days, 95% confidence interval -7.03 to 10.62).

01.15 Incidence of necrotising enterocolitis (NEC)

Two studies reported on this outcome (Lago 1998; Simons 2003). Both studies show no significant difference in the incidence of NEC in the opioid group compared with control. The meta-analysis of the two trials shows no significant effect (relative risk 0.93; 95% confidence interval 0.36 to 2.37).

01.16 Incidence of any intraventricular haemorrhage (IVH)

Six studies reported on incidence of all grades of IVH (Anand 1999; Dyke 1995; Orsini 1996; Quinn 1992; Quinn 1993; Simons 2003). Only Simons (Simons 2003) found a significant reduction in incidence of any IVH in favour of the morphine group, (relative risk 0.58; 95% confidence interval 0.35 to 0.95, number needed to treat 5.9; 95% confidence interval 3.2 to 43.5). The meta-analysis shows no significant effect (relative risk 0.84; 95% confidence interval 0.60 to 1.17). When only high quality studies were considered (Anand 1999; Dyke 1995; Orsini 1996; Quinn 1993; Simons 2003), the relative risk was 0.67, (relative risk 0.67; 95% confidence interval 0.45 to 1.00). The results of the only study that considered very preterm infants only (Anand 1999) showed no significant effect (relative risk 0.66; 95% confidence interval 0.17 to 2.60). With pooling across all studies, considerable heterogeneity was found. When only the high quality studies

were considered (Anand 1999; Dyke 1995; Orsini 1996; Quinn 1993; Simons 2003), heterogeneity was no longer statistically significant.

01.17 Incidence of severe intraventricular haemorrhage (IVH) Papile grade 3/4

None of the five trials that reported on incidence of severe IVH found any significant differences (Anand 1999; Anand 2004; Lago 1998; Simons 2003; Siwiec 1999). The meta-analysis showed no significant effect (relative risk 0.98; 95% confidence interval 0.70 to 1.38). Meta-analysis of only high quality studies (Anand 1999; Anand 2004; Simons 2003) showed no significant effect (relative risk 1.04; 95% confidence interval 0.73 to 1.46). When studies with very preterm infants only were analysed (Anand 1999; Anand 2004) no significant effect was found (relative risk 1.12; 95% confidence interval 0.78 to 1.60). The meta-analysis showed only minor heterogeneity. Anand (Anand 2004) did a post hoc analysis with participants divided into a morphine group and a placebo group without receiving additional morphine. He found a significantly increased risk of developing a severe IVH in the morphine group compared to placebo. If the meta-analyses were repeated with data from this post hoc analysis, the results did not change and no significance was reached (data not shown).

01.18 Incidence of periventricular leucomalacia (PVL)

None of the five studies reporting on the incidence of PVL could find a significant difference between the opioid group and control. The meta-analyses of all studies (Anand 1999; Anand 2004; Lago 1998; Simons 2003; Siwiec 1999), high quality studies (Anand 1999; Anand 2004; Simons 2003), and studies including very preterm babies only (Anand 1999; Anand 2004), showed no significant effect (relative risk 0.79; 95% confidence interval 0.51 to 1.22; relative risk 0.81; 95% confidence interval 0.51 to 1.29; relative risk 0.80; 95% confidence interval 0.49 to 1.29, respectively). None of the meta-analyses showed any heterogeneity. When entering the data for the post hoc analysis of the groups without receiving additional morphine of the NEOPAIN study (Anand 2004), the relative risks for all studies was 1.06 (relative risk 1.06; 95% confidence interval 0.56 to 2.01). The effects for high quality studies and studies including very preterm babies were not significant either (data not shown).

02. OPIOID VERSUS SEDATIVE

02.01 - 02.11 All outcomes

Only one study was found comparing an opioid (morphine) to a sedative (midazolam) in ventilated newborns (Anand 1999).

In selected pain scores (02.01), Anand reported a significant reduction in PIPP score during tracheal suctioning in the morphine and in the midazolam group (Mean (standard deviation) PIPP score decreased from 11.5 (4.0) to 7.9 (2.3) in the morphine group versus 10.5 (4.1) to 8.9 (3.3) in the midazolam group). Decrease in

PIPP score was not significantly different between the two groups. Decrease in mean COMFORT score (outcome 02.02) was also not significantly different between the two groups.

Duration of mechanical ventilation (outcome 02.03) was lower in the morphine group (mean difference -6.70 days; 95% confidence interval -12.40 to -1.00). No deaths occurred in the morphine group, but one neonate died in the midazolam group. No statistically significant difference was noted between the morphine group and the midazolam group in mortality to discharge (outcome 02.04); neurodevelopmental outcome at 36 weeks corrected age (NAPI scores, outcome 02.05); days to reach full enteral feeding (outcome 02.06); or length of hospital stay (outcome 02.08). Weight gain at 36 to 40 weeks adjusted age was reported as not significant, but data were not available. Weight gain at discharge was not significantly different (outcome 02.07). The incidence of any IVH (outcome 02.09) was significantly lower in the morphine group (relative risk 0.28; 95% confidence interval 0.09 to 0.87); severe IVH (02.10) and PVL (02.11) were not significantly different between the two groups.

DISCUSSION

The review found a number of fair to good quality studies, and even the oldest studies were well designed and conducted. In the last three years a number of large studies have been published, with a high total of patients randomised. Most outcomes were measured appropriately and were comparable across studies.

One major problem regarding the primary outcomes of this review is the differences in measuring pain across studies. Pain was assessed with well validated, and less well validated, scales. When subgroup analysis was performed to account for this issue it yielded different results, indicating problems in measuring the real outcome.

For validated pain scales, e.g. PIPP score, the weighted mean difference of 1.71 points is statistically significant in favour of the opioid group, but this difference is not considered clinically significant (Ballantyne 1999). Marked statistical heterogeneity was found in this analysis. Heterogeneity can be caused by the small group examined in the Anand 1999 study, or by the method of measuring PIPP score. Only the abstract by Siwiec (Siwiec 1999) evaluated PIPP score without any stimulus and found a PIPP score below six in the morphine group, which is considered minimal pain (Ballantyne 1999). The other studies measured PIPP during suctioning and did not find any reduction of the PIPP score below 7.9 points (i.e. incomplete control of pain).

Heterogeneity was significantly high in all the analyses involving pain. Exclusion of lower quality studies and limitation to very preterm newborns did not diminish the heterogeneity. Causes of heterogeneity were not formally analysed in a post hoc analysis. Possible explanations include: inconsistencies in opioids used, dif-

ferences in dosages of opioids used, differences in outcome measures and differences in the statistical reporting of results. The 'extra protocol' use of opioids in more recent studies may dilute the effect of the intervention being studied. On the other hand, this issue confirms the fact that opioids are now widely accepted for use in the neonatal intensive care unit, and that it is considered unethical not to give newborns the analgesic relief they need, if clinically justified.

Most studies evaluated the effect of an opioid started at the beginning of mechanical ventilation, assuming that mechanical ventilation is a painful procedure. The overall effect of opioids in this setting was found to be small and quite inconsistent. Given the pharmacological characteristics of opioids, possible explanations for this finding are numerous: pain could not have been measured correctly or newborns on mechanical ventilation may not always feel pain. The effect of opioids given 'on demand' in studies that allowed for extra protocol opioid administration could have altered the measurements of pain. Non-drug interventions that were not mentioned in the papers could reduce pain and stress in newborns on the ventilator, thus reducing the need for drug control of pain. Indeed, a recent study (Simons 2003) found very low pain scores; a situation in which a lack of effect of opioids would be expected.

One of the objectives of the review - to test the effect of opioids according to the administration of the drugs on an 'as needed' basis based on signs of pain - was addressed by only one study (Lago 1998). That showed a significant reduction of pain when fentanyl was titrated (administered in proportion to need) according to the assessment of pain of the newborn. However, the limitations (a limited number of patients evaluated with a not well validated scale) of this trial do not allow conclusions to be drawn.

Other primary outcomes of the review were mortality and duration of ventilation. No major adverse effects were found for these in the meta-analysis of all studies. For another important primary outcome, medium and long term neurodevelopment, only limited data from one study were available. Given the hypothesis that opioids could influence neurological outcomes, allowing both for better outcomes (if the opioids reduce the adverse effects of pain) or worse outcomes (if the opioids interfere with neurotransmitters), there is an urgent need for data addressing this subject, specifically for very preterm and vulnerable infants. These data could come in a few years time from follow up studies from the more recent, large randomised clinical trials.

With regard to secondary outcomes, no significant effects were found, with the exception of an increase in days to reach full enteral feeding. These results were found to be consistent across studies, and meta-analysis could yield valid estimates of effects.

The analysis of the effects of opioids in very preterm babies yielded similar results, with a small reduction of pain scores and no major clinical adverse effects (with the exception, again, of days to reach full enteral feeding).

Different dosage regimens were used across studies but no clear relationship with effect could be found. A note of caution came from more recent studies (Anand 1999; Anand 2004) that showed a tendency toward more frequent adverse neurological effects for higher opioid doses in smaller babies.

Finally, the comparison between opioids and sedatives is based on just one study (Anand 1999). Comparing morphine to midazolam showed similar pain scores between the two groups but fewer adverse effects with morphine.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review found insufficient evidence to support a recommendation for the routine use of opioids in mechanically ventilated newborns. In the absence of firm evidence to support a routine policy, we suggest that opioids be used selectively - based on clinical judgment and evaluation of pain indicators - although there are limitations to pain measurement in newborns. When pain relief is required, morphine is recommended over midazolam because of fewer adverse effects, although this conclusion is based on the results from one small study.

Implications for research

This review recommends selective use of opioids in mechanically ventilated newborns. However, there is a need to investigate this issue fully in large, well-conducted studies. Future studies should enrol only newborns who express indicators of pain (based on best available pain scores) when on mechanical ventilation. Data are specifically needed for very preterm babies. Medium (one to three years) and long term (more than three years) neurodevelopmental consequences of opioid treatment have not been adequately addressed to date, so if data could be obtained from follow up studies of patients enrolled in recent trials they would be very valuable.

POTENTIAL CONFLICT OF INTEREST

None

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*Indicates the major publication for the study

T A B L E S

Characteristics of included studies

Study	Anand 1999
Methods	Multicentre randomised, placebo controlled trial. Randomisation was performed by an automated procedure in blocks, stratified by centre. Allocation concealment was ensured by an automated telephone response system. Carers and assessors were blinded to the treatment. Outcomes were reported for all patients enrolled.
Participants	67 preterm infants (24–32 weeks) on ventilator by < 8 h were eligible for inclusion. Exclusion criteria: postnatal age >72 h, positive pressure ventilation >=8 h, major congenital anomalies, severe intrapartum asphyxia (Apgar score <=3 at 5 min), and participation in other studies interfering with the NOPAIN trial procedures criteria: postnatal age >72 h, positive pressure ventilation >=8 h, major congenital anomalies, severe intrapartum asphyxia (Apgar score <=3 at 5 min)

Characteristics of included studies (Continued)

Interventions Morphine group (n=24): loading dose 100, 200 or 300 mcg/kg followed by an infusion of 10, 20 or 30 mcg/kg/h for infants of gestational ages 24-26, 27-29 and 30-32 weeks respectively. Midazolam group (n=22): loading dose 200 mcg/kg followed by an infusion of 20, 40 or 60 mcg/kg/h for infants of gestational ages 24-26, 27-29 and 30-32 weeks respectively.
Placebo group (n=21): dextrose 5%
treatment continued as long as necessary (written protocol for stopping drugs), max 14 days. Additional analgesia with morphine bolus doses was allowed. The amount and frequency of additional morphine was recorded as an outcome measure.

Outcomes Primary outcome: incidence of adverse neurological events (neonatal death, grade III/IV intraventricular haemorrhage, periventricular leucomalacia). Secondary outcomes: level of sedation (measured by the COMFORT score); and pain response to tracheal suctioning (assessed by the PIPP) - all scores assessed before starting treatment, after 24 h of infusion, and at 10-12 h after treatment was discontinued; incidence of pneumothorax; days of ventilatory support; continuous positive airway pressure and oxygen; length of intensive care unit and hospital stay; and neurodevelopmental outcome (measured by Neurobehavioral Assessment of the NAPI cluster scores at 36 weeks corrected for gestational age).

Notes

Allocation concealment A – Adequate

Study **Anand 2004**

Methods Multicentre randomised, placebo controlled trial. Randomisation was performed by an automated procedure, stratified by centre and groups of gestational age at birth. Allocation concealment was ensured by an automated telephone response system. Carers and assessors were blinded to the treatment. Outcomes were reported for all patients enrolled.

Participants 898 preterm (23-32 weeks) babies intubated within 72 h of birth and ventilated for <8 h at enrolment. Exclusion criteria: major congenital anomalies, asphyxia, intrauterine growth retardation, maternal opioid addiction, participation to other clinical trials.

Interventions Morphine group (n=449): loading dose 100 mcg/kg followed by an infusion of 10, 20 or 30 mcg/kg/h for infants of gestational ages 23-26, 27-29, or 30-32 weeks, respectively. Placebo group (n=449): Additional analgesia with morphine bolus doses was allowed.

Outcomes Primary outcomes: a composite of neonatal death, grade III/IV intraventricular haemorrhage and periventricular leucomalacia. Secondary outcomes: pain response to tracheal suctioning (assessed by the PIPP) - scores were assessed before starting treatment, after 24 and 72 h of infusion, and at 12 h after treatment was discontinued; days of ventilatory support; days of oxygen supplementation days to full volume feeding.

Notes Data on PIPP scores, duration of ventilation, days to reach full enteral feeding were obtained by personal communication with the author

Allocation concealment A – Adequate

Study **Dyke 1995**

Methods Randomised double blind, placebo controlled trial. Randomisation was performed by a computer generated list in the pharmacy. Allocation concealment was adequate. Carers and assessors were blinded to the treatment. There was no loss to follow up.

Participants 26 preterm infants (29-36 weeks) requiring mechanical ventilation for hyaline membrane disease. Exclusion criteria: major congenital malformations.

Interventions Morphine group (n=12) loading dose 100 mcg/kg over 30 min followed by continuous infusion 10 mcg/kg/h. Placebo group (n=14): dextrose 5%. Infusion continued until weaning from intermittent mandatory ventilation or for a maximum of 48 h therapy. Pancuronium allowed for infants not stabilized by ventilatory adjustment and markedly asynchronous with their ventilator (2/12 infants in morphine group, 3/14 in placebo group).

Characteristics of included studies (Continued)

Outcomes	Primary outcomes: heart rate, blood pressure, respiratory rate hourly; severity of respiratory distress; interaction of the infant with positive pressure ventilation. Secondary outcomes: duration of oxygen therapy; ventilator therapy and hospitalisation; incidence of bronchopulmonary dysplasia; periventricular haemorrhage and pneumothorax.
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Notes

Allocation concealment A – Adequate

Study **Guinsburg 1998**

Methods	Randomised double blind, placebo controlled trial. Method of randomisation was not stated; the use of sealed envelopes was stated, but it is not clear how allocation concealment was dealt with. Assessors were stated to be blinded to the treatment. Outcomes were reported for all patients enrolled.
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Participants	22 preterm infants (≤ 32 weeks) mechanically ventilated since birth, with postnatal age 12-48 h, with an indwelling arterial umbilical line. Exclusion criteria: maternal opioid use or abuse during pregnancy, labour, or delivery. Administration of muscle relaxants, analgesics, or sedatives before or during the study period; grade III-IV intraventricular haemorrhage; central nervous system malformations; gross neurological abnormalities; intubation or reintubation within 4 h before patient observation.
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Interventions	Intervention (n=11) with single dose of fentanyl (3 mcg/kg) over 2 min control (n=11) with 0.2 ml normal saline.
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Outcomes	Serum cortisol and growth hormone; blood glucose and lactate; vital signs. Behavioral pain scales: modified postoperative COMFORT scale and NFCS for 10 min. All outcomes measured before treatment, at 30 min and at 60 min after treatment.
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Notes

Allocation concealment B – Unclear

Study **Lago 1998**

Methods	Randomised double blind, controlled trial. Method of randomisation was not stated; the use of sealed envelopes was reported (author's communication). Assessors were stated to be blinded to the treatment, but blinding was unlikely. Carers were not blinded.
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Participants	55 preterm infants (26-34 weeks) requiring mechanical ventilation for hyaline membrane disease, with indwelling catheters. Exclusion criteria: asphyxia (Apgar < 5 at 5min) foetal drug exposure, sepsis, major congenital anomalies. Two infants died (one in fentanyl group and one in control group) and were excluded from analysis.
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Interventions	Fentanyl group (n=26): continuous infusion at 0.5-2 mcg/kg/h adjusted to render the neonate sedated but arousable (according to the behavioural sedation score). Control group (n=27): no intervention.
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Outcomes	Urine metapinephrine: normetapinephrine molar ratio Concentration; behavioural sedation score (assessed every 2 h during the study period); severity of hyaline membrane disease; need for surfactant replacement; evidence of clinically significant patent ductus arteriosus; days of ventilatory support and oxygen treatment; air leak; intraventricular haemorrhage; periventricular leucomalacia; bronchopulmonary dysplasia; days to exclusive enteral feeding; days to reach birth weight; length of hospital stay.
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Notes

Allocation concealment B – Unclear

Study **Lago 1999**

Methods	Randomised double-blind, placebo controlled trial. Method of randomisation was not stated; the use of sealed envelopes was reported (author's communication). Assessors were stated to be blinded to the treatment. Carers were unaware of the treatment.
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Participants	31 preterm infants (>28 weeks - <37 weeks) ventilated for hyaline membrane disease. Exclusion criteria: not stated.
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Characteristics of included studies (Continued)

Interventions	Fentanyl group (n=15): continuous infusion of 1.5 mcg/kg/h scaled down by 0.5 mcg/kg/h every 24 h, for a total of 72 h. Placebo group (n=16): 5% glucose.
Outcomes	Ventilator setting; sedation score (not described) every 4 h; severity of respiratory disorder; radiological score; duration of ventilation; need for surfactant therapy; duration of oxygen dependence; electromyographic activity of the intercostal muscles.
Notes	Data, methods and details were obtained by personal communication with the author.
Allocation concealment	B – Unclear

Study **Orsini 1996**

Methods	Randomised double-blind, placebo controlled trial. Randomisation was performed in the pharmacy by random number generation (not otherwise specified); allocation concealment was adequate. Carers and assessors were blinded to the treatment. There was no loss to follow up.
Participants	20 preterm infants (26-36 weeks), >1000 g birth weight, undergoing mechanical ventilation for respiratory distress syndrome, with an indwelling arterial catheter. Exclusion criteria: any analgesic, sedating agent or muscle relaxant given before informed consent could be obtained.
Interventions	Fentanyl group (n=11): loading dose 5 mcg/kg over 20 min followed by a continuous infusion of 2 mcg/kg/h for 72 h, 1 mcg/kg/h for the next 24 h, and 0.5 mcg/kg/h for the final 24 h (total: 5 days). Placebo group (n=9): dextrose 5% in water.
Outcomes	Behavioral score; vital signs every 2 h; cortisol and 11-deoxycortisol levels at baseline and the daily 3-methyl histidine/urinary creatinine ratio and urea excretion (as indicators of catabolism); incidence of intraventricular haemorrhage, patent ductus arteriosus; bronchopulmonary dysplasia; sepsis.
Notes	Data on pain, incidence of CLD and IVH were obtained by personal communication with the author.
Allocation concealment	A – Adequate

Study **Pokela 1994**

Methods	Randomised double-blind, placebo controlled trial. Randomisation was performed by the pharmacy using randomisation table (personal communication with the author); allocation concealment was therefore adequate. Carers and assessors were blinded to the treatment. There was no loss to follow up.
Participants	84 newborns (term and preterm) requiring sedation for mechanical ventilation during the first week after birth. Other inclusion criteria: respiratory distress, age < 1 week, documentation of hypoxaemia during the previous nursing care and need of sedation or analgesia. Exclusion criteria: fatal anomalies.
Interventions	Meperidine group (n=42): 1 mg/kg intravenously over 1 min before 15 min of tracheal suction or daily routine treatment procedures (2 h study period). Placebo group (n=42) 0.9% saline.
Outcomes	Heart rate, tcPO ₂ , SaO ₂ , mean arterial blood pressure, ventilatory parameters monitored continuously and recorded at 1min intervals from 10 min before the treatment to 2 h afterward; pain during the 2 h period scored with a behavioural pain score (facial expression, movements, response to handling and consolability, rigidity of the limbs and body); plasma beta-endorphin, serum cortisol.
Notes	
Allocation concealment	A – Adequate

Study **Quinn 1992**

Methods	Randomised double-blind, controlled trial (morphine vs morphine + pancuronium vs pancuronium). Authors stated that randomisation was performed by drawing a sealed envelope; allocation concealment was inadequate. The authors did not state how the list of randomisation was generated. Blinding of interventions and outcomes was not clearly ensured. A power calculation was made for differences in catecholamines levels. Loss to follow up was 0 in “control” (pancuronium) group, 10/38 in “treated” group (morphine+pancuronium). Analysis of clinical data was performed on an intention to treat basis.
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Characteristics of included studies (Continued)

Participants	95 preterm newborns. Entry criteria: newborns with hyaline membrane disease who were fighting against the ventilator (on clinical impression); postnatal age >4 h and < 48 h; no prior treatment with narcotic analgesic or neuromuscular blocking agent.
Interventions	Morphine group (n=29): 50 mcg/kg/h by continuous infusion, increased to 100 mcg/kg/h if the newborn was still struggling after 2 h. Pancuronium group (n=28): 100 mcg/kg per dose given as required to inhibit breathing. Morphine + pancuronium group (n=38): continuous morphine at 50 mcg/kg/h + intermittent pancuronium at 100 mcg/kg as required; morphine not increased above 50 mcg/kg/h. Drug therapy continued until FiO ₂ < 0.45. Babies in the Morphine group were allowed to receive pancuronium if still fighting the ventilator after 4 h (n=7). Babies in Pancuronium group were given morphine for painful procedures (n=4). One baby stopped treatment within 24 h because FiO ₂ fell below 0.45. Data from the Morphine + pancuronium group and Pancuronium group were used; in this way pancuronium given in the same way in the two groups is a co-intervention. Clinical outcomes are presented for 28 infants in the Morphine + pancuronium group and for 28 in the Pancuronium group.
Outcomes	Catecholamines plasma levels; blood pressure; heart rate; peak inspiratory pressure; FiO ₂ on entry to the study and after 6 h treatment; days on ventilator; air leaks; intraventricular haemorrhage; PDA ; death.
Notes	
Allocation concealment	C – Inadequate

Study **Quinn 1993**

Methods	Randomised double-blind, placebo controlled trial. Randomisation was performed using stratified table; pharmacy allowed for adequate allocation concealment; carers and assessors were stated to be blinded, except for the consultant physician responsible for the baby. There was no loss of follow up for clinical outcomes. A power calculation was made for differences in catecholamines levels. Analysis of clinical data was performed on an intention to treat basis. The trial was terminated after an interim analysis showed differences in the adrenaline concentration.
Participants	41 preterm (<34 weeks) infants who required mechanical ventilation and received surfactant (Curosurf) for hyaline membrane disease. Exclusion criteria: babies who did not have an arterial line in situ.
Interventions	Morphine group (n=21): loading dose 100 mcg/kg/h for 2 h followed by 25 mcg/kg/h as a continuous infusion. Treatment was continued until the baby was on ventilator. Placebo group (n=20): dextrose 5%.
Outcomes	Catecholamines plasma levels; blood pressure; heart rate and ventilator setting (peak inspiratory pressure and oxygen concentration) at study entry and after 6 h treatment; arterial/alveolar oxygen ratio at 0 h and 24 h; pain score (based on the level of consciousness, crying, posture, and facial expression); days on ventilator; air leaks; intraventricular haemorrhage; PDA ; death during first 6 months of life.
Notes	
Allocation concealment	A – Adequate

Study **Saarenmaa 1996**

Methods	Randomised, controlled, double blind, crossover trial in one centre. Method of randomisation was not stated; the use of sealed envelopes was stated, but it is not clear how allocation concealment was dealt with. Crossover occurred after a period longer than the duration of action of the given drug, so this is actually a single intervention study.
Participants	Ten intubated and ventilated newborns (>= 24 weeks gestational age) without chromosomal aberrations or major anomalies, with an indwelling arterial line, without other continuous analgesics. Seven newborns completed the protocol.
Interventions	Two different doses of alfentanil (10 mcg/kg and 20 mcg/kg) or placebo (saline) in random order two min before three separate endotracheal suction, at least six h apart.
Outcomes	Behavioural pain scores (one developed from the Children's Hospital of East Ontario Pain scale, and the NIPS) performed before, during and after suction by a blinded researcher; heart rate; arterial blood pressure and

oxygen saturation measured before and after suction; plasma adrenaline, nor-adrenalin and beta-endorphin measured before and 30 min after the procedure.

Notes

Allocation concealment B – Unclear

Study Simons 2003

Methods Randomised double-blind, placebo controlled trial in 2 NICUs. Method of randomisation: computer generated randomisation list to select 10 random permuted blocks stratified into 5 groups of gestational age ranges. Allocation concealment was ensured. Binding of carers and assessors was obtained. There was no loss to follow up.

Participants 150 ventilated neonates. Inclusion criteria: all neonates admitted to NICU who required mechanical ventilation, postnatal age < 3 days, ventilation <8 h. Exclusion criteria: severe asphyxia, severe IVH, major congenital malformations, facial malformations, neurological disorders, continuous or intermittent treatment with neuromuscular blockers.

Interventions Morphine group (n=73): loading dose 100 mcg/kg followed by 10 mcg/kg/h continuous infusion. Placebo group (n=77): sodium chloride in 5% glucose. Masked treatment was continued for 7 days or less (as for clinical conditions); after 7 days' study medication was weaned or stopped, or replaced by open-label morphine infusion. During study period additional morphine was allowed if patients from either groups were judged to be in pain or distress based on decisions of the attending physician.

Outcomes Primary outcomes: pain response: PIPP, NIPS, and Visual Analogue Scale at standardized time points. Secondary outcomes: incidence of all grades of intraventricular haemorrhage and poor neurologic outcome (severe intraventricular haemorrhage, periventricular leukomalacia or death). Other outcomes: duration of ventilation; length of NICU stay; incidence of co-morbidity (chronic lung disease; sepsis; necrotizing enterocolitis; patent ductus arteriosus); number of painful procedures.

Notes Data on duration of ventilator days were presented for the first period (NICU stay) and as total duration of ventilator days during admission. Data from the first period were used for the meta-analysis.

Allocation concealment A – Adequate

Study Siwicz 1999

Methods Randomised double-blind controlled trial; method of randomisation was not stated; the use of sealed envelopes was reported (author's communication). Carers and assessors were stated not to be blinded.

Participants 20 preterm infants (26-35 weeks), birth weight 810-2750 g, receiving mechanical ventilation. Exclusion criteria: not stated.

Interventions Morphine group (n=10): loading dose 100 mcg/kg over 30 min followed by continuous infusion of 20 mcg/kg/h for 1-5 days. Control group (n=10): no intervention.

Outcomes PIPP and COMFORT scores; ventilatory setting; mean airways pressure, ventilatory rate, FiO2. Clinical outcomes: pneumothorax; grade IV intraventricular haemorrhage; periventricular leukomalacia; BPD.

Notes Data on pain scores were obtained by personal communication with the author.

Allocation concealment B – Unclear

Characteristics of excluded studies

Study Reason for exclusion

Barker 1995 Comparison of one opioid to another

Saarenmaa 1999 Comparison of one opioid to another

Characteristics of excluded studies (Continued)

Wood 1998 Comparison of one opioid to another

ANALYSES

Comparison 01. Opioids versus placebo or no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain (PIPP)			Weighted Mean Difference (Random) 95% CI	Subtotals only
02 Pain (NFCS)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
03 Pain (NIPS)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
04 Pain (other scales)			Standardised Mean Difference (Random) 95% CI	Subtotals only
05 Duration of ventilation (days)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
06 Neonatal mortality			Relative Risk (Fixed) 95% CI	Subtotals only
07 Mortality to discharge			Relative Risk (Fixed) 95% CI	Subtotals only
08 Neurodevelopmental outcome (NAPI)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
09 Neurodevelopmental outcome at 5-6 years (disability)			Relative Risk (Fixed) 95% CI	Subtotals only
10 Oxygen at 28 days of life			Relative Risk (Fixed) 95% CI	Subtotals only
11 Oxygen at 36 weeks postconceptional age			Relative Risk (Fixed) 95% CI	Subtotals only
12 Days to reach full enteral feeding			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
13 Weight gain at discharge (g/kg per day)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
14 Length of stay in hospital (days)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
15 Necrotising enterocolitis			Relative Risk (Fixed) 95% CI	Subtotals only
16 Any intraventricular haemorrhage (IVH)			Relative Risk (Fixed) 95% CI	Subtotals only
17 Severe intraventricular haemorrhage (Papile grade 3/4)			Relative Risk (Fixed) 95% CI	Subtotals only
18 Periventricular leucomalacia (PVL)			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 02. Opioids versus sedatives

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain (PIPP)	1	46	Weighted Mean Difference (Fixed) 95% CI	-1.00 [-2.66, 0.66]
02 Pain (COMFORT)	1	46	Weighted Mean Difference (Fixed) 95% CI	-0.20 [-2.51, 2.11]
03 Duration of mechanical ventilation (days)	1	46	Weighted Mean Difference (Fixed) 95% CI	-6.70 [-12.40, 1.00]
04 Mortality to discharge	1	46	Relative Risk (Fixed) 95% CI	0.31 [0.01, 7.16]
05 Neurodevelopmental outcome (NAPI)	1	46	Weighted Mean Difference (Fixed) 95% CI	5.20 [-5.84, 16.24]
06 Days to reach full enteral feeding	1	46	Weighted Mean Difference (Fixed) 95% CI	1.70 [-7.09, 10.49]
07 Weight gain at discharge (g/kg per day)	1	46	Weighted Mean Difference (Fixed) 95% CI	-0.19 [-0.66, 0.28]

Opioids for neonates receiving mechanical ventilation (Review)

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08 Length of stay in hospital (days)	1	46	Weighted Mean Difference (Fixed) 95% CI	-21.90 [-43.56, -0.24]
09 Any intraventricular heamorrhage (IVH)	1	46	Relative Risk (Fixed) 95% CI	0.28 [0.09, 0.87]
10 Severe intraventricular heamorrhage (Papile grade 3/4)	1	46	Relative Risk (Fixed) 95% CI	0.08 [0.00, 1.43]
11 Periventricular leucomalacia (PVL)	1	46	Relative Risk (Fixed) 95% CI	0.23 [0.03, 1.90]

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [*therapeutic use]; Infant, Newborn; Pain [*drug therapy; etiology]; Pain Measurement; Randomized Controlled Trials; Respiration, Artificial [*adverse effects]

MeSH check words

Humans

COVER SHEET

Title Opioids for neonates receiving mechanical ventilation

Authors Bellù R, de Waal KA, Zanini R

Contribution of author(s)

R. Bellu:
 Development and writing of protocol
 Literature search and identification of trials for inclusion
 Evaluation of methodologic quality of included trials
 Abstraction of data independently of co-reviewer
 Entering data into Revman
 Writing the description of studies section
 Writing of results section
 Writing of discussion section

K.A. de Waal:
 Literature search and identification of trials for inclusion
 Evaluation of methodologic quality of included trials
 Abstraction of data independently of co-reviewer
 Entering data into RevMan
 Writing the description of studies section
 Writing of results section
 Writing of discussion section

R. Zanini:
 Development of protocol
 Writing of discussion section
 Revision of the final review

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Date new studies found but not yet included/excluded	30 June 2004
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Roberto Bellù Neonatal Intensive Care Unit Ospedale "Manzoni" -Lecco Via Eremo 9 Lecco 23900 ITALY E-mail: r.bellu@ospedale.lecco.it Tel: +39-0341-489231 Fax: +39-0341-489247
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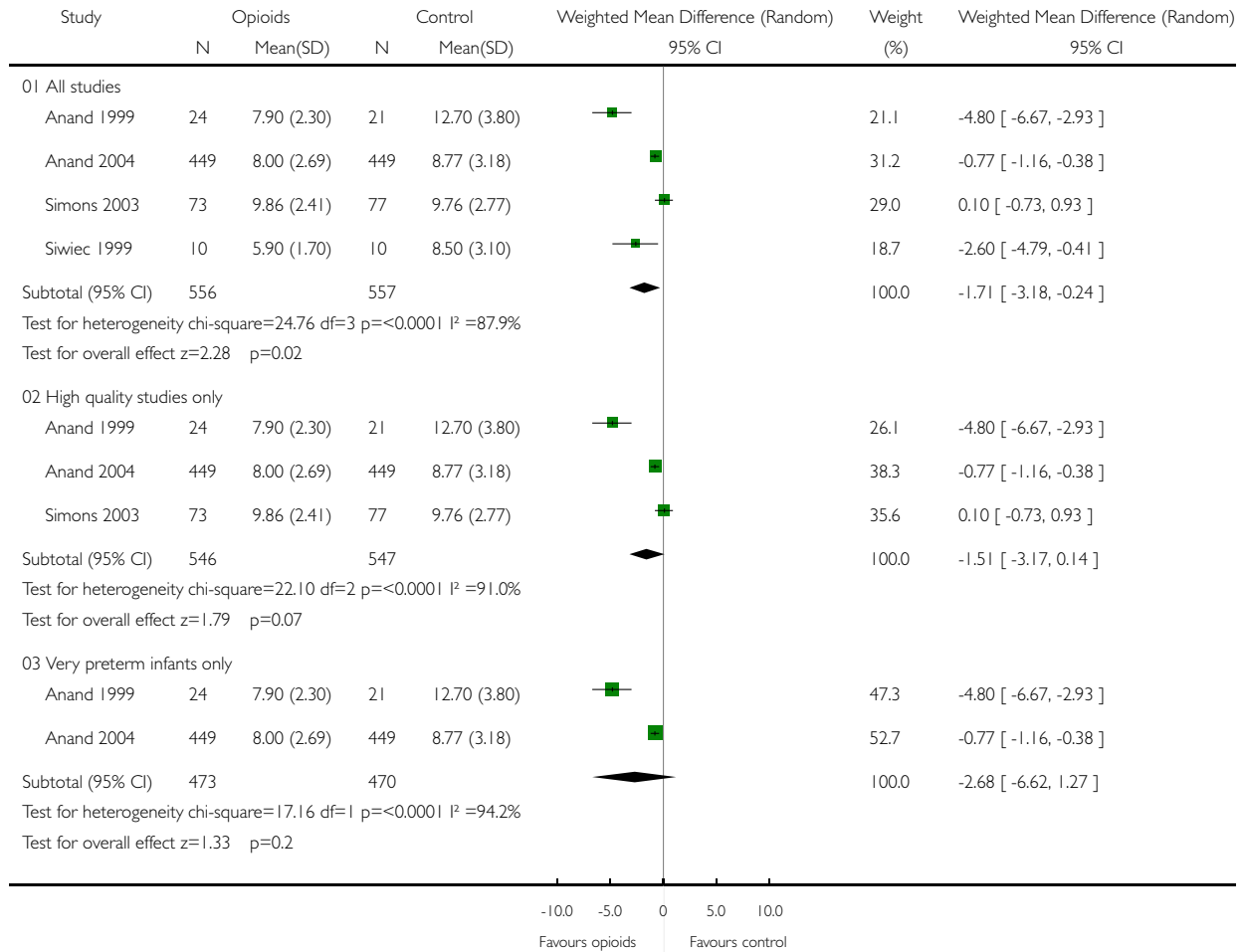
GRAPHS AND OTHER TABLES

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Comparison: 01 Opioids versus placebo or no treatment

Outcome: 01 Pain (PIPP)

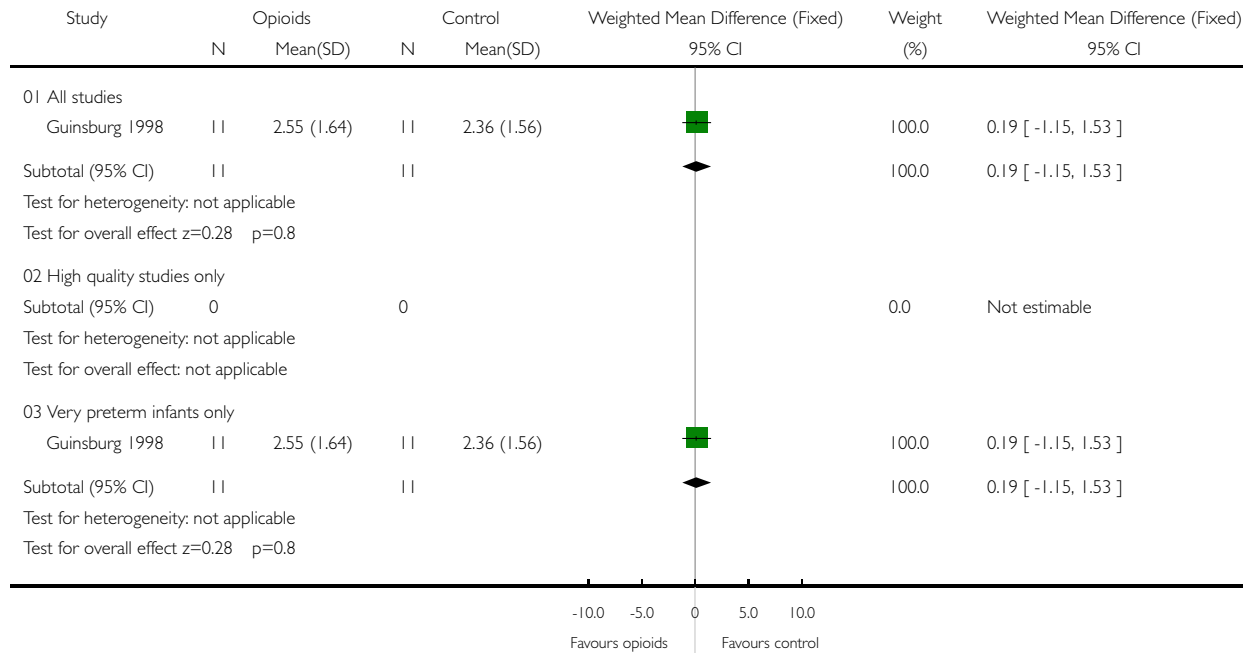


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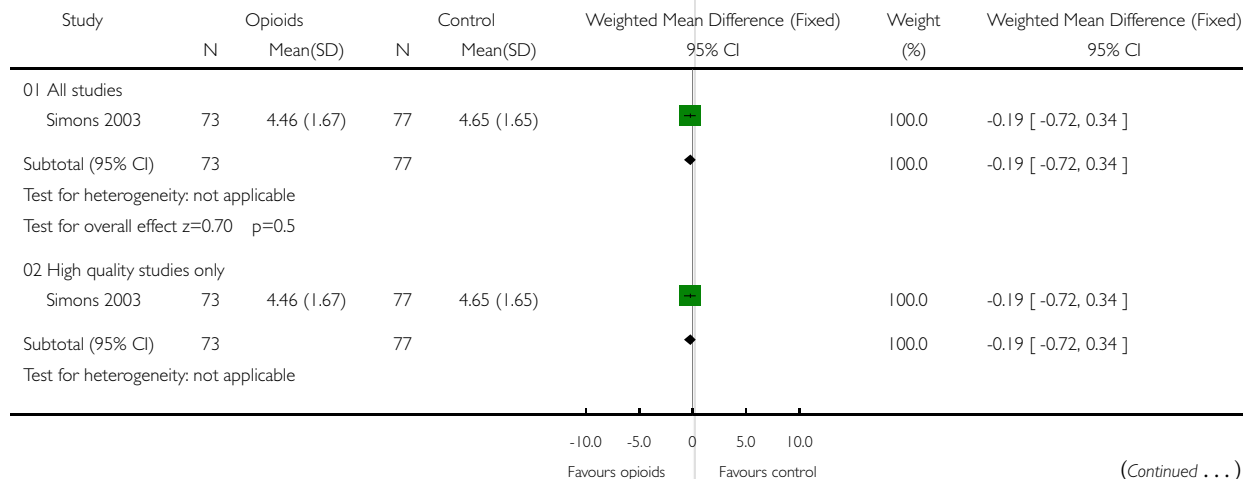


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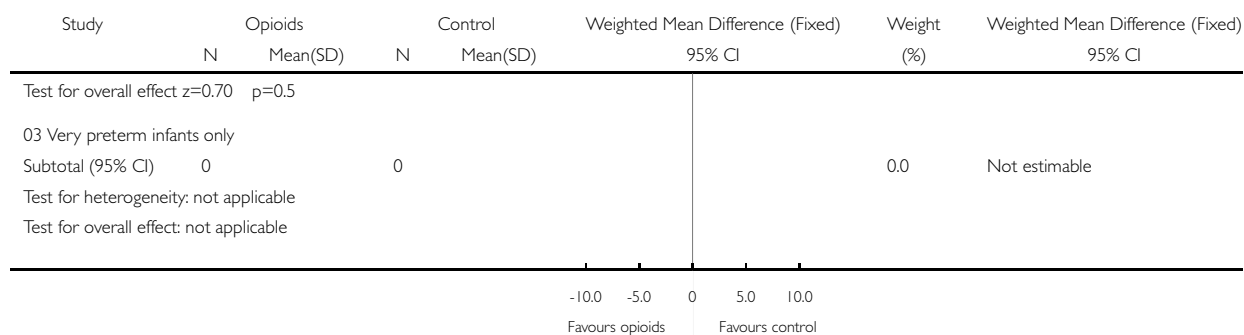
Review: Opioids for neonates receiving mechanical ventilation

Comparison: 01 Opioids versus placebo or no treatment

Outcome: 03 Pain (NIPS)



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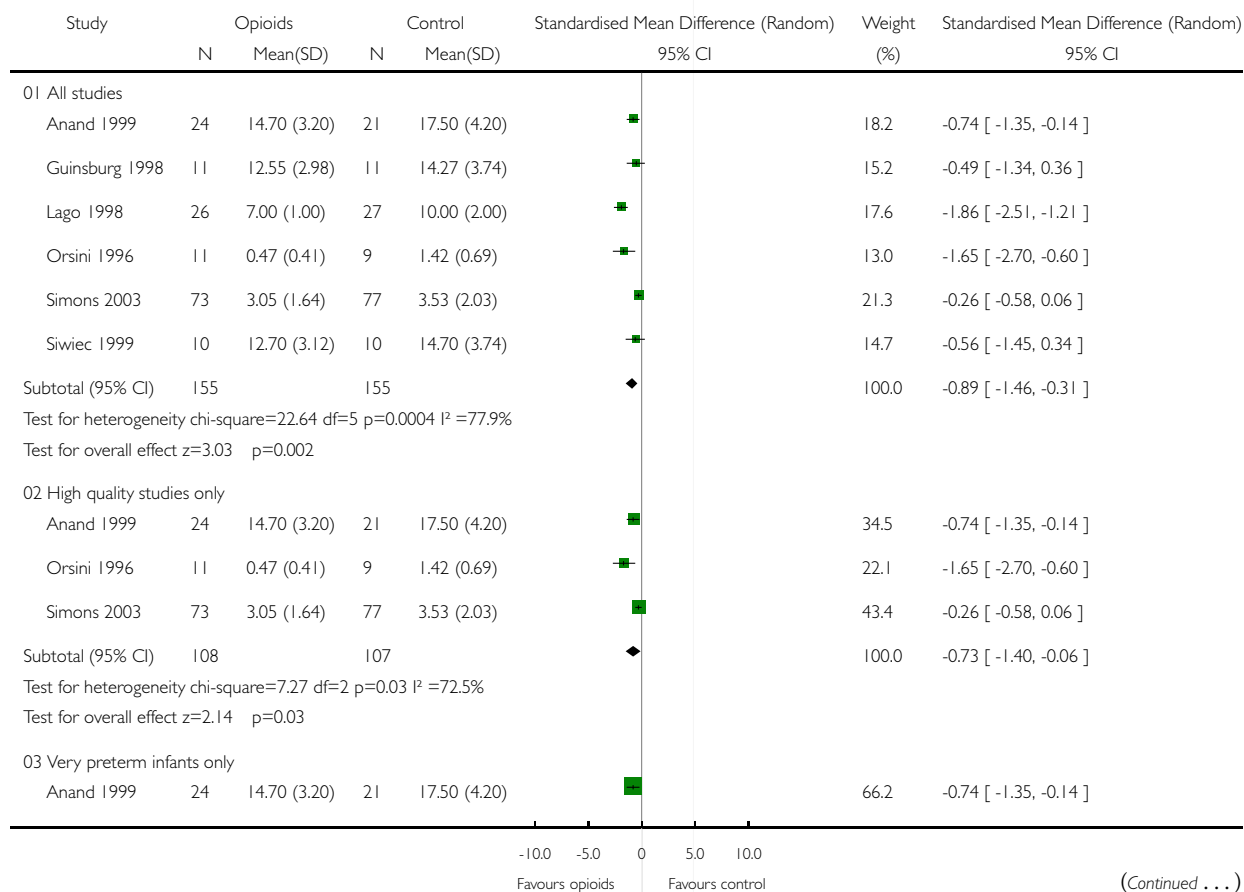


Analysis 01.04. Comparison 01 Opioids versus placebo or no treatment, Outcome 04 Pain (other scales)

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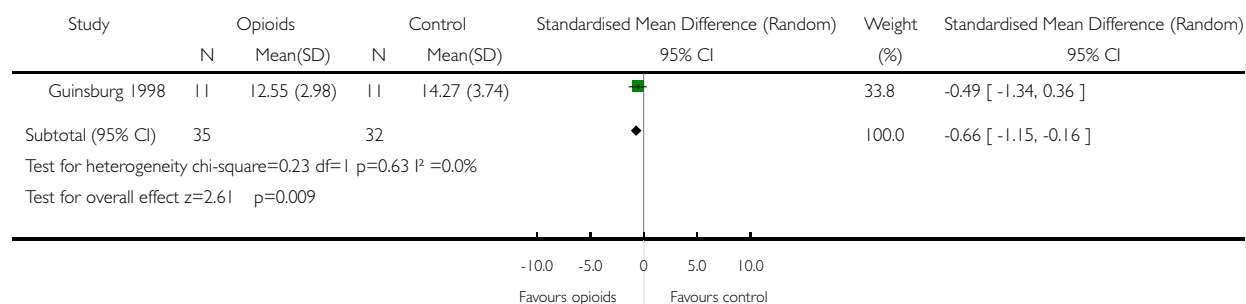
Comparison: 01 Opioids versus placebo or no treatment

Outcome: 04 Pain (other scales)



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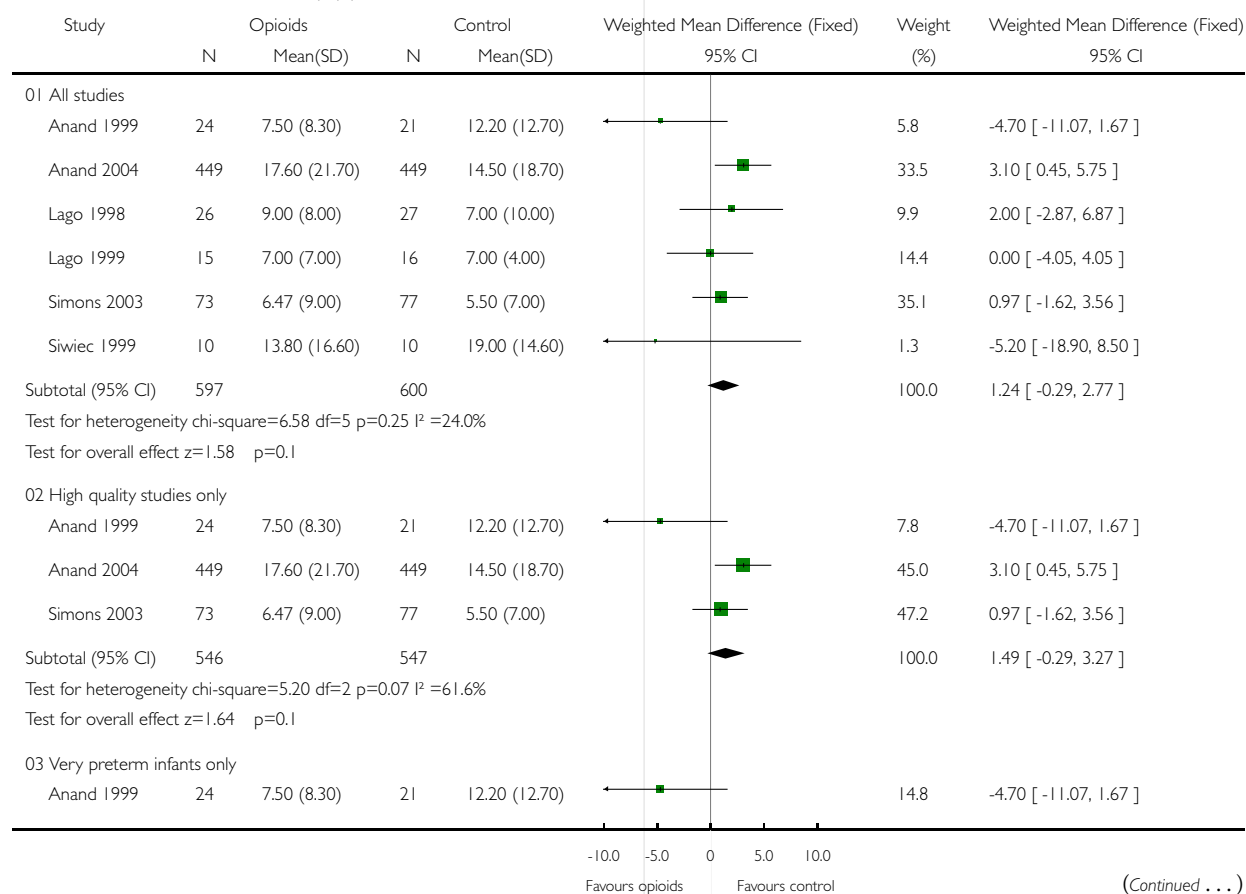


Analysis 01.05. Comparison 01 Opioids versus placebo or no treatment, Outcome 05 Duration of ventilation (days)

Review: Opioids for neonates receiving mechanical ventilation

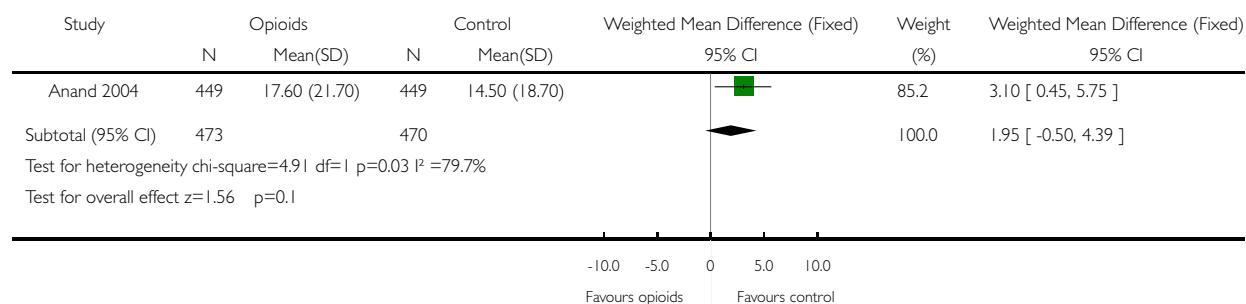
Comparison: 01 Opioids versus placebo or no treatment

Outcome: 05 Duration of ventilation (days)



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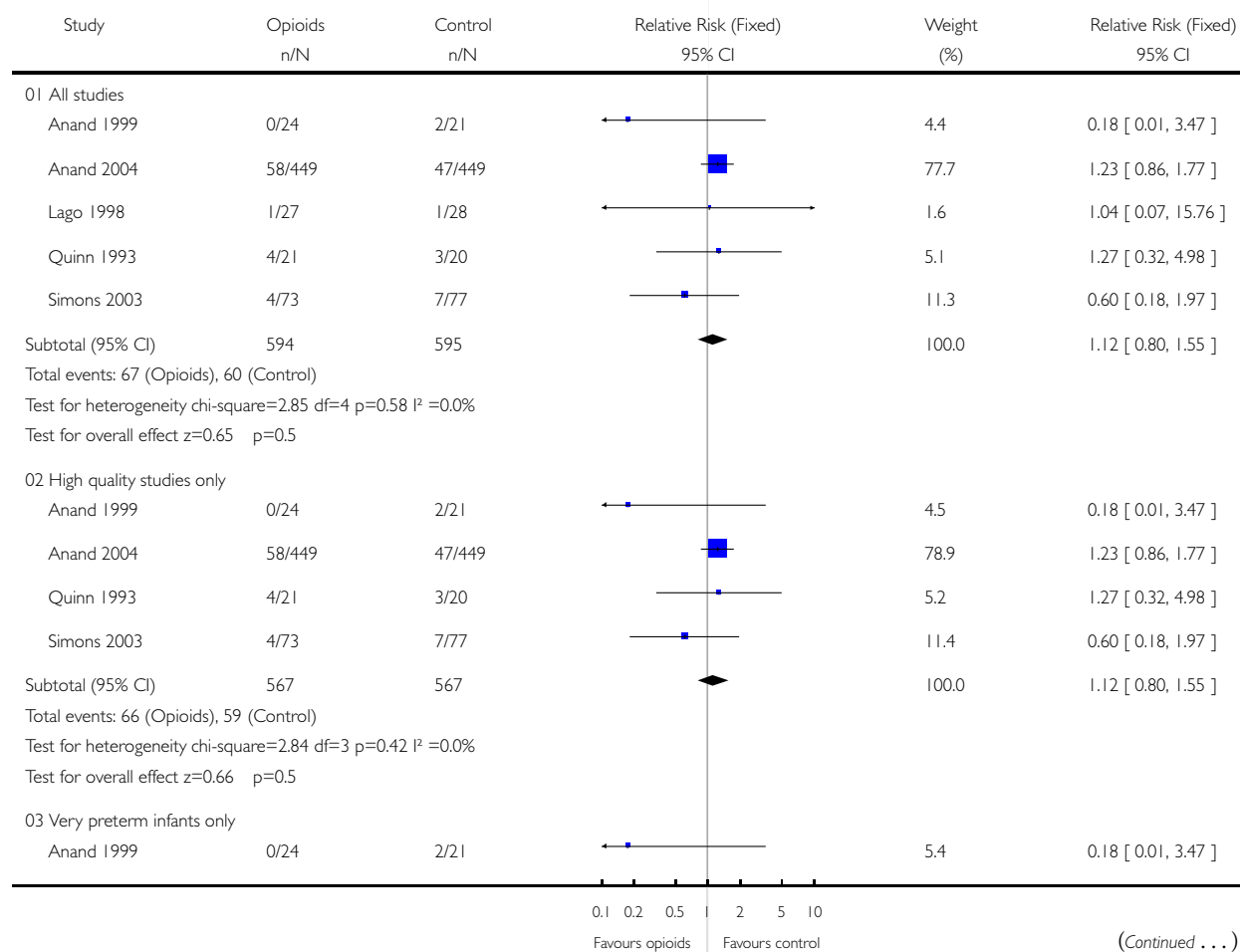


Analysis 01.06. Comparison 01 Opioids versus placebo or no treatment, Outcome 06 Neonatal mortality

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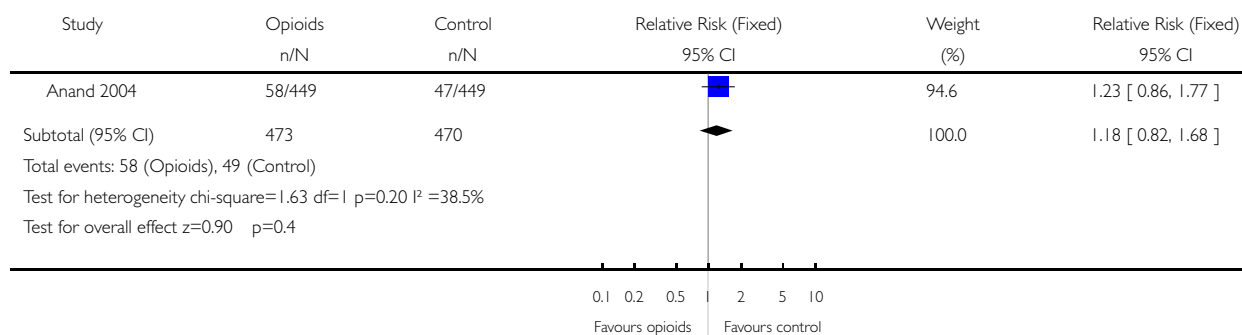
Comparison: 01 Opioids versus placebo or no treatment

Outcome: 06 Neonatal mortality



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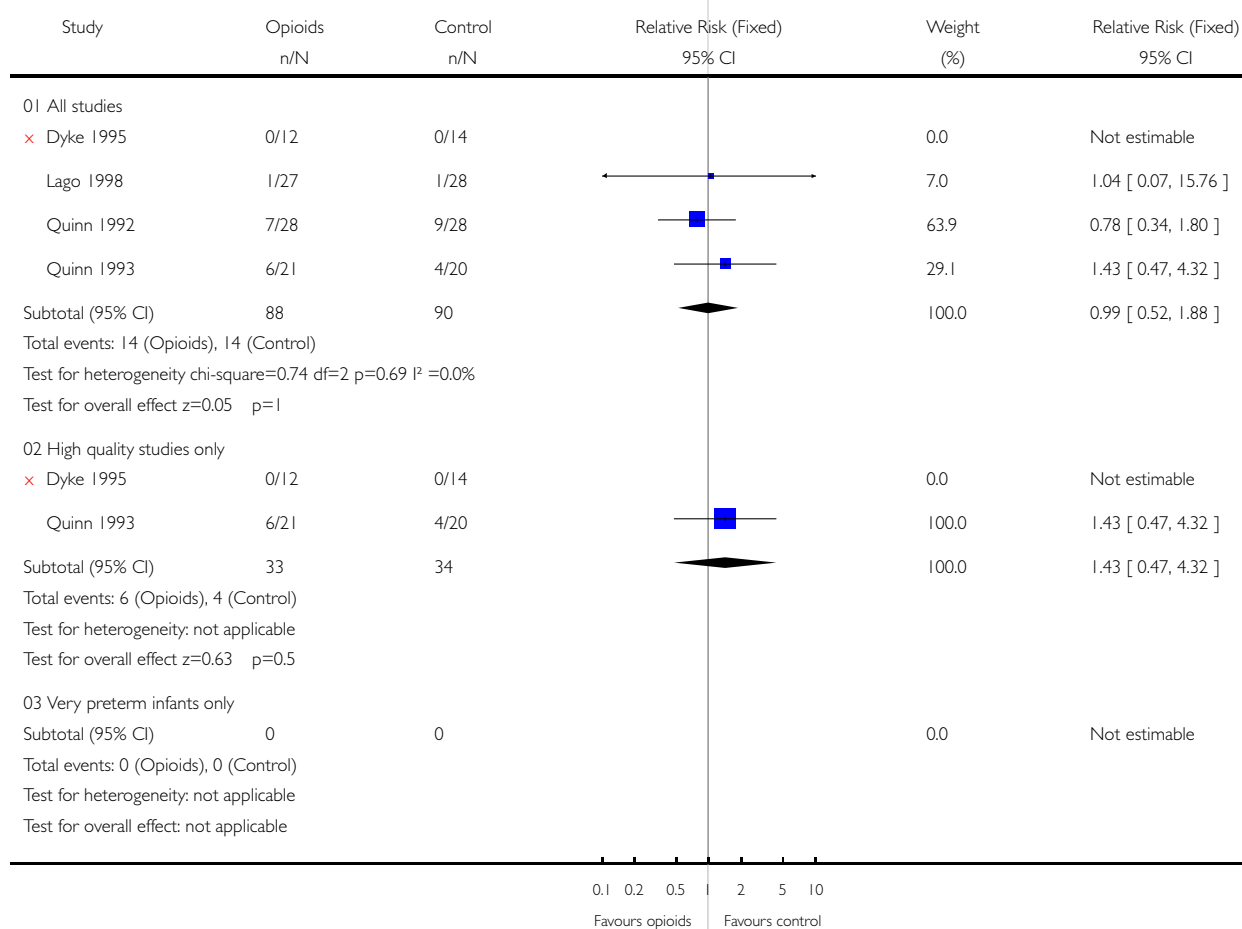


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Comparison: 01 Opioids versus placebo or no treatment

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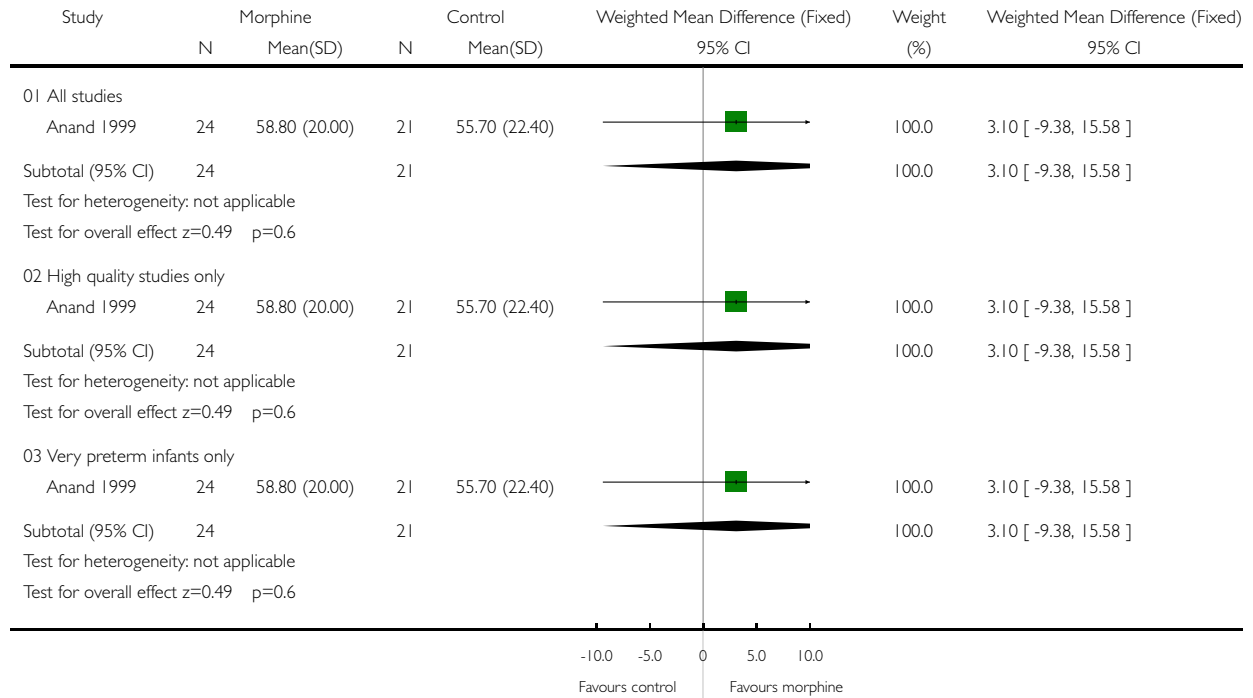


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Review: Opioids for neonates receiving mechanical ventilation

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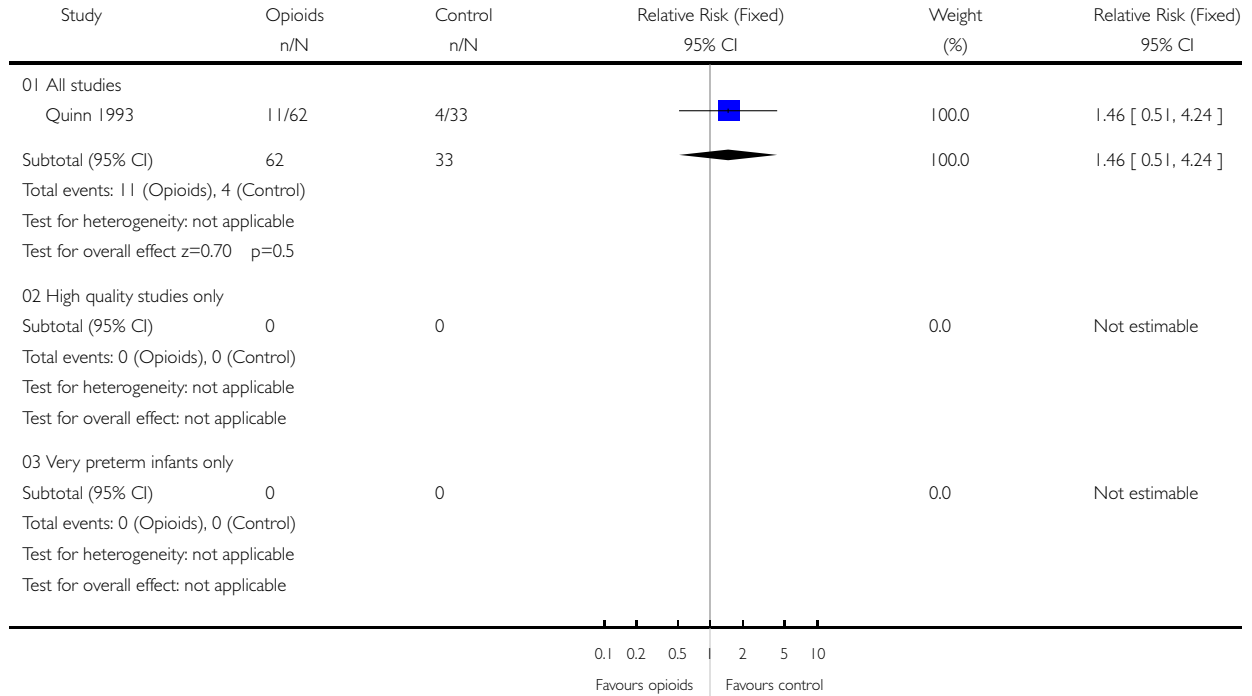


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Review: Opioids for neonates receiving mechanical ventilation

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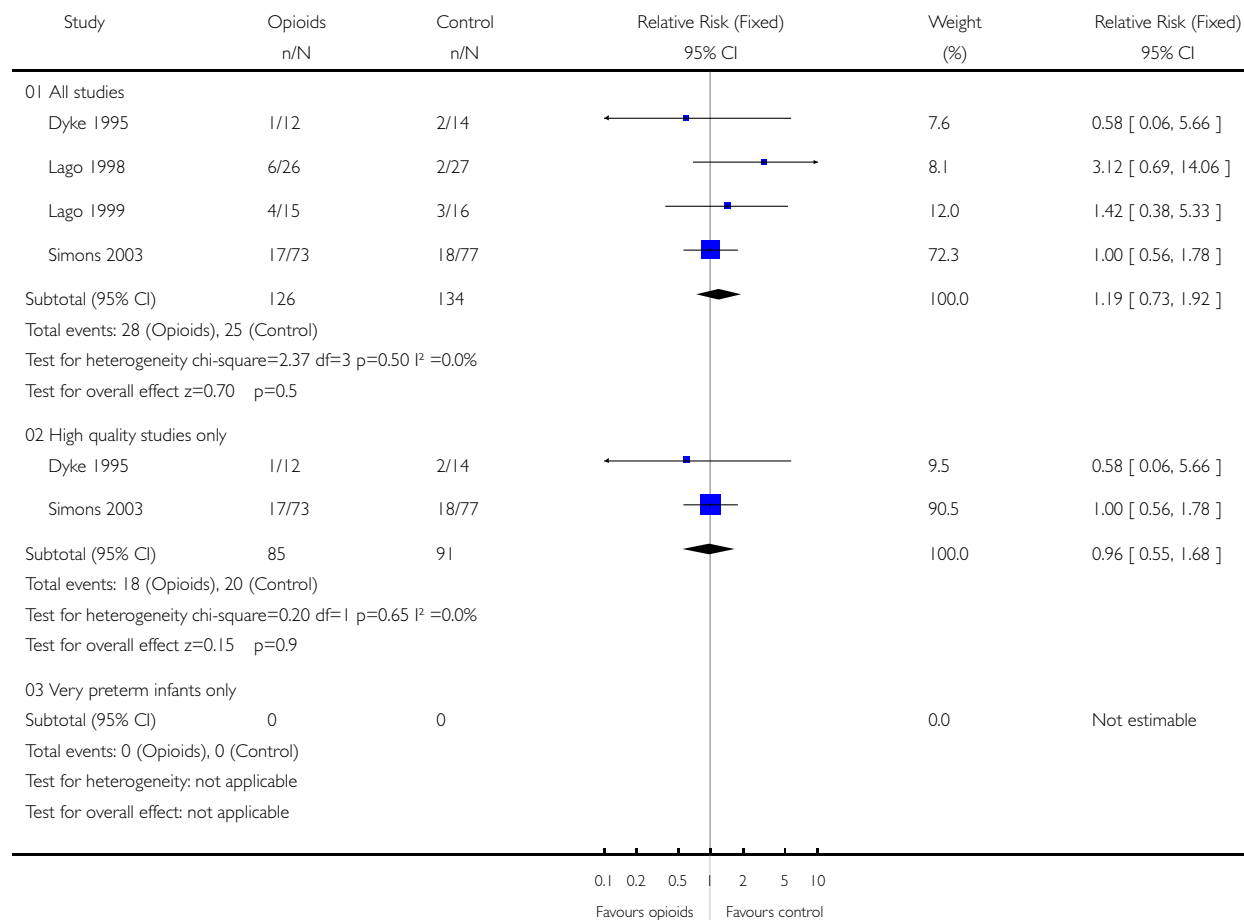


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Comparison: 01 Opioids versus placebo or no treatment

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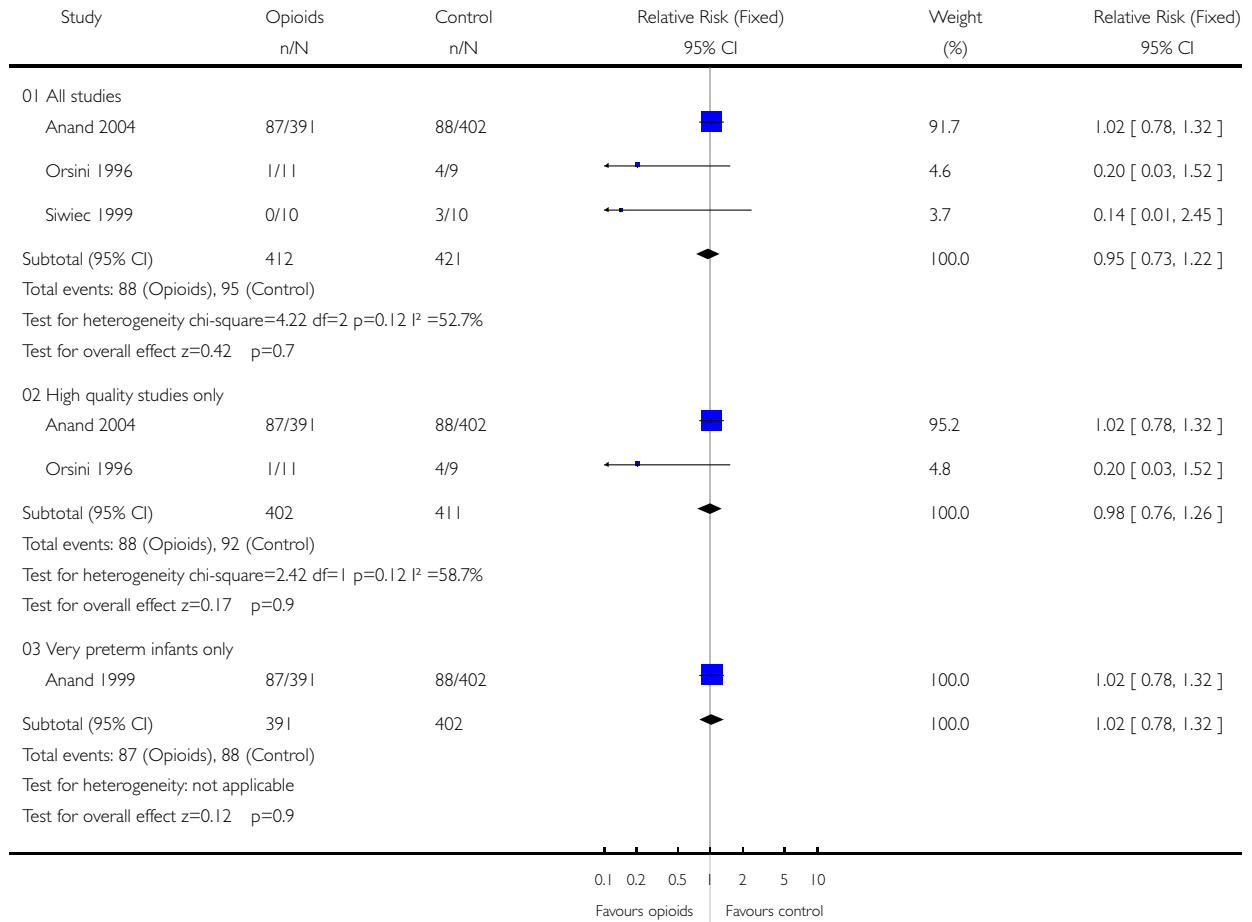


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Review: Opioids for neonates receiving mechanical ventilation

Comparison: 01 Opioids versus placebo or no treatment

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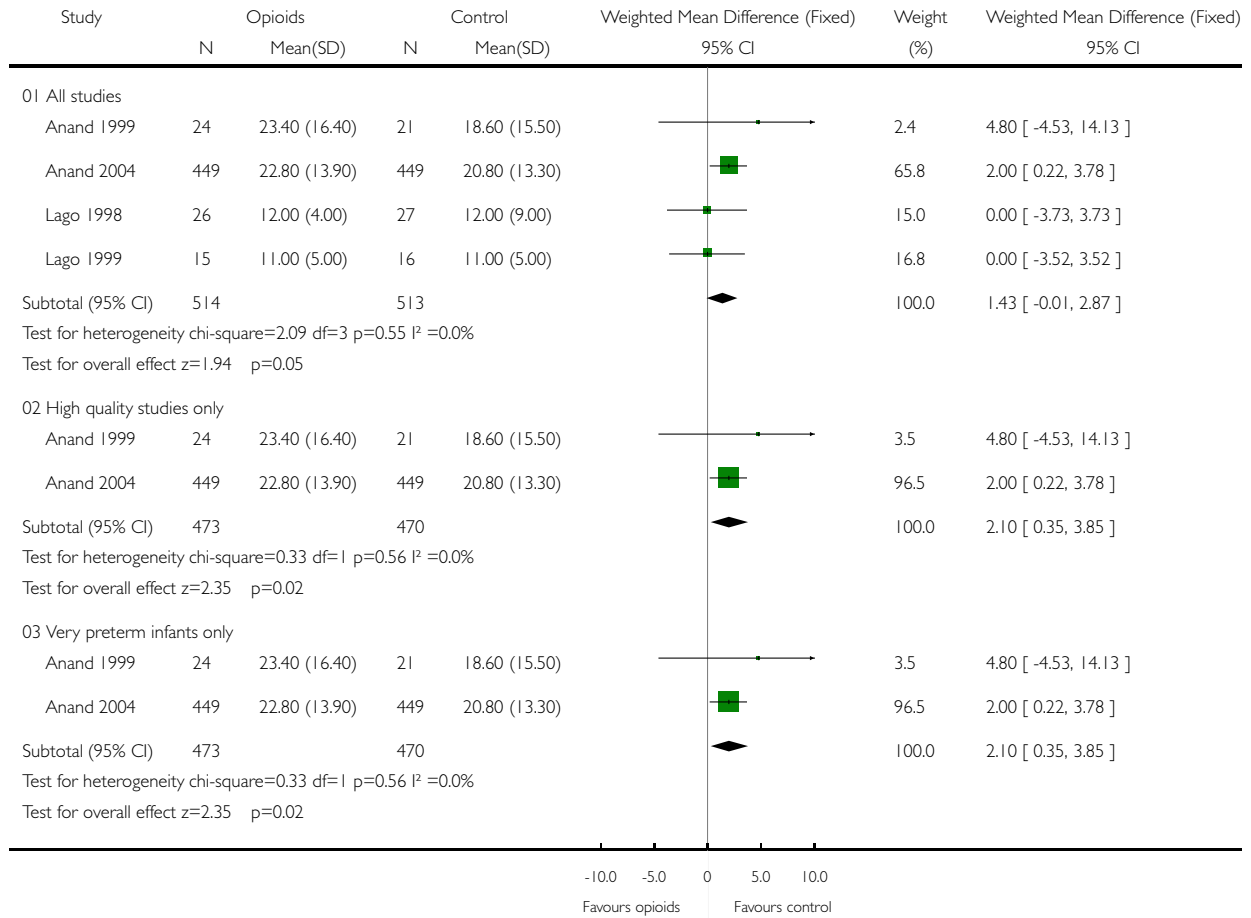


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Comparison: 01 Opioids versus placebo or no treatment

Outcome: 12 Days to reach full enteral feeding

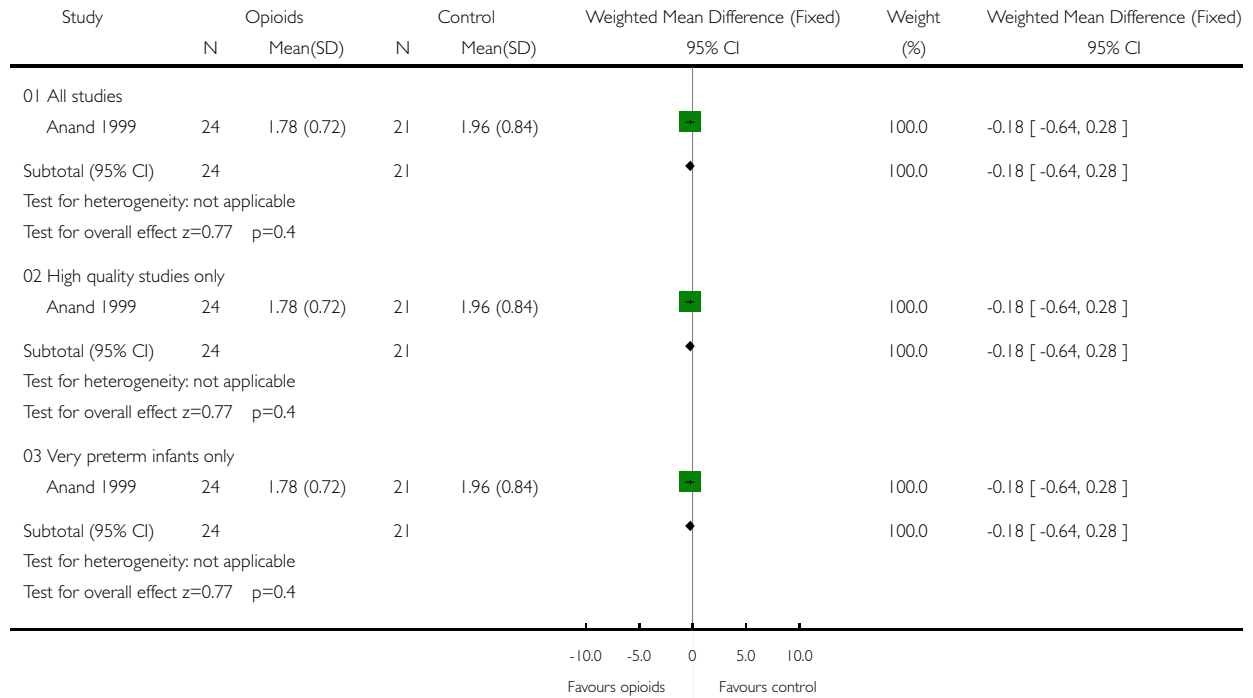


Analysis 01.13. Comparison 01 Opioids versus placebo or no treatment, Outcome 13 Weight gain at discharge (g/kg per day)

Review: Opioids for neonates receiving mechanical ventilation

Comparison: 01 Opioids versus placebo or no treatment

Outcome: 13 Weight gain at discharge (g/kg per day)

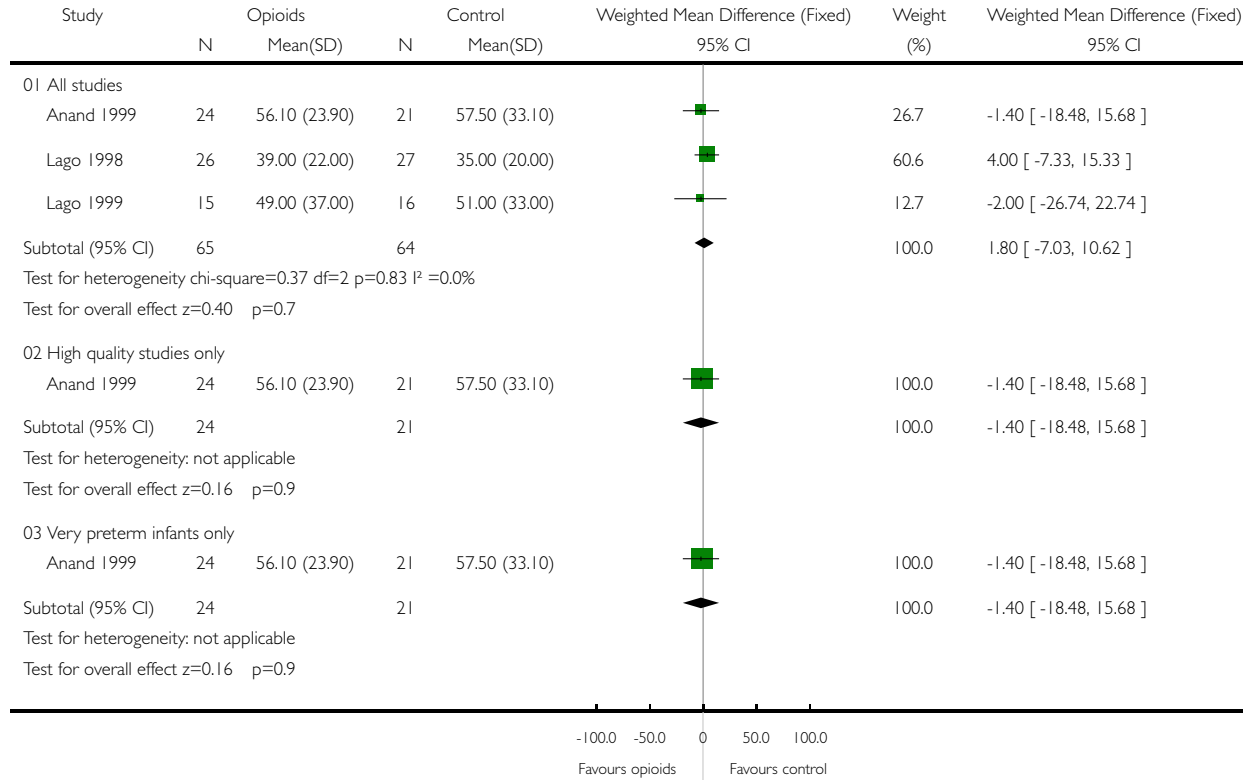


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Comparison: 01 Opioids versus placebo or no treatment

Outcome: 14 Length of stay in hospital (days)

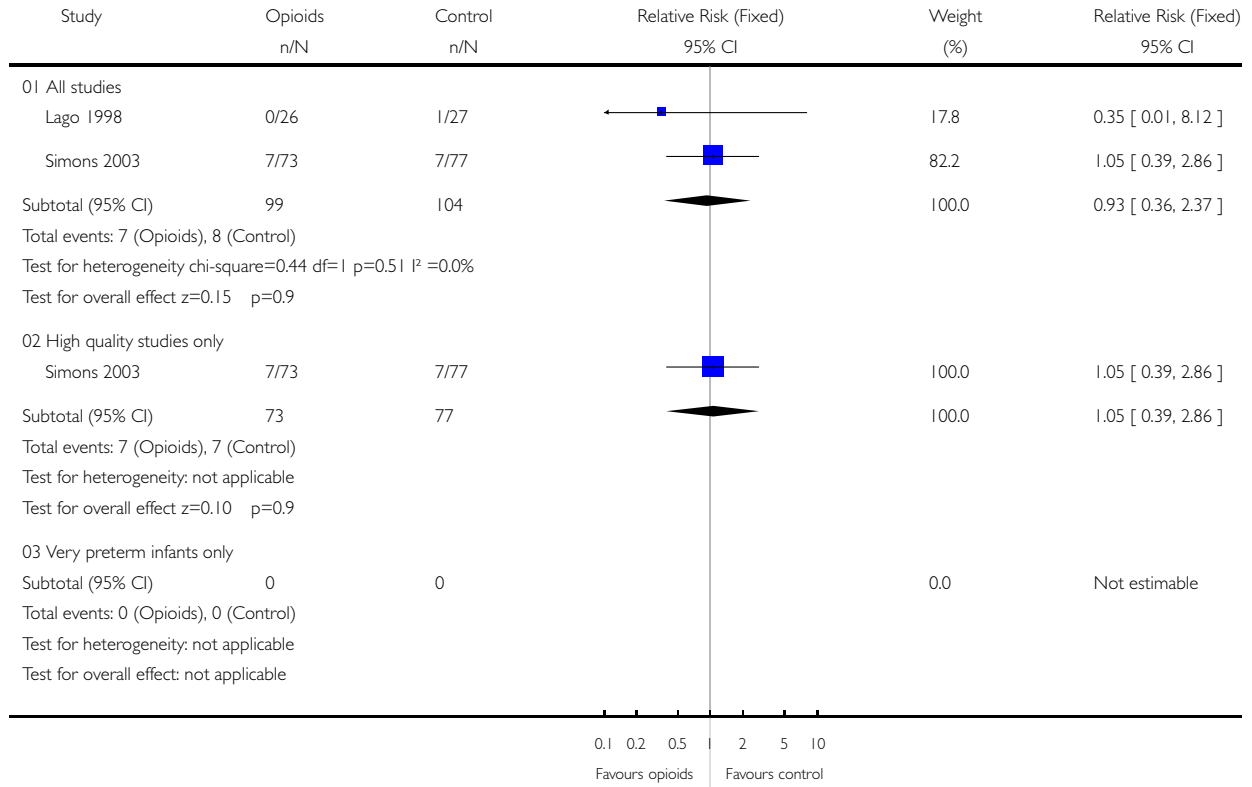


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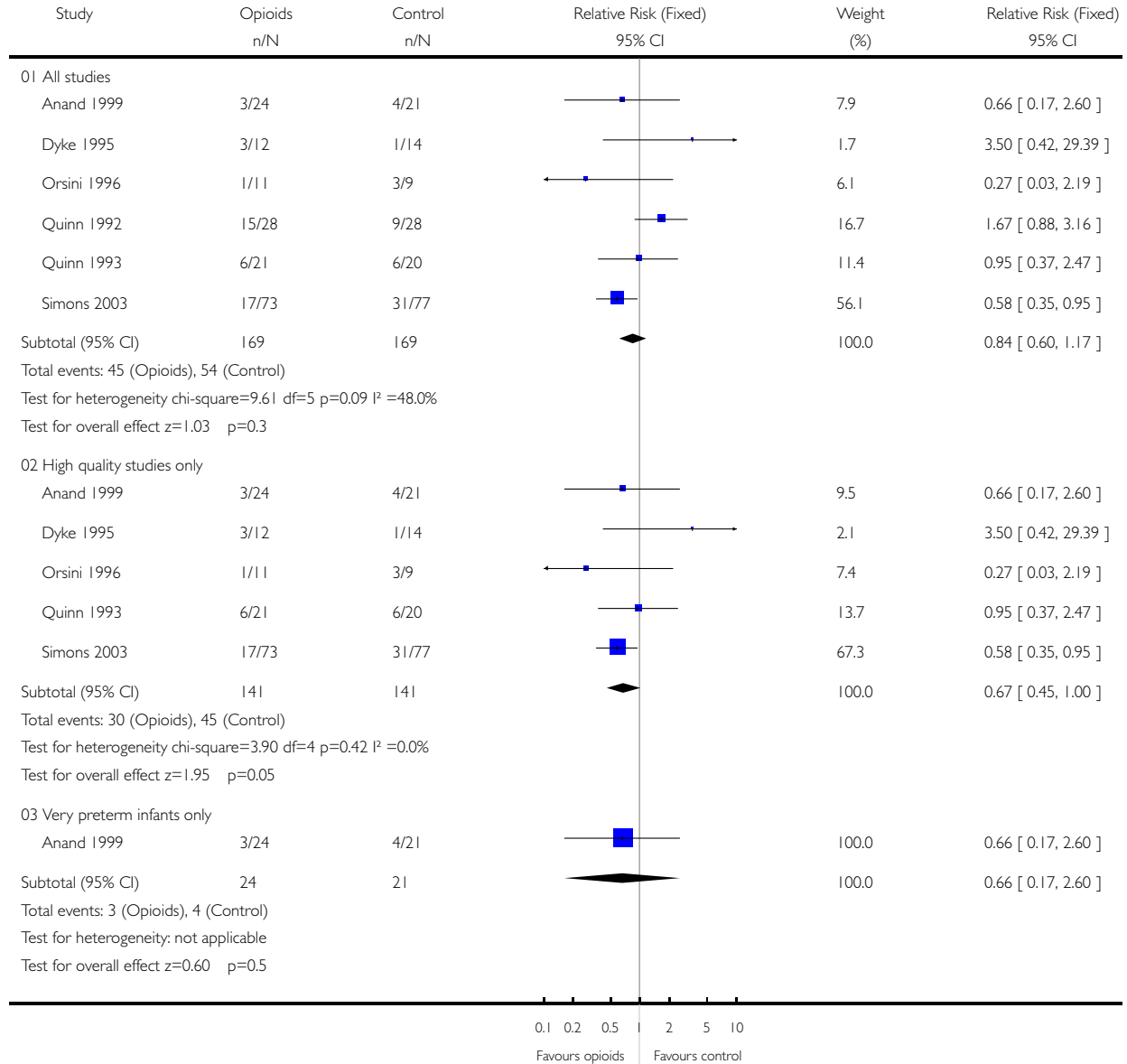


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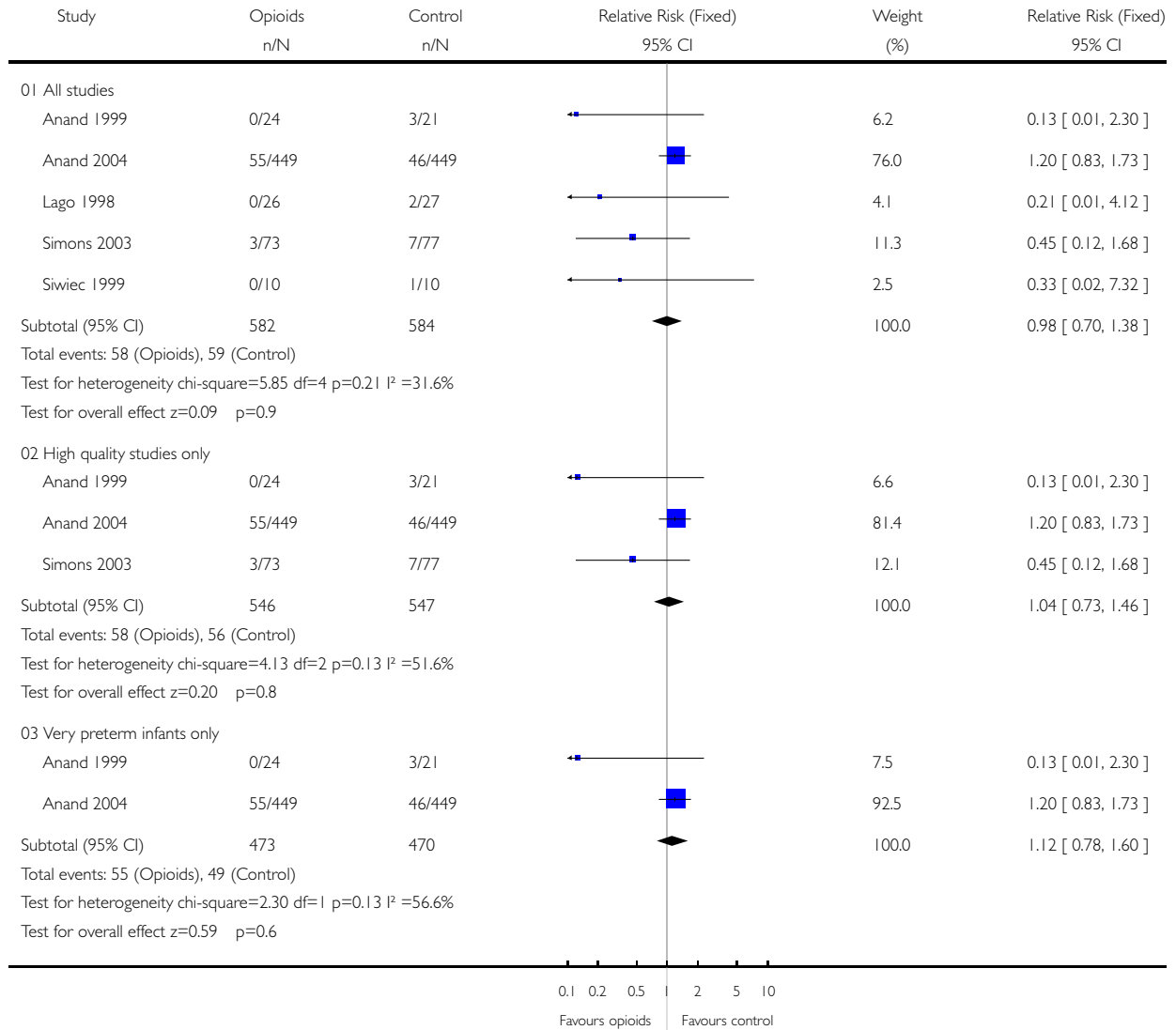
Comparison: 01 Opioids versus placebo or no treatment

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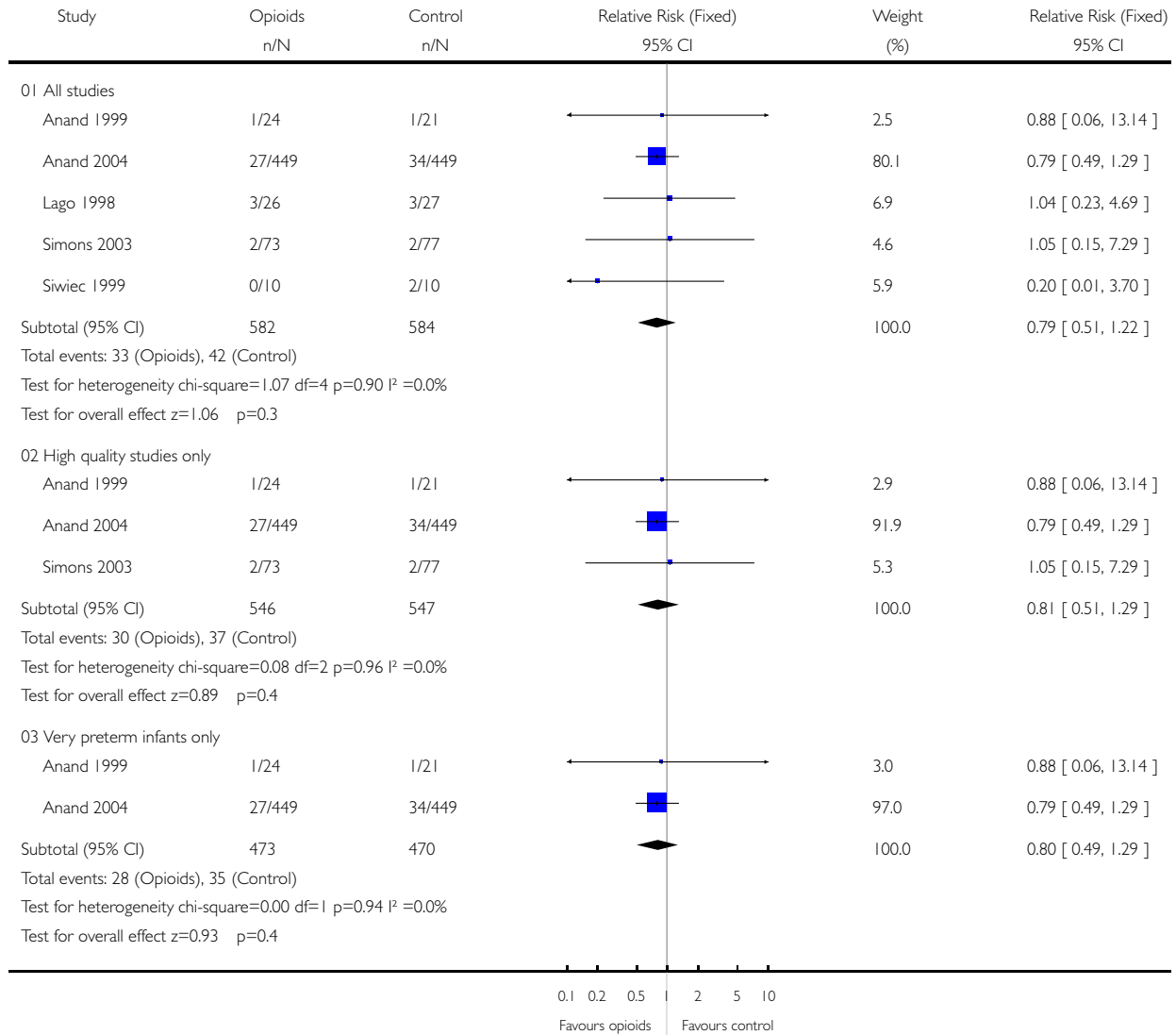
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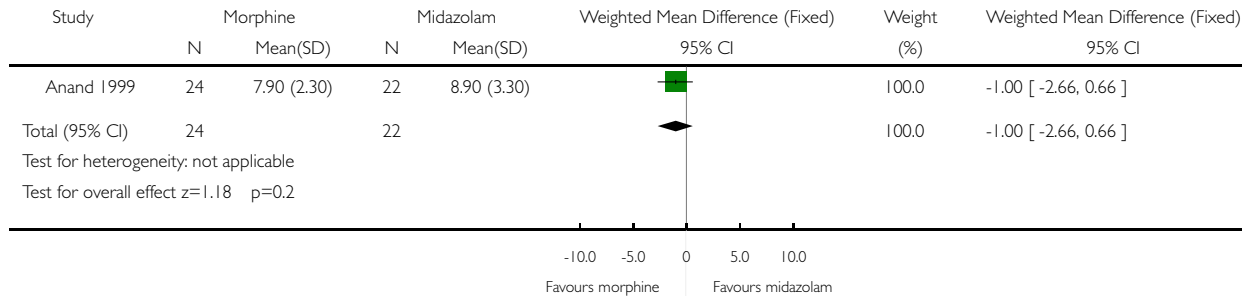


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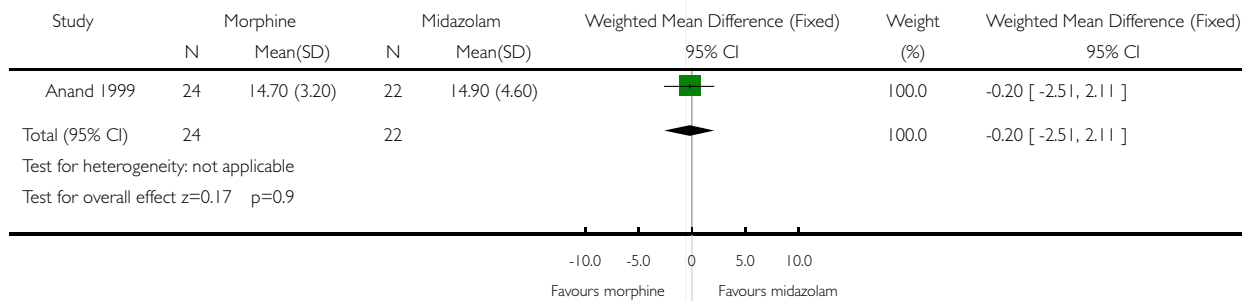


Analysis 02.02. Comparison 02 Opioids versus sedatives, Outcome 02 Pain (COMFORT)

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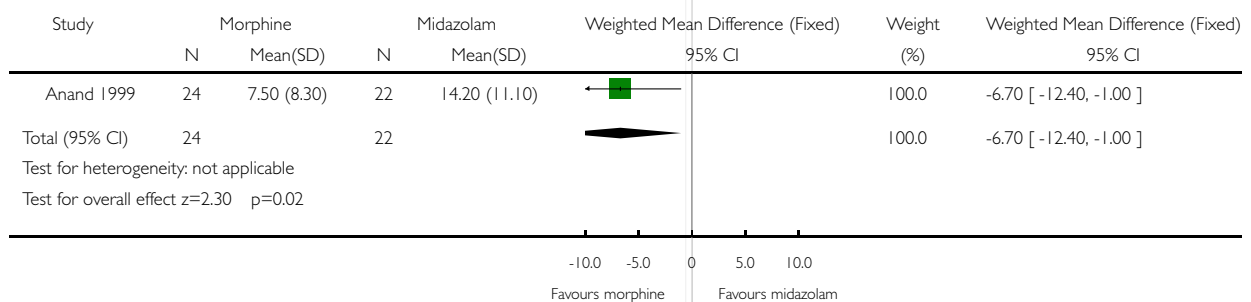


Analysis 02.03. Comparison 02 Opioids versus sedatives, Outcome 03 Duration of mechanical ventilation (days)

Review: Opioids for neonates receiving mechanical ventilation

Comparison: 02 Opioids versus sedatives

Outcome: 03 Duration of mechanical ventilation (days)

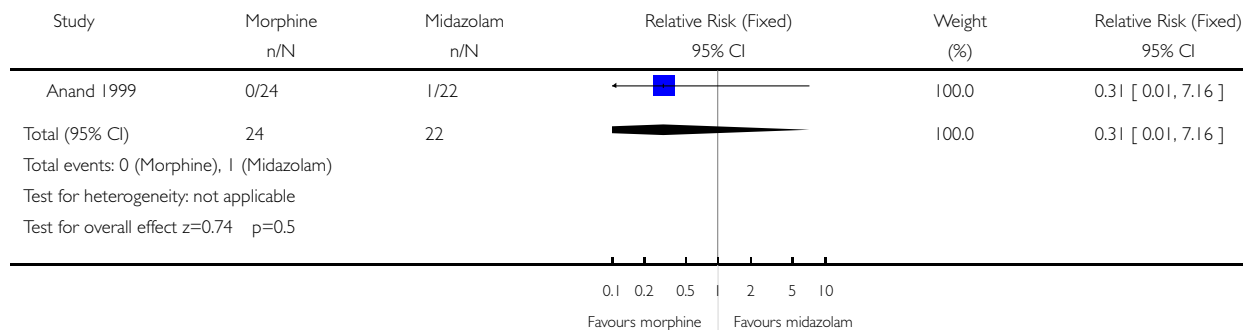


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Review: Opioids for neonates receiving mechanical ventilation

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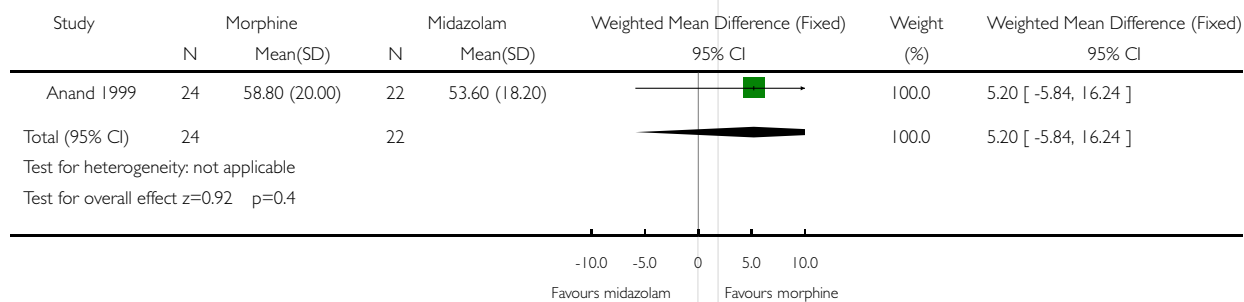


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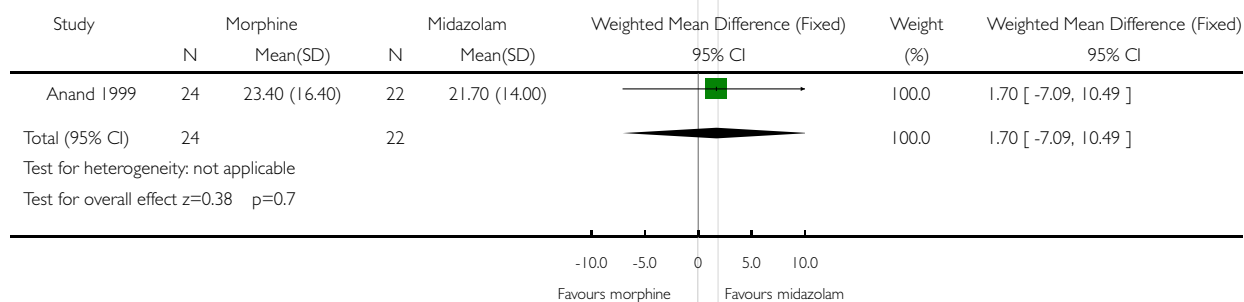


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Review: Opioids for neonates receiving mechanical ventilation

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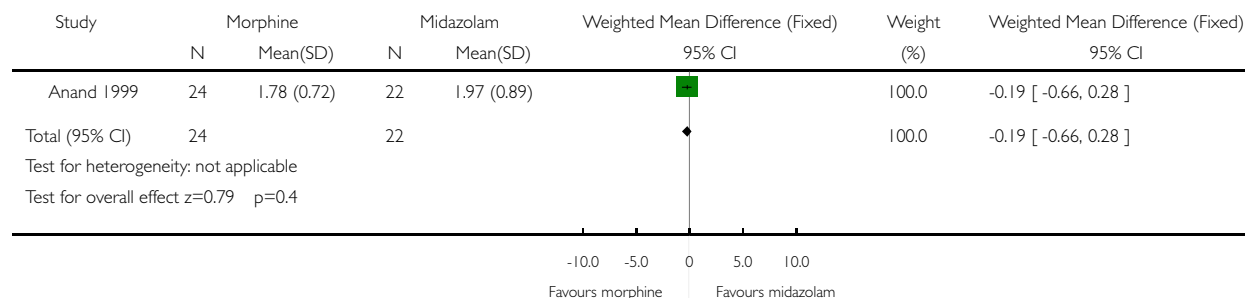


Analysis 02.07. Comparison 02 Opioids versus sedatives, Outcome 07 Weight gain at discharge (g/kg per day)

Review: Opioids for neonates receiving mechanical ventilation

Comparison: 02 Opioids versus sedatives

Outcome: 07 Weight gain at discharge (g/kg per day)

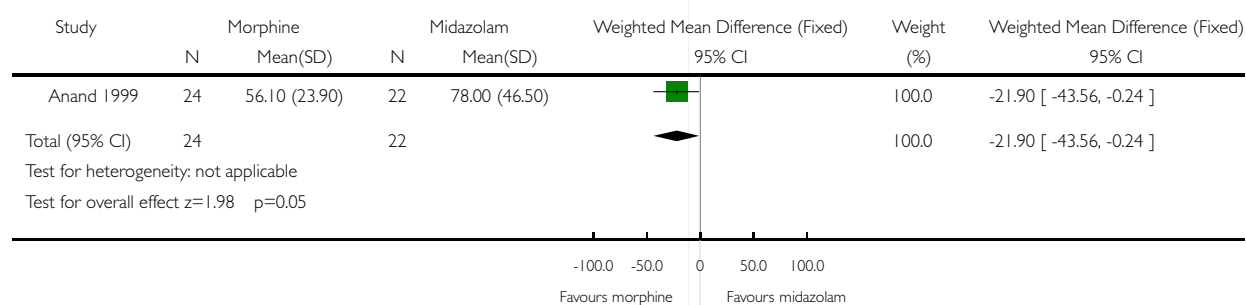


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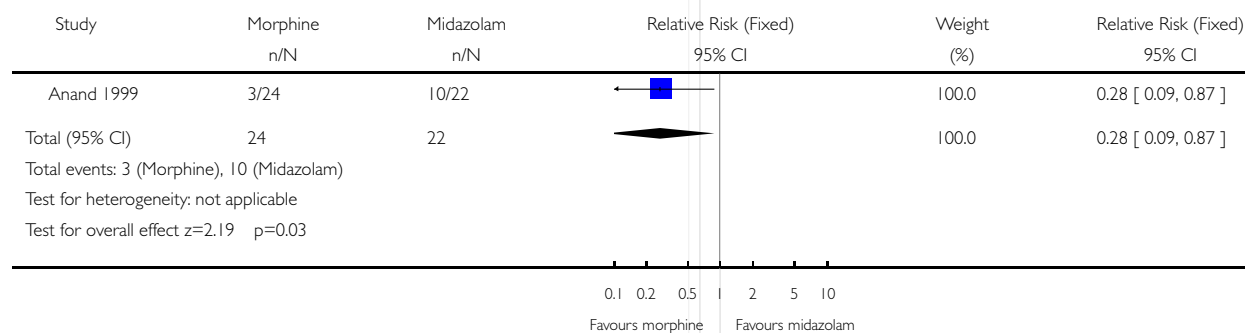


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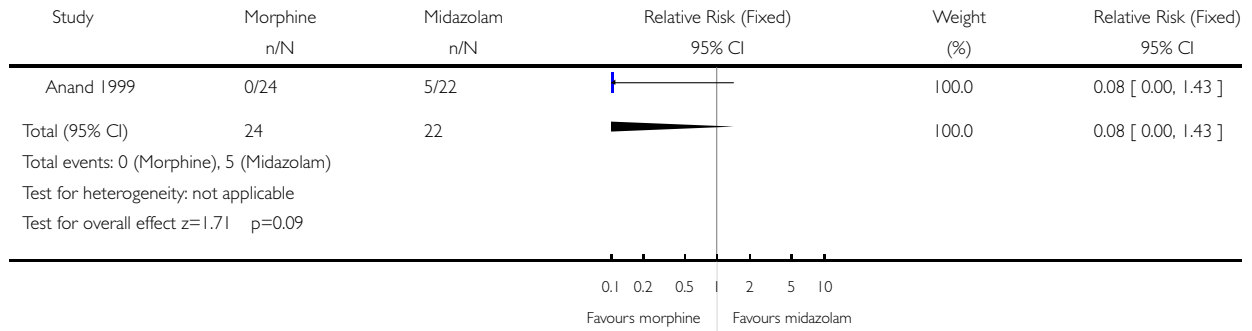
Comparison: 02 Opioids versus sedatives

Outcome: 09 Any intraventricular haemorrhage (IVH)



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Review: Opioids for neonates receiving mechanical ventilation
 Comparison: 02 Opioids versus sedatives
 Outcome: 10 Severe intraventricular heamorrhage (Papile grade 3/4)



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Review: Opioids for neonates receiving mechanical ventilation
 Comparison: 02 Opioids versus sedatives
 Outcome: 11 Periventricular leucomalacia (PVL)

