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Pharmacological pain and sedation interventions for the prevention of intraventricular hemorrhage in preterm infants on assisted ventilation - an overview of systematic reviews (Review)

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[Overview of Reviews]

Pharmacological pain and sedation interventions for the prevention of intraventricular hemorrhage in preterm infants on assisted ventilation - an overview of systematic reviews

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ABSTRACT

Background

Germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) may contribute to neonatal morbidity and mortality and result in long-term neurodevelopmental sequelae. Appropriate pain and sedation management in ventilated preterm infants may decrease the risk of GMH-IVH; however, it might be associated with harms.

Objectives

To summarize the evidence from systematic reviews regarding the effects and safety of pharmacological interventions related to pain and sedation management in order to prevent GMH-IVH in ventilated preterm infants.

Methods

We searched the Cochrane Library August 2022 for reviews on pharmacological interventions for pain and sedation management to prevent GMH-IVH in ventilated preterm infants (< 37 weeks' gestation). We included Cochrane Reviews assessing the following interventions administered within the first week of life: benzodiazepines, paracetamol, opioids, ibuprofen, anesthetics, barbiturates, and antiadrenergics. Primary outcomes were any GMH-IVH (aGMH-IVH), severe IVH (sIVH), all-cause neonatal death (ACND), and major neurodevelopmental disability (MND). We assessed the methodological quality of included reviews using the AMSTAR-2 tool. We used GRADE to assess the certainty of evidence.

Main results

We included seven Cochrane Reviews and one Cochrane Review protocol. The reviews on clonidine and paracetamol did not include randomized controlled trials (RCTs) matching our inclusion criteria. We included 40 RCTs (3791 infants) from reviews on paracetamol for patent ductus arteriosus (3), midazolam (3), phenobarbital (9), opioids (20), and ibuprofen (5). The quality of the included reviews was high. The certainty of the evidence was moderate to very low, because of serious imprecision and study limitations.

Germinal matrix hemorrhage-intraventricular hemorrhage (any grade)

Compared to placebo or no intervention, the evidence is very uncertain about the effects of paracetamol on aGMH-IVH (risk ratio (RR) 0.89, 95% confidence interval (CI) 0.38 to 2.07; 2 RCTs, 82 infants; very low-certainty evidence); midazolam may result in little to no difference in the incidence of aGMH-IVH (RR 1.68, 95% CI 0.87 to 3.24; 3 RCTs, 122 infants; low-certainty evidence); the evidence is very uncertain about the effect of phenobarbital on aGMH-IVH (RR 0.99, 95% CI 0.83 to 1.19; 9 RCTs, 732 infants; very low-certainty evidence); opioids may result in little to no difference in aGMH-IVH (RR 0.85, 95% CI 0.65 to 1.12; 7 RCTs, 469 infants; low-certainty evidence); ibuprofen likely results in little to no difference in aGMH-IVH (RR 0.99, 95% CI 0.81 to 1.21; 4 RCTs, 759 infants; moderate-certainty evidence).

Compared to ibuprofen, the evidence is very uncertain about the effects of paracetamol on aGMH-IVH (RR 1.17, 95% CI 0.31 to 4.34; 1 RCT, 30 infants; very low-certainty evidence). Compared to midazolam, morphine may result in a reduction in aGMH-IVH (RR 0.28, 95% CI 0.09 to 0.87; 1 RCT, 46 infants; low-certainty evidence). Compared to diamorphine, the evidence is very uncertain about the effect of morphine on aGMH-IVH (RR 0.65, 95% CI 0.40 to 1.07; 1 RCT, 88 infants; very low-certainty evidence).

Severe intraventricular hemorrhage (grade 3 to 4)

Compared to placebo or no intervention, the evidence is very uncertain about the effect of paracetamol on sIVH (RR 1.80, 95% CI 0.43 to 7.49; 2 RCTs, 82 infants; very low-certainty evidence) and of phenobarbital (grade 3 to 4) (RR 0.91, 95% CI 0.66 to 1.25; 9 RCTs, 732 infants; very low-certainty evidence); opioids may result in little to no difference in sIVH (grade 3 to 4) (RR 0.98, 95% CI 0.71 to 1.34; 6 RCTs, 1299 infants; low-certainty evidence); ibuprofen may result in little to no difference in sIVH (grade 3 to 4) (RR 0.82, 95% CI 0.54 to 1.26; 4 RCTs, 747 infants; low-certainty evidence). No studies on midazolam reported this outcome.

Compared to ibuprofen, the evidence is very uncertain about the effects of paracetamol on sIVH (RR 2.65, 95% CI 0.12 to 60.21; 1 RCT, 30 infants; very low-certainty evidence). Compared to midazolam, the evidence is very uncertain about the effect of morphine on sIVH (grade 3 to 4) (RR 0.08, 95% CI 0.00 to 1.43; 1 RCT, 46 infants; very low-certainty evidence). Compared to fentanyl, the evidence is very uncertain about the effect of morphine on sIVH (grade 3 to 4) (RR 0.59, 95% CI 0.18 to 1.95; 1 RCT, 163 infants; very low-certainty evidence).

All-cause neonatal death

Compared to placebo or no intervention, the evidence is very uncertain about the effect of phenobarbital on ACND (RR 0.94, 95% CI 0.51 to 1.72; 3 RCTs, 203 infants; very low-certainty evidence); opioids likely result in little to no difference in ACND (RR 1.12, 95% CI 0.80 to 1.55; 5 RCTs, 1189 infants; moderate-certainty evidence); the evidence is very uncertain about the effect of ibuprofen on ACND (RR 1.00, 95% CI 0.38 to 2.64; 2 RCTs, 112 infants; very low-certainty evidence).

Compared to midazolam, the evidence is very uncertain about the effect of morphine on ACND (RR 0.31, 95% CI 0.01 to 7.16; 1 RCT, 46 infants; very low-certainty evidence). Compared to diamorphine, the evidence is very uncertain about the effect of morphine on ACND (RR 1.17, 95% CI 0.43 to 3.19; 1 RCT, 88 infants; very low-certainty evidence).

Major neurodevelopmental disability

Compared to placebo, the evidence is very uncertain about the effect of opioids on MND at 18 to 24 months (RR 2.00, 95% CI 0.39 to 10.29; 1 RCT, 78 infants; very low-certainty evidence) and at five to six years (RR 1.6, 95% CI 0.56 to 4.56; 1 RCT, 95 infants; very low-certainty evidence). No studies on other drugs reported this outcome.

Authors' conclusions

None of the reported studies had an impact on aGMH-IVH, sIVH, ACND, or MND. The certainty of the evidence ranged from moderate to very low.

Large RCTs of rigorous methodology are needed to achieve an optimal information size to assess the effects of pharmacological interventions for pain and sedation management for the prevention of GMH-IVH and mortality in preterm infants. Studies might compare interventions against either placebo or other drugs. Reporting of the outcome data should include the assessment of GMH-IVH and long-term neurodevelopment.

PLAIN LANGUAGE SUMMARY

Medicines to manage pain and discomfort in premature babies assisted with breathing machines and at risk of brain bleeding

Overview question

Do pain medicines reduce brain bleeding and death and improve long-term development in babies born too early ('preterm' babies) who need mechanical breathing assistance?

Background

Preterm babies, especially babies born before 28 weeks of pregnancy are completed, sometimes develop brain bleeding. Babies with less severe bleeding may make a full recovery or have only mild problems later in life. Babies with more serious bleeding may die or have problems later in life. Currently, there are no approaches to prevent or treat brain bleeding.

What did we do?

We searched for Cochrane Reviews that investigated pain medicines for preventing brain bleeding in preterm babies. We assessed the quality of the reviews and summarized their results, thus bringing all the current relevant evidence about these treatments into one place.

What did we find?

We included seven Cochrane Reviews and one protocol (plan) for a Cochrane Review. Two reviews included studies outside our area of interest; for example, they focused on babies born normally at the end of the pregnancy, or babies not needing breathing machines. The other five reviews investigated these medicines: paracetamol (3 studies), midazolam (3 studies), phenobarbital (9 studies), opioids (20 studies), and ibuprofen (5 studies).

Main results

• Less severe brain bleeding

We are moderately confident in the evidence for ibuprofen, which likely results in no important difference in the amount of brain bleeding compared to placebo (an inactive or 'dummy' medicine) (ranging from 19% reduction to 21% increase). We are not confident in the evidence for: morphine compared to diamorphine; other medicines compared to placebo. None of the studies investigating other comparisons between two different medicines looked at this outcome.

• Severe brain bleeding

We are not confident in the evidence for paracetamol, phenobarbital, opioids, and ibuprofen compared to placebo. Similarly, we are not confident in the evidence for: paracetamol compared to ibuprofen; morphine compared to midazolam and fentanyl. No studies on midazolam compared to placebo and morphine to diamorphine reported severe brain bleeding.

• Deaths (from any cause) at 28 days of life

We are moderately confident in the evidence for opioids, which likely results in no important difference compared to placebo (ranging from 20% reduction to 55% increase). We are not confident in the evidence for: phenobarbital and ibuprofen compared to placebo; morphine compared to midazolam and diamorphine. No studies on paracetamol and midazolam compared to placebo, paracetamol to ibuprofen, and morphine to fentanyl reported deaths (from any cause) at 28 days of life.

• Long-term development

We are not confident in the evidence for opioids compared to placebo on babies' long-term development at 18 to 24 months old and at five to six years old. None of the other studies looked at long-term development.

We identified one Cochrane Review protocol on dexmedetomidine, a medicine to manage pain and help babies relax. We plan to include evidence from this review when it is published.

What are the limitations of the evidence?

We are moderately confident in the evidence for ibuprofen on less severe brain bleeding and opioids on deaths (from any cause) compared to placebo. We are not confident in the evidence for the other comparisons and outcomes. The studies either did not report information that we could use or produced findings in which we have very little confidence. These studies were small and used methods likely to introduce errors in their results.

How up to date is this evidence?

The evidence is up to date to August 2022.

BACKGROUND

Description of the condition

Prematurity remains the major risk factor for developing germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH), which occurs in approximately 20% of very low birth weight infants (Siffel 2021). Complications of GMH-IVH, including periventricular hemorrhagic infarction (PVHI), posthemorrhagic ventricular dilatation (PHVD), cerebellar hemorrhagic injury (CHI), and periventricular leukomalacia (PVL), are critical determinants of neonatal morbidity, mortality, and long-term neurodevelopmental sequelae (Sherlock 2005). Although modern perinatal medicine has led to a significant decrease in the overall incidence of GMH-IVH in preterm infants (from 50% in the late 1970s to the current 15% to 25% (Hamrick 2004; Horbar 2002; Philip 1989)), GMH-IVH continues to be a significant problem in the modern neonatal intensive care unit. Advances in neonatal-perinatal medicine have led to a higher incidence of preterm births and a major increase in the survival of preterm infants, reaching as high as 85% to 90% (EXPRESS 2009; Ishii 2013). In addition, the incidence of birth and survival of the smallest preterm infants, who are at the highest risk for developing GMH-IVH and its complications, has increased during the last decade. Specifically, the incidence of GMH-IVH reaches 45% in infants with a birth weight of less than 750 grams, and 35% of these lesions are severe (Wilson-Costello 2005). It has been suggested that the encouraging decrease in the overall incidence of GMH-IVH may have reached a plateau during the last decade (Horbar 2002; Horbar 2012).

These trends may lead to the survival of more critically ill infants, and as a consequence, increase the rate of neurodevelopmental problems caused both by extreme prematurity and GMH-IVH. Approximately 50% to 75% of preterm survivors with GMH-IVH (any grade) develop cerebral palsy, mental retardation, PHVD, or a combination of these conditions, with serious sequelae on neurodevelopmental outcome (Luu 2009). Moreover, around a quarter of non-disabled survivors develop psychiatric disorders and problems with executive function (Indredavik 2010; Nosarti 2007; Whitaker 2011). Hence, GMH-IVH and its resultant neurologic and psychiatric sequelae continue to be an important public health concern worldwide. GMH-IVH in preterm infants is typically diagnosed during the first days of life, 50% on the first day and 90% within the first four days. Between 20% and 40% of these infants undergo progression of hemorrhage during these first days of life (Volpe 2008). The incidence of antenatal GMH-IVH is unclear, although an estimate for intracranial bleeding of 1 in 10,000 pregnancies has been suggested (Vergani 1996). Antenatal fetal intracranial hemorrhages may occur spontaneously or in association with various maternal or fetal conditions. Predisposing maternal conditions include platelet and coagulation disorders, medications (warfarin), illicit drugs (cocaine), seizure, smoking, trauma, amniocentesis, and febrile disease; fetal conditions include twin–twin transfusion, demise of a co-twin, hydrops fetalis, congenital tumors, and feto-maternal hemorrhage (Kutuk 2014). GMH-IVH may undergo spontaneous resolution or, especially for grades 3 and 4, may cause the development of PHVD.

Furthermore, both low- and high-grade GMH-IVH may affect cerebellar growth, resulting in reduced cerebellum volumes and impaired white matter and motor tract microstructure (Morita 2015; Sancak 2016; Sancak 2017; Srinivasan 2006; Tam 2009; Tam 2011). The cerebellum is the fastest growing portion of the brain, its volume increasing five-fold from 24 to 40 weeks of postmenstrual age (Volpe 2009). During this period, extravasation of hemoglobin due to GMH-IVH into cerebrospinal fluid (CSF) and further hemolysis of free hemoglobin may result in deposition of hemosiderin on the cerebellar surface, disturbing the normal development of the cerebellar cortex (Fukumizu 1995; Koeppen 2008; Messerschmidt 2005). It is well recognized that the cerebellum plays a crucial role not only in motor function but also in many higher-order cognitive and affective functions, such as executive functions, working memory, and emotional processing (Van Overwalle 2014; Volpe 2009). Thus, preventing GMH-IVH would also help to preserve cerebellum integrity.

The etiology of GMH-IVH is multifactorial, complex, and heterogeneous. An inherent fragility of the germinal matrix vasculature predisposes for hemorrhage, and fluctuation in the cerebral blood flow induces the rupture of vasculature (Romantsik 2019). The association between cerebral blood flow (CBF) fluctuations and GMH-IVH appearance in ventilated neonates with respiratory distress syndrome (RDS) in the first day of life was suggested by Perlman and colleagues (Perlman 1983). In a subsequent study of the same group, it has been shown that the elimination of CBF fluctuation by neuromuscular paralysis (pancuronium) resulted in reduction of GMH-IVH (Perlman 1985). The question remained whether the fluctuations in CBF were due to breathing against the respirator, which could be explained by increased pleural pressure fluctuations. Two studies confirmed that CBF fluctuations were related to RDS extent and pleural pressure fluctuations and that those could be damped by mechanical ventilation (Mullaart 1994; Perlman 1988). To date, it has been suggested that loss of cerebral autoregulation, which is important to maintain constant CBF, may predispose preterm infants to hemorrhagic and ischemic cerebral injury (Boylan 2000; Tsuji 1998). Impaired autoregulation might correlate to higher mortality (Soul 2007; Wong 2008), and lower cerebral oxygenation predicts higher risk of GMH-IVH (Schwab 2022). Vaginal delivery, low Apgar score, severe respiratory distress syndrome, pneumothorax, hypoxia, hypercapnia, seizures, patent ductus arteriosus, infection, and other conditions seem to increase primarily the fluctuations in the cerebral blood flow and thus represent important risk factors to the development of GMH-IVH (Ballabh 2014). If there are associated platelet or coagulation disorders, the homeostasis mechanisms are impaired, which might accentuate the hemorrhage. Furthermore, the germinal matrix lies within an arterial end zone, and it is directly connected to the deep galenic venous system (Nakamura 1990; Pape 1979), thereby exposing it to insults of arterial ischemia-reperfusion and to venous congestion (Pape 1979; Takashima 1978). The immature deep galenic system is prone to venous congestion and stasis, making it of potentially major importance for the development of GMH-IVH and its complications (Pape 1979; Volpe 2008).

Besides the interventions aimed at possibly halting GMH-IVH progression and reducing its complications, several preventive approaches to GMH-IVH have been proposed, including antenatal and postnatal measures. Several antenatal pharmacologic interventions have been proposed. Antenatal corticosteroids are currently the only modality repeatedly shown in several studies to be associated with a reduction in the incidence of GMH-IVH and overall reduction in mortality rates (McGoldrick 2020). Another appealing antenatal treatment is magnesium sulfate, commonly used for tocolysis but also with vascular stabilizing,

anti-inflammatory, and neuroprotective properties. Some authors have suggested a reduction in the incidence of GMH-IVH following maternal administration of magnesium sulfate (Di Renzo 2005); however, most data do not show any benefit on the incidence of GMH-IVH per se. Other antenatal therapeutics, such as phenobarbital and vitamin K, seemed not to be beneficial for the prevention of GMH-IVH (Whitelaw 2001).

Because GMH-IVH is strongly associated with both intrinsic and extrinsic hemodynamic effectors, optimal ventilation and strict hemodynamic control of the preterm infant are among the cornerstones of preventing GMH-IVH and its progression. Pharmacological interventions used for pain and sedation may impact an incidence of GMH-IVH. This overview analyzes these intervention measures.

Description of the interventions

Neonatal pain has been poorly understood and was often unrecognized until the 1980s, when research describing the developmental physiology of nociception and adverse responses of neonates to noxious stimuli emerged (Anand 1987a; Anand 1987b). Despite early maturation of the ascending neural pathways responsible for nociception, the descending inhibitory pathways, which localize and mitigate pain, do not form until later in maturation (Fitzgerald 1986). Moreover, normal brain development is abruptly interrupted by preterm birth, which results in a unique susceptibility to neurologic remodeling after repetitive noxious stimuli (Taddio 2009). Despite the growing knowledge about the long-term consequences of neonatal pain and discomfort, consensus regarding a safe and effective strategy for controlling these complications in many routine clinical situations is still missing. Non-pharmacological therapies, including non-nutritive sucking and swaddling, form the foundation of neonatal pain and agitation relief, but, alone, they are unlikely to be adequate to provide comfort for moderate to intense pain (Brummelte 2012; Golianu 2007).

The most common indication for sedation is distress during mechanical ventilation. In this setting, sedation may be needed to alleviate stress and facilitate mechanical ventilation (Quinn 1993), thus preventing some of its complications, such as pneumothorax and GMH-IVH (Greenough 1983; Perlman 1985).

How the intervention might work

Multiple pharmacological interventions might help to prevent the occurrence of GMH-IVH, the onset of which is typically in the first days of life. A reduction in GMH-IVH could be achieved by avoiding the pain, stress, and discomfort caused by multiple manual procedures and mechanical ventilation.

Benzodiazepines

Benzodiazepines are used to provide sedation in several clinical settings. Midazolam is the benzodiazepine of choice in the neonatal intensive care unit (NICU). Midazolam is a short-acting benzodiazepine that is very lipophilic in physiological pH, which contributes to its rapid onset of action. It is two to three times more potent than diazepam due to its increased affinity for benzodiazepine receptors, and is preferred to other benzodiazepines because of its water solubility and rapid clearance (Jacqz-Aigrain 1994). The effect of midazolam on the appearance of GMH-IVH was studied in preterm infants undergoing mechanical ventilation (Anand 1999; Jacqz-Aigrain 1994). Concerns have been raised about the potential harms of benzodiazepines on brain development, including an increase in the rate of neuroapoptosis and a decrease in the number of neurons in the dentate gyrus (Stefovska 2008; Young 2005).

Opioids

Opioids act through opioid receptors, which are found in the central and peripheral nervous system and the gastrointestinal tract. Morphine and fentanyl are the most commonly used opioids in the NICU. Recommendations have been issued to promote a more aggressive approach to treatment and prevention of pain in the neonate (AAP 2000). However, uncertainty on long-term effects of opioid treatment remains. Several studies reported occurrence of GMH-IVH during opioid sedation. Small studies conducted before 2000 observed no change on GMH-IVH occurrence between opioid group infants compared to control group infants (Anand 1999; Dyke 1995; Orsini 1996; Quinn 1993), while a larger randomized control trial (RCT) published in 2003 demonstrated a reduction of GMH-IVH rate in the morphine group (Simons 2003).

Anesthetic drugs

Propofol is a short-acting anesthetic agent and its clinical effect lasts for only a few minutes. It acts both through potentiation of gamma-aminobutyric acid-A (GABA-A) receptor activity, thereby slowing the channel-closing time (Krasowski 2001), and also by acting as a sodium channel blocker (Haeseler 2008). The distribution of propofol in neonates is notably different from its distribution in children and adults (Allegaert 2007), and its clearance is slower in cardiopathic and preterm neonates, thus the accumulation risk is increased (Rigby-Jones 2002). Based on the experience in the pediatric population, propofol has been used in neonates and proved to be especially effective in neonates with oropharyngeal complications (Golden 2001). However, serious side effects associated with propofol use have been reported (Welzing 2010). Data on propofol influence on GMH-IVH rate are not available.

Barbiturates

Phenobarbital is a long-acting barbiturate and one of the most commonly used to treat neonatal seizures (Booth 2004). It acts through GABA-A receptors in the central nervous system. It is thought that phenobarbital could act by stabilizing blood pressure, thereby reducing cerebral flow fluctuation (Wimberley 1982). The evidence from animal experimental data showed that barbiturates could be protective against hypoxic/ischemic damage (Steen 1979), and they could act as free radical scavengers after cerebral hypoxic/ischemic injury (Ment 1985). However, phenobarbital might be detrimental to preterm infants by causing respiratory depression, cardiac depression, and hypotension.

Alpha-2 agonists

Alpha-2 agonists (e.g. clonidine and dexmedetomidine) are used as adjunctive (or alternative) sedative agents alongside opioids and benzodiazepines. They have a wide range of effects, including sedation, analgesia, and relief of anxiety (Mantz 2011; Pichot 2012). These effects are mediated through alpha-2 adrenergic receptor subtypes, located in the locus ceruleus. Both clonidine and dexmedetomidine reduce the activity of neurons in the locus ceruleus without affecting the respiratory drive (Hoy 2011).

Moreover, it has been suggested that alpha-2 agonists might have neuroprotective function (Laudenbach 2002; Paris 2006), and anti-inflammatory action (Mantz 2011). The adverse events of alpha-2 agonists, such as bradycardia and hypotension, are mediated via the alpha-2 adrenoreceptors in the medullary dorsal motor nucleus and motor complex, and thus they are independent of sedative effect (Gregoretti 2009; Pichot 2012). A randomized placebo-controlled trial in ventilated term newborns showed that continuous infusion of clonidine decreased fentanyl and midazolam demand, with deeper levels of analgesia and sedation without substantial side effects (Hünseler 2014).

Paracetamol and ibuprofen

In preterm infants, paracetamol and ibuprofen are primarily used for the prevention and treatment of patent ductus arteriosus. However, these drugs are also administered for pain management. Indications for their use include both minor and more invasive procedures, such as pain management during drainage of pneumothorax.

Why it is important to do this overview

There are now numerous intervention reviews available for the prevention of GMH-IVH in preterm infants. The totality of evidence from RCTs of postnatal pharmacological interventions for pain and sedation management has never been assembled before in a systematic and comprehensive way. An 'overview of reviews' provides a clinically meaningful summary of one of the most important topics in neonatology. The overview provides a coherent and up-to-date summary of the totality of evidence, without the need to access many individual systematic reviews. This may help clinicians, policymakers, childbirth educators, and consumers.

OBJECTIVES

To summarize the evidence from systematic reviews regarding the effects and safety of pharmacological interventions related to pain and sedation management in order to prevent GMH-IVH in ventilated preterm infants.

METHODS

Criteria for considering reviews for inclusion

Types of studies

We included any published Cochrane Review on postnatal pharmacological interventions for pain and sedation management in ventilated preterm infants. We identified Cochrane Review protocols and titles for future inclusion.

Types of participants

We included reviews on preterm infants of less than 37 weeks of gestational age on assisted ventilation. As incidence of GMH-IVH dramatically decreases with advancing gestational age, we planned to perform a subgroup analysis for both extreme and very preterm infants.

Types of interventions and comparison

We assessed the following categories of interventions: benzodiazepines, paracetamol, opioids, ibuprofen, anesthetics, barbiturates, and antiadrenergics (Description of the interventions). We excluded other comfort measures and non-pharmacological interventions, such as sucrose.

Interventions must have been started within the first week of life as GMH-IVH commonly occurs in this period. Although causes of GMH-IVH might originate before birth (Kutuk 2014), we excluded reviews on antenatal interventions.

This is an overview of systematic reviews and not a review of primary studies. Due to the large number of possible comparisons among these interventions, we did not plan to specify in advance the comparisons to be included. We expected to retrieve reviews comparing the above-mentioned interventions to:

- placebo or no treatment;
- other interventions.

Types of outcome measures

As the objective of this overview is the prevention of GMH-IVH, we considered only reviews that include GMH-IVH among their outcomes.

Primary outcomes

- Any germinal matrix hemorrhage-intraventricular hemorrhage: any GMH-IVH, ultrasound diagnosis grades 1 to 4 (according to the Papile classification (Papile 1978))
- Severe intraventricular hemorrhage (sIVH), ultrasound diagnosis grades 3 and 4 (according to the Papile classification (Papile 1978))
- All-cause neonatal death (death within 28 days of birth)
- Major neurodevelopmental disability: cerebral palsy, developmental delay (Bayley Mental Developmental Index (Bayley 1993; Bayley 2006) or Griffiths Mental Development Scale assessment more than two standard deviations (SD) below the mean (Griffiths 1954)), intellectual impairment (intelligence quotient (IQ) more than two standard deviations below the mean), blindness (vision < 6/60 in both eyes), or sensorineural deafness requiring amplification (Jacobs 2013). We planned to evaluate each of these components as a separate outcome and to extract data on this long-term outcome from studies that evaluated children after 18 months of chronological age. We planned to assess separately data on children aged 18 to 24 months and those aged three to five years.

Secondary outcomes

- All-cause death during initial hospitalization
- Any retinopathy of prematurity: any stage (ICROP 1984)
- Severe retinopathy of prematurity: stage 3 or greater (ICROP 1984)
- Cerebellar hemorrhage at brain ultrasound in the first month of life (yes/no; Graça 2013)
- Cystic periventricular leukomalacia at brain ultrasound in the first month of life (yes/no); or at term equivalent age (yes/no)
- Brain magnetic resonance imaging (MRI) abnormalities at term equivalent age (yes/no), defined as white matter lesions (i.e. cavitations; Rutherford 2010) and punctate lesions (Cornette 2002); GMH-IVH (Parodi 2015); or cerebellar hemorrhage (Limperopoulos 2007)

Search methods for identification of reviews

The Information Specialist of Cochrane Sweden searched the Cochrane Library on 30 August 2022 for reviews on pharmacological interventions for pain and sedation management to prevent GMH-IVH in ventilated preterm infants (< 37 weeks' gestation) (Appendix 1).

Data collection and analysis

The methodology for data collection and analysis is based on Chapter 22 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Selection of reviews

Two review authors (AS, TP) independently checked reviews on postnatal pharmacological interventions for pain and sedation management in ventilated preterm infants for inclusion. We planned to resolve any disagreement through discussion or, if required, to consult a third review author (MB). As the objective of this overview is the prevention of GMH-IVH, we considered only reviews that included GMH-IVH among their outcomes.

Data extraction and management

Two review authors (AS, TP) independently extracted data from the reviews using a predefined data extraction form. We resolved discrepancies through discussion or, if required, we consulted a third review author (MB).

We extracted the following key information from each review:

- objective or clinical research question;
- date that the review was assessed as up to date;
- number of included trials;
- number and characteristics of participants (sex, gestational age);
- interventions and comparisons;
- outcome measures;
- effect measurements for variables such as GMH-IVH occurrence and severity, death, and other secondary outcomes (risk ratio (RR) with the 95% confidence interval (CI); number of studies; number of participants reporting on each outcome);
- overall judgment on the certainty of evidence included (GRADE table);
- strengths and limitations of the review.

We planned to retrieve this information from the reports of the included reviews. However, we expected that some details needed for this overview were only available from the original primary studies (e.g. gestational age, GMH-IVH in different subpopulations). In these cases, we analyzed the reports of the studies included in each review and presented the effects sizes from these adapted forest plots in the overview, in Table 1.

We entered data into Review Manager 5 software and checked for accuracy (Review Manager 2020). When the information was unobtainable from the published reports, we planned to contact the review authors or authors of the original reports to provide clarification and further details.

Assessment of methodological quality of included reviews

Quality of included reviews

Two review authors (AS, TP) independently assessed the methodological quality of the included reviews using the AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) measurement tool (Shea 2017). This instrument has good inter-rater agreement, test-retest reliability, and face and construct validity (Shea 2017). Specifically, we addressed the following questions.

- Did the research questions and inclusion criteria for the review include the components of PICO (Population, Intervention, Comparison(s), Outcome)?
- Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? *
- Did the review authors explain their selection of the study designs for inclusion in the review?
- Did the review authors use a comprehensive literature search strategy? *
- Did the review authors perform study selection in duplicate?
- Did the review authors perform data extraction in duplicate?
- Did the review authors provide a list of excluded studies and justify the exclusions? *
- Did the review authors describe the included studies in adequate detail?
- Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? *
- Did the review authors report on the sources of funding for the studies included in the review?
- If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? *
- If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
- Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? *
- Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
- If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? *
- Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Possible responses to each question are 'yes' and 'no'. A 'partial yes' response is applicable in some instances (Shea 2017). We provided a rationale for judgments for each AMSTAR-2 item. Seven of 16 domains (marked with an * in the list above) are defined as critical because they can "critically" affect the validity of a review. We did not report a summary score, as recommend by developers of AMSTAR-2 (Shea 2017). However, we did consider the potential impact of an inadequate rating for each item.

Because three authors of this overview are also the authors of one (MGC) and three (OR, MB) of the included reviews, AS and TP conducted the quality assessments.

Certainty of the body of evidence in included reviews

We created summary of findings tables for the four primary outcomes (Table 1), and used the GRADE approach to assess the certainty of evidence for the effects of interventions for pain and sedation on GMH-IVH and mortality (Guyatt 2011). When summary of findings tables were not available in the included reviews or did not completely match the PICO of this overview (e.g. different gestational age or definition of the outcomes), we planned to prepare them ourselves. When such tables were reported in the included reviews, we 're-graded' the certainty of evidence of the four primary outcomes to ensure a homogeneous assessment. Potential discrepancies with the original reviews are discussed in this overview (Differences between protocol and review). We graded the certainty of evidence considering the following criteria: study limitations (that is, risk of bias), consistency of effect, imprecision, indirectness, and publication bias.

Data synthesis

We provided a narrative summary of the method and results of each of the included reviews and summarized this information using tables (e.g. characteristics of included reviews, summary of quality of evidence within individual systematic reviews, AMSTAR-2 evaluation for each systematic review).

For primary and secondary outcomes, we reported the effect estimates and 95% CIs as reported in the meta-analyses conducted by the authors of the systematic reviews, when available.

We reformatted data in text, table, and figures. A table on outcomes shows: comparison; number of participants and studies; measure of effect with 95% CI; I^2; certainty of evidence (GRADE).

We did not pool data deriving from different reviews in meta-analyses, as we expected substantial heterogeneity. We did not draw inferences about the comparative effectiveness of multiple interventions; that is, we avoided any ranking (which would require network meta-analysis). However, we planned to classify the interventions that were effective for the prevention of GMH-IVH and the ones that were not, according to effect estimates and 95% CIs, as reported in the meta-analyses conducted by the authors of the systematic reviews. However, if some details needed for this overview were only available from the original primary studies (e.g. gestational age, GMH-IVH in different subpopulations), we planned to analyze the reports of the studies included in each review to re-calculate effect estimates and 95% CIs (fixed-effect model). Whenever feasible, we summarized data on primary outcomes in summary of findings tables as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 11 (Higgins 2021). We constructed tables based on each comparison using the GRADE profiler (GRADEpro; tech.cochrane.org/revman/gradepro). For future updates of this overview, if the data allow, we may perform some indirect comparisons of interventions across reviews for the primary outcomes.

We planned to present data from the following subgroups (if these data were available within the included systematic reviews).

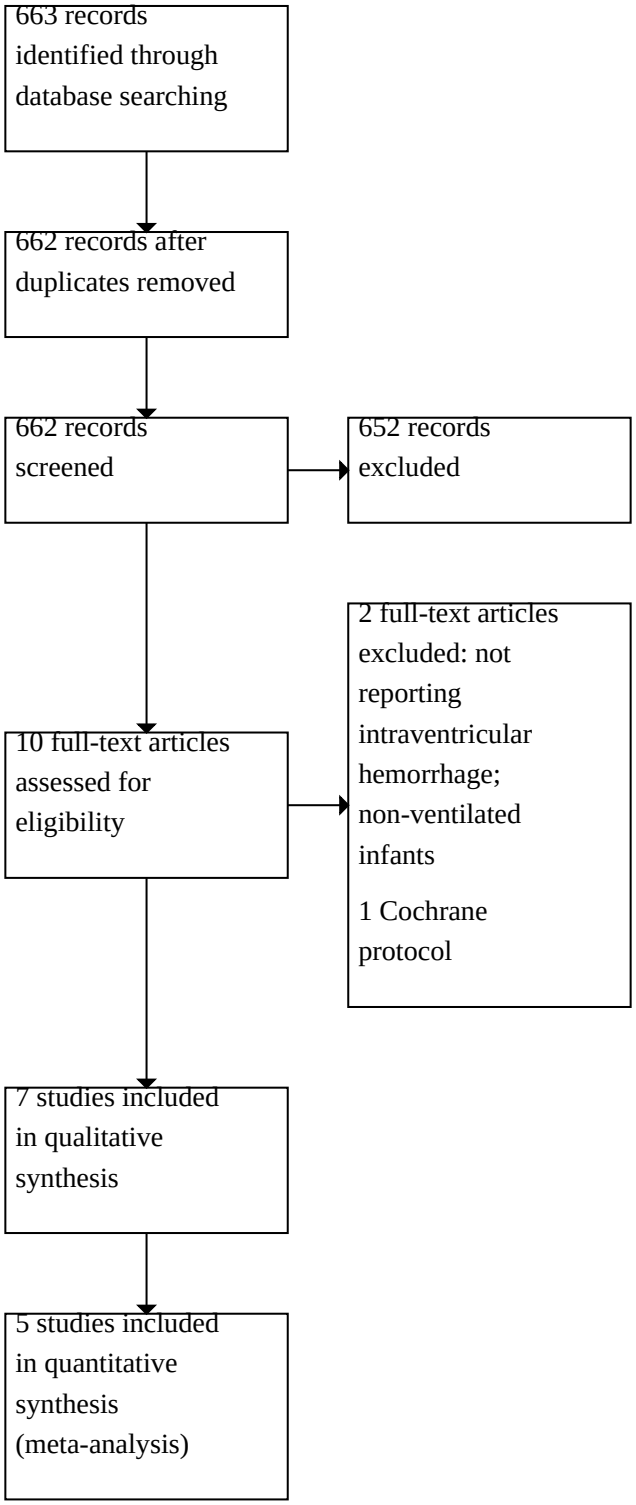
- Gestational age, with three subgroups: extreme preterm (< 28 weeks) versus very preterm (≥ 28 but < 32 weeks) versus preterm infants (≥ 32 but < 37 weeks).
- Birth weight, with three subgroups: very low birth weight (less than 1500 grams) versus low birth weight (≥ 1500 grams but < 2500 grams) versus 2500 grams or higher.
- Timing of initiation of intervention, with three subgroups: within less than 12 hours of life versus within less than 72 hours of life versus at 72 hours of life or higher but within seven days of life.

RESULTS

Results of the search

The literature search identified 662 references. We excluded 652 based on title/abstract, and reviewed 10 full-texts. We excluded two reviews: Bäcke 2022 did not report GMH-IVH; Shah 2011 included non-ventilated infants. We included seven reviews (Bellù 2021; Jasani 2022; Ng 2017; Ohlsson 2020a; Ohlsson 2020b; Romantsik 2017a; Romantsik 2023). We identified one protocol for a Cochrane Review (Ibrahim 2016). The selection process is presented in Figure 1. Characteristics of the included reviews are provided in Table 2.

Figure 1. Review flow diagram



From the seven included reviews, we identified 39 trials. We excluded studies not meeting our inclusion criteria from the reviews on paracetamol (Jasani 2022); phenobarbitol (Romantsik 2017a); ibuprofen (Ohlsson 2020b); and opioids (Bellù 2021). We included all three studies included in the review on midazolam (Ng 2017). The Anand 1999 study was found in both the midazolam (Ng 2017) and opioids (Bellù 2021) reviews.

Description of included reviews

Search strategies in each review were run between May 2016 (Ohlsson 2020a) and January 2022 (Romantsik 2023). Two reviews did not include any RCTs matching the inclusion criteria of this overview: Romantsik 2017a included only one RCT with term infants and Ohlsson 2020a included RCTs with either not-ventilated infants, term infants, or intervention after seven days of life (see Table 2 for additional information).

We excluded trials from the remaining reviews, except for the review on midazolam, where all three of the included RCTs matched the inclusion criteria of this Cochrane Overview. We summarize the population, intervention, and comparison of the reviews on paracetamol (Jasani 2022), midazolam (Ng 2017), phenobarbital (Romantsik 2023), opioids (Bellù 2021), and ibuprofen (Ohlsson 2020b) in Table 3, Table 4, Table 5, Table 6 and Table 7, respectively.

Effect estimates for the primary and secondary outcomes of this overview are shown compared to placebo or active comparators in Table 8 and Table 9, respectively. The risk of bias of the five informative reviews (i.e. those reviews that included RCTs meeting this *overview's* inclusion criteria) is depicted in Table 10, as assessed by the authors of the Cochrane Reviews, but only for those RCTs included in this overview. The summary of findings table for the primary outcomes of this overview, as assessed by the authors of this overview, is shown in Table 1. We assessed the quality of the included reviews with AMSTAR-2 and have reported these assessments in Table 11.

The three RCTs on paracetamol included in Jasani 2022 enrolled 112 infants. Paracetamol was compared to ibuprofen in one study (Jafari 2019); and to placebo in two studies (Hochwald 2018; Schindler 2021).

From the Bellù 2021 review on opioids, we included 19 RCTs enrolling 1978 infants. Eight RCTs compared opioids to other active pharmacological interventions (i.e. three RCTs compared morphine to fentanyl (Ionides 1994; Naderi 2017; Saarenmaa 1999), two trials compared morphine to midazolam (Anand 1999; Liem 1999), one trial compared morphine to diamorphine (Wood 1998), one compared morphine to remifentanil (e Silva 2008), and one morphine with pancuronium (Quinn 1992)). Two of these RCTs had three study arms: in Anand 1999, the other comparison was placebo; in Quinn 1992, opioids were also compared to opioids and another active pharmacological intervention. The remaining 11 RCTs compared opioids to placebo or no intervention: in those, five RCTs assessed the effects of morphine (Anand 2004; Dyke 1995; Quinn 1993; Simons 2003; Siwiec 1999); and six RCTs evaluated fentanyl (Ancora 2013; Guinsburg 1998; Lago 1998; Lago 1999; Orsini 1996; Qiu 2019).

The three RCTs on midazolam included in the Ng 2017 review enrolled 146 infants. Two of the RCTs compared midazolam to placebo (Arya 2001; Jacqz-Aigrain 1994). The remaining RCT included three arms (morphine, midazolam, and placebo arms) (Anand 1999), and was also included in the opioids review (Bellù 2021).

The nine RCTs on phenobarbital (Romantsik 2023), and five on ibuprofen (Ohlsson 2020b), enrolled 742 and 813 infants, respectively. Phenobarbital was compared to an unspecified control group in three RCTs (Bedard 1984; Donn 1981; Ruth 1985), no treatment in four RCTs (Mas-Munoz 1993; Morgan 1982; Porter 1985; Ruth 1988), supportive care in one RCT (Anwar 1986), and non-specified placebo in one RCT (Kuban 1986). Ibuprofen was compared to placebo in four RCTs (Dani 2005; Gournay 2004; Sangtawesin 2008; Van Overmeire 2004), and no treatment in one RCT (De Carolis 2000).

Overall, the five informative reviews (out of seven reviews) included in this overview enrolled 40 RCTs (3791 infants).

Methodological quality of included reviews

Risk of bias in the included trials is summarized in Table 10. The certainty of the evidence for the primary outcomes of this overview is summarized in Table 1.

We assessed the quality of the included reviews with AMSTAR-2 and reported this in Table 11. Overall, the quality of the included reviews was high, with all of them fulfilling the critical domains of AMSTAR 2.

Effect of interventions

The comparator was placebo or ibuprofen in the review on paracetamol (Jasani 2022). The comparator was placebo, no intervention, or unspecified control group in the reviews on phenobarbital (Romantsik 2023), ibuprofen (Ohlsson 2020b), and in two of the three RCTs on midazolam (Ng 2017). As the third trial included in the Ng 2017 review included three arms (midazolam, placebo, and morphine) (Anand 1999), the comparison to morphine is listed in the opioids review (Bellù 2021). In the Bellù 2021 review on opioids, the opioids were also compared to other analgesics/sedatives (midazolam), and other opioids (diamorphine and fentanyl), which were analyzed separately. We did not conduct subgroup analyses because of the paucity of studies included in each analysis.

Comparisons to placebo or no intervention

Primary outcomes

Primary outcomes are shown in Table 1.

Any grade GMH-IVH

- **Paracetamol.** Two studies reported this outcome (Hochwald 2018; Schindler 2021; in the Jasani 2022 review). The evidence is very uncertain about the effects of paracetamol on GMH-IVH (any grade) compared to placebo or no intervention (RR 0.89, 95% CI 0.38 to 2.07; 2 RCTs, 82 infants; very low-certainty evidence).
- **Midazolam.** Three studies reported this outcome (Anand 1999; Arya 2001; Jacqz-Aigrain 1994; in the Ng 2017 review). Midazolam may result in little to no difference in reducing GMH-IVH (any grade) compared with placebo or no intervention (RR 1.68, 95% CI 0.87 to 3.24; 3 RCTs, 122 infants; low-certainty evidence).

- **Phenobarbital.** Nine studies reported this outcome (Anwar 1986; Bedard 1984; Donn 1981; Kuban 1986; Mas-Munoz 1993; Morgan 1982; Porter 1985; Ruth 1985; Ruth 1988; in the Romantsik 2023 review). Compared to placebo or no intervention, the evidence is very uncertain about the effect of phenobarbital on GMH-IVH (any grade) (RR 0.99, 95% CI 0.83 to 1.19; 9 RCTs, 732 infants; very low-certainty evidence).
- **Opioids.** Seven studies reported this outcome (Anand 1999; Ancora 2013; Dyke 1995; Orsini 1996; Quinn 1992; Quinn 1993; Simons 2003; in the Bellù 2021 review). Opioids may result in little to no difference in reducing GMH-IVH (any grade) compared with placebo or no intervention (RR 0.85, 95% CI 0.65 to 1.12; 7 RCTs, 469 infants; low-certainty evidence).
- **Ibuprofen.** Four studies reported this outcome (Dani 2005; Gournay 2004; Sangtawesin 2008; Van Overmeire 2004; in the Ohlsson 2020b review). Ibuprofen likely results in little to no difference in reducing GMH-IVH (any grade) compared with placebo or no intervention (RR 0.99, 95% CI 0.81 to 1.21; 4 RCTs, 759 infants; moderate-certainty evidence).

Severe IVH (sIVH) (grade 3 to 4)

- **Paracetamol.** Two studies reported this outcome (Hochwald 2018; Schindler 2021; in the Jasani 2022 review). The evidence is very uncertain about the effects of paracetamol on sIVH (grade 3 to 4) compared to placebo or no intervention (RR 1.80, 95% CI 0.43 to 7.49; 2 RCTs, 82 infants; very low-certainty evidence).
- **Midazolam.** No studies reported this outcome.
- **Phenobarbital.** Nine studies reported this outcome (Anwar 1986; Bedard 1984; Donn 1981; Kuban 1986; Mas-Munoz 1993; Morgan 1982; Porter 1985; Ruth 1985; Ruth 1988; in the Romantsik 2023 review). Compared to placebo or no intervention, the evidence is very uncertain about the effect of phenobarbital on sIVH (grade 3 to 4) (RR 0.91, 95% CI 0.66 to 1.25; 9 RCTs, 732 infants; very low-certainty evidence).
- **Opioids.** Six studies reported this outcome (Anand 1999; Anand 2004; Ancora 2013; Lago 1998; Simons 2003; Siwiec 1999; in the Bellù 2021 review). Opioids may result in little to no difference in reducing sIVH (grade 3 to 4) compared with placebo or no intervention (RR 0.98, 95% CI 0.71 to 1.34; 6 RCTs, 1299 infants; low-certainty evidence).
- **Ibuprofen.** Four studies reported this outcome (Dani 2005; De Carolis 2000; Gournay 2004; Van Overmeire 2004; in the Ohlsson 2020b review). Ibuprofen may have little or no effect in reducing sIVH (grade 3 to4) compared with placebo or no intervention (RR 0.82, 95% CI 0.54 to 1.26; 4 RCTs, 747 infants; low-certainty evidence).

All-cause neonatal death

- **Paracetamol.** No studies reported this outcome.
- **Midazolam.** No studies reported this outcome.
- **Phenobarbital.** Three studies reported this outcome (Bedard 1984; Mas-Munoz 1993; Ruth 1988; in the Romantsik 2023 review). Compared to placebo or no intervention, the evidence is very uncertain about the effect of phenobarbital on all-cause neonatal death (RR 0.94, 95% CI 0.51 to 1.72; 3 RCTs, 203 infants; very low-certainty evidence).
- **Opioids.** Five studies reported this outcome (Anand 1999; Anand 2004; Lago 1998; Quinn 1993; Simons 2003; in the Bellù 2021 review). Opioids likely result in little to no difference in reducing all-cause neonatal death compared with placebo or no intervention (RR 1.12, 95% CI 0.80 to 1.55; 5 RCTs, 1189 infants; moderate-certainty evidence).
- **Ibuprofen.** Two studies reported this outcome (De Carolis 2000; Sangtawesin 2008; in the Ohlsson 2020b review). Compared to placebo or no intervention, the evidence is very uncertain about the effect of ibuprofen on all-cause neonatal death (RR 1.00, 95% CI 0.38 to 2.64; 2 RCTs, 112 infants; very low-certainty evidence).

Major neurodevelopmental disabilities

- **Paracetamol.** No studies reported this outcome.
- **Midazolam.** No studies reported this outcome.
- **Phenobarbital.** No studies reported this outcome.
- **Opioids.**
  - One study reported this outcome at 18 to 24 months (Ancora 2013; in the Bellù 2021 review). Compared to placebo or no intervention, the evidence is very uncertain about the effect of opioids in reducing major neurodevelopmental disability at 18 to 24 months (RR 2.00, 95% CI 0.39 to 10.29; 1 RCT, 78 infants; very low-certainty evidence).
  - One study reported this outcome at five to six years (Quinn 1993; in the Bellù 2021 review). Compared to placebo or no intervention, the evidence is very uncertain about the effect of opioids in major neurodevelopmental disability at five to six years (RR 1.6, 95% CI 0.56 to 4.56; 1 RCT, 95 infants; very low-certainty evidence).
- **Ibuprofen.** No studies reported this outcome.

Secondary outcomes

Secondary outcomes for this comparison are reported in Table 8.

All-cause death during initial hospitalization

- **Paracetamol.** No studies reported this outcome.
- **Midazolam.** Three studies reported this outcome (Anand 1999; Arya 2001; Jacqz-Aigrain 1994; in the Ng 2017 review). Midazolam likely results in little or no effect in reducing all-cause death during initial hospitalization compared with placebo or no intervention (RR 0.79, 95% CI 0.40 to 1.56; 3 RCTs, 122 infants; moderate-certainty evidence).
- **Phenobarbital.** Eight studies reported this outcome (Anwar 1986; Bedard 1984; Donn 1981; Kuban 1986; Mas-Munoz 1993; Morgan 1982; Porter 1985; Ruth 1988; in the Romantsik 2023 review). Compared to placebo or no intervention, the evidence is very uncertain about the effect of phenobarbital on death during initial hospitalization (RR 0.90, 95% CI 0.64 to 1.26; 8 RCTs, 680 infants; very low-certainty evidence).
- **Opioids.** Four studies reported this outcome (Dyke 1995; Lago 1998; Quinn 1992; Quinn 1993; in the Bellù 2021 review). Compared to placebo or no intervention, the evidence is very uncertain about the effect of opioids on death during initial hospitalization (RR 0.99, 95% CI 0.52 to 1.88; 4 RCTs, 178 infants; very low-certainty evidence).
- **Ibuprofen.** Three studies reported this outcome (Dani 2005; De Carolis 2000; Van Overmeire 2004; in the Ohlsson 2020b review). Ibuprofen may have little or no effect in reducing all-cause death during initial hospitalization compared with placebo or no intervention (RR 0.91, 95% CI 0.63 to 1.33; 3 RCTs, 620 infants; low-certainty evidence).

Any retinopathy of prematurity (ROP) (any stage)

- **Paracetamol.** One study reported this outcome (Schindler 2021; in the Jasani 2022 review). The evidence is very uncertain about the effect of paracetamol in reducing ROP of any grade compared with placebo or no intervention (RR 0.93, 95% CI 0.53 to 1.61; 1 RCT, 58 infants; very low-certainty evidence).
- **Midazolam.** No studies reported this outcome.
- **Phenobarbital.** No studies reported this outcome.
- **Opioids.** No studies reported this outcome.
- **Ibuprofen.** Two studies reported this outcome (Dani 2005; Sangtawesin 2008; in the Ohlsson 2020b review). Ibuprofen may have little or no effect in reducing ROP of any grade compared with placebo or no intervention (RR 1.09, 95% CI 0.75 to 1.60; 2 RCTs, 213 infants; low-certainty evidence).

Severe ROP (stage 3 or greater)

- **Paracetamol.** No studies reported this outcome.
- **Midazolam.** No studies reported this outcome.
- **Phenobarbital.** No studies reported this outcome.
- **Opioids.** No studies reported this outcome.
- **Ibuprofen.** One study reported this outcome (Sangtawesin 2008; in the Ohlsson 2020b review). The evidence is very uncertain about the effect of ibuprofen in reducing severe ROP (stage 3 or greater) compared with placebo or no intervention (RR not estimable; RD 0.00, 95% CI -0.06 to 0.06; 1 RCT, 62 infants; very low-certainty evidence).

Cerebellar hemorrhage

- No studies out of the five included reviews reported this outcome (Bellù 2021; Jasani 2022; Ng 2017; Ohlsson 2020b; Romantsik 2023).

Cystic periventricular leukomalacia (PVL)

- **Paracetamol.** No studies reported this outcome.
- **Midazolam.** One study reported this outcome (Anand 1999; in the Ng 2017 review). Compared to placebo or no intervention, the evidence is very uncertain about the effect of midazolam on PVL (RR 3.82, 95% CI 0.46 to 31.43; 1 RCT, 43 infants; very low-certainty evidence).
- **Phenobarbital.** No studies reported this outcome.
- **Opioids.** Six studies reported this outcome (Anand 1999; Anand 2004; Ancora 2013; Lago 1998; Simons 2003; Siwiec 1999; in the Bellù 2021 review). Opioids may have little or no effect in reducing PVL compared to placebo or no intervention (RR 0.79, 95% CI 0.49 to 1.14; 6 RCTs, 1299 infants; low-certainty evidence).
- **Ibuprofen.** Four studies reported this outcome (Dani 2005; De Carolis 2000; Gournay 2004; Van Overmeire 2004; in the Ohlsson 2020b review). Ibuprofen may have little or no effect in reducing PVL compared to placebo or no intervention (RR 1.19, 95% CI 0.64 to 2.18; 4 RCTs, 747 infants; low-certainty evidence).

Brain MRI abnormalities

- No studies out of the five included reviews reported this outcome (Bellù 2021; Jasani 2022; Ng 2017; Ohlsson 2020b; Romantsik 2017a).

Paracetamol versus ibuprofen

Primary outcomes

Primary outcomes are shown in Table 1.

Any GMH-IVH

One study reported this outcome (Jafari 2019; in the Jasani 2022 review). The evidence is very uncertain about the effects of paracetamol on GMH-IVH (any grade) compared to ibuprofen (RR 1.17, 95% CI 0.31 to 4.34; 1 RCT, 30 infants; very low-certainty evidence).

sIVH (grade 3 to 4)

One study reported this outcome (Jafari 2019; in the Jasani 2022 review). The evidence is very uncertain about the effects of paracetamol on sIVH compared to ibuprofen (RR 2.65, 95% CI 0.12 to 60.21; 1 RCT, 30 infants; very low-certainty evidence).

All-cause neonatal death

No studies reported this outcome.

Major neurodevelopmental disabilities

No studies reported this outcome.

Secondary outcomes

Secondary outcomes for this comparison are reported in Table 9.

All-cause death during initial hospitalization

One study reported this outcome (Jafari 2019; in the Jasani 2022 review). The evidence is very uncertain about the effects of paracetamol on all-cause death during initial hospitalization compared to ibuprofen (RR 0.88, 95% CI 0.14 to 5.42; 1 RCT, 30 infants; very low-certainty evidence).

Any ROP (any stage)

One study reported this outcome (Jafari 2019; in the Jasani 2022 review). The evidence is very uncertain about the effects of paracetamol on any ROP (any stage) compared to ibuprofen (RR 4.41, 95% CI 0.24 to 84.79; 1 RCT, 30 infants; very low-certainty evidence).

Severe ROP (stage 3 or greater)

No studies reported this outcome.

Cerebellar hemorrhage

No studies reported this outcome.

PVL

No studies reported this outcome.

Brain MRI abnormalities

No studies reported this outcome.

Opioids versus other analgesic/sedative

Primary outcomes

Primary outcomes are shown in Table 1.

Any GMH-IVH

One study reported this outcome (Anand 1999; in the Bellù 2021 review). Morphine may result in a reduction in GMH-IVH (any grade) compared to midazolam, (RR 0.28, 95% CI 0.09 to 0.87; 1 RCT, 46 infants; low-certainty evidence).

sIVH (grade 3 to 4)

One study reported this outcome (Anand 1999; in the Bellù 2021 review). Compared to midazolam, the evidence is very uncertain about the effect of morphine in sIVH (grade 3 to 4) (RR 0.08, 95% CI 0.00 to 1.43; 1 RCT, 46 infants; very low-certainty evidence).

All-cause neonatal death

One study reported this outcome (Anand 1999; in the Bellù 2021 review). Compared to midazolam, the evidence is very uncertain about the effect of morphine on all-cause neonatal death (RR 0.31, 95% CI 0.01 to 7.16; 1 RCT, 46 infants; very low-certainty evidence).

Major neurodevelopmental disabilities

No studies reported this outcome.

Secondary outcomes

Secondary outcomes for this comparison are reported in Table 9.

All-cause death during initial hospitalization

No studies reported this outcome.

Any ROP (any stage)

No studies reported this outcome.

Severe ROP (stage 3 or greater)

No studies reported this outcome.

Cerebellar hemorrhage

No studies reported this outcome.

PVL

One study reported this outcome (Anand 1999; in the Bellù 2021 review). Compared to midazolam, the evidence is very uncertain about the effect of opioids on PVL (RR 0.23, 95% CI 0.03 to 1.90; 1 RCT, 46 infants; very low-certainty evidence).

Brain MRI abnormalities

No studies reported this outcome.

Opioids versus other opioids

Primary outcomes

Primary outcomes are shown in Table 1.

Any GMH-IVH

One study reported this outcome within this comparison; that is, opioids to other opioids (Wood 1998; in the Bellù 2021 review). Compared to diamorphine, the evidence is very uncertain about the effect of morphine on GMH-IVH (any grade) (RR 0.65, 95% CI 0.40 to 1.07; 1 RCT, 88 infants; very low-certainty evidence).

sIVH (grade 3 to 4)

One study reported this outcome within this comparison (i.e. opioids to other opioids) (Saarenmaa 1999; in the Bellù 2021 review). Compared to fentanyl, the evidence is very uncertain about the effect of morphine on sIVH (grade 3 to 4) (RR 0.59, 95% CI 0.18 to 1.95; 1 RCT, 163 infants; very low-certainty evidence).

All-cause neonatal death

One study reported this outcome within this comparison (i.e. opioids to other opioids) (Wood 1998; in the Bellù 2021 review). Compared to diamorphine, the evidence is very uncertain about the effect of morphine on all-cause neonatal death (RR 1.17, 95% CI 0.43 to 3.19; 1 RCT, 88 infants; very-low certainty evidence).

Major neurodevelopmental disabilities

No studies reported this outcome.

Secondary outcomes

Secondary outcomes for this comparison are reported in Table 9.

All-cause death during initial hospitalization

One study reported this outcome within this comparison (i.e. opioids to other opioids) (Saarenmaa 1999; in the Bellù 2021 review). Compared to fentanyl, the evidence is very uncertain about the effect of opioids on all-cause death during initial hospitalization (RR 1.21, 95% CI 0.43 to 3.45; 1 RCT, 163 infants; very low-certainty evidence).

Any ROP (any stage)

No studies reported this outcome.

Severe ROP (stage 3 or greater)

No studies reported this outcome.

Cerebellar hemorrhage

No studies reported this outcome.

PVL

No studies reported this outcome.

Brain MRI abnormalities

No studies reported this outcome.

DISCUSSION

Summary of main results

We included seven Cochrane Reviews and one Cochrane Protocol on pain and sedation interventions for the prevention of GMH-IVH in preterm infants on assisted ventilation, corresponding to 3791 infants enrolled in 40 trials. However, two of these reviews – on clonidine (Romantsik 2017a) and paracetamol (Ohlsson 2020a) – included no trials in ventilated preterm infants exposed to the intervention in the first week of life. Among the included reviews, the number of trials included in each review ranged from three to 20: the review on opioids included 20 trials; phenobarbital: nine trials; ibuprofen: five trials; paracetamol and midazolam: three trials each. The certainty of the evidence ranged from moderate to very low for the primary outcomes of this overview.

Compared to placebo, opioids and midazolam may result in little to no difference in reducing GMH-IVH (any grade), and there is likely also little to no difference between ibuprofen and placebo for this outcome; the evidence is very uncertain about the effect of paracetamol and phenobarbital on this outcome. Morphine may result in a reduction in GMH-IVH (any grade) compared to midazolam, whereas the evidence is very uncertain about the effect of morphine on this outcome compared to diamorphine, and of paracetamol compared to ibuprofen.

Compared to placebo, opioids and ibuprofen may result in little to no difference in reducing severe IVH (sIVH; grade 3 to 4). The evidence is very uncertain about the effect of paracetamol and phenobarbital on this outcome. No studies on midazolam reported this outcome. The evidence is very uncertain about the effect of morphine on sIVH (grade 3 to 4) compared to midazolam and fentanyl, and of paracetamol to ibuprofen. No studies on morphine versus diamorphine reported this outcome.

Compared to placebo, opioids likely result in little to no difference in reducing all-cause neonatal death. The evidence is very uncertain about the effect of paracetamol, ibuprofen, and phenobarbital on this outcome. No studies on midazolam reported this outcome. The evidence is very uncertain about the effect of morphine on all-cause neonatal death compared to midazolam and diamorphine, and of paracetamol to ibuprofen. No studies on morphine versus fentanyl reported this outcome.

Compared to placebo, the evidence is very uncertain about the effect of opioids in reducing major neurodevelopmental disability at 18 to 24 months and at five to six years. No studies on other drugs reported this outcome.

Most of the reviews, and to a limited extent also their included trials, considered harms associated with treatments. No relevant adverse events were reported. However, a much larger information size would be needed to estimate the incidence of events which might be rare. Additionally, this result should be interpreted with caution, as the trials did not have enough statistical power (due to small sample sizes) to find possible increases in harms such as seizures, gastrointestinal perforation, or hypotension.

Most of the ongoing studies to be included in future updates of this Cochrane Overview are exploring the effects of paracetamol and ibuprofen. Two trials protocols on opioids have been identified (CTRI/2020/08/027144; IRCT2017082417413N26), but none on phenobarbital or midazolam. We identified one Cochrane Review protocol on dexmedetomidine (Ibrahim 2016).

Overall completeness and applicability of evidence

We found Cochrane Reviews for all of our prespecified interventions; however, two of the seven reviews included no trials matching the inclusion criteria of this Cochrane Overview (Ohlsson 2020a; Romantsik 2017a). The review of opioids included multiple comparisons; namely, opioids versus placebo, other drugs, and other opioids. The paracetamol review compared that intervention to either placebo or ibuprofen. The Bellù 2021 opioids review and the Ibrahim 2016 protocol on dexmedetomidine specifically include trials in ventilated infants, whereas most of the other reviews might have included studies regardless of assisted ventilation. The paracetamol and ibuprofen reviews focused on the prevention of patent ductus arteriosus, thus including trials in ventilated preterm infants administered these interventions in the first days of life (Jasani 2022; Ohlsson 2020b). Of note, ibuprofen is used for pain management during screening for retinopathy of prematurity (Bulut 2022), and paracetamol for painful procedures.

The external validity of our overview is limited for several analyses, mainly because of the few studies that have been published and their limitations in study design. However, we are moderately confident in the effect estimates on ibuprofen for GMH-IVH (any grade) and opioids for all-cause neonatal death compared to placebo. For some interventions identified in this overview, we found a lack of evidence for their use in the prevention of GMH-IVH; however, these drugs might be effective in preterm infants treated for procedural pain.

Most of the reviews had similar outcomes to the primary ones defined in our overview. However, the original studies rarely reported long-term neurodevelopment, which should be a primary concern for those assessing the consequences of GMH-IVH.

Quality of the evidence

The quality of the included reviews was high, with all of them fulfilling the critical domains of the AMSTAR-2 (Table 11). One of the domains, question 3 (‘Did the review authors explain their selection of the study designs for inclusion in the review?’), was of special interest: none of the included reviews reported an explanation for including only RCTs. In systematic reviews assessing the effects of an intervention, the inclusion of only RCTs is a standard approach. However, for some research questions, inclusion criteria limited only to RCTs may lead to an incomplete summary of important outcomes (Shea 2017). Four of the seven Cochrane Reviews did not report funding for included trials (AMSTAR-2 question 10: 'Did the review authors report on the sources of funding for the studies included in the review?'). This item has not consistently been reported in Cochrane Reviews, despite being specified in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement and the *Cochrane Handbook for Systematic Reviews of Interventions,* although figures have improved in recent years (Turner 2020). Four of the seven Cochrane Reviews did not construct funnel plots because they included few RCTs (i.e. fewer than 10 trials).

For most outcomes, the certainty of evidence according to the GRADE approach was low or very low, except for GMH-IVH (any grade) for ibuprofen versus placebo and neonatal mortality for opioids versus placebo, both of which we downgraded by one level for imprecision. We further downgraded the certainty of evidence for all other outcomes. This was mostly for imprecision, by one to three levels, associated with low event rates and wide confidence intervals overlapping no effect, and one or two levels for the risk of bias in several domains (mostly related to selection bias). Some outcomes only included a single RCT with a very low event rate and sample size; therefore, we downgraded the evidence by two or three levels because of very serious or extremely serious imprecision. We downgraded the evidence certainty for sIVH for opioids versus placebo for publication bias. We identified moderate inconsistency in two RCTs, and did not make any downgrades for indirectness.

Potential biases in the overview process

We are confident that this overview is a comprehensive summary of all currently available Cochrane Reviews on this topic. Only three of the included reviews have a search strategy run since 2020 (Bellù 2021; Jasani 2022; Romantsik 2023); the reviews on paracetamol and ibuprofen included the highest number of ongoing studies (Jasani 2022; Ohlsson 2020b). At least two overview authors independently assessed reviews for inclusion, carried out data extraction and quality assessment, and assessed the certainty of evidence using the GRADE approach. A potential source of bias is related to the fact that three overview authors are authors of several of the included reviews. Two other overview authors (AS and TP), who were not authors of these reviews, carried out data extraction and quality assessment for these reviews in order to minimize intellectual bias.

Agreements and disagreements with other studies or reviews

We did not find any other overview or systematic reviews on pain and sedation interventions for the prevention of GMH-IVH in preterm infants. Similar to our findings, two network meta-analyses investigating indomethacin, acetaminophen, ibuprofen, and placebo did not find a significant effect on GMH-IVH incidence or mortality with any of these treatment modalities (Jones 2011; Mitra 2018). Another review on analgesia and sedation during mechanical ventilation in neonates found no difference between morphine and placebo in reducing GMH-IVH and neonatal mortality in preterms (Aranda 2005). The review by Aranda and colleagues reported that infants receiving morphine spent more days on mechanical ventilation than the control group. However, this finding was not detected in the more recent Cochrane Review on opioids (Bellù 2021), included in this overview.

AUTHORS' CONCLUSIONS

Implications for practice

We identified seven Cochrane Reviews and one Cochrane Review protocol regarding the effects and safety of pharmacological interventions related to pain and sedation management to prevent germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) in ventilated preterm infants. None of the reported studies found a major impact on GMH-IVH (any grade), severe intraventricular hemorrhage (sIVH), all-cause neonatal death, or major neurodevelopmental disability. Certainty of the evidence ranged from moderate to very low.

Implications for research

Large randomized trials of rigorous methodology are needed to achieve an optimal information size to assess the effects of pharmacological interventions for pain and sedation management for the prevention of GMH-IVH and mortality in preterm infants. Studies might compare the interventions against either placebo or other drugs. Reporting of the outcome data should include the assessment of GMH-IVH and long-term neurodevelopment. Prospective, observational studies might provide valuable information on harms.

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ADDITIONAL TABLES

Table 1. Summary of findings: all comparisons for the primary outcomes

Outcome	Intervention and comparison	Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
Intervention versus placebo					
Germinal matrix hemorrhage -intraventricular hemorrhage (GMH-IVH) (any grade)	Paracetamol vs placebo Jasani 2022	RR 0.89 (0.38 to 2.07)	82 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[a]	The evidence is very uncertain about the effects of paracetamol on GMH-IVH (any grade) compared to placebo.
	Midazolam vs placebo Ng 2017	RR 1.68 (0.87 to 3.24)	122 (3 RCTs)	⊕⊕⊖⊖ LOW[b]	Midazolam may result in little to no difference in reducing GMH-IVH (any grade) compared to placebo.
	Phenobarbital vs placebo/no intervention/unspecified control Romantsik 2023	RR 0.99 (0.83 to 1.19)	732 (9 RCTs)	⊖⊖⊖⊖ VERY LOW[c]	The evidence is very uncertain about the effect of phenobarbital on GMH-IVH (any grade) compared to placebo.
	Opioids vs placebo Bellù 2021	RR 0.85 (0.65 to 1.12)	469 (7 RCTs)	⊕⊕⊖⊖ LOW[b]	Opioids may result in little to no difference in GMH-IVH (any grade) compared to placebo.
	Ibuprofen vs placebo Ohlsson 2020b	RR 0.99 (0.81 to 1.21)	759 (4 RCTs)	⊕⊕⊕⊖ MODERATE[d]	Ibuprofen likely results in little to no difference in GMH-IVH (any grade) compared to placebo.
Severe intraventricular hemorrhage (sIVH) (grade 3 to4)	Paracetamol vs placebo Jasani 2022	RR 1.80 (0.43 to 7.49)	82 (2 RCTs)	⊖⊖⊖⊖ VERY LOW[a]	The evidence is very uncertain about the effects of paracetamol and ibuprofen on sIVH (grade 3 to 4) compared to ibuprofen.
	Midazolam vs placebo Ng 2017	NR	-	-	No studies reported this outcome.
	Phenobarbital vs placebo/no intervention/unspecified control Romantsik 2023	RR 0.91 (0.66 to 1.25)	732 (9 RCTs)	⊕⊖⊖⊖ VERY LOW[e]	The evidence is very uncertain about the effect of phenobarbital on sIVH (grade 3 to 4) compared to placebo.
	Opioids vs placebo Bellù 2021	RR 0.98 (0.71 to 1.34)	1299 (6 RCTs)	⊕⊕⊖⊖ LOW[f]	Opioids may result in little to no difference in sIVH (grade 3 to4) compared to placebo.

Table 1. Summary of findings: all comparisons for the primary outcomes *(Continued)*

	Ibuprofen vs placebo Ohlsson 2020b	RR 0.82 (0.54 to 1.26)	747 (4 RCTs)	⊕⊕⊖⊖ LOW[b]	Ibuprofen may result in little to no difference in sIVH (grade 3 to4) compared to placebo.
All-cause neonatal death	Paracetamol vs placebo Jasani 2022	NR	-	-	No studies reported this outcome.
	Midazolam vs placebo Ng 2017	NR	-	-	No studies reported this outcome.
	Phenobarbital vs placebo/no intervention/unspecified control Romantsik 2023	RR 0.94 (0.51 to 1.72)	203 (3 RCTs)	⊖⊖⊖⊖ VERY LOW[g]	The evidence is very uncertain about the effect of phenobarbital on all-cause neonatal death compared to placebo/no intervention/unspecified control.
	Opioids vs placebo Bellù 2021	RR 1.12 (0.80 to 1.55)	1189 (5 RCTs)	⊕⊕⊕⊖ MODERATE[h]	Opioids likely results in little to no difference in all-cause neonatal death compared to placebo.
	Ibuprofen vs placebo Ohlsson 2020b	RR 1.00 (0.38 to 2.64)	112 (2 RCTs)	⊖⊖⊖⊖ VERY LOW[i]	The evidence is very uncertain about the effect of ibuprofen on all-cause neonatal death compared to placebo.
Major neurodevelopmental disability	Paracetamol vs placebo Jasani 2022	NR	-	-	No studies reported this outcome.
	Midazolam vs placebo Ng 2017	NR	-	-	No studies reported this outcome.
	Phenobarbital vs placebo/no intervention/unspecified control Romantsik 2023	NR	-	-	No studies reported this outcome.
	Opioids vs placebo Bellù 2021	At 18 to 24 months: RR 2.00 (0.39 to 10.29)	78 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a]	The evidence is very uncertain about the effect of opioids in reducing major neurodevelopmental disability at 18 to 24 months and at 5 to 6 years
		At 5 to 6 years: RR 1.6 (0.56 to 4.56)	95 (1 RCT)	⊖⊖⊖⊖ VERY LOW[a]	
	Ibuprofen vs placebo Ohlsson 2020b	NR	-	-	No studies reported this outcome.
Opioids versus other analgesic/sedative					

Table 1. Summary of findings: all comparisons for the primary outcomes *(Continued)*

Germinal matrix hemorrhage -intraventricular hemorrhage (GMH-IVH) (any grade)	Morphine vs midazolam Bellù 2021	RR 0.28 (0.09 to 0.87)	46 (1 RCT)	⊕⊕⊖⊖ LOW[j]	Morphine may result in a reduction in GMH-IVH (any grade) compared to midazolam.
Severe intraventricular hemorrhage (grade 3 to 4)	Morphine vs midazolam Bellù 2021	RR 0.08 (0.00 to 1.43)	46 (1 RCT)	⊖⊖⊖⊖ VERY LOW[a]	The evidence is very uncertain about the effects of morphine on sIVH (grade 3 to 4) compared to midazolam.
All-cause neonatal death	Morphine vs midazolam Bellù 2021	RR 0.31 (0.01 to 7.16)	46 (1 RCT)	⊖⊖⊖⊖ VERY LOW[a]	The evidence is very uncertain about the effect of morphine on all-cause neonatal death compared to midazolam.
Major neurodevelopmental disability	Morphine vs midazolam Bellù 2021	NR	-	-	No studies reported this outcome.
Opioids versus other opioids					
Germinal matrix hemorrhage - intraventricular hemorrhage (GMH-IVH) (any grade)	Morphine vs diamorphine Bellù 2021	RR 0.65 (0.40 to 1.07)	88 (1 RCT)	⊖⊖⊖⊖ VERY LOW[k]	The evidence is very uncertain about the effect of morphine on GMH-IVH (any grade) compared to diamorphine.
	Morphine vs fentanyl Bellù 2021	-	-	-	No studies reported this outcome.
Severe intraventricular hemorrhage (grade 3 to 4)	Morphine vs diamorphine Bellù 2021	-	-	-	No studies reported this outcome.
	Morphine vs fentanyl Bellù 2021	RR 0.59 (0.18 to 1.95)	163 (1 RCT)	⊖⊖⊖⊖ VERY LOW[l]	The evidence is very uncertain about the effect of morphine on sIVH (grade 3 to 4) compared to fentanyl.
All-cause neonatal death	Morphine vs diamorphine Bellù 2021	RR 1.17 (0.43 to 3.19)	88 (1 RCT)	⊖⊖⊖⊖ VERY LOW[k]	The evidence is very uncertain about the effect of morphine on all-cause neonatal death compared to diamorphine.
	Morphine vs fentanyl Bellù 2021	-	-	-	No studies reported this outcome.
Major neurodevelopmental disability	Morphine vs diamorphine Bellù 2021	NR	-	-	No studies reported this outcome.
	Morphine vs fentanyl Bellù 2021	NR	-	-	No studies reported this outcome.
Paracetamol versus ibuprofen					
Germinal matrix hemor-	Paracetamol vs ibuprofen	RR 1.17 (0.31 to 4.34)	30 (1 RCT)	⊖⊖⊖⊖ VERY LOW[a]	The evidence is very uncertain about the effects of paracetamol on GMH-

Table 1. Summary of findings: all comparisons for the primary outcomes *(Continued)*

rhage - intraventricular hemorrhage (GMH-IVH) (any grade)	Jasani 2022				IVH (any grade) compared to ibuprofen.
Severe intraventricular hemorrhage (grade 3 to 4)	Paracetamol vs ibuprofen Jasani 2022	RR 2.65 (0.12 to 60.21)	30 (1 RCT)	⊖⊖⊖⊖ VERY LOW[a]	The evidence is very uncertain about the effects of paracetamol on sIVH (grade 3 to 4) compared to ibuprofen.
All-cause neonatal death	Paracetamol vs ibuprofen Jasani 2022	NR	-	-	No studies reported this outcome.
Major neurodevelopmental disability	Paracetamol vs ibuprofen Jasani 2022	NR	-	-	No studies reported this outcome.

CI: confidence interval; **NR**: not reported; **RCT:** randomized controlled trial; **RD:** risk difference; **RR:** risk ratio; **vs:** versus

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Highcertainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderatecertainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Lowcertainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Verylowcertainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded three levels for extremely serious imprecision: only one small study with a small event rate, wide CI overlapping no effect
[b]Downgraded two levels for serious imprecision: low event rate, and wide confidence intervals overlapping no effect
[c]Downgraded two levels for study limitations: seven of nine RCTs had a high risk of performance bias, six of nine RCTs had a high or unclear risk of selection bias (both sequence generation and allocation concealment); and one level for significant heterogeneity (I^2 = 63%)
[d]Downgraded by one level for serious imprecision: low event rate
[e]Downgraded by two levels for study limitations: seven of nine RCTs had a high risk of performance bias, six of nine RCTs had a high or unclear risk of selection bias (both sequence generation and allocation concealment), and one level for serious imprecision: wide confidence intervals overlapping no effect
[f]Downgraded one level for serious imprecision (low events rate) and one level for publication bias
[g]Downgraded one level for study limitations: high risk of performance bias in all RCTs, an unclear risk of bias in at least one domain, one level for serious imprecision (low event rate, and wide confidence intervals overlapping no effect), and one level for significant heterogeneity (I^2 = 65%)
[h]Downgraded one level for serious imprecision: wide confidence intervals overlapping no effect (assessed by original authors and reassessed)
[i]Downgraded one level for study limitations: one of two RCTs had a high risk of performance bias, all had unclear risk of selection bias (both sequence generation and allocation concealment), and two levels for very serious imprecision: low event rate, and wide confidence intervals overlapping no effect
[j]Downgraded two levels for very serious imprecision: only one small study with a small event rate
[k]Downgraded one level for study limitations: high or unclear risk of bias in four domains (selection, attrition and reporting bias), and two levels for very serious imprecision: low event rate, and wide confidence intervals overlapping no effect
[l]Downgraded one level for study limitations: high or unclear risk of bias in three domains (selection and reporting bias), and two levels for very serious imprecision: low event rate, and wide confidence intervals overlapping no effect

Table 2. Characteristics of included reviews

	Clonidine Romantsik 2017a	Paracetamol for pain Ohlsson 2020a	Paracetamol for PDA Jasani 2022	Midazolam Ng 2017	Phenobarbital Romantsik 2023	Opioids Bellù 2021	Ibuprofen Ohlsson 2020b
Up to date	January 2017	May 2016	October 2021	June 2016	January 2022	September 2020	October 2018
# included RCTs in the original review (# infants)	1 (112)	9 (728)	27 (2278 infants)	3 (146)[a]	10 (792)	23 (2023)[a]	9 RCTs (1070)
RCTs excluded (with reason)	• Term infants: 1 (Hünseler 2014)	• Not mechanically ventilated infants: 4 (Badiee 2009; Seifi 2013; Tinner 2013; Van Lingen 2001) • Term or most term: 3 (Bonetto 2008; Ceelie 2013; Shah 1998) • Intervention after 7 days of life: 2 (Kabataş 2016; Manjunatha 2009)	• Not mechanically ventilated infants: 22 (Al-Lawama 2017; Asadpour 2018; Asbagh 2015; Babaei 2018; Bagheri 2016; Bagheri 2018; Balachander 2020; Dang 2013; Dani 2021; Dash 2015; Davidson 2021; El-Farrash 2019; El-Mashad 2017; Ghaderian 2019a; Ghaderian 2019b; Härkin 2016; Kumar 2020; Oboodi 2020; Oncel 2017; Shahmirzadi 2021; Tauber 2020; Yang 2016) • Intervention after 7 days of life: 2 (Kluckow 2019; Meena 2020)	0	• Not all mechanically ventilated: 1 (Whitelaw 1983)	• Term or most term: 2 (Schmidt 2010; Welzing 2012) • Intervention after 7 days of life (Jiang 2012)	• No information on mechanical ventilation and no response from the authors: 2 (Kalani 2016; Sangtawesin 2006) • Not all mechanically ventilated: 1 (Kanmaz 2013) • Ineligible comparator: 1 (Dani 2000)
# included RCTs in the overview (# infants)	0	0	3 (112) See Table 3	3 (146) See Table 4	9 (742) See Table 5	20 (1978) See Table 6	5 (813) See Table 7

[a]Anand 1999 has 3 study arms (midazolam, morphine and placebo) and is therefore included in both the midazolam (Ng 2017) and opioids (Bellù 2021) reviews.
PDA: patent ductus arteriosus; RCT: randomized controlled trial

Table 3. Paracetamol

RCT ID	Population	Intervention	Comparison	Outcomes	Notes
Jafari 2019	30 preterm infants, postnatal age 48 to 72 hours with moderate to large hsPDA. Mean GA ± SD: not reported. Mean BW (g) ± SD: not reported.	Paracetamol iv 15 mg/kg BW every 6 hours for 3 days. N = 16	Ibuprofen iv 10 mg/kg of BW on the first day and 5 mg/kg on the second and third day. N = 14	Primary outcomes: postintervention PDA grades, length of stay, duration of MV, patient outcomes (i.e. death, discharge). Other outcomes: germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) (grade 1 to 4 or no GMH-IVH); retinopathy of prematurity, pneumothorax, bronchopulmonary dysplasia.	
Hochwald 2018	24 preterm infants, 24 to 31 weeks GA, with diagnosis of hsPDA. Mean GA ± SD: 27.7 ± 1.3 in ibuprofen + paracetamol group; 27.2 ± 1.4 in ibuprofen + placebo group. Mean BW (g) ± SD: 1120 ± 171 in IBU + PAR group; and 951 ± 157 in IBU + PLA group. NIPPV, n (%): 2(17) in IBU + PAR group; and 3 (25) in IBU + PLA group. SIMV, n (%): 6 (50) in IBU + PAR group; and 5 (42) in IBU + PLA group. HFOV, n (%): 2 (17) in IBU + PAR group; and 4 (33) in IBU + PLA group.	Ibuprofen (initial dose: 10 mg/kg, followed by 5 mg/kg at 24 and 48 hours) and paracetamol (Perfalgan, Bristol-Meyer Squibb; a loading dose of 20 mg/kg (2 ml/kg) followed by 10 mg/kg (1 ml/kg) given every 6 hours for 3 days (a total of 12 doses). N = 12	Ibuprofen (identical to intervention group) and placebo (similar volume of saline 0.9% was given at the same time intervals). N = 12	Primary outcome: closed duct on echocardiography after the completion of the pharmacologic treatment (1 or 2 courses) or a trivial and constrictive PDA after treatment without the need for treatment until discharge. Secondary outcomes: need for a second course, need for surgical ligation, rates of ductal reopening, clinical parameters including mode and duration of ventilation, pneumothorax, pulmonary hemorrhage, bronchopulmonary dysplasia, GMH-IVH, NEC, gastrointestinal bleeding, retinopathy of prematurity, definite sepsis, death. Safety parameters also included increase in serum creatinine, decrease in urine output to < 1 ml/kg/h, AST/ALT levels and paracetamol level	First dose of study drug (paracetamol) or placebo was given within 1 hour of starting the first ibuprofen dose. If hsPDA persisted after the first course, a second course of the same treatment was given. If hsPDA persisted after the second course, a surgical PDA ligation was considered.
Schindler 2021	58 infants born at < 29 weeks GA, < 6 hours old and with PDA ≥ 1.0 mm with < 30% right to left shunt. Mean GA (wks)(SD): 26.6 (1.6) in PAR group, 26.5 (1.6) in PLA group. Mean BW (g) ± SD: 924.1 ± 240.7 in PAR	Paracetamol iv at a dose of 15 mg/kg (1.5 mL/kg) initially, followed by every 6 hours at a dose of 7.5 mg/kg (0.75 mL/kg) for 5 days. N = 29	5% dextrose (placebo) iv 1.5 mL/kg initially, followed by 0.75 mL every 6 hours for 5 days. N = 29	Primary outcome: any intervention for management of PDA up to 5-day postnatal age. Secondary outcomes: closure of ductus arteriosus at 5-day postnatal age; size of the ductus arteriosus at 48-hours and 5-day postnatal age; ductal reopening during admission; ductus arteriosus parameters; systemic blood flow measurements; adverse events during the treatment period; clinical outcomes including mortality and significant morbidities (pul-	

Table 3. Paracetamol *(Continued)*

	group, 951.6 ± 266.9 in PLA group.			monary hemorrhage, necrotizing enterocolitis, early-onset sepsis, late-onset sepsis, GMH-IVH, periventricular leukomalacia, chronic lung disease, or retinopathy of prematurity). Safety measures were also reported.	

ALT = alanine transaminase; AST = aspartate transaminase; BW = body weight; d = days; GA = gestational age; GMH-IVH = germinal matrix hemorrhage-intraventricular hemorrhage; HFOV = high frequency oscillatory ventilation; hsPDA = hemodynamically significant patent ductus arteriosus; IBU = ibuprofen; iv = intravenous; MV = mechanical ventilation; NEC = necrotizing enterocolitis; NIPPV =; nasal intermittent positive pressure ventilation; PAR = paracetamol; PDA = patent ductus arteriosus; PLA = platelet; SD = standard deviation; SIMV = synchronized intermittent mandatory ventilation.

Table 4. Midazolam

RCT ID	Population	Intervention	Comparison	Outcomes	Notes
Anand 1999 (reported also in Table 7)	67 preterm infants; 24 to 32 GA; intubated and required ventilatory support for less than 8 h postnatal age ≤ 72 h Mean GA ± SD: 28.6 ± 2.5 in MID group, 29.2 ± 2.2 in MOR group, 28.1 ± 2.2 in PLA group Mean BW ± SD: 1245±445 in MID group; 1230±475 in MOR group; 1049±419 in PLA group	Midazolam hydrochloride (0.1 mg/ml in 10% dextrose). N = 22	Placebo (10 % dextrose). N = 21	Level of sedation, PIPP after 24 h of continued infusion and at 10 to 12 h after stopping infusion. ITT analyses for: neonatal death (poor neurologic outcomes at 0 to 28 days of age without discharge from the NICU); germinal matrix hemorrhage -intraventricular hemorrhage (GMH-IVH) grade III or IV; PVL; severity of illness (with Neonatal Medical Index Grade). Secondary outcomes: analgesia and sedation, weight gain, incidence of pneumothorax, duration of respiratory support (ventilatory support, continuous positive airway pressure, oxygen), length of NICU stay and hospital stay, neurobehavioral assessment scores at 36 weeks after conception. Outcomes related to enteral feeding (full strength, full-volume NG and PO). Number of children receiving additional doses of morphine sulfate analgesia on day 1, 2, 3, 4 and 14 after starting the drug infusion.	Both (MID and PLA) were received as infusion. Additional analgesia provided with intravenous morphine doses was allowed. Characteristics for all study population included in this overview. This was a 3-arm study; third arm was morphine sulfate infusion (reported in Table 7).
Arya 2001	33 neonates with BW < 2000 g who were MV within first 7 d of life. Mean GA ± SD: 31.5 ± 2.4 in MID group, 32.3 ± 2.2 in PLA group Mean BW ± SD: 1263 ± 326 in MID group; 1337 ± 297 in PLA group	Midazolam (1 mg /ml solution), initiated by administering a bolus of 0.2 ml/kg followed by continuous infusion of 0.06 ml/kg/h (0.06 mg/kg/h); FulsedTM, Ranbaxy Laboratories Ltd.)	Placebo (0.9% saline; a similar volume of placebo was administered to the control group) N = 16	The primary outcome variable was adequacy of sedation before drug therapy, therefore till next 48 h after initiating MID infusion. Other measures: mortality within 48 h, heart rate, blood pressure and ventilatory requirements (FiO_2, PIP, PEEP, bpm); arterial blood gas; ventilatory complications; side effects of treatment.	Infants in both groups received MOR by continuous infusion at a dose of 10 µg/kg/h. All study population included in this overview.

Table 4. Midazolam *(Continued)*

		N = 17			
Jacqz-Aigrain 1994	46 newborns on mechanical ventilation for respiratory distress syndrome; with postnatal age of 48 h or less. Mean GA ± SD: 32.1 ± 2.8 in MID group; 32.8 ± 2.6 in PLA group Mean BW ± SD: 1820 ± 647 in MID group; 2000 ± 548 in PLA group	Midazolam (≥ 33 wk of GA: of 1.2 mL/h, giving 60 µg/kg per h (1.44 mg/kg/d); < 33 wk of GA: 1.2 mL/ h during the first 24 h, followed by 0,6 ml/h, giving 30 µg/kg/h (0.82 mg/kg/d). Maximum 5 days. Infusion could stop after 24 h. N = 24 Sedation with midazolam could be continued if prescribed.	Unspecified placebo N = 22	Behavior (on a 5-item scale). Sedation scores. Heart rate, blood pressure. Ventilatory requirements (FiO_2, mean positive airway pressure). Saturation transcutaneous oxygen and CO pressures were also monitored. Side effects of treatment (i.e. pneumothorax, pulmonary interstitial emphysema, hypotension, chronic lung disease, NEC, GMH-IVH, persistence of pulmonary hypertension of the newborn, death), duration of ventilatory support, stay in ICU, duration of oxygen support. Course of RDS: duration of respiratory support, subject withdrawn because of inadequate sedation, stay in ICU, duration of oxygenation, max FIO_2, duration of FiO_2 > 60% and > 40% max MAP, PaO_2/FiO_2. Concomitant administration of drugs used in ICU was allowed. Fentanyl and/or muscle relaxants were permitted.	Both MID and PLA supplied by manufacturer (Roche Laboratories); both were provided as a continuous infusion. Concomitant administration of drugs used in ICU was allowed. Fentanyl and/or muscle relaxants were permitted. All study population included in this overview.

bpm = beats per minute; BW = birth weight; CO = carbon dioxide; d = days; GA = gestational age, in weeks; GMH-IVH = germinal matrix hemorrhage-intraventricular hemorrhage; h = hours; ICU = intensive care unit; ITT= intention to treat; MAP = mean airway pressure; MID = midazolam; MOR = morphine; MV = mechanical ventilation; NEC = necrotizing enterocolitis; NICU = neonatal intensive care unit; NG = nasogastric; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; PO = per os; PIPP = Premature Infant Pain Profile; PLA = placebo; RCT = randomized controlled trial; RDS = respiratory distress syndrome; SD = standard deviation

Table 5. Phenobarbital

RCT ID	Population	Intervention	Comparison	Outcomes	Notes
Anwar 1986	58 preterm infants (BW less than 1500 g) who had no congenital malformations and whose mother had not received PHE before their delivery. Mean/median GA: not reported. Number of ventilated infants: not reported.	PHE (a loading dose of 20 mg/kg divided into 2 equal doses administered intravenously 12 h apart, following a maintenance dose of 2 to 5 mg/kg every 12 h); for the first week of life, starting at less than 6 h of age. N = 30	Supportive care N = 28	Germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) incidence and degree (ultrasound brain scans were performed on days 1, 3, and 7 of life and subsequently at weekly intervals in infants with GMH-IVH), posthemorrhagic hydrocephalus, deaths. Blood concentration of PHE before the first maintenance dose and then at 3 to 5 days of age was also measured.	Additional treatment: not reported (with exception of indomethacin, bicarbonate). Cerebral ultrasound was not carried out prior to trial entry so it was not possible to exclude babies who already had GMH-IVH before the first dose of PHE.

Table 5. Phenobarbital *(Continued)*

Bedard 1984	42 premature infants (< 37 wks of GA), less than 24 h of age with normal admission encephalograms; infants < 1500 g or less than 33 wks of GA were eligible regardless of the need for MV; larger or older infants were eligible only if required MV for hyaline membrane disease. Mean GA ± SD: 32.2 ± 1.7 in PHE group; 31.1 ± 2.7 in CON group. Mean BW: 1491 ± 421 in PHE group; 1271 ± 422 in CON group. n of MV: 19/21 in PHE group; 17/21 in CON group.	PHE (2 intravenous loading doses of 10 mg/kg 12 h apart, followed by a maintenance dose of 2.5 mg/kg every 12 h for 6 days, latter one, given intravenously or orally). N = 21	Unspecified control group N = 12	Incidence of central nervous system (periventricular) hemorrhage and its severity (mild, moderate and severe based on Shankaran 1982), and age at diagnosis (diagnosed by ultrasound imaging). Deaths. Need for mechanical ventilation, the incidence of pneumothorax. Frequency of hypotension acidosis, hypercarbia, hypocarbia, all during the first 3 days. Sodium bicarbonate administration and volume expansion. Serum phenobarbital levels (measured, but not an outcome).	Additional treatment not reported (with exception of bicarbonates and blood-volumes expanders).
Donn 1981	60 infants with BW less than 1500 g and who were less than 6 h old, without obvious congenital malformations, and whose mothers had not taken barbiturates during pregnancy. Mean GA ± SD: 28.9 ± 1.9 in PHE group; 28.6 ± 1.8 in CON group. MV: 25/30 in PHE group; 21/30 in CON group	PHE (intravenously, 2 loading dose of 10 mg/kg each administered intravenously 12 h apart; following the maintenance doses of 2 to 5 mg/kg every 12 h begun 12 h after the second loading dose and continued intravenously/ intramuscularly or orally for 6 days; at third postnatal day dosages were adjusted to maintain levels in 20 to 30 mcg/ml range). N = 30 At the end of the seventh day therapy was stopped.	Unspecified control group N = 30	GMH-IVH (diagnosed with cranial ultrasonography at third, fourth or fifth postnatal day, CT or postmortem examination), and graded using Papile 1978 classification. Deaths. Need for MV, oxygen therapy only, continuous distending pressure, thoracostomy drainage. Hyperoxia, hypoxia, hypercapnia, hypocapnia, acidosis, hypotension were also reported. Sodium bicarbonate and blood-volumes expanders administration.	Additional treatment not reported (with exception of bicarbonates and blood-volumes expanders).
Kuban 1986	280 intubated newborns with BW less than 1751 g; with endotracheal intubation before 12 h of age; without major con-	PHE (10 mg/ml; or 25 mg/ml; all were single lot; first dose of 10 mg/kg administered intravenous-	Non-specified placebo (at the same rate as PHE). N = 135	Incidence of any hemorrhage (subependymal hemorrhage/GMH-IVH; diagnosed with ultrasound) and grading using the Papile 1978 classification.	Additional treatment: not reported (with exception of morphine).

Table 5. Phenobarbital *(Continued)*

	genital anomaly; and with no evidence of intracranial hemorrhage on US before drug administration; neonatal PHE level less than 5 mcg/ml (measured only if mother received PHE before delivery). Mean GA: 29.5 in PHE group; 30.1 in CON group.	ly at or before 12 h of age, second dose administered 0.5 h later (20 mg of a loading dose in sum); 12 h later, the first of 9 maintenance doses of 2.5 mg/kg was given intravenously or orally, then at 12 h intervals). N = 145		Pneumothorax or pulmonary interstitial emphysema on day 1, mean arterial pressure < 30 mmHg on day 1, use of morphine on day 1, cranial bruising, and days of ventilation were also reported. Serum PHE level between the third and fifth day was measured, and then, again between 7 h and 10th day in half of infants.	Mortality data were by personal communication between Dr Kuban and Dr Horbar, although age at death was not clear.
Mas-Munoz 1993	60 preterm neonates (27 to 34 wks of GA), who required mechanical ventilation from birth, without GMH-IVH in the first 6 h of life (by cranial ultrasound). Mean GA ± SD: 31.5 ± 2 in PHE group; 31 ± 2 in CON group	PHE (intravenously, a loading dose of 20 mg/kg, followed by the 2.5 mg/kg at 12 h apart as the maintenance dose for 5 d). N =30	Control group: no placebo was used N = 30	GMH-IVH incidence, graded following the Papile 1978 classification (diagnosed by cranial ultrasound). Glycemia, blood pressure, $PaCo_2$, PaO_2, pH, and pressure in mean pressure in ventilatory vessels; were also reported. Postnatal complications, i.e. membrane hyaline disease, sepsis, pneumothorax, hypotension, pulmonary hypertension, pneumonia, mortality. Additional treatment not reported.	Additional treatment not reported.
Morgan 1982	60 VLBW infants (all < 1250 g of BW and all infants 1250 to 1500 BW who required artificial ventilation in the first 24 h of life), without hemorrhage on ultrasound imaging at entry. Mean GA ± SD: 30.1 ± 2.7 in PHE group; 28.8 ± 2.8 in CON group	PHE (20 mg/kg administered intramuscularly at a median time of 2 h after birth (range 1 to 22 h) N = 30	No placebo injection was given to untreated infants – no treatment N = 30	Periventricular hemorrhage (by real-time ultrasound scanning performed daily or more frequently for the first 5 d and at least once thereafter; if needed, confirmed postmortem); graded 1 to 4 following the Papile 1978 classification. Need for ventilation. Serum PHE level, frequency of pneumothorax, hypercapnia, acidosis, and survival were also measured.	Additional treatment not reported.
Porter 1985	19 newborns, < 1500 BW, admitted to NICU within the first 6 h of life; without GMH-IVH on initial ultrasound screening, congenital malformations; with a diagnosis of respiratory disease requiring respiratory support. Mean GA ± SD: 29.4 ± 2.8 in PHE group; 28.8 ± 2.2 in CON group.	PHE (intravenously, within 6 h of delivery in a loading dose of 30 mg/kg, a level within the therapeutic range, followed by the maintenance dose of 5 mg/kg/24 h for 72 h. N = 7	Placebo injections were not administered, nor PHE levels controlled; equal management as in PHE group but without PHE. N = 12	GMH-IVH incidence (diagnosed by ultrasound scanning), and severity (graded following the Papile system); ventilation (intermittent positive pressure ventilation, continuous positive airway pressure), pneumothorax, hypercapnia, acidosis, survivals; frequency of movements (limbs, extremities, trunk). Serum PHE levels were measured (only in PHE group.	Serum phenobarbital levels were measured at 36 h of age

Table 5. Phenobarbital *(Continued)*

Ruth 1985	52 premature infants with BW < 1500 g, admitted at NICU at the age of < 2 h; without malformations, and epileptic mothers. Mean GA ± SD: 28.7 ± 2.1 in PHE group; 29.3 ± 1.8 in CON group MV: 21/25 in PHE group; 22/27 in CON group	PHE (administered intravenously; a loading dose of 15 mg/kg 4 h apart starting before the age of 2 h to achieve 200 to 300 µmol/l of serum level, followed by the maintenance dose of 5 mg/kg starting 24 h after the first dose, and given once a day for 5 days). N = 25	Unspecified control N = 27	Incidence of GMH-IVH, graded following the Papile 1978 classification (by cranial US; EEG during first week; neurological follow-up with cranial US performed at 4 and 9 mo of age); ventricular dilatation (central atrophy), hydrocephalus and neurological abnormalities, pneumothorax, need for mechanical ventilation, death.	
Ruth 1988	111 preterm (≥ 25 wks of GA or more) infants, admitted to NICU, ≤ 1500 g of BW at birth, without major congenital malformation, with no history of maternal barbiturate treatment, and early admission to allow randomization before the age of 4 h.	PHE (a first dose of 15 mg/kg was infused intravenously for 15 minutes as soon as possible after birth, followed by the maintenance dose of 5 mg/kg at 24-h intervals after the loading dose for 5 days) N = 54	Control group (routine intravenous glucose infusion) N = 57	GMH-IVH (measured by real-time ultrasound scanning on the brain performed on the first, third, fifth and seventh day, if possible, and then once a week; it was repeated at 4 and 9 months old; classified according to Papile 1978 classification). Neurodevelopmental assessment was done at 4, 9, 15, and 27 months of postnatal age.	10 infants excluded after randomization (finally, 47 in PHE group and 54 in CON group); Mean BW and GA only for 101 infant included in final analysis.

BW = birth weight, in grams; CON = control group; CT = computer tomography; d = days; EEG = electroencephalogram; GA = gestational age, in weeks; GMH-IVH = germinal matrix hemorrhage-intraventricular hemorrhage; h = hour; mo = month; MV = mechanical ventilation; n = number; NICU = neonatal intensive care unit; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; PaO_2 = partial pressure of oxygen in arterial blood; PHE = phenobarbital; RCT = randomized controlled trial; RDS = respiratory distress syndrome; SD = standard deviation; US = ultrasound; VLBW: very low birth weight; wks = weeks.

Table 6. Opioids

RCT ID	Population	Intervention	Comparison	Outcomes	Notes
Anand 1999	67 preterm infants; 24 to 32 GA; intubated and required ventilatory support for less than 8 h; postnatal age ≤ 72 h Mean GA ± SD: 28.6 ± 2.5 in midazolam group, 29.2 ± 2.2 in morphine group, 28.1 ± 2.2 in PLA group Mean BW ± SD: 1245 ± 445 in midazolam group; 1230 ± 475 in morphine group; 1049 ± 419 in PLA group	Group 1: morphine sulfate (0.05 mg/mL in 10% dextrose) as infusion. N = 24	Group 2: midazolam hydrochloride (0.1 mg/ml in 10% dextrose). N = 22 Group 3: placebo (10 % dextrose). N = 21	Level of sedation, PIPP after 24 h of continued infusion and at 10 to 12 h after stopping infusion. ITT analyses for: neonatal death (poor neurologic outcomes at 0 to 28 days of age without discharge from the NICU); germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) grade III or IV, PVL; severity of illness (with Neonatal Medical Index Grade).	All (morphine, midazolam and PLA) were received as infusion. Additional analgesia provided with intravenous morphine doses was allowed. All study population in-

Table 6. Opioids *(Continued)*

				Secondary outcomes: analgesia and sedation, weight gain, incidence of pneumothorax, duration of respiratory support (ventilatory support, continuous positive airway pressure, oxygen), length of NICU stay and hospital stay, neurobehavioral assessment scores (NAPI) at 36 weeks after conception. Outcomes related to enteral feeding (full strength, full-volume NG and PO). Number of children receiving additional doses of morphine sulfate analgesia on day 1, 2, 3, 4 and 14 after starting the drug infusion.	cluded in this overview.
Anand 2004	898 ventilated preterm neonates (23 to 32 wk of GA), intubated within 72 h of birth, and ventilated for less than 8 h. Mean/median GA not reported.	Morphine (n = 449): loading dose 100 mcg/kg infused over 1 h, followed by a continuous infusion of 10, 20 or 30 mcg/kg/h for infants of GA 23 to 26, 27 to 29, or 30 to 32 weeks, respectively; continued as long as clinically justified (maximum 14 days).	Unspecified placebo N = 449	Primary outcomes: GMH-IVH (grade III or IV); PVL, neonatal death, composite outcome (sIVH, PVL, and/or neonatal death.	Analgesia with bolus doses of the study drug or increases in the infusion rate were not permitted. All study population included in this overview.
Ancora 2013	131 newborns (≤ 32 + 6 wk of GA; 22 to 32 weeks), mechanically ventilated through an endotracheal tube during first 72 hours of life. Median GA with range: 26 (22 to 32 in PHE group; 26 (22 to 31 in PLA group. Infants with sIVH and intraparenchymal hemorrhage according to the Volpe classification, cystic periventricular leukomalacia were excluded.	Fentanyl (intravenous loading dose of 1 µg/kg in 30 min, followed by a continuous intravenous infusion of 1µg/kg/h Infants treated with a bolus of fentanyl for endotracheal intubation did not receive the loading dose if fentanyl had to be initiated within 1 hour	Placebo (continuous infusion of placebo) N = 67	Primary outcome: analgesic efficacy of continuous fentanyl infusion with pain scale. Safety measures: use of mechanical ventilation at 1 wk of age; duration of the first cycle of mechanical ventilation (hrs), age at full enteral feeding, age at first meconium passage (hours); GMH-IVH, cystic periventricular leukomalacia, or death within 28 days of life; chest wall rigidity; and bladder size during the first week of life; diuresis, blood pressure, and the use of vasopressors.	Additional treatment: open-label boluses of fentanyl.

Table 6. Opioids *(Continued)*

		after intubation. N = 64			
Chen 2015	30 neonates who received mechanical ventilation (28 to 39 wks of GA; birth weight 1050 to4070 g); ventilated for more than 24 h; with diseases including neonatal pneumonia, neonatal respiratory distress syndrome, neonatal aspiration pneumonia, and neonatal wet lung. Median/mean GA not reported. Age at the time of intervention not specified.	Fentanyl (an intravenous bolus injection, 2 μg/kg for > 10 min, followed by continuous intravenous infusion, 2 μg/kg per hour (dose according to the degree of pain). N = 15 Additionally, the drug intervention group received fentanyl as the analgesic treatment.	Control group: no analgesics given N = 15	HR, respiratory rate, blood pressure changes, and PIPP score measured before treatment and at 30 min, 2 h, and 4 h after treatment; mental development index and psychomotor development index measured at 3, 6, 9 and 12 mo after discharge.	
Dyke 1995	26 preterm infants (29 to 36 wks of GA) with hyaline membrane disease requiring ventilatory assistance on the first day after birth.	Morphine (1 mg/ml in 5% dextrose; a loading dose 100 μg/k over 30 min followed by continuous intravenous infusion at 10 μg/kg per h). N=12	Placebo (5% dextrose, infused as intervention) N=14	Primary outcomes: HR, blood pressure, respiratory rate and interaction of spontaneous respiration with mechanical ventilation. Secondary outcomes: duration of oxygen therapy, ventilator therapy, hospitalization, incidence of bronchopulmonary dysplasia, periventricular hemorrhage and pneumothorax.	Infusion continued until weaning from MV or for a maximum of 48 h therapy. Pancuronium allowed for infants not stabilized by ventilatory adjustment and markedly asynchronous with their ventilator. All study population included in this overview.
e Silva 2008	20 premature neonates (28 to 34 wks) with respiratory distress syndrome, mechanically ventilated; requiring elective tracheal intubation and surfactant therapy. Mean GA ± SD: 31.35 ± 1.67 in morphine group; 31.27 ± 1.46 in remifentanil group	Morphine (intravenous bolus 150 $\mu g/kg^{-1}$) N = 10	Remifentanil (intravenous bolus 1 $\mu g/kg^{-1}$) N = 10	The length of time to awaken and extubate the neonate after interrupting opioid administration; stress (COMFORT scale), pain response (NIPS), hemodynamic and ventilatory variables; adverse effects secondary to infusion of the specific opioid.	Additional treatment: midazolam 200 μg/kg-1.

Table 6. Opioids *(Continued)*

	Infants with birth weight < 1000 g were excluded.				
Guinsburg 1998	22 preterm infants (≤ 32 wks; postnatal age of 12 to 48 h), intubated and mechanically ventilated since birth; with an indwelling arterial umbilical line. Mean GA ± SD: 31 ± 1 in fentanyl group; 30 ± 2 in PLA group. Infants with grade III to IV intraventricular hemorrhage were excluded.	Fentanyl (single dose, 3 µg/kg) N = 11	Placebo (0.2 ml of normal saline) N = 11	HR, blood pressure, arterial blood gases, ventilator settings, and behavioral measures (Neonatal Facial Coding System and Modified Postoperative Comfort Score) at 30 and 60 min after drug administration; blood cortisol, growth hormone, glucose, and lactate were measured before and at 60 min after analgesia; behavioral measures were assessed at the bedside and from video films recorded during each observation period.	Both fentanyl and placebo were injected slowly over 2 min. All study population included in this overview.
Ionides 1994	25 MV infants Mean GA ± SD: 33.9 ± 1.8 in fentanyl group; 32.9±1.6 in morphine group	Fentanyl citrate (single intravenous dose, 3 µg/kg) N = 10	Morphine sulfate (single intravenous dose, 0.1 mg/kg) N = 12	Plasma B-endorphin level, HR, blood pressure.	In our analysis, only preterm groups (fentanyl and morphine) were included. 9 infants received pancuronium, and 6 of these infants also received opiates.
Lago 1998	55 preterm infants (26 to 34 wks GA), requiring intermittent mandatory ventilation for hyaline membrane disease with indwelling catheters, first 24 hours of life. Mean GA ± SD: 31(2) in fentanyl group, 31 (2) in control group	Fentanyl (given at 0.5 to 2.0 µg/kg/h and adjusted to render the neonate sedated) N = 26	No treatment N = 27	Behavioral sedation score, urinary metanephrine, the normetanephrine: creatinine molar ratio measured at 0, 24, 48 and 72 h; ventilatory indexes; need for surfactant replacement, evidence of clinically significant patent ductus arteriosus, incidence of air leak (pulmonary emphysema and pneumothorax), bronchopulmonary dysplasia, GMH-IVH, periventricular leukomalacia, days of ventilatory support and oxygen treatment, days of exclusive enteral feeding, growth and hospital stay.	All study population included in this overview.
Lago 1999 (conference abstract)	27 preterm (> 28 wks GA) with RDS and conventionally ventilated Mean/median GA not reported	Fentanyl (continuous venous infusion 1.5 µg/kg/h, scaled down by 0.5 µg/kg/h every	Placebo (infusion of 5% glucose solution) N = 14	Peak inspiratory pressure, respiratory rate, tidal volume and minute ventilation, along with arterial blood gas and electromyographic activity, a sedation score.	All study population included in this overview.

Table 6. Opioids *(Continued)*

	Age at the time of intervention not specified.	24 h, for a total 72 h of infusion) N = 13			
Liem 1999	8 preterm infants (29.9 to 32.1 wks GA) who needed MV Ranges of GA: 30.7 to 32 in midazolam group; 29.9 to 32.1 in morphine group. Age at the time of intervention not specified.	Morphine (a loading dose of 0,05 mg/kg, maintenance 0.001 mg/kg/h) N = 4	Midazolam (a loading dose 0.2 mg/kg, maintenance 0.2 mg/kg/h) N = 4	Concentration changes of oxyhemoglobin, deoxyhemoglobin, and total hemoglobin in the brain, changes in cerebral blood flow velocity in the internal carotid artery (in %) determined before and at 15, 30, and 60 min after sedation.	
Naderi 2017	32 newborns (26 to 38 wks of GA) undergoing intubation and mechanical ventilation (for at least 24 h); following RDS, bacterial pneumonia, viral pneumonia, and other respiratory problems for at least 24 h during a period of 12 months. Mean GA ± SD: 31.6 ± 4.7 in fentanyl group; 31.0 ± 4.2 in morphine group	Morphine (a loading dose of 100 mcg/kg in the first hour, and a maintenance dose of 12 mcg/kg/h for the next 24 h, injected intravenously) n = 16	Fentanyl (loading dose of 2 mcg, and with a maintenance dose of 0.25 mcg/kg/h, intravenously injected slowly) n = 16	Ultrasonographic measurements of gallbladder dimensions (length, width, depth and volume) as well as the occurrence of hydrops of gall bladder.	
Orsini 1996	20 premature infants undergoing MV for RDS in the first 24 h of life, with indwelling arterial catheter, > 1000 g BW Mean GA ± SD: 31.6 ± 2.8 in fentanyl group, 29.9 ± 3.2 in PLA group	Fentanyl (continuous infusion; a 5 mcg/kg bolus infused for 20 min, followed by 2 mcg/kg/h for 72 h, then decreased to 1 mcg/kg/h for the next 24 h and 0.5 mcg/kg/h for the final 24 h; then the infusion was discontinued; total: 5 days) N=11	Placebo (5% dextrose in water; volume-matched infusion) N = 9	Behavioral state score, cortisol and 11-deoxycortisol levels, 24-h urine collection for 3-methyl histidine/creatinine molar ratio and urea excretion, arterial blood gases, heart rate, IMV, PIP, PEEP	Other analgesics, sedatives, and muscle relaxants were precluded from being administered. All study population included in this overview.
Qiu 2019	60 preterm infants (< 32 wks of GA), admitted in the first 72 h after birth and mechanically ventilated	Fentanyl (an intravenous loading dose of 1 μg/kg in 30 min, followed by a continuous intravenous in-	Placebo (continuous infusion of 5% glucose at the same rate as fentanyl) n = 30	Gas analysis (pH, PaO_2, $PaCO_2$, SaO_2), cardiovascular parameters (MABP, HR, cardiac output), ventilatory parameters (PIP, positive end-expiratory pressure, MAP and FiO_2) before administration,	Dose of fentanyl/glucose was decreased to 0.5 mcg/kg/hour when default parameters for MV were as

Table 6. Opioids *(Continued)*

	Mean GA ± SD: 31.08 ± 2.02 in fentanyl group; 30.32 ± 2.03 in PLA group Infants with significant parenchymal brain injury (grade IV GMH-IVH or PVL) were excluded.	fusion of 1 µg/kg/h, immediately after using MV) n = 30		and 1, 12, 24, 48 and 72 h after start of infusion. PIPP, cerebral blood flow velocity, neuron-specific enolase concentrations in plasma samples, cerebral function monitoring.	follows: FiO_2 < 25%, RR < 25 bpm, and MAP < 7 cmH_2O. 30 minutes later, MV was stopped after discontinuation of infusion.
Quinn 1992	95 premature newborns (≤ 34 wks of GA), with hyaline membrane disease, RDS requiring MV; postnatal age > 4 h and < 48 h; no prior treatment with narcotic analgesics or neuromuscular blocking agents; struggling against the ventilator. Median GA with range: 29 (24 to 34) in morphine group; 28 (24 to 32) in pancuronium group; 28 (24 to 33) in morphine+pancuronium group	Group 1: morphine (continuous infusion at a dose of 50 mcg/kg/h, increased to 100 mcg/kg/h if infant continued to struggle after 2 h on lower dose) N = 29	Group 2; pancuronium (100 mcg/kg/h, given as required to inhibit spontaneous respiration) N = 28 Group 3: morphine with pancuronium (morphine by infusion at a dose of 50 mcg/kg/h and intermittent pancuronium 100 mcg/kg as required; dosage of morphine was not increased) N = 38	Plasma catecholamine levels, BP, HR. ventilatory requirements (peak inspiratory pressure and oxygen concentration), at entry and at 6 h. Outcomes: GMH-IVH, air leak, patent ductus arteriosus, duration of mechanical ventilation in days, drug therapy, death of the infants.	Babies in morphine group who continued to 'light the ventilator' after 4 h on the morphine infusion (2 h at 50 pg/kg per h + 2 h at 100 kg per h) were allowed to be given pancuronium (N = 7). Babies in pancuronium group were given morphine analgesia if a painful procedure was performed (N = 4). Drug therapy continued until FiO_2 < 0.45; 1 infant stopped treatment within 24 h because FiO_2 fell below 0.45. Group 3 (morphine with pancuronium) was not included in our review.
Quinn 1993	41 MV infants (≤ 34 wks of GA) who were treated with surfactant (Curosurf) for hyaline membrane disease (clinically and radiologically confirmed), and have arterial line in situ, and an arterial/alveolar oxygen ratio below 0.22.	Morphine (in 5% dextrose; 2 mL per h for each kg birthweight for 2 h as a loading infusion, then 0 to 5 mL per h for each kg birthweight as	Placebo (5 % dextrose) N = 20	Pain assessment (with validated score); GMH-IVH, pneumothorax, patient ductus arteriosus, duration of intubation in completed days, death during the first 6 months of life. Blood pressure, HR and ventilator settings (i.e. peak inspiratory pressure, oxygen concentration), and catecholamine,	Infusion of both started 1h after first dose of Curosurf. All study population included in this overview. Treatment until the baby had

Table 6. Opioids *(Continued)*

		infusion; 100 mcg/kg/h for 2 h, followed by 25 mcg/kg/h of continuous infusion) N = 21		adrenaline, noradrenaline concentrations were reported.	recovered sufficiently to be weaned from ventilation.
Saarenmaa 1999	163 newborns (≥ 24 wks of GA) who underwent intubation and MV after birth (for at least 1 day), an indwelling arterial line, no chromosomal aberrations or major abnormalities, during first days of life Median GA with IQR: 31.7 (29.4 to 37.0) in fentanyl group, 31.0 (28.9 to 35.3) in morphine group	Fentanyl (a loading dose of 10.5 mcg/kg over 1 h, followed by a maintenance rate of 1.5 mcg/kg/h for at least 24 h) N = 83	Morphine (a loading dose of 140 mcg/kg over 1 h, followed by a maintenance rate of 20 mcg/kg/h for at least 24 h) N = 80 .	The severity of pain, behavioral pain (adapted NIPS scale), stress hormone concentrations (catecholamines; beta-endorphin) before and 2 and 24 h after start of intervention; decreased gastrointestinal motility, necrotizing enterocolitis, retention.	Additional analgesia with opioid boluses was allowed. The bolus, equal to a 1-h maintenance infusion dose, could be given 4 times a day at the most. Muscle relaxation could be used if the infant was struggling against the ventilator despite analgesia. All study population included in this overview.
Simons 2003	150 newborns who had received ventilatory support, postnatal age < 3 d and ventilation for less than 8 h, indwelling (peripheral or umbilical) arterial catheter, admitted to NICU. Median GA (IQR) of 29.1 wks (27.4 to 31.6) in morphine group; and 29.2 wks (27.3 to 31.4) in placebo group Infants with sIVH were excluded.	Morphine (intravenous; a loading dose of 100 mcg/kg, followed by continuous infusion of 10 mcg/kg per h) N = 73	Placebo (sodium chloride infusion, the same dosages as morphine) N = 77	Primary outcome: analgesic effect (measured before, 30 min after loading dose and twice daily at a standardized time point before, during and after endotracheal suctioning; NIPS, Visual Analogue Score and PIPP). Secondary outcomes: poor neurologic outcome defined as sIVH, PVL, or death within 28 days and the incidence of all grades of GMH-IVH. Other: duration of artificial ventilation, length of NICU stay, incidence of comorbidity, number of painful procedures.	Both morphine and PLA were dissolved in 5% glucose, and both were given for 7 days (or less because of clinical necessity in severe cases). Additional morphine based on physician decision was allowed. All study population included in this overview.
Siwiec 1999 (conference abstract)	20 infants (26 to 35 wks of GA), receiving MV, BW 810 to 2750 g	Morphine (loading dose 100 mcg/kg over 30 min followed by continuous	Control: no treatment N = 10 (reported in the	Pain (PIPP), comfort score, assessed prior to the treatment then at 6, 12, 24 hrs of age, HR, blood pressure, and ventilatory parameters assessed more	All study population included in this overview.

Table 6. Opioids *(Continued)*

	Mean/median GA not reported.	infusion of 20 mcg/kg/h for 1 to 5 days) N = 10 (reported in the Cochrane Review)	Cochrane Review)	frequently. Mean airway pressure, ventilatory rate or FIO_2, pneumothorax, GMH-IVH, PVL, bronchopulmonary dysplasia.
Wood 1998	88 preterm neonates (< 35 wks of postconceptional age at birth), 2 to 48 h of postnatal age at trial entry, requiring IPPV and sedation; indwelling intra-arterial access. Median GA with IQR: 28 (26 to 30) in morphine group; 27 (26 to 29) in diamorphine group	Morphine (a loading dose of 200 mcg/kg over 2 h, followed by maintenance infusion of 25 mcg/kg/h) N = 44	Diamorphine (120 mcg/kg over 2 h, followed by maintenance infusion of 15 mcg/kg/h) N = 44	Arterial blood pressure, HR, PaO_2 (or SaO_2), temperature, intermittent arterial blood gas sampling; mean arterial blood pressure recorded when starting infusion and at 2, 6, 24 h. The use of initiation of inotropic support over the first 24 h of infusion.

BW = birth weight; CPAP = continuous positive airway pressure; FiO_2 = fraction of inspired oxygen; GA = gestational age, in weeks; GMH-IVH = germinal matrix hemorrhage-intraventricular hemorrhage; h = hour; HR = heart rate; IMV = intermittent mechanical ventilation; IPPV = intermittent positive pressure ventilation; IQR = interquartile range; ITT= intention to treat; MAP = mean airway pressure; MABP = mean arterial blood pressure; min = minute; mo = months; MV = mechanical ventilation; NAPI = neurobehavioral assessment scores; NG = nasogastric; NICU = neonatal intensive care unit; NIPS = Neonatal Infant Pain Scale; PEEP = positive end-expiratory pressure ; PIP = peak inspiratory pressure; PIPP = premature infant pain profile; PLA = placebo; PO = per os; PVL = periventricular leukomalacia; RCT = randomized controlled trial; RDS = respiratory distress syndrome; RR = respiratory rate; SaO_2 = oxygen saturation; sIVH = severe intraventricular hemorrhage; wk = week.

Table 7. Ibuprofen

RCT ID	Population	Intervention	Comparison	Outcomes	Notes
Dani 2005	155 preterm infants (< 28 wks of GA), < 6 h of postnatal age, without 2 to 4 grade GMH-IVH, ≥ 50,000 platelets/mm3, serum creatinine concentration ≤ 1.5 mg/dL Mean BW ± SD (in grams): 832 ± 215 in ibuprofen group; and 812 ± 209 in PLA group Mean GA ± SD (wks): 25.3 ± 1.2 in ibuprofen group; and 25.9 ± 1.1 in PLA group MV: SIMV/SIPPV: 57/77 (74%) in ibuprofen group; 53/78 (68%) in PLA group	3 doses of ibuprofen (Arfen, Lisapharma, Erba, Italy; 10 mg/kg within 6 h after birth, followed by 5 mg/kg after 24 and 48 h) N = 77	Indistinguishable non-specified placebo N = 78	Incidence of germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) at 7 days of life with grading (no or 1 – success; 2 to4 – failure; serial ECG was performed at days 7, 15, 30 and at 40 wks' of postconceptional age); the rates of ductal closure on day 3; adverse events and complications (i.e. bronchopulmonary dysplasia, NEC, retinopathy of prematurity, sepsis). Length of stay in hospital, death; severity of infant respiratory distress syndrome; serum creatinine level (at 1, 3 and 5 d of life), urine output (first 5 d of life), fluid intake (during first week of life), hematuria, gastric bleeding, blood in the endotracheal aspirate or stools, oozing from puncture sites – to evaluate bleeding.	Both, ibuprofen and placebo were infused continuously in period of 15 min. In patients with ductus arteriosus still patent, ibuprofen was administered as a nonrandomized rescue treatment. If this therapy also failed to promote ductal closure or if there was a contraindication to repeated pharmacologic treatment, then surgical ligation of the ductus arte-

Table 7. Ibuprofen *(Continued)*

	HFOV: 26/77 (34%) in ibuprofen group, 17/78 (22%) in PLA group				riosus was performed. Additional treatment: dopamine and/or dobutamine for hypotension Postnatal dexamethasone for severe respiratory failure
De Carolis 2000	50 preterm neonates (< 31 wks of GA), at 2 h of life; BW ≥ 500 g, platelet count ≥ 50 x 109/l), without neonatal indomethacin administration. All children were mechanically ventilated. Mean GA with SD (wks): 28.1 ± 1.1 in ibuprofen group 28.0 ± 1.9 in control group Mean BW ± SD (g): 934 ± 288 in ibuprofen group; 993 ± 308 in control group	Ibuprofen lysine salt (Arfen, Lysafarma, Erba-Como, Italy; 10 mg/kg infused over 20 min via peripheral vein and within 2 h after birth, followed by 2 doses of 5 mg/kg after 24 and 48 h using the same modality; intravenously) N = 25 (23 analyzed)	Control group: no intervention, i.e. no placebo administration N = 25 (23 analyzed)	PDA (assessed with ECG evaluation, after birth, at day 3 of life, and whenever suspicion occurred). Adverse events. Hemoglobin, hematocrit, platelet count, serum electrolytes, blood urea nitrogen, and serum creatine were monitored. Coagulation tests: at birth and then following the clinical indications. Renal function evaluated daily (urine output, blood urea nitrogen, serum creatinine concentrations, creatinine clearance, fractional excretion of sodium on second and third day after birth. Clinical bleeding tendency and occurrence of sepsis assessed the first 3 day of life. Abdominal distension, food tolerance and NEC were also monitored. GMH-IVH, PVL, cerebral flow patterns were measured with Doppler ultrasound on days 1, 3, 7 and weekly until discharge. Pulmonary parameters (FiO_2, mean arterial pressure, bronchopulmonary dysplasia, days of mechanical ventilation, days of oxygen therapy). Need for treatment with indomethacin after 72 hs, surgical ligation, mortality at 28 days of age.	In the presence of significant PDA at the completion of ibuprofen cycle, treatment with indomethacin (3 x 0.2 mg/kg at 12 h intervals, by intravenous infusion over 20 min) was carried out; the same in control group with significant PDA at day 3. Failure to respond was indication for surgical ligation. Additional treatment: 200 mg/kg of Curosurf.
Gournay 2004	131 preterms (< 28 wks of GA, i.e. up to 27 wks and 6 d), within 6 h of birth; whose mother did not use nephrotoxic medications within 3d before delivery); without GMH-IVH grade 3 or 4.	Ibuprofen (Orphan, Paris, France) 3 doses, within 6 h of birth; loading dose of 10 mg/kg, followed by two maintenance doses of 5 mg/	Placebo (saline, equivalent volumes) N = 66	Primary outcome: need for surgical ligation, based on presence of significant PDA on the echocardiogram, resulting in clinical manifestation of increased pulmonary blood flow, steal flow to peripheral organs, or a combination of these criteria. Secondary criteria: frequency of PDA at day 3; rate of curative	Analysis per protocol. Both ibuprofen and PLA were supplied by Orphan Europe (Paris, France).

Table 7. Ibuprofen *(Continued)*

	Mean GA with SD (wks): 26.3 ± 0.9 in ibuprofen group; 26.0 ± 0.9 in PLA group. Mean BW ± SD (g): 844 ± 181 in ibuprofen group; 851 ± 164 in PLA group. Majority of infants were mechanically ventilated (88% in ibuprofen and 94% in PLA groups).	kg at 24 h intervals N = 65 After day 3, symptomatic PDA was treated by open curative ibuprofen, then back-up indomethacin, surgery, or both.		treatment with ibuprofen; frequency of backup treatment with indomethacin; rate of cystic PVL; frequency of GMH-IVH grade 3 or 4 (Volpe classification); rate of NEC, intestinal perforation, or both; duration of MV; frequency of bronchopulmonary dysplasia (defined as the need for supplementary oxygen at 36 wks after conception; effects on renal function; the actuarial curve of survival during the study period.	
Sangtawesin 2008	62 VLBW (≤ 1500 g) premature neonates (26 to 32 wks of GA), admitted to the neonatal unit, with open ductus arteriosus; without maternal non-steroid anti-inflammatory drug use; with serum creatinine < 1.5 mg/dl and/or blood urinary nitrogen < 30 mg/dl, and platelet count > 75000 cells/mm3 Mean age of drug administration ± SD (h): 18.14 ± 6.03 in ibuprofen group; and 20.09 ± 5.67 in PLA group. Mean GA ± SD (wks): 29.32 ± 1.94 (range: 26 to32) in ibuprofen group; 29.29 ± 2.16 (range: 26 to32) in PLA group Mean BW ± SD (g): 1156.90 ± 263.6 (range: 765 to 1500) in ibuprofen group; 1162.90 ± 261.0 (range: 690 to 1500) in PLA group Majority of infants had ventilator assistant (93.55% in ibuprofen group; 87.1% in PLA group).	Oral ibuprofen suspension (Junifen, Boots Company, Thailand; 3 doses; at a dosage of 10 mg/kg for first dose within 24 h of life and 5 mg/kg for the second and third doses after 24 and 48 h; given via orogastric tube, followed by 0.5 ml of distilled water). N = 31 Patients with any significant adverse drug reactions which required treatment were excluded.	Oral placebo (3 doses of orange starch suspension, administered with the same method and time schedule as oral ibuprofen). N = 31	Primary outcome: PDA: incidence of symptomatic (defined as echocardiographic and clinical evidence of hemodynamically significant PDA); size in mm, close on day 3, weight in grams (≤ 1200 or 1201 to 1500). Secondary outcomes: Respiratory system (persistent pulmonary hypertension, bronchopulmonary dysplasia, ventilatory days, days of oxygen therapy); renal function (serum blood urea nitrogen, serum creatinine); gastrointestinal system (days of start and full feeding, local gastrointestinal bleeding), NEC ≥ stage II); GMH-IVH (total, grade 1 and 2 to 3; retinopathy of prematurity (total, stage 1 and 2); length of hospital stay; death. Complete blood count, blood urinary nitrogen, creatinine, electrolyte, coagulogram were evaluated 24 h after the fully course of drug administration. ECG was performed each dose, of ibuprofen administration and on days 7, 14 and 28 of life.	Additional treatment: if during the course of the study, symptomatic PDA did occur, standard treatment with intravenous indomethacin was given. Surgical ligation was performed in cases of medication failure.
Van Overmeire 2004	415 low-birthweight preterm infants (24 to 30 wks of GA), within	Ibuprofen lysine (an initial dose of 10	Placebo (intravenously; 3 doses of	Primary outcome: occurrence of sIVH (cranial ultrasonography was done at baseline, and then	Both ibuprofen and placebo were infused

Table 7. Ibuprofen *(Continued)*

	mitted to NICU; without GMH-IVH higher than grade 1 and contradiction for ibuprofen administration (i.e. serum creatinine level > 115 µmol/L or serum bilirubin > 85 µmol/L, platelet count < 60 x 109/L, tendency to bleed). Mean GA with SD (wks): 28.1 ± 1.7 in ibuprofen group; and, 28.1 ± 1.6 in PLA group. Mean BW with SD (g): 1048 ± 215 in ibuprofen group; and, 1065 ± 315 in PLA group. Majority of infants were mechanically ventilated from birth: 85% in ibuprofen group and 84% in PLA group.	the first 6 h of life, followed by 2 doses of 5 mg/kg after 24 h and 48 h). N = 205 Vials contained 20 mg of ibuprofen with 14 mg of lysine in water or normal saline.	initial dose of 1 ml/kg, followed by 0.5 ml/kg after 24 and 48 h). N = 210	28 of life, or before discharge; GMH-IVH was graded from 1 to 4, according to standard classification systems). The presence of cystic PVL after age of 2 wks was also reported. Secondary outcomes: the presence of confirmed with ECG open PDA after 3 d of life, and the need for its pharmacological rescue treatment or surgical ligation; occurrence of renal dysfunction (measured by urine production); NEC; and death. Adverse effect.	Fluids were given following the standard guidelines. ITT analysis. Additional treatment: a non-randomized intravenous pharmacological rescue treatment was given with either indomethacin (3 doses of 0·2 mg/kg with 12-h intervals) or ibuprofen-lysine (first dose of 10 mg/kg followed by 2 doses of 5 mg/kg at 24 h and 48 h). If the infant was still on mechanical ventilation without decrease of the ductal shunt after rescue intervention, the ductus was surgically ligated. Half of patients received surfactant treatment (60% in PLA and 55% in ibuprofen group).

BW = body weight; d = days; ECG = echocardiography; GA = gestational age; GMH-IVH = germinal matrix hemorrhage-intraventricular hemorrhage; h = hour; HFOV = high-frequency oscillatory ventilation; ITT= intention to treat; iv = intravenous; min = minute; MV = mechanical ventilation; NEC = necrotizing enterocolitis; NICU = neonatal intensive care unit; PDA = patent ductus arteriosus; PLA = placebo; PVL = periventricular leukomalacia; SD = standard deviation; SIMV = synchronized intermittent mandatory ventilation; SIPPV = Synchronized intermittent positive pressure ventilation; sIVH = severe intraventricular hemorrhage; VLBW: very low birth weight; wks = week

Table 8. Effect estimates, intervention versus placebo/no intervention

Outcomes	Paracetamol	Midazolam	Phenobarbital	Opioids	Ibuprofen
	Jasani 2022	Ng 2017	Romantsik 2023	Bellù 2021	Ohlsson 2020b
Any GMH-IVH[a]	RR 0.89, 95% CI 0.38 to 2.07; 2 RCTs, 82 infants	RR 1.68, 95% CI 0.87 to 3.24; I^2 = 0%; 3 RCTs, 122 infants	RR 0.99, 95% CI 0.83 to 1.19; I^2 = 63%; 9 RCTs, 732 infants	RR 0.85, 95% CI 0.65 to 1.12; I^2 = 38%; 7 RCTs, 469 infants	RR 0.99, 95% CI 0.81 to 1.21; I^2 = 0%; 4 RCTs, 759 infants

Table 8. Effect estimates, intervention versus placebo/no intervention *(Continued)*

Severe IVH[b]	RR 1.80, 95% CI 0.43 to 7.49; 2 RCTs, 82 infants	No RCTs reported this outcome	RR 0.91, 95% CI 0.66 to 1.25; I^2 = 29%; 9 RCTs, 732 infants	RR 0.98, 95% CI 0.71 to 1.34; I^2 = 15%; 2 RCTs; 1299 infants	RR 0.82, 95% CI 0.54 to 1.26; I^2 = 0%; 4 RCTs, 747 infants
Neonatal death[c]	Not reported	No RCTs reported this outcome	RR = 0.94, 0.51 to 1.72); I^2= 65%; 3 RCTs, 203 infants	RR 1.12, 95% CI 0.80 to 1.55; I^2 = 0%; 5 RCTs, 1189 infants	Neonatal mortality at < 28 days of life: I (IV) versus placebo: RR 1.00, 0.38 to 2.64; I^2= 0%; 2 RCTs, 112 infants Mortality before 36 wks PMA: RR 0.96, 0.56 to 1.66; 1 RCT, 131 infants
Major neurodevelopmental disability[d]	Not reported	No RCTs reported this outcome	No RCTs reported this outcome	At 18 to 24 months (moderate to severe disability): RR 2.0, 95% CI 0.39 to 10.29; 1 RCT, 78 infants At 5 to 6 years (disability): RR 1.6, 95% CI 0.56 to 4.56; 1 RCT, 95 infants	No RCTs reported this outcome
Death during initial hospitalization[e]	Not reported	RR 0.79, 95% CI 0.40 to 1.56; I^2 = 0%; 3 RCTs, 122 infants	RR 0.90, 95% CI 0.64 to 1.26; I^2 = 15%; 8 RCTs, 680 infants	RR 0.99, 95% CI 0.52 to 1.88; I^2 = 0%; 4 RCTs, 178 infants	RR 0.91, 95% CI 0.63 to 1.33; I^2 = 0%; 3 RCTs, 620 infants
Any ROP[f]	RR 0.93, 95% CI 0.53 to 1.61; 1 RCT, 58 infants	No RCTs reported this outcome	No RCTs reported this outcome	No RCTs reported this outcome	RR 1.09, 95% CI 0.75 to 1.60; I^2 = 11%; 2 RCTs, 213 infants
Severe ROP[g]	Not reported	No RCTs reported this outcome	No RCTs reported this outcome	No RCTs reported this outcome	RD 0.00, 95% CI -0.06 to 0.06; 1 RCT, 62 infants
Cerebellar hemorrhage[h]	Not reported	No RCTs reported this outcome	No RCTs reported this outcome	No RCTs reported this outcome	No RCTs reported this outcome
PVL[i]	Not reported	RR 3.82, 95% CI 0.46 to 31.43; 1 RCT; 43 infants	No RCTs reported this outcome	RR 0.79, 95% CI 0.49 to 1.14; I^2 = 0%; 6 RCTs, 1299 infants	RR 1.19, 95% CI 0.64 to 2.18; I^2 = 0%; 4 RCTs, 747 infants
Brain MRI abnormalities[j]	Not reported	No RCTs reported this outcome	No RCTs reported this outcome	No RCTs reported this outcome	No RCTs reported this outcome

I^2 = not applicable where only one RCT
List of outcomes:
[a]Any germinal matrix hemorrhage-intraventricular hemorrhage: any GMH-IVH, ultrasound diagnosis grade 1 to 4 (according to Papile classification (Papile 1978)).

[b]Severe intraventricular hemorrhage (IVH), ultrasound diagnosis grade 3 and 4 (according to Papile classification (Papile 1978)).
[c]All-cause neonatal death (death within 28 days of birth).
[d]Major neurodevelopmental disability: cerebral palsy, developmental delay (Bayley Mental Developmental Index (Bayley 1993; Bayley 2006) or Griffiths Mental Development Scale assessment (Griffiths 1954) more than two SD below the mean), intellectual impairment (IQ more than two standard deviations below mean), blindness (vision < 6/60 in both eyes), or sensorineural deafness requiring amplification (Jacobs 2013). We planned to evaluate each of these components as a separate outcome and to extract data on this long-term outcome from studies that evaluated children after 18 months of chronological age. We planned to assess separately data on children aged 18 to 24 months and those aged three to five years.
[e]All-cause death during initial hospitalization.
[f]Any retinopathy of prematurity: any stage (ICROP 1984).
[g]Severe retinopathy of prematurity: stage 3 or greater (ICROP 1984).
[h]Cerebellar hemorrhage at brain ultrasound in the first month of life (yes/no, Graça 2013).
[i]Cystic periventricular leukomalacia at brain ultrasound in the first month of life (yes/no); or at term equivalent age (yes/no).
[j]Brain magnetic resonance imaging (MRI) abnormalities at term equivalent age (yes/no), defined as white matter lesions (i.e. cavitations; Rutherford 2010) and punctate lesions (Cornette 2002); GM-IVH (Parodi 2015); or cerebellar hemorrhage (Limperopoulos 2007).
CI = confidence interval; IV= intravenous; GMH-IVH = germinal matrix hemorrhage-intraventricular hemorrhage; MRI = magnetic resonance imaging; NA = not applicable; PMA = postmenstrual age; PVL = periventricular leukomalacia; RCT = randomized controlled trial; RD = risk difference; ROP = retinopathy of prematurity; RR= risk ratio; wks = week.

Table 9. Effect estimates, intervention versus other active interventions

Outcomes	Paracetamol versus Ibuprofen Jasani 2022	Morphine versus midazolam Bellù 2021	Morphine versus diamorphine Bellù 2021	Morphine versus fentanyl Bellù 2021
Any GMH-IVH[a]	RR 1.17, 95% CI 0.31 to 4.34; 1 RCT, 30 infants	RR 0.28, 95% CI 0.09 to 0.87; 1 RCT, 46 infants	RR 0.65, 95% CI 0.40 to 1.07; 1 RCT, 88 infants	Not reported
Severe IVH[b]	RR 2.65, 95% CI 0.12 to 60.21; 1 RCT, 30 infants	RR 0.08, 95% CI 0.00 to 1.43; 1 RCT, 46 infants	Not reported	RR 0.59, 95% CI 0.18 to 1.95; 1 RCT, 163 infants
Neonatal death[c]	Not reported	RR 0.31, 95% CI 0.01 to 7.16; 1 RCT, 46 infants	RR 1.17, 95% CI 0.43 to 3.19; 1 RCT, 88 infants	Not reported
Major neurodevelopmental disability[d]	Not reported	Not reported	Not reported	Not reported
Death during initial hospitalization[e]	RR 0.88, 95% CI 0.14 to 5.42; 1 RCT, 30 infants	Not reported	Not reported	RR 1.21, 95% CI 0.43 to 3.45; 1 RCT, 163 infants
Any ROP[f]	RR 4.41, 95% CI 0.24 to 84.79; 1 RCT, 30 infants	Not reported	Not reported	Not reported
Severe ROP[g]	Not reported	Not reported	Not reported	Not reported
Cerebellar hemorrhage[h]	Not reported	Not reported	Not reported	Not reported
PVL[i]	Not reported	RR 0.23, 95% CI 0.03 to 1.90; 1 RCT, 46 infants	Not reported	Not reported

Table 9. Effect estimates, intervention versus other active interventions *(Continued)*

Brain MRI abnormalities[j]	Not reported	Not reported	Not reported	Not reported

Studies comparing morphine versus midazolam, diamorphine, or fentanyl: their results are shown in this table; I^2 was not applicable because there was only one study in each analysis.

List of outcomes

[a]Any germinal matrix hemorrhage-intraventricular hemorrhage: any GMH-IVH, ultrasound diagnosis grade 1 to 4 (according to Papile classification (Papile 1978)).

[b]Severe intraventricular hemorrhage (IVH), ultrasound diagnosis grade 3 and 4 (according to Papile classification (Papile 1978)).

[c]All-cause neonatal death (death within 28 days of birth).

[d]Major neurodevelopmental disability: cerebral palsy, developmental delay (Bayley Mental Developmental Index (Bayley 1993; Bayley 2006) or Griffiths Mental Development Scale assessment (Griffiths 1954) more than two SD below the mean), intellectual impairment (IQ more than two standard deviations below mean), blindness (vision < 6/60 in both eyes), or sensorineural deafness requiring amplification (Jacobs 2013). We planned to evaluate each of these components as a separate outcome and to extract data on this long-term outcome from studies that evaluated children after 18 months of chronological age. We planned to assess separately data on children aged 18 to 24 months and those aged three to five years.

[e]All-cause death during initial hospitalization.

[f]Any retinopathy of prematurity: any stage (ICROP 1984).

[g]Severe retinopathy of prematurity: stage 3 or greater (ICROP 1984).

[h]Cerebellar hemorrhage at brain ultrasound in the first month of life (yes/no, Graça 2013).

[i]Cystic periventricular leukomalacia at brain ultrasound in the first month of life (yes/no); or at term equivalent age (yes/no).

[j]Brain magnetic resonance imaging (MRI) abnormalities at term equivalent age (yes/no), defined as white matter lesions (i.e. cavitations; Rutherford 2010) and punctate lesions (Cornette 2002); GM-IVH (Parodi 2015); or cerebellar hemorrhage (Limperopoulos 2007).

CI = confidence interval; GMH-IVH = germinal matrix hemorrhage-intraventricular hemorrhage; MRI = magnetic resonance imaging; PVL = periventricular leukomalacia; ROP = retinopathy of prematurity; RR = risk ratio

Table 10. Risk of bias assessments from included reviews

Review ID	Summary of trial limitation (risk of bias assessment)
Paracetamol	**Sequence generation:** 3 RCTs low risk
Jasani 2022	**Allocation concealment:** 2 RCTs low risk; 1 RCT unclear risk
	Blinding (participants and personnel): 2 RCTs low risk; 1 RCT unclear risk
	Blinding (outcome assessors): 1 RCT low risk; 2 RCTs unclear risk
	Incomplete outcome data: 3 RCTs low risk
	Selective reporting: 2 RCTs low risk; 1 RCT unclear risk
	Other: 3 RCTs low risk
Midazolam	**Sequence generation:** 2 RCTs low risk; 1 RCT unclear risk
Ng 2017	**Allocation concealment:** 3 RCTs low risk
	Blinding (participants and personnel): 3 RCTs low risk
	Blinding (outcome assessors): 3 RCTs low risk
	Incomplete outcome data: 3 RCTs low risk
	Selective reporting: 3 RCTs unclear risk
	Other: 3 RCTs low risk
Phenobarbital	**Sequence generation:** 3 RCTs low risk; 5 RCTs unclear risk; 1 RCT high risk

Table 10. Risk of bias assessments from included reviews *(Continued)*

Romantsik 2023	**Allocation concealment:** 2 RCTs low risk; 6 RCTs unclear risk; 1 RCT high risk
	Blinding (participants and personnel): 1 RCT low risk; 1 RCT unclear risk; 7 RCTs high risk
	Blinding (outcome assessors): 5 RCTs low risk; 4 RCTs unclear risk
	Incomplete outcome data: 8 RCTs low risk; 1 RCT unclear risk
	Selective reporting: 1 RCT low risk; 8 RCTs unclear risk
	Other: 9 RCTs low risk
Opioids	**Sequence generation:** 8 RCTs low risk; 11 RCTs unclear risk; 1 RCT high risk
Bellù 2021	**Allocation concealment:** 10 RCTs low risk; 8 RCTs unclear risk; 2 RCTs high risk
	Blinding (participants and personnel): 14 RCTs low risk; 2 RCTs unclear risk; 4 RCTs high risk
	Blinding (outcome assessors): 14 RCTs low risk; 4 RCTs unclear risk; 2 RCTs high risk
	Incomplete outcome data: 13 RCTs low risk; 5 RCTs unclear risk; 2 RCTs high risk
	Selective reporting: 2 RCTs low risk; 18 RCTs unclear risk
	Other: 19 RCTs low risk; 1 RCT unclear risk
Ibuprofen	**Sequence generation:** 1 RCT low risk; 4 RCTs unclear risk
Ohlsson 2020b	**Allocation concealment:** 3 RCTs low risk; 2 RCTs unclear risk
	Blinding (participants and personnel): 4 RCTs low risk; 1 RCTs high risk
	Blinding (outcome assessors): 4 RCTs low risk; 1 RCT high risk
	Incomplete outcome data: 5 RCTs low risk
	Selective reporting: 5 RCTs unclear risk
	Other: 4 RCTs low risk; 1 RCT unclear risk

Risk of bias assessment is reported only for those trials matching the inclusion criteria of this Overview, as shown in Table 1.
All included Cochrane Reviews used version one of the Cochrane tool for assessing risk of bias (Higgins 2017).
RCT = randomized controlled trial

Table 11. AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews)

AMSTAR-2 domains	Clonidine Romantsik 2017a	Paracetamol for pain Ohlsson 2020a	Paracetamol for PDA Jasani 2022	Midazolam Ng 2017	Phenobarbital Romantsik 2023	Opioids Bellù 2021	Ibuprofen Ohlsson 2020b
1	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Yes	Yes	Yes	Yes	Yes	Partial yes	Partial yes
3	No	No	No	No	No	No	No
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Not applicable	Yes	Yes	Yes	Yes	Yes	Yes
8	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Yes	No	No	Yes	Yes	No	No
11	Not applicable	Not applicable	No	Yes	Yes	Yes	Yes
12	Not applicable	Not applicable	No	Yes	Yes	Yes	No
13	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14	Not applicable	Not applicable	No	Yes	Yes	Yes	No
15	Funnel plot was not constructed (< 10 RCTs)	Funnel plot was not constructed (< 10 RCTs)	Yes	Funnel plot was not constructed (< 10 RCTs)	Yes	Funnel plot was not constructed (< 10 RCTs)	Yes
16	Yes	Yes	Yes	Yes	Yes	Yes	Yes

The AMSTAR-2 domains are:
1. Did the research questions and inclusion criteria for the review include the components of PICO?

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? *
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy? *
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions? *
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? *
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? *
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? *
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? *
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

The seven critical domains are marked with an *.
PDA = patent ductus arteriosus; RCT = randomized controlled trial

APPENDICES

Appendix 1. Search strategy

Information specialist: Maria Björklund, Krister Aronsson

Affiliation: Lund University, Faculty of Medicine, Library & ICT, Sweden

CENTRAL via Cochrane Library Online (Issue 8 of 12, August 2022)

Date of search: 30 August 2022

No publication date limitations or language limitations were used.

[Population block, Cochrane Neonatal standard search strategy https://neonatal.cochrane.org/Literature-Search-Filters-for-Neonatal-Reviews]

#1 MeSH descriptor: [Infant, Newborn] explode all trees
17650 records

#2 MeSH descriptor: [Intensive Care, Neonatal] this term only

353 records

#3 MeSH descriptor: [Intensive Care Units, Neonatal] this term only
867 records

#4 MeSH descriptor: [Gestational Age] this term only

2784 records

#5 ("babe" or "babes" or baby* or "babies" or "gestational age?" or infant? or "infantile" or infancy or "low birth weight?" or "low birthweight?" or neonat* or "neo-nat*" or newborn* or "new born?" or "newly born" or "premature" or "pre-mature" or "pre-matures" or prematures or prematurity or "pre-maturity" or "preterm" or "preterms" or "pre term?" or "preemie" or "preemies" or "premies" or "premie" or "VLBW" or "VLBWI" or "VLBW-I" or "VLBWs" or "LBW" or "LBWI" or "LBWs" or "ELBW" or "ELBWI" or "ELBWs" or "NICU" or "NICUs"):ti,ab,kw

99625 records

#6 #1 OR #2 OR #3 OR #4 OR #5

99625 records

[Anesthesia/sedation/pharmacological interventions block]

#7 MeSH descriptor: [Anesthesia and Analgesia] explode all trees

29200 records

#8 MeSH descriptor: [Anesthesia, Local] explode all trees

2285 records

#9 MeSH descriptor: [Deep Sedation] explode all trees

173 records

#10 MeSH descriptor: [Conscious Sedation] explode all trees

1478 records

#11 anesthesia OR anaesthesia OR anest* OR anaest* OR sedat*:ti,ab,kw

143786 records

#12 #7 OR #8 or #9 OR #10 OR #11

146620 records

#13 MeSH descriptor: [Analgesics, Opioid] explode all trees

8485 records

#14 MeSH descriptor: [Morphine Derivatives] explode all trees

7521 records

#15 opioid* OR opiat*:ti,ab,kw

31155 records

#16 MeSH descriptor: [Fentanyl] explode all trees

5869 records

#17 MeSH descriptor: [Alfentanil] explode all trees

706 records

#18 MeSH descriptor: [Sufentanil] explode all trees

1022 records

#19 MeSH descriptor: [Meperidine] explode all trees

1185 records

#20 MeSH descriptor: [Codeine] explode all trees

1834 records

#21 MeSH descriptor: [Remifentanil] explode all trees

1876 records

#22 MeSH descriptor: [Piperidines] explode all trees

19307 records

#23 MeSH descriptor: [Phenylpropionates] explode all trees

2996 records

#24 MeSH descriptor: [Ibuprofen] explode all trees

2147 records

#25 MeSH descriptor: [Fenoprofen] explode all trees

39 records

#26 MeSH descriptor: [Indoprofen] explode all trees

38 records

#27 MeSH descriptor: [Ketoprofen] explode all trees

583 records

#28 MeSH descriptor: [Suprofen] explode all trees

38 records

#29 MeSH descriptor: [Benzodiazepines] this term only

1927 records

#30 MeSH descriptor: [Midazolam] explode all trees

3229 records

#31 MeSH descriptor: [Lorazepam] explode all trees

839 records

#32 MeSH descriptor: [Chloral Hydrate] explode all trees

129 records

#33 MeSH descriptor: [Propofol] explode all trees

5292 records

#34 MeSH descriptor: [Ketamine] explode all trees

2508 records

#35 MeSH descriptor: [Receptors, N-Methyl-D-Aspartate] explode all trees

381 records

#36 MeSH descriptor: [Analgesics, Non-Narcotic] explode all trees

9639 records

#37 MeSH descriptor: [Analgesics, Short-Acting] explode all trees

0 records

#38 MeSH descriptor: [Calcitonin Gene-Related Peptide Receptor Antagonists] explode all trees

80 records

#39 MeSH descriptor: [Narcotics] explode all trees

9317 records

#40 MeSH descriptor: [Acetaminophen] explode all trees

3486 records

#41 alfentanil OR sulfentanil OR morphine OR meperidine OR codeine OR remifentanil OR piperidines OR opioid* OR fentanyl OR alfentanil OR sufentanil OR diamorphine OR meperidine OR pethidine OR codeine OR remifentanil OR ibuprofen OR fenoprofen OR indoprofen OR ketoprofen OR suprofen OR Phenylpropionate* OR midazolam OR lorazepam OR Benzodiazepine* OR propofol OR chloral hydrate OR ketamine OR NMDA OR N-Methylaspartate OR N-Methyl-D-Aspartate OR CGRPra OR acetaminophen OR paracetamol:ti,ab,kw

91388 records

#42 #7OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41

106899 records

[Pain block]

#43 MeSH descriptor: [Pain] explode all trees

56027 records

#44 MeSH descriptor: [Pain Management] explode all trees

4384 records

#45 MeSH descriptor: [Pain Measurement] explode all trees

22861 records

#46 MeSH descriptor: [Pain Threshold] explode all trees

1809 records

#47 MeSH descriptor: [Anxiety] explode all trees

9244 records

#48 MeSH descriptor: [Crying] explode all trees

338 records

#49 MeSH descriptor: [Facial Expression] explode all trees

707 records

#50 MeSH descriptor: [Fear] explode all trees

1705 records

#51 MeSH descriptor: [Gestures] explode all trees

72 records

#52 MeSH descriptor: [Heart Rate] explode all trees

20060 records

#53 MeSH descriptor: [Infant Behavior] explode all trees

342 records

#54 MeSH descriptor: [Oxygen Consumption] explode all trees

6948 records

#55 MeSH descriptor: [Panic] explode all trees

265 records

#56 MeSH descriptor: [Wakefulness] explode all trees

1056 records

#57 “procedural pain” OR “pain* procedur*” OR anxiet* OR anxious OR behavior* OR behaviour* OR crying OR discomfort* OR distress* OR Douleur Aigue du Nouveau ne OR DAN OR facial expression* OR fear* OR fright* OR gesture* OR grimac* OR heart rate* OR Median Premature Infant Pain Profile score* OR Neonatal Facial Action* OR Neonatal Facial Activity Coding System OR Neonatal Facial Coding Score* OR NFCS OR neonatal facial coding system OR nociceptive reaction* OR sensorial antinociceptive effect* OR oxygen consumption OR oxygen saturation* OR pain* OR panic* OR sleep wake state* OR wakefulness:ti,ab,kw

518060 records

#58 #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57

522912 records

[Mechanical ventilation block]

#59 MeSH descriptor: [Respiration, Artificial] explode all trees

6986 records

#60 artificial respiration OR respiration OR mechanical ventilation OR ventilat* OR intubat* OR extubat*:ti,ab,kw

65987 records

#61 #59 OR #60

66740 records

Combination search [Population block AND (Pharmacological OR sedation OR pain blocks) AND mechanical ventilation block]

#62 #6 AND (#42 OR #58) AND #61

5423 records

Total number of records of systematic reviews: 612

Total number of Cochrane protocols: 51

Total number of records: 5423

Annotation: The population block combined with the (pharmacology OR sedation OR pain) block only retrieves many irrelevant records. Combining the population and the pharmacology block with and AND together with the pain block may miss relevant records.

The pain and the pharmacology block retrieves the same number of records, indicating that there is an overlap between the blocks. We still prefer to add both blocks, in combination with the mechanical ventilation block.

Adding the mechanical ventilation block balances the number of records with relevant results, as in the suggested search strategy above.

HISTORY

Protocol first published: Issue 6, 2017

CONTRIBUTIONS OF AUTHORS

AS and TP screened search results, organized retrieval of papers, screened retrieved papers against eligibility criteria, appraised quality of papers, extracted data from papers.

OR conceived the overview, and contributed to data collection, quality appraisal of papers, and clinical interpretation.

MGC contributed to data management for the overview, entered data into Review Manager, and provided a methodological perspective.

RB contributed to data management for the overview and provided a methodological perspective.

DL provided general advice on the overview and interpretation of data.

MB conceived the overview, contributed to data collection, quality appraisal of papers, and clinical interpretation, and coordinated the overview.

All authors reviewed the overview and approved its final version.

DECLARATIONS OF INTEREST

AS was employed as an independent contractor (consultant; 25 April 2022) by US Pharmacia to develop a brochure (authorship), and undertake an interview and workshop. This consultancy focuses on functional constipation in children and has no bearing on this review.

TP has no interest to declare.

OR is an author of the following included Cochrane Reviews: Bellù 2021; Romantsik 2017a; Romantsik 2023.

MGC is an author of the following included Cochrane Review: Romantsik 2017a.

RB has no interest to declare.

DL has no interest to declare.

MB is an Associate Editor for the Cochrane Neonatal Group. He had no involvement in the editorial processing of this overview. Skåne University Hospital received a public grant to fund MB's salary 0.5 FTE for basic research, not related to his Cochrane Work. He is an author of the following included Cochrane Reviews: Bellù 2021; Romantsik 2017a; Romantsik 2023.

SOURCES OF SUPPORT

Internal sources

- Institute for Clinical Sciences, Lund University, Lund, Sweden

  OR, MB and DL are employed by this organization.

- Istituto Giannina Gaslini, Genoa, Italy

  MGC is employed by this organization.

External sources

- Vermont Oxford Network, USA

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- Region Skåne, Skåne University Hospital, Lund University and Region Västra Götaland, Sweden

  Cochrane Sweden is supported from Region Skåne, Skåne University Hospital Lund University and Region Västra Götaland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Romantsik 2017b).

1. We planned to use AMSTAR (A MeaSurement Tool to Assess systematic Reviews) as the critical appraisal tool (Shea 2007). Following the publication of the protocol of this overview (Romantsik 2017b), the revised version AMSTAR-2 became available (Shea 2017). We therefore employed this tool in our assessments.
2. We included reviews on ibuprofen and paracetamol, though these were not explicitly listed in the protocol, to ensure that we included all relevant interventions.
3. Following editorial feedback, we moved the outcome 'major neurodevelopmental disability' from the secondary to the primary outcomes, and included it in the summary of findings table (Table 1).
4. We did not conduct any subgroup analyses because of the paucity of studies included in each analysis.
5. Agata Stróżyk and Themistoklis Paraskevas joined the authors team of the overview.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [therapeutic use]; Analgesics, Opioid [adverse effects]; Cerebral Hemorrhage [chemically induced] [prevention & control]; Heroin; *Ibuprofen [therapeutic use]; Infant, Premature; Midazolam [adverse effects]; Pain [drug therapy]; *Perinatal Death; Phenobarbital [therapeutic use]; Respiration, Artificial [adverse effects]; Systematic Reviews as Topic

MeSH check words

Female; Humans; Infant, Newborn