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[Intervention Protocol]

Systemic opioids versus other analgesics and sedatives for postoperative pain in neonates

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To determine the effects of systemic opioid analgesics in neonates (term or preterm) undergoing surgery, on mortality, pain and major neurodevelopmental disability, compared to placebo or no drug, non-pharmacological intervention, other opioids, or other analgesics or sedatives.

BACKGROUND

Description of the condition

According to the United States' National Surgical Quality Improvement Program-Pediatric (NSQIP-P), during 2012 to 2017, 19,312 neonates received inpatient surgery (Mpody 2020). NSQIP-P was designed to prospectively and nationally collect the perioperative data of children from across hospitals (Mpody 2020). Newborn infants undergo surgeries for treatment of congenital abnormalities and neonatal morbidities, and are managed in the neonatal intensive care unit (NICU) thereafter. Malformations range from conditions such as diaphragmatic hernia and gastroschisis that require surgical repair immediately or relatively early after birth, to conditions such as congenital heart disease and hypertrophic pyloric stenosis that can wait several weeks during the neonatal period. Neonatal morbidities include complications often due to prematurity, such as necrotizing enterocolitis (NEC), spontaneous intestinal perforation, and retinopathy of prematurity (ROP) that requires surgical treatment. Such surgical interventions result in acute pain during and after surgery, and also easily mount to chronic pain, due to hyperalgesia, during a vital period of complex brain development (Fitzgerald 1989). Major surgeries involving larger incisions (e.g. thoracotomy, laparotomy) are considered to be more painful than minor surgeries limited to a local area (e.g. circumcision). The plasticity of the neonatal brain might increase its vulnerability to these early adverse events, thereby leading to abnormal neurodevelopmental, behavioral, and cognitive outcomes (Anand 1998; Anand 2000; Duerden 2014; Ranger 2014; Vinall 2014). Moreover, preterm infants with even more immature brains are already predisposed to developing such sequelae from inadequately treated pain, while being more likely to be exposed to more pain during their longer NICU hospitalization. The unique character of the neonatal population strengthens the rationale to establish the best therapeutic approach for adequate analgesia.

Neonatal pain might have a negative impact not only on neonates' clinical recovery in the NICU, but also on their neuropsychological long-term development. Therefore, it is of utmost importance to accurately identify and appropriately manage pain, for which reviews and guidelines have been continuously updated (Carter 2017; Derieg 2016; Maitra 2014; Maxwell 2019). However, major gaps in knowledge exist regarding the objective assessment of pain, the most effective way to prevent and relieve pain as well as the long-term effects of drug therapy. Systematic evaluation of pain has increased the awareness of treating pain, but pain assessment continues to pose a challenge (Olsson 2021). Pain assessment tools like NIPS (Neonatal Infant Pain Scale), and CRIES (Crying, Requires oxygen saturation, Increased vital signs, Expression, Sleeplessness) have been developed and their use in postoperative neonates has been validated (Maitra 2014). In the Poppi study, a randomized controlled trial (RCT) investigating the analgesic efficacy of oral morphine for retinopathy of prematurity (ROP) screening, investigators revised an existing pain measure specifically for the study (Monk 2019). Nonetheless, a fully reliable and objective assessment method is still lacking (Eriksson 2019; Olsson 2021).

Investigators have made various attempts to find treatment strategies to prevent or minimize neonates' pain, stress and discomfort to improve outcomes. Currently, healthcare providers routinely adopt an approach that uses both non-pharmacological and pharmacological interventions in the NICU (Allegaert 2013; Allegaert 2016; Lim 2017). However, a significant portion of the drugs administered is used 'off-label' and according to clinical experience extrapolated from adults and older children, thus administered on the basis of experience rather than evidence. This practice highlights the reality that the pharmacokinetics (PK) and pharmacodynamics (PD) are not known for the neonatal population. In the daily NICU setting, healthcare providers constantly weigh the potential and actual benefits against harms in choosing the right intervention based on available evidence, taking extra caution when considering medications for which neonatal data is sparse. Such a balanced approach is to be recommended (Lim 2017). To better meet the needs of newborn sick infants, we need more thorough knowledge of the pharmacokinetics and pharmacodynamics, as well as the pharmacogenetics, in this specific immature population, which is in all respects very different from older children (Allegaert 2013; Allegaert 2016).

A recent review of pediatric perioperative controlled trials published between 2008 and 2018 reported that outcomes related to patient comfort, including pain management, were the most frequent domain across age groups beyond infancy, while clinical variables such as cardiorespiratory or medication-related adverse events were the most common outcome for neonates and infants under 60 weeks of age (Muhly 2020). The review also pointed out that the youngest age group of neonates and infants under 60 weeks of age were significantly under-represented in perioperative trials (Muhly 2020). This could be due to the higher perioperative risk of morbidity and mortality in neonates compared to older children (Kuan 2020), as well as to neonatal pharmacokinetics, which is not yet well characterized (Euteneuer 2020). The present reality is that optimal pain management in newborns is yet to be achieved, with further primary studies and updated systematic reviews needed for this unique age group.

Description of the intervention

For mild to moderate pain, the use of non-pharmacological strategies (e.g. non-nutritive sucking, swaddling, facilitated tucking, kangaroo care, music therapy, multi-sensorial stimulation, acupuncture) with or without oral sucrose should always be considered (Bucsea 2019). For moderate to severe pain, as in the postoperative setting, opioids have traditionally been used, but they have several side effects such as respiratory depression, hypotension, constipation, as well as development of tachyphylaxis and abstinence (Kinoshita 2020).

Morphine, fentanyl, and remifentanil are the opioids most often used during neonatal intensive care, whereas the fentanyl derivatives, alfentanil and sufentanil, are less frequently used. These opioids have varying pharmacokinetic and pharmacodynamic profiles and should optimally be administered in an individualized way according to the need, clinical state, and expected course of hospitalization. Fentanyl and remifentanil are administered intravenously in very sick infants, whereas morphine can be administered by both intravenous and oral routes.

Morphine has the longest duration of onset, half-life, and elimination time, followed by fentanyl and remifentanil (Thigpen 2019; Van Gonge 2018; Ziesenitz 2018). Remifentanil is a short-acting opioid with ultra-rapid onset and very fast elimination profile, thus very suitable for rapid painful procedures such as tracheal intubations (McPherson 2018). Pharmacodynamic studies

on opioids report hypotension as the most common adverse effect (Thigpen 2019). Several larger studies have questioned the effects of opioids and reported on negative outcomes (Anand 2004; Hall 2005; Simons 2003). There are accumulating data on the negative impact of opioids on the structure and function of the developing brain, including neuronal apoptosis (McPherson 2015; Sanders 2013; Zwicker 2016).

How the intervention might work

After major surgery (e.g. cardiothoracic or brain surgery), opioids are indicated due to the associated rapid onset of action (typically less than five minutes), and a moderate duration of action (four to five hours). However, drugs such as methadone (preferably given intravenously) are more likely to exhibit an accentuated duration of action, particularly due to their slow elimination. The decision to initiate or replace opioids in neonates should rely cautiously on parameters of age, body weight, and both hepatic and renal function, as neonates tend to have immature metabolism during the first two to four weeks of life compared to older infants and children (Hong 2010; Van der Marel 2007). Morphine is unusual among opioids in that it requires an age-adjusted dose regimen. In neonates, morphine is administered in a starting lower dose of 50 mcg/kg per hour for a two-hour loading period, followed by 10 mcg/kg per hour, with regular neonate assessment to examine clinical progression and response (Anand 2004). Taking into account the limited literature on the other opioid-class representatives (fentanyl, sufentanil and alfentanil), fewer problems regarding their pharmacodynamic and pharmacokinetic features have been observed, as these drugs undergo expedited renal clearance in comparison to morphine. When neonates have been on continuous or intermittent use of any opioid-class drug for fewer than three days, and in the absence of severe pain, a complete and abrupt cessation is usually recommended (Balda 2019). However, for treatment over longer periods, a gradual withdrawal is advised, in order to minimize potential effects from abstinence syndrome. Besides the analgesic effects of opioids, euphoria and systemic effects (respiratory or cardiovascular) may also be correlated with their use. Additionally, it is noteworthy that the use of opioids in neonates might be linked to adverse effects - including hypotension, bradycardia, and chest wall rigidity - and can create tolerance over time (Anand 2006; Mitchell 2000).

In addition to opiate painkillers, other pharmacological interventions (such as traditional non-opioid analgesics and sedative medications) play an important role in post-surgical pain control among neonates (Silva 2007). It has been suggested that opioids can be combined with other drugs to achieve a balanced analgesic status among neonates suffering from postoperative pain. Most commonly used for control of mild pain or as co-adjuvants in inflammatory processes, non-steroidal anti-inflammatory drugs (NSAIDs) act by inhibiting circulating cyclo-oxygenase enzymes (I and II), thereupon diminishing inflammatory biomarkers throughout peripheral targets (Antonucci 2009). For instance, intermittent and intravenous acetaminophen (up to 48 hours after surgery) appears to intensify pain relief when used in combination with morphine or fentanyl for most major surgeries, and impact positively on decreasing opioid-related side effects, such as abstinence syndrome (Hong 2010). Wong and colleagues have referred to this as the ‘opioid-sparing effect’ of co-adjuvants (Wong 2013). Their research has shown that neonates who received continuous acetaminophen as the primary choice of analgesia required less morphine and, significantly, had fewer adverse effects (Wong 2013). Furthermore, a growing literature describes potential synergic action from the use of ketorolac in combination with opioids, mainly because of ketorolac's prominent safety and adequate pain control outcomes (Dawkins 2009; Moffett 2006). Several advantages associated with the use of NSAIDs have been described, but the most important benefits are regarding their safety (low hepatotoxicity and nephrotoxicity), reduction of gastrointestinal disorders, as well as improvement in ventilation parameters (Mather 1992). Along with acetaminophen and NSAIDs, ketamine has also been suggested to decrease postoperative pain and opioid consumption (Zhu 2017). Ketamine has anxiolytic, analgesic, and amnestic effects, with few cardiovascular and respiratory effects (Carter 2017; Saarenmaa 2001).

In addition to pharmacological interventions, the establishment of an adequate environment, including reducing noise and light, has been suggested to reduce neonatal pain in a holistic way (Anand 2007).

Why it is important to do this review

Based on previous systematic reviews (Cochrane Reviews and non-Cochrane reviews), the American Academy of Pediatrics has highlighted both the conflicting findings and lack of findings published in recent years about the use of opioids for analgesia in neonates (American Academy of Pediatrics 2016). Some particular populations have been widely evaluated for the use of opioids, such as mechanically ventilated neonates (Bellù 2021), and those requiring non-emergency intubation (Ayed 2017). It has become evident that inadequate pain management in early human life, besides causing neuropsychological impairment, can be related to neuronal apoptosis, which directly impacts human neurodevelopment (Pacifici 2014; Schiller 2018). Therefore, the assessment of the contemporary practice of analgesic and sedative procedures is of utmost importance, especially for infants in substantial pain during the postoperative period. A systematic review of opioids for postoperative pain in neonates is called for to summarize concrete evidence from existing literature, provide updated guidance for clinical practice, as well as to determine current gaps that entail additional clinical research. The use of different regimens to administer systemic opioids for postoperative pain in neonates is assessed in a separate ongoing Cochrane Review (Kinoshita 2021).

OBJECTIVES

To determine the effects of systemic opioid analgesics in neonates (term or preterm) undergoing surgery, on mortality, pain and major neurodevelopmental disability, compared to placebo or no drug, non-pharmacological intervention, other opioids, or other analgesics or sedatives.

METHODS

Criteria for considering studies for this review

Types of studies

We will include prospective randomized controlled trials (RCTs), quasi-RCTs, cluster-RCTs and cross-over RCTs.

Types of participants

We will include preterm and term infants of a postmenstrual age (PMA) up to 46 weeks and 0 days, irrespective of their gestational age at birth, receiving opioids following neonatal surgery where the surgery was performed in the operating room under general anesthesia (e.g. hernia repair surgery) or in the neonatal ward for minor surgery (e.g. patent ductus arteriosus ligation, surgery for retinopathy of prematurity, positioning of surgical drainage for air leak, thoracocentesis, placement of reservoir, or peritoneal dialysis for acute kidney failure).

We will exclude:

- infants receiving opioids during mechanical ventilation for respiratory morbidity;
- infants receiving opioids pre-intubation;
- infants receiving opioids for procedural pain;
- infants treated for neonatal abstinence syndrome; and
- infants undergoing hemodialysis.

Types of interventions

We will include studies on any opioids (e.g. morphine, diamorphine, fentanyl, alfentanil, sufentanil, pethidine, meperidine, codeine) following neonatal surgery. The following acceptable comparisons will be included.

- Comparison 1: opioids versus no treatment or placebo.
- Comparison 2: opioids versus non-pharmacological intervention (oral sugar solution, skin-to-skin contact, music exposure, non-nutritive sucking, swaddling, etc.).
- Comparison 3: head to head comparisons of different opioids (e.g. morphine versus fentanyl).
- Comparison 4: opioids versus other analgesics (e.g. acetaminophen), N-methyl-D-aspartate (NMDA) receptor antagonists (e.g. ketamine), and sedatives (e.g. benzodiazepines such as midazolam).

We will include any systemic route of administration (e.g. enteral, rectal, and intravenous).

We will exclude spinal administration (i.e. intrathecal, epidural, caudal), intraosseous infusion, nerve blocks or wound infusions.

We will include studies where the interventions are started during surgery, if their administration is continued postoperatively.

Studies comparing different regimens of the same opioid are included in the ongoing Cochrane Review, 'Systemic opioids regimens for postoperative pain in neonates' (Kinoshita 2021).

Types of outcome measures

Outcome measures do not form part of the eligibility criteria.

Primary outcomes

- Pain assessed with validated methods during the administration of selected drugs. The following scales, developed to assess pain, fulfill validity and reliability criteria for newborn infants (term and preterm on mechanical ventilation for any respiratory disease) when critically reviewed (Giordano 2019): NIPS (Lawrence 1983); Premature Infant Pain Profile (PIPP) (Stevens 1996); COMFORTneo (Van Dijk 2009); and Neonatal Pain, Agitation and Sedation Scale (N-PASS) (Hummel 2008).
- All-cause mortality during initial hospitalization.
- Major neurodevelopmental disability: cerebral palsy; developmental delay (Bayley Scales of Infant Development - Mental Development Index Edition II (BSID-MDI-II; Bayley 1993), Bayley Scales of Infant and Toddler Development - Edition III Cognitive Scale (BSITD-III) (Bayley 2005), or Griffiths Mental Development Scale - General Cognitive Index (GCI) (Griffiths 1954; Griffiths 1970), assessment greater than two standard deviations (SDs) below the mean); intellectual impairment (intelligence quotient (IQ) greater than two SDs below the mean); blindness (vision less than 6/60 in both eyes); or sensorineural deafness requiring amplification (Jacobs 2013). We will assess data on children aged 18 to 24 months and aged three to five years separately.
- Cognitive and educational outcomes in children more than five years old.

Secondary outcomes

- All-cause neonatal mortality (death until postnatal day 28).
- Episodes of bradycardia defined as a fall in heart rate of more than 30% below the baseline or less than 100 beats per minute for 10 seconds or longer.
- Hypotension requiring medical therapy (vasopressors or fluid boluses).
- Retinopathy of prematurity (ROP) in infants examined (all stages (stage 1 or greater) and severe (defined as stage 3 or greater)) (ICCROP 2005).
- Intraventricular hemorrhage (IVH; all (grade 1 or 2) or severe (grade 3 or greater) on cranial ultrasound, as per Papile classification (Papile 1978).
- Periventricular leukomalacia (PVL) (any grade (grade 1 or greater), on basis of ultrasound or magnetic resonance imaging (De Vries 1992).
- Necrotizing enterocolitis (NEC) (modified Bell stage 2/3; Walsh 1986).
- Bronchopulmonary dysplasia/chronic lung disease:
  * 28 days (NIH 1979);
  * 36 weeks' postmenstrual age (Jobe 2001);
  * physiological definition (Walsh 2004).
- Constipation defined as a delay in defecation sufficient to cause significant distress to the infant.
- Focal gastrointestinal perforation.
- Duration of mechanical ventilation (days).
- Duration of oxygen supplementation (days).
- Hospital stay (days).
- Time to full enteral feeding (days).
- Cost of neonatal care.

Search methods for identification of studies

We will use the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register). We will search for errata or retractions for included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed).

Electronic searches

We will conduct a comprehensive search including: the Cochrane Central Register of Controlled Trials (CENTRAL 2021, current issue) in the Cochrane Library; MEDLINE via PubMed (1966 to current); and CINAHL (Cumulative Index to Nursing and Allied Health Literature; 1982 to current). We will search clinical trials databases, conference proceedings, and the reference lists of retrieved articles for RCTs and quasi-RCTs. We will use Cochrane Neonatal's search strategy for neonates and RCTs (see Appendix 1 for the full search strategies for each database). We will not apply any language restrictions.

We will search clinical trials registries for ongoing or recently completed trials. We will search the World Health Organization's International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en/), and the United States' National Library of Medicine's ClinicalTrials.gov (clinicaltrials.gov), via Cochrane CENTRAL. Additionally, we will search the ISRCTN Registry for any unique trials not found through the Cochrane CENTRAL search.

Searching other resources

We will also review the reference lists of all identified articles for relevant articles not located in the primary search.

Data collection and analysis

We will collect information regarding the method of randomization, blinding, intervention, stratification, and whether the trial was single or multicenter for each included study. We will note information regarding trial participants including birth weight, gestational age, number of participants, modality of administration and dose of opioids. We will analyze the clinical outcomes noted above in Types of outcome measures.

Selection of studies

If the search yields more than 200 results, we will use Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and labeled as an 'RCT' or as 'Not an RCT'; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs; and if appropriate, Cochrane Crowd (https://crowd.cochrane.org) – Cochrane's citizen science platform where the Crowd help to identify and describe health evidence.

For more information about Screen4Me, please visit: https://community.cochrane.org/organizational-info/resources/resources-groups/information-specialists-portal/crs-videos-and-quick-reference-guides#Screen4Me. Detailed information regarding evaluations of the Screen4Me components can be found in the following publications: Marshall 2018; Noel-Storr 2020; Noel-Storr 2021; Thomas 2020.

We will include all randomized, quasi-randomized, cluster-randomized and cross-over controlled trials fulfilling our inclusion criteria. Two review authors (IJBN; KS) will review the results of the search and independently select studies for inclusion. We will resolve any disagreements through discussion or, when necessary, by involving a third review author.

We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

Two review authors (MK, KS) will independently extract data using a data extraction form integrated with a modified version of the Cochrane Effective Practice and Organisation of Care Group data collection checklist (Cochrane EPOC Group 2017). We will pilot the form within the review team using a sample of included studies.

We will extract these characteristics from each included study:

- administrative details: study author(s); published or unpublished; year of publication; year in which study was conducted; presence of vested interest; details of other relevant papers cited;
- study: study design; type, duration, and completeness of follow-up (e.g. greater than 80%); country and location of study; informed consent; ethics approval;
- participants: sex, birth weight, gestational age, number of participants;
- interventions: initiation, dose, and duration of administration; and
- outcomes as mentioned above under Types of outcome measures.

We will resolve any disagreements through discussion. We will describe ongoing studies identified by our search, when available, detailing the primary author, research question(s), methods, and outcome measures, together with an estimate of the reporting date and report them in the 'Characteristics of ongoing studies' table.

Should any queries arise (e.g. discrepancies in the definitions of the outcomes in the trials and under Types of outcome measures), or in cases for which additional data are required, we will contact study investigators or authors for clarification. Two review authors (MK, IJBN) will use Cochrane statistical software for data entry (Review Manager 2020). We will replace any standard error of the mean (SEM) with the corresponding SD.

Assessment of risk of bias in included studies

Two review authors (MK, KS) will independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2011).

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Any other bias.

We will resolve any disagreements through discussion or, if necessary, by consulting a third review author (IJBN). See Appendix 1 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We will perform the statistical analyses using Review Manager 5 software (Review Manager 2020). We will summarize the data in a meta-analysis if they are sufficiently homogeneous, both clinically and statistically.

Dichotomous data

For dichotomous data, we will present results using risk ratios (RR) and risk differences (RD) with 95% confidence intervals (CIs). We will calculate the number needed to treat for an additional beneficial outcome (NNTB), or number needed to treat for an additional harmful outcome (NNTH) with 95% CIs if there is a statistically significant reduction (or increase) in RD.

Continuous data

For continuous data, we will used the mean difference (MD) when outcomes were measured in the same way between trials. We will use the standardized mean difference (SMD) to combine trials that measured the same outcome but used different methods. Where trials reported continuous data as median and interquartile range (IQR) and data passed the test of skewness, we will convert median to mean and estimate the standard deviation as IQR/1.35.

Unit of analysis issues

The unit of analysis will be the participating infant in individually randomized trials, and an infant will be considered only once in the analysis. The participating neonatal unit or section of a neonatal unit or hospital will be the unit of analysis in cluster-randomized trials. We will analyze them using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), or from a similar trial, or from a study with a similar population, as described in Section 16.3.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). If we use ICCs from a similar trial or from a study with a similar population, we will report this and conduct a sensitivity analysis to investigate the effect of variation in the ICC.

If we identify both cluster-randomized trials and individually randomized trials, we will only combine the results from both if there is little heterogeneity between the study designs, and the interaction between the effect of the intervention and the choice of randomization unit is considered to be unlikely.

In the event that we identify cross-over trials, in which the reporting of continuous outcome data precludes paired analysis, we will not include these data in a meta-analysis, in order to avoid unit of analysis error. Where carry-over effects are thought to exist, and where sufficient data exist, we will only include data from the first period in the analysis (Higgins 2021).

We will acknowledge any possible heterogeneity in the randomization unit and perform a sensitivity analysis to investigate possible effects of the randomization unit.

Dealing with missing data

Where feasible, we intend to carry out analysis on an intention-to-treat basis for all outcomes. Whenever possible, we will analyze all participants in the treatment group to which they were randomized, regardless of the actual treatment received. If we identify important missing data (in the outcomes) or unclear data, we will request the missing data by contacting the original investigators. We will make explicit the assumptions of any methods used to deal with missing data. We may perform sensitivity analyses to assess how sensitive results are to reasonable changes in the undertaken assumptions. We will address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

We will estimate the treatment effects of individual trials and examine heterogeneity among trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. We will grade the degree of heterogeneity as:

- less than 25%: no heterogeneity;
- 25% to 49%: low heterogeneity;
- 50% to 75%: moderate heterogeneity;
- more than 75%: substantial heterogeneity.

If we note statistical heterogeneity (I^2 > 50%), we will explore the possible causes (e.g. differences in study quality, participants, intervention regimens, or outcome assessments).

Assessment of reporting biases

We intend to conduct a comprehensive search for eligible studies and will be alert for duplication of data. If we identify 10 or more trials for meta-analysis, we will assess possible publication bias by inspection of a funnel plot. If we uncover reporting bias that could, in the opinion of the review authors, introduce serious bias, we will conduct a sensitivity analysis to determine the effect of including and excluding these studies in the analysis.

Data synthesis

If we identify multiple studies that we consider to be sufficiently similar, we will perform meta-analysis using Review Manager 5 (Review Manager 2020). For categorical outcomes, we will calculate the typical estimates of RR and RD, each with its 95% CI. For continuous outcomes, we will calculate the MD or the SMD, each with its 95% CI. We will use a fixed-effect model to combine data where it is reasonable to assume that studies were estimating the same underlying treatment effect. If we judge meta-analysis to be inappropriate, we will analyze and interpret individual trials separately. If there is evidence of clinical heterogeneity, we will try to explain this based on the different study characteristics and subgroup analyses.

Subgroup analysis and investigation of heterogeneity

We will explore high statistical heterogeneity in the outcomes by visually inspecting the forest plots and by removing the outlying studies in the sensitivity analysis (Higgins 2020). Where statistical heterogeneity is significant, we will interpret the results of the meta-analyses accordingly; and we will downgrade the certainty of evidence in the 'Summary of findings' tables, according to the GRADE recommendations.

We will consider the following groups for subgroup analysis where data are available.

- Gestational age (GA): term; moderately preterm (32 to 36 weeks' GA); very preterm (less than 32 weeks' GA).

- Duration of opioids administration: up to 72 hours after surgery; beyond 72 hours.
- Studies where the administration is started during the surgery; after the surgery.
- Surgery performed in the operating room under general anesthesia; surgery in the neonatal ward for minor surgery such as patent ductus arteriosus ligation, surgery for retinopathy of prematurity, positioning of surgical drainage for air leak, thoracocentesis or peritoneal dialysis for acute kidney failure.
- Within studies that accepted the use of co-interventions: studies where investigators allowed co-interventions for pain management; and studies that obligated its use, as well as by the type of co-interventions (corticosteroids or non-steroidal anti-inflammatory drugs).

We will restrict these analyses to the primary outcomes.

Sensitivity analysis

Where we identify substantial heterogeneity, we will conduct sensitivity analysis to determine if the findings are affected by inclusion of only those trials considered to have used adequate methodology with a low risk of bias (selection and performance bias). We will report results of sensitivity analyses for primary outcomes only.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence for the following (clinically relevant) outcomes.

- Pain assessed with validated methods during the administration of selected drugs.
- Major neurodevelopmental disability in children aged 18 to 24 months: cerebral palsy, developmental delay assessment greater than two standard deviations (SDs) below the mean), intellectual impairment (intelligence quotient (IQ) greater than two SDs below the mean), blindness (vision less than 6/60 in both eyes), or sensorineural deafness requiring amplification (Jacobs 2013).
- Major neurodevelopmental disability (see above) in children aged three to five years.
- Cognitive and educational outcomes in children more than five years old.
- All-cause mortality during initial hospitalization.
- Severe (defined as stage 3 or greater) retinopathy of prematurity in infants examined.
- Severe (grade 3 or greater) intraventricular hemorrhage (IVH) on cranial ultrasound.

Two review authors (MK, MB) will independently assess the certainty of the evidence for each of the outcomes above. We will consider evidence from RCTs as high certainty, downgrading the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We will use GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the certainty of the evidence.

The GRADE approach results in an assessment of the certainty of a body of evidence in one of the following four grades.

- High: we are very confident that the true effect lies close to that of the estimate of the effect;
- Moderate: 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;
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of findings and assessment of the certainty of the evidence

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- Severe (defined as stage 3 or greater) retinopathy of prematurity in infants examined.
- Severe (grade 3 or greater) intraventricular hemorrhage (IVH) on cranial ultrasound.

Two review authors (MK, MB) will independently assess the certainty of the evidence for each of the outcomes above. We will consider evidence from RCTs as high certainty, downgrading the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We will use GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the certainty of the evidence.

The GRADE approach results in an assessment of the certainty of a body of evidence in one of the following four grades.

- High: we are very confident that the true effect lies close to that of the estimate of the effect;
- Moderate: 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;

- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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APPENDICES

Appendix 1. 'Risk of bias' tool

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the trials. For each trial, we will seek information regarding the method of randomization, blinding, and reporting of all outcomes of all the infants enrolled in the trial. We will assess each criterion as being at a low, high, or unclear risk of bias. Two review authors will separately assess each study. We will resolve any disagreements by discussion. We will add this information to the 'Characteristics of included studies' table. We will evaluate the following issues and enter the findings into the 'Risk of bias' table.

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we will categorize the method used to generate the allocation sequence as:

1. low risk (any truly random process, e.g. random number table; computer random number generator);
2. high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
3. unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we will categorize the method used to conceal the allocation sequence as:

1. low risk (e.g. telephone or central randomization; consecutively numbered, sealed, opaque envelopes);
2. high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
3. unclear risk

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we will categorize the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or class of outcomes. We will categorize the methods as:

1. low risk, high risk, or unclear risk for participants; and
2. low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we will categorize the methods used to blind outcome assessment. We will assess blinding separately for different outcomes or class of outcomes. We will categorize the methods as:

1. low risk for outcome assessors;
2. high risk for outcome assessors; or
3. unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorize the methods as:

1. low risk (< 20% missing data);
2. high risk (≥ 20% missing data); or
3. unclear risk.

6. Selective reporting bias. Are reports of the study free of the suggestion of selective outcome reporting?

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as:

1. low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
2. high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; the study fails to include results of a key outcome that would have been expected to have been reported); or
3. unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at high risk of bias?

For each included study, we will describe any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as:

1. low risk;
2. high risk;
3. unclear risk.

If needed, we plan to explore the impact of the level of bias by undertaking sensitivity analyses.

Appendix 2. Search strategy

Pubmed

#1 (((infant, newborn[MeSH] OR newborn*[TIAB] OR "new born"[TIAB] OR "new borns"[TIAB] OR "newly born"[TIAB] OR baby*[TIAB] OR babies*[TIAB] OR premature[TIAB] OR prematurity[TIAB] OR preterm[TIAB] OR "pre term"[TIAB] OR “low birth weight”[TIAB] OR "low birthweight"[TIAB] OR VLBW[TIAB] OR LBW[TIAB] OR infan*[TIAB] OR neonat*[TIAB])))

#2 (((((morphine OR diamorphine OR fentanyl OR alfentanil OR sufentanil OR pethidine OR meperidine OR codeine OR methadone))) OR ("Narcotics"[Majr] OR "Analgesia"[Majr] OR sedation[Title/Abstract] OR opioid*[Title/Abstract] OR remifentanil)) OR (((((((("Morphine"[Mesh]) OR "Heroin"[Mesh]) OR "Fentanyl"[Mesh]) OR "Alfentanil"[Mesh]) OR "Sufentanil"[Mesh]) OR "Meperidine"[Mesh]) OR "Codeine"[Mesh]) OR "Methadone"[Mesh] OR “Remifentanil”[Mesh]))

#3 ("Surgical Procedures, Operative"[Mesh] OR surgery[TIAB] OR surgical[TIAB] OR "postoperat*"[TIAB] OR "post operat*"[TIAB] OR "postsurg*"[TIAB] OR "post surg*"[TIAB] OR operative[TIAB] OR operation*[TIAB] OR ligation*[TIAB] OR repair[TIAB])

#4 ((((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab])) NOT (animals[MH] NOT humans[MH])))

#5 #1 AND #2 AND #3 AND #4

Cochrane Library / CENTRAL via Wiley

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

#2 (infan* or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm* or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU):ti,ab,kw (Word variations have been searched)

#3 (morphine OR diamorphine OR fentanyl OR alfentanil OR sufentanil OR pethidine OR meperidine OR codeine OR methadone OR remifentanil):ti,ab,kw (Word variations have been searched)

#4 (surgery OR surgical OR postoperat* OR "post operat*" OR postsurg* OR "post surg*" OR operative OR operation*):ti,ab,kw (Word variations have been searched)

#5 MeSH descriptor: [Surgical Procedures, Operative] explode all trees

#6 #1 OR #2

#7 #4 OR #5

#8 #3 AND #6 AND #7

CINAHL via EBSCOHost

#1 (infant or infants or infant's or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW)

#2 (morphine OR diamorphine OR fentanyl OR alfentanil OR sufentanil OR pethidine OR meperidine OR codeine OR methadone OR MH morphine OR MH diamorphine OR MH fentanyl OR MH alfentanil OR MH sufentanil OR MH pethidine OR MH meperidine OR MH codeine OR MH methadone OR MH remifentanil OR MJ narcotics OR MJ sedation OR MJ analgesia OR TI opioid* OR AB opioid*)

#3 (MH "Surgery, Operative+")

#4 surgery OR surgical OR postoperat* OR "post operat*" OR postsurg* OR "post surg*" OR operative OR operation*

#5 #3 OR #4

#6 (randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

#7 #1 AND #2 AND #3 AND #4

HISTORY

Protocol first published: Issue 4, 2021

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: MK, KS, MB

Designing the review: MK, KS, MB

Coordinating the review: MB

Data collection for the review: MK, KS, IJBN

Screening search results: MK, KS, IJBN

Organizing retrieval of papers: MK, KS, IJBN

Screening retrieved papers against eligibility criteria: MK, KS, IJBN

Appraising quality of papers: MK, KS, IJBN

Extracting data from papers: MK, KS, IJBN

Writing to authors of papers for additional information: MK, KS, IJBN

Data management for the review: MK, MB

Entering data into RevMan: MK, KS

Analysis of data: MK, KS, MB

Interpretation of data: MK, KS, MB

Providing a methodological and a clinical perspective: MB

Writing the protocol: MK, KS, IJBN, MB

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MK has received a PhD scholarship funded by the Erasmus + Programme of the European Union (Framework Agreement number: 2013-0040). MK has been employed by Fundació Clínic per a la Recerca Biomèdica (a non-profit organization) for research projects not related to the review.

KS has no interests to declare.

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