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[Intervention Protocol]

Systemic opioid regimens for postoperative pain in neonates

Mari Kinoshita[1,2], Israel Junior Borges do Nascimento[3,4], Lea Styrmisdóttir[5], Matteo Bruschettini[6,7]

[1]Fetal Medicine Research Center, University of Barcelona, Barcelona, Spain. [2]Department of Pediatrics, Lund University, Lund, Sweden. [3]School of Medicine and University Hospital, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil. [4]Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, USA. [5]Faculty of Medicine, Lund University, Lund, Sweden. [6]Department of Clinical Sciences Lund, Paediatrics, Lund University, Skåne University Hospital, Lund, Sweden. [7]Cochrane Sweden, Lund University, Skåne University Hospital, Lund, Sweden

Contact address: Matteo Bruschettini, matteo.bruschettini@med.lu.se, matbrus@gmail.com.

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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 different regimens of systemic opioid analgesics in neonates (term or preterm) undergoing surgery, on mortality, pain and major neurodevelopmental disability. These different regimens may include: different doses of the same opioid; different routes of administration of the same opioid; continuous infusion versus bolus administration; or 'as needed' administration versus 'as scheduled' administration.

BACKGROUND

Description of the condition

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, spontaneous intestinal perforation, and retinopathy of prematurity, which require 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).

Neonatal pain might affect neuropsychological development in the long-term. Therefore, it is important to accurately identify and appropriately manage pain. However, major gaps in knowledge exist regarding both 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). Although there are many validated scales for the assessment of both acute and continuous pain, a fully reliable and objective assessment method is still lacking (Eriksson 2019; Olsson 2021).

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. 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

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 (PK) and pharmacodynamic (PD) profiles and should optimally be administered in an individualized way, according to the need, clinical state, and expected course of the 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 endotracheal intubation (McPherson 2018). Pharmacodynamic studies on opioids report hypotension as the most common adverse effect (Thigpen 2019). Several larger studies have questioned the effect of opioids and reported on negative outcomes (Anand 2004; Hall 2005; Simons 2003). Accumulating data report on the negative impact on the structure and function of the developing brain, including neuronal apoptosis (McPherson 2015; Sanders 2013; Zwicker 2016).

How the intervention might work

Opioids have been commonly used in postoperative management after major procedures (such as to correct cardiac or other thoracoabdominal abnormalities, and otorhinolaryngological surgeries or neurosurgeries), particularly among preterm infants (Van Dijk 2001). Their analgesic function is related to interaction with the mu, kappa, and delta receptors present in the entire central nervous system which, as a final outcome, decrease neuronal excitability and reduce neurotransmission of nociceptive impulses (Trescot 2008). The overall efficacy of opioids administered directly to the central compartment is evident even when administered at low doses. However, in the case of peripheral administration in post-surgery, post-trauma or inflammatory state situations, their effectiveness is not as reliable. In recent years, recommendations on time-scheduled opioid-dosing protocols and pain-contingent ('as needed') control have become more common (American Academy of Pediatrics 2016). For neonates during the postoperative period, it is thought that continuous administration of opioids results in steadier serum concentration of the active metabolite, establishing better pain relief, fewer adverse effects and side effects, reduced augmentation of pain behaviors and decreased risk of abstinence syndrome.

As far as routes of administration are concerned, several possibilities can be listed. Oral administration may be difficult immediately after the surgery due to the consciousness of the infant as well as the condition of the gastrointestinal system, which is affected by administered drugs and by the surgery itself. Potential physical-chemical interaction with milk and other frequently used medications during hospitalization (such as antibiotics) may also need to be considered (O'Brien 2019; Papai 2010). Likewise, intramuscular and subcutaneous injections are uncommon methods of opioid delivery in neonates, due to limited muscle mass, impact on skeletal muscle vascularizations, and increased discomfort generated by these routes of administration (Costa 2013; Strolin 2003). Conversely, intravenous administration of opioids is most often the preferred route of administration, particularly among critically ill infants (WHO 2012). Close monitoring should be undertaken in order to prevent excess administration of total fluids to the neonate: a regular intravenous fluid infusion rate can be as low as 10 mL per hour for full-term neonates and as low as 2 mL per hour for extremely preterm infants.

Morphine, one of the most used candidates in this category and a first-line opioid, is typically administered through a continuous intravenous infusion, with a dose ranging from 1 to 30 mcg/kg per hour, until no more improvement in pain control is observed, indicating a dose appropriate to the individual's current need (Anand 2004; Balda 2019). Interestingly, morphine starts working as an analgesic five minutes after the start of administration and reaches a peak effect in 15 minutes. Alternatively, an intermittent

dose might be offered to the neonate, at 0.05 to 0.20 mg/kg per dose every four to six hours, preferably intravenously. Fentanyl, which begins its onset of action two to three minutes after injection, also can be given intermittently (at 0.3 to 4.0 mcg/kg per dose every two to four hours, intravenously) or as a continuous infusion (with a starting dose of slow 0.3 mcg/kg per hour, reaching a maximum dose of 5.0 mcg/kg per hour) (Anand 2004; Balda 2019). Similarly, tramadol is typically given at an increasing dose pattern (frequently administered as an intermittent medication at the dose of 5 mg/kg per day divided every 6 or 8 hours, intravenously or orally, or continuously at the dose of 0.10 to 0.25 mg/kg per hour) (Anand 2004; Balda 2019). In spite of many alternatives for pain control among neonates, the best dose regimen, route of administration and most appropriate opiate for neonates post-surgery is still uncertain, mainly due to the physiologic and metabolic immaturity of the neonate and the potential risk of toxicity.

Why it is important to do this review

Based on previous systematic reviews (Cochrane Reviews and non-Cochrane reviews), the American Academy of Pediatrics highlights the conflicting findings and lack of findings published in recent years associated with the use of opioids for analgesia in neonates (American Academy of Pediatrics 2016). Some particular populations have already been widely evaluated for the use of opioids, such as mechanically ventilated neonates (Bellù 2021), and those requiring non-emergency intubation (Ayed 2017). 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. An ongoing Cochrane Review of opioids compared to placebo or no drug, to oral sugar solution or non-pharmacological intervention, or to other analgesics or sedatives is under preparation (Kinoshita 2021). In this review, we assess different regimens to administer systemic opioids for postoperative pain in neonates.

OBJECTIVES

To determine the effects of different regimens of systemic opioid analgesics in neonates (term or preterm) undergoing surgery, on mortality, pain and major neurodevelopmental disability. These different regimens may include: different doses of the same opioid; different routes of administration of the same opioid; continuous infusion versus bolus administration; or 'as needed' administration versus 'as scheduled' administration.

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: different doses of the same opioid.
- Comparison 2: different routes of administration of the same opioid (e.g. enteral versus parenteral).
- Comparison 3: continuous infusion versus bolus administration.
- Comparison 4: 'as needed' administration (e.g. based on pain scales) versus 'as scheduled' administration (e.g. a predefined time interval).

We will include any systemic route of administration (e.g. enteral 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 opioids to other interventions are included in the ongoing Cochrane Review, 'Systemic opioids versus other analgesics and sedatives 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): Neonatal Infant Pain Scale (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 separately assess data on children aged 18 to 24 months and aged three to five years.

- Cognitive and educational outcomes in children older 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 (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 been 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, LS) will independently review the results of the search and select studies for inclusion. We will resolve any disagreements through discussion or, when necessary, by involving a third 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, LS) 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;
- 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/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) by the corresponding SD.

Assessment of risk of bias in included studies

Two review authors (MK, LS) 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 by consulting a third 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 mean to median 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).
- According to drug dose regimen: continuous drug administration; 'as needed' based on signs of pain, discomfort, stress or following medical advisory.

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 three to five years old.
- 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.

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- 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 categorise 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:

- low risk, high risk, or unclear risk for participants; and
- 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

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CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: MK, LS, MB

Designing the review: MK, LS, MB

Coordinating the review: MB

Data collection for the review: MK, LS, IJBN

Screening search results: MK, LS, IJBN

Organising retrieval of papers: MK, LS, IJBN

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

Appraising quality of papers: MK, LS, IJBN

Extracting data from papers: MK, LS, IJBN

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

Data management for the review: MK, MB

Entering data into RevMan: MK, LS

Analysis of data: MK, LS, MB

Interpretation of data: MK, LS, MB

Providing a methodological and a clinical perspective: MB

DECLARATIONS OF INTEREST

MK has no interests to declare.

LS has no interests to declare.

IJBN has no interests to declare.

MB has no interests to declare.

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Internal sources

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

  MB is employed by this organization
- University Hospital at the Federal University of Minas Gerais, Brazil

  IJBN is currently enrolled in a paid research project in this institution

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