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Clonidine for painful procedures or conditions in infants (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Clonidine for painful procedures or conditions in infants

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ABSTRACT

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

To determine the efficacy and safety of clonidine for the prevention or treatment of procedural or postoperative pain, or pain associated with clinical conditions in neonates. Clonidine will be compared to placebo, no treatment, dexmedetomidine, paracetamol, and opioids. In addition, the safety of clonidine administration will be assessed for potential harms.

BACKGROUND

Description of the condition

The importance of pain in the neonate was not recognized until the late 1980s when research describing the developmental physiology of nociception emerged (i.e. the sensory nervous system's response to harmful stimuli, frequently manifested as pain) (Anand 1987a; Anand 1987b). In newborn infants, there is an imbalance between the excitatory neural pathways accountable for nociception and the inhibitory neural pathways responsible for localization and alleviation of noxious stimuli (Fitzgerald 1986). Pain perception develops slowly and advances with postnatal age. In addition, normal brain development is abruptly interrupted by preterm birth, and repetitive painful stimuli may lead to developmental alterations of the nociceptive pathways (Taddio 2009).

Critically ill newborn infants undergo numerous and repeated invasive procedures during their early life in the neonatal intensive care unit (NICU). The "Epidemiology of Procedural Pain in Neonates" (EPIPPAIN) study reported that 430 preterm and term infants experienced a total of 60,969 first-attempt procedures during the first two weeks in the NICU. They went through a median of 16 stressful procedures per day, of which 10 were considered not only to be stressful, but also painful (Carbajal 2008). Other investigators have reported a similar number of painful procedures: Barker 1995 reported an average of 60 painful procures per patient in 54 preterm infants, while Benis 2001 described a total of 5663 procedures in a cohort of 15 preterm infants. In the Johnston 1997 study, a mean of two procedures per patient per day were performed, and some neonates had as many as eight procedures per day during the first week of NICU care. Additionally, in a Dutch cohort of 151 neonates admitted to the NICU, neonates experienced a mean of 14 procedures each day during the first two weeks (Simons 2003).

Despite the growing knowledge about long-term consequences of neonatal pain and discomfort, a safe and effective strategy to min-

imize these complications remains a challenge in everyday clinical care (McPherson 2012). Non-pharmacologic support and interventions, such as non-nutritive sucking and wrapping, are well accepted first-hand strategies, but are insufficient to provide comfort for moderate and severe pain (Brummelte 2012; Golianu 2007).

Oral sucrose and glucose are commonly used in the NICUs to provide analgesia or comfort infants, or both, during mild to moderately painful procedures (Lim 2017). Both have been extensively studied as possible analgesic agents in newborns, however many gaps of knowledge still remain, including appropriate dosing and long-term consequences (Bueno 2013; Stevens 2016). Nevertheless, neither glucose nor sucrose may be effective for longer or more painful procedures (Costa 2013).

Opioids are the pharmacological agents most commonly administered to treat pain in newborn infants, with fentanyl and morphine most commonly used. The dosage of these drugs varies between studies and the reports of long-term effects of opioids given during the neonatal period are conflicting (de Graaf 2013; Roze 2008). Rodent models have demonstrated that early opiate exposure diminishes neuronal density and dendritic length (i.e. density and length of brain cells), as well as to increase apoptosis (natural death of cells that occurs during growth or development) (Hammer 1989; Ricalde 1990; Seatriz 1993). Furthermore, rodents exposed to postnatal morphine exhibited reduced brain growth (Zagon 1977), persistently decreased motor activity and impaired learning ability (Handelmann 1985; McPherson 2007; Ma 2007). Several other pharmacological agents, such as methadone, ketamine and propofol have been suggested, and used, for analgesia during neonatal intensive care, but data regarding appropriate dosage and short- and long-term safety in this vulnerable population are currently insufficient, and further research is needed before these drugs are introduced to clinical practice (Allegaert 2007; Anand 2004; Chana 2001; Cravero 2011; Simons 2003).

It has been shown that co-administration of morphine and paracetamol (acetaminophen) in the management of neonatal postoperative pain may reduce the final amount of opioid needed (Ceelie 2013). However, concerns have been raised about the safety of paracetamol (Bauer 2013; Viberg 2014). The use of nonsteroidal anti-inflammatory agents, such as ibuprofen and indomethacin, is restricted to the pharmacological management of patent ductus arteriosus (i.e. a neonatal heart problem) because of possible adverse effects, e.g. renal insufficiency, platelet dysfunction and pulmonary hypertension (Ohlsson 2016).

Description of the intervention

A limited experience with alpha2-agonists (α2-agonists), chiefly clonidine and dexmedetomidine, in term and preterm infants, suggests that they may provide an analgesic and sedative effect. Alpha2-agonists may induce sedation, provide analgesia and ameliorate anxiety (Chen 2015; Mantz 2011; Pichot 2012). These effects are mediated through α2-adrenergic receptor subtype agonism located in the locus coeruleus, which is a nucleus in the pons of the brainstem and the main site for brain synthesis of norepinephrine (noradrenaline). Both clonidine and dexmedetomidine reduce the neuronal activity in the locus coeruleus without affecting the respiratory drive (Hoy 2011). Moreover, it has been suggested that α2-agonists might have a neuroprotective and anti-inflammatory effect (Mantz 2011). In animal models of endotoxic shock, both drugs preserve neutrophil function and inhibit the cytokine response (i.e. in cells that regulate the immune response) (Nishina 1999; Taniguchi 2004; Taniguchi 2008). Furthermore, both α2-agonists protect neurons from damage in vitro and diminish brain lesion size in animal models (Laudenbach 2002; Paris 2006). The two main side effects of α2-agonists are bradycardia (slow heart beat) and hypotension (low blood pressure). These are mediated through the α2-adenoreceptors in the medullary dorsal motor nucleus and motor complex and have been shown to be independent of the sedative effect (Gregoretti 2009; Pichot 2012).

Traditionally, clonidine has been used in management of attention deficit hyperactivity disorder (ADHD) (Hazell 2003), opioid withdrawal (Gold 1978), and as an anaesthetic adjuvant (i.e. added to the anaesthetic to improve performance) (Gregoretti 2009; Lambert 2014). Its use as sedative agent persists 'off label' in many countries. In the critically ill paediatric and neonatal population, clonidine is routinely prescribed as an adjunct to opioids or benzodiazepines, or both, aiming to reduce the doses of these drugs that are required for analgesia or sedation, or to facilitate weaning from mechanical ventilation (Duffett 2012). Furthermore, clonidine has been shown to reduce pain, discomfort and agitation in a paediatric population following sevoflurane anaesthesia (Tesoro 2005). A Cochrane Review showed that clonidine premedication might have a positive effect on postoperative pain in the paediatric population (neonates not included) (Lambert 2014). Moreover, the addition of clonidine to bupivacaine for spinal anaesthesia in newborns may double the duration of the block (Rochette 2004). It is worth noting that a study in newborn rats showed that intrathecal administration (via the spine) of clonidine did not induce signs of spinal histopathology (Walker 2012).

The current literature on practices for procedural and postoperative pain in critically ill newborn infants lacks a comprehensive data summary about the efficacy and safety of clonidine as a potential agent. In 2016, a systematic review was published on clonidine for sedation, analgesia and iatrogenic drug withdrawal in critically ill infants and children (Capino 2016). However, this review by Capino and colleagues included only mechanically ventilated infants and children.

Cochrane Reviews have also focused on pain management with other interventions, e.g. paracetamol (Ohlsson 2016); breastfeeding or breast milk (Shah 2012); and non-pharmacological management, which included 4905 infants from 63 studies (Pillai Riddell 2015).

How the intervention might work

Clonidine is a centrally acting α2-selective adrenergic agonist. It has been suggested that clonidine mediates its sedative effects through the stimulation of the presynaptic α2- adrenoceptors of the locus coeruleus, leading to a decrease in the release of norepinephrine (Jamadarkhana 2010). As well as exerting a sedative effect, clonidine also acts on the cholinergic, purinergic and serotonergic pathways, to produce analgesia (Jamadarkhana 2010). This analgesic action is thought to be optimal when combined with other agents. Moreover the administration of clonidine may exert neuroprotective effects by preventing apoptosis induced by agents such as ketamine (Pontén 2012). The ability of α2-agonists to protect the neuronal culture from damage in vitro and to reduce the brain lesion size in animal models is promising in the view of neuroprotection (Laudenbach 2002). An expanded description of how clonidine might work in the newborn is provided in a separate review (Romantsik 2017).

Why it is important to do this review

Despite the theoretical advantages of α2-agonists, the safety and efficacy of their short-term and long-term use remain unclear. It is important to note that clonidine is not licensed for use in infants and its effectiveness and safety for pain management in non-ventilated newborns has not been systematically reviewed.
Clonidine is an alfa2-agonist with sedative and analgesic characteristics. In contrast to other analgo-sedatives, clonidine does not reduce respiratory drive. Clonidine has been shown to be neuroprotective in animal research. For serious painful conditions (e.g. necrotizing enterocolitis and postoperative care) the additive use of clonidine might reduce the dose of opioid treatment and subsequent negative effects. However, clonidine pharmacokinetics (PK), pharmacodynamics (PD), pharmacogenetics (PG) or the PK/PD/PG relation has not been tested in this population. It has been used for adults and older children, and the newborn population is treated accordingly. Clonidine was introduced for treatment of hypertension in adults; hypotension and bradycardia are well known side effects in that population. The PK, PD, PG or the PK/PD/PG relation needs to be studied in the newborn term and preterm population. Both general vital parameters and specific effects of cerebral activity (EEG) and cerebral hemodynamics (NIRS) are of major interest for the evaluation of the drug effects and side effects in this vulnerable population.
Pain and stress are still a problem in the NICU and evidence-based consensus and clear guidelines are lacking. Clonidine is increasingly used because of the side effects of opioids, however more knowledge about the drug is needed in order to make safe recommendations.

OBJECTIVES

To determine the efficacy and safety of clonidine for the prevention or treatment of procedural or postoperative pain, or pain associated with clinical conditions in neonates. Clonidine will be compared to placebo, no treatment, dexmedetomidine, paracetamol, and opioids. In addition, the safety of clonidine administration will be assessed for potential harms.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials, quasi-randomised controlled trials, and cluster-randomised trials. We will exclude cross-over trials.

Types of participants

Full term and preterm (gestational age < 37 weeks) infants less than 44 weeks' postmenstrual age (PMA) requiring pain management for one or more of the following procedures or clinical conditions during their hospital stay or as outpatients:

- painful procedures: heel lance, venipuncture, lumbar puncture, bladder tap, insertion of nasogastric tube, insertion of venous or arterial catheter/line or chest drain, or surgery (including neonatal circumcision, any surgery performed in the operating room); or
- painful clinical conditions: including a fractured long bone, necrotizing enterocolitis, open skin lesions from an inherited skin disorder, or pain from an assisted vaginal birth.

We will exclude studies where clonidine infusion is administered in ventilated newborns, as this has been addressed in another Cochrane Review (Romantsik 2017). However, we will include studies where clonidine infusion is administered in ventilated newborns if the intervention specifically aims to treat procedural or postoperative pain, or pain associated with clinical conditions.

Types of interventions

Clonidine administered at any dose for the prevention or treatment of pain. Clonidine may be delivered intravenously, orally (or via nasogastric tube), or transdermally. We will include studies that report on single administration of clonidine or multiple (repeated) doses of clonidine over a prolonged period during the initial hospital stay. We will exclude studies that compare clonidine with local or regional anaesthesia.
Procedural pain, postoperative pain, and pain associated with clinical conditions will be assessed in separate comparisons.

Clonidine will be compared with placebo or no intervention; opioids; paracetamol; dexmedetomidine; or non-pharmacological pain-reducing intervention, e.g. sucrose, glucose, other sweet-tasting solutions, breast milk, breastfeeding, non-nutritive sucking, skin-to-skin care, or other intervention.

Comparison 1: Clonidine compared to placebo or no treatment for the prevention or treatment of procedural, postoperative pain or pain associated with clinical conditions in neonates.

Comparison 2: Clonidine compared to opioids for the prevention or treatment of procedural, postoperative pain or pain associated with clinical conditions in neonates.

Comparison 3: Clonidine compared to paracetamol for the prevention or treatment of procedural, postoperative pain or pain associated with clinical conditions in neonates.

Comparison 4: Clonidine compared to dexmedetomidine for the prevention or treatment of procedural, postoperative pain or pain associated with clinical conditions in neonates.

Comparison 5: Clonidine compared to non-pharmacologic pain-reducing interventions (e.g. sucrose, glucose, other sweet-tasting solution, breast milk, breastfeeding, non-nutritive sucking, skin-to-skin care) for the prevention or treatment of procedural, postoperative pain or pain associated with clinical conditions in neonates.

We plan to perform subgroup analyses according to gestational age (term; preterm; extreme preterm infants), birth weight (normal; low; very low), type of pain, dose, duration and route of clonidine administration, and pharmacologic sedation as a co-intervention (see Subgroup analysis and investigation of heterogeneity).

Types of outcome measures

Primary outcomes

Analgesia assessed using the pain scales listed in Table 1.

For procedural pain, we will report the mean values of each analgesia scale assessed during the procedure and at one to two hours after the procedure.

For postoperative pain and for pain associated with clinical conditions, we will report the mean values of each analgesia scale assessed: at 30 minutes, three hours, and 12 hours after the administration of the intervention.

Secondary outcomes

- Neonatal mortality: during initial hospitalisation
- Completion of the targeted objective (relief of either procedural or postoperative pain, or pain associated with clinical conditions) without use of any other agent.
- Any intraventricular hemorrhage (IVH) (yes/no): any IVH, grades 1 to 4 (according to the Papile 1978 classification); severe IVH (grades 3 and 4)
- Cystic periventricular leukomalacia at brain ultrasound in the first month of life (yes/no)
- Retinopathy of prematurity (ICROP 1984; yes/no): any; requiring laser therapy
- Duration of mechanical ventilation (days)
- Duration of hospital stay (days)
- Bronchopulmonary dysplasia/chronic lung disease (yes/no): 28 days; 36 weeks' PMA (Jobe 2001); "physiological definition" (Walsh 2004)
- Necrotizing enterocolitis (yes/no): any grade; requiring surgery
- Time to full enteral feeding (days)
- Episodes of apnoea spells (mean rates of apnoea)
- 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, occurring:
    - for procedural pain, during the procedure and at one to two hours after the procedure;
    - for postoperative or pain associated with clinical conditions, at 30 minutes, three hours, and 12 hours after administration of the intervention.
- Altered reactions to painful stimuli following NICU discharge, as reported by study authors
- Parent satisfaction with care provided in the NICU (as measured by a validated instrument/tool) (Butt 2013)
- 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 (SDs) below the mean (Griffiths 1954));
    - intellectual impairment (intelligence quotient > 2 SD below the mean);
    - blindness (vision < 6/60 in both eyes);
    - or sensorineural deafness requiring amplification (Jacobs 2013).
    - We plan 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. Data on children aged 18 to 24 months and those aged three to five years are to be assessed separately.

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 from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Electronic searches

We will conduct a comprehensive search including: the Cochrane Central Register of Controlled Trials (CENTRAL, current issue) in the Cochrane Library; MEDLINE via PubMed (1996 to current); Embase (1980 to current); and CINAHL (1982 to current) using the following search terms: (clonidine OR alpha-2 agonists), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). We will not apply language restrictions. We will search clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International Trials Registry and Platform, and the ISRCTN Registry).

Searching other resources

Additionally, we will review the reference lists of all identified articles for any relevant articles that were not identified in the primary search.

Data collection and analysis

Selection of studies

Independently, two review authors (OR, MB) will search and identify eligible trials that meet the inclusion criteria. We will screen the titles and abstracts to identify potentially relevant citations, retrieve the full texts of all potentially relevant articles, and assess independently the eligibility of the studies by filling out eligibility forms designed in accordance with the specified inclusion criteria. We will review studies for relevance based on study design, types of participants, interventions and outcome measures. We will resolve any disagreements by discussion and, if necessary, by consulting a third author (MGC). We will provide details of studies excluded from the review in the 'Characteristics of excluded studies' table along with the reasons for exclusion. We will contact the trial authors if the details of the primary trials are not clear to request further information.

Data extraction and management

Independently, two reviewers (OR, MB) will undertake data abstraction using a data extraction form developed and integrated with a modified version of the Cochrane Effective Practice and Organisation of Care Group (EPOC) data collection checklist (Cochrane EPOC 2013).

We will extract the following characteristics from each included study:

- administrative details: author(s); whether published or unpublished; year of publication; year in which study was conducted; details of other relevant papers cited;
- details of the study: study design; type, duration and completeness of follow-up (e.g. > 80%); country and location of study informed consent and ethics approval;
- details of participants: birth weight, gestational age, and number of participants;
- details of intervention: modality of administration and dose of clonidine;
- details of outcomes, as listed in Types of outcome measures.

We will resolve any disagreement by discussion between the reviewers.

We will describe any on-going studies identified, detailing the primary author, research question(s), methods and outcome measures, together with an estimate of the reporting date.

When queries arise or when additional data are required, we will contact the authors of the trial reports. MGC and MB will use Review Manager 5 software to enter all the data (Review Manager 2014).

Assessment of risk of bias in included studies

Independently, two review authors (OR, MGC) will assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains:

- 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 by discussion or through a third assessor (MB).

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality (to meet the validity criteria) of the trials. For each trial, we will seek information regarding the method of randomisation, and the blinding and reporting of all outcomes of all the infants enrolled in the trial. We will assess each criterion as being at low, high, or unclear risk. Separately, two review authors will assess each study. We will resolve any disagreement 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.

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:

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

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:

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

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. Blinding will be assessed 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.

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. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorize the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors;
- unclear risk for outcome assessors.

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 randomised 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 used to deal with missing data as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data);
- unclear risk.

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

For each included study, we will investigate the possibility of selective outcome reporting bias. For studies in which study protocols were published in advance (clinicaltrials.gov), 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 likelihood of selective reporting bias as:

- 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);
- 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; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk.

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

For each included study, we will describe any important concerns we had about other possible sources of bias (for example, 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 the degree to which each study was free of other problems that could put it at risk of bias and categorize them as:

- low risk;
- high risk;
- unclear risk.

If needed, we will explore the impact of the level of bias through undertaking sensitivity analyses.

Measures of treatment effect

We will extract categorical data for each intervention group and calculate risk ratios (RRs) and absolute risk differences (RDs). We will obtain means and standard deviations for continuous data, and perform analyses using mean differences (MDs). We will calculate standardized MDs when combining different pain scales. For each measure of effect we will also calculate the corresponding 95% confidence intervals (CIs). We will present the number needed to treat to benefit and number needed to treat to harm (NNTB and NNTH, respectively) when RDs are found to be statistically significant (P value < 0.05).

Unit of analysis issues

The unit of analysis will be individual infants. For multiple painful procedures we will consider the first procedure performed in the randomised infant. The unit of analysis for cluster-randomised trials will be the randomising treating centre or cluster. We plan to include cluster-randomised trials in the analyses, using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), or from another source, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We will contact the original study investigators to request additional data where information about critical and important outcomes is missing. We will investigate attrition rates (e.g. dropouts, losses to follow-up, and withdrawals). We plan to perform a sensitivity analysis to evaluate the overall results with and without the inclusion of studies with significant drop-out rates. If a study reports outcomes only for participants completing the trial, or only for participants who followed the protocol, we plan to contact the author(s) and ask them to provide additional information to facilitate an intention-to-treat analysis; and in instances where this is not possible we will perform a complete case analysis. We will address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

We plan to assess clinical heterogeneity by comparing the distribution of important participant factors between trials and trial factors (randomisation concealment, blinding of outcome assessment, loss to follow-up, treatment type, co-interventions). We will assess statistical heterogeneity by examining the I^2 statistic (Higgins 2011), a quantity that describes the proportion of variation in point estimates that is due to variability across studies rather than sampling error.

We will interpret the I^2 statistic as described by Higgins 2003:

- < 25%: no heterogeneity;
- 25% to 49%: low heterogeneity;
- 50% to 74%: moderate heterogeneity;
- ≥ 75%: high heterogeneity.

In addition, we will employ the Chi^2 test of homogeneity to determine the strength of evidence that heterogeneity is genuine. We will explore clinical variation across studies by comparing the distribution of important participant factors among trials and trial factors (randomisation concealment, blinding of outcome assessment, loss to follow-up, treatment type and co-interventions). We will consider a threshold P value of < 0.1 as an indicator of whether heterogeneity (genuine variation in effect sizes) is present.

Assessment of reporting biases

We will investigate publication by using funnel plots if at least 10 clinical trials are included in the meta-analysis (Egger 1997; Higgins 2011)

Data synthesis

We will perform statistical analyses according to the recommendations of the Cochrane Neonatal Review Group (neonatal.cochrane.org/en/index.html). We will analyse all infants randomised on an intention-to-treat basis. For any meta-analyses we will synthesize data using RR, RD, NNTB, NNTH, MD, and 95% confidence intervals (CI). We plan to analyse and interpret individual trials separately when we judge meta-analysis to be inappropriate.

Quality of evidence

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the GRADE Handbook (Schu¨ nemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes:

- pain scale measure (the two scales which are reported more often across the included trials);
- neonatal mortality;
- completion of the targeted objective without use of any other agent;
- intraventricular hemorrhage;
- episodes of bradycardia; and
- parent satisfaction with care provided in the NICU.

Two authors will independently assess the quality of the evidence for each of the outcomes above. We will consider evidence from randomised controlled trials as high quality but downgrade 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 the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence as being 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.

Subgroup analysis and investigation of heterogeneity

We plan to present data from the following subgroups:

- gestational age: term infants (≥ 37 weeks); preterm infants (≥ 28 but < 37 weeks); extreme preterm (< 28 weeks);
- birth weight: under 1500 grams; 1500 grams or more;
- type of pain: 1) painful procedures: heel lance, venipuncture, lumbar puncture, bladder tap, insertion of nasogastric tube, insertion of venous or arterial catheter/line or chest drain, or surgery (including neonatal circumcision, any surgery performed in the operating room); 2) painful clinical conditions: including a fractured long bone, necrotizing enterocolitis, open skin lesions from an inherited skin disorder, or pain from an assisted vaginal birth.
- dose of clonidine. For infusion administration: < 0.3 µg/kg/hour) versus 0.3 µg to 1 µg/kg/hour versus > 1 µg/kg/hour. For bolus administration: < 2 µg/kg versus 2 µg to 4 µg/kg versus > 4 µg/kg;
- duration of treatment (< 24 hours; one to five days; ≥ five days);
- route of administration: parenteral; enteral; transdermal;
- with versus without pharmacologic sedation and pain management as co-interventions;
- within studies that included co-interventions: studies in which the protocol allowed co-interventions for sedation and pain management for one or both of the intervention groups; studies in which the protocol mandated sedation with co-interventions.

Sensitivity analysis

We will conduct sensitivity analyses to explore the effect of the methodological quality of the trials, checking to ascertain if studies with a high risk of bias over-estimate the effect of treatment.

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The methods section of this protocol is based on a standard template used by Cochrane Neonatal.

REFERENCES

Additional references

Allegaert 2007
Allegaert K, Peeters MY, Verbesselt R, Tibboel D, Naulaers G, de Hoon JN, et al. Inter-individual variability in propofol pharmacokinetics in preterm and term neonates. *British Journal of Anaesthesia* 2007;**99**(6):864-70. DOI: 10.1093/bja/aem294; PUBMED: 17965417

Anand 1987a
Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. *New England Journal of Medicine* 1987;**371**(21):1321–9. DOI: 10.1056/NEJM198711193172105; PUBMED: 3317037

Anand 1987b
Anand KJ, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet* 1987;**1**(8524):62–6. [PUBMED: 2879174]

Anand 2004
Anand KJ, Hall RW, Desai N, Shephard B, Bergqvist LL, Young TE, et al. NEOPAIN Trial Investigators Group. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet* 2004;**363**(9422):1673–82. DOI: 10.1016/S0140-6736(04)16251-X; PUBMED: 15158628

Barker 1995
Barker DP, Rutter N. Exposure to invasive procedures in neonatal intensive care unit admissions. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 1995;**72**(1):F47–8. [PUBMED: 7743285]

Bauer 2013
Bauer AZ, Kriebel D. Prenatal and perinatal analgesic exposure and autism: an ecological link. *Environmental Health* 2013;**12**:41. DOI: 10.1186/1476-069X-12-41; PUBMED: 23656698

Bayley 1993
Bayley N. *Bayley Scales of Infant Development*. 2nd Edition. San Antonio (TX): Psychological Corporation, 1993.

Bayley 2006
Bayley N. *Bayley Scales of Infant and Toddler Development*. 3rd Edition. San Antonio (TX): Harcourt Assessment, 2006.

Bellieni 2005
Bellieni CV, Bagnoli F, Sisto R, Neri L, Cordelli D, Buonocore G. Development and validation of the ABC pain scale for healthy full-term babies. *Acta Paediatrica* 2005;**94**(10):1432–6. [PUBMED: 16299876]

Benis 2001
Benis MM, Suresh GK. Frequency of invasive procedures in very low birth weight (VLBW) infants in the neonatal intensive care unit (NICU). Pediatric Research 2001; Vol. 49, issue 4:392A.

Brummelte 2012
Brummelte S, Grunau RE, Chau V, Poskitt KJ, Brant R, Vinall J, et al. Procedural pain and brain development in premature newborns. *Annals of Neurology* 2012;**71**(3):385–96. DOI: 10.1002/ana.22267; PUBMED: 22374882

Bueno 2013
Bueno M, Yamada J, Harrison D, Khan S, Ohlsson A, Adams-Webber T, et al. A systematic review and meta-analyses of non-sucrose sweet solutions for pain relief in neonates. *Pain Research and Management* 2013;**18**(3):153-61. [PUBMED: 23748256]

Butt 2013
Butt ML, McGrath JM, Samra HA, Gupta R. An integrative review of parent satisfaction with care provided in the neonatal intensive care unit. *Journal of Obstetric, Gynecologic, and Neonatal Nursing* 2013;**42**(1):105–20. DOI: 10.1111/1552-6909.12002; PUBMED: 23316895

Capino 2016
Capino AC, Miller JL, Johnson PN. Clonidine for sedation and analgesia and withdrawal in critically ill infants and children. *Pharmacotherapy* 2016;**36**(12):1290–9. DOI: 10.1002/phar.1850; PUBMED: 27779775

Carbajal 1997
Carbajal R, Paupe A, Hoenn E, Lenclen R, Olivier-Martin M. APN: evaluation behavioral scale of acute pain in newborn infants. *Archives de Pediatrie* 1997;**4**(7):623–8. [PUBMED: 9295899]

Carbajal 2008
Carbajal R, Rousset A, Danan C, Coquery S, Nolent P, Ducrocq S, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA* 2008; **300**(1):60–70. [PUBMED: 18594041]

Ceelie 2013
Ceelie I, de Wildt SN, van Dijk M, van den Berg MM, van den Bosch GE, Duivenvoorden HJ, et al. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. *JAMA* 2013;**309**(2):149–54. DOI: 10.1001/jama.2012.148050; PUBMED: 23299606

Chana 2001
Chana SK, Anand KJ. Can we use methadone for analgesia in neonates?. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2001;**85**(2):F79–81. [PUBMED: 11517197]

Chen 2015
Chen K, Lu Z, Xin YC, Cai Y, Chen Y, Pan SM. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. *Cochrane Database of Systematic Reviews* 2015, Issue 1. DOI: 10.1002/14651858.CD010269; PUBMED: 25879090

Cochrane EPOC 2013
Cochrane Effective Practice, Organisation of Care (EPOC). Data extraction and management. EPOC Resources for review authors, 2013. Available at: epoc.cochrane.org/epoc-specific-resources-review-authors.

Costa 2013
Costa MC, Eckert GU, Fortes BG, Fortes Filho JB, Silveira RC, Procianoy RS. Oral glucose for pain relief during examination for retinopathy of prematurity: a masked randomized clinical trial. *Clinics (Sao Paulo, Brazil)* 2013; **68**(2):199–204. [PUBMED: 23525316]

Cravero 2011
Cravero JP, Havidich JE. Pediatric sedation--evolution and revolution. *Paediatric Anaesthesia* 2011;**21**(7):800–9. DOI: 10.1111/j.1460-9592.2011.03617.x; PUBMED: 21585616

de Graaf 2013
de Graaf J, van Lingen RA, Valkenburg AJ, Weisglas-Kuperus N, Groot Jebbink L, Wijnberg-Williams B, et al. Does neonatal morphine use affect neuropsychological outcomes at 8 to 9 years of age?. *Pain* 2013;**154**(3):449–58. DOI: 10.1016/j.pain.2012.12.006; PUBMED: 23352760

Debillon 2001
Debillon T, Zupan V, Ravault N, Magny JF, Dehan M. Development and initial validation of the EDIN scale, a new tool for assessing prolonged pain in preterm infants. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2001;**85**(1):F36–41. [PUBMED: 11420320]

Duffett 2012
Duffett M, Koop A, Menon K, Meade MO, Cook DJ. Clonidine for the sedation of critically ill children: a systematic review. *Journal of Pediatric Intensive Care* 2012;**1** (1):5–15.

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**(7109):629–34. [PUBMED: 9310563]

Fitzgerald 1986
Fitzgerald M, Koltzenburg M. The functional development of descending inhibitory pathways in the dorsolateral funiculus of the newborn rat spinal cord. *Brain Research* 1986;**389**(1-2):261–70. [PUBMED: 3948011]

Gibbins 2014
Gibbins S, Stevens BJ, Yamada J, Dionne K, Campbell-Yeo M, Lee G, et al. Validation of the Premature Infant Pain Profile-Revised (PIPP-R). *Early Human Development* 2014; **90**(4):189–93. DOI: 10.1016/j.earlhumdev.2014.01.005; PUBMED: 24491511

Gold 1978
Gold M, Redmond DE, Kleber H. Clonidine blocks acute opiate-withdrawal symptoms. *Lancet* 1978;**2**(8090): 599–602. [PUBMED: 80526]

Golianu 2007
Golianu B, Krane E, Seybold J, Almgren C, Anand KJ. Non-pharmacological techniques for pain management in neonates. *Seminars in Perinatology* 2007;**31**(5):318–22. DOI: 10.1053/j.semperi.2007.07.007; PUBMED: 17905187

GRADEpro GDT [Computer program]
Grade Working Group, McMaster University. GRADEpro GDT. Version accessed 10 August 2017. Hamilton (ON): Grade Working Group, McMaster University, 2014.

Gregoretti 2009
Gregoretti C, Moglia B, Pelosi P, Navalesi P. Clonidine in perioperative medicine and intensive care unit: more than an anti-hypertensive drug. *Current Drug Targets* 2009;**10**(8):799–814. [PUBMED: 19702526]

Griffiths 1954
Griffiths R. *The abilities of babies: a study in mental measurement*. New York (NY): McGraw-Hill Book Co. Inc, 1954.

Grunau 1986
Grunau RE, Oberlander T, Holsti L, Whitfield MF. Bedside application of the Neonatal Facial Coding System in pain assessment of premature neonates. *Pain* 1998;**76**(3):277–86. [PUBMED: 9718246]

Hammer 1989
Hammer RP Jr, Ricalde AA, Seatriz JV. Effects of opiates on brain development. *Neurotoxicology* 1989;**10**(3):475–83. [PUBMED: 2696899]

Handelmann 1985
Handelmann GE, Dow-Edwards D. Modulation of brain development by morphine: effects on central motor systems and behavior. *Peptides* 1985;**6**(Suppl 2):29–34. [PUBMED: 4080616]

Hazell 2003
Hazell PL, Stuart JE. A randomized controlled trial of clonidine added to psychostimulant medication for hyperactive and aggressive children. *Journal of the American Academy of Child and Adolescent Psychiatry* 2003;**42**(8):886–94. DOI: 10.1097/01.CHI.0000046908.27264.00; PUBMED: 12874489

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical Research Ed.)* 2003;**327**(7414):557–60. DOI: 10.1136/bmj.327.7414.557; PUBMED: 12958120

Higgins 2011
Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hodgkinson 1994
Hodgkinson K, Bear M, Thorn J, Van Blaricum S. Measuring pain in neonates: evaluating an instrument and developing a common language. *Australian Journal of Advanced Nursing* 1994;**12**(1):17–22. [PUBMED: 7786451]

Holsti 2008
Holsti L, Grunau RE, Oberlander TF, Osiovich H. Is it painful or not? Discriminant validity of the Behavioral Indicators of Infant Pain (BIIP) scale. *Clinical Journal of Pain* 2008;**24**(1):83–8. DOI: 10.1097/AJP.0b013e318158c5e5; PUBMED: 18180641

Hoy 2011
Hoy SM, Keating GM. Dexmedetomidine: a review of its use for sedation in mechanically ventilated patients in an intensive care setting and for procedural sedation. *Drugs* 2011;**71**(11):1481–501. DOI: 10.2165/11207190-000000000-00000; PUBMED: 21812509

Hummel 2008
Hummel P, Puchalski M, Creech SD, Weiss MG. Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain. *Journal of Perinatology* 2008;**28**(1):55–60. DOI: 10.1038/sj.jp.7211861; PUBMED: 18165830

Hummel 2010
Hummel P, Lawlor-Klean P, Weiss MG. Validity and reliability of the N-PASS assessment tool with acute pain. *Journal of Perinatology* 2010;**30**(7):474–8. DOI: 10.1038/jp.2009.185; PUBMED: 19924132

ICROP 1984
Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Pediatrics* 1984;**74**(1):127–33. [PUBMED: 6547526]

Jacobs 2013
Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database of Systematic Reviews* 2013, Issue 1. DOI: 10.1002/14651858.CD003311.pub3

Jamadarkhana 2010
Jamadarkhana S, Gopal S. Clonidine in adults as a sedative agent in the intensive care unit. *Journal of Anaesthesiology, Clinical Pharmacology* 2010;**26**(4):439–45. [PUBMED: 21547166]

Jobe 2001
Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *American Journal of Respiratory and Critical Care Medicine* 2001;**163**(7):1723–9. DOI: 10.1164/ajrccm.163.7.2011060; PUBMED: 11401896

Johnston 1997
Johnston CC, Collinge JM, Henderson SJ, Anand KJ. A cross-sectional survey of pain and pharmacological analgesia in Canadian neonatal intensive care units. *Clinical Journal of Pain* 1997;**13**(4):308–12. [PUBMED: 9430811]

Krechel 1995
Krechel SW, Bildner J. CRIES: a new neonatal postoperative pain measurement score. Initial testing of validity and reliability. *Paediatric Anaesthesia* 1995;**5**(1):53–61. [PUBMED: 8521311]

Lambert 2014
Lambert P, Cyna AM, Knight N, Middleton P. Clonidine premedication for postoperative analgesia in children. *Cochrane Database of Systematic Reviews* 2014, Issue 1. DOI: 10.1002/14651858.CD009633.pub2

Laudenbach 2002
Laudenbach V, Mantz J, Lagercrantz H, Desmonts JM, Evrard P, Gressens P. Effects of alpha(2)-adrenoceptor agonists on perinatal excitotoxic brain injury: comparison of clonidine and dexmedetomidine. *Anesthesiology* 2002;**96**(1):134–41. [PUBMED: 11753013]

Lawrence 1993
Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. *Neonatal Network* 1993;**12**(6):59–66. [PUBMED: 8413140]

Lim 2017
Lim Y, Godambe S. Prevention and management of procedural pain in the neonate: an update, American Academy of Pediatrics, 2016. *Archives of Disease in Childhood. Education and Practice Edition* 2017;**102**(5): 254–6. [PUBMED: 28724533]

Lundqvist 2014
Lundqvist P, Kleberg A, Edberg AK, Larsson BA, Hellström-Westas L, Norman E. Development and psychometric properties of the Swedish ALPS-Neo pain and stress assessment scale for newborn infants. *Acta Paediatrica* 2014; **103**(8):833–9. DOI: 10.1111/apa.12672; PUBMED: 24813238

Ma 2007
Ma MX, Chen YM, He J, Zeng T, Wang JH. Effects of morphine and its withdrawal on Y-maze spatial recognition memory in mice. *Neuroscience* 2007;**147**(4):1059–65. DOI: 10.1016/j.neuroscience.2007.05.020; PUBMED: 17601672

Mantz 2011
Mantz J, Josserand J, Hamada S. Dexmedetomidine: new insights. *European Journal of Anaesthesiology* 2011;**28**(1): 3–6. DOI: 10.1097/EJA.0b013e32833e266d; PUBMED: 20881501

McPherson 2007
McPherson RJ, Gleason C, Mascher-Denen M, Chan M, Kellert B, Juul SE. A new model of neonatal stress which produces lasting neurobehavioral effects in adult rats. *Neonatology* 2007;**92**(1):33–41. DOI: 10.1159/000100084; PUBMED: 17596735

McPherson 2012
McPherson C. Sedation and analgesia in mechanically ventilated preterm neonates: continue standard of care or experiment?. *Journal of Pediatric Pharmacology and Therapeutics : JPPT : the official journal of PPAG* 2012;**17** (4):351–64. [PUBMED: 23413121]

Milesi 2010
Milesi C, Cambonie G, Jacquot A, Barbotte E, Mesnage R, Masson F, et al. Validation of a neonatal pain scale adapted to the new practices in caring for preterm newborns. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2010;**95**(4):F263–6. DOI: 10.1136/adc.2008.144758; PUBMED: 19221401

Nishina 1999
Nishina K, Akamatsu H, Mikawa K, Shiga M, Maekawa N, Obara H, et al. The effects of clonidine and dexmedetomidine on human neutrophil functions. *Anesthesia and Analgesia* 1999;**88**(2):424–8. [PUBMED: 9972773]

Ohlsson 2016
Ohlsson A, Shah PS. Paracetamol (acetaminophen) for prevention or treatment of pain in newborns. *Cochrane Database of Systematic Reviews* 2016, Issue 10. DOI: 10.1002/14651858.CD011219.pub3; PUBMED: 27716943

Papile 1978
Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *Journal of Pediatrics* 1978;**92**(4):529–34. [PUBMED: 305471]

Paris 2006
Paris A, Mantz J, Tonner PH, Hein L, Brede M, Gressens P. The effects of dexmedetomidine on perinatal excitotoxic brain injury are mediated by the alpha2A-adrenoceptor subtype. *Anesthesia and Analgesia* 2006;**102**(2):456–61. DOI: 10.1213/01.ane.0000194301.79118.e9; PUBMED: 16428542

Peters 2003
Peters JW, Koot HM, Grunau RE, de Boer J, van Druenen MJ, Tibboel D, et al. Neonatal Facial Coding System for assessing postoperative pain in infants: item reduction is valid and feasible. *Clinical Journal of Pain* 2003;**19**(6): 353–63. [PUBMED: 14600535]

Pichot 2012
Pichot C, Ghignone M, Quintin L. Dexmedetomidine and clonidine: from second-to-first-line sedative agents in the critical care setting?. *Journal of Intensive Care Medicine* 2012;**27**(4):219–37. DOI: 10.1177/0885066610396815; PUBMED: 21525113

Pillai Riddell 2015
Pillai Riddell RR, Racine NM, Turcotte K, Uman LS, Horton RE, Din Osmun L, et al. Non-pharmacological management of infant and young child procedural pain. *Cochrane Database of Systematic Reviews* 2015, Issue 12. DOI: 10.1002/14651858.CD006275.pub3

Pontén 2012
Pontén E, Viberg H, Gordh T, Eriksson P, Fredriksson A. Clonidine abolishes the adverse effects on apoptosis and behaviour after neonatal ketamine exposure in mice. *Acta Anaesthesiologica Scandinavica* 2012;**56**(8):1058–65. DOI: 10.1111/j.1399-6576.2012.02722.x; PUBMED: 22694670

Review Manager 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ricalde 1990
Ricalde AA, Hammer RP Jr. Perinatal opiate treatment delays growth of cortical dendrites. *Neuroscience Letters* 1990;**115**(2-3):137–43. [PUBMED: 2172870]

Rochette 2004
Rochette A, Raux O, Troncin R, Dadure C, Verdier R, Capdevila X. Clonidine prolongs spinal anesthesia in newborns: a prospective dose-ranging study. *Anesthesia and Analgesia* 2004;**98**(1):56–9. [PUBMED: 14693584]

Romantsik 2017
Romantsik O, Calevo MG, Norman E, Bruschettini M. Clonidine for sedation and analgesia for neonates receiving mechanical ventilation. *Cochrane Database of Systematic Reviews* 2017, Issue 5. DOI: 10.1002/14651858.CD012468.pub2

Roze 2008
Roze JC, Denizot S, Carbajal R, Ancel PY, Kaminski M, Arnaud C, et al. Prolonged sedation and/or analgesia and 5-year neurodevelopment outcome in very preterm infants: results from the EPIPAGE cohort. *Archives of Pediatrics & Adolescent Medicine* 2008;**162**(8):728–33. DOI: 10.1001/archpedi.162.8.728; PUBMED: 18678804

Schu¨ nemann 2013
Schünemann H, Broż ek J, Guyatt G, Oxman A, editors. GRADE Working Group. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations. Available from gdt.gradepro.org/app/handbook/handbook.html Updated October 2013.

Seatriz 1993
Seatriz JV, Hammer RP Jr. Effects of opiates on neuronal development in the rat cerebral cortex. *Brain Research Bulletin* 1993;**30**(5-6):523–7. [PUBMED: 8384517]

Shah 2012
Shah PS, Herbozo C, Aliwalas LL, Shah VS. Breastfeeding or breast milk for procedural pain in neonates. *Cochrane Database of Systematic Reviews* 2012, Issue 12. DOI: 10.1002/14651858.CD004950.pub3; PUBMED: 23235618

Simons 2003
Simons SH, van Dijk M, van Lingen RA, Roofthooft D, Duivenvoorden HJ, Jongeneel N, et al. Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. *JAMA* 2003;**290**(18):2419–27. DOI: 10.1001/jama.290.18.2419; PUBMED: 14612478

Spence 2005
Spence K, Gillies D, Harrison D, Johnston L, Nagy S. A reliable pain assessment tool for clinical assessment in the neonatal intensive care unit. *Journal of Obstetric, Gynecologic, and Neonatal Nursing* 2005;**34**(1):80–6. DOI: 10.1177/0884217504272810; PUBMED: 15673649

Stevens 1996
Stevens B, Johnston C, Petryshen P, Taddio A. Premature Infant Pain Profile: development and initial validation. *Clinical Journal of Pain* 1996;**12**(1):13–22. [PUBMED: 8722730]

Stevens 2016
Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database of Systematic Reviews* 2016, Issue 7. DOI: 10.1002/14651858.CD001069.pub5; PUBMED: 27420164

Taddio 2009
Taddio A, Shah V, Atenafu E, Katz J. Influence of repeated painful procedures and sucrose analgesia on the development of hyperalgesia in newborn infants. *Pain* 2009;**144**(1-2):43-8. DOI: 10.1016/j.pain.2009.02.012; PUBMED: 19329255

Taniguchi 2004
Taniguchi T, Kidani Y, Kanakura H, Takemoto Y, Yamamoto K. Effects of dexmedetomidine on mortality rate and inflammatory responses to endotoxin-induced shock in rats. *Critical Care Medicine* 2004;**32**(6):1322–6. [PUBMED: 15187514]

Taniguchi 2008
Taniguchi T, Kurita A, Kobayashi K, Yamamoto K, Inaba H. Dose- and time-related effects of dexmedetomidine on mortality and inflammatory responses to endotoxin-induced shock in rats. *Journal of Anesthesia* 2008;**22**(3):221–8. DOI: 10.1007/s00540-008-0611-9; PUBMED: 18685927

Tesoro 2005
Tesoro S, Mezzetti D, Marchesini L, Peduto VA. Clonidine treatment for agitation in children after sevoflurane anesthesia. *Anesthesia and Analgesia* 2005;**101**(6):1619–22. DOI: 10.1213/01.ANE.0000184204.81877.53; PUBMED: 16301230

van Dijk 2009
van Dijk M, Roofthooft DW, Anand KJ, Guldemond F, de Graaf J, Simons S, et al. Taking up the challenge of measuring prolonged pain in (premature) neonates: the COMFORTneo scale seems promising. *Clinical Journal of Pain* 2009;**25**(7):607–16. DOI: 10.1097/AJP.0b013e3181a5b52a; PUBMED: 19692803

Viberg 2014
Viberg H, Eriksson P, Gordh T, Fredriksson A. Paracetamol (acetaminophen) administration during neonatal brain development affects cognitive function and alters its analgesic and anxiolytic response in adult male mice. *Toxicological Sciences* 2014;**138**(1):139–47. DOI: 10.1093/toxsci/kft329; PUBMED: 24361869

Walker 2012
Walker SM, Grafe M, Yaksh TL. Intrathecal clonidine in the neonatal rat: dose-dependent analgesia and evaluation of spinal apoptosis and toxicity. *Anesthesia and Analgesia* 2012;**115**(2):450–60. DOI: 10.1213/ANE.0b013e3182501a09; PUBMED: 22467896

Walsh 2004
Walsh MC, Yao Q, Gettner P, Hale E, Collins M, Hensman A, et al. National Institute of Child Health and Human Development Neonatal Research Network. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics* 2004;**114**(5):1305–11. DOI: 10.1542/peds.2004-0204; PUBMED: 15520112

Zagon 1977
Zagon IS, McLaughlin PJ. Morphine and brain growth retardation in the rat. *Pharmacology* 1977;**15**(3):276–82. [PUBMED: 866403]

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Pain scales

Pain scale	Population	Type of pain
ABC pain scale (Bellieni 2005)[a]	Preterm and term infants	Procedural pain
Astrid Lindgren and Lund Children's Hospitals Pain and Stress Assessment Scale for Preterm and sick Newborn Infants (ALPS-Neo) (Lundqvist 2014)	Preterm and term infants	Prolonged pain/stress
Behavioral Indicators of Infant Pain (BIIP) (Holsti 2008)	Preterm infants	Procedural pain
Comfort Neo (van Dijk 2009)	Preterm and term infants	Postoperative and prolonged pain/stress
CRIES (Krechel 1995)	Preterm and term infants	Procedural and postoperative pain
Douleur Aiguë du Nouveau-né (DAN) (Acute pain in newborn infants, APN, English version) (Carbajal 1997)	Preterm and term infants	Procedural pain
Echelle Douleur Incomfort Nouveau-né (EDIN) (Debillon 2001)	Preterm infants	Prolonged pain
'Faceless' Acute Neonatal pain Scale (FANS) (Milesi 2010)	Preterm and term infants	Procedural pain
Neonatal Facial Coding System (NFCS) (Grunau 1986; Peters 2003)	Preterm and term infants	Procedural, postoperative and prolonged pain/stress
Neonatal Infant Pain Scale (NIPS) (Lawrence 1993)	Preterm and term infants	Procedural pain
Neonatal Pain, Agitation, and Sedation Scale (N-PASS) (Hummel 2008; Hummel 2010)	Preterm and term infants	Procedural, postoperative and prolonged pain/stress
Pain Assessment Tool (PAT) (Hodgkinson 1994; Spence 2005)	Preterm and term infants	Postoperative and prolonged pain/discomfort
Premature Infant Pain Profile (PIPP and PIPP-R) (Gibbins 2014; Stevens 1996)	Preterm and term infants	Procedural and postoperative pain

[a] Publication of development or validation, or both, within parentheses

APPENDICES

Appendix 1. Standard search methodology

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (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]))
Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)
CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
Cochrane Library: (infant or newborn or neonate or neonatal or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

CONTRIBUTIONS OF AUTHORS

OR and MB reviewed the literature and wrote the protocol.

MGC assisted in the review of literature and in writing of the protocol.

EN commented on and reviewed the protocol.

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