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Clonidine for neonates receiving mechanical ventilation (Protocol)

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[Intervention Protocol]

Clonidine for neonates receiving mechanical ventilation

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ABSTRACT

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

To assess whether clonidine infusion in term and preterm newborn infants receiving mechanical ventilation reduces the rate of mortality and morbidity. The intervention will be compared to placebo, no treatment and dexmedetomidine. In addition, the safety of clonidine infusion will be assessed for potential harms.

We will perform subgroup analyses according to gestational age; birth weight; dose, duration and route of clonidine administration; and presence of pharmacological sedation as co-intervention.

BACKGROUND

Description of the condition

Neonatal pain has been poorly understood and often unrecognized till the 1980s, when research describing the developmental physiology of nociception and adverse responses of neonates to noxious stimuli emerged (Anand 1987a; Anand 1987b). Despite early maturation of the ascending neural pathways responsible for nociception, the descending inhibitory pathways, which localize and mitigate pain, do not form until later in maturation (Fitzgerald 1986). Moreover, normal brain development is abruptly interrupted by preterm birth, which results in a unique susceptibility to neurologic remodeling after repetitive noxious stimuli (Taddio 2009). Despite the growing knowledge about long-term consequences of neonatal pain and discomfort, the consensus regarding a safe and effective strategy for controlling these complications in many routine clinical situations is still missing.

Mechanical ventilation is a common stressful experience in preterm neonates (Hall 2007). Non-pharmacologic therapies, including non-nutritive sucking and swaddling, form the foundation of neonatal pain and agitation relief, but in many cases pharmacological support is needed to provide comfort during invasive ventilation (Golianu 2007). Though routine administration of pharmacologic sedation or analgesia during mechanical ventilation in preterm neonates is not recommended, the use of benzodiazepines and opiates in clinical practice remains common due to the lack of available alternative therapies (Clark 2006; Kumar 2008). Benzodiazepines have no analgesic effect and the data from two randomized controlled trials showed that midazolam may increase the incidence of brain injury (Anand 1999; Jacqz-Aigrain 1994). Furthermore, the Cochrane review 'Intravenous midazolam infusion

for sedation of infants in the neonatal intensive care unit' reported controversial data on neurological effects of midazolam, raising a question regarding the safety of this drug (Ng 2012). Additionally, studies in rodent models have shown widespread neuroapoptosis and suppressed neurogenesis elicited by early benzodiazepine exposure (Stefovska 2008; Young 2005).

Morphine and fentanyl are the most commonly utilized opiates in neonates (Clark 2006; Kumar 2008). Three large randomized controlled trials examined the impact of morphine on acute brain injury in mechanically ventilated preterm neonates (Anand 1999; Anand 2004; Simons 2003). The first was the Neonatal Outcome and Prolonged Analgesia in Neonates (NOPAIN) trial, which demonstrated that the incidence of the composite outcome of severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), or death was decreased in the morphine group (4%) compared to the midazolam (32%) and placebo (24%) groups (Anand 1999). However, in the two following randomized controlled trials no difference was detected in the composite outcome of severe IVH, PVL, or death (Anand 2004; Simons 2003). In addition, no impact of fentanyl was detected on the incidence of the composite outcome of severe IVH, PVL, or death (Lago 1998). This finding has been confirmed by Cochrane review, where the authors have described that infants receiving morphine need a longer time to achieve full enteral feeding (Bellù 2008).

Early opiate exposure in rodent models has been demonstrated to diminish neuronal density and dendritic length, as well as to increase apoptosis (Hammer 1989; Ricalde 1990; Seatriz 1993). Further, rodents exposed to postnatal morphine exhibited reduced brain growth (Zagon 1977), persistently decreased motor activity and impaired learning ability (Handelmann 1985; Ma 2007; McPherson 2007). Conflicting results exist in human neonates with regard to the long-term neurodevelopmental impact of early morphine exposure. It has been shown that morphine-treated children had smaller head circumference, impaired short-term memory, and more social problems compared to placebo-treated children (Ferguson 2012).

The data about morphine therapy impact on intelligence quotient are controversial (de Graaf 2011; Ferguson 2012). Children treated with morphine displayed a lower overall intelligence quotient compared to placebo (de Graaf 2011). Such a difference disappeared after correction for treatment condition, open-label morphine consumption over the first 28 days, and a propensity score for clinically relevant co-variables in multiple regression analyses. Of note: scores on one intelligence quotient (IQ) subtest, "visual analysis," were significantly negatively related to having received morphine and to open-label morphine consumption in the first 28 days. In a small pilot follow-up study (NEOPAIN population), children treated with morphine completed 27% less of the short-term memory task than children in the placebo group, though overall IQ did not differ between the two groups (Ferguson 2012).

Description of the intervention

Thus, alternative sedation strategies have been tested. Alpha-2 agonists, mainly clonidine and dexmedetomidine, are used as adjunctive (or alternative) sedative agents alongside opioids and benzodiazepines. They have a wide range of effects, including sedation, analgesia and relief of anxiety (Mantz 2011; Pichot 2012). These effects are mediated through alpha2-adrenergic receptor subtype agonism, located in the locus ceruleus. Both clonidine and dexmedetomidine reduce the activity of neurons in the locus ceruleus without affecting the respiratory drive (Hoy 2011). Moreover, it has been suggested that alpha-2 agonists might have neuroprotective and anti-inflammatory action (Mantz 2011). Both drugs preserve neutrophil function and inhibit the cytokine response in animal models of endotoxic shock (Nishina 1999; Taniguchi 2004; Taniguchi 2008). The impact of dexmedetomidine on cytokine levels has been confirmed in septic adult humans (Tasdogan 2009). Both alpha-2 agonists reduced the number of damaged neurons in vitro and reduced the size of the lesions in vivo (Laudenbach 2002; Paris 2006). The adverse events of alpha-2 agonists, such as bradycardia and hypotension, are mediated via the alpha-2 adenoreceptors in the medullary dorsal motor nucleus and motor complex, and are thus independent of sedative effect (Gregoretti 2009; Pichot 2012). Traditionally, clonidine has been used to treat attention deficit hyperactivity disorder (ADHD) (Hazell 2003), opioid withdrawal (Gold 1978), or as an anaesthetic adjuvant (Gregoretti 2009; Lambert 2014). Its use for sedation remains 'off label' in many countries. However, in the critically ill pediatric population, clonidine is frequently used as a sedative agent, particularly as an adjunctive agent when there is an inadequate response to opioids and benzodiazepines, or to help facilitate weaning from mechanical ventilation (Duffett 2012). Dexmedetomidine has a higher alpha- 2/alpha-1 selectivity ratio (dexmedetomidine 1620:1, clonidine 220:1) (Virtanen 1988). Dexmedetomidine was approved by the United States Food and Drug Administration in 1999 for short-term sedation in adults. Currently, dexmedetomidine is not approved for pediatric use. Nevertheless, it is widely used in critically ill children and infants (Mason 2011). The first case report was published in 2009 regarding the use of dexmedetomidine in an extremely preterm newborn (O'Mara 2009); subsequently the retrospective description of the efficacy and safety of dexmedetomidine infusion in mechanically ventilated preterm neonates emerged (O'Mara 2012).

How the intervention might work

Clonidine is a centrally acting alpha-2 selective adrenergic agonist. It has been postulated that alpha-2 agonists exert their sedative effects via stimulation of the pre-synaptic alpha-2 adrenoceptors of the locus ceruleus, decreasing norepinephrine release (Jamadarkhana 2010). Clonidine also has action on the cholinergic, purinergic, and serotonergic pathways, resulting in analgesia

(Jamadarkhana 2010). Mechanically ventilated preterm neonates treated with dexmedetomidine infusion required less adjunctive sedation compared to historical controls treated with fentanyl infusion (O'Mara 2012). These data support the findings of randomized controlled trials in adult patients (Riker 2009; Ruokonen 2009). Moreover the administration of clonidine may exert neuroprotective effects by preventing apoptosis induced by anesthesia (Pontén 2012).

Why it is important to do this review

Cochrane reviews have been published on the pharmacological management of newborns receiving mechanical ventilation (Bellù 2008; Ng 2012). Important issues are raised by the authors of these reviews, including the lack of data on safety and on long-term neurodevelopmental effects of midazolam and opioid treatment; however extremely preterm infants, who constitute the largest population requiring mechanical ventilation in neonatal intensive care units, are under-represented in these clinical trials.

The use of clonidine has not been systematically assessed for neonatal sedation during ventilation: neonates were excluded from the Cochrane review 'Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients' (Chen 2015). One systematic review, which focused only on pediatric ICU patients, found that adjunctive clonidine use decreased the requirement for other sedative agents, decreased withdrawal symptoms when weaning off benzodiazepines or opiates, and was associated with minimal clinically significant adverse effects (Duffett 2012). A Cochrane review on 'Dexmedetomidine for analgesia and sedation in newborn infants receiving mechanical ventilation' is in preparation (Ibrahim 2016); however, despite the theoretical advantages of clonidine, safety and efficacy for both short-term and long-term use remain unclear. A comprehensive synthesis is therefore needed to assess whether clonidine is safe and whether it has advantages over traditional sedatives for long-term sedation.

OBJECTIVES

To assess whether clonidine infusion in term and preterm newborn infants receiving mechanical ventilation reduces the rate of mortality and morbidity. The intervention will be compared to placebo, no treatment and dexmedetomidine. In addition, the safety of clonidine infusion will be assessed for potential harms.

We will perform subgroup analyses according to gestational age; birth weight; dose, duration and route of clonidine administration; and presence of pharmacological sedation as co-intervention.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

Full-term and preterm newborns receiving mechanical ventilation via an endotracheal tube.

Types of interventions

1. Clonidine vs placebo
2. Clonidine vs no intervention
3. Clonidine vs dexmedetomidine

We will include any route of administration, dose, frequency, timing of initiation and duration for clonidine, dexmedetomidine and co-interventions.

The presence of pharmacological co-interventions within sedation and pain management (e.g. morphine, fentanyl, midazolam) will be assessed in the subgroup analyses.

Types of outcome measures

Primary outcomes

1. All-cause neonatal death (death within 28 days of birth)
2. All-cause death during initial hospitalization
3. Duration of mechanical ventilation (days)

Secondary outcomes

1. Sedation assessed utilising tools or scales such as COMFORT (Ista 2005). We will report the mean values of the sedation scales assessed at 30 minutes and 3 hours post-administration of the drug in question
2. Analgesia assessed using validated pain scales with age-appropriate behavioural measures and physiological parameters such as Comfort-Neo (van Dijk 2009), Échelle Douleur Inconfort Nouveau-Né (neonatal pain and discomfort scale, EDIN) (Debillon 2001), Astrid Lindgren and Lund Children's Hospitals Pain and Stress Assessment Scale for Preterm and sick Newborn Infants (ALPS-Neo) (Lundqvist 2014), Neonatal Infant Pain Scale (NIPS) (Lawrence 1993), and Pain Assessment Tool (PAT) (Hodgkinson 1994). See Appendix 1 for a more detailed list. We will report the mean values of the analgesia scales assessed at 30 minutes and 3 hours post-administration of the drug in question.

3. Duration of any co-interventions (e.g. morphine, fentanyl, midazolam) (days). We plan not to report this outcome if the study protocol mandates sedation with a co-intervention.
4. Any Intraventricular hemorrhage: any IVH, grade 1 to 4 (according to Papile classification (Papile 1978)); severe IVH (grade 3 and 4)
5. Cerebellar hemorrhage on brain ultrasound in the first month of life (yes/no, Graça 2013)
6. Cystic periventricular leukomalacia at brain ultrasound in the first month of life (yes/no)
7. Brain MRI abnormalities at term equivalent age (yes/no), defined as: white matter lesions, i.e. cavitations (Rutherford 2010), and punctate lesions (Cornette 2002); GM-IVH (Parodi 2015); cerebellar hemorrhage (Limperopoulos 2007)
8. Retinopathy of prematurity (ICROP 1984): any; requiring laser therapy
9. Pneumothorax (on chest x-ray)
10. Duration of respiratory support (IPPV or continuous positive airway pressure, days)
11. Duration of oxygen therapy (days)
12. Duration of hospital stay (days)
13. Bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD): 28 days (NIH 1979); 36 weeks postmenstrual age (Jobe 2001); physiological definition (Walsh 2004).
14. Necrotizing enterocolitis (any grade; requiring surgery)
15. Need for treatment (medical; surgical) for persistent ductus arteriosus (PDA)
16. Time to full enteral feeding (days)
17. 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, during exposure to intervention
18. Major neurodevelopmental disability: cerebral palsy, developmental delay (Bayley Mental Developmental Index (Bayley 1993; Bayley 2006) or Griffiths Mental Development Scale (Griffiths 1954) assessment more than two SD below the mean), intellectual impairment (IQ more than two standard deviation below 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

Electronic searches

We will use the criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group. We will undertake a comprehensive search in the following electronic sources:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE (January 1996 to current date);
- Embase (January 1980 to current date);
- CINAHL (1982 to current date);
- conference proceedings of the Perinatal Society of Australia and New Zealand (from 2005 to current date);
- conference proceedings of the Pediatric Academic Societies (from 2000 to current date);

The full search strategies for each database are included in Appendix 2. We will not apply any language restrictions. We will also screen the reference lists of any cited articles.

Searching other resources

We will search clinical trials' registries for ongoing or recently completed trials (e.g. ClinicalTrials.gov (ClinicalTrials.gov) and the International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.controlled-trials.com)).

Data collection and analysis

We will use the standard methods of the Cochrane Neonatal Review Group as described below.

Selection of studies

Two review authors (OR, MB) will independently search and identify eligible trials that meet the inclusion criteria. We will screen the titles and abstracts to identify potentially relevant citations, and retrieve the full texts of all potentially relevant articles and independently assess 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.

Data extraction and management

Two authors (OR, MB) will independently extract data using a data extraction form developed ad hoc and integrated with a modified version of the Cochrane Effective Practice and Organisation of Care Group data collection checklist (Cochrane EPOC Group 2013).
We will extract the following characteristics from each included study.

- Administrative details: author(s); 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 (i.e. > 80%); country and location of study informed consent and ethics approval.
- Details of participants: sex, birth weight, gestational age, and number of participants.
- Details of intervention: initiation, dose and duration of the intervention (clonidine); and of the co-interventions, if any.
- Details of outcomes as mentioned above in Types of outcome measures.

We will resolve any disagreement by discussion. We will describe ongoing studies identified from our search, where available, detailing the primary author, research question(s), methods and outcome measures together with an estimate of the reporting date. Should any queries arise or in cases where additional data are required, we will contact the study investigators/authors for clarification. Two review authors (MGC, MB) will use Cochrane statistical software, Revman 2014, for data entry.

Assessment of risk of bias in included studies

Two authors (OR, MGC) will independently assess risk of bias in all the included studies using Cochrane's tool for assessing risk of bias (Higgins 2011).

We will assess the following items.

1. Selection bias: random sequence generation and selection bias, i.e.
    - random sequence generation (biased allocation to interventions) due to inadequate generation of a randomized sequence;
    - allocation concealment: selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment;
2. blinding of participants and personnel: performance bias due to knowledge of the allocated interventions by participants and personnel during the study;
3. blinding of outcome assessment: detection bias due to knowledge of the allocated interventions by outcome assessors;
4. incomplete outcome data: attrition bias due to amount, nature or handling of incomplete outcome data;
5. selective reporting: reporting bias due to selective outcome reporting;
6. other bias: bias due to problems not covered elsewhere in the table.

We will use a 'Risk of bias' graph to illustrate risk across studies. We will resolve any disagreements by consensus and, if necessary, by consulting a third author (MB).

1. Random sequence generation (Selection bias)

For each included study, we will categorize the risk of bias regarding random sequence generation as follows.

- Low risk: the investigators describe a random component in the sequence generation process such as referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, minimization.
- High risk: the investigators describe a non-random component in the sequence generation process (sequence generated by odd or even date of birth, sequence generated by some rule based on date or day of admission, sequence generated by some rule based on hospital or clinic record number, allocation by judgment of the clinician, allocation by preference of the participant, allocation based on the results of a laboratory test or a series of tests, allocation by availability of the intervention).
- Unclear risk: no or unclear information provided.

2. Allocation concealment (Selection bias)

For each included study, we will categorize the risk of bias regarding allocation concealment as follows.

- Low risk: participant and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomization), sequentially numbered drug containers of identical appearance, sequentially numbered sealed opaque envelopes.
- High risk: participants and investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on open random allocation schedule (e.g. a list of random numbers), unsealed or non-opaque envelopes, alternation or rotation, date of birth, case record number.
- Unclear risk: no or unclear information provided.

3. Blinding of study participants and personnel (Performance bias)

For each included study, we will categorize the methods used to blind study participants and personnel from knowledge of which intervention a participant received as follows.

- Criteria of a judgment of 'low risk' of bias: no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; or blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Criteria of a judgment of 'high risk' of bias: no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have

been broken, and the outcome is likely to be influenced by lack of blinding.

- Unclear risk: no or unclear information provided.

4. Blinding of outcome assessors (Detection bias)

For each included study, we will categorize the methods used to blind outcome assessors from knowledge of which intervention a participant received as follows.

- Criteria of a judgment of 'low risk' of bias: no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; or blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Criteria of a judgment of 'high risk' of bias: no blinding of outcome assessment, and the outcome is likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
- Unclear risk: no or unclear information provided.

5. Incomplete outcome data (Attrition bias)

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis as follows.

- Criteria of a judgment of 'low risk' of bias:
  - no missing outcome data;
  - reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);
  - missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
  - for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
  - for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
  - missing data have been imputed using appropriate methods.
- Criteria of a judgment of 'high risk' of bias:
  - reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
  - for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
  - for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
  - 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;
  - potentially inappropriate application of simple imputation.
- Unclear risk: no or unclear information provided.

6. Selective reporting (Reporting bias)

For each included study, we will describe how we investigated the risk of selective outcome reporting bias and what we found. We will attempt to access all the protocols of the included studies through clinical trials' registries (e.g. ClinicalTrials.gov (ClinicalTrials.gov), the International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.controlled-trials.com)) and direct contact with the authors.

We will assess the methods as follows.

- Low risk: the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; or the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
- High risk: not all of the study's pre-specified primary outcomes have been reported; or one or more primary outcomes is reported using measurements, or analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; or one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); or one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; or the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
- Unclear risk: no or unclear information provided (the study protocol was not available).

7. Other potential sources of bias (Other 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 used).

We will assess whether each study was free of other problems that could put it at risk of bias as follows.

- Low risk: the study appears to be free of other sources of bias.
- High risk: the study has at least one important risk of bias (for example, the study had a potential source of bias related to

the specific study design used or has been claimed to have been fraudulent or had some other problem).

- Unclear risk: there may be a risk of bias, but there is either: insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.

Measures of treatment effect

We will follow the standard methods of the Cochrane Neonatal Review Group for data synthesis. 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). For each measure of effect we will also calculate the corresponding 95% confidence intervals (CIs). We will present the number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) when RDs are found to be statistically significant (P value < 0.05).

Unit of analysis issues

The unit of randomization will be the intended unit of analysis (individual neonate). If we identify any cluster-randomized trials for inclusion, we will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* Section 16.3.4 or 16.3.6 using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population (Higgins 2011). If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC.

Dealing with missing data

Where data are missing, we will contact the original study investigators to request the missing data. We will obtain a drop-out rate for each study. If we find a significant drop-out rate (greater than 20%), we will contact the author(s) to provide additional data. We will perform a sensitivity analysis to evaluate the overall results with and without the inclusion of studies with significant drop-out rate. If a study reports outcomes only for participants completing the trial or only for participants who followed the protocol, we will contact 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.

Assessment of heterogeneity

We plan to assess clinical heterogeneity by comparing the distribution of important participant factors between trials and trial factors (randomization 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.

We will consider statistical heterogeneity to be substantial when I^2 is greater than 50%. 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 (randomization concealment, blinding of outcome assessment, loss to follow-up, treatment type and co-interventions). We will consider a threshold P value of less than 0.1 as 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 systematic review (Egger 1997; Higgins 2011).

Data synthesis

We will summarize all eligible studies in Review Manager 5 (Revman 2014). We will utilize standard methodologies for meta-analysis as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will use the fixed-effect model and present all our results with 95% CI. We will calculate the RR, RD, and NNTB or NNTH if RD is significant, each with 95% CI, for categorical outcomes; and MD with 95% CI for continuous outcomes. Where continuous outcomes are measured using different scales, the treatment effect will be expressed as standardized mean difference (SMD) with 95% CI. For any outcomes where the included studies are not sufficiently homogeneous, or where insufficient data are available for meta-analysis, we will present a narrative synthesis.

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: all-cause neonatal death, all-cause death during initial hospitalization, duration of mechanical ventilation (days); important outcomes:

intraventricular hemorrhage; duration of mechanical ventilation; major neurodevelopmental disability.

Two authors will independently assess the quality of the evidence for each of the outcomes above. We will consider evidence from randomized 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 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 in one of four grades:

1. High: We are very confident that the true effect lies close to that of the estimate of the effect.
2. 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.
3. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. 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:

1. gestational age: preterm (< 37 weeks' gestational age) vs term infants (≥ 37 weeks); extreme preterm (< 28 weeks) vs preterm infants (≥ 28 but < 37 weeks)
2. birth weight: less than 1500 grams versus greater than or equal to 1500 grams
3. parenteral vs enteral administration of the intervention
4. dose of clonidine (low: < 0.1 mcg/kg/hr; standard: 0.1 to 0.3 mcg/kg/hr; high: ≥ 0.1 to 0.3 mcg/kg/hr)
5. duration of treatment (< 24 hr; 1 to 5 days; ≥ 5 days)
6. with versus without pharmacological sedation and pain management as co-intervention
7. within studies which include co-interventions: studies in which the protocol allows co-interventions for sedation and pain management for one or both of the intervention groups versus studies in which the protocol mandates 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 overestimate the effect of treatment.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Neonatal Pain Scores

1. Comfort-Neo (van Dijk 2009)
2. Échelle Douleur Inconfort Nouveau-Né (neonatal pain and discomfort scale, EDIN) (Debillon 2001)
3. Astrid Lindgren and Lund Children's Hospitals Pain and Stress Assessment Scale for Preterm and sick Newborn Infants (ALPS-Neo) (Lundqvist 2014)
4. Neonatal Infant Pain Scale (NIPS) (Lawrence 1993)
5. Pain Assessment Tool (PAT) (Hodgkinson 1994
6. Premature Infant Pain Profile (PIPP) (Stevens 1996)
7. APN: evaluation behavioral scale of acute pain in newborn infants (Carbajal 1997)
8. Neonatal Facial Coding System (NFCS) (Grunau 1986; Peters 2003)
9. DAN (Douleur Aiguë du Nouveau-né) (Carbajal 2005)
10. ABC Pain Scale (Bellieni 2005)
11. Neonatal Pain, Agitation, and Sedation Scale (N-PASS) (Hummel 2010)
12. 'Faceless' Acute Neonatal pain Scale (FANS) (Milesi 2010)
13. Premature Infant Pain Profile-Revised (PIPP-R) (Gibbins 2014)

Appendix 2. Search methodology

Review-specific terms: (clonidine OR clonidine[MeSH] OR alpha-2 agonists)
Plus database-specific limiters for RCTs and neonates:
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.

DECLARATIONS OF INTEREST

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