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[Intervention Review]

Clonidine for pain in non-ventilated infants

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ABSTRACT

Background

Critically ill newborn infants undergo a variety of painful procedures or experience a variety of painful conditions during their early life in the neonatal unit. In the critically ill paediatric and neonatal population, clonidine is prescribed as an adjunct to opioids or benzodiazepines aiming to reduce the doses of these drugs that are required for analgesia or sedation, or to facilitate weaning from mechanical ventilation. It has been shown that clonidine premedication might have a positive effect on postoperative pain in children.

Objectives

To assess the benefit and harms of clonidine for the prevention or treatment of procedural pain; postoperative pain; or pain associated with clinical conditions in non-ventilated neonates.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the CENTRAL, MEDLINE via PubMed, Embase, and CINAHL to December 2018. We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials. We ran an updated search from 1 January 2018 to 11 March 2020 in CENTRAL via CRS Web, MEDLINE via Ovid, and CINAHL via EBSCOhost.

Selection criteria

Randomised controlled trials, quasi-randomised controlled trials, and cluster trials comparing clonidine to placebo or no treatment, opioids, paracetamol, dexmedetomidine, or non-pharmacological pain-reducing interventions for the management of procedural pain, postoperative pain, and pain associated with clinical conditions in preterm and term newborns.

Data collection and analysis

Two review authors independently planned to extract data (e.g. number of participants, birth weight, gestational age, modality of administration, and dose of clonidine) and assess the risk of bias (e.g. adequacy of randomisation, blinding, completeness of follow-up). The primary outcome considered was pain: for procedural pain, 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, the mean values of each analgesia scale assessed at 30 minutes, three hours, and 12 hours after the administration of the intervention. We planned to use the GRADE approach to assess the quality of evidence.

Main results

Our search strategy yielded 3383 references. Two review authors independently assessed all references for inclusion. We did not find any completed studies for inclusion. We excluded three trials where clonidine was administered for spinal anaesthesia.

Authors' conclusions

We did not find any studies that met our inclusion criteria and hence there is no evidence to recommend or refute the use of clonidine for the prevention or treatment of procedural or postoperative pain, or pain associated with clinical conditions in neonates.

PLAIN LANGUAGE SUMMARY

Clonidine for painful procedures and conditions in infants

Review question: does clonidine administration reduce pain in newborns exposed to painful procedures or conditions?

Background: newborns admitted to the hospital are exposed to a number of painful procedures which might include blood sampling, lumbar puncture (a medical procedure where a needle is inserted into the spinal canal, usually to collect cerebrospinal fluid for testing), tubes in the stomach, different types of catheters, and minor surgical procedures such as neonatal circumcision. In addition, newborns might have pain because of clinical conditions, such as, fractured bone, pain following traumatic vaginal birth, disease of the skin (open skin lesions from an inherited skin disorder), or intestines (necrotising enterocolitis (inflammation)). All babies, and especially those born too early (preterm), are very sensitive to pain. Moreover, the experience of repeated episodes of pain might cause problems, such as an altered development of the nervous system, in early life and an increased pain sensitivity when they grow up. Most of the medicines to manage pain and stress in babies have side effects, and might also harm the immature developing brain by inducing death of cells (apoptosis) in the brain.

Study characteristics: we searched for studies up to 11 March 2020. The aim of this review was to assess if clonidine could reduce pain in newborns. This medicine can be given through injections, using a tube in the stomach (nasogastric tube), through the skin, and as spinal anaesthesia. However, the latter is not in the focus of this review as it is used for babies undergoing specific surgical procedures. Clonidine works on the brain modifying responses and reducing stress and agitation. Furthermore, clonidine may reduce pain, especially if used in combination with other medicines.

Key results: we found no studies for our review. Three studies were excluded because clonidine was given for spinal anaesthesia, whereas our review focuses on other indications.

BACKGROUND

Description of the condition

The importance of pain in neonates was not recognised 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 localisation 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 stressful and painful (Carbajal 2008). Other investigators have reported a similar number of painful procedures: Barker 1995 reported a mean 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 one 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 minimise these complications remains a challenge in everyday clinical care (McPherson 2012). Non-pharmacological 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 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 for procedures such as chest tube insertion, for premedication for intubation or for conditions such as necrotising enterocolitis. The dosage of these drugs varies between studies, the effects are uncertain at procedural pain (Anand 2004; Simons 2003), 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 neuroapoptosis (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; Ma 2007; McPherson 2007). Several other pharmacological agents, such as methadone, ketamine, and propofol have been suggested, and used, for analgesia and sedation 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 total amount of opioid needed (Ceelie 2013). However, concerns on neurodevelopment have been raised about the safety of paracetamol (Bauer 2013; Viberg 2014). The use of non-steroidal 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), mainly 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 located in the locus coeruleus, which is a nucleus in the pons of the brainstem and the main site for brain synthesis of noradrenaline (norepinephrine). 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). It is worth noting that one study in newborn rats showed that intrathecal administration (via the spine) of clonidine did not induce signs of spinal histopathology (Walker 2012). The two main adverse effects of α2-agonists are bradycardia (slow heartbeat) 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).

In the critically ill paediatric and neonatal population, clonidine is routinely prescribed as an adjunct to opioids, benzodiazepines, or both, aiming at reducing the doses of these drugs required for analgesia or sedation, to facilitate weaning from mechanical ventilation, or for the management of neonatal abstinence syndrome (Duffett 2012). Furthermore, clonidine has been shown

to reduce pain, discomfort, and agitation in a paediatric population following sevoflurane anaesthesia (Tesoro 2005). One Cochrane Review showed that clonidine premedication might have a positive effect on postoperative pain in the paediatric population (neonates not included) (Lambert 2014).

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, one systematic review was published on clonidine for sedation, analgesia, and iatrogenic drug withdrawal in critically ill infants and children (Capino 2016). However, this review included only mechanically ventilated infants and children. Similarly, one Cochrane Review including one trial (Hünseler 2014) assessed the effects of clonidine in ventilated newborns (Romantsik 2017).

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 noradrenaline (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, for the management of postoperative pain and pain associated with clinical conditions in neonates. 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 α2-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. necrotising 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 adverse effects in that population. The PK, PD, PG, or 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 (electroencephalogram (EEG)) and cerebral haemodynamics (near-infrared spectrophotometry (NIRS)) are of major interest for the evaluation of the drug effects and adverse 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 adverse effects of opioids; however, more knowledge about the drug is needed in order to make safe recommendations.

OBJECTIVES

To assess the benefit and harms of clonidine for the prevention or treatment of procedural pain; postoperative pain; or pain associated with clinical conditions in non-ventilated neonates.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials, quasi-randomised controlled trials, and cluster-randomised trials. We excluded cross-over trials.

Types of participants

Full-term and preterm infants less than 44 weeks' postmenstrual age (PMA) requiring pain management during their hospital stay or as outpatients for:

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

We excluded studies where clonidine infusion was administered in ventilated newborns, as this was addressed in another Cochrane Review (Romantsik 2017). However, we included studies where clonidine infusion was administered in ventilated newborns if the intervention specifically aimed 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 have been delivered intravenously, orally (or via nasogastric tube), or transdermally. We included studies that reported on single administration of clonidine or multiple (repeated) doses of clonidine over a prolonged period during the initial hospital stay. We excluded studies that compared clonidine with local or regional anaesthesia.

We assessed procedural pain, postoperative pain, and pain associated with clinical conditions in separate comparisons.

Clonidine was compared with placebo or no intervention; opioids; paracetamol; dexmedetomidine; or non-pharmacological pain-reducing interventions (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-pharmacological 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 planned to perform subgroup analyses according to gestational age (term 37 weeks' gestation or greater); preterm (less than 37 weeks' gestation); extreme preterm infants (less than 28 weeks' gestation); birth weight for gestational age (small, appropriate, large for gestational age); type of pain; dose, duration, and route of clonidine administration; and pharmacological sedation as a co-intervention (see Subgroup analysis and investigation of heterogeneity).

Types of outcome measures

Primary outcomes

- Pain assessed using the pain scales listed in Table 1.

For procedural pain, we planned to 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 planned to 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

For procedural pain – low-intensity pain.

- Completion of the targeted objective (relief of procedural pain) without use of any other agent.
- Episodes of apnoea (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 during the procedure and at one to two hours after the procedure.
- Parent satisfaction with care provided in the NICU (as measured by a validated instrument/tool) (Butt 2013).

For procedural pain – high-intensity pain.

- Completion of the targeted objective (relief of procedural pain) without use of any other agent.
- Any intraventricular haemorrhage (IVH) (yes/no): any IVH, grades 1 to 4 (according to the Papile 1978 classification); severe IVH (grades 3 and 4).
- Episodes of apnoea (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 during the procedure and at one to two hours after the procedure.
- 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).

For postoperative pain and for pain associated with clinical conditions.

- Neonatal mortality.
- Mortality during initial hospitalisation.
- Completion of the targeted objective (relief of pain associated with clinical conditions) without use of any other agent.
- Any 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).
- Necrotising enterocolitis (yes/no): any grade; requiring surgery.
- Time to full enteral feeding (days).
- Episodes of apnoea (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 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);
  - sensorineural deafness requiring amplification (Jacobs 2013);
  - we planned to evaluate each of these components as a separate outcome and to extract data on this long-term

outcome from studies that evaluated children after 18 months of chronological age. Data on children aged 18 to 24 months and those aged three to five years were to be assessed separately.

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal Standard Search Strategy; neonatal.cochrane.org/resources-authors/author-resources-new-reviews). We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and reported the date this was done.

Electronic searches

We conducted a comprehensive search including: the Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 12) in the Cochrane Library; MEDLINE via PubMed (1996 to 3 December 2018); Embase (1980 to 3 December 2018); and CINAHL (1982 to 3 December 2018) using the following search terms: (clonidine[MeSH] OR clonidine OR alpha-2 agonists), plus database-specific limiters for randomised controlled trials and neonates (see Appendix 1 for the full search strategies for each database). We applied no language restrictions. We searched clinical trials registries for ongoing or recently completed trials (ClinicalTrials.gov (clinicaltrials.gov); the World Health Organization's International Clinical Trials Registry Platform (apps.who.int/trialsearch/), and the ISRCTN Registry (www.isrctn.com/)).

We conducted a comprehensive update search in March 2020 including: Cochrane Central Register of Controlled Trials (CENTRAL 2020, Issue 3) in the Cochrane Library; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) (1 January 2018 to 11 March 2020); and CINAHL (1 January 2018 to 11 March 2020). We included the search strategies for each database in Appendix 2. We applied no language restrictions.

We searched clinical trial registries for ongoing or recently completed trials. We searched the World Health Organization's International Clinical Trials Registry Platform (apps.who.int/trialsearch/) and the U.S. National Library of Medicine's ClinicalTrials.gov (clinicaltrials.gov) via Cochrane CENTRAL. Additionally, we searched the ISRCTN Registry (www.isrctn.com/) for any unique trials not found through the Cochrane CENTRAL search.

Searching other resources

Additionally, we reviewed 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

Two review authors (OR, MB) independently screened the titles and abstracts to identify potentially relevant citations, retrieved the full texts of all potentially relevant articles, and assessed the eligibility of the studies by filling out eligibility forms designed in accordance with the specified inclusion criteria. We reviewed studies for relevance based on study design, types of participants, interventions, and outcome measures. We resolved any disagreements by discussion and, if necessary, by consulting a third review author (MC). We provided details of studies excluded from the review in the Characteristics of excluded studies table along with the reasons for exclusion. We planned to contact the trial authors if the details of the primary trials were unclear to request further information.

Data extraction and management

Two review authors (OR, MB) planned to independently 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 2017).

We planned to 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 study: study design; type, duration, and completeness of follow-up (e.g. greater than 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 planned to resolve any disagreement by discussion between the review authors.

We described any ongoing studies identified, detailing the primary author, research question(s), methods and outcome measures, and an estimate of the reporting date.

When queries arose or when additional data were required, we planned to contact the authors of the trial reports. Two review authors (MC, MB) planned to use Review Manager 5 software to enter all the data (Review Manager 2014).

Assessment of risk of bias in included studies

Two review authors (OR, MC) planned to independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2011):

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- any other bias.

We planned to resolve any disagreements by discussion or through a third review author (MB). See Appendix 3 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We planned to extract categorical data for each intervention group and calculate risk ratios (RRs) and absolute risk differences (RDs). We planned to obtain means and SDs for continuous data, and perform analyses using mean differences (MDs) when studies used the same pain scale. We planned to calculate standardised mean differences (SMDs) when studies used different pain scales. For each measure of effect, we planned to calculate the corresponding 95% confidence intervals (CIs). We planned to 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 were statistically significant ($P < 0.05$).

Unit of analysis issues

The unit of analysis was the individual infant. For multiple painful procedures, we considered the first procedure performed in the randomised infant. The unit of analysis for cluster-randomised trials was the randomised treating centre or cluster. We planned 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 planned to contact the original study investigators to request additional data where information about critical and important outcomes was missing (see the list of the clinically relevant outcomes in Data synthesis). We planned to investigate attrition rates (e.g. dropouts, losses to follow-up, and withdrawals). We planned to perform a sensitivity analysis to evaluate the overall results with and without the inclusion of studies with significant dropout rates. If a study reported outcomes only for participants completing the trial, or only for participants who followed the protocol, we planned to contact the author(s) and ask them to provide additional information to facilitate an intention-to-treat analysis; and in instances where this was not possible we would have performed a complete-case analysis. We planned to address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

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

- less than 25%: no heterogeneity;
- 25% to 49%: low heterogeneity;
- 50% to 74%: moderate heterogeneity;
- 75% or greater: high heterogeneity.

In addition, we planned to employ the Chi^2 test of homogeneity to determine the strength of evidence that heterogeneity is genuine. We planned to 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 planned to consider a threshold P value of less than 0.1 as an indicator of whether heterogeneity (genuine variation in effect sizes) is present.

Assessment of reporting biases

We planned to investigate publication bias using funnel plots if at least 10 clinical trials were included in the meta-analysis (Egger 1997; Higgins 2011)

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

We planned to present data from the following subgroups:

- gestational age: term infants (37 weeks' gestation or greater); preterm infants (less than 37 weeks' gestation); extreme preterm (less than 28 weeks' gestation);
- birth weight: under 1500 g; 1500 g or more;
- type of pain:
  - 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);
  - painful clinical conditions: including a fractured long bone, necrotising enterocolitis, open skin lesions from an inherited skin disorder, or pain from an assisted vaginal birth;
- dose of clonidine:
  - for infusion administration: less than 0.3 µg/kg/hour) versus 0.3 µg/kg/hour to 1 µg/kg/hour versus greater than 1 µg/kg/hour;
  - for bolus administration: less than 2 µg/kg versus 2 µg/kg to 4 µg/kg versus greater than 4 µg/kg;
- duration of treatment (less than 24 hours; one to five days; five days or greater);
- route of administration: parenteral; enteral; transdermal;
- with versus without pharmacological 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 planned to 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 overestimated the effect of treatment.

Summary of findings and assessment of the certainty of the evidence

We planned to use the GRADE approach, as outlined in the GRADE Handbook to assess the quality of evidence for the following (clinically relevant) outcomes (gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html; Schünemann 2013):

- For procedural pain – low-intensity pain:
  - validated pain scale (Table 1);
  - completion of the targeted objective (relief of procedural pain) without use of any other agent;
  - episodes of apnoea (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 during the procedure and at one to two hours after the procedure;
  - parent satisfaction with care provided in the NICU (as measured by a validated instrument/tool) (Butt 2013).
- For procedural pain – high-intensity pain:
  - validated pain scale (Table 1);
  - completion of the targeted objective (relief of procedural pain) without use of any other agent;
  - episodes of apnoea (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 during the procedure and at one to two hours after the procedure;
  - parent satisfaction with care provided in the NICU (as measured by a validated instrument/tool) (Butt 2013).
- For postoperative pain and for pain associated with clinical conditions:
  - validated pain scale (Table 1);
  - neonatal mortality;
  - episodes of apnoea (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;
  - parent satisfaction with care provided in the NICU (as measured by a validated instrument/tool) (Butt 2013).

Two review authors planned to independently assess the certainty of the evidence for each of the outcomes above. We planned to consider evidence from randomised controlled trials as high certainty 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 planned to use GRADEpro GDT to create a 'Summary of findings' table to report the certainty of the evidence.

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

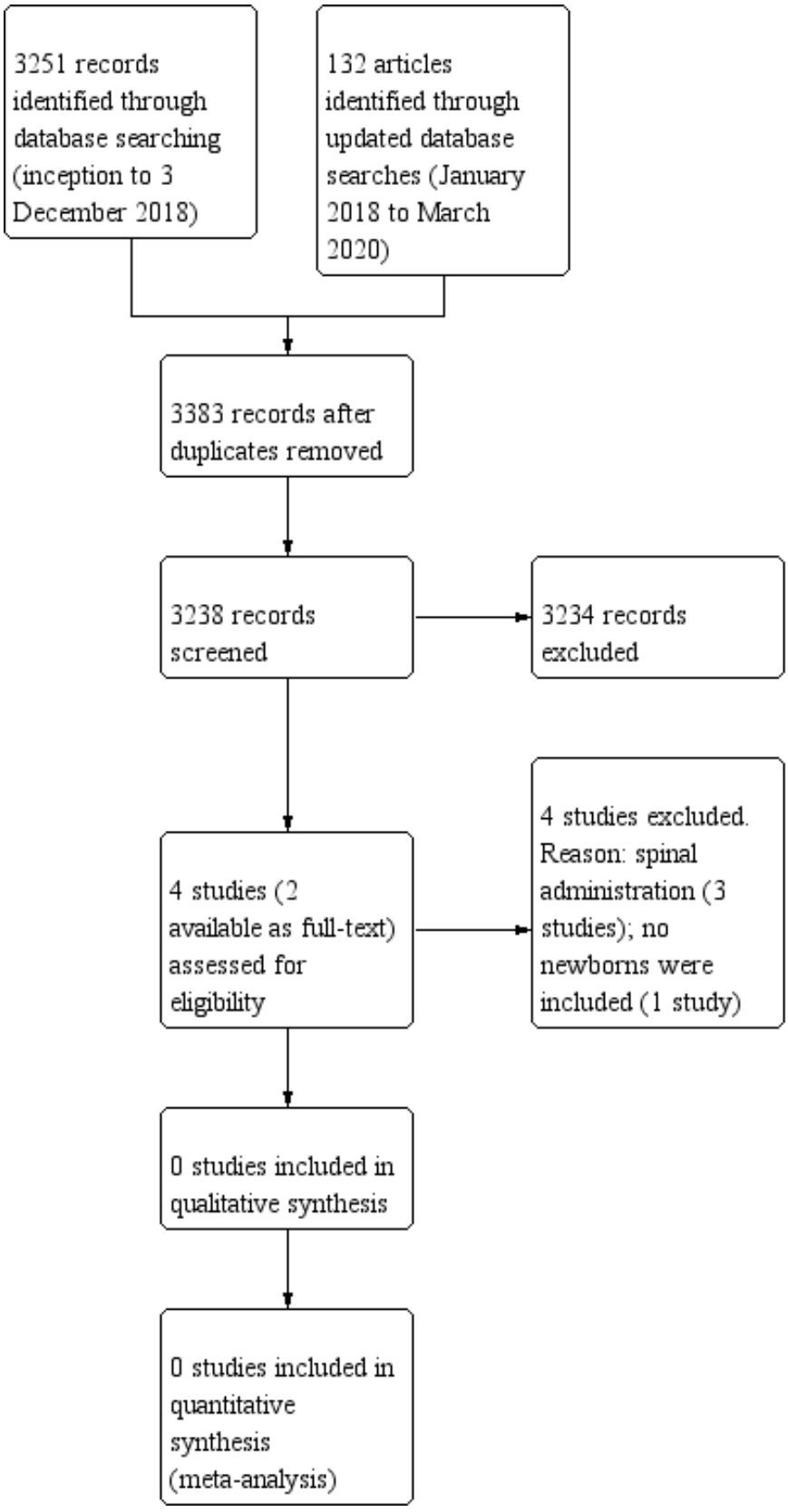
- high: we are very confident that the true effect lies close to that of the estimate of the effect;
- moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- low: 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.

RESULTS

Description of studies

We provided results of the search in the study flow diagram (Figure 1).

Figure 1. Study flow diagram.



See Characteristics of excluded studies, Characteristics of ongoing studies, and Characteristics of studies awaiting classification tables.

Results of the search

The literature search conducted in December 2018 and March 2020 identified 3383 references after removing duplicates. After screening, we assessed four studies for eligibility: three trials were excluded because of the route of administration (Batra 2010; Delous 2010; Rochette 2004). In addition, one study was classified as 'awaiting classification' because the abstract was not available (we tried to contact the study authors with no success) (Rochette 1998).

Our search of ClinicalTrials.gov identified 27 registered studies, ICTRP identified 10, ISRCTN registry identified one, and Luxid Biopharma Navigator identified 58. Only one ongoing trial was eligible (NCT01075490; see Characteristics of ongoing studies table). However, it is possible that this study has been completed and corresponds to one of the 'Excluded studies' described above (likely Delous 2010).

Included studies

We identified no trials that matched our inclusion criteria.

Excluded studies

We excluded three trials because they administered clonidine for spinal anaesthesia (Batra 2010; Delous 2010; Rochette 2004). In addition, one studies included no newborns (Batra 2010).

Two studies compared clonidine to placebo (Delous 2010; Rochette 2004); Rochette 2004 was a dose-ranging study with four different doses of clonidine. The third excluded study had four arms: no intervention; clonidine; fentanyl; clonidine plus fentanyl (bupivacaine as co-intervention in each arm of the study) (Batra 2010).

Risk of bias in included studies

No study met the eligibility criteria of this review.

Effects of interventions

No study met the eligibility criteria of this review.

DISCUSSION

Summary of main results

We identified no eligible randomised controlled trials for inclusion that compared clonidine versus placebo, no intervention, or other interventions for the prevention or treatment of procedural or postoperative pain, or pain associated with clinical conditions in neonates. We excluded three studies that administered clonidine for spinal anaesthesia (Batra 2010; Delous 2010; Rochette 2004). Moreover, there were no newborns in the study of Batra 2010. Two of studies reported longer spinal anaesthesia when clonidine 1 µg/kg was co-administered (Delous 2010; Rochette 2004).

We identified one ongoing trial (NCT01075490), which might be the protocol of one of the 'Excluded studies' described above (Delous 2010).

Overall completeness and applicability of evidence

We identified no eligible studies for inclusion.

Quality of the evidence

We identified no eligible studies for inclusion.

Potential biases in the review process

We used the standard methods of Cochrane Neonatal to conduct this systematic review. Our inclusive search strategy would theoretically have included all relevant studies. We minimised any potential biases, though the choice of the criteria for considering studies for inclusion in this review (namely Types of interventions) led to the exclusion of three studies where clonidine was administered for spinal anaesthesia (Batra 2010; Delous 2010; Rochette 2004).

Agreements and disagreements with other studies or reviews

One prospective observational study on clonidine in newborns has been reported by the same group as one of the excluded studies in this review (Rochette 2005). The cohort included 124 preterm and term infants undergoing herniorrhaphy under spinal anaesthesia with bupivacaine and clonidine. Apnoea episodes increased in the postoperative period, whereas desaturation episodes and mean arterial pressure were not affected. Short, transient bradycardias occurred in former preterm infants.

One Cochrane Review including 11 studies (neonates not included) on clonidine premedication in children undergoing surgery showed that oral administration of clonidine at 4 µg/kg reduced the need for additional analgesia without the usual adverse effects (Lambert 2014). However, some of the included studies administered atropine prophylactically to prevent bradycardia and hypotension. The interpretation of the effect of clonidine on pain scales was complicated because of the use of different pain scales and heterogeneity in the characteristics of the interventions and study design.

One systematic review of randomised controlled trials reported prolonged duration of analgesia when clonidine was used as an additive in spinal anaesthesia administered to children (neonates not included) (Ansermino 2003). The addition of clonidine 1 µg/kg to 2 µ/kg to local anaesthetic prolonged the duration of analgesia by two to three hours and increased sedation scores. However, there was respiratory depression in some infants. More evidence appears to be available for spinal administration rather than other routes of administration.

AUTHORS' CONCLUSIONS

Implications for practice

We found no studies that met our inclusion criteria and hence there is no evidence to recommend or refute the use of clonidine for the prevention or treatment of procedural or postoperative pain, or pain associated with clinical conditions in neonates.

Implications for research

Future research might assess the effects in the neonatal population, in both term and preterm newborns, by using validated and

adequate pain scales. In addition, the use of clonidine might be explored for other routes of administration and in combination with opioids.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Batra 2010	No newborns included.
Delous 2010	Spinal administration of clonidine. RCT in 47 preterm and 63 term newborns. Infants were randomised to either clonidine 1 µg/kg or saline. Both groups received spinal anaesthesia with bupivacaine 1 mg/kg. Spinal anaesthesia was prolonged in the clonidine group in both preterm and term infants. Incidence and severity of apnoea did not differ between clonidine and control. Available as an abstract only.
Rochette 2004	Spinal administration of clonidine. RCT in 75 neonates, including 50% of former preterm infants, undergoing elective inguinal herniorrhaphy. Used clonidine 0.25 µg/kg, 0.5 µg/kg, 1 µg/kg, or 2 µg/kg, or no intervention. Both groups received spinal anaesthesia with bupivacaine 1 mg/kg. Infants receiving clonidine 1 µg/kg doubled the duration of spinal block compared to the control group. Infants receiving the highest dose of clonidine (2 µg/kg) were affected more often with transient hypotension and need for caffeine administration.

RCT: randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Rochette 1998

Methods	Not reported in the title of the publication. Abstract and full-text not available
Participants	Newborns
Interventions	Clonidine + bupivacaine during spinal anaesthesia
Outcomes	Not reported in the title of the publication. Abstract and full-text not available
Notes	We tried to contact the study authors without success.

Characteristics of ongoing studies *[ordered by study ID]*

NCT01075490

Trial name or title	Neonatal spinal anaesthesia: effects of the addition of clonidine
Methods	Randomised controlled trial
Participants	Preterm and term infants, requiring inguinal hernia or lower limbs surgery. Sample size: 120
Interventions	Addition of clonidine 1 µg/kg or saline to bupivacaine 1 mg/kg as spinal anaesthesia
Outcomes	Primary outcome: number of rescue general anaesthesia

NCT01075490 *(Continued)*	Secondary outcomes: apnoea and desaturation occurrence; duration of spinal anaesthesia
Starting date	November 2006
Contact information	Alain Rochette, Montpellier, France; E-mail: a-rochette@chu-montpellier.fr
Notes	We tried to contact the study authors without success. It is possible that this study has been completed and corresponds to 1 of the 'Excluded studies'.

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 1998; 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
Preterm 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. 2018 Search methods

PubMed, 3 December 2018

#1 (((randomized controlled trial [pt]) OR controlled clinical trial [pt]) OR (((randomized[Title/Abstract] OR randomized[Title/Abstract] OR randomly[Title/Abstract] OR placebo[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract] OR study[Title/Abstract])) OR drug therapy[MeSH Subheading])) OR cluster[Title/Abstract] 9,569,823

#2 ((((premature OR prematures OR prematurity OR preterms OR preterm OR very low birth OR low birth weight* OR vlbw OR lbw OR "Infant, Extremely Premature"[Mesh] OR "Infant, Premature"[Mesh] OR "Infant, Low Birth Weight"[Mesh])) OR (newborn OR newborns OR neonate OR neonates OR neonatal OR neonat* OR infant OR infants OR infan* OR "Infant, Newborn"[Mesh]))) 1,547,106

#3 (("Clonidine"[Mesh] OR clonidine)) OR ("Adrenergic alpha-2 Receptor Agonists" [Pharmacological Action] OR "Adrenergic alpha-2 Receptor Agonists"[Mesh]) 29,248

#4 #1 AND #2 AND #3 840

Embase, 4 December 2018

#1. 'infant'/exp OR infant* OR infan* OR 'neonate'/exp OR neonate* OR neonat* OR 'newborn'/exp OR newborn* OR 'low birth weight'/exp OR 'low birth weight*' OR vlbw OR lbw OR 'very low birth weight'/exp OR 'very low birth' OR 'prematurity'/exp OR prematurity OR premature* OR preterm* 1,662,161

#2. 'clonidine'/exp OR clonidine 42,568

#3. 'alpha 2 adrenergic receptor stimulating agent'/exp 98,020

#4. #2 OR #3 99,698

#5. #1 AND #4 4,232

#6. 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'controlled clinical trial'/exp OR 'controlled clinical trial' OR randomized:ti,ab OR randomised:ti,ab OR randomly:ti,ab OR placebo:ti,ab OR trial:ti,ab OR study:ti,ab OR 'clinical trial'/exp OR cluster:ti,ab 10,165,392

#7. #1 AND #4 AND #6 1,676

#8. #5 AND 'drug therapy'/lnk 1,868

#9. #1 AND #4 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) 246

#10. #7 OR #8 OR #9 2,814

CINAHL, 6 December 2018

S1	(MH "Clonidine") OR clonidine	1,632
S2	alpha 2 agonists	664
S3	premature* OR prematurity OR preterm* OR very low birth OR low birth weight* OR vlbw OR lbw OR infant OR infan* OR newborn* OR neonate* OR neonat*	407,226
S4	(MH "Infant+") OR (MH "Infant, Newborn+")	217,072
S5	S3 OR S4	407,226

(Continued)

S6	S1 OR S2	2,193
S7	randomized controlled trial* OR controlled clinical trial OR randomized OR randomised OR randomly OR placebo OR trial OR groups OR study OR PT clinical trial OR clinical trial as topic OR cluster	2,230,803
S8	S5 AND S6 AND S7	139

The Cochrane Library, 6 December 2018

#1 (clonidine):ti,ab,kw (Word variations have been searched) 3,497

#2 MeSH descriptor: [Clonidine] explode all trees 1,809

#3 MeSH descriptor: [Adrenergic alpha-2 Receptor Agonists] explode all trees 225

#4 #1 OR #2 OR #3 3,636

#5 (infant OR infants OR newborn OR newborns OR neonate OR neonates OR neonatal OR premature OR prematures OR preterm OR preterms OR low birth weight OR vlbw OR lbw):ti,ab,kw (Word variations have been searched) 66,171

#6 #4 AND #5 168

Searches in clinical trial registries, 16 December 2018

Clinicaltrials.gov

Advanced search

Intervention/treatment: clonidine
Other terms: premature OR prematurity OR preterms OR preterm OR “very low birth” OR “low birth weight” OR newborn OR newborns OR neonate OR neonates OR infant OR infants
No further limits applied
27 results

https://clinicaltrials.gov/ct2/results?term=premature+OR+prematurity+OR+preterms+OR+preterm+OR+%E2%80%9Cvery+low+birth%E2%80%9D+OR+%E2%80%9Clow+birth+weight%E2%80%9D+OR+newborn+OR+newborns+OR+neonate+OR+neonates+OR+infant+OR+infants&intr=clonidine&age_v=&gndr=&type=&rslt=&Search=Apply

ICTRP / WHO

Advanced search

Title: premature OR prematurity OR preterms OR preterm OR very low birth OR low birth weight OR newborn OR newborns OR neonate OR neonates OR infant OR infants
Intervention: clonidine
Ticked box: search for clinical trials in children
Recruitment status: ALL, Phases: ALL

Simple search

Infant* AND clonidine

Prematur* AND clonidine

Preterm* AND clonidine

Low birth AND clonidine

Newborn* AND clonidine

Neonate* AND clonidine

10 results

ISRCTN registry
Text search: Clonidine AND (premature OR prematurity OR preterms OR preterm OR newborn OR newborns OR neonate OR neonates OR infant OR infants)

1 result

http://www.isrctn.com/search?q=Clonidine+AND+%28premature+OR+prematurity+OR+preterms+OR+preterm+OR+newborn+OR+newborns+OR+neonate+OR+neonates+OR+infant+OR+infants%29

Luxid Biopharma Navigator

"Clonidine" AND (premature OR prematurity OR preterms OR preterm OR newborn OR newborns OR neonate OR neonates OR infant OR infants)

58 results

Appendix 2. 2020 Search methods

The RCT filters have been created using Cochrane's highly sensitive search strategies for identifying randomised trials (Higgins 2019). The neonatal filters were created and tested by the Cochrane Neonatal Information Specialist.

CENTRAL via CRS Web:

Date ranges: 01 January 2018 to 11 March 2020
Terms:
1 MESH DESCRIPTOR Clonidine EXPLODE ALL AND CENTRAL:TARGET
2 clonidine AND CENTRAL:TARGET
3 MESH DESCRIPTOR Adrenergic alpha-2 Receptor Agonists EXPLODE ALL AND CENTRAL:TARGET
4 (adrenergic ADJ2 "alpha 2" ADJ2 agonist*) AND CENTRAL:TARGET
5 (adrenergic ADJ2 "alpha 2" ADJ2 receptor ADJ2 agonist*) AND CENTRAL:TARGET
6 MESH DESCRIPTOR Adrenergic alpha-Agonists EXPLODE ALL AND CENTRAL:TARGET
7 (adrenergic ADJ2 alpha ADJ2 agonist*) AND CENTRAL:TARGET
8 (alpha ADJ2 adrenergic ADJ2 receptor ADJ2 agonist*) AND CENTRAL:TARGET
9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10 MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND CENTRAL:TARGET
11 infant or infants or infant's or "infant s" or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU AND CENTRAL:TARGET
12 #11 OR #10 AND CENTRAL:TARGET
13 #12 AND #9
14 2018 TO 2020:YR AND CENTRAL:TARGET
15 #14 AND #13

MEDLINE via Ovid:

Date ranges: 01 January 2018 to 11 March 2020
Terms:
1. exp Clonidine/
2. clonidine.mp.
3. exp Adrenergic alpha-2 Receptor Agonists/
4. (adrenergic adj2 "alpha 2" adj2 agonist*).mp.
5. (adrenergic adj2 "alpha 2" adj2 receptor adj2 agonist*).mp.
6. exp Adrenergic alpha-Agonists/
7. (adrenergic adj2 alpha adj2 agonist*).mp.
8. (alpha adj2 adrenergic adj2 receptor adj2 agonist*).mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp infant, newborn/
11. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or 'infant s' or infant's or infantile or infancy or neonat*).ti,ab.
12. 10 or 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.

16. placebo.ab.
17. drug therapy.fs.
18. randomly.ab.
19. trial.ab.
20. groups.ab.
21. or/13-20
22. exp animals/ not humans.sh.
23. 21 not 22
24. 12 and 23
25. randomi?ed.ti,ab.
26. randomly.ti,ab.
27. trial.ti,ab.
28. groups.ti,ab.
29. ((single or doubl* or tripl* or treb*) and (blind* or mask*)).ti,ab.
30. placebo*.ti,ab.
31. 25 or 26 or 27 or 28 or 29 or 30
32. 11 and 31
33. limit 32 to yr="2018 -Current"
34. 24 or 33
35. 9 and 34
36. limit 35 to yr="2018 -Current"

CINAHL via EBSCOhost:

Date ranges: 01 January 2018 to 11 March 2020
Terms:
(clonidine OR (adrenergic AND "alpha 2" AND agonist*) OR (adrenergic AND "alpha 2" AND receptor AND agonist*) OR (adrenergic AND alpha AND agonist*) OR (alpha AND adrenergic AND receptor AND agonist*)) AND
(infant or infants or infant's or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW) AND
(randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
Limiters - Published Date: 20180101-20200331

ISRCTN:

Date ranges: 2018 to 2020
Terms: Clonidine AND (premature OR prematurity OR preterms OR preterm OR newborn OR newborns OR neonate OR neonates OR infant OR infants)

Appendix 3. 'Risk of bias' tool

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

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

For each included study, we planned to categorise 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); or
- unclear risk.

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

For each included study, we planned to categorise 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);
- or unclear risk.

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

For each included study, we planned to categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

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

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

For each included study, we planned to categorise the methods used to blind outcome assessment. Blinding was to be assessed separately for different outcomes or class of outcomes. We planned to categorise the methods as:

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

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

For each included study and for each outcome, we planned to describe the completeness of data including attrition and exclusions from the analysis. We planned to 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 was reported or supplied by the trial authors, we planned to re-include missing data in the analyses. We planned to categorise the methods as:

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

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

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

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

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

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

WHAT'S NEW

Date	Event	Description
21 April 2020	Amended	Duplicate text ' Summary of findings and assessment of the certainty of the evidence' removed from Data synthesis section

CONTRIBUTIONS OF AUTHORS

OR: reviewed the literature and wrote the review.

MC: assisted in the review of literature and in writing of the review.

EN: commented on and reviewed the review.

MB: reviewed the literature and wrote the review.

DECLARATIONS OF INTEREST

OR: none.

MC: none.

EN: none.

MB: none.

SOURCES OF SUPPORT

Internal sources

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

  to OR, EN and MB
- Istituto Giannina Gaslini, Genoa, Italy.

  to MC

External sources

- Vermont Oxford Network, USA.

  Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title has been changed from "Clonidine for painful procedures or conditions in infants" to "Clonidine for pain in non-ventilated infants" to reflect the broad inclusion criteria for both low-intensity and high-intensity painful procedures or conditions (Romantsik 2018).

The search strategy has been updated following the publication of the protocol and is reported in Appendix 1.

The description of the outcomes has been rearranged. We further limited the outcomes in the 'Summary of findings' table based on editorial input.

As of July 2019, Cochrane Neonatal no longer searches Embase for its reviews. Randomised controlled trials and controlled clinical trials from Embase are added to the Cochrane Central Register of Controlled Trials (CENTRAL) via a robust process (see 'How CENTRAL is created' at www.cochranelibrary.com/central/central-creation). Cochrane Neonatal has validated their searches to ensure that relevant Embase records are found while searching CENTRAL.

Also starting in July 2019, Cochrane Neonatal no longer searches for randomised controlled trials and controlled clinical trials from ClinicalTrials.gov (clinicaltrials.gov) or from World Health Organization's International Clinical Trials Registry Platform (apps.who.int/trialsearch/), as records from both platforms are added to CENTRAL on a monthly basis (see 'How CENTRAL is created' at www.cochranelibrary.com/central/central-creation). Comprehensive search strategies are executed in CENTRAL to retrieve relevant records. The ISRCTN Registry (at www.isrctn.com/, formerly Controlled-trials.com), is searched separately.

For the 2020 update, we ran searches in the following databases: CENTRAL via CRS Web, MEDLINE via Ovid, and CINAHL via EBSCOhost. The search strategies are available in Appendix 2. The previous search methods are available in Appendix 1.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics [*therapeutic use]; Clonidine [*therapeutic use]; Pain, Postoperative [*prevention & control]; Pain, Procedural [*drug therapy] [prevention & control]

MeSH check words

Humans; Infant, Newborn