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[Intervention Protocol]

Pharmacological interventions for pain and sedation management in newborn infants undergoing therapeutic hypothermia

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ABSTRACT

Objectives

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

To determine the effects of pharmacological interventions for pain and sedation management in newborn infants undergoing therapeutic hypothermia.

BACKGROUND

Description of the condition

Hypoxic-ischemic encephalopathy is a leading cause of mortality and long-term neurological sequelae, affecting more than one million newborn infants every year (Lee 2013). Standard management in neonatal intensive care units (NICUs) consists of providing supportive care to maintain cerebral perfusion and metabolic balance. Therapeutic hypothermia can improve survival without disability in infants with moderate to severe hypoxic-ischemic encephalopathy following peripartum asphyxia (Gunn 2017; Jacobs 2013). Additional therapies are under investigation and include erythropoietin, allopurinol, xenon, topiramate, and magnesium sulphate; findings from trials on stem cell-based interventions for hypoxic-ischemic encephalopathy are not yet available (Bruschettini 2020). Therapeutic hypothermia should be initiated within six hours after birth and is maintained for 72 hours (Wassink 2019). So far only late-preterm and full-term asphyxiated infants are treated with therapeutic hypothermia; limited results are available on therapeutic hypothermia in preterm infants (Herrera 2018; Laptook 2016). The main modalities are selective head cooling, which is performed with a helmet, and total-body cooling, where the infant lies on a thermal mattress. The latter is more widely used also because it is associated with servo-controlled temperature regulation (Wassink 2019). Infants undergoing therapeutic hypothermia are in need of adequate management for pain and sedation due to their clinical condition and the need for intensive care, such as cooling and respiratory support. The therapeutic hypothermia by itself seems to be associated with stress and pain (Axelin 2013; Hoffman 2013; Üner 2019). Painful procedures in the newborn period can affect pain responses later in life (Walker 2019), impair brain development (Williams 2020), and possibly have a long-term negative impact on neurodevelopment and quality of life (Chau 2019; Walker 2017).

Description of the intervention

The newborn infant undergoing therapeutic hypothermia is exposed to a higher number of painful procedures than other infants admitted to the NICU (Axelin 2013). The discomfort and pain, which the newborn infant may experience as stress, is caused by procedures (such as intubation, mechanical ventilation, or blood sampling) and might be augmented by the therapeutic hypothermia itself. Induced hypothermia produces significant stress, together with the painful procedures and interventions the asphyxiated infant often undergoes such as blood tests and ventilator treatment (Wassink 2015). It is recommended that infants treated with therapeutic hypothermia be provided with optimal analgesia and sedation (de Haan 2012; McPherson 2020; Üner 2019). However, there is no consensus regarding the use of analgesia or sedation during neonatal therapeutic hypothermia (Üner 2019). Protocols for sedation and analgesia management are rarely reported in studies on therapeutic hypothermia. To further complicate the treatment of pain and stress in this already vulnerable patient group, the encephalopathic newborn often has subtle signs of pain and neurological symptoms that can resemble symptoms of pain (Üner 2019), making the use of pain scales otherwise used in a neonatal context more difficult. Since hypothermia causes a reduction in heart rate by 10/min, with each degree celsius a well-sedated newborn is expected to have a heart rate of around 100/min. A heart rate of greater than 110 to 120 has been suggested to be a sign of inadequate sedation and analgesia (Ergenekon 2016).

Opioids have varying pharmacokinetic and pharmacodynamic profiles, and should optimally be administered in an individualized way according to the need, clinical state, and expected course of the hospitalization. Morphine can be administered by both intravenous and oral routes, whereas fentanyl and remifentanil are only used intravenously. Morphine is an agonist of the μ and k receptors (Pacifici 2016), and acts by binding to opiate receptors in the central and peripheral nervous system, exerting analgesic effect by stimulation of descending inhibitory pathways. Morphine is primarily metabolized by the liver, and pharmacokinetics differ considerably between neonates (Donato 2020). Adverse effects include miosis, pruritus, respiratory depression, constipation, urinary retention, and hypotension. Fentanyl is frequently used due to its effectiveness and high lipid solubility. It is a synthetic opioid and, compared to morphine, crosses the blood-barrier more rapidly, and its half-life time is shorter. Fentanyl has an onset of action of 3 minutes and a duration of effect of 30 minutes (Pacifici 2014; Schiller 2018). If opioids are administered to the infant for less than three days and in the absence of severe pain, a complete and abrupt cessation is recommended (Balda 2019).

Alpha-2 agonists such as clonidine and dexmedetomidine activate the alpha-2 receptors in the central nervous system, decreasing sympathetic activity (Donato 2020). Clonidine has analgesic properties and can reduce the need for opiates and benzodiazepines. Clearance in infants is reduced because of pathway immaturity or renal disease. Adverse effects include hypotension, rebound hypertension, atrioventricular block, and bradycardia. Contrary to opioids, alpha-2 agonists such as clonidine do not cause respiratory depression. Though primarily used as adjunctive therapy to opioids, alpha-2 agonists might be administered in monotherapy (O'Mara 2018).

Ketamine, an N-Methyl-d-aspartate (NMDA) receptor antagonist, has been suggested to decrease pain and opioid consumption in infants, due to its anxiolytic and analgesic effects, with few cardiovascular and respiratory effects (Carter 2017; Saarenmaa 2001).

Paracetamol (acetaminophen) is a non-opioid, central-acting analgesic used to treat mild and moderate pain (Donato 2020). It is generally used to treat fever or pain, or both, and can be used for the management of patent ductus arteriosus (Ohlsson 2020). The analgesic effect of paracetamol is mediated by activation of descending serotonergic pathways, inhibition of prostaglandin synthesis, and the formation of an active metabolite influencing cannabinoid receptors (Allegaert 2017). In postoperative pain management, paracetamol might reduce pain when used in combination with morphine or fentanyl, and impact positively on decreasing opioid-related side effects, such as abstinence syndrome (Hong 2010). The main adverse effect of paracetamol is hepatotoxicity generated by the metabolite N-acetyl-p-benzoquinone imine (Donato 2020).

Midazolam is a short-acting benzodiazepine exercising the sedative effect through binding to gamma-aminobutyric acid (GABA) receptors (Donato 2020). It induces sedation, amnesia, and muscle relaxation, but no analgesia. Elimination of midazolam is reduced in newborn infants; when used in adults undergoing therapeutic hypothermia, there is a fivefold increase in serum levels (Ainsworth

2015). Adverse effects include hypotension and neurological irregularities (Donato 2020).

In addition to possible multi-organ failure impacting drug pharmacokinetics due to the hypoxic insult at birth, the therapeutic hypothermia itself may impact responses to drugs in the asphyxiated infant. Therapeutic hypothermia causes redistribution of blood flow, which can significantly influence both drug distribution and clearance and could potentially impair renal excretion of drugs in humans (Ainsworth 2015). Phenobarbital administered under therapeutic hypothermia results in higher plasma concentrations and longer half-lives than expected in normothermic newborns (Filippi 2011). Therapeutic hypothermia reduces morphine's affinity for the μ opioid receptor, making it less effective, though at the same time the clearance of morphine is lower in infants, and accumulation could occur if higher doses are used (Pacifici 2016). The use of more than one drug for pain and sedation management during therapeutic hypothermia requires considering potential pharmacological interactions. As phenobarbital is an inducer of cytochrome P450 (CYP) 3A, while midazolam is a CYP3A substrate, phenobarbital increases midazolam clearance by a factor 2.3 (Favié 2019). The co-administration of these two drugs therefore requires dosing adjustment.

How the intervention might work

Pharmacological interventions are commonly used during neonatal therapeutic hypothermia. A large, multicenter observational study conducted in 2621 infants reported that the use of opioids was more common in the case of more severe hypoxic-ischemic encephalopathy, although it varied widely between centers (Berube 2020). The use of morphine and benzodiazepine increased from 38% to 68% and from 40% to 53% between 2008 and 2015, respectively (Berube 2020).

The use of drugs during neonatal therapeutic hypothermia should be based on reliable pain and sedation evaluation. A Cochrane Review on scales for evaluating pain in newborn infants is under preparation (Bruschettini 2021). However, assessing the pain and effect of pain medication in the asphyxiated and hypothermic infant is associated with several difficulties. Neurological symptoms stemming from encephalopathy can mask or mimic pain symptoms, thus the assessment of pain is complex (Üner 2019). Moreover, the infant is often sedated during therapeutic hypothermia, which further complicates the pain assessment. It has been reported in a case report that pain and agitation correlate with physiological variables such as skin conductance algesimeter during therapeutic hypothermia (Hoffman 2013). Sedation of the infant receiving active therapeutic hypothermia during transport has been found to protect against incident hypocapnia (Szakmar 2018), which could be an issue in non-ventilated infants. A systematic review reported that the expected reduction in neonatal mortality did not appear among hypothermia-treated infants in low- and middle-income countries (Pauliah 2013). Sedation was not routinely given to hypothermia-treated infants, possibly due to fears of respiratory compromise and a lack of facilities for providing optimal ventilatory support. This lack of satisfactory sedation might have negated the neuroprotective effects of the hypothermia treatment. Of note, the Cochrane Review on opioids in ventilated infants, which included 23 trials, concluded that it is uncertain whether morphine or fentanyl has an effect on pain, and probably have little or no effect in reducing the duration of mechanical ventilation and neonatal mortality (Bellù 2021).

The use of sedative and anticonvulsant drugs during neonatal therapeutic hypothermia should be based on the available evidence, which is scarce (Young 2016), making it difficult to recommend routine use of these agents and to identify the optimal drug (Wassink 2015). Furthermore, the risk of long-lasting neurological sequelae of anesthetic, sedative, and analgesic drugs on newborn infants' developing brain further complicates treatment choice (McCann 2012; Wassink 2015).

Non-pharmacological interventions for pain management such as swaddling, sweet solutions, facilitated tucking, and non-nutritive sucking are considered to have a low risk for adverse effects and to be effective on mild pain (Mangat 2018; Pillai Riddell 2015). These interventions engage environmental and behavioral approaches through activation of a 'gate control mechanism' preventing the pain sensation from being carried to the central nervous system (Mangat 2018). Non-pharmacological interventions can include the infant's parents as part of the pain treatment, hence facilitating parental bonding. Of note, signs induced by therapeutic hypothermia such as shivering may be perceived by parents as infant discomfort (Craig 2020).

Why it is important to do this review

Pain and sedation need to be adequately managed in all patients. The therapeutic effect of cooling might be suboptimal if the newborn infant experiences stress and discomfort during treatment. Painful procedures and inadequate pain management in early life may lead to long-term negative effects (Walker 2019). Drugs such as sedatives and analgesics might be used to optimize the outcome of the therapeutic hypothermia. It is important to assess which drugs should be used, as they might have different benefits, harms, and different levels of neuroprotection. Cochrane Reviews on postoperative pain (Kinoshita 2021a; Kinoshita 2021b), procedural pain (Kinoshita 2021c), sedation during mechanical ventilation (Bellù 2021; Ibrahim 2016; Romantsik 2017), prophylactic barbiturate use following perinatal asphyxia (Young 2016), and other indications in the newborn (Pirlotte 2019; Romantsik 2020), are available or are currently under preparation. However, no systematic reviews have been conducted on pain or sedation management during therapeutic hypothermia.

OBJECTIVES

To determine the effects of pharmacological interventions for pain and sedation management in newborn infants undergoing therapeutic hypothermia.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

We will include studies on pharmacological interventions for pain and sedation management in late preterm (i.e. 34 to 36 weeks'

gestational age) and full-term (i.e. more than 36 weeks' gestational age) newborn infants undergoing therapeutic hypothermia.

Types of interventions

We will include studies using drugs used for the management of pain or sedation, or both, during therapeutic hypothermia. This will include any opioids (e.g. morphine, fentanyl), alpha-2 agonists (e.g. clonidine, dexmedetomidine), N-Methyl-D-aspartate (NMDA) receptor antagonist (e.g. ketamine), other analgesics (e.g. paracetamol), and sedatives (e.g. benzodiazepines such as midazolam).

We will include the following comparisons.

Comparison 1. Opioids (e.g. morphine, fentanyl) versus placebo, no intervention, or non-pharmacological interventions

1. Opioids versus placebo or no intervention (e.g. morphine versus placebo)
2. Opioids versus non-pharmacological interventions (e.g. non-nutritive sucking, sweet solutions (oral glucose or sucrose), swaddling, music therapy, therapeutic touch/massage, sensorial saturation, or acupuncture)

Comparison 2. Alpha-2 agonists (e.g. clonidine, dexmedetomidine) versus placebo, no intervention, or non-pharmacological interventions

1. Alpha-2 agonists (e.g. clonidine, dexmedetomidine) versus placebo or no intervention (e.g. clonidine versus placebo)
2. Alpha-2 agonists (e.g. clonidine, dexmedetomidine) versus non-pharmacological interventions (e.g. non-nutritive sucking, sweet solutions (oral glucose or sucrose), swaddling, music therapy, therapeutic touch/massage, sensorial saturation, or acupuncture)

Comparison 3. N-Methyl-D-aspartate (NMDA) receptor antagonist (e.g. ketamine) versus placebo, no intervention, or non-pharmacological interventions

1. NMDA receptor antagonist (e.g. ketamine) versus placebo or no intervention (e.g. ketamine versus placebo)
2. NMDA receptor antagonist (e.g. ketamine) versus non-pharmacological interventions (e.g. non-nutritive sucking, sweet solutions (oral glucose or sucrose), swaddling, music therapy, therapeutic touch/massage, sensorial saturation, or acupuncture)

Comparison 4. Other analgesics (e.g. paracetamol) versus placebo, no intervention, or non-pharmacological interventions

1. Other analgesics (e.g. paracetamol) versus placebo or no intervention (e.g. paracetamol versus placebo)
2. Other analgesics (e.g. paracetamol) versus non-pharmacological interventions (e.g. non-nutritive sucking, sweet solutions (oral glucose or sucrose), swaddling, music therapy, therapeutic touch/massage, sensorial saturation, or acupuncture)

Comparison 5. Sedatives (e.g. benzodiazepines such as midazolam, barbiturates such as phenobarbital) versus placebo, no intervention, or non-pharmacological interventions

1. Sedatives (e.g. midazolam, phenobarbital) versus placebo or no intervention (e.g. midazolam versus placebo)
2. Sedatives (e.g. midazolam, phenobarbital) versus non-pharmacological interventions (e.g. non-nutritive sucking, sweet solutions (oral glucose or sucrose), swaddling, music therapy, therapeutic touch/massage, sensorial saturation, or acupuncture)

Comparison 6. Drug type A versus drug type B (e.g. morphine versus fentanyl or morphine versus midazolam)

This can include comparisons within or between classes of interventions (opioids, alpha-2 agonists, NMDA receptor antagonists, other analgesics, and sedatives).

We will include any dose, duration, and route of administration.

We will include studies where the interventions are initiated to prevent or treat pain or discomfort associated with therapeutic hypothermia, including the use of sedatives and antiseizure medications to prevent seizures.

Types of outcome measures

Outcome measures are not part of the eligibility criteria.

Primary outcomes

1. Analgesia and sedation assessed with validated scales in the neonatal population: the Echelle Douleur Inconfort Nouveau-ne (EDIN) scale (Debillon 2001), COMFORTneo (van Dijk 2009), Neonatal Pain, Agitation and Sedation Scale (N-PASS) (Hummel 2008), pain assessment tool, the Astrid Lindgren and Lund Children's Hospital's Pain and Stress Assessment Scale for Preterm and Sick Newborn Infants (ALPS-neo) (Lundqvist 2014), Neonatal Facial Coding System (NFCS) (Grunau 1986; Peters 2003), and CRIES (Crying, Requires oxygen, Increased vital signs, Expression, Sleepless) scale (Krechel 1995). However, none of these scales are validated for assessing pain during therapeutic hypothermia. We plan to report the mean values of each scale assessed at 30 minutes, three hours, and 12 hours after the administration of the intervention. We plan to report analgesia and sedation scores separately.
2. All-cause mortality to discharge.

Secondary outcomes

1. All-cause neonatal mortality (death until postnatal day 28).
2. Sinus bradycardia (heart rate < 80 beats/minute).
3. Hypotension requiring medical therapy (inotropes, vasopressors, and/or fluid boluses).
4. Constipation, defined as difficulty in defecation causing significant distress to the newborn.
5. Focal gastrointestinal perforation.
6. Duration of mechanical ventilation (days).
7. In studies where infants might not be ventilated: apneic spells occurring after commencement of therapy.
8. In studies where infants might not be ventilated: need for mechanical ventilation occurring after commencement of therapy.

9. Hospital stay (days).
10. Time to full enteral feeding (days).
11. Need for gavage feeds at time of discharge.
12. Abnormal neurological examination at time of discharge.
13. Seizure, defined as a transient occurrence of signs or symptoms, or both, due to abnormal excessive or synchronous neuronal activity in the brain (Fisher 2005). The American Clinical Neurophysiology Society has defined a seizure as "a sudden, abnormal EEG [electroencephalography] event, defined by a repetitive and evolving pattern with a minimum 2 µV peak-to-peak voltage and duration of at least 10 seconds" (Pressler 2021; Tsuchida 2013).
14. Major neurodevelopmental disability: cerebral palsy, developmental delay (Bayley Scales of Infant Development - Mental Development Index Edition II (BSID-MDI-II) (Bayley 1993), Bayley Scales of Infant and Toddler Development - Edition III Cognitive Scale (BSITD-III) (Bayley 2005), Griffiths Mental Development Scale - General Cognitive Index (GCI) (Griffiths 1954; Griffiths 1970) assessment greater than two standard deviations (SDs) below the mean), intellectual impairment (intelligence quotient (IQ) greater than two SDs below the mean), blindness (vision less than 6/60 in both eyes), or sensorineural deafness requiring amplification (Jacobs 2013). We will assess data separately for children aged 18 to 24 months and those aged three to five years.
15. Each component of major neurodevelopmental disability. We will assess data separately for children aged 18 to 24 months and aged three to five years.
16. Cognitive and educational outcomes in children aged more than five years old. We will assess data separately for children aged 6 to 12 years and those aged more than 12 years.

Search methods for identification of studies

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

Electronic searches

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

We will search clinical trial registries for ongoing or recently completed trials. We will search the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/) and the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov), via CENTRAL. We will also search the ISRCTN registry (www.isrctn.com/) for any unique trials not found through the CENTRAL search.

Searching other resources

We will review the reference lists of all included articles for any relevant articles not identified by the primary search.

Data collection and analysis

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

Selection of studies

If the search yields more than 1000 results, we will use Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises the following three components:

1. known assessments: a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labeled as an 'RCT' or as 'Not an RCT';
2. the RCT classifier: a machine learning model that distinguishes RCTs from non-RCTs;
3. and if appropriate, Cochrane Crowd (crowd.cochrane.org), Cochrane's citizen science platform where the Crowd help to identify and describe health evidence.

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

We will include all RCTs, quasi-RCTs, cluster-RCTs, and cross-over RCTs fulfilling our inclusion criteria. Two review authors (PB, YTB) will review the results of the search and separately select studies for inclusion. Any disagreements will be resolved by discussion or by consulting a third review author when necessary.

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

Data extraction and management

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

We will extract the following characteristics from each included study:

1. administrative details: study author(s); published or unpublished; year of publication; year in which the study was conducted; presence of vested interest; details of other relevant papers cited;

2. study: study design; type, duration, and completeness of follow-up (e.g. greater than 80%); country and location of study; informed consent; ethics approval;
3. participants: sex, birth weight, gestational age, number of participants;
4. interventions: initiation, dose, and duration of administration;
5. outcomes as described in Types of outcome measures.

Any disagreements will be resolved by discussion. For any ongoing studies identified by our search, we will detail the primary author, research question(s), methods, and outcome measures, together with an estimate of the reporting date, and report the study in the 'Characteristics of ongoing studies' table.

We will contact study investigators/authors in cases where clarification or additional data are required. Two review authors (PB, YTB) will enter data into Review Manager 5 software (Review Manager 2020). We will replace any standard error of the mean (SEM) by the corresponding SD.

Assessment of risk of bias in included studies

Two review authors (PB, YTB) will independently assess risk of bias (low, high, or unclear) of all the included trials using the Cochrane risk of bias tool, based on the following domains (Higgins 2011).

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Any other bias

Any disagreements will be resolved by discussion or by consulting a third review author. A more detailed description of risk of bias for each domain is provided in Appendix 1.

Measures of treatment effect

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

Dichotomous data

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

Continuous data

For continuous data, we will use the mean difference (MD) when outcomes are measured in the same way between trials. We will use the standardized mean difference (SMD) to combine trials that measure the same outcome but employ different methods of measurement. Where trials report continuous data as median and interquartile range (IQR), and data pass the test of skewness, we will convert mean to median and estimate the SD as IQR/1.35.

Unit of analysis issues

The unit of analysis will be the participating infant in individually randomized trials, and an infant will be considered only once in the analysis. The participating neonatal unit or section of a neonatal unit or hospital will be the unit of analysis in cluster-randomized trials; these will be analyzed using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), or from a similar trial or from a study with a similar population as described in Section 16.3.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). If we use ICCs from a similar trial or from a study with a similar population, we will report this and conduct a sensitivity analysis to investigate the effect of variation in the ICC.

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

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

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

Dealing with missing data

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

Assessment of heterogeneity

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

1. less than 25%: no heterogeneity;
2. 25% to 49%: low heterogeneity;
3. 50% to 75%: moderate heterogeneity;
4. more than 75%: substantial heterogeneity.

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

Assessment of reporting biases

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

Data synthesis

If we identify multiple studies considered to be sufficiently similar, we will perform meta-analysis using Review Manager 5 (Review Manager 2020). For categorical outcomes, we will calculate the typical estimates of RR and RD, each with its 95% CI; for continuous outcomes, we will calculate the MD or the SMD, each with its 95% CI. If we consider different pain or sedation scales to be inappropriate to be combined by means of SMD, we will analyze and interpret them separately. We will use a fixed-effect model to combine data where it is reasonable to assume that studies have estimated the same underlying treatment effect. If we judge meta-analysis to be inappropriate, we will analyze and interpret individual trials separately. If there is evidence of clinical heterogeneity, we will attempt to provide an explanation based on the different study characteristics and subgroup analyses.

Subgroup analysis and investigation of heterogeneity

We will explore high statistical heterogeneity in the outcomes by visually inspecting the forest plots and by removing the outlying studies in the sensitivity analysis (Higgins 2021a). Where statistical heterogeneity is significant, we will interpret the results of the meta-analyses accordingly and downgrade the certainty of evidence in the summary of findings tables according to the GRADE recommendations.

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

1. Severity of hypoxic-ischemic encephalopathy, e.g. mild, moderate, or severe encephalopathy according to Sarnat criteria (Sarnat 1976).
2. Indication, e.g. procedural pain, premedication, analgesia-sedation for ventilation and for cooling.
3. High versus low dose.
4. By route of administration.
5. Low-, middle-, and high-income settings.

We will restrict these analyses to the primary outcomes.

Sensitivity analysis

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

Summary of findings and assessment of the certainty of the evidence

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

1. Analgesia and sedation assessed at 30 minutes after the administration of the intervention with validated scales in the neonatal population: the Echelle Douleur Inconfort Nouveaune (EDIN) scale (Debillon 2001), COMFORTneo (van Dijk 2009), Neonatal Pain, Agitation and Sedation Scale (N-PASS) (Hummel 2008), pain assessment tool, the Astrid Lindgren and Lund Children's Hospital's Pain and Stress Assessment Scale for Preterm and Sick Newborn Infants (ALPS-neo) (Lundqvist 2014), Neonatal Facial Coding System (NFCS) (Grunau 1986; Peters 2003), and CRIES (Crying, Requires oxygen, Increased vital signs, Expression, Sleepless) scale (Krechel 1995). However, none of these scales are validated for assessing pain during therapeutic hypothermia. We plan to report analgesia and sedation scores separately. If we judge different scales to be inappropriate to be combined by means of SMD, we will report the scale with the best validity and reliability for the type of population investigated (Bruschettini 2021).
2. Analgesia and sedation (see above) assessed at three hours after the administration of the intervention.
3. All-cause mortality to discharge.
4. Major neurodevelopmental disability in children aged 18 to 24 months: cerebral palsy, developmental delay assessment greater than two SDs below the mean, intellectual impairment (IQ greater than two SDs below the mean), blindness (vision less than 6/60 in both eyes), or sensorineural deafness requiring amplification (Jacobs 2013).
5. Major neurodevelopmental disability (see above) in children aged three to five years.

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

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

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APPENDICES

Appendix 1. Risk of bias tool

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the trials. For each trial, we will seek information regarding the method of randomization, blinding, and reporting of all outcomes of all infants enrolled in the trial. We will assess each criterion listed below as being at a low, high, or unclear risk of bias. Two review authors will separately assess each study. Any disagreements will be resolved by discussion. We will enter our findings in the risk of bias table in the 'Characteristics of included studies' table.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1. low risk (< 20% missing data);

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

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

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

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

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

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

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

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

Appendix 2. Search strategy

MEDLINE via PubMed

(((((infant, newborn[MeSH] OR newborn*[TIAB] OR "new born"[TIAB] OR "new borns"[TIAB] OR "newly born"[TIAB] OR baby*[TIAB] OR babies*[TIAB] OR premature[TIAB] OR prematurity[TIAB] OR preterm[TIAB] OR "pre term"[TIAB] OR "low birth weight"[TIAB] OR "low birthweight"[TIAB] OR LBW[TIAB] OR infan*[TIAB] OR neonat*[TIAB]) NOT (animals [mh] NOT humans [mh]))))

AND ((hypoxic-ischemic[Title/Abstract]) OR (encephalopathies, hypoxic ischemic[MeSH Terms]) OR (encephalopath*[Title/Abstract]) OR (asphyxia[MeSH Terms]) OR (asphyxi*[Title/Abstract])))

AND ((hypothermia, induced[MeSH Terms]) OR (hypothermia[Title/Abstract]) OR (induced hypothermia[Title/Abstract]) OR (therapeutic hypothermia[Title/Abstract]) OR (cooling[Title/Abstract]) OR (temperature management[Title/Abstract]))

AND

((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type])) OR ((((randomized[Title/Abstract] OR randomly[Title/Abstract] OR randomised[Title/Abstract]) OR (placebo[Title/Abstract] OR drug therapy[Title/Abstract])) OR (groups[Title/Abstract] OR trial[Title/Abstract])) OR (((single[Title/Abstract] OR doubl*[Title/Abstract] OR tripl*[Title/Abstract] OR treb*) AND (blind*[Title/Abstract] OR mask*))))

CINAHLComplete (Ebsco)

(infant or infants 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 LBW)

AND

MH Hypoxia-Ischemia, Brain, Neonatal OR (hypoxic-ischemic OR encephalopath* OR asphyxi*)

AND

MH Hypothermia, Induced OR (hypothermia OR induced hypothermia OR therapeutic hypothermia OR temperature management OR cooling)

AND

PT randomized controlled trial OR PT controlled clinical trial OR (randomized OR randomly OR randomised OR placebo OR drug therapy OR groups OR trial OR) OR (single OR doubl* OR tripl* OR treb*) AND (blind* OR mask*))

Cochrane CENTRAL

MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND CENTRAL:TARGET

OR 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

AND

(MeSH descriptor: [Hypoxia-Ischemia, Brain] explode all trees OR MeSH descriptor: [Hypoxia-Ischemia, Brain] explode all trees OR hypoxic-ischemic OR encephalopath* OR asphyxi*)

AND

(MeSH descriptor: [Hypothermia, Induced] explode all trees OR hypothermia OR induced hypothermia OR therapeutic hypothermia OR temperature management OR cooling)

Scopus

((TITLE-ABS-KEY ((infant OR infants OR infantile OR infancy OR newborn* OR "new born" OR "new born" OR "newly born" OR neonat* OR baby* OR babies OR premature OR premature OR prematurity OR preterm OR preterm OR "pre term" OR premises)) OR TITLE-ABS-KEY (("low birth weight" OR "low birthweight" OR lbw OR nicu)))) AND ((TITLE-ABS-KEY ((hypoxic-ischemi* OR encephalopath* OR asphyxi*)) AND TITLE-ABS-KEY ((hypothermia OR induced AND hypothermia OR therapeutic AND hypothermia OR temperature AND management OR cooling)))) not TITLE-ABS-KEY (animals AND not AND humans)

AND

TITLE-ABS-KEY (randomized OR randomly OR randomised OR placebo OR drug AND therapy OR groups OR trial OR (single OR doubl* OR tripl* OR treb*) AND (blind* OR mask*))

Web of Science

TOPIC: ((infant OR infants OR infantile OR infancy OR newborn* OR "new born" OR "new born" OR "newly born" OR neonat* OR baby* OR babies OR premature OR premature OR prematurity OR preterm OR preterm OR "pre term" OR premises OR "low birth weight" OR "low birthweight" OR lbw OR nicu)) AND TOPIC: ((hypoxic-ischemi* OR encephalopath* OR asphyxi*)) AND TOPIC: ((hypothermia OR induced AND hypothermia OR therapeutic AND hypothermia OR temperature AND management OR cooling)) NOT TOPIC: ((animals NOT humans)) AND

TOPIC: (TITLE-ABS-KEY (randomized OR randomly OR randomised OR placebo OR drug AND therapy OR groups OR trial OR (single OR doubl* OR tripl* OR treb*) AND (blind* OR mask*)))

Clinicaltrials.gov

Other terms

(Hypoxic* OR ischemi* OR encephalopaht* OR hypothermia OR induced AND hypothermia OR therapeutic AND hypothermia OR temperature AND management OR cooling)

AND

randomized OR randomly OR randomised OR placebo OR drug therapy OR groups OR trial OR ((single OR doubl* OR tripl* OR treb*) AND (blind* OR mask*))

Filter: Child (birth-17 years)

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: PB, MB, YTB, EO

Designing the review: PB, MB, YTB, GS, EO

Co-ordinating the review: MB

Data collection for the review: PB, YTB

Screening search results: PB, YTB

Organizing retrieval of papers: PB, GS, YTB, EO

Screening retrieved papers against eligibility criteria: PB, YTB

Appraising quality of papers: PB, YTB

Extracting data from papers: PB, YTB

Writing to authors of papers for additional information: GS

Data management for the review: MB, GS, EO

Entering data into Review Manager 5: PB, YTB

Analysis of data: MB, GS, EO

Interpretation of data: MB, GS, EO

Providing a methodological and a clinical perspective: MB

DECLARATIONS OF INTEREST

PB has no interests to declare.

MB has no interests to declare.

GS has no interests to declare.

YTB has no interests to declare.

EO has no interests to declare.

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