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[Intervention Protocol]

Pain and sedation management for screening or treatment of retinopathy of prematurity

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ABSTRACT

Objectives

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

To assess the benefits and harms of pain and sedation management for screening or treatment of retinopathy of prematurity in preterm infants compared to placebo, no intervention, or other interventions.

BACKGROUND

Description of the condition

Retinopathy of prematurity is a neurovascular developmental disorder that may lead to vision impairment and even blindness. It occurs mainly among infants born preterm (i.e. less than 32 weeks' gestational age), and has a higher incidence in extremely preterm newborns (i.e. less than 28 weeks' gestational age) [1]. The condition is caused by abnormal neurovascular growth that can progress to retinal detachment [2].

Screening of retinopathy of prematurity

To detect infants requiring treatment for retinopathy of prematurity, regular screenings are conducted in accordance with national/local guidelines. Screening policies differ internationally. For example, India screens infants at less than 34 weeks' gestational age or weighing less than 2000 g [3]; the UK at less than 32 weeks' gestational age or less than 1501 g [4]; Germany at less than 31 weeks' gestational age or less than 1500 g [5]; and Sweden and the USA at less than 30 weeks' gestational age or less than 1500 g [6, 7]. Screening is performed using subjective indirect ophthalmoscopy, which has historically been the method of choice [1]. However, objective fundus imaging has become more widespread and commonly used [1]. With either technique, mydriatic eye drops must be administered before examination. Pain during retinopathy of prematurity screening can result from several factors: discomfort from mydriatic eye drops [8, 9]; the insertion of an eyelid speculum to access the ocular fundus; exposure to bright light for fundus illumination; and scleral indentation due to eye manipulation during the exam [10, 11].

Treatment of retinopathy of prematurity

Treatment for retinopathy of prematurity is based on severity. Most cases resolve; however, approximately 5% to 10% require interventions such as laser therapy or intravitreal antivascular endothelial growth factor (anti-VEGF) injections to prevent abnormal blood vessel growth in the retina [12]. Laser photocoagulation involves the destruction of the peripheral retina using a diode laser; the procedure lasts about one hour and may be painful and stressful for the infant. In rare cases when laser or intravitreal anti-VEGF treatments (or both) have been unsuccessful, surgery such as cerclage or vitrectomy may be required to reattach the retina [12].

Both screening and treatment of retinopathy of prematurity are painful. Given that retinopathy of prematurity screenings are performed regularly until retinal vascularization is adequately completed, or retinopathy of prematurity must be treated, providing safe and effective pain relief during screening and treatment is essential.

Description of the intervention and how it might work

Management of procedural pain may be non-pharmacologic or pharmacologic. Non-pharmacologic strategies include parent-led interventions [13], such as skin-to-skin contact, singing [14, 15], breastfeeding [16], and swaddling [17]. These interventions have the benefit of being safe to use with minimal or no adverse effects typically reported [18, 19, 20], and engage parents, which is a benefit to both infants and parents [13]. Pharmacologic strategies can include oral sweet solutions such as sucrose [16], non-opioids such as acetaminophen (paracetamol) [16] or clonidine [21], and opioids such as morphine [22]. Topical anesthetic agents can, depending on the procedure, also be used [16]. For newborns requiring laser photocoagulation or anti-VEGF injections, achieving the appropriate level of anesthesia is crucial to ensure both effective pain relief and immobility, the latter ensuring the treatment is performed safely and accurately. Various options for analgosedation (i.e. pain and sedation management) are available, including general anesthesia with intubation and mechanical ventilation, regional anesthesia, topical anesthesia, or combinations of these methods, depending on local practices and available resources [23].

Topical anesthesia, such as oxybuprocaine and proxymetacaine eye drops, is often used as an adjunct in less invasive ophthalmic procedures. Additionally, intravenous or intramuscular sedatives, including midazolam, propofol, or ketamine, are sometimes combined with opioids (e.g. morphine, fentanyl) to enhance pain control and procedural tolerance. Dexmedetomidine, a selective α_2-adrenergic agonist, is increasingly being explored for its ability to provide sedation with minimal respiratory depression, though its use in neonates remains an area of ongoing research.

General anesthesia with sevoflurane and halothane ensures complete immobility and effective pain relief but is associated with a higher risk of systemic complications, including hypotension and respiratory depression. In contrast, sedation with opioids and benzodiazepines, while often preferred for its ease of administration, may lead to prolonged apnea and desaturation episodes, necessitating careful monitoring in preterm infants. Although topical anesthesia is considered a less invasive alternative, it has been associated with the highest degree of postoperative cardiorespiratory instability, surpassing both sedation and general anesthesia in terms of risk [23].

Despite the availability of multiple sedation options, protocols remain highly variable, with no universally established guidelines on optimal dosing, safety, or long-term effects, making their use challenging [24].

Assessing pain in this non-verbal population is difficult, and pain scales are often used to assess the infant's behavior as well as physiologic reactions to pain [25]. Although the validity of pain scales is questionable [26], their use is recommended [25]. There are many pain assessment scales for the neonatal population; however, only a few of these are used in most research studies [27]. Acute pain scales include Premature Infant Pain Profile (PIPP)/Premature Infant Pain Profile – Revised (PIPP-R), Neonatal Facial Coding System (NFCS), Neonatal Pain Agitation and Sedation Scale (N-PASS), and Behavioral Indicators of Infant Pain (BIIP). Prolonged pain is measured using scales such as Neonatal Pain Agitation and Sedation Scale (N-PASS), COMFORTneo, and Échelle de Douleur et d'Inconfort du Nouveau-né (EDIN/EDIN6) [28]. Neurophysiologic measurements such as near-infrared spectroscopy, electroencephalography [29], and galvanic skin conductance [30] are also used to assess neonatal pain.

Why it is important to do this review

Pain relief recommendations for retinopathy of prematurity screening vary, and are often multifaceted (e.g. topical anesthesia alongside non-pharmacologic measures such as pacifiers,

swaddling, and oral sucrose). Despite extensive research related to pharmacologic and non-pharmacologic pain relief interventions for premature infants [8, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23], there is no global consensus on the ideal approach to analgosedation for pain relief in general, or retinopathy of prematurity treatment in particular. Given that repeated painful procedures can result in long-term negative effects on pain response [31], brain development [32, 33], and cognitive function [34], and that retinopathy of prematurity screening has been linked to physiologic stress and higher rates of apnea [10, 11], providing safe and effective pain relief during screening and treatment is essential.

OBJECTIVES

To assess the benefits and harms of pain and sedation management for screening or treatment of retinopathy of prematurity in preterm infants compared to placebo, no intervention, or other interventions.

METHODS

For this protocol, we have followed methodologic guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* and reporting guidance per PRISMA-P [35, 36]. For the review, we will follow methodologic guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* [35] and MECIR (Methodological Expectations for Cochrane Intervention Reviews) [37], and we will report the review following PRISMA [35, 38, 39].

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) or quasi-RCTs (trials using strategies of allocating interventions which are not truly random, e.g. allocation by patient ID number), and cluster-RCTs.

We will exclude cross-over randomized trials because they will not be able to report on neurodevelopmental outcomes that develop over time [40]. We will exclude non-randomized cohort studies because they are prone to bias due to confounding by indication or by residual confounding, both of which may influence the results of the studies [41, 42].

Where included studies only partially overlap with our intended population, we will attempt to acquire participant-level data. Where this is not possible, we will include studies where a majority (greater than 50%) meet our inclusion criteria. Specific decisions will be assessed case-by-case, and documented clearly in the review. Sensitivity analyses will be undertaken to assess the impact of these decisions [35].

Types of participants

We will include studies enrolling preterm infants (born at less than 37 weeks' completed gestation) undergoing pain management for screening or treatment for retinopathy of prematurity.

Types of interventions

We will include studies of any intervention used for the management of pain or sedation, or both, during screening or treatment for retinopathy of prematurity. We will include both pharmacologic and non-pharmacologic interventions. We will include any dose, duration, or route of administration.

Pharmacologic interventions will include sweet solutions (e.g. oral glucose or sucrose), opioids (e.g. morphine, fentanyl), α_2-agonists (e.g. clonidine, dexmedetomidine), N-methyl-D-aspartate (NMDA) receptor antagonists (e.g. ketamine), other analgesics (e.g. acetaminophen), and sedatives (e.g. benzodiazepines such as midazolam).

Non-pharmacologic interventions will include non-nutritive sucking, skin-to-skin contact, swaddling, music therapy (including singing), therapeutic touch/massage, sensorial saturation, acupuncture, or multisensorial stimulation (the use of two or more non-pharmacologic interventions). Non-pharmacologic interventions may be provided by parents, other caregivers, medical staff, or combinations of these (e.g. skin-to-skin provided by a parent and singing by medical staff).

We will analyze studies on screening and treatment of retinopathy of prematurity separately due to the different intensity and duration of pain (e.g. laser treatment being more painful than screening). We will include studies with or without the use of sedation or general anesthesia.

We will include the following comparisons.

Opioids versus placebo, no intervention, or non-pharmacologic interventions

- Opioids versus placebo or no intervention (e.g. morphine versus placebo)
- Opioids versus non-pharmacologic interventions (e.g. fentanyl versus sensorial saturation)

α_2-Agonists versus placebo, no intervention, or non-pharmacologic interventions

- α_2-Agonists versus placebo or no intervention (e.g. clonidine versus placebo)
- α_2-Agonists versus non-pharmacologic interventions (e.g. dexmedetomidine versus acupuncture)

N-methyl-D-aspartate receptor antagonist versus placebo, no intervention, or non-pharmacologic interventions

- NMDA receptor antagonist versus placebo or no intervention (e.g. ketamine versus placebo)
- NMDA receptor antagonist versus non-pharmacologic interventions (e.g. ketamine versus music therapy)

Other analgesics versus placebo, no intervention, or non-pharmacologic interventions

- Other analgesics versus placebo or no intervention (e.g. acetaminophen versus placebo)
- Other analgesics versus non-pharmacologic interventions (e.g. acetaminophen versus non-nutritive sucking)

Sedatives versus placebo, no intervention, or non-pharmacologic interventions

- Sedatives versus placebo or no intervention (e.g. midazolam, phenobarbital versus placebo)

- Sedatives (e.g. midazolam, phenobarbital) versus non-pharmacologic interventions (e.g. phenobarbital versus oral glucose)

Topical anesthetics versus placebo, no intervention, or non-pharmacologic interventions

- Topical anesthetics versus placebo or no intervention (e.g. lidocaine versus placebo)
- Topical anesthetics versus non-pharmacologic interventions (e.g. lidocaine versus oral glucose)

Sweet solutions (glucose, sucrose) versus placebo, no intervention, or non-pharmacologic interventions

- Sweet solutions versus placebo or no intervention
- Sweet solutions versus non-pharmacologic intervention

Drug type A versus drug type B

This could include comparisons within or between classes of interventions such as opioids, α_2-agonists, NMDA receptor antagonists, other analgesics, or sedatives.

Non-pharmacologic interventions versus placebo or no intervention

- Non-pharmacologic interventions versus placebo or no intervention (e.g. sensorial saturation versus placebo)

Outcome measures

Outcome measures are detailed below. We will include studies even if the study reports no data for that outcome.

Critical outcomes

- **Analgesia** assessed with a neonatal scale. No pain scales have been validated in the neonatal population [26]. We will consider any pain scale and then consider downgrading the certainty of the evidence for indirectness. We plan to report the mean values of each scale assessed during the procedure (primary time point) and at the end of the procedure.
- **Sedation** assessed with a neonatal scale. We plan to report the mean values of each scale assessed during the procedure (primary time point) and at the end of the procedure.
- **Pain** assessment by electrophysiologic devices, such as electrocardiography, electromyography, electrodermal activity (galvanic skin conductance, near-infrared spectroscopy, photoplethysmography, or combinations of these). We plan to report the mean values of each scale assessed during the procedure (primary time point) and at the end of the procedure.
- **Adverse events/reactions to the drugs used for pain management** during the procedure (primary time point) and at the end of the procedure.

Important outcomes

- **Apnea** (in studies where infants might not be ventilated): number of infants with at least one episode (defined as interruption of breathing for more than 20 seconds, or any interruption of breathing less than 20 seconds but with associated bradycardia or frequent periodic breathing) assessed during the procedure (primary time point) and at the end of the procedure.
- **Hypotension requiring medical therapy** (inotropes, vasopressors, or fluid boluses) assessed during the procedure (primary time point) and at the end of the procedure.
- **Increased oxygen requirement** assessed during the procedure (primary time point) and at the end of the procedure.
- **Requirement of respiratory stimulant** (e.g. caffeine) assessed during the procedure (primary time point) and at the end of the procedure.
- **Sinus bradycardia** (heart rate less than 80 beats per minute) assessed during the procedure (primary time point) and at the end of the procedure.
- **Enteral feeding tolerance** assessed at the end of the procedure.

Search methods for identification of studies

Electronic searches

An Information Specialist (MF) drafted a search strategy, which is provided in Supplementary material 1. The strategy is preceded by a search narrative per Cooper and colleagues [43]. There will be no publication type or language limits. There will be no date limits, but searches for systematic reviews will be limited to the most recent two years. An Information Specialist will peer-review the search strategies based on the Peer Review of Electronic Search Strategies checklist [44, 45]. We will search the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) via CRS
- Ovid MEDLINE All, 1946 to date of search
- Ovid Embase, 1974 to date of search
- Ovid Emcare, 1995 to date of search
- Epistemonikos (https://www.epistemonikos.org/en/)

We will report the results of the search in the text of the review and in a PRISMA diagram [38, 39].

Searching other resources

We will search the following trial registries.

- National Library of Medicine trial registry (https://clinicaltrials.gov/)
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (https://trialsearch.who.int/Default.aspx)

We will search the following for conference abstracts, published during the past five years, as available.

- Perinatal Society of Australia and New Zealand (PSANZ)
- Pediatric Academic Societies (PAS)
- European Academy of Paediatric Societies (EAPS)

We will check the reference lists of systematic reviews related to the topic of this review.

We will search for errata or retractions of studies selected for inclusion in this review via PubMed and Retraction Watch.

Data collection and analysis

Selection of studies

Review authors will screen references identified by the literature searches using Covidence [46]. We will use the RCT Classifier in

Covidence, which is based on Cochrane's Screen4Me technology [47, 48, 49, 50], to remove non-RCT references and tag potential RCTs. Both of these features help to reduce manual screening burden. Results found by the search for systematic reviews will be screened before activating the RCT Classifier. If results are unduly high (in excess of 4000), we may use Cochrane Crowd (Cochrane's crowdsourcing platform) to identify further non-RCT records. We will report the number of references categorized as non-RCTs in Covidence in the review; if we use Cochrane Crowd, we will document its results in the review.

Two review authors (EO and OR) will independently screen the remaining titles/abstracts. Two review authors (EO and OR) will independently assess the full text of references included after the title/abstract review. At any point in the screening process, we will resolve disagreements by discussion or by consultation with a third review author (MB). We will exclude studies that do not meet our inclusion criteria as described in the Criteria for considering studies for this review. We will document the reason for excluding studies during full-text review in the 'Characteristics of excluded studies' table. We will collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram [38, 39].

In cases where there are questions about the data reported in a study, we will attempt to contact study investigators for clarification or additional information. If we identify studies in languages not read by the review authors, we will use an online translation service such as Google Translate. If the translation is sufficient, we will use it. If it is insufficient, we will attempt to identify an individual conversant in the language of the report to translate the study.

Data extraction and management

Two review authors (EO, AS) will independently extract data using a form based on the Cochrane Effective Practice and Organisation of Care data collection checklist [51]. We will pilot the form within the review team using a sample of three included studies. We will compare the data from each review author and resolve disagreements by discussion. We will extract the following information.

- Administrative details: study author(s), published or unpublished, year of publication, year in which study was conducted, presence of vested interest.
- Study setting, number of study centers and location, informed consent, ethics approval, completeness of follow-up (e.g. greater than 80%).
- Participants: number randomized, number lost to follow-up/ withdrawn, number analyzed, mean gestational age, gestational age range, mean corrected age or corrected age range, inclusion criteria, place of residence, race/ethnicity/culture/language, occupation, sex, religion, education, socioeconomic status, social capital, age, and disability and exclusion criteria.
- Type of intervention, according to Types of interventions.
- Outcomes: outlined above, under Outcome measures.

If we identify ongoing studies, we will document available information such as the primary author, research question(s), methods, and outcome measures, and the estimated date of completion in the 'Characteristics of ongoing studies' table.

Should any queries arise, or in cases for which additional data are required, we will contact study investigators/authors for clarification.

One review author (MB) will import data from Covidence into Review Manager [46, 52]. We will replace any standard error of the mean with the corresponding standard deviation.

Risk of bias assessment in included studies

We will use the Cochrane RoB 2 tool to assess the risk of bias in RCTs included in the review. We will use an RoB 2 Excel tool to implement RoB 2 (https://www.riskofbias.info/welcome/rob-2-0-tool) [53]. The outcomes to be assessed for each study are those described in Certainty of the evidence assessment.

Two review authors (EO, AS) will independently assess the risk of bias (low, high, or some concerns) for each outcome. We will resolve discrepancies in judgments through discussion or by consultation with a third review author (OR). We will assess the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* [53].

- Bias arising from the randomization process
- Bias due to deviations from intended interventions (we will assess the effect of assignment to the intervention at baseline, i.e. the 'intention-to-treat effect')
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

To address these types of bias, we will use the signaling questions recommended in the RoB 2 tool and make a judgment using the following options.

- 'Yes': if there is firm evidence that the question was fulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'Probably yes': a judgment was made that the question was fulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'No': if there was firm evidence that the question was unfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'Probably no': a judgment was made that the question was unfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'No information': if the study report provided insufficient information to allow any judgment.

We will then use the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias.

- Low risk of bias
- Some concerns
- High risk of bias

This approach will allow the review authors to derive an overall risk of bias rating for each outcome in each study in accordance with the following suggestions.

- Low risk of bias: we judged the trial at low risk of bias for all domains for this result.
- Some concerns: we judged the trial to raise some concerns in at least one domain for this result, but not at high risk of bias for any domain.
- High risk of bias: we judged the trial at high risk of bias in at least one domain for the result, or we judged the trial to have some concerns for multiple domains in a way that substantially lowered confidence in the results.

If we include cluster-RCTs, we will use RoB 2 for cluster-randomized trials and follow the guidance in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* [54].

Measures of treatment effect

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 the number needed to treat for an additional harmful outcome (NNTH) with 95% CIs if there is a significant reduction (or increase) in RD.

Continuous data

For continuous data, we will use the mean difference (MD) when trials measured outcomes on the same scale. We will use the standardized mean difference to combine data from trials that measured the same outcome but used different scales. Where trials report continuous data as median and interquartile range (IQR), and data pass the test of skewness, we will convert the median to the mean and estimate the standard deviation as IQR/1.35 [55].

Count data

For counts and rates, we will calculate data as described in Rose and colleagues [56].

Unit of analysis issues

The unit of analysis will be the participating infant in individually randomized trials; 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-RCTs. For cluster-RCTs, we will abstract information on the study design and unit of analysis for each study, indicating whether clustering of observations is present due to allocation to the intervention at the group level or clustering of individually randomized observations (e.g. infants within clinics). We will abstract available statistical information needed to account for the implications of clustering on the estimation of outcome variances, such as design effects or intracluster correlations (ICCs), and whether the study adjusted results for the correlations in the data. In cases where the study does not account for clustering, we will ensure that appropriate adjustments are made to the effective sample size following Cochrane guidance [35]. Where possible, we will derive the ICC for these adjustments from the trial itself or from a similar trial. If an appropriate ICC is unavailable, we will conduct sensitivity analyses to investigate the potential effect of clustering, by imputing a range of values of ICC.

If trials have multiple arms compared against the same control condition that will be included in the same meta-analysis, we will either combine groups to create a single pair-wise comparison or select the pair of interventions that most closely match the definitions given in Types of interventions and exclude the others. We will include the arm where multiple interventions are used and the control group where no specific intervention was introduced. If there are several arms with multiple different interventions, we will combine them into one group. If there are several arms with single interventions, we will also combine them and treat them as one comparative group. We will acknowledge this potential selective bias of data used for analysis in the 'Discussion' section.

Dealing with missing data

We intend to carry out analysis on an intention-to-treat basis for all included outcomes. Whenever possible, we will analyze all participants in the intervention group to which they were randomized, regardless of the actual intervention received. If we identify important missing data (in the outcomes) or unclear data, we will contact the original investigators and request the missing data. We will make explicit the assumptions of any methods used to deal with missing data. Where missing data are thought to introduce serious bias (defined as 20% or greater of missing data), we will perform sensitivity analyses to evaluate the impact of missing outcome data.

For missing dichotomous outcomes, we will include participants with incomplete or missing data in the sensitivity analysis by imputing them according to the following scenarios.

- Extreme-case analysis favoring the experimental intervention (best-worst case scenario): none of the dropouts/participants lost from the experimental arm, but all the dropouts/participants lost from the control arm experienced the outcome, including all randomized participants in the denominator.
- Extreme-case analysis favoring the control (worst-best case scenario): all dropouts/participants lost from the experimental arm, but none from the control arm experienced the outcome, including all randomized participants in the denominator.

The scenarios are constructed with reference to an outcome label that is negative in polarity (e.g. mortality). For the positive equivalent (e.g. survival), we will reverse the direction in the scenario.

For continuous outcomes, we will calculate missing standard deviations using reported P values or CIs [35]. If the calculation is not possible, we will impute a standard deviation as the highest standard deviation reported in the other trials for the corresponding treatment group and outcome.

We will address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Reporting bias assessment

We will assess reporting bias by comparing the stated primary and secondary outcomes, and reported outcomes. When study protocols are available, we will compare these to the full publications to determine the likelihood of reporting bias. We will document studies using the interventions in a potentially eligible infant population but not report on any of the primary and secondary outcomes in the characteristics of the included study tables.

We will use funnel plots to screen for publication bias when there are a sufficient number of studies (more than 10) reporting the same outcome. If publication bias is suggested by a significant asymmetry of the funnel plot on visual assessment, we will incorporate this in our assessment of the certainty of evidence [57]. If our review includes fewer than 10 studies eligible for meta-analysis, the ability to detect publication bias will be largely diminished, and we will simply note our inability to rule out possible publication bias or small-study effects.

Synthesis methods

If we identify multiple studies that we consider to be sufficiently similar, we will perform a meta-analysis using Review Manager [52]. For categorical outcomes, we will calculate the typical estimates of RR and RD, each with its 95% CI; for continuous outcomes, we will calculate the MD or the SMD, each with its 95% CI. We will use a fixed-effect model to combine data where it is reasonable to assume that studies are estimating the same underlying treatment effect [58]. Cochrane Neonatal reviews have typically used a fixed-effect model as preterm neonates are relatively similar in terms of their general condition as they are less likely to be influenced by confounding factors that take time to develop. Interventions administered to neonates are also considered relatively easily standardized due to a controlled environment in the neonatal intensive care unit and standard basic care protocol. Taking this into consideration, a fixed-effect model is more sensitive in detecting small effect sizes.

If there is evidence of clinical heterogeneity, we will try to explain this based on the different study characteristics and subgroup analyses. We will use forest plots to provide graphical representation of the study data.

If we judge meta-analysis to be inappropriate, we will refer to methodologic guidance from Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* [59] and Synthesis Without Meta-analysis (SWiM) reporting guidance [60]. We will create a table with studies ordered by risk of bias, and calculate standardized effect estimates for each study. This table will be modeled on the worked example as presented in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* [59]. We will use a forest plot to provide graphical representation of the data.

Investigation of heterogeneity and subgroup analysis

We will interpret any test results for subgroup differences with caution, considering the potential for confounding with other study characteristics and the observational nature of comparisons, as described in Section 10.11.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* [35]. We will consider any subgroup analyses with fewer than five studies per category as not producing meaningful results and will not therefore present these. If and when subgroup analyses are possible, we will perform meta-analysis and a formal statistical test for interaction to examine subgroup differences (e.g. Cochran's Q test, meta-regression) [58, 61].

Given the potential of intervention effectiveness to be related to gestational age, we plan to conduct subgroup analyses to determine whether the intervention is more effective.

We plan to carry out the following subgroup analysis that may contribute to heterogeneity in the effects of the intervention.

- Gestational age: less than 27 weeks of gestation; 27 weeks of gestation or greater

We will use the main outcomes (those specified for the summary of findings table) in subgroup analyses if there are enough studies reporting the outcomes to support valid subgroup comparisons (at least five studies per subgroup).

Equity-related assessment

We will report any relevant characteristics that are included in the acronym PROGRESS-Plus (place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, social capital, age, sexual orientation, and disability), and whether our neonatal population would be subject to any health inequity in terms of the interventions that we will assess [62]. We anticipate differences in terms of financing between high-, middle-, or low-income country settings and populations in terms of the interventions included in our review. We will descriptively assess this in our review. In our summary of findings table, we will highlight and present any differences in baseline risks in our neonatal population that might cause disadvantages.

Sensitivity analysis

We will conduct sensitivity analyses to explore the effect of the methodologic quality of studies and ascertain whether studies with a high risk of bias (in at least two domains) overestimate the effect of treatment.

Differences in the study design of included studies might also affect the systematic review results. We will perform a sensitivity analysis to compare the effects of multisensory stimulation in truly randomized trials instead of quasi-randomized trials.

For cluster-RCTs, we will abstract available statistical information needed to account for the implications of clustering on the estimation of outcome variances, such as design effects or ICCs, and whether the study adjusted results for the correlations in the data. If an appropriate ICC is unavailable, we will conduct sensitivity analyses to investigate the potential effect of clustering, by imputing a range of values of ICC.

Certainty of the evidence assessment

We will use the GRADE approach, as outlined in the GRADE Handbook to assess the certainty of evidence for the following (clinically relevant) outcomes [63].

- Analgesia
- Sedation
- Pain
- Adverse events/reactions to the drugs used for pain management during the procedure
- Apnea
- Hypotension requiring medical therapy

We will include three summary of findings tables.

- Opioids versus placebo or no intervention, for studies on treatment of retinopathy of prematurity
- α_2-Agonists versus placebo or no intervention, for studies on screening of retinopathy of prematurity

- Sedatives versus placebo or no intervention, for studies on screening of retinopathy of prematurity

Two review authors (EO, MB) will independently assess the certainty of the evidence for each of the outcomes above for each comparison where at least one study is included. We will use the overall RoB 2 assessments to inform our GRADE judgments. We will consider evidence from RCTs as high certainty, downgrading the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We will use GRADEpro GDT to create summary of findings tables to report the certainty of the evidence [64].

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

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

Consumer involvement

This review protocol has been developed with the involvement of consumers, with assistance from the parents of preterm children who have required neonatal intensive care and the consumers' network of the Lund Hospital Library, Sweden. We expect that this will have made an important contribution to the research question and design, and will further be of importance when interpreting data, and in the dissemination and in the translation of findings (Supplementary material 2).

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016171.

Supplementary material 1 Search strategies

Supplementary material 2 Consumer involvement

ADDITIONAL INFORMATION

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The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Professor James I Hagadorn, Division of Neonatology, Connecticut Children's Medical Center/University of Connecticut School of Medicine.
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Jenny Bellorini, Cochrane Central Editorial Service.
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported the editorial team): Cynthia Stafford, Cochrane Central Editorial Service.
- Copy Editor (copy editing and production): Anne Lawson.
- Peer-reviewers (provided comments and recommended an editorial decision): Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review); Jo Platt, Central Editorial Information Specialist (search review). One additional peer reviewer provided clinical/content peer review but chose not to be publicly acknowledged.

Contributions of authors

EO co-ordinated the review, reviewed the literature to inform the protocol, wrote the first draft of the protocol, and reviewed and approved the final version of the protocol.

OR reviewed the literature to inform the protocol, wrote the first draft of the protocol, and reviewed and approved the final version of the protocol.

PL provided clinical insight, reviewed and approved the final version of the protocol.

MF revised the Methods section, wrote search methods and search strategies, and reviewed and approved the final version of the protocol.

AS provided clinical insight, reviewed and approved the final version of the protocol.

AH provided clinical insight, reviewed and approved the final version of the protocol.

MB co-ordinated the review, reviewed the literature to inform the protocol, wrote the first draft of the protocol, and reviewed and approved the final version of the protocol.

Declarations of interest

EO: no commercial or non-commercial conflicts of interest relevant to this review.

OR: no commercial or non-commercial conflicts of interest relevant to this review.

PL: no commercial or non-commercial conflicts of interest relevant to this review.

MF: is the Managing Editor and Information Specialist of Cochrane Neonatal; she did not participate in the editorial assessment or acceptance of this review.

AS: no commercial or non-commercial conflicts of interest relevant to this review.

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Registration and protocol

Cochrane approved the proposal for this review in May 2024.

Data, code and other materials

Data sharing is not applicable to this article as it is a protocol, so no datasets were generated or analyzed.

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