# Pain relieving interventions for retinopathy of prematurity: a network meta-analysis

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## Review question

What is the most effective intervention, or combination of interventions, for reducing pain during retinopathy of prematurity eye exams?

## Searches

Search strategy was developed in consultation with a library professional and conducted February, 2017. Databases searched include: MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and Embase. As there are no consensus guidelines regarding the impact of language restriction in systematic reviews, and conflicting evidence regarding the value of reducing language restrictions, only studies published in English will be considered for inclusion. Unpublished studies will be included if provided in a format that provides the opportunity for critical appraisal. No time limits will be included.

## Types of study to be included

Eligible studies included parallel group randomized controlled trials comparing at least two interventions intended to reduce pain from retinopathy of prematurity eye exams. Participants must be preterm neonates (e.g. <37 weeks gestational age) undergoing an ROP exam in the NICU. Trials must be published in a peer-reviewed journal or contain enough information to allow for critical appraisal.

## Condition or domain being studied

Since the early 80s, untreated neonatal pain has been recognized as having important ethical and clinical implication. Untreated pain was most famously associated with increased mortality within the surgical environment, and as a result there have been substantial improvements in the treatment of surgical and palliative pain. Following the recognition of the importance of treating surgical pain, the potential harmful role of repeated procedural pain has also been highlighted. While these studies have been limited by the non-randomized nature of pain exposure, we have seen consistent evidence that increased exposure to procedural pain is associated with numerous short and long-term sequalae including changes in physiological stability, alterations in white and gray matter development, and internalizing and externalizing behaviours.

Retinopathy of prematurity (RoP) is a potentially serious disease that arises from the immature vasculature of the preterm retinopathy. If left untreated, RoP can result in blindness. Current guidelines recommend that infants born less than 30 weeks receive repeat serial eye exams until their retina reach maturity. Standard practice for eye exams involves indirect ophthalmic examines which require eyelid retraction and scleral indentation. This procedure is widely recognized as being painful, with neonates showing both immediate pain behaviours and prolonged physiological arousal.

In order to reduce the pain associated with RoP eye examination, researchers have identified a number of pharmacological, non-pharmacological, and procedural interventions. While this is a positive development, the plurality of approaches makes a direct comparison of all interventions unfeasible without a very large multi-centre trial. As a result, despite the topic being the subject of at least three systematic reviews, it has not been possible to provide a statistically derived estimate of the most effective treatment. The purpose of this systematic review will be to combine all existing randomized and quasi-randomized trials of pain-relieving interventions for RoP exams using network meta-analysis in order to allow for comparison of direct and indirect evidence.

## Participants/population
Preterm neonates who require screening for retinopathy of prematurity

## Intervention(s), exposure(s)
1. Pharmacological interventions (e.g. paracetamol, anesthetic eye drops)
2. Sweet tasting solutions (e.g. sucrose, expressed breast milk)
3. Procedural modifications (e.g. use of wide-field digital camera versus binocular ophthalmoscopy)
4. Non-pharmacological interventions (e.g. non-nutritive sucking)

## Comparator(s)/control
Any active control, or no intervention.

## Context

## Primary outcome(s)
Validated pain assessment scale (e.g. premature infant pain profile, neonatal infant pain scale, etc..)

*Timing and effect measures*
Pain reactivity: Measurements within one minute of the start of the procedure
Pain recovery: Measurements taken after the procedure is completed

## Secondary outcome(s)
Behavioural measures (e.g. cry time)
Physiologic measures (e.g. heart rate, oxygen saturation)
Adverse events (e.g. bradycardia, apnea)

*Timing and effect measures*
Same as primary outcomes for behavioural and physiologic. Adverse events timing as defined by individual studies.

## Data extraction (selection and coding)
Abstract and title screen, full-text screening, and data extraction, will be conducted independently by two reviewers using Covidence. All conflicts will be resolved by reviewers and, if necessary, consultation with a third reviewer. Data will be extracted using standardized forms. Abstract and title screen, full-text screening, and data extraction, will be conducted independently by two reviewers using Covidence. All conflicts will be resolved by reviewers and, if necessary, consultation with a third reviewer. Data will be extracted using standardized forms.

## Risk of bias (quality) assessment
Critical appraisal will be conducted using the Cochrane risk of bias tool for randomized controlled trials. All studies will be assessed by two reviewers. Conflicts will be solved through consensus or, if necessary, resolved by a third reviewer.

## Strategy for data synthesis
For studies that provide binary outcome measures, we will calculate relative risks (RRs) to inform relative effectiveness. Weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis.
Unit of analysis issues:
CROSS-OVER TRIALS
Cross-over trials can lead to unit of analysis issues if correlations between treatment and control are unaccounted for. If treated as if the data was generated by parallel design, the precision of the trial will be underestimated and will receive less weighting in the analysis. The Cochrane handbook outlines several methods for addressing this issue, including imputation of missing correlation coefficient. Where possible, we will request data required for an exact calculation, but otherwise impute the correlation coefficient as outlined

by the handbook. Sensitivity analyses will be conducted on the values of the correlation coefficient, as well as results with cross-overs only, parallel trials only, and both combined.
Heterogeneity will be assessed visually in addition to using the standard deviation of the random effect distribution (tau). Previously established bench marks of measures of heterogeneity of the network (tau) will be used, which identify values of 0.1 to 0.49 as reasonable, 0.5-0.9 as moderate, and greater than 1 as potentially indicative of serious heterogeneity. If possible, sources of heterogeneity will be explored through subgroup analyses and/or meta-regression.
Assessment of inconsistency within the network (e.g. agreement between direct and indirect evidence) will be conducted using methods outlined by the National Institutes for Health and Care Excellence (NICE) technical support documents. Specifically, it will be assessed through the development of a consistency and inconsistency model. Point estimates of treatment comparisons will be compared between the two models, and deviation information critera (DIC) will be used as a measure of model fit. Generally, a reduction in DIC of greater than 4-5 points in the inconsistency model indicates signs on inconsistency. In addition to these methods, we will develop plots of residuals comparing the consistency and inconsistency models to facilitate identification of potentially problematic studies and/or study arms.
Relevant clinical and study design characteristics will be compared between eligible trials in order to assess acceptability for synthesis. These will include infant gestational age, birthweight, and year of publication.
Pooled treatment effects will be estimated using pairwise random-effects meta-analysis with a normal likelihood and identity link for continuous data, and a binomial likelihood with logit link for dichotomous data. Results will be expressed in mean difference or relative risk as appropriate and accompanied with their 95% credible intervals. Network meta-analysis was conducted using WinBugs through the freely available NetMetaXL interface. Rankograms and surface under the cumulative ranking curve (SUCRA) will be used to estimate the probability that a given treatment would be ranked first, second, etcetera.
SKEWED DATA
Many authors report that pain scales often produce skewed data, which may have important implications for pooled analyses. We will use methods outlined by the Cochrane handbook to test data reported as mean and SD for signs of skewness. When results are reported as median and IQR, we will assess whether the assumption of symmetry was supported. In the absence of signs of skewness, we used scores as reported, treated medians and the mean and imputed the standard deviation using method outlined by the Cochrane handbook. When assumptions of symmetry were not supported by the reported results, we conducted analysis using ratio of means.

## Analysis of subgroups or subsets

We will conduct two a priori sensitivity analyses: The first will be based on categorical specification of trials as “high risk of bias” or “low risk of bias”, and the second will investigate the potential influence of different control conditions (e.g. swaddling vs containment).

## Contact details for further information

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## Organisational affiliation of the review

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## Review team members and their organisational affiliations

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01 February 2017

## Anticipated completion date

30 April 2017

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Supported by student funding

## Conflicts of interest
None known

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English

## Country
Canada

## Stage of review
Ongoing

## Subject index terms status
Subject indexing assigned by CRD

## Subject index terms
Humans; Infant, Newborn; Infant, Premature; Network Meta-Analysis; Pain; Retinopathy of Prematurity

## Date of registration in PROSPERO
27 February 2017

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## Stage of review at time of this submission

| Stage | Started | Completed |
|---|---|---|
| Preliminary searches | No | Yes |
| Piloting of the study selection process | No | Yes |
| Formal screening of search results against eligibility criteria | Yes | No |
| Data extraction | No | No |
| Risk of bias (quality) assessment | No | No |
| Data analysis | No | No |

## Versions
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