**Pain relieving interventions for retinopathy of prematurity: Systematic review and network meta-analysis**

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To be submitted to: JAMA Pediatrics

Guidelines:

Maximum length: 4000 words of text, not including abstract, tables, figures, acknowledgments, references, and only-only material.

**Abstract**

**Context:** Despite substantial research effort to identify effective pain relieving interventions, there has been no systematic review that compares all available interventions.

**Methods:** Systematic review and network meta-analysis.

**Data sources:** MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and the WHO ICTRP (2004-Feb 2017).

**Study Selection:** Interventions intended to provide pain relief and could include pharmacological, non-pharmacological, multisensory, or procedural modifications (e.g. the use of wide-field digital retina imaging) were included.

**Data Extraction:** Abstract and title screen, full-text screening, and data extraction were conducted independently by two reviewers. The primary outcome waspain in during the exam period (pain reactivity) with pain following the exam (pain recovery) and adverse events as secondary outcomes.

**Results:** Seventeen studies (n = 1187) investigating nine interventions assessed pain reactivity phase. Only multisensory interventions combined with topical anesthetic showed statistically significant improvement over topical anesthetic alone (Random effect MD = 2.96, 95% Credible Interval = -5.23 to -0.62). Eleven studies (n = 630) assessed pain recovery with multisensory interventions showing a statistically significant decrease in pain (Random effect MD = -4.79, 95% Credible Interval = -8.81 to 0.79). No differences were detected in adverse events.

**Limitations:** We found evidence that vague priors artificially inflated network heterogeneity. Additional heterogeneity within nodes could not be explained through sensitivity analyses.

**Conclusions:** Recommendations for best treatments for ROP eye exams is complicated by significant heterogeneity. Use of informative priors may improve precision, but significant unexplained heterogeneity is likely to remain. Multisensory interventions are likely optimal, but results should be interpreted with caution.

**Background**

Preterm neonates,are at higher risk for pain exposures, which have been associated with numerous short and long-term sequelae including altered cortical development and changes in response to later pain1,2. Retinopathy of prematurity (RoP) is a potentially serious disease that arises from the immature vasculature of the preterm retina3. If left untreated, RoP can result in blindness. Current guidelines recommend that infants born less than 30 weeks receive eye serial eye exams until their retina reach maturity3. Standard practice for eye exams involves indirect ophthalmic examines which require eyelid retraction and scleral pressure3. This procedure is widely recognized as being painful, with neonates showing both immediate pain behaviors and prolonged physiological arousal4.

Methods to reduce the pain associated with RoP eye examination, include pharmacological, non-pharmacological, and procedural modification interventions4. The plurality of approaches makes a direct comparison of all interventions unfeasible without a large multi-centre trial. As a result, despite the topic being the subject of at least three recent reviews4–6, 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 trials of pain-relieving interventions for RoP exams using network meta-analysis to allow for comparison of direct and indirect evidence.

**Objectives**

To conduct a systematic review and network meta-analysis comparing all available pain-relieving strategies for RoP eye examinations.

**Methods**

**Protocol and registration**

**Study Design**

Systematic review with Bayesian network meta-analysis using the gemtc package in R for statistics7,8. A pre-specified protocol was followed (PROSPERO 2017: CRD42017058231).

**Search Strategy and Selection Criteria**

A database search was conducted and July 2017. The search strategy was developed in partnership with a library professional and included searches of the Cochrane Library Central Registry of Controlled Trials (1966-present), MEDLINE (1946-present), Embase (1974-present), and Web of Science (1900-present). A complete search strategy for MEDLINE can be found in the supplemental material. Eligible trials designs included randomized clinical trials comparing at least two pain-relieving strategies for ROP eye exams conducted in preterm neonates.

**Study Selection and Data Extraction**

Parallel group and cross-over designs were included. Eligible interventions included those that were intended to provide pain relief and could include pharmacological (e.g. sucrose, glucose, nitric oxide, topical anesthetic), non-pharmacological (e.g. facilitated tucking, bundling, holding, skin-to-skin contact, non-nutritive sucking), combined interventions, or procedural modifications (e.g. the use of wide-field digital retina imaging).

Abstract and title screen, full-text screening, and data extraction were conducted independently by two reviewers using Covidence9. All conflicts were resolved by reviewers and, if necessary, consultation with a third reviewer. Data was extracted using standardized forms.

**Outcomes**

The primary outcome was pain score as measured by validated pain assessment tools. All tools were converted to a common scale (the premature infant pain profile)10,11. Following the approach outlined in Pillai Riddell et al.’s12 Cochrane review of nonpharmacologic pain relieving interventions in neonates, we selected one time point measured during the procedure (pain reactivity), and the first time point after completion of the procedure (pain recovery). Secondary outcomes included physiological response (e.g. heart rate) and adverse events. When multiple adverse events were reported, the most serious were used for meta-analysis.

**Quality Assessment – Risk of Bias**

Critical appraisal was conducted using the Cochrane risk of bias tool for randomized controlled trials13. Two reviewers assessed each study, with conflicts resolved through consultation or, if required, consultation with a third reviewer.

**Statistical Analysis**

Relevant clinical and study design characteristics were compared between eligible trials to assess acceptability to synthesis. These included infant postmenstrual age at the time of the procedure, birth weight, use of a speculum and scleral depression during the procedure, and infant positioning (e.g. swaddled or contained). Pairwise and network meta-analysis was conducted using gemtc8. Standard errors for cross-over trials were adjusted by converting paired t-tests to standard error in order to appropriately capture precision for these trials14. All analyses were run on four chains with 20,000 iterations a chain including a burn in period of 5000 runs. Convergence was monitored using the Brooks-Gelman-Rubin diagnostic, with values less than 1.05 considered acceptable if consistent with visual inspection of convergence and time series plots15,16. Results of continuous scales were expressed in mean difference and accompanied with their 95% credible intervals (CrI). Adverse events were expressed as odds ratios (ORs). Surface under the cumulative ranking (SUCRA) statistics were calculated to express the probability that a treatment is optimal17. Results of the largest trial were used to estimate the absolute PIPP reactivity score, and this value was used to convert mean differences to absolute scores for the top three treatments15. Mean absolute scores were used to calculate the number of infants expected with scores indicating low, moderate, and severe pain assuming pain scores are normally distributed. Heterogeneity was assessed through the standard deviation of the random effect distribution. Assessment of inconsistency within the network (e.g. agreement between direct and indirect evidence) was conducted primarily through the use of an inconsistency model with node-splitting methods used as a secondary assessment18.

**Results**

**Search results**

The database search returned 831 citations after removal of duplicates, of which 29 studies met all inclusion criteria (Supplementary figure 1).

**Study characteristics**

Twenty-one trials were parallel randomized controlled trials19–40, with six studies41–46 reported as randomized crossover trials. Based on consultation with clinicians and pain researchers, interventions were grouped based on underlying mechanism of action (supplementary table 1). Studies were similar in infant and procedure characteristics (e.g. use of speculum) (supplementary table 2). Ten studies stated that infants were swaddled during the procedure23,25–27,29–31,44–46, and the remainder stating infants were contained.

**Risk of bias within studies**

Studies assessing interventions that were easily blinded (e.g. sweet taste, oral acetaminophen) were considered to be at an overall low risk of bias (supplementary figure 2). Details of sequence generation and allocation concealment were unclear in most studies. Studies that tested interventions which were difficult or impossible to the blind (e.g. sensorial saturation) scored as high risk of bias on outcome assessors.

**Publication Bias**

We intended to use funnel plots to investigate signs of publication bias, although no comparisons had sufficient studies13. We identified several trial registries indicating trials that are or should realistically be complete without an identifiable publication of results in abstract or manuscript form47–52. One of these was a trial assessing the efficacy of acetaminophen which was stopped early because the intervention showed no effect49. None of the contacts listed responded to e-mails.

**Validated Pain Assessment Scales**

Twenty-two (n = 1187) investigating nine interventions reported results of a validated pain assessment scale during the pain reactivity phase (Fig 2A). Adding additional interventions resulted in incrementally larger differences in treatment effect (Fig 3).

Eleven studies assessing nine interventions (n = 630, Fig 2B) were included in the analysis. The most common interventions were anesthetic eye drops (8 studies, n = 211) followed by multisensory interventions combined with anesthetic drops (4 studies, n = 91). As in the case of the reactivity analyses, large amounts of network heterogeneity resulted in wide credible intervals that prevented any intervention except anesthetic drops combined with a multi-sensory intervention from reaching statistical significance (Table 2). Except sweet taste being considered the most-likely best intervention, ranking based on such followed the trend that increased number of interventions was associated with increased pain relieving effects (Figure 4). Sensitivity analyses were conducted removing studies with scaled scores or imputed means, cross-over designs, and residual deviance greater than 1.5 (Table 2). Direction and magnitude of effect did not meaningfully change for any comparison. The inconsistency model for this comparison only offered a slight improvement in DIC (0.13 points lower).

**Heart rate**

Seventeen studies (n = 1187) investigating nine interventions reported results of a validated pain assessment scale during the pain reactivity phase (Fig 2A). Adding additional interventions resulted in incrementally larger differences in treatment effect (Fig 3).

Eleven studies assessing nine interventions (n = 630, Fig 2B) were included in the analysis. The most common interventions were anesthetic eye drops (8 studies, n = 211) followed by multisensory interventions combined with anesthetic drops (4 studies, n = 91). As in the case of the reactivity analyses, large amounts of network heterogeneity resulted in wide credible intervals that prevented any intervention except anesthetic drops combined with a multi-sensory intervention from reaching statistical significance (Table 2). Except sweet taste being considered the most-likely best intervention, ranking based on such followed the trend that increased number of interventions was associated with increased pain relieving effects (Figure 4). Sensitivity analyses were conducted removing studies with scaled scores or imputed means, cross-over designs, and residual deviance greater than 1.5 (Table 2). Direction and magnitude of effect did not meaningfully change for any comparison. The inconsistency model for this comparison only offered a slight improvement in DIC (0.13 points lower).

**Oxygen saturation**

Seventeen studies (n = 1187) investigating nine interventions reported results of a validated pain assessment scale during the pain reactivity phase (Fig 2A). Adding additional interventions resulted in incrementally larger differences in treatment effect (Fig 3).

Eleven studies assessing nine interventions (n = 630, Fig 2B) were included in the analysis. The most common interventions were anesthetic eye drops (8 studies, n = 211) followed by multisensory interventions combined with anesthetic drops (4 studies, n = 91). As in the case of the reactivity analyses, large amounts of network heterogeneity resulted in wide credible intervals that prevented any intervention except anesthetic drops combined with a multi-sensory intervention from reaching statistical significance (Table 2). Except sweet taste being considered the most-likely best intervention, ranking based on such followed the trend that increased number of interventions was associated with increased pain relieving effects (Figure 4). Sensitivity analyses were conducted removing studies with scaled scores or imputed means, cross-over designs, and residual deviance greater than 1.5 (Table 2). Direction and magnitude of effect did not meaningfully change for any comparison. The inconsistency model for this comparison only offered a slight improvement in DIC (0.13 points lower).

**Adverse events**

Few studies reported the frequency of adverse events, with two distinct networks preventing a complete comparison of the include treatments. The first network consisted of two studies comparing anesthetic drops, anesthetic drops in addition to acetaminophen, and anesthetic drops with a sweet taste (n = 160, Fig. 2D). Adverse events in all cases were bradycardia, but there was a large unexplained in the baseline risk of events between studies. The second network consisted of two studies comparing anesthetic drops with NNS against anesthetic drops with a multisensory intervention (n = 104, Fig 2C). All arms in all included studies had at least one event. Because all nodes were single study connections, a fixed-effect model was used. In both networks, there were no statistically significant differences found between interventions (Fig 5).

**Discussion**

To our knowledge, this is the first attempt at a network meta-analyses of interventions intended to decrease procedural pain in preterm neonates. While most comparisons failed to reach statistical significance, probabilistic results support the hypothesis that engaging more sensory systems likely results in improved pain relief. The exception is during the recovery period where sweet taste was the optimal intervention, although it should be considered that this was the result of a single trial. Point estimates were robust to sensitivity analyses, which provides some degree of confidence in their findings although all results should be interpreted with caution.

Interpretation of the findings is complicated by profound heterogeneity across all networks. This is especially problematic considering pairwise meta-analyses results showed that acetaminophen, and multisensory interventions combined with topical anesthetic, were superior to topical anesthetic alone. No sensitivity analysis could meaningfully reduce heterogeneity, which was driven in all cases by disparate results in the current studies. Investigation of potential sources of heterogeneity was further limited by incomplete procedure reporting which made it difficult to know the exact timing of the recording of the pain response, and potentially important procedural modifiers (e.g. presence or absence of eyelid speculum or scleral depression). While these factors may explain some additional heterogeneity, it should be noted that this appears to be a consistent problem faced in meta-analysis pain-relieving interventions in neonates. Two recently updated Cochrane systematic reviews assessed nonpharmacologic12 and skin-to-skin contact53 as interventions for reducing pain from commonly performed painful procedures in preterm and term neonates. In both cases, moderate the high heterogeneity was a commonly cited reason for downgrading the level of evidence from combined analysis. The recently updated review of sucrose for painful procedures did not experience the same difficulty. However, most analyses were limited to single studies54. No reviews have had success in identifying explanations for this heterogeneity, and thus it is unclear whether it is the result of methodological or clinical heterogeneity.

An unexpected challenge in interpreting these results arises from the need to compare interventions which are amenable to blinding with those that are not. For example, it is relatively simple to blind, sterile water against sweet-tasting solutions, but not possible to do so when comparing anesthetic drops alone to a multisensory intervention (e.g. NIDCAP, or sensorial saturation). As a result, it is possible that estimates of multisensory interventions are biased which may make them appear to be superior to sweet taste alone when in fact they are not. This may have clinical implications, as multisensory interventions are more resource intensive to implement.

While using cut scores to determine mild, moderate, or severe pain shouldgenerally be avoided, it is important to comment on the relative inability of any intervention to meaningfully reduce average raw scores. For example, when assessing pain during eye exam 12 of the 17 studies reported PIPP scores of 11 or greater in both groups with six of those documenting scores considered to reflect severe pain. This is placed in comparison to the same interventions used to reduce pain from vaccination, heel lance, or venepuncture where scores in intervention groups are routinely lying within four and six points on the same scale12,53–55. Strong conclusions from these findings are not warranted. However, it does draw our attention to two points of consideration: Whether existing pain scales valid for assessment of pain from RoP exams, and should we be giving greater consideration to more powerful interventions? The PIPP was the most used pain scale included in this review, however, in the most recent review of validation and reliability authors have not reported validation studies for RoP exams54. This is of relevance because the exam itself includes direct manipulation of the face including eyelid speculum and a bright light, which makes up three domains (and a possible 9 points) on the PIPP. The lowest raw score on the PIPP came from a unit that did not use the eyelid speculum28, and while it is tempting to suggest this as an approach to relieve pain, it is difficult to say whether this is an artifact created by the scale not being valid for these procedures. Others have suggested that persistently high raw pain scores suggest that stronger analgesics should be investigated (e.g., opiates). One ongoing clinical trial will investigate the use of morphine for pain reduction during an eye exam and use the PIPP to assess pain. While this will undoubtedly provide important information, it will need to be interpreted within the possibility that the tool itself is not a valid measure of pain perse.

**Conclusions**

Substantial network heterogeneity limits confidence in findings and may disguise real differences in treatment effects observed in the pairwise meta-analysis. Current evidence suggests that the optimal treatments are likely to be anesthetic eye drops in combination with either sweet taste or multisensory interventions, although the evidence is of very low quality. Estimates for all interventions include potentially clinically meaningful benefit or harm, introducing substantial uncertainty in recommendations for practice and future research. Assumptions about the validity of pain scores for ROP exams may need to be revisited. Future studies should be careful to report exactly when pain scores were assessed, and provide all relevant details of the procedure including the use of a speculum and scleral depression, and infant positioning.

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