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Review: Pain relief for premature babies during ophthalmology assessment

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Abstract

Background: Ophthalmological examination commonly carried out for ROP screening in premature infants is a painful and uncomfortable procedure. However, it is an essential part in the management of a premature baby.

Methods: Literature search was carried out using MEDLINE (January 1980 to January 2011) and Cochrane Central register of Controlled Trials Issue 1 of 4, January 2011 to determine the currently available evidence on methods pain relief for premature babies.

Results: There are various studies that have investigated the benefits of topical anesthesia, oral sucrose, non nutritive sucking, developmental care and ROP examination techniques on pain relief. Eyelid speculum insertion appears to be the most uncomfortable aspect of the screening examination. Oral sucrose did not result in a significant reduction in pain scores (weighted mean difference -0.65 (95% CI -1.88, 0.59). Topical proparacaine marginally decreased pain without any side effects (pain score ≥ 11 in 65% of the examination in control group compared to 27% in the treatment group; p=0.04). The infants randomized to pacifiers had lower pain scores compared to those without pacifiers (95% CI -4.23, -0.96; p = 0.003). Infants who were nested experienced less distress (duration of crying for nested and non-nested was 11.8 sec and 92.4 sec respectively; p<0.01). There was conflicting data on the benefits of different ROP screening techniques.

Conclusion: Topical anesthetic agent marginally reduces pain during eye examination in premature infants. Non pharmacological interventions such as non-nutritive sucking with a pacifier and nesting may be beneficial.
Background

Preterm birth, defined as childbirth occurring at less than 37 completed weeks or 259 days of gestation, is a major cause of neonatal mortality and morbidity and has long-term adverse consequences for health. The World Health Organization estimates that there are more than 12 million preterm births per year and the numbers are increasing. A significant proportion of these babies will develop Retinopathy of Prematurity (ROP). The current joint policy statement on ROP screening produced by the American Academy of Pediatrics (AAP), American Academy of Ophthalmology and the American Association for Pediatric Ophthalmology and Strabismus recommends that babies with a birth weight of less than 1500 g or gestational age (GA) of 30 weeks or less and high risk infants undergo retinal examination to detect ROP. This guideline also recommends that efforts should be made to minimize discomfort and systemic effects of eye examination by pretreatment of the eyes with a topical anesthetic agent such as proparacaine and to use other methods such as pacifiers and oral sucrose although it does not provide any references to support these recommendations. Adequate pain relief is important in neonates. Neonates, unlike adults are unable to express the amount of pain they are feeling. Inadequate pain relief may result in neonates developing increased pain sensitivity over time and altered responses to pain later in life. Animal studies on brain and spinal cord development suggest that repetitive pain during the neonatal period may cause permanent or long-term changes in the immature brain. This review assesses the currently available evidence on pain relief for premature infants during this uncomfortable procedure.
Currently available evidence shows that ROP examination is a painful and distressing procedure for a premature baby. The neonatal pain management policy produced by AAP recognizes that ROP examination is a painful and uncomfortable procedure and cautions that the currently available methods of pain relief with topical anesthetic agents or oral sucrose may be insufficient. There are various methods which can be used to assess pain in babies. One of the more commonly used and established scoring methods developed to assess acute pain in preterm is the Premature Infant Pain Profile (PIPP) score. This is a 7-indicator composite measure that includes behavioral, physiologic and contextual indicators. PIPP consists of 3 behavioral (facial actions: brow bulge, eye squeeze, and nasolabial furrow) and 2 physiological (heart rate and oxygen saturation) indicators, and 2 contextual [gestational age (GA) and behavioral state] variables that modify pain. Possible scores range from 1 to 21. PIPP scores <7 are indicative of no pain, PIPP scores 7 to 12 are indeterminate and >12 are indicative of significant pain. First introduced approximately 14 years ago, this tool has been validated in numerous reviews and continues to be a reliable method of assessing pain in preterm neonates. The AAP recommends that whatever pain assessment tools are used, continual multidisciplinary training of staff in the recognition of neonatal pain and in the use of the chosen pain-assessment tools should be provided.

Local Anesthesia

Topical anesthesia such as proparacaine hydrochloride is often used as a pre-treatment for the eyes prior to examination. This is a rapidly acting local anesthetic agent which has duration of action of 10 to 20 minutes. The efficacy of topical anesthesia during
ROP screening has been rather controversial. Table 1 compares four different studies on the effects of topical anesthetic agent on pain relief in premature infants during ROP examination. All studies used proparacaine as topical anesthesia. In an earlier study by Saunder et al., 55 patients were recruited but the data was only available for 42 patients. No standardized method of pain scoring was used. Instead, patient’s vitals signs and cry intensity was recorded. The investigators found that there was no difference in any of these parameters between the two patients groups and concluded that topical anesthetic agents offered no advantage over normal saline eye drops during the examination of premature infants.

Subsequent clinical studies however, have shown that the use of topical anesthetic agent does have a significant effect on pain relief in premature infants. The authors’ however differed in their conclusions. Study by Marsh et al. concluded that topical anesthetic pretreatment with proparacaine during speculum insertion significantly reduces the PIPP score compared with saline and the authors proposed it should become routine practice. In a study by Mehta et al., the investigators suggested that proparacaine eye drops should be routinely used for the short term, immediate relief of pain during ROP screening in preterm infants of lesser GA. In this study, the patients underwent assessment at GA 33.3 and 35.3 weeks. There was significant difference in PIPP scoring during the first examination between the treatment and control group. However, PIPP scores at 1 and 5 minutes during the 2nd examination were significantly lower compared to first examination regardless of type of drops instilled (1 minute 11.9 vs. 10.15 , p =0.03 and at 5 minutes 5.7 vs. 4.475 , p =0.025 ). Mature infants felt less pain and tolerated ROP screening better. These investigators concluded that proparacaine is not beneficial for mature infant. In a more recent study, Cogen at al. investigated the benefit of proparacaine compared to
artificial tears during ROP eye examination. PIPP score from was measured during the assessment of right eyes on three separate occasion (speculum insertion, indirect ophthalmoscopy and indirect ophthalmoscopy with scleral depression). Corneal clarity was subjectively assessed by the examiner. There was no difference in PIPP score between treatment and control group on all three phases of examination (p > 0.05). PIPP score was highest during scleral indentation in both groups but the significance of this was not determined in this study. Although the individual percentage of PIPP score being ≥ 11 was not different between treatment and control groups, the final cumulative comparison showed 65% of the examination in the control group had a score of ≥ 11 compared to only 27% in the treatment group (p = 0.04). There was no effect on corneal clarity. The authors concluded that topical anesthesia can marginally decrease pain in premature infants without any adverse effect.

**Oral sucrose**

Non pharmacological agents such as oral sucrose are being used for pain relief in neonates. A Cochrane systematic review on sucrose for analgesia in newborn infants undergoing painful procedures concluded that sucrose is safe and effective for reducing procedural pain. The majority of the studies reviewed involved the effect of sucrose as pain relief in babies who had their heel lanced. However, an optimal dose could not be identified due to inconsistency in effective sucrose dosage among studies (ranges between 12 to 50% sucrose). This review analyzed forty-four studies enrolling 3,496 infants. The authors also carried out a systematic review of five published articles on the effect of sucrose during ROP assessment in premature infants which are summarized in table 2. The overall pooled results however
showed that oral sucrose did not cause a significant reduction in PIPP score in premature infants undergoing eye ROP assessment (weighted mean difference -0.65 (95% CI -1.88, 0.59).

Interestingly, another recently published study showed that oral sucrose does not significantly affect activity in neonatal brain or spinal cord nociceptive circuits, and therefore might not be an effective analgesic agent. In this double-masked, randomised controlled trial, 59 newborn infants were randomly assigned to receive 0.5 ml 24% sucrose solution or 0.5 ml sterile water 2 minutes before undergoing a clinically required heel lance. The primary outcome was pain specific brain activity evoked by one time-locked heel lance, recorded with electroencephalography and identified by principal component analysis. Secondary measures were the PIPP score, and spinal nociceptive reflex withdrawal activity. The PIPP score was significantly lower in infants given sucrose than in those given sterile water and significantly more infants had no change in facial expression after sucrose administration (mean 5·8, 95% CI 3·7–7·8 vs 8·5, 7·3–9·8; p=0·02). However, the nociceptive brain activity after the noxious heel lance did not differ significantly between infants who received sucrose and those who received sterile water (sucrose: mean 0·10, 95% CI 0·04–0·16; sterile water: mean 0·08, 0·04–0·12; p=0·46). No significant difference was recorded between the sucrose and sterile water groups in the magnitude or latency of the spinal nociceptive reflex withdrawal recorded from the biceps femoris of the stimulated leg. The investigators in this study concluded that the ability of sucrose to reduce clinical observational pain scores after noxious events in newborn infants should not be interpreted as pain relief. Perhaps oral sucrose distracts the baby from the painful stimuli giving a lower PIPP score which is misinterpreted as pain relief.
Non-nutritive sucking has been investigated as an option for pain relief during screening for ROP. Boyle et al.\textsuperscript{21} (Table 2) evaluated the use of oral sucrose and/or pacifier for reducing pain responses during eye examinations. The infants randomized to pacifiers scored lower than those without pacifiers and there was no difference between groups receiving sucrose and those receiving water. The authors concluded that non-nutritive sucking with a pacifier reduced distress responses in infants undergoing screening for ROP.

Developmental Care

Other non-pharmacological interventions have been investigated as a possible method of pain relief. The Newborn Individualized Developmental Care and Assessment Program (NIDCAP) is an intervention program aiming at optimizing and adapting neonatal care for preterm infants.\textsuperscript{27-30} It is believed that NIDCAP-based interventions ("developmental care" interventions) may exert positive influences on pain and stress responses during routine care procedures, for example, diaper changes or weighing.

Slevin et al.\textsuperscript{31} investigated the degree of distress caused by ROP screening in a cohort of preterm infants and the effects of nesting in reducing their discomfort. This nesting concept was derived from developmental recommendations about the nursing care of preterm infants.\textsuperscript{29} Before screening, the nested infants were placed on a soft padded surface with boundaries that helped to maintain and support them in a flexed position but still allowed unrestricted movement of their body and limbs. The non-nested infants were placed on a standard cot blanket without any boundaries. Both groups of infants were thus able to move freely without any restriction. From
In another study, Kleberg et al.\textsuperscript{32} evaluated the effect of NIDCAP on newborn stress during ROP assessment. NIDCAP is a whole educational program but for the purpose of this study, short-NIDCAP based interventions ("developmental care" interventions) were used. This involved developmental care strategies such as undisturbed periods, incubator covers, bed support, and reduction in environmental light and noise. In this study, the first two eye examinations in thirty six preterm infants were evaluated. The infants were randomly assigned at the first eye examination to receive either NIDCAP or standard care. The investigators assessed PIPP scores and salivary cortisol at defined time points up to four hours after the eye examination. There was no difference in PIPP score between the two care strategies before or after the eye examination. Salivary cortisol increased from baseline to 30 minutes after the eye examination independent of care strategy and decreased significantly between 30 and 60 minutes when infants were subjected to NIDCAP but not after standard care. The investigators concluded that NIDCAP-based intervention during eye examination does not decrease pain responses but results in faster recovery, as measured by lower salivary cortisol 60 minutes after the examination. The limitation of this study is that there is no control group in which no eye study is performed to assess the response of the baby to the study procedures independent of the eye examination itself.
Rush et al. investigated the benefit of combined comfort care and pacifier soaked with 24% sucrose solution (Table 2). The investigators found that the vital signs did not vary significantly between the two groups. The participants in the control group had a trend towards a longer crying time, but this trend did not reach statistical significance. In addition, the time required for the vital signs to return to their baseline values did not vary significantly. The authors concluded the routine use of comfort care to reduce pain during the examination could not be supported by this study. The limitation of this study is that the authors used different methods of pain relief (swaddling, pacifier and sucrose 24%) which could have confounded the final results.

ROP screening technique

Do examination techniques for ROP screening of babies have an impact on pain? There is currently conflicting information on the severity of pain experienced by a baby undergoing different modes of ophthalmology examination. Mehta et al. compared the physiological and behavioral changes in premature infants undergoing three different methods of screening for ROP. In this prospective randomized crossover study, fifteen premature infants requiring screening for ROP were recruited, and physiological and behavioral responses produced by three different methods of screening were compared. The screening methods used a retinal camera with eyelid speculum and an indirect ophthalmoscope with and without an eyelid speculum. Physiological indices (change in pulse, mean blood pressure and oxygen saturation) and facial responses to pain (brow bulge, eye squeeze, nasolabial fold, mouth opening and the presence of cry) were recorded at five points: before, during and immediately after screening and 10 and 30 min after examination. The investigators found that screening with the retinal camera and the indirect ophthalmoscope with a speculum
both caused a greater change in pulse and mean blood pressure and an increase in facial responses during and immediately after screening as compared to the indirect ophthalmoscope without the speculum.

Muherjee et al.\textsuperscript{34} carried out a study on a larger cohort of preterm infants and compared the impact of ROP screening examination between a digital retinal camera and conventional binocular indirect ophthalmoscope (BIO) using cardio respiratory indices as a measure of distress. The investigators did not use the PIPP score. Eighty-six preterm infants with a birth weight of $\leq 1500$ g or gestational age of $\leq 32$ weeks and undergoing ROP screening were included. Heart rate (HR), oxygen saturation, respiratory rate (RR), and mean blood pressure (BP) were recorded before, during, and 1 hour after examination. The increase in HR (mean $23.4 \pm 28.6$ vs $13.7 \pm 25.2$; $p = 0.038$) and RR (mean $11.1 \pm 17.9$ vs $1.3 \pm 15.3$; $p = 0.01$) was significantly higher in the indirect ophthalmoscope group than in the digital camera group. The investigators concluded that screening for ROP with a digital retinal camera was associated with a significantly lower stress-related response than with a conventional indirect ophthalmoscope.

In a recently published prospective, randomised comparative study, 76 premature infants with a mean GA of 28.6 weeks needing ROP examination were randomized to undergo either examination with BIO or with a wide field retinal camera.\textsuperscript{35} A lid speculum and scleral indenter were routinely used for indirect ophthalmoscope examination. The digital retinal examination was carried out with a lid speculum but scleral indentation was not routinely performed. Infants were examined on a cot blanket. They were unswaddled and non-nested. Pacifiers were not used and oral sucrose was not given. The PIPP scoring system was used to determine the severity of pain experience by the patients. Baseline observations were recorded
and during the first minute of the examination. The PIPP score was assessed by an independent observer, who could not be masked to the type of examination. From this study, the investigators found that PIPP score was elevated during both types of examination (mean PIPP score for retinal camera 15.0±2.1, BIO 15.2±2.4; p=0.47) but there was no statistically significant difference between the two different types of examination. The conclusion from this study was that both types of examination with eyelid speculum are similarly painful for infants. The authors proposed that the eyelid speculum rather than the examination method contributed most to the pain experienced.

**Effects of feeding of pain during ROP examination**

The effect of feeding on pain during ROP examination was investigated by Strube et al.\textsuperscript{36} This prospective, randomized, single-masked study involved infants in the neonatal intensive care unit who required an ROP eye examination and who received normal or full enteral feeding. Infants were randomly assigned to 1 of 2 study arms: feeding 1 hour before examination (arm 1) or feeding schedule adjusted to ensure no feeding within 2 hours before examination (arm 2). No formal pain scoring was used; instead blood pressure and pulse rate, before, during and after examination, crying time during the examination was recorded. The presence of vomiting and gastric aspirates volume 24 hours after the examination, were recorded. The investigators found that there was 19% less crying (p = 0.016) in arm 1 versus arm 2. Vomiting or gastric aspirates were same between both groups. They concluded that feeding neonatal intensive care unit infants 1 hour before compared with withholding feeding 2 or more hours before ROP examinations may reduce stress during the examination.
A Cochrane review on effect of breast feeding or breast milk for procedural pain in neonates concluded that breast milk should be used to alleviate pain in neonates undergoing a single painful procedure compared to placebo. Breast milk was found to be as effective as sucrose. However, all 11 studies reviewed in the systematic review were on babies undergoing venepuncture or heel lancing for neonatal screening and none were from babies undergoing ROP eye examination.

Conclusion

Ophthalmological examination is a painful procedure. However, it is a very essential part in the management of premature infants. Topical anesthetic agent marginally decreases pain and could be used during examination. Speculum insertion appears to be the most uncomfortable aspect of the examination. Non pharmacological intervention such as non-nutritive sucking with a pacifier and nesting may be beneficial. There is no role for routine use of oral sucrose and there is evidence to suggest that it might not have any effect on pain perception. Currently available data suggest that babies should be fed as usual during eye examination and delaying feeds has no recognized benefit. Breast milk is a possible alternate for pain relief but more studies are needed to establish its benefit during ROP examination.

Literature search

Literature search was conducted by the authors using MEDLINE (January 1980 to January 2011) and Cochrane Central register of Controlled Trials Issue 1 of 4, January 2011, using the following keywords: retinopathy of prematurity, screening examination, neonates, pain relief and stress. Only articles published in English were considered.
Acknowledgement: Nil

References


Table 1. Studies comparing the use topical of anesthesia in infants undergoing eye examination for ROP

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saunders et al16</td>
<td>Randomized double masked control trial</td>
<td>42 infants, GA from 35 to 45 weeks (corrected age)</td>
<td>Proparacaine HCL 0.5% (cases) and normal saline (control)</td>
<td>No formal pain scoring – vital signs and cry recorded*</td>
<td>Analysis of variance used to compare parameter at 0, 2 and 5 minutes. p value &gt;0.05 for all comparisons</td>
</tr>
<tr>
<td>Marsh et al17</td>
<td>Randomized double masked cross-over control trial</td>
<td>22 infants, GA from 24 to 32 weeks</td>
<td>Proparacaine HCL 0.5% (cases) and normal saline (control)</td>
<td>PIPP (baseline score measured prior to examination and then 0, 1 and 5 minutes during examination)</td>
<td>PIPP score at speculum insertion(0 minute) is lower in treatment group (paired difference -2.5± 3.4; p=0.001) 1 minute, paired difference -1.2 ± 4.0, p = 0.09 5 minutes paired difference -1.3±3.6,p =0.06</td>
</tr>
<tr>
<td>Mehta et al18</td>
<td>Randomized double masked cross-over trial</td>
<td>50 infants, GA 26 to 31 weeks (assessment done at GA 33.3 and 35.3 weeks)</td>
<td>Proparacaine HCL 0.5% (cases) and normal saline (control)</td>
<td>PIPP (baseline score measured 1 minute prior and then 1 and 5 minutes during examination)</td>
<td>For 1st examination, PIPP score at 1 minute 11.725 (saline) vs. 10.375 (Proparacaine) (p=0.013) PIPP score at 5 minutes 5.225 (saline) vs. 6.550 (Proparacaine) (p=0.767)</td>
</tr>
<tr>
<td>Cogen et al19</td>
<td>Randomized double masked control trial</td>
<td>34 infants, GA 31 to 40 weeks</td>
<td>Proparacaine 0.5% (cases) and artificial tears (control)</td>
<td>PIPP (scores measured at speculum insertion, indirect ophthalmoscopy with and without sclera depression)</td>
<td>PIPP score ≥ 11 during 65% of the examinations without topical anesthesia compared with 27% examination with anesthesia ( p = 0.04)</td>
</tr>
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</table>

*Heart rate, respiration rate, BP, and transcutaneous oxygen saturation, infant cry and corneal opacity.
GA (gestational age), PIPP (Premature Infant Pain Profile)
Table 2. Studies using oral sucrose for pain relief in infants undergoing eye examination for ROP

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyle et al.</td>
<td>Randomized controlled trial</td>
<td>40 preterm infants with GA 24-34 weeks (median 29 weeks)</td>
<td>Sucrose 33% and sterile water ± pacifier (randomized to four interventions):</td>
<td>PIPP (during examination of first eye)</td>
<td>Mean PIPP scores were 15.3, 14.3, 12.3, and 12.1 for groups 1, 2, 3, and 4 respectively. ANOVA showed a significant difference score between groups (p = 0.023).</td>
</tr>
</tbody>
</table>
| Gal et al.     | Randomized double-masked controlled trial | 23 preterm infants with GA 24-29 weeks | 2ml Sucrose 24% and 2 ml sterile water (both groups also received proparacaine HCl) | PIPP (baseline scores 1 and 5 minutes pre-exam, at initial placement of the eye speculum and 1 and 5 minutes after examination) | Score during speculum insertion lower in sucrose group (paired difference –2.2 ± 3.9, p = 0.01)  
Effects not sustained at 1 and 5 minutes, paired difference –0.6 ± 4.1, p= 0.24; paired difference –0.9 ± 2.7, p= 0.07 respectively |
<table>
<thead>
<tr>
<th>Study</th>
<th>Trial Type</th>
<th>Number of Infants</th>
<th>Intervention Details</th>
<th>Pain Assessment Method</th>
<th>Pain Scores During Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grabska et al.</td>
<td>Randomized masked control trial</td>
<td>32</td>
<td>Sucrose 24% and sterile water (both groups received topical tetracaine, swaddled, and given pacifier; sucrose adjusted to body weight)</td>
<td>PIPP (Baseline measurement, during examination and at 1 minute intervals post examination)</td>
<td>PIPP score during examination 14±3 for both group (no significant difference)</td>
</tr>
<tr>
<td>Mitchell et al.</td>
<td>Randomized double-masked controlled trial</td>
<td>30</td>
<td>Sucrose 24% 0.1 ml (3 doses) and sterile water 0.1 (3 times) Both groups were given pacifier and received proparacaine HCl</td>
<td>PIPP (Baseline measurement, during examination and at 30, 60, 90, and 120 seconds post examination)</td>
<td>PIPP scores during examination for the sucrose group was significantly lower than in control group 8.8 ± 0.7 and 11.4 ±0.6 respectively, ( p =0.0077 )</td>
</tr>
<tr>
<td>Rush et al.</td>
<td>Randomized control trial</td>
<td>30</td>
<td>Pacifier soaked with Sucrose 24% and swaddling for treatment group. Study group received none of the above (both group received proparacaine)</td>
<td>None (Pulse rate, respiratory rate and oxygen saturation monitored 30 and 5 minutes before, during and 5 minutes after the examination)</td>
<td>No significant difference in the measured parameters between both groups ( (P&gt;0.05) )</td>
</tr>
</tbody>
</table>

GA (gestational age), PIPP (Premature Infant Pain Profile)