Topical Anesthesia or Oral Dextrose for the Relief of Pain in Screening for Retinopathy of Prematurity: a Randomized Controlled Double-blinded Trial

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Summary

Objective: Compare efficacy of 0.5% proparacaine eye drops and oral 25% dextrose in reducing pain during screening for retinopathy of prematurity (ROP).
Patients and Methods: Double-blinded randomized controlled trial. Twenty eligible babies were randomized. Group I received 0.5% proparacaine eye drops at first ROP screening, while Group II received 25% dextrose orally. At second examination, babies received no intervention. Pain was assessed using Premature Infant Pain Profile (PIPP) score.
Results: The mean ($\pm$SD) PIPP during procedure in Group I were 15.5 ± 2.06 and 14 ± 2.4 at first and second screening ($p = 0.259$). The mean ($\pm$SD) PIPP in Group II were 14.2 ± 1.8 and 14.9 ± 2.5 at the first and second screening ($p = 0.428$). Differences were not statistically significant. The PIPP scores of Group I and Group II at the first screening were also not significantly different ($p = 0.165$).
Conclusion: ROP screening causes moderate to severe pain and neither proparacaine nor dextrose is an effective analgesic.

Key words: ROP screening, dextrose, PIPP, proparacaine, pain.

Introduction

The incidence of retinopathy of prematurity (ROP) in various neonatal intensive care units (NICUs) is 27–35% in babies with birth weight of <1500 g, and 16–48% in babies <1000g [1]. ROP can be treated by laser and cryotherapy. If left untreated, severe ROP can lead to blindness. As the survival of preterm babies is steadily increasing with the focus on intact survival, screening for ROP in a susceptible population becomes absolutely necessary.

Screening for ROP involves a retinal examination usually done using an indirect ophthalmoscope. This examination involves the use of mydriatics to dilate the pupils, eye speculums to separate the eyelids and scleral indentation to facilitate examination of the peripheral retina. These, along with increased handling of the baby, lead to pain and discomfort. Repeated painful events in preterm babies may cause changes in the pain thresholds, perception and tolerance of pain during subsequent painful events and may have a negative impact on neurodevelopment outcomes [2, 3]. As there is an increasing need for ROP screening and hence a need to find a good analgesic for ROP screening, studies have been done using oral sucrose and topical anesthesia. The evidence for their use has been inconclusive. This study was planned to compare the efficacy of topical

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anesthesia and oral dextrose in reducing pain associated with ROP screening.

Patients and Methods

This was a prospective double-blinded randomized controlled trial in a level III NICU of a tertiary care hospital, from March to November 2007. All neonates requiring an ROP screening and likely to be in hospital for at least 2 ROP examinations were included in the study with parental consent. Babies with an Apgar score of <5/10 at 5 min, who were unable to take oral glucose, who were on opioid analgesics, sedatives or anticonvulsants were excluded. Neonates on mechanical ventilation including continuous positive airway pressure too were excluded. Babies who had an unanticipated discharge from hospital, prior to the second ROP examination returned for the ROP screen in the NICU.

The current NICU protocol in this institution is to do a ROP screen for all babies with a birth weight of <1750 g or <35 weeks of gestation (as determined by the New Ballard score) at 14 days of life. All babies satisfying the inclusion criteria were enrolled in the study. At the time of the first ROP screening, the babies were randomized into one of the two groups. Group I received the topical anesthetic and the group II received oral 25% dextrose. At the next ROP screen, usually done after 1–2 weeks, the babies received neither the topical anesthetic nor the oral dextrose. Thus each baby acted as his/her own control.

Randomization was done using random number table. Topical anesthesia was administered with one drop of 0.5% proparacaine eye drops instilled 10 min prior to examination. Two milliliters of oral dextrose 25% was administered orally by pallada or with a syringe 2 min prior to the procedure. The anesthetic drops and the oral dextrose were administered by the nurse who was uninvolved in the scoring of pain or the analysis. The ophthalmologist and the observer were thus blinded. All the babies were nested during the procedure.

The eye examination was performed by the same ophthalmologist (SN) using an indirect ophthalmoscope with a 20 diopter lens, after mydriasis with tropicamide 0.5% and phenylephrine 2.5%. The time interval between two examinations was 2 weeks or less as determined by the ophthalmologist, depending on the severity of the disease.

Pain was assessed by PIPP—Premature Infant Pain Profile. This measures physiological and behavioral indicators (three facial reactions: eye squeeze, brow bulge and nasolabial furrow) to pain. The PIPP has been tested for reliability, validity and clinical utility with good results [4].

The baby's gestational age was noted on the performa. Just prior to the examination, the behavioral state, baseline heart rate and oxygen saturations were recorded. While the ophthalmologist examined the eye, one observer noted the vital parameters—maximum heart rate, minimum oxygen saturations and another observer videotaped the face of the neonate. This was done during examination of the left eye alone for each baby to allow for clear visualization of the baby's face. The three facial reactions—brow bulge, eye squeeze and presence of nasolabial furrow—were assessed by videotaping for 30 s. These same parameters were also noted at 1 and 5 min after the procedure.

The three facial responses to pain were assessed separately later by three replays of the video recording. Pain was scored on PIPP scale based on the seven parameters from 0 to 3 giving a maximum total score of 21. Care was taken to see that the videography and analysis of pain were done by the same blinded observer (Saudamini V Nesargi) for all the neonates to avoid interobserver variation.

Babies were monitored for side effects of the mydriatics like apnea, vomiting and feed intolerance for 12 h after the procedure.

A written informed consent was taken from either parent. The study was approved by the institutional ethics committee.

The sample size was calculated with reference to the study by Boyle with 90% power and 5% level of significance [5]. A total of 20 babies were enrolled to detect a two-point difference in the PIPP scores between the two groups within a standard deviation of 1.6.

All data were recorded on a predesigned performa, tabulated and the results analyzed statistically by SPSS statistical software (version 13). The paired *t*-test, independent sample *t*-test and repeated measures analysis of variance were used for analysis.

Results

A total of 65 babies required an ROP screening during the study period. Of these, 30 babies did not satisfy the inclusion criteria and 8 parents refused consent; 20 babies were enrolled, with 10 babies in each group. This resulted in a total of 40 examinations. Figure 1 shows enrollment details. The baseline characteristics were similar in both groups (Table 1).

The mean ($\pm$SD) PIPP score during the procedure in Group I (proparacaine) were 15.5 ± 2.06 and 14 ± 2.4 at the first and second screening, respectively, which was not statistically significant ($p = 0.259$; Table 2). The mean ($\pm$SD) PIPP scores in Group II (25% dextrose) were 14.2 ± 1.8 and 14.9 ± 2.5 at the first and second screening, respectively, and this difference was not statistically significant ($p = 0.428$; Table 2). On comparing proparacaine and dextrose, the PIPP scores were not significantly different ($p = 0.165$) (Table 2). There was a statistical difference in the mean PIPP scores during the procedure when compared with the PIPP scores at 1 and 5 min. The pain perceived by the baby during the procedure was moderate to severe

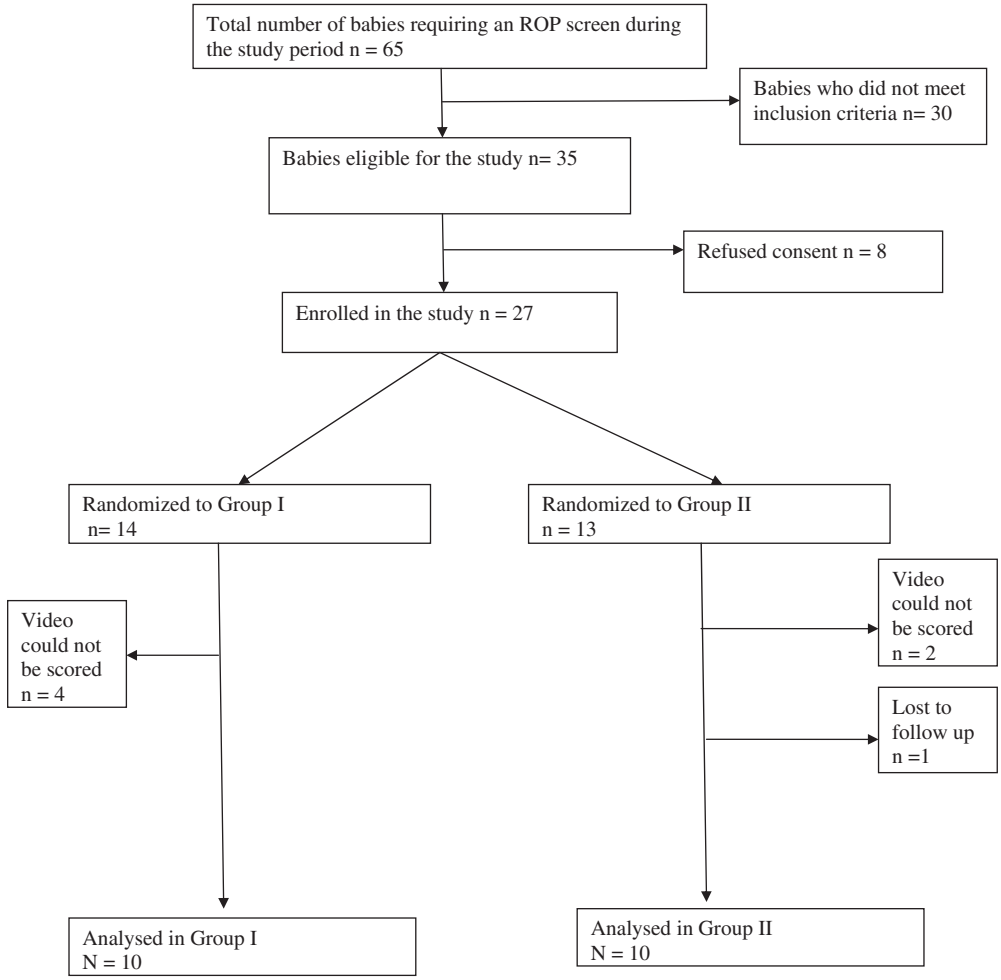

FIG. 1. Trial flow.

(PIPP > 12), while the pain after 5 min was mild or absent (PIPP < 6). No adverse reactions were noted.

Discussion

As the survival of smaller babies increases, the need for ROP screening also increases to ensure intact survival. The procedure however is painful [6] and repeated exposure to pain in the neonatal period alters the perception of pain later in the baby's life. There is also evidence to suggest that the babies exposed to pain have poor neurodevelopmental outcomes, in terms of emotional, behavioral and learning disabilities [2, 3]. The developing brain of preterm babies is more prone to these changes and they are also most vulnerable to developing ROP.

The American Academy of Pediatrics recommendation for pain relief during ROP screening is to use proparacaine [7]. There was no difference in the PIPP scores when proparacaine was used. Conflicting results have been reported by other authors. Saunders *et al.* [8] found no decrease in pain when proparacaine was used, while Cogen [9] found a decrease but not reaching statistical significance. Two studies have reported a beneficial effect; Mehta [10] and Marsh [11] both showed a decrease in PIPP scores at the time of speculum insertion and at 1 min, respectively; however there was no difference at 5 min in either studies and hence the benefit was not sustained.

Oral sucrose is well documented as an effective analgesic for painful procedures like heel lancing and venipuncture [12]. Its mechanism of action is thought to be through indirect release of endogenous opioids or through the release of dopamine, similar to that of sucrose [13, 14]. Its use during ROP screening has been investigated with varying results. Gal [6] and Mitchel [15] found that it decreased pain in contrast to Boyle, Grabska and Rush who found no analgesic effect [5, 16, 17]. In countries like India,

TABLE 1
Demographic data

Characteristics	Group I (Proparacaine group)	Group II (Dextrose group)	*p*-value
Gestational age(weeks)	31.7 ± 9.48	32.1 ± 2.5	0.032
Birth weight (g)	1102 ± 172	1232 ± 244	>0.05
Male:female	2:3	1:1	
Day of life of first screen	16.8 ± 1.6	16.3 ± 1.5	
Resuscitation required at birth %	30%	40%	
Ventilation required %	60%	80%	

TABLE 2
PIPP scores

PIPP Mean ± SD	Group I (proparacaine)			Group II (dextrose)			Comparison of group I and Group II *p*
	First screening	Second screening	*p*	First screening	Second screening	*p*	
During	15.5 ± 2.0	14.0 ± 2.4	0.259	14.2 ± 1.8	14.5 ± 2.5	0.428	0.165
1 min	8.1 ± 1.9	6.6 ± 3.4	0.224	9.0 ± 2.8	7.6 ± 2.7	1.05	0.147
5 min	5.6 ± 1.6	5.8 ± 3.8	0.619	3.7 ± 2.2	4.1 ± 2.1	0.657	0.147
p	<0.05	<0.05		<0.05	<0.05		

sucrose is not commercially available and hence dextrose was used. Studies report a similar efficacy as with sucrose when used for heel lance [18]. Various concentrations have been tried, 30% was found to better than 10 or 20% dextrose [19]. A 25% solution is readily available and hence was used. The dose administered was 2 ml given orally 2 min before the procedure, as in previous studies [20]. The present study did not find that the PIPP scores were lower in the group receiving dextrose. This is in concordance with a recent article [21].

The pain in ROP is due to insertion of the speculum, sclera depression and manipulation of the globe during visualization, bright light and physical restraints all of which cause deep pain [22]. Thus, proparacaine, a local anesthetic, might not alleviate this deeper pain [15]. Oral 25% dextrose has been found to alleviate the moderate pain of venipuncture and heel lance. The average pain as measured by the PIPP score in heel lancing and venipuncture is 5.8 [23] and 7–9 [24]. However 25% dextrose did not decrease the pain during ROP screening which is a more severe type of pain, PIPP score >12. A recent study also published that although the PIPP scores may decrease with sucrose, the Electroencephalogram findings were still suggestive of pain and hence sucrose in these situations may be only masking the pain [23]. Other studies have suggested that the use of a pacifier along with sucrose may be more effective [5]. Multiple doses of dextrose also may be better analgesics [25].

Other methods of pain relief that have been studied include nonnutritive sucking (pacifier), nesting and NIDCAP (newborn individualized development care and assessment program) [26] and nitrous oxide [27]. Of these, Non nutritive sucking appears to be promising. Alternative methods to indirect ophthalmoscopy for ROP screening—the use of a Retcam—has been investigated and found that the pain decreased when the speculum was not used, rather than with Retcam [28, 29]. The use of a Fabry lens has also been found to be less painful [30].

The strengths of this study are that it is a double-blinded randomized controlled trial. The babies were all videotaped and each of the parameters of the PIPP score was separately assessed by replaying the tape. The SN performed all the examinations. Each baby served as its own control because there is some variability in the pain perceived by an individual baby.

At the time the present study was conducted, there was no protocol for pain management in the institute nor were there any national guidelines. Subsequent to the study a pain protocol has been established in the unit. Recently national guidelines have been published which recommend swaddling, local anesthesia and 0.5–1 ml of 24% sucrose solution 1–2 min prior to the procedure. This sucrose solution is now commercially available in the country since the past 1 year.

This study showed that screening for ROP causes severe pain and may need a multimodal approach to decrease it—oral dextrose, local anesthesia, NIDCAP and possibly minimizing the use of the speculum.

Conclusions

The conclusions of the study are that neither oral 25% dextrose nor the topical anesthetic proparacaine was effective in decreasing the severe pain associated with screening for ROP. However, the pain is most during the procedure, and by 5 min there is minimal or no pain. More studies are needed using multimodal measure to find an effective way to reduce the pain during screening for ROP.

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