The Indian Journal of Pediatrics (May 2020) 87(5):353–358
https://doi.org/10.1007/s12098-020-03182-6

ORIGINAL ARTICLE

Prevention of Pain During Screening for Retinopathy of Prematurity: A Randomized Control Trial Comparing Breast Milk, 10% Dextrose and Sterile Water

Ramya Nayak[1] · Kalale Nikhil Nagaraj[2] · Girish Gururaj[3]

Received: 8 March 2019 / Accepted: 1 January 2020 / Published online: 27 January 2020

Abstract

Objectives To compare the efficacy of orally administered 10% dextrose, breast milk and sterile water on pain prevention during screening examination for Retinopathy of prematurity (ROP) in preterm neonates as measured by Premature infant pain profile (PIPP).

Methods A three-limbed double-blinded randomized control trial was conducted in a Level 3 neonatal intensive care unit. Forty five preterm neonates undergoing ROP screening were included. Eligible babies were randomly assigned to one of the three groups that orally received either expressed breast milk ($n = 14$), 10% dextrose solution (n = 14) or sterile water ($n = 17$), one minute before eye examination. The outcome measure was PIPP score.

Results All 3 groups were similar in baseline characteristics. The mean PIPP scores were comparable ($p = 0.18$) in the three groups (11.8 ± 2.8 *vs.* 9.8 ± 3.3 *vs.* 10.2 ± 2.9). The behavioral and physiological variables were also similar across all three groups.

Conclusions Expressed breast milk, 10% dextrose or sterile water administered orally before ROP screening in preterm neonates have similar analgesic effects and do not significantly alleviate pain during the procedure.

Keywords Procedural pain · Premature infant · Pain perception · Analgesia

Introduction

Preterm neonates do perceive pain and pain in these neonates has both short term and long term deleterious effect. Repeated experiences of pain in the neonatal period can cause altered cortical development and pain processing, such as decreased pain threshold, hyperalgesia, and allodynia [1–4]. Preterm babies are exposed to a variety of painful experiences during their neonatal intensive care unit (NICU) stay. Screening for ROP is one such procedure, where neonates show both immediate pain behavior and prolonged physiologic arousal [5]. During eye examinations, babies display well-defined pain responses [6].

Various interventions have been tried to reduce this pain response but have not been found to be very effective [7–9]. Both dextrose and expressed breast milk (EBM) have been found to have an analgesic effect during venipuncture, a relatively less painful procedure than ROP screening [10–12]. Studies have shown conflicting results on the use of oral sucrose/dextrose for prevention of pain during ophthalmoscopy [13–16]. Recent studies have used EBM for pain prevention during ROP screening [17–19]. EBM had better analgesic effect when compared to the use of topical anesthesia or sucrose in these studies. In the present study, authors compared the analgesic effects of EBM with 10% dextrose which is safe and easily available. Sterile water was used as a placebo.

Material and Methods

This was a three-limbed, randomized controlled double-blinded study. All the neonates included in the trial were eligible for ROP screening as per National Neonatology Forum (NNF) guidelines. Babies who were (1) nil by mouth, (2) had congenital malformation, (3) on a mechanical ventilator and (4) those who were on concurrent analgesic medication were

✉ Ramya Nayak
dr.ramyanayak@gmail.com

[1] Department of Pediatrics, Melaka Manipal Medical College, Manipal Academy of Higher Education, Manipal, India

[2] Department of Pediatrics, Motherhood Hospital, Sahakarnagar, Bangalore, India

[3] Department of Neonatology, Apollo BGS Hospitals, Mysore, India

excluded from the study. Forty-five neonates were randomized into three groups, who received either 10% dextrose, expressed breast milk or sterile water. Randomization was performed using computer-generated random numbers. Stratification of cases was done for weight < 1250 g and ≥ 1250 g at the time of enrollment. Babies with weight less than 1250 g received 2 ml and babies with weight more than 1250 g received 5 ml of either breast milk, 10% dextrose solution or sterile water one minute before the start of the examination as depicted in Fig. 1. Allocation concealment was done by storing the randomized group numbers in sealed opaque envelopes which were opened just before administration of intervention. The study solutions were prepared by members of the staff who were otherwise not involved with the study. Expressed breast milk was collected for all the babies in a sterile container before the start of the examination. Mydriatics used were cyclopentolate 0.5% and phenylephrine 2.5% one drop in each eye, repeated three times every 10 min. Infants also received the topical anesthetic proparacaine just before the eye examination. Eye examinations were carried out by an experienced ophthalmologist. Approval from the ethical committee of the hospital where the study was conducted was taken before initiating the study and written parental consent was obtained. Demographic details and baseline characteristics were recorded on a pre-designed proforma. Pain was assessed by Premature Infant Pain Profile (PIPP) score. This score incorporates maximum heart rate, minimum oxygen saturation, gestational age and three facial reactions—the presence of nasolabial furrow, brow bulge and eye squeeze. It was graded as mild (<6), moderate (6–12) and severe (>12) [20].

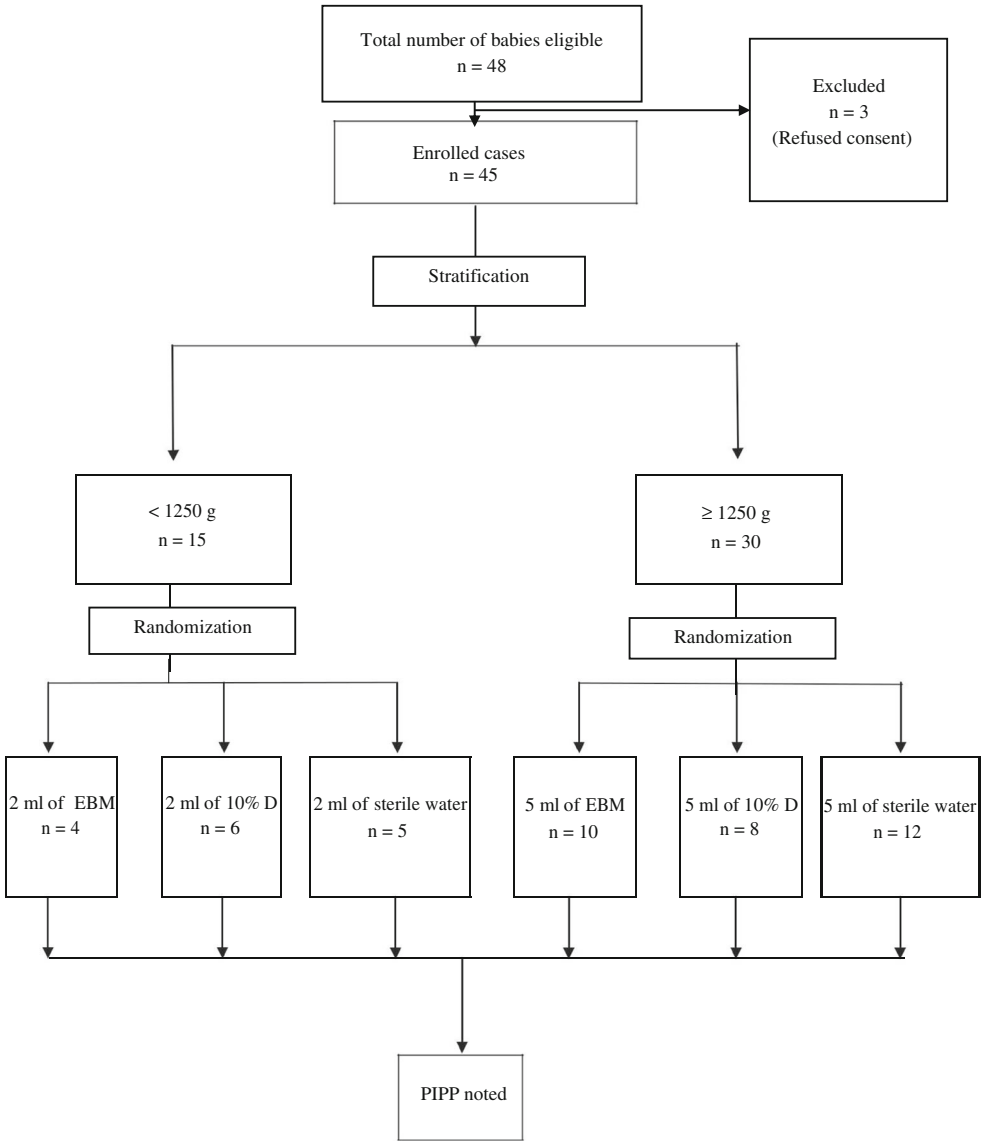

Fig. 1 Flow of participants in the study. *D* Dextrose; *EBM* Expressed breast milk; *PIPP* Premature infant pain profile

A difference in mean PIPP score of 2 was expected between the two groups with a standard error of mean being 1.5. With α error of 0.05 and power of the study being 90%, 13 neonates were needed in each group.

The gestational age was noted from the case records and weight on the day of enrolment was recorded. Eligible neonates were randomly assigned to one of the three groups to receive either expressed breast milk or 10% dextrose solution or sterile water, one minute before the start of examination which was taken from the time of insertion of lid speculum in the first eye being examined.

Primary investigator, parents and the person assessing the PIPP score were blind to the identity of the study solution. A trained nurse who was not involved in the study analysis delivered the solution directly into the mouth of the baby using a sterile syringe, one minute before the onset of the eye exam in the NICU and then the baby was shifted to RETCAM examination bassinet. The study ended one minute after the completion of the first eye exam. Throughout the procedure, non-nutritive sucking was given to all the babies using a sterile dry cotton wick. Each infant was observed before, during and until one minute after completion of the examination. Examination of only the first eye was used for recording PIPP score.

Heart rate and oxygen saturation were continuously measured and recorded on the bedside pulse oximeter. Baseline physiological parameters were collected before the start of the examination. Maximum heart rate and minimum oxygen saturation values were noted during the procedure by the primary investigator. A blinded person observed the facial expression of the babies before, during and up to one minute after the examination and timed the duration of brow bulge, eye squeeze and nasolabial furrow on the PIPP scale in all examinations. All the parameters were recorded on the study proforma, which was designed based on the objective of the study.

The data was entered in Microsoft Excel 2007 spreadsheet. Statistical analysis was done using Microsoft Excel and Epiinfo software (version 7.2.2). PIPP scores in the three groups were compared using a one-way ANOVA test.

Results

Forty-five neonates were included in this study. Fourteen neonates received 10% dextrose, 14 neonates received breast milk, and 17 neonates received sterile water. The baseline parameters across all the three groups were similar and are given in Table 1. There was no difference in the mean gestational age, birth weight, age and weight at the time of screening. Even though, babies who received dextrose have been examined at earlier postnatal age; this difference was not significant.

The physiological and behavioral parameters of the PIPP score have been detailed in Table 2. At baseline, there was no statistical difference between the three groups in mean heart rate and SPO_2. During the procedure, higher heart rate and lower oxygen saturation were noted in babies who received EBM. However, the difference was not significant. Babies in the dextrose group scored relatively less in behavioral parameters, but this difference did not attain statistical significance. The mean PIPP scores were comparable ($p = 0.18$) in the three groups (11.8 ± 2.8 *vs.* 9.8 ± 3.3 *vs.* 10.2 ± 2.9) which received EBM, 10% dextrose and sterile water respectively. The dextrose group had marginally lower mean PIPP score. However, this was statistically insignificant.

Discussion

Early diagnosis of ROP by screening at-risk neonates is essential for good visual outcome. Screening is done by indirect ophthalmoscopy, a potentially painful procedure which involves the insertion of a speculum, use of an indenter, and a considerable amount of handling. Despite the use of local anesthetic drops before eye examination, screening remains a painful procedure [8].

Various non-pharmacological interventions have been tried to alleviate the pain during ROP screening. Though sucrose is a widely studied agent for analgesia in newborns, authors used dextrose because sterile dextrose solution was readily available than sucrose solution. Further, oral dextrose is safe and has also been found to reduce pain perception in newborns undergoing painful procedures [21, 22]. Among the analgesics studied for neonatal pain, breastfeeding/breast milk is a natural, easily available, easy to use and potentially risk-free intervention. The potential mechanisms by which breast milk might provide an analgesic effect is the presence of lactose in breast milk [23]. Breast milk contains a higher concentration of tryptophan, a precursor of melatonin. Melatonin is shown to increase the concentration of beta-endorphins and could be one of the mechanisms for the nociceptive effects of breast milk [24].

In the present study, authors compared the efficacy of orally administered 10% dextrose, EBM and sterile water for pain prevention during ROP screening. There was no significant difference in the analgesic effect of either 10% dextrose or expressed breast milk in preterm neonates during ROP screening as measured by PIPP ($p = 0.18$). Oral dextrose had a better effect on the behavioral parameters of PIPP score as compared to EBM or sterile water. However, this was not statistically significant. Infants who received dextrose had lesser peak heart rate and oxygen desaturation during the screening procedure compared to those who received breast milk. This was not statistically significant. Infants in all 3 groups experienced moderate pain during ROP screening in the current study.

Table 1 Baseline variables of enrolled cases

Baseline characteristics	Group D (n = 14) Mean (SD)	Group W (*n* = 17) Mean (SD)	Group M (*n* = 14) Mean (SD)
Gestational age at birth (weeks)	32.1 (2.1)	32.1 (2.6)	32.0 (1.9)
Corrected gestational age at the time of examination (weeks)	36.7 (2.4)	38.5 (4.7)	38.7 (2.8)
Age at the time of examination (days)	33.0 (13.0)	45.8 (27.1)	47.2 (18.7)
Birth weight (grams)	1421.4 (393.1)	1375.9 (234.7)	1358.6 (354.4)
Weight at the time of examination (grams)	1851.4 (570.9)	2234.1 (873.5)	2198.6 (932.9)
Sex ratio (M:F)	8:6	9:8	9:5

Group D 10% Dextrose; *Group W* Sterile water; *Group M* Expressed breast milk

Various studies have shown conflicting results on the use of oral sucrose or dextrose in pain prevention during ROP screening. Grabska et al. did not find a significant difference in PIPP score between infants receiving sucrose and sterile water [25]. Boyle et al. found a significant difference in mean PIPP score of 14.3 in sucrose and pacifier group and 15.3 for the placebo group during ROP screening [26]. However, the mean PIPP score indicated severe pain in both groups. Gal et al. also found no significant difference in the pain responses between sucrose and placebo groups during the ROP screening [27]. Nesargi et al. compared the efficacy of oral 25% dextrose and topical proparacaine and they concluded that both the interventions did not provide effective analgesia during ROP screening [15]. Dilli et al. evaluated oral sucrose combined with non-nutritive sucking for reducing pain associated with ROP screening. The intervention group had a significantly lower mean PIPP score ($p = 0.001$) compared to the control group [13.7(2.1) *vs.* 16.4(1.8)] [13]. However, the mean PIPP scores in both the groups indicated severe pain. Kataria et al. studied the effect of oral dextrose on pain management during laser treatment of ROP and concluded that it does not provide additional pain relief in neonates under topical anesthesia [16]. Mitchell et al. observed reduced pain scores in infants receiving repeated doses of oral sucrose during ROP screening [14]. It is possible that had repeated doses of the intervention been given in the present study, a positive effect may have been seen.

Recently, the efficacy of EBM in reducing pain during ROP screening has been studied. Rosali et al. concluded that the group receiving EBM had significantly lower PIPP score of 12.7(1.69) *vs.* 15.5(1.78) in the control group [19]. Taplak compared sucrose, breast milk and distilled water for reducing pain during ROP screening. They found that breast milk group had better recovery from pain after the procedure [18]. The present study scored the pain only during the procedure. Ribeiro et al. evaluated breast milk and sucrose for pain relief during retinal eye examinations and concluded that they have similar analgesic effects [17].

Table 2 Physiological and behavioral variables of PIPP score

Variables	Group D *n* = 14 (Mean ± SD)	Group W *n* = 17 (Mean ± SD)	Group M *n* = 14 (Mean ± SD)	*P* value
Baseline HR (beats/min)	149.1 ± 22.4	145.7 ± 20.0	150.9 ± 19.6	0.768
Baseline SpO_2 (%)	97.4 ± 1.5	97.9 ± 1.3	98.0 ± 1.4	0.492
Peak HR (beats/min)	180.6 ± 17.3	174.2 ± 27.6	194.5 ± 26.3	0.078
Lowest SpO_2 (%)	94.0 ± 3.5	94.1 ± 3.4	93.4 ± 3.5	0.814
Increase in HR from baseline (beats/min)	31.5 ± 19.5	28.5 ± 13.8	43.6 ± 25.5	0.103
Percentage decrease in SpO_2 from baseline (%)	3.5 ± 2.7	3.8 ± 2.9	4.6 ± 2.8	0.533
HR 1-min post eye examination (beats/min)	164.9 ± 16.4	151.2 ± 27.9	171.1 ± 26.9	0.080
SPO_2 1 min post eye examination (%)	97.3 ± 2.3	97.8 ± 1.9	97.6 ± 1.7	0.757
Behavioral state	1.6 ± 0.7	1.4 ± 0.9	1.4 ± 1.1	0.633
Brow bulge	1.2 ± 0.9	1.5 ± 0.6	1.6 ± 0.6	0.295
Nasolabial furrow	1.2 ± 0.9	1.5 ± 0.6	1.6 ± 0.6	0.295
Eye squeeze	1.2 ± 0.9	1.5 ± 0.6	1.6 ± 0.6	0.295
Mean PIPP score ± SD	9.8 ± 3.3	10.2 ± 2.9	11.8 ± 2.8	0.186

Group D 10% Dextrose; *Group W* Sterile water; *Group M* Expressed breast milk; *HR* Heart rate; *PIPP* Premature infant pain profile

Non-pharmacological measures like swaddling and nesting are known to reduce pain but may not be enough for ROP screening, which is a severe type of pain [28]. A recent meta-analysis, which included twenty-nine studies ($N = 1487$), compared the benefits of various pharmacological and non-pharmacological interventions used for pain management during ROP screening [9]. It was concluded that topical anesthetic (TA) combined with a sweet taste and an adjunct intervention (*e.g.*, non-nutritive sucking) had the highest probability of being the optimal treatment *vs.* TA alone. However, absolute scores suggested that no pain treatment was effective in absolute terms (*i.e.*, 62% of trial arms had mean scores >12). Of trials included in this review, the lowest absolute scores were observed in a unit that does not use a speculum [29] and the only study in which the authors assessed the effect of speculum on pain found evidence to support avoiding its use [30].

It is possible that the degree of discomfort from forceful lid retraction, and scleral depression cannot be ameliorated by the relatively mild analgesic effect of oral dextrose or EBM used in present study. Hence, future researchers must study the combined effect of newer pharmacological and non-pharmacological interventions in pain management during ROP screening.

There were limitations to present study. The sample size was small. The authors did not document sleep state and last feeding time, which could have had an impact on pain scores. The strengths of present study are the use of PIPP scale for pain evaluation which is a reliable, validated pain scale and double-blinding. The study results cannot be generalized as babies on ventilator, sick babies and those, not on oral feeds who require eye examination for detection of ROP were not included.

Conclusions

ROP screening is a painful procedure and requires adequate pain prevention in preterm infants. In this study, 10% dextrose and EBM given orally before ROP screening had a similar analgesic effect. Babies in all 3 groups experienced moderate pain as indicated by PIPP score. Hence, future investigators must assess the efficacy and safety of higher doses of dextrose or EBM or other more potent pharmacological interventions to reduce the pain and distress during ROP screening.

Acknowledgements The authors thank Dr Anand Vinekar, Consultant in Pediatric Vitreoretina, Narayana Nethralaya - 1 for his cooperation and screening the babies for retinopathy of prematurity.

Authors' Contribution RN: Principal investigator and preparation of manuscript; KNN: Collection of literature and co-investigator; GG: Co-investigator and reviewer of the paper. GG is the guarantor for this paper.

Compliance with Ethical Standards

Conflict of Interest None.

References

1. Volpe JJ. Brain injury in the premature infant–current concepts of pathogenesis and prevention. Biol Neonate. 1992;62:231–42.
2. Danford DA, Miske S, Headley J, Nelson RM. Effects of routine care procedures on transcutaneous oxygen in neonates: a quantitative approach. Arch Dis Child. 1983;58:20–3.
3. Brummelte S, Grunau RE, Chau V, et al. Procedural pain and brain development in premature newborns. Ann Neurol. 2012;71:385–96.
4. Valeri BO, Holsti L, Linhares MB. Neonatal pain and developmental outcomes in children born preterm: a systematic review. Clin J Pain. 2015;31:355–62.
5. Francis K. What is best practice for providing pain relief during retinopathy of prematurity eye examinations? Adv Neonatal Care. 2016;16:220–8.
6. International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. Arch Pediatr Adolesc Med. 2001;155:173–80.
7. Sun X, Lemyre B, Barrowman N, O'Connor M. Pain management during eye examinations for retinopathy of prematurity in preterm infants: a systematic review. Acta Paediatr. 2010;99:329–34.
8. Dempsey E, McCreery K. Local anaesthetic eye drops for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity. Cochrane Database Syst Rev. 2011:CD007645.
9. Disher T, Cameron C, Mitra S, Cathcart K, Campbell-Yeo M. Pain-relieving interventions for retinopathy of prematurity: a meta-analysis. Pediatrics. 2018;142: pii: e20180401.
10. Shah PS, Aliwalas LI, Shah V. Breastfeeding or breast milk for procedural pain in neonates. Cochrane Database Syst Rev. 2006;3:CD004950.
11. Bueno M, Yamada J, Harrison D, et al. A systematic review and meta-analyses of non sucrose sweet solutions for pain relief in neonates. Pain Res Manag. 2013;18:153–61.
12. Dilen B, Elseviers M. Oral glucose solution as pain relief in newborns: results of a clinical trial. Birth. 2010;37:98–105.
13. Dilli D, İlarslan NE, Kabataş EU, Zenciroğlu A, Şimşek Y, Okumuş N. Oral sucrose and nonnutritive sucking goes some way to reducing pain during retinopathy of prematurity eye examinations. Acta Paediatr. 2014;103:e76–9.
14. Mitchell A, Stevens B, Mungan N, et al. Analgesic effects of oral sucrose and pacifier during eye examinations for retinopathy of prematurity. Pain Manag Nurs. 2004;5:160–8.
15. Nesargi S, Nithyanandam S, Rao S, Nimbalkar S, Bhat S. Topical anaesthesia or oral dextrose for the relief of pain in screening for retinopathy of prematurity: a randomized controlled double blinded trial. J Trop Pediatr. 2015;61:20–4.
16. Kataria M, Narang S, Chawla D, Sood S, Gupta PC. Oral dextrose for pain management during laser treatment of retinopathy of prematurity under topical anaesthesia. Indian J Pediatr. 2015;82:694–7.
17. Ribeiro LM, Castral TC, Montanholi LL, et al. [Human milk for neonatal pain relief during ophthalmoscopy.] (Article in Portuguese). Rev Esc Enferm USP. 2013;47:1039–45.
18. Taplak AS, Erdem E. A comparison of breast milk and sucrose in reducing neonatal pain during eye exam for retinopathy of prematurity. Breastfeed Med. 2017;12:305–10.
19. Rosali L, Nesargi S, Mathew S, Vasu U, Rao SP, Bhat S. Efficacy of expressed breast Milk in reducing pain during ROP screening—a randomized controlled trial. J Trop Pediatr. 2015;61:135–8.

20. Stevens B, Johnston C, Taddio A, Gibbins S, Yamada J. The premature infant pain profile: evaluation 13 years after development. Clin J Pain. 2010;26:813–30.
21. Skogsdal Y, Eriksson M, Schollin J. Analgesia in newborns given oral glucose. Acta Paediatr. 1997;86:217–20.
22. Deshmukh LS, Udani RH. Analgesic effect of oral glucose in preterm infants during venipuncture–a double-blind, randomized, controlled trial. J Trop Pediatr. 2002;48:138–41.
23. Blass EM. Milk-induced hypoalgesia in human newborns. Pediatrics. 1997;99:825–9.
24. Barrett T, Kent S, Voudoris N. Does melatonin modulate beta-endorphin, corticosterone, and pain threshold. Life Sci. 2000;66:467–76.
25. Grabska J, Walden P, Lerer T, et al. Can oral sucrose reduce the pain and distress associated with screening for retinopathy of prematurity? J Perinatol. 2005;25:33–5.
26. Boyle EM, Freer Y, Khan-Orakzai Z, et al. Sucrose and non-nutritive sucking for the relief of pain in screening for retinopathy of prematurity:a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2006;91:F166–8.
27. Gal P, Kissling GE, Young WO, et al. Efficacy of sucrose to reduce pain in premature infants during eye examinations for retinopathy of prematurity. Ann Pharmacother. 2005;39:1029–33.
28. O'Sullivan A, O'Connor M, Brosnahan D, McCreery K, Dempsey EM. Sweeten soother and swaddle for retinopathy of prematurity screening: a randomized placebo controlled trial. Arch Dis Child Fetal Neonatal Ed. 2010;95:F419–22.
29. Olsson E, Eriksson M. Oral glucose for pain relief during eye examinations for retinopathy of prematurity. J Clin Nurs. 2011;20:1054–9.
30. Mehta M, Adams GGW, Bunce C, Xing W, Hill M. Pilot study of the systemic effects of three different screening methods used for retinopathy of prematurity. Early Hum Dev. 2005;81:355–60.