

BRIEF ARTICLE

Efficacy of expressed breast milk alone or in combination with paracetamol in reducing pain during retinopathy of prematurity screening: A randomized controlled trial

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ABSTRACT

Background: The aim of this study was to determine the efficacy of expressed breast milk (EBM) alone or in combination with oral paracetamol for pain reduction during retinopathy of prematurity (ROP) screening.

Methods: A randomized control trial was conducted in two departments of Bangabandhu Sheikh Mujib Medical University. A total of 60 pre-term neonates who underwent ROP screening were randomized into three equal groups. Group A got nesting and swaddling as per institutional protocol (control). Group B received 2 ml EBM two minutes prior to the ROP screening and Group C received 15 mg/kg syrup paracetamol 30 minutes prior to the ROP screening and EBM like Group B. Premature infant pain profile (PIPP) scores was used prior, during and 2 minutes after ROP screening procedure.

Results: The three groups were similar in terms of baseline characteristics. The mean (standard deviation) PIPP scores during the procedure were 16.4 (1.1), 15.0 (1.8) and 13.4 (1.8) in control, EBM, and EBM with paracetamol groups respectively. The PIPP scores were significantly lower in the EBM and EBM with paracetamol groups during the procedure compared to control group. The mean difference in PIPP scores (during minus before procedure) of the EBM (10.2; 95% CI 9.4 – 10.9) and EBM with paracetamol (8.9; 95% CI 8.1 – 9.7) groups, were also substantially lower.

Conclusion: Breast milk alone or in combination with paracetamol can reduce significant pain during ROP screening than control group.

Keywords: retinopathy of prematurity, premature infant pain profile, PIPP

INTRODUCTION

Retinopathy of prematurity (ROP) has been widely acknowledged to be the primary cause of preventable childhood blindness in developing countries. It is recommended for preterm infants with gestational age <35 weeks or birth weight <2000 grams and infants of a gestational age greater than 35 weeks who are believed to be at high risk for ROP.¹ However, the procedure for ROP is painful and is known to cause stress and physical debilitation among preterm neonates, especially because of the use of eyelid speculum and scleral indentation. Globally, most newborns admitted to neonatal intensive care units (NICUs) are subjected to repeat these painful procedures which have short- and long-term sequelae. It may lead to permanent

changes in brain processing and maladaptive behavior later.² As evident that most premature neonates are capable of feeling pain therefore, experiencing such pain in early stage of life may have long term neurological consequences.³

Neonates are unable to express their pain verbally. They rely on their caregivers to recognize, assess, and manage their pain.⁴ Surrogate markers have been studied and widely used to assess neonatal pain. These include motor responses, facial expressions, crying, and changes in physiologic parameters such as heart rate, blood pressure, oxygen saturation, and respiratory rate. Validated pain assessment scores include the Neonatal Facial Coding System, the Neonatal Infant Pain Scale, and the Premature Infant Pain Profile (PIPP).⁵

HIGHLIGHTS

1. Expressed breast milk alone or in combination with paracetamol relief pain significantly among premature neonate during ROP screening compared to control group.
2. Premature infant pain profile (PIPP) scores were used to measure pain.

Many pharmacological and nonpharmacological interventions have been studied to alleviate neonates' pain during various procedures.⁶ Expressed breast milk (EBM) sweet solutions (oral sucrose or glucose solutions), and various drugs such as paracetamol have been studied in the various clinical trials to relieve procedural pain with equivocal results.^{7,8} ROP screening in newborns causes severe pain during the procedure, with residual pain lasting up to 30 minutes afterward. Breast milk has higher levels of tryptophan. Tryptophan is a precursor to melatonin, which has been shown in animal studies to increase concentrations of beta endorphin, a naturally occurring endorphin that is thought to be one of the mechanisms responsible for breast milk's analgesic effect.⁹

In this study, we tried to compare two commonly used methods to relieve procedural pain, namely EBM and paracetamol. The purpose of this study was to determine the efficacy of EBM alone or in combination of EBM with oral paracetamol for pain reduction during retinopathy of prematurity (ROP) screening among preterm infants.

METHODS

This double blinded randomized control trial was conducted in neonatal intensive care unit of the Department of Neonatology and ROP clinic of the Department of Ophthalmology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from November 2021 to April 2022. One hundred preterm neonate, with gestational age (assessed using New Ballard Score) <35 weeks and/or birth weight <1500 grams were enrolled in the study. Sample size was based on a study by Rosali, et al.¹⁰ A sample size of 20 per group was calculated to allow 80% probability of detecting a three-point difference in PIPP score with 5% level of significance. Written informed

consent was obtained from the parents. Newborns with multiple congenital anomalies, patient who is on mechanical ventilator during ROP examination, neonate receiving narcotic or sedative drugs and neonate not receiving oral feed were excluded from this study.

The neonates who are eligible for the study were allocated into three groups randomly. These were Group A (control group), Group B (EBM alone group) and Group C (EBM with paracetamol). Mydriatics were used before eye examination. These are Tropicamide 0.8% and Phenylephrine 5% (Tropfen ophthalmic solution). This drop is diluted with 1:1 proportion with polyethylene Glycol drop (Tearon eye drop). One drop of this combined drop was instilled every 10 – 15 minutes for four times starting 1 hour before the scheduled time for the examination. The procedure for screening involved the use of indirect ophthalmoscopy using a 20D lens and this was performed by an experienced ophthalmologist who was blind about the intervention. After instilling a topical anesthetic drop (Proparacaine), a wire speculum was inserted to keep the eyelids apart, and a scleral indenter was used whenever required.

All the neonates were swaddled during the procedure. Group A was served as the control group; babies in this group were nested and swaddled which is the standard practice in the unit. Group B received 2 ml of EBM (collected from mother in a sterile container) administered through a sterile syringe into the baby's mouth 2 minutes prior to procedure: Group C receiving syrup paracetamol at a dose of 15 mg/kg administered 30 minutes before procedure along with breastmilk as in Group B. 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 a resident.

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, presence of nasolabial furrow, brow bulge and eye squeeze. It was graded as mild (<6),

TABLE 1 Background status of the enrolled cases

Background characteristics	Group A (n=20) (Control)	Group B (n=20) (Expressed breast milk)	Group C (n=20) (Expressed breast milk and paracetamol)	P
	n (%)	n (%)	n (%)	
Age during examination*	33.5 (10.0)	33.3 (7.7)	35.4 (10.1)	0.73
Gestational age at birth (weeks)*	31.6 (2.1)	31.3 (2.3)	31.2 (2.1)	0.88
Gestational age				
≤31 weeks	6 (30)	6 (30)	7 (35)	0.93
31 – 34 weeks	14 (70)	14 (70)	13 (70)	
Birth weight (grams)*	1438.2 (330.1)	1399.0 (334.2)	1454.5 (326.0)	0.86
Birth weight category				
<1499 grams	8 (40)	10 (50)	9 (45)	0.82
1500 – 2000 grams	12 (60)	10 (50)	11 (55)	
Sex				
Male	9 (45)	9 (45)	10 (50)	0.94
Female	11 (55)	11 (55)	10 (50)	
Delivery type				
Vaginal delivery	9 (45)	6 (30)	5 (25)	0.38
Lower Uterine Caesarean Section	11 (85)	14 (70)	15 (75)	
Birth weight category				
Appropriate for gestational age	17 (85)	17 (85)	18 (90)	0.87
Small for gestational age	3 (15)	3 (15)	2 (10)	

* Mean (standard deviation)

moderate (6 – 12) and severe (>12). The ROP screening examinations were video recorded by the resident physician. The video recording taken 20 seconds before procedure served as baseline (PIPP 1). The other two videos were taken during and 2 minutes post procedure and these were leveled as PIPP 2 and PIPP 3, respectively. Both Ophthalmologist and the researcher were blinded. Researcher who was blinded about the procedure observed the facial expression of the babies in video before, during and 2 minutes after the examination and timed the duration of brow bulge, eye squeeze and nasolabial furrow on the PIPP scale in all examinations. Video recordings that were found incomplete at this time, were discarded. Each video was replayed thrice, and the mean PIPP score was calculated and used for analysis.

Data was analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp, Armonk, New York, USA). Variables were expressed in the percentages, mean, standard deviation and 95% confidence interval. Data were analyzed with the Chi-square test and one-way analysis of variance (ANOVA). The mean difference between before and during and, before and after were further analyzed between and within the groups. Comparison between groups were done by post hoc test. The difference was considered significant for $P < 0.05$.

RESULTS

The baseline parameters among all the three groups were similar and no significant difference in the mean gestational age, birth weight, age at the time of screening among the three groups (TABLE 1). The mean (standard deviation) PIPP scores during the procedure were significantly lower in the EBM group [15.0 (1.8)] and EBM with paracetamol group [13.4 (1.8)] compared to control group [16.4 (1.1)]. No significant differences were found before and after procedure of the PIPP scores among the three groups (TABLE 2).

TABLE 2 Mean (standard deviation) of Premature infant pain profile score in the study population of the three groups

Premature infant pain profile (PIPP) score	Group A (n=20) (Control)	Group B (n=20) (Expressed breast milk)	Group C (n=20) (Expressed breast milk and paracetamol)	P
	n (%)	n (%)	n (%)	
Before procedure	5.0 (0.8)	4.8 (0.7)	4.5 (0.5)	0.06
During the procedure	16.5 (1.1)	15.0 (1.8)	13.4 (1.8)	<0.001
Post procedure	10.3 (1.0)	10.2 (1.5)	9.5 (1.0)	0.08

The mean difference (95% confidence interval) of PIPP scores between during minus before procedure was 11.4 (10.9 – 11.9), 10.2 (9.4 – 10.9) and 8.9 (8.1 – 9.7) in Control group, EBM group and EBM with paracetamol group respectively. The differences were also substantially lower in EBM group and EBM with

paracetamol group compared to Control group. No differences were found among the three groups regarding mean difference of PIPP score between before and after procedure. However, it is also noted that all groups were different from each other as per Tukey's test (TABLE 3).

DISCUSSION

We aimed to assess the efficacy of EBM alone or combination of EBM with paracetamol for relieving pain during ROP screening among premature neonates. Although several nonpharmacological and pharmacological agents are being used to treat neonatal pain, none of them are well established. Among the analgesics studied for newborn pain, breastfeeding/breast milk is a natural, readily available, easy to use, and potentially risk-free option. The presence of lactose in breast milk

effects of breast milk and sucrose during retinal eye examinations are equivalent¹⁶. Several studies have been conducted to determine the effectiveness of breastmilk as a procedural pain analgesic. It was shown to reduce pain during treatment in studies conducted by Sahoo JP et al and Upadhyay and Gupta. Despite the fact that venipuncture was used in these studies.^{17,18}

We observed that in the EBM and EBM with paracetamol groups, the mean difference in PIPP scores (between before and during the procedure) was also substantially lower. No differences were found among three groups regarding mean difference of PIPP score between before and after procedure. But difference was found within group comparison. Naik A, et al reported that the control and study groups had equal PIPP scores during the ROP.^{14,19}

TABLE 3 Mean difference (95% confidence interval) of Premature Infant Pain Profile scores between measurements in three groups

Premature infant pain profile (PIPP) score	Group A (n=20) (Control)	Group B (n=20) (Expressed breast milk)	Group C (n=20) (Expressed breast milk and paracetamol)	P
PIPP "during minus before" procedure	11.4 (10.9 – 11.9)	10.2 (9.4 – 10.9)	8.9 (8.1 – 9.7)	<0.001*
PIPP "after minus before" procedure	5.4 (4.7 – 5.8)	5.4 (4.7 – 6.0)	5.1 (4.5 – 5.6)	0.65

*All groups were different from each other as per Tukey's test

may be one of the reasons it has analgesic properties.⁹⁻¹¹ Our study observed that the PIPP scores were significantly lower in the EBM and EBM with paracetamol groups during the procedure compared to control group, which is consistent with previous findings.^{10,13,14} Despite the fact that topical anesthetic eye drops were administered prior to the ROP exams, as is standard clinical practice, preterm infants still required pain relief and assistance in recovering quickly afterward.¹⁵

Rosali et al investigated the effectiveness of expressed breast milk in reducing pain during ROP screening. During the procedure, the expressed breast milk group had a significantly lower PIPP score than the control group. A significant difference between the two groups was observed 1 minute and 5 minutes after the procedure¹⁰. Moreover, Taplak et al investigated the pain-relieving effects of sucrose, breast milk, and distilled water and found that the breast milk group recovered from the procedure with less pain.¹⁴ On the other hand Ribeiro et al. reported that the analgesic

There were some limitations in this study. Last feeding time was not documented, which could have impact on pain scores. The study results cannot be generalized as neonate on ventilator, sick babies and those not on oral feeds who require eye examination for detection of ROP were not included in this study.

Conclusion

The breastmilk alone or in combination with paracetamol may alleviate pain during ROP screening among premature infants compared to standard practice like nested and swaddled. Future investigators may assess the efficacy and safety of higher doses of expressed breast milk or other more potent drugs to reduce the pain during ROP screening.

Acknowledgments

Authors of this study are thankful to the authority of the Department of Ophthalmology and Neonatology of Bangabandhu Sheikh Mujib Medical University for their nice cooperation and also thankful to study subjects for their active and enthusiastic participation. Special thanks to Mr Rijwan Bhuiyan (ORCID: 0000-0003-0005-8889) for doing final analysis and critically revising the manuscript.

Author Contributions

Conception and design: RMC; Acquisition, analysis, and interpretation of data: RMC, AJ; Manuscript drafting and revising it critically: RMC, KPD, SKD, AJ, MAM, TRA, NC; Approval of the final version of manuscript: RMC, KPD, SKD, AJ, MAM, TRA, NC; Guarantor accuracy and integrity of the work: RMC.

Funding

Research grant from Bangabandhu Sheikh Mujib Medical University, memo number: BSMMU/2022/3712(48).

Conflict of Interest

The authors declare no conflict of interest.

Ethical Approval

The protocol for this study was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University.

Trial Registration

Clinical Trial.gov NCT05354479

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REFERENCES

- Costa MC, Eckert GU, Fortes BG, Fortes Filho JB, Silveira RC, Procianny RS. Oral glucose for pain relief during examination for retinopathy of prematurity: a masked randomized clinical trial. *Clinics (Sao Paulo)*. 2013;68(2):199-204. DOI: [10.6061/clinics/2013\(02\)0a13](https://doi.org/10.6061/clinics/2013(02)0a13).
- Anand KJ, Scalzo FM. Can adverse neonatal experiences alter brain development and subsequent behavior? *Biol Neonate*. 2000 Feb;77(2):69-82. DOI: [10.1159/000014197](https://doi.org/10.1159/000014197).
- Lago P, Garetti E, Merazzi D, Pieragostini L, Ancora G, Pirelli A, Bellieni CV; Pain Study Group of the Italian Society of Neonatology. Guidelines for procedural pain in the newborn. *Acta Paediatr*. 2009 Jun;98(6):932-9. DOI: [10.1111/j.1651-2227.2009.01291.x](https://doi.org/10.1111/j.1651-2227.2009.01291.x).
- Cooper S, Petty J. Promoting the use of sucrose as analgesia for procedural pain management in neonates: A review of the current literature. *J Neonatal Nurs*. 2012; 18:121-8. DOI: [10.1016/j.jnn.2012.05.003](https://doi.org/10.1016/j.jnn.2012.05.003).
- Stevens BJ, Gibbins S, Yamada J, Dionne K, Lee G, Johnston C, Taddio A. The premature infant pain profile-revised (PIPP-R): initial validation and feasibility. *Clin J Pain*. 2014 Mar;30(3):238-43. DOI: [10.1097/AJP.0b013e3182906aed](https://doi.org/10.1097/AJP.0b013e3182906aed).
- Pillai RRR, Racine NM, Turcotte K, Uman LS, Horton RE, Din Osmun L, Ahola Kohut S, Hillgrove Stuart J, Stevens B, Gerwitz-Stern A. Non-pharmacological management of infant and young child procedural pain. *Cochrane Database Syst Rev*. 2011 Oct 5;(10):CD006275. DOI: [10.1002/14651858.CD006275](https://doi.org/10.1002/14651858.CD006275).
- Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev*. 2016 Jul 16;(7):CD001069. DOI: [10.1002/14651858.CD001069.pub5](https://doi.org/10.1002/14651858.CD001069.pub5).
- Ohlsson A, Shah PS. Paracetamol (acetaminophen) for prevention or treatment of pain in newborns. *Cochrane Database Syst Rev*. 2020 Jan 27;1(1):CD011219. DOI: [10.1002/14651858.CD011219.pub4](https://doi.org/10.1002/14651858.CD011219.pub4).
- Barrett T, Kent S, Voudouris N. Does melatonin modulate beta-endorphin, corticosterone, and pain threshold? *Life Sci*. 2000;66(6):467-76. DOI: [10.1016/S0024-3205\(99\)00616-5](https://doi.org/10.1016/S0024-3205(99)00616-5).
- 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 Apr;61(2):135-8. DOI: [10.1093/tropej/fmu073](https://doi.org/10.1093/tropej/fmu073).
- Blass EM. Milk-induced hypoalgesia in human newborns. *Pediatrics*. 1997 Jun;99(6):825-9. doi: [10.1542/peds.99.6.825](https://doi.org/10.1542/peds.99.6.825).
- Shah PS, Herbozo C, Aliwalas LL, Shah VS. Breastfeeding or breast milk for procedural pain in neonates. *Cochrane Database Syst Rev*. 2012 Dec 12;12(12):CD004950. DOI: [10.1002/14651858.CD004950.pub3](https://doi.org/10.1002/14651858.CD004950.pub3).
- Bozlak S, Dolgun G. Effect of Nonpharmacologic Pain Control During Examination for Retinopathy of Prematurity. *J Obstet Gynecol Neonatal Nurs*. 2017 Sep-Oct;46(5):709-715. DOI: [10.1016/j.jogn.2017.06.008](https://doi.org/10.1016/j.jogn.2017.06.008).
- Şener TA, Erdem EA. Comparison of Breast Milk and Sucrose in Reducing Neonatal Pain During Eye Exam for Retinopathy of Prematurity. *Breastfeed Med*. 2017 Jun;12:305-310. DOI: [10.1089/bfm.2016.0122](https://doi.org/10.1089/bfm.2016.0122).
- Committee on Fetus and newborn and section on Anesthesiology and pain medicine. Prevention and Management of Procedural Pain in the Neonate: An Update. *Pediatrics*. 2016 Feb;137(2):e20154271. DOI: [10.1542/peds.2015-4271](https://doi.org/10.1542/peds.2015-4271).
- Ribeiro LM, Castral TC, Montanholi LL, Daré MF, Silva AC, Antonini SR, Scochi CG. Human milk for neonatal pain relief during ophthalmoscopy. *Rev Esc Enferm USP*. 2013 Oct;47(5):1039-45. Portuguese. DOI: [10.1590/S0080-623420130000500005](https://doi.org/10.1590/S0080-623420130000500005).
- Sahoo JP, Rao S, Nesargi S, Ranjit T, Ashok C, Bhat S. Expressed breast milk vs 25% dextrose in procedural pain in neonates, a double blind randomized controlled trial. *Indian Pediatr*. 2013 Feb;50(2):203-7. DOI: [10.1007/s13312-013-0067-3](https://doi.org/10.1007/s13312-013-0067-3).
- Upadhyay A, Gupta NK. Retinopathy of Prematurity (ROP) and its Associated Pain. *Indian J Pediatr*. 2015 Aug;82(8):673-4. DOI: [10.1007/s12098-015-1812-5](https://doi.org/10.1007/s12098-015-1812-5).
- Naik A, D'Lima S, Sreekumar K, Silveira MP. Efficacy of Expressed Breast Milk Alone or in Combination with Paracetamol in Reducing Pain during ROP Screening: A Randomized Controlled Trial. *Journal of Clinical Neonatology* 10(2):p 73-78, Apr-Jun 2021. DOI: [10.4103/jcn.jcn_198_20](https://doi.org/10.4103/jcn.jcn_198_20).