Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/4rs59530

COMPARATIVE ANALGESIC EFFICACY OF EXPRESSED BREAST MILK VERSUS ORAL 25% DEXTROSE DURING VENIPUNCTURE IN CLINICALLY STABLE PRETERM NEONATES ON ORAL FEEDS: A RANDOMIZED COMPARATIVE STUDY

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ABSTRACT

Background: Neonates undergo multiple painful procedures in early life, and adequate pain relief is crucial due to the long-term neurodevelopmental consequences of unrelieved pain. Among the various non-pharmacological strategies, expressed breast milk (EBM) and oral dextrose have shown promise. This study aimed to compare the analgesic efficacy of EBM versus oral 25% dextrose in clinically stable preterm neonates undergoing venipuncture.

Methods: A hospital-based randomized controlled study was conducted in the postnatal ward of a tertiary care centre in New Delhi from January to June 2020. A total of 110 preterm neonates (gestational age 30–36+6 weeks, birth weight 1500–2500 g) were randomized to receive either 2 mL of EBM (n=55) or 2 mL of oral 25% dextrose (n=55) one minute before venipuncture. Pain was assessed using the Premature Infant Pain Profile (PIPP) at four intervals up to 5.5 minutes after the procedure. Secondary outcomes included crying time, heart rate, and oxygen saturation.

Results: Baseline characteristics were comparable between the two groups. Mean crying time was significantly lower in the 25% dextrose group (69.09 ± 16.59 s) compared to the EBM group (86.91 ± 18.84 s; $p<0.001$). Post-procedural heart rate was lower and oxygen saturation higher in the dextrose group. Mean PIPP scores were significantly lower in the dextrose group at all time points ($p<0.001$), confirming superior analgesic effect.

Conclusion: Oral 25% dextrose is more effective than expressed breast milk in alleviating venipuncture pain in preterm neonates. Its low cost, availability, and ease of use make it a practical choice in routine neonatal care.

Keywords: Premature infants; Procedural pain; Expressed breast milk; Dextrose 25%; Neonatal analgesia; PIPP score; Non-pharmacological pain relief

Introduction

Pain in neonates is now recognized as a real and significant clinical concern. The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience

associated with actual or potential tissue damage" [1]. Contrary to earlier assumptions, research has shown that even premature infants have the anatomical and neurochemical capacity to perceive pain, and may actually respond more intensely than term neonates [2,3].

Hospitalized neonates frequently undergo painful procedures such as venipuncture, heel pricks, and suctioning. Repeated exposure to such stimuli without adequate pain relief can lead to altered neurodevelopment, abnormal stress responses, and long-term behavioral changes [4,5]. Yet, despite the clinical importance of neonatal pain management, it is often under-addressed in routine care [6].

Non-pharmacological interventions such as oral sweet solutions and expressed breast milk (EBM) have gained attention due to their safety, simplicity, and ease of implementation [7]. Sweet-tasting solutions like sucrose and glucose (dextrose) act via stimulation of the orogustatory system, triggering endogenous opioid pathways and thereby reducing pain perception [8]. EBM may exert similar analgesic effects through the presence of lactose and tryptophan, which can enhance endorphin levels [9].

Although both 25% dextrose and EBM have been independently shown to reduce pain in neonates, direct comparisons between the two yield inconsistent findings. Some studies suggest superior efficacy of dextrose, while others report comparable or even better results with EBM [10,11].

Given the frequency of minor invasive procedures in neonatal units and the need for simple and effective analgesic options, this study aimed to compare the analgesic efficacy of oral 25% dextrose versus EBM during venipuncture in clinically stable preterm neonates using the Premature Infant Pain Profile (PIPP).

Materials and Methods

Study Design and Participants

This was a hospital-based, randomized, controlled, comparative trial conducted in the postnatal ward of the Department of Pediatrics, Deen Dayal Upadhyay Hospital, New Delhi, over a 6month period (January to June 2020). After obtaining approval from the institutional scientific and ethical committee and informed parental consent, clinically stable preterm neonates were enrolled.

Inclusion criteria were:

- Gestational age between 30 weeks and 36 weeks 6 days
- Birth weight between 1500 and 2500 grams
- Tolerance of oral feeds
- Indication for venipuncture (e.g., thyroid profile or serum bilirubin estimation) within 24 hours to 7 days after birth.

Exclusion criteria included congenital anomalies, genetic syndromes, perinatal asphyxia, sepsis, meconium aspiration syndrome, birth trauma, and neonates not tolerating oral feeds.

Sample size was calculated based on previous data [12], using a 1% significance level and 90% power, yielding 49 per group. To compensate for potential attrition, 55 neonates were enrolled in each group. A total of 110 neonates were randomized into two groups of 55 each using computer-generated random numbers. Allocation concealment was ensured through sequentially numbered, opaque, sealed envelopes. Group 1 received 2 mL of expressed breast milk (EBM), and Group 2 received 2 mL of 25% dextrose (25D), administered orally 1 minute before venipuncture using a sterile paladay. All procedures were performed by trained residents using a 23-gauge needle without a tourniquet, with dorsum of the hand as the preferred site.

During the procedure 2 ml of test solution was administered to the baby through a sterile paladay (a traditional cup with a spout) by mouth by one staff nurse. The excess amount of test solution and the paladay was cleared before the entry of observers into the room to mask the test solution given.

Outcome Assessment and Statistical Analysis

Pain was assessed using the **Premature Infant Pain Profile (PIPP)**, a validated scoring system that includes behavioral (brow bulge, eye squeeze, nasolabial furrow), physiological (heart rate, SpO_2), and contextual variables (gestational age and behavioral state). Scores range from 0 to 21:

- 0–6: minimal/no pain
- 7–12: moderate pain • 12: severe pain [13].

PIPP scores were recorded at four intervals: 0–30 seconds, 1–1.5 minutes, 3–3.5 minutes, and 5–5.5 minutes after venipuncture. Secondary outcomes included crying time (in seconds), maximum heart rate, and minimum oxygen saturation post-procedure. Baseline HR and SpO_2 were recorded before sampling.

Data were analyzed using SPSS version 21.0. Continuous variables were expressed as mean ± standard deviation and compared using the independent t-test. Categorical data were analyzed using chi-square test. Repeated measures (PIPP score) were compared using ANOVA with Bonferroni post-hoc correction. A p-value <0.05 was considered statistically significant.

Observation & Results

A total of 110 preterm neonates were enrolled and randomized equally into the expressed breast milk group (EBM, n=55) and the 25% dextrose group (25D, n=55). All neonates completed the study protocol without dropouts.

Baseline Characteristics

The two groups were comparable in baseline characteristics including sex distribution, birth weight, gestational age, mode of delivery, and postnatal age. The mean birth weight was 2.087 ± 0.311 kg in the EBM group and 2.092 ± 0.352 kg in the 25D group (p=0.931). Mean gestational age was 34.15 ± 1.70 weeks in EBM vs 34.42 ± 1.66 weeks in 25D (p=0.398). There was no statistically significant difference in gender (p=0.697), mode of delivery (p=0.695), or postnatal age (p=0.596) (table 1).

Table 1. Baseline Characteristics of the Study Population (n = 110)

Parameter	**EBM Group (n = 55)**	**25D Group (n = 55)**	**p-value**
Gender			
Male	23 (42%)	21 (38%)	0.697
Parameter	**EBM Group (n = 55)**	**25D Group (n = 55)**	**p-value**
Female	32 (58%)	34 (62%)	
Mean Birth Weight (kg)	2.087 ± 0.311	2.092 ± 0.352	0.931
Gestational Age (weeks)	34.15 ± 1.70	34.42 ± 1.66	0.398
Mode of Delivery			
Vaginal	22 (40%)	20 (36%)	0.695
Caesarean	33 (60%)	35 (64%)	
Postnatal Age (hours)	77.71 ± 36.15	73.84 ± 40.17	0.596
Sampling Time (sec)	47.00 ± 8.09	44.45 ± 10.39	0.155

Crying Time and Physiological Parameters

Mean crying time was significantly lower in the 25D group (69.09 ± 16.59 seconds) compared to the EBM group (86.91 ± 18.84 seconds; **p<0.001**). Post-procedural mean heart rate was also significantly lower in the 25D group (132.38 ± 3.90 bpm) than in the EBM group (133.95 ± 3.59 bpm; **p=0.031**). Conversely, mean SpO_2 was significantly higher in the 25D group postvenipuncture (96.67 ± 0.90%) compared to the EBM group (95.71 ± 1.08%; **p<0.001**). No significant differences were noted in baseline heart rate or oxygen saturation prior to the procedure (table 2).

Table 2. Crying Time and Physiological Parameters Pre- and Post-Venipuncture

Parameter	EBM Group (n = 55)	25D Group (n = 55)	p-value
Crying Time (sec)	86.91 ± 18.84	69.09 ± 16.59	**<0.001**
Heart Rate (bpm)			
Before Sampling	122.78 ± 3.99	123.36 ± 5.04	0.503
After Sampling	133.95 ± 3.59	132.38 ± 3.90	**0.031**
SpO_2 (%)			
Before Sampling	99.29 ± 0.79	99.07 ± 0.90	0.178
After Sampling	95.71 ± 1.08	96.67 ± 0.90	**<0.001**

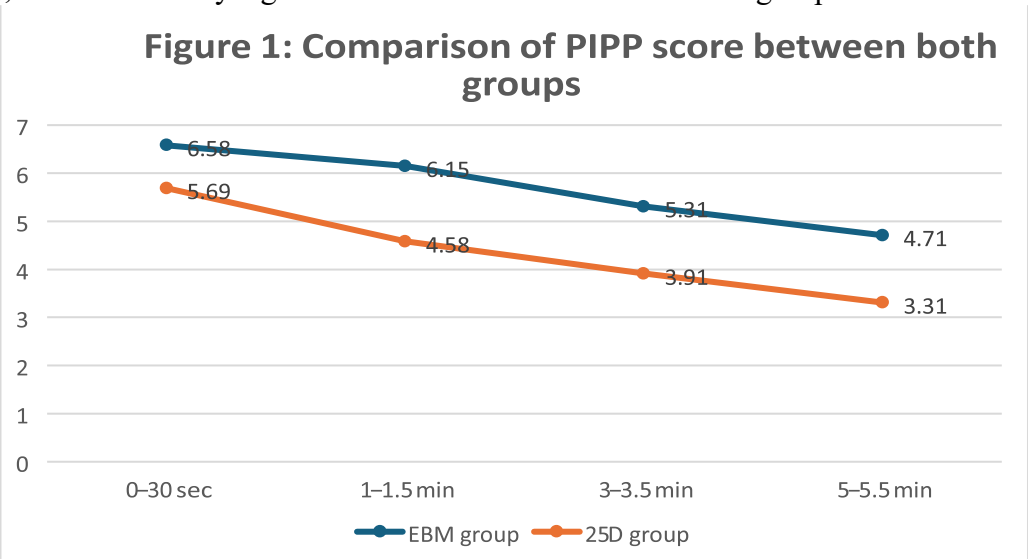
PIPP Score and Pain Intensity

The Premature Infant Pain Profile (PIPP) score was used to assess pain at four time intervals following venipuncture: 0–30 sec, 1–1.5 min, 3–3.5 min, and 5–5.5 min. At all intervals, the mean PIPP scores were significantly lower in the 25D group compared to the EBM group:

Table 3: Comparison of PIPP score between both groups

Time Interval	EBM Group (n = 55)	25D Group (n = 55)	p-value
0–30 sec	6.58 ± 1.23	5.69 ± 0.96	**<0.001**
1–1.5 min	6.15 ± 0.93	4.58 ± 0.96	**<0.001**
3–3.5 min	5.31 ± 0.94	3.91 ± 0.78	**<0.001**
5–5.5 min	4.71 ± 0.74	3.31 ± 0.92	**<0.001**

Pain was classified based on PIPP score as mild (0–6), moderate (7–12), or severe (>12). No neonates in either group experienced severe pain. A greater proportion of neonates in the 25D group experienced **mild pain** at all intervals up to 5 minutes (e.g., 84% vs 53% at 0–30 sec; **p<0.001**). Repeated measures ANOVA with Bonferroni post-hoc correction confirmed that the mean PIPP score in the 25D group was significantly lower than the EBM group at all time points ($p<0.001$), with statistically significant differences between all intra-group time intervals as well.



These findings indicate a **superior analgesic effect of oral 25% dextrose** over expressed breast milk in reducing venipuncture-related pain among clinically stable preterm neonates.

Discussion

Effective pain management in neonates, especially those born preterm, is essential given the heightened pain sensitivity and potential long-term neurodevelopmental consequences of repeated untreated pain [1,4,13]. This randomized controlled trial compared the analgesic efficacy of **expressed breast milk (EBM)** and **oral 25% dextrose (25D)** in clinically stable preterm neonates undergoing venipuncture. The findings demonstrate that **25D significantly reduced pain**, as measured by the Premature Infant Pain Profile (PIPP), compared to EBM at all time intervals.

Baseline Comparability and Study Integrity

The demographic and clinical characteristics of neonates in both groups were statistically comparable, which strengthens the internal validity of the study. Parameters such as gestational age, birth weight, mode of delivery, and postnatal age were similar across groups, minimizing confounding variables.

Analgesic Effect: PIPP Score and Crying Time

Our study found significantly lower PIPP scores at all time points (0–30 sec, 1–1.5 min, 3–3.5 min, and 5–5.5 min) in the 25D group. This is consistent with studies by Sahoo et al. [11], Bueno et al. [10], and Rawal et al. [14], which also demonstrated superior pain relief with 25% dextrose compared to EBM. The mean crying time, another reliable behavioral marker of procedural pain, was significantly shorter in the 25D group—an observation also noted by Malngiang et al. [15] and Ravishankar et al. [16].

Physiological Response: Heart Rate and SpO_2

Post-procedural heart rate was lower and SpO_2 was higher in the 25D group, both statistically significant. These findings indicate better autonomic stability post-pain stimulus and are in agreement with reports by **Deshmukh et al.** [17] and **Nimbalkar et al.** [18]. Although **Upadhyay et al.** [19] found EBM beneficial, its analgesic effect was comparatively milder than 25D in our trial.

Mechanisms and Biological Plausibility

The analgesic action of **dextrose** is believed to be mediated by the activation of the **endogenous opioid system**, triggered via the gustatory-sweet pathway [8,20]. On the other hand, **EBM** contains lactose and tryptophan, which may increase melatonin and β-endorphin levels, contributing to analgesia [9]. However, as our findings and others suggest [10,14,15], the sweet taste of concentrated glucose provides a stronger and faster-acting analgesic effect.

Comparison with International Evidence

Studies from diverse populations support our results. **Carbajal et al.** and **Dilen et al.** demonstrated that higher concentrations of glucose or sucrose provide better pain relief than placebo or lower concentration solutions [7,21]. In contrast, a few studies such as by **Singh et al.** [22] and **Kumari et al.** [23] observed either comparable effects or mild advantage with breast milk, particularly in term neonates or under specific conditions.

Conclusion

This randomized controlled trial found that oral 25% dextrose is significantly more effective than expressed breast milk in reducing venipuncture pain in clinically stable preterm neonates. The 25D group had lower PIPP scores, reduced crying time, more stable heart rates, and better oxygen saturation following the procedure. Given its safety, low cost, and ease of administration, 25% dextrose can be recommended as a first-line non-pharmacological analgesic during minor painful procedures in preterm neonates.

Limitations

This study had several limitations. First, it was conducted exclusively in clinically stable preterm neonates, so the findings may not be generalizable to term neonates or critically ill infants. Second, although the Premature Infant Pain Profile (PIPP) is a validated and widely used tool, pain perception is multifactorial, and relying on a single assessment tool may limit the depth of evaluation. Third, the

absence of a placebo or no-intervention control group—due to ethical concerns—limits the ability to measure absolute analgesic effects. Lastly, the study focused on the short-term efficacy of a single intervention during one procedure; thus, it does not provide data on the cumulative effects of repeated dosing or long-term neurodevelopmental outcomes.

Recommendations

Based on the results, the routine use of oral 25% dextrose can be recommended as a simple, safe, effective, and low-cost intervention for procedural pain relief in preterm neonates undergoing minor procedures such as venipuncture. Neonatal care protocols, especially in resource-limited settings, should incorporate non-pharmacological analgesic strategies like dextrose administration. In addition, training healthcare providers in recognizing and managing neonatal pain is crucial. Future research should explore the combined use of EBM with other comfort measures such as non-nutritive sucking or kangaroo care, assess dose-response relationships for oral dextrose, and evaluate the long-term neurodevelopmental outcomes of repeated procedural pain and its management.

References

1. Merskey H, Albe FD, Bonica JJ, Carmon A, Dubner R, Kerr FWL, et al. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. Pain. 1979;6(3):249–52.
2. Anand KJ, Carr DB. The neuroanatomy, neurophysiology, and neurochemistry of pain, stress, and analgesia in newborns and children. Pediatr Clin North Am. 1989;36(4):795–822.
3. Anand KJ. Clinical importance of pain and stress in preterm neonates. Biol Neonate. 1998;73(1):1–9.
4. Peterson BS, Vohr B, Staib LH, Cannistraci CJ, Dolberg A, Schneider KC, et al. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. JAMA. 2000;284(15):1939–47.
5. Lago P, Garetti E, Merazzi D, Pieragostini L, Ancora G, Pirelli A, et al. Guidelines for procedural pain in the newborn. Acta Paediatr. 2009;98(6):932–9.
6. Anand KJ, Aranda JV, Berde CB, Buckman S, Capparelli EV, Carlo W, et al. Summary proceedings from the neonatal pain-control group. Pediatrics. 2006;117(3):9–22.
7. Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database Syst Rev. 2016;7:CD001069.
8. Blass E, Fitzgerald E, Kehoe P. Interactions between sucrose, pain and isolation distress. Pharmacol Biochem Behav. 1987;26(3):483–9.
9. Barrett T, Kent S, Voudouris N. Does melatonin modulate beta-endorphin, corticosterone, and pain threshold? Life Sci. 2000;66(6):467–76.
10. Bueno M, Costa P, Oliveira J, Cardoso R, Linhares M. Breast milk versus glucose for pain relief in preterm infants undergoing heel lancing: a randomized controlled trial. Pain. 2012;153(5):953–8.
11. Sahoo JP, Manasa S, Gowda NR, Kumar P. Comparison of expressed breast milk, 25% dextrose and sterile water for relieving venepuncture pain in neonates: a randomized controlled trial. Indian Pediatr. 2013;50(2):153–7.
12. Stevens B, Johnston C, Petryshen P, Taddio A. Premature Infant Pain Profile: development and initial validation. Clin J Pain. 1996;12(1):13–22.
13. Witt N, Coynor S, Edwards C, Bradshaw H. A Guide to Pain Assessment and Management in the Neonate. Curr Emerg Hosp Med Rep. 2016;4(3):1–10.
14. Rawal S, Chakrabarti S, Dasgupta S, Rajan R. Efficacy of oral dextrose and expressed breast milk for reducing procedural pain in neonates: A randomized controlled trial. J Trop Pediatr. 2019;65(5):459–65.
15. Malngiang B, Singh LR, Nongthombam RS. Analgesic effects of expressed breast milk and glucose in neonates during venipuncture. J Clin Neonatol. 2016;5(3):167–71.

16. Ravishankar A, Dutta S, Paul VK, et al. Oral dextrose for pain relief during nasogastric tube insertion in neonates: A randomized controlled trial. Indian J Pediatr. 2014;81(1):15–20.
17. 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(3):138–41.
18. Nimbalkar S, Patel D, Patel M, Sethi A. Randomized control trial of 25% dextrose for orogastric tube insertion pain in neonates. Indian Pediatr. 2013;50(1):39–42.
19. Upadhyay A, Aggarwal R, Narayan S. Analgesic effect of expressed breast milk in procedural pain in term neonates. Acta Paediatr. 2004;93(4):518–22.
20. Gibbins S, Stevens B. Mechanisms of sucrose and non-nutritive sucking in procedural pain management in infants. Pain Res Manag. 2001;6(1):21–8.
21. Dilen B, Elseviers M, Vanderhaegen J, Vercauteren J, Vanderbruggen N, Van den Broeck K, et al. Oral glucose solution as pain relief in newborns: results of a clinical trial. Pediatrics. 2010;126(5):e1015–20.
22. Singh B. Breastfeeding versus oral glucose during heel lance in neonates: a prospective study. J Neonatol. 2019;33(2):77–81.
23. Kumari S, Singhal PK, Anupama N, Jain A, Shukla R, Kumar R, et al. Comparison of 24% sucrose and 25% glucose for analgesia during heel lance in preterm neonates. Indian J Pediatr. 2017;84(8):606–10.