RESEARCH PAPER

Expressed Breast Milk *vs* 25% Dextrose in Procedural Pain in Neonates: *A Double Blind Randomized Controlled Trial*

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Objective: To compare the effect of expressed breast milk (EBM), 25% dextrose (25 D) and sterile water (SW) on procedural pain in neonates as assessed by the premature infant pain profile (PIPP), changes in heart rate (HR), oxygen saturation (SpO_2) and duration of crying.

Design: Prospective, double blind, randomized controlled trial.

Setting: Postnatal ward of a tertiary-care hospital.

Participants: 210 babies who required venipuncture for blood sampling and who were on oral feeds were recruited into the study after parental informed consent.

Methods: The enrolled babies were randomized into intervention groups (EBM, 25% dextrose) and control group (sterile water). Two ml of test solution was given to baby by *paladay* (a traditional cup with a spout) 2 min before venipuncture. The face and crying of baby were video graphed by an independent, blinded observer. The facial response to pain (brow bulge, eye squeeze, nasolabial furrow) was analysed from the video. Maximum HR and minimum SpO_2 were recorded during, and 1, 3 and 5 min after venipuncture by another blinded observer.

Outcome variable: :PIPP score, HR, SpO_2 and crying time at 0/ 1/3/5 min after sampling.

Results: 160 babies were considered for final analysis with 50 in 25 D, 62 in EBM and 48 in SW group. The mean PIPP score in the 3 groups were 5.22, 6.84 and 11.22 at 0-30 sec after venipuncture; 4.52, 6.34, and 10.88 at 1-1 ½ min; 3.96, 6.15 and 9.35 at 3-3 ½ min; and 3.12, 4.68 and 7.83 at 5-5 ½ min; respectively (P< 0.001). The median crying time was 10 ,37.5 and 162 seconds in 25 D, EBM and SW groups, respectively (P< 0.001).

Conclusions: EBM significantly reduces procedural pain in neonates though to a lesser extent as compared to 25% dextrose.

Key words: *25% dextrose, Expressed breast milk, Neonates, Procedural pain, PIPP score.*

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Most newborns routinely undergo painful invasive procedures in the hospital. It is now well recognized that even preterm neonates are anatomically and physiologically capable of feeling pain. Pain in neonates can evoke negative behavioral, physiologic, or metabolic responses [1], and may be associated with long term consequences. As neonates cannot verbalize their pain, they depend on others to recognize, assess and manage their pain.

Many pharmacologic and non-pharmacologic methods have been proposed for pain control in neonates [2-5]. Despite these, the pain during various neonatal procedures is inadequately controlled. Expressed breast milk [6,7], sucrose [7,8] and glucose (10-33%) [9,10] have been used in various trials for reducing procedural pain in neonates with equivocal effects. We hypothesized that both expressed breast milk and 25% dextrose are equally effective in reducing pain from venipuncture. We tried to compare the efficacy of expressed breast milk and 25% dextrose in comparison with sterile water in reducing pain during venipuncture in neonates as assessed by the Premature Infant Pain Profile.

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METHODS

This prospective randomized controlled trial was conducted in the post-natal ward of a tertiary care hospital in southern India from April 2010 to September 2010. Babies ≥34 week gestations that required venipuncture for blood sampling and who were on oral feeds were included in the study after informed parental consent. Neonates who were sick, had perinatal asphyxia (Apgar score <5 at 5 minutes), congenital malformations or were on opioid analgesics, sedatives or phenobarbi-tone were excluded from the study. After inclusion, all neonates who cried before venipuncture or passed stool/urine during sampling or had more than one prick were excluded from analysis, as decided *a priori*. The study was cleared by the Institutional ethical review board.

The eligible babies were randomized into 3 groups: two intervention groups - Expressed breast milk group (EBM), 25% dextrose group (25D) and sterile water group (SW) – the control group; using computer generated random numbers. Allocation concealment was achieved by using sequentially numbered opaque sealed envelope containing the codes for intervention (EBM for expressed breast milk, 25D for 25% dextrose, SW for sterile water). The envelopes were exclusively accessed by the principal investigator.

The neonates requiring venipuncture were taken to a quiet room. It was ensured that time interval between the procedure and previous breast milk intake was at least one hour. The babies' gestational age was determined by New Ballard Score and behavioral state was recorded. Oxygen saturation (SpO_2) and heart rate (HR) were monitored by a pulse oxymeter (MASIMO). Two 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* were cleared before the entry of observers into the room. All venipunctures were done with 23 gauge needle 2 minutes after the test solution was administered. All venipunctures were done by one of a selected group of staff nurses who had adequate experience in neonatal care to minimize variation in pain during venipuncture. Two observers were present during sampling time. One observer videographed the face of baby for later analysis; the other observer was responsible for recording the HR, SpO_2 and duration of venipuncture. The observers entered the room after test solution was administered, and thus were masked to the test solution given. HR and SpO_2 were recorded at baseline, and at 0, 1, 3, 5 min after venipuncture. Maximum HR and minimum SpO_2 were noted between 0-30 seconds, 1-1½ min, 3-3½ min and 5-5½ min after the venipuncture. Crying time was defined as the total duration of audible cry which was recorded from the video recording. Sampling time was defined as the time gap between the times of insertion of needle for venipuncture to the time the needle was removed from the baby. The facial response to pain (brow bulge, eye squeeze, nasolabial furrow) in this period was recorded and subsequently analyzed from the video by a single observer. The primary outcome of the study was the PIPP score [11]. The PIPP score is a composite pain measure that includes contextual (behavioral state and gestational age), behavioral (brow bulging, eye squeezing and nasolabial furrowing), and physiologic (heart rate and oxygen saturation) indicators of pain. Each indicator is scored in a 4 point scale (0-3) and pain intensity scores range from 0-21. Scores of 6 or less represent absence of pain or minimal pain. PIPP score was not calculated in case of difficulty in analyzing the facial response from the videos. The secondary outcomes were change in HR, SpO_2 and crying time.

The sample size was calculated based on the study by Taddio, *et al.* [8], where the mean difference of PIPP score was 1.8 between the two study groups (24% sucrose and placebo) group. Considering the standard deviation for the group 1 as 2.9 and standard deviation for the group 2 as 2.5, with 1% level of significance and 90% power, 201 subjects were to be recruited, 67 subjects in each arm (breast milk, 25% dextrose, sterile water). However the sample was increased to 210 (70 in each group) to account for the possible loss of data.

Statistical analysis was done with ANOVA (analysis of variance) to assess the effect within and between the groups. Analysis was done with SPSS statistical software package 16. Post-hoc analysis was done using Bonferroni test. Crying time was analyzed by Kruskal Wallis test. Repeated measures ANOVA were used to compare the heart rate and SpO_2 over time and it's interaction with the intervention group. A *P* value of 0.01 was considered a statistically significant level of difference.

RESULTS

A total of 210 babies were randomly allocated to the 3 groups (25 D, EBM, and SW). 50 neonates were excluded from the analysis because of incomplete data **(*Fig* 1).** The analysis included 160 babies (50 in 25 D, 62 in EBM and 48 in SW group). No differences were observed bet-ween the groups with regard to baseline variables **(*Table* I).**

The crying time [median (IQR)] was lower in the 25% dextrose group [10(0-70)] as compared with the EBM [37.5 (5-142)] and sterile water group [162 (59-200)]. The difference between crying time in 25D and EBM group was not significant. A significant difference was found between SW group compared to 25D and EBM groups.

There was a significant change in HR and SpO_2 over time ($P<0.001$). The HR and SpO_2 observed in the sterile water group were significantly higher and lower, respectively when compared to the other two groups for all time points except baseline (***Table* II**).

The mean PIPP score was significantly lower at 0-30 sec, 1- 1 ½ min, 3-3 ½ min, and 5- 5 ½ minutes after the procedure in the 25 D, and EBM groups *vs* SW group. Further, the PIPP score was higher in EBM group than 25 D group at all time points. The PIPP score was not significantly different at 30 sec between the 25D and EBM group ($P=0.58$) **(*Table* III).**

There were no adverse events in any of the groups except for 1 baby having transient bradycardia (HR <100) in the 25D group.

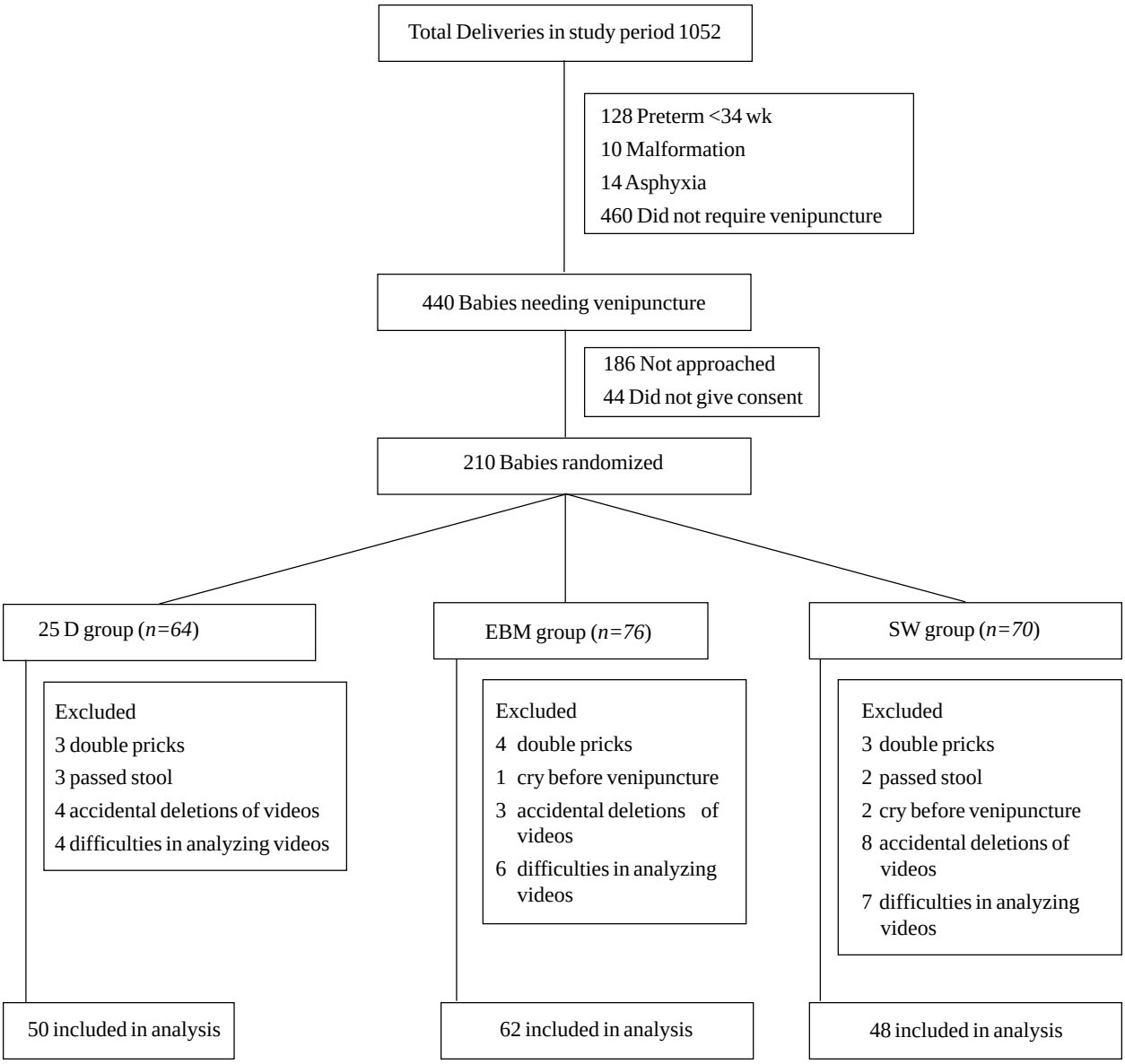

FIG. 1 *Trial profile and participant flow.*

TABLE I BASELINE CHARACTERISTICS OF STUDY POPULATION

Parameter	*25D group (n=50)*	*EBM group (n=62)*	*SW group (n=48)*
Birth weight* (g)	2965 (2507-3287)	2605 (2226-2992)	2720 (2297-3000)
Gestation# (wk)	37.94 (1.64)	37.66 (1.88)	37.93 (1.61)
Male	30 (60%)	44 (70%)	28 (58%)
Vaginal delivery	25 (50%)	35 (56%)	23 (48%)
Postnatal age (hr)*	77 (55.5-102)	84 (61.5-97.5)	89 (54-98)
Time since last feed# (min)	59.7 (8.1)	56.84 (7.4)	58.54 (6.6)
Sampling time* (sec)	50 (38.5-60)	51.5 (41.2-63.7)	55 (43.7-65)

**median (IQR); #Mean (SD); EBM – Expressed breast milk; SW – Sterile Water; 25 D – 25% dextrose.*

TABLE II HEART RATE AND SPO_2 [MEAN (SD)] IN THE STUDY SUBJECTS

	Heart rate (beats/min)			*SPO_2 (%)*		
	25D	*EBM*	*SW*	*25 D*	*EBM*	*SW*
Baseline	131.7 (13.9)	127.4 (16.2)	125.3 (14.7)	97.5 (1.9)	97.9 (1.8)	98.2 (1.4)
After venipuncture						
0 - 30 sec	142.2 (13.6)	142.5 (17.4)	153.8 (15.5)	95.2 (3.6)	95.8 (2.1)	95.1 (1.9)
1 min- 1 ½ min	140.0 (14.9)	142.5 (21.4)	156.4 (19.1)	95.5 (2.7)	95.4 (3.1)	93.7 (2.4)
3 min- 3½min	138.4 (17.0)	142.0 (21.3)	155.2 (18.9)	95.7 (2.3)	95.7 (2.9)	93.9 (2.5)
5 min-5 ½ min	132.6 (17.0)	137.6 (20.9)	149.4 (17.4)	96.0 (2.2)	96.52 (2.4)	94.4 (2.4)

EBM – Expressed breast milk; SW – Sterile Water; 25 D – 25% dextrose.

DISCUSSION

This study showed that both 25% dextrose and breast milk decrease pain response (behavioral and physiologic) in newborn babies as assessed by the PIPP score. The mean crying time, heart rate and oxygen saturation changes at 0, 1, 3, 5 minute after venipuncture were significantly reduced in the 25% dextrose or breast milk group as compared to placebo (sterile water), and the analgesic effect persisted till 5 minutes after the procedure. The analgesic effect of 25% dextrose or expressed breast milk is probably based on the link that exists between the oro-gustatory effects of sweet solution given orally and the endogenous opioid pathway [12, 13]. In all probability this is due to the sweet taste perception, a sense well developed even in premature infants at birth.

Though oral sucrose has been widely studied as an analgesic tool and has been found to be safe and effective [14], we preferred to use 25% dextrose, as sucrose is not readily available in the neonatal units in India. Compared to sucrose, glucose is 0.75 times as sweet [15] and 25% dextrose is commercially available as sterile ampoules. Breast milk also has analgesic properties and has been found to reduce pain from procedures. The analgesic effect of breast milk may be related to the sweetness of breast milk (presence of lactose in breast milk) [16] or higher concentration of tryptophan, a precursor of melatonin that increase the concentration of beta endorphins [17]. Being a natural food, it would be the most ideal and safe analgesic. Also it is readily available, easy to use and can be repeated without risk.

Similar analgesic effects of expressed breast milk were observed in studies by Upadhyaya, *et al.* [6]. They had; however, used a higher volume (5 mL) of EBM. Others found a better response with higher glucose concentration (25-30%) compared to 10% glucose or breast milk [9,10]. In contrast to our study, Desmukh, *et al.* [10] did not find significant reduction in heart rate and oxygen saturation in their study on preterm infants. Ors, *et al.* [7] also concluded that the antinociceptive effect of human milk is not as effective as an analgesic as 25% sucrose solution.

We observed that though EBM and 25% dextrose reduced the mean PIPP score after venipuncture, 25% dextrose was better. Mariano, *et al.* [18] compared the efficacy of expressed breast milk *vs* 25% glucose on pain responses of late preterm infants during heel lancing. They also observed lower incidence of cry and shorter duration of crying in the 25% dextrose group. They concluded that the results based on PIPP score and crying time indicate better effects of 25% glucose compared to EBM during heel lancing.

One of the strength of the study is that we have used a very objective, validated and reliable tool for assessment of pain response - the PIPP tool [19]. The PIPP adjusts for gestational age and is also validated for use in term neonates [20]. The other strength of the study is that the observers were masked to the analgesic used. The main

TABLE III PIPP SCORE IN THE STUDY SUBJECTS

	*25 D group**	*EBM group*	*SW group*
0 - 30 sec	5.22 (4.3-6.1)	6.84 (5.8-7.8)	11.21 (10.1-12.2)
1 min- 1½ min	4.52 (3.6-5.4)	6.34 (5.2-7.4)	10.88 (9.7-12)
3 min- 3½ min	3.96 (3.2-4.6)	6.15 (5.1-7.1)	9.35 (8.2-10.4)
5 min-5½ min	3.12 (2.4-3.8)	4.68 (3.8-5.5)	7.83 (6.7-8.8)

** PIPP score in 25 D vs. EBM group at 1- 1 ½min, 3- 3 ½ min, 5- 5 ½ min P=0.042, P= 0.003, P=0.036, respectively.*

WHAT IS ALREADY KNOWN?

- Expressed breast milk (EBM) and 25% dextrose have pain relieving property.

WHAT THIS STUDY ADDS?

- EBM significantly reduces procedural pain in neonates, though to a lesser extent as compared to 25% dextrose.

limitation of our study is the post-randomization exclusions, because of video errors (difficulty in analyzing/ accidental deletion of some videos). We have neither studied the long term effect of painful stimuli nor the effect of multiple punctures.

This study further emphasizes that venipuncture is a painful procedure with pain scores as high as 11 immediately after the procedure and high scores persisting after 5 minutes; though we did not record the median recovery time. The use of analgesics, either glucose or breast milk, does not totally alleviate the pain. Pain management in newborns must thus be multi- pronged.

Pain in newborn should be recognized and treated. We conclude that 25% dextrose and expressed breast milk cause effective reduction in pain response in newborn babies during venipuncture and there is a better response with 25% dextrose. EBM which is easily available and useful for alleviating pain response does not totally alleviate pain and further studies should evaluate groups of intervention for pain reduction.

Contributors: JPS: conceiving and designing the study, protocol development, patient screening and analysis of video for PIPP score, outcome assessment, and writing of manuscript; SR: study design, writing of manuscript; SN: randomization of study population and statistical analysis; TR & AC: patient screening, collection of data, video recording; and SB: supervised the design and execution of study, outcome assessment, writing of manuscript. She will act as guarantor of the study. The final manuscript was approved by all the authors.
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