

# Comparison of 25% Dextrose versus Expressed Breast Milk in Reducing Pain while Heel Prick Procedure in Preterm Neonates in a Tertiary Care Hospital, Vadodara, Gujarat, India: A Randomised Clinical Trial

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## ABSTRACT

**Introduction:** Preterm infants undergo repeated painful procedures during a period of rapid brain development and programming of stress systems. Newborn babies including preterm infants do feel pain. Although different interventions, such as skin-to-skin contact, glucose solutions, breastfeeding, and local anaesthetic agents, have been evaluated to reduce infants' pain, there is no clinical trial available to identify the best method.

**Aim:** To compare the dextrose 25% versus Expressed Breast Milk (EBM) in reducing pain while heel prick procedure in preterm neonates in a tertiary care hospital.

**Materials and Methods:** The present randomised clinical trial was conducted at Neonatal Intensive Care Unit (NICU) of Kashiben Gordhandas Patel Children Hospital, Vadodara, Gujarat, India, from September 2019 to May 2020. Total 125 neonates with Gestational age between 28 weeks to 36 weeks were included in the study. Babies were divided into two groups by randomisation: Group-A: EBM and Group-B: Dextrose 25%.

Premature Infant Pain Profile (PIPP) score was calculated from worst state of individual recovery period (0-½ minute, 1-1½ minute, 3-3½ minute) and compared to baseline period PIPP.

**Results:** Mean gestational age on examination in Group-A was 34.48±6.14 weeks and in Group-B were 34.51±5.89 weeks. Out of total 125 preterm babies (Group-A-62, group B-63), 71 (56.8%) were male and 54 (43.2 %) were females. Comparison of PIPP at 1-1½ min of heel prick in EBM and Dextrose 25% group was statistically significant (p-value <0.003) suggestive of continued analgesic effect of dextrose 25% better than EBM and PIPP scores after 3-3½ min of heel prick having no statistically significant difference. (p>0.05) Mean difference between the PIPP score in the dextrose 25% and EBM groups was -1.25 and -1.33 at 0 and 1 minute after procedure (p-value, <0.001), so pain relief was better in dextrose 25% group than EBM group.

**Conclusion:** Dextrose 25% was better effective in reducing mean crying duration than EBM. Dextrose 25% had a better analgesic effect than EBM in 28 to 36 weeks gestational age neonates.

**Keywords:** Premature infant pain profile, analgesia, Postoperative pain, Newborn

## INTRODUCTION

Infants that are born prematurely and at full term experience pain. Premature infants undergo a variety of gruelling procedures as their brains develop quickly and their stress response systems are programmed. Many studies in preterm infants have provided evidence that repeated painful interventions in neonatal period contribute to hyperalgesia that is more profound and more long lasting in comparison with term infants [1-5]. The high prevalence of painful procedures being performed with preterm newborns without analgesia (79%), with a median of 75% painful procedures being received during hospitalisation and as many as 51% painful procedures per day highlights the importance of this problem [2].

Additionally, both preterm and term newborns requiring more intensive care, such as respiratory support, are exposed to an increased amount of acute procedures. While it was previously believed that newborns did not feel pain, research findings have not only refuted this belief, but have also revealed that newborns' threshold for pain is likely to be lower than that of older infants and children due to developing abilities to modulate pain both cognitively and physically [3]. Moreover, preterm neonates' pain thresholds

are seen as substantially lower than full-term newborns. Given the ubiquitous nature of painful and invasive medical procedures in the NICU, the implications of repetitive painful procedures have also been studied in the literature [4].

As part of the NHS's immunisation programme, infants in India's first year of life are regularly exposed to 12 potentially painful intramuscular injections, given on four separate occasions. Procedure-related pain in newborns and infants cannot be managed in the same way as it is in older children or adults, so non-pharmacological treatments are prioritised [5,6]. Pharmacological interventions and their side effects and non-pharmacological therapies are also reviewed including sucrose, milk and non nutritive sucking, using of pacifier which have been effective but thought to negatively affect breast-feeding [5,7].

As per recent survey, the use of non-pharmacological measures has been increased significantly between 2000 and 2017 from 84 to 97% [7]. Sugary solutions, such as dextrose, glucose, or sucrose solutions bind to the sweet taste receptors and cause a surge of endorphins, which leads to lowering the sensation of pain and elevating the pain threshold level; however, its efficacy for

analgesia has been reported differently in recent studies [8-11]. It assumes that breast milk feeding, as another method for analgesia, reduces the pain sensation through three different mechanisms, i.e., endorphin release due to sweet taste, skin contact and cradling during breastfeeding, and the sucking reflex [12-17].

The non-pharmacological modalities of pain relief work not merely by distraction but also due to soothing effect of sucrose and by release of endogenous feel good neuropeptides and endorphins [18].

Many palliative methods have been studied for children [12]. Also, pain relief in infants has been the subject of many studies [10,11]. However, methods that are merely applicable to the emergency department are less well considered. Most pain reduction methods require analgesic injections or applications which are not suitable for infants. Also, most non-pharmacological methods are time-consuming and are therefore not applicable within the emergency sector. The authors hypothesised that both EBM and 25% dextrose are equally effective in reducing pain from venipuncture. Present study was done with an aim to investigate if instilling breast milk or dextrose water into oral cavity can reduce pain of heel prick in preterm neonates and to compare with each other.

## MATERIALS AND METHODS

The present randomised crossover clinical trial was conducted in Kashiben Gordhandas Patel Children Hospital, Vadodara, Gujarat, India, from September 2019 to May 2020 over a period of nine months. Study was commenced after approval from the Ethical Committee and Scientific Committee (KGPC/179/2022/pedia). This trial was registered with (CTRI no: 231-22109-191-223691). A written informed consent was taken from each patient.

**Inclusion criteria:** Haemodynamically stable preterm neonates of 28-36 weeks gestational age, who required heel prick, were included.

**Exclusion criteria:** Neonates with ventilator or CPAP, use of sedatives within last 24 hours, with clinically evident abnormal neurological sign or encephalopathy, birth asphyxia, cardiorespiratory instability, neuromuscular dysfunction, congenital anomalies were excluded.

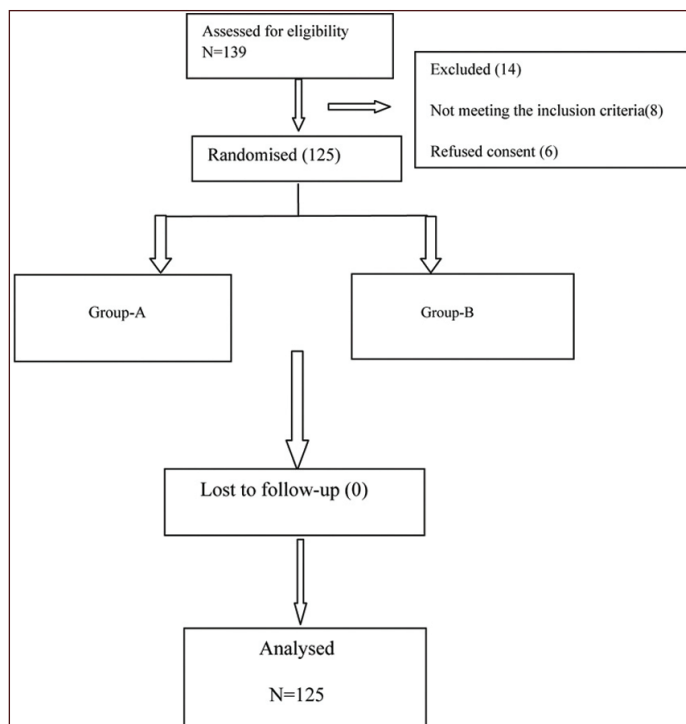
**Sample size:** To assess the difference in mean reduction of pain score between two groups by one with SD of two at 95% confidence and 80% power, a total of 125 preterm neonates were needed.

$$n = 2 * \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 * SD^2}{d^2}$$

Where,  $Z_{1-\alpha/2} = 1.96$ ,  $Z_{1-\beta} = 0.842$ ,  $SD = 2$ ,  $d = 1$

To achieve expected sample size, in view of error in procedures like multiple pricks, difficulty in analysing video and vomiting while examination (as per data from previous literature) [7], the authors considered 10% extra sample size to the calculated sample size of 125. Hence, total of had included total 139 neonates which were randomly allocated in two groups, out of which eight patients from Group-A and six patients from Group-B were excluded due to above mentioned reasons. So finally, 62 patients from Group-A and 63 patients from Group-B were analysed [Table/Fig-1].

Randomisation of baby was done by previously generated random number. Allocation concealment was done by storing the randomised group numbers in sealed opaque envelopes which were opened just before administration of intervention.



[Table/Fig-1]: CONSORT flowchart of the study.

## Procedure

**Data collection:** The data were gathered and details were filled into the performa. The gestational age was noted from the case records and as per New Ballard Score and weight on the day of enrolment was recorded [4].

Babies were divided into two groups by randomisation:

Group A: EBM first followed by dextrose 25% in same group with 6-8 hours of gap while heel prick procedure.

Group B : Dextrose25% first followed by EBM in same group with 6-8 hours of gap while heel prick procedure.

The study solutions were prepared by members of the staff who were otherwise not involved with the study. EBM was collected for all the babies in a sterile container before the start of the examination.

Study interventions were done on babies expected to heel prick, as per routine management and requirement of baby, No additional heel prick were done. Each study case received heel prick two times with 6-8 hours gap in routine care of preterm. Commercially, available dextrose 25% was taken in 1 ml syringe and used in 24 hours. During Intervention period, 0.2 ml/kg dextrose 25% or 2 ml EBM was instilled into mouth using sterile syringe by staff nurse respectively according to random order of group allocation [7].

Each evaluation process had four sections:

- Baseline period of one minute;
- Intervention period of one minute;
- Heel prick of 30 seconds;
- Recovery period of three minute.

Neonates were placed in semi-reclining position on a couch or remained in their radiant warmers during procedure. A non-invasive vital sign monitor was applied to infant's foot or hand to monitor heart rate or oxygen saturation. (Medsun MD5100 Vital Sign Cardiac Monitor) After baseline period of one minute and baseline PIPP score evaluation, decided amount of solution of dextrose 25% or EBM were given to the neonate over anterior part of tongue by staff nurse over period of one minute. After one minute, heel prick was done after

cleaning heel of neonate with sterile spirit swab by trained staff nurse within 30 seconds. Video recording of neonatal facial expression to pain was done by investigator during baseline period of one minute and recovery period of three minutes during and after heel prick along with continuous heart rate and SpO<sub>2</sub> monitoring by pulse oximetry.

PIPP score was calculated from worst state of individual recovery period minute and compared to baseline period PIPP [4]. The PIPP is a seven-item multidimensional measure of pain. The seven items include three behavioural (facial actions: brow bulge, eye squeeze, nasolabial furrow), two physiological (changes in heart rate and oxygen saturation), and two contextual (GA and behavioural state) items. The maximum score is 21 for preterm infants GA and 18 for full-term infants. PIPP scoring criteria was: 0-½ minute, 1-1½ minute, 3-3½. The PIPP score is a composite pain measure that includes contextual (behavioural state and gestational age), behavioural (brow bulging, eye squeezing and nasolabial furrowing), and physiologic (heart rate and oxygen saturation) indicators of pain. Each indicator is scored in a four point scale (0-3) and pain intensity scores range from 0-21. Scores of six or less represent absence of pain or minimal pain. Crying time was defined as the total duration of audible cry which was recorded from the video recording.

Primary investigator, parents and person assessing the PIPP score were blinded to identity of the study solution. A trained staff nurse who was not involved in the study analysis delivered solution directly into the mouth of the baby. Heart rate and oxygen saturation were continuously measured and recorded on the bedside pulse oximetry. Baseline physiological parameters were collected before start of examination.

## STATISTICAL ANALYSIS

Data analysis was done by STATA/IC-13 statistical software. Descriptive statistics like frequency table, mean, median, standard deviation, percentage for baseline variable comparison and PIPP Score. Students t-test was used to compare two groups of mean quantitative data. The chi-square test was used for comparison of categorical variables. For all tests, statistical significance was defined as p-value of less than 0.05.

## RESULTS

Out of total 125 preterm babies (Group-A- 62, Group-B-63), 71 (56.8%) were male and 54 (43.2%) were females. Out of which Group-A had 35 (56.5%) male and 27 (43.5%) females, with similar distribution of Group-B had 36 males (57.1%) and 27 (42.9%) females [Table/Fig-2].

Gender	Group-A n (%)	Group-B n (%)	p-value
Males	35 (56.5)	36 (57.1)	0.07
Females	27 (43.5)	27 (42.9)	
Total	62 (49.6)	63 (50.4)	

**[Table/Fig-2]:** Gender Distribution of study participants. Statistically significance at p<0.05, chi-square test

Gestational age wise distribution included 97 late preterm (>34 weeks) out of 125 preterm neonates and 28 early preterm (<34 weeks) out of 125 preterm neonates.

Mean gestational age on examination in Group-A was 34.48±6.14 weeks and in Group-B was 34.51±5.89 weeks. Mean age on procedure for Group-A was 6.13±0.23 days and median was 3.5 days, and for Group-B mean was 7.65±0.87 days and median was four days. Cases of LSCS delivery in Group-A was 47 and Group-B was 45 [Table/Fig-3]. Mean and median crying duration in EBM group were 5.32±3.72 and 5.0 (2-9) respectively and in dextrose 25% group were 4.2±3.31 and 4.0 (2-7), respectively. Mean crying duration in Group-A was significantly higher than the Group-B [Table/Fig-4].

Variable	Group-A (Mean±SD)	Group-B (Mean±SD)	p-value
Mean gestational age (years)	34.48±6.14	34.51±5.89	0.05
<b>Mode of delivery</b>			
LSCS:	47 (75.80%)	45 (71.42%)	0.001*
Vaginal	15 (24.19%)	18 (28.57%)	
Mean weight	1.74±0.54	1.63±0.68	0.09
Mean age at the time of procedure (Days)	6.13±0.23	7.65±0.87	0.03*

**[Table/Fig-3]:** Comparison of demographic variables in both groups. \*Indicates statistically significance at p<0.05, student t-test and chi-square test

The mean (SD) PIPP scores, before heel prick (Baseline PIPP) to after heel prick at 0 minute, 1 and 3 minute in EBM groups and in dextrose 25% groups were high at the time period of 0-½ min and declining trend at 1-1½ min and at 3-3½ min, the condition nearly returns to the baseline. Difference between both groups was significant statistically [Table/Fig-4].

PIPP Score	EBM (n=125)	Dextrose 25% (n=125)	p-value
<b>Time after heel prick procedure</b>			
0-1/2 min	3.22±0.54	3.12±0.31	0.002*
1-11/2 min	8.1±1.03	6.85±0.89	
3-31/2 min	5.76±0.08	4.43±0.12	
3 min	3.15±0.41	3.02±0.09	
Crying (Minutes)	5.32±0.11	4.2±3.31	0.004*

**[Table/Fig-4]:** Premature infant pain profile score. \*Indicates statistically significance at p<0.05, student t-test

## DISCUSSION

Intensive care treatment of preterm and sick term infants in the neonatology unit entails a period of hospitalisation which may last from several weeks to several months. These children are exposed to an environment characterised by highly variable, sometimes excessive stimulation lack of diurnal variation and frequently changing caregivers [19]. A pre-condition for an adequate pain treatment procedure is the accurate assessment of the pain. Recently, a growing number of reliable and valid measurement tools for neonates have been developed [20].

Upto 80-90% of the medications which are used among sick preterm and term neonates in an intensive care unit are either not approved for the illness concerned (off-label use), or are administered in a form other than that officially approved. As a rule, their use is based on clinical guidelines. The reticence in systematic application for routine short interventions can be justified with a view to their long-term effects and possible side-effects [20,21].

Non-pharmacological pain intervention is a prophylactic and complementary approach to reduce pain. It is assumed that non pharmacological interventions activate the gate control mechanism. Some of them lead to an endogenous endorphine dispersal, which contributes to the modulation of the pain pulse at the level of the spinal cord, and have the effect of relieving pain. These interventions can also activate the attention of neonates, distract them from the pain, and thus modify the pain. It is postulated that they reduce the pain by pre-empting hypersensitivity [21].

This study showed that both 25% dextrose and breast milk decrease pain response (behavioural and physiologic) in newborn babies as assessed by the PIPP score. Gradin M and Schollin J argued orally administered dextrose has more significant effect because it reduces the pain of painful procedures by stimulating the secretion

of endorphins [22]. Similarly, Cohen LL et al., indicated that oral dextrose has a more significant impact on pain reduction [23].

Jatana SK et al., examined the effects of 10, 25 and 50% of oral dextrose, EBM and sterile water (the control group) on the amount of heel blood sampling pain in 125 infants. Their results indicate that the use of dextrose with different concentrations and EBM has an effective analgesic result in full-term infants and can be used as a cost-effective method with many benefits and low side effects in reducing neonatal pain [24]. The results of the study by Golestan M et al., showed that the pain response and duration of crying of newborns in the infants who received oral dextrose group (25 and 50%) before painful procedures was reduced more than infants who received 10% oral dextrose and EBM group [25].

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) or higher concentration of tryptophan, a precursor of melatonin that increase the concentration of beta endorphins [26]. 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 EBM were observed in studies by Upadhyay A et al., [27]. 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 [28,29].

Desmukh LS and Udani RH did not find significant reduction in heart rate and oxygen saturation in their study on preterm infants [29]. Ors R et al., also concluded that the antinociceptive effect of human milk is not as effective as an analgesic as 25% sucrose solution [30]. Buenno M et al., compared the efficacy of EBM vs 25% glucose on pain responses of late preterm infants during heel lancing [31]. 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.

Heel prick was significant painful procedure which increased PIPP scores immediately during procedure which returned to nearly baseline at three minutes in both groups, but it didn't alleviated the pain. In this study, non-pharmacological interventions- dextrose 25% and EBM were given before heel prick to reduce procedural pain, which had significant analgesic effect [32].

Preterm pain score before, during and after heel prick was suggestive of babies had significant pain during heel prick procedure and pain level observed was minimum to mild mainly. Dextrose 25% had better effect in reducing pain in comparison with EBM. Dextrose 25% was better effective in reducing mean crying duration than EBM. Dextrose 25% had a better analgesic effect than EBM in 28 to 36 weeks gestational age neonates in term of less PIPP score, less crying duration and sustained analgesic effect during and after the procedure.

### Limitation(s)

The post-randomisation exclusions, because of video errors (difficulty in analysing/accidental deletion of some videos). Long-term effect of painful stimuli and the effect of multiple punctures were not recorded in the present study.

### CONCLUSION(S)

Dextrose 25% had better effect in reducing pain in comparison with EBM. Dextrose 25% was better effective in reducing mean crying duration than EBM. Dextrose 25% had a better analgesic effect than EBM in 28 to 36 weeks gestational age neonates in term of less PIPP

score, less crying duration and sustained analgesic effect during and after the procedure. Non-pharmacological interventions to reduce pain should be used whenever possible because of their effectiveness, low cost and safety. Based on prolonged NICU stay of preterm neonates, requirement of multiple painful procedures and to prevent long-term pain related adverse effects; future studies are needed to identify the best method of pain reduction for procedures in these settings.

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#### PLAGIARISM CHECKING METHODS: <sup>[Jain H et al.]</sup>

- Plagiarism X-checker: Aug 01, 2022
- Manual Googling: Apr 28, 2022
- iThenticate Software: May 08, 2022 (20%)

#### ETYMOLOGY: Author Origin

#### AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jul 29, 2022**  
Date of Peer Review: **Sep 19, 2022**  
Date of Acceptance: **May 09, 2023**  
Date of Publishing: **Jun 30, 2023**