DOI: 10.7860/IJNMR/2023/59294.2377

Original Article

Paediatrics Section

Efficacy of Enhanced Dose of Expressed Breast Milk in Neonatal Procedural Pain Relief: A Randomised Placebo-controlled Study

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ABSTRACT

Introduction: Procedural pain remedies in neonates is an area of active research due to better understanding of short and long-term outcomes of neonatal painful exposures. Non pharmacological interventions are especially attractive as it avoids unnecessary drug exposure. While dextrose is known to be effective, results with small volumes (2 mL) of Expressed Breast Milk (EBM) are equivocal. There is recent theoretical evidence to show that larger doses of EBM may be more efficacious.

Aim: To compare the efficacy of a larger volume of EBM 5 mL and 2 mL of 25% Dextrose (25D) in relief of procedural pain from venipuncture in term and preterm neonates.

Materials and Methods: A single center randomised placebo-controlled study was conducted at Bokaro General Hospital, Bokaro Steel City, Jharkhand, India, between March 2014 and February 2016. Neonates ≥34 week gestation, requiring venipuncture in a neonatal care unit were randomly allocated into 3 equal groups using a random number table- Sterile Water (SW), 2mL 25D, 5 mL EBM was given two minutes prior to venipuncture. Video of facial response, cry times, Maximal Heart Rate (MHR), and minimum Oxygen Saturation (SpO_2) were recorded till five minutes after venipuncture. The Premature Infant Pain Profile (PIPP) score was used to assess the effect of the interventions on procedural pain. Subgroup analysis was done in term and preterm neonates. Continuous variables were presented as mean±SD or median. Categorical variables were expressed as frequencies and percentages. The comparison of normally distributed continuous variables between the groups was performed using Analysis of Variance (ANOVA).

Results: The PIPP score in the 25D group (2.94±1.41) was significantly lower than the EBM (7.42±1.69) and SW (10.56±1.69) groups (p-value<0.001). MHR was significantly lower in the 25D group, but no difference was found between the EBM and SW groups (p-value=0.23). SpO_2 was significantly higher in the 25D group but for the initial 2.5 minutes only. Cry times were significantly lower in the intervention groups. There was no difference in outcomes in term vs. preterm infants.

Conclusion: The use of 2 mL 25D was more effective in reducing procedural pain from venipuncture compared to 5 mL EBM. The return of physiological markers (MHR and SpO_2) to baseline were faster and more complete in the 25D group.

Keywords: Analgesia, Infant, Newborn, Nociceptive pain, Pain management, Pain measurement

INTRODUCTION

Neonates admitted in neonatal care units undergo various procedures for diagnostic and therapeutic purposes, many of which are painful. A recent study estimated that such newborns undergo around 90-100 painful procedures, averaging 13.9 per baby per day [1]. Neonates sometimes don't have similar behavioural or motor responses as adults, leading historically, to a pervasive view that neonates do not feel and experience pain in the same way as adults do [2]. It is however clear that such painful exposures in the neonatal phase can lead to adverse short and long-term neurodevelopmental and behavioural outcomes [3,4]. It is thus quite distressing that in a recent report, just 13% of painful procedures were preceded by analgesic measures [5]. The knowledge and attitude of healthcare workers towards neonatal procedural pain is also far from reassuring [6]. Several pharmacological interventions have been tried in neonates for pain relief with variable success [7-9]. Although these interventions are effective, it sometimes raises ethical issues of excessive or unnecessary drug exposure in neonates. Some studies have used distraction measures like cartoons in relatively older children [10]. Non pharmacological interventions, such as preprocedure administration of sweet solutions such as dextrose or sucrose have been shown effective to various extents in alleviating procedural pain in neonates [11,12]. EBM on the other hand has provided more equivocal results, especially when used in smaller volumes [13-15]. Interestingly, studies using a large dose of EBM were more effective [16]. The lower lactose content in breast milk (7%) and lower apparent sweetness compared to stronger dextrose solutions may explain the better efficacy of larger volumes of EBM. Keeping in view this unmet need relating to a 'neglected' area of neonatal medicine, and the lack of studies comparing larger doses of EBM to 25D, the present study was conducted. The aim was to evaluate if a 5 mL dose of EBM was non inferior to 2 mL of 25D in relieving procedural pain due to venipuncture in neonates.

MATERIALS AND METHODS

A single center randomised placebo-controlled study with interpreter blinding conducted in the neonatal care unit in a tertiary care hospital at Bokaro General Hospital, Bokaro Steel City, Jharkhand, India, between March 2014 and February 2016. The protocol was reviewed and approved by the Institutional Ethics Committee (Permission letter dated 15th March, 2014).

Sample size calculation: Considering 5% level of significance, power of 90% and allowing for loss of data, sample size was calculated as 165.

Inclusion criteria: After written informed consent from parents, neonates of >34 weeks gestation requiring venipuncture for blood sampling and who were on oral feeds were included.

Exclusion criteria: Sick neonates, those receiving sedatives or analgesics, those crying before venipuncture or having received recent feed, failed first attempt at venipuncture or neonates with congenital neurologic or craniospinal abnormalities were excluded.

Procedure

The neonates were randomised into two intervention groups and a control group, using a random number table in a 1:1:1 ratio. The intervention agent (5 mL EBM or 2 mL 25D) or placebo (2 mL SW) was given two minutes prior to the venipuncture. The agent was administered orally using a taped syringe (covered with micropore tape) for interpreter blinding. The venipunctures were carried out with 23G (gauge) needle by a selected group of staff nurses or residents to minimise variation in pain during the venipuncture.

A video recording of the procedure and the postprocedural period till the infant stopped crying was done. The video was assessed for total duration of brow bulge, eye squeeze and nasolabial furrowing by a blinded interpreter. The heart rate and saturation were recorded using a finger pulse oximeter for 30s spans immediately after the prick and at 1, 2, 3, 4 and 5 minutes (the highest heart rate and the lowest saturation recorded). The PIPP scores were calculated from the video and the recordings detailed above [17,18]. The primary outcome measure was the difference in PIPP score between the groups. The secondary outcomes evaluated include duration of cry, maximum heart rate and lowest SpO_2 in the intervention and placebo groups. A secondary analysis was also performed to compare the effect of the interventions in term and preterm infants.

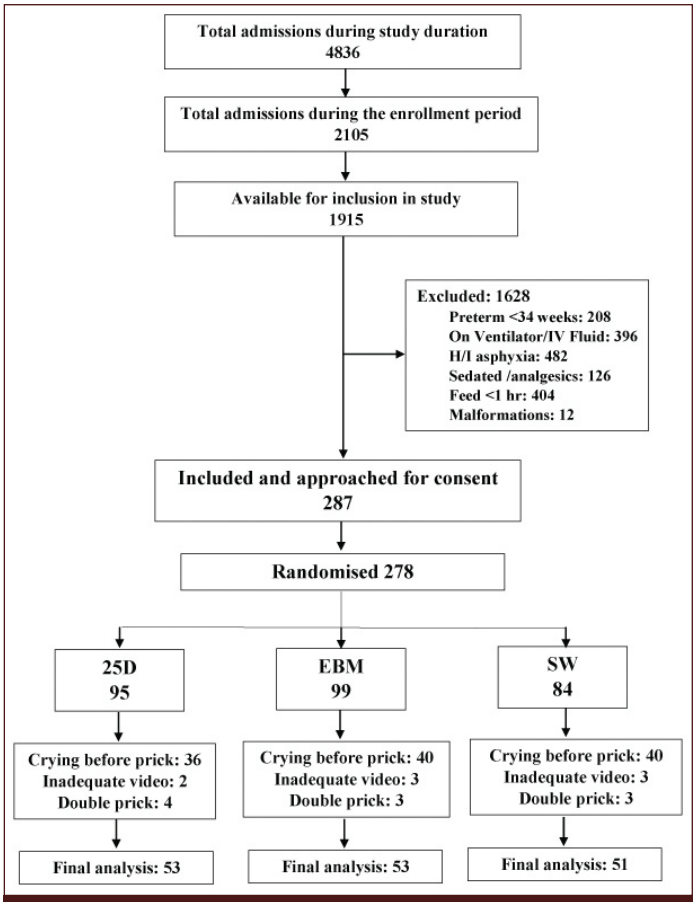
STATISTICAL ANALYSIS

Statistical testing was conducted with the Statistical Package for the Social Science (SPSS) system version 20.0. (Armonk, NY: IBM Corp.). Continuous variables were presented as mean±SD or median. Categorical variables were expressed as frequencies and percentages. The comparison of normally distributed continuous variables between the groups was performed using ANOVA. Nominal categorical data between the term and preterm were compared using Chi-squared test. Non normally distributed continuous variables were compared using Kruskal Wallis test. A p-value less than 0.05 was as significant.

RESULTS

A total of 278 babies were randomly allocated to the study groups. Although the initial plan was to include 165 neonates, after the study began, a lot of dropouts were encountered, esp. due to babies crying before the actual prick. Thus enrolment was continued, to reach as close to the target of 165 as possible. Finally, 157 neonates were included in the final analysis [Table/Fig-1]. Baseline parameters including age, sex, birth weight, heart rate and SpO_2 were normally distributed [Table/Fig-2].

There was a significant difference in the PIPP scores between the groups, with 25D being significantly better than EBM and EBM significantly better than SW [Table/Fig-3]. Similarly, 25D was superior to both EBM and SW, while EBM was significantly superior to SW (p-value<0.001) with respect to cry times. Thus, 25D was more effective in decreasing the pain perception than EBM and similarly, EBM was superior to SW in controlling pain after venipuncture.



[Table/Fig-1]: Overview of study.

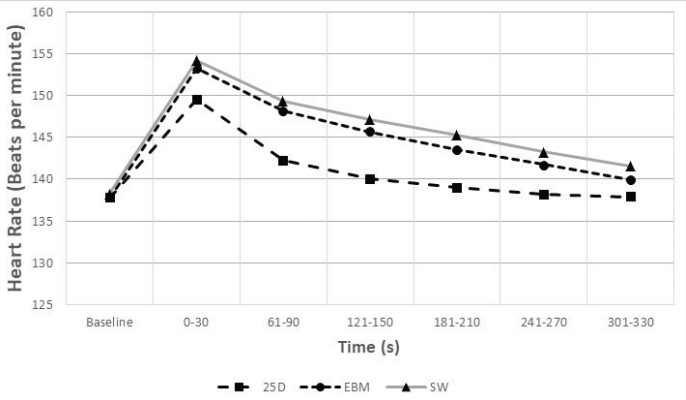
Variables	Total (n=157)	25D (n=53)	EBM (n=53)	SW (n=51)	p-value
Gestational age (weeks)	37.90± 1.47	37.97± 1.53	38.1± 1.49	37.65± 1.36	0.27
Term: preterm	132:25	45:8	45:8	42:9	0.92
Sex (M:F)	81:76	28:25	29:24	24:27	0.72
Mean age (days)	3.20± 1.20	3.42± 1.34	3.02± 1.38	3.17± 1.16	0.28
Birth weight (kg)	2.82± 0.33	2.84± 0.32	2.83± 0.36	2.80± 0.38	0.83
Baseline HR (bpm)	137.95± 6.79	137.75± 7.13	137.75± 6.21	138.27± 6.32	0.89
Baseline SO_2 (%)	97.29± 1.03	97.22± 0.94	97.22± 1.04	97.42± 1.04	0.50

[Table/Fig-2]: Baseline characteristics of the neonates.
Where, 25D: 25% Dextrose; EBM: Expressed breast milk; SW: Sterile water; Values represent Mean±SD; A p-value less than 0.05 was as significant

Outcome analysis	25D	EBM	SW	p-value
PIPP Score	2.94±1.41	7.42±1.69	10.56±1.69	<0.001
Cry times (s)	6.47±5.75	38.58±15.21	91.67±38.99	<0.001
Post-hoc analysis	**25D vs EBM**	**EBM vs SW**	**25D vs SW**	
PIPP Score	<0.001	<0.001	<0.001	
Cry times (s)	<0.001	<0.001	<0.001	

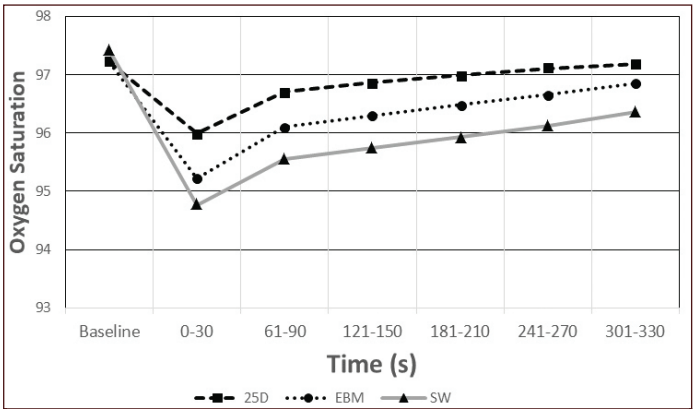
[Table/Fig-3]: Comparison of PIPP scores and cry times.
Where, 25D: 25% Dextrose; EBM: Expressed breast milk: SW: Sterile water; Values represent Mean±SD; A p-value less than 0.05 was as significant and all values are p-values

Maximal HR showed a statistically significant difference between groups throughout the observation period. Post-hoc analysis showed that 25D performed better than SW throughout but performed better than EBM only in the first 4 minutes. EBM was not superior to SW in control of MHR [Table/Fig-4]. Similarly, for SpO_2, difference between the 25D group and the SW group were maintained throughout the observation time. The difference between the 25D and the EBM groups were significant in the first 2.5 minutes only. Although the initial dip in SpO_2 was similar in the EBM and SW groups, the recovery of SpO_2 was significantly faster in the EBM group [Table/Fig-5].



	Baseline	0-30s	61-90s	121-150s	181-210s	241-270s	301-330s
25D vs EBM	0.718	0.010	<0.001	<0.001	0.001	0.007	0.085
25D vs SW	0.299	0.005	<0.001	<0.001	<0.001	0.001	0.010
EBM vs. SW	0.752	0.571	0.552	0.329	0.244	0.270	0.232

[Table/Fig-4]: Comparison of inter group Maximal Heart Rate (MHR). A p-value less than 0.05 was as significant; all values are p-values mentioned at different time intervals



	Baseline	0-30s	61-90s	121-150s	181-210s	241-270s	301-330s
25D vs EBM	1.00	0.002	0.013	0.025	0.050	0.083	0.258
25D vs SW	0.624	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
EBM vs. SW	0.630	0.136	0.027	0.024	0.029	0.042	0.064

[Table/Fig-5]: Comparison of inter group Minimal Oxygen Saturation (SpO_2). All values given in table are p-value A p-value less than 0.05 was as significant

Comparison of PIPP scores and cry times between term and preterm infants showed no significant differences between the study groups [Table/Fig-6]. Maximal HR, minimum SpO_2, for preterm and term neonates also failed to show any significant differences between the intervention groups and the control group [Table/Fig-7]. No adverse effects were observed during the study.

	Group	Term	n	Preterm	n	p-value
PIPP score	25D	2.78±1.22	45	3.88±2.03	8	0.130
	EBM	7.40±1.78	45	7.50±1.19	8	0.801
	SW	10.55±2.03	42	10.78±1.39	9	0.616
Cry time	25D	6.93±5.74	45	3.88±3.79	8	0.139
	EBM	37.38±14.58	45	45.38±17.87	8	0.263
	SW	91.12±40.96	42	94.22±29.96	9	0.263

[Table/Fig-6]: Comparison of PIPP Score and cry times between term and preterm infants.
Where, 25D: 25% Dextrose; EBM: Expressed breast milk; SW: Sterile water; Values represent Mean±SD; *p-values represent comparison of PIPP scores and cry times between term and preterm neonates in each intervention group; A p-value less than 0.05 was as significant

25D		Term	Preterm	p-value
Maximum Heart Rates (beats per min)	0-30s	149.56±8.01	149.50±7.95	0.893
	61-90s	142.67±7.95	140.25±5.70	0.533
	121-150s	140.40±7.82	138.00±5.53	0.550
	181-210s	139.27±7.53	137.63±5.31	0.687
	241-270s	138.60±7.46	136.25±5.73	0.486
	301-330s	138.24±7.52	135.88±5.44	0.441
Minimal Oxygen saturation (%)	0-30s	95.88±1.02	96.72±0.93	0.053
	61-90s	96.61±0.93	97.25±0.98	0.128
	121-150s	96.76±0.93	97.40±1.00	0.142
	181-210s	96.89±0.95	97.53±1.00	0.149
	241-270s	97.02±0.93	97.63±1.01	0.560
	301-330s	97.10±0.93	97.98±1.00	0.176
EBM		**Term**	**Preterm**	**p-value**
Maximum Heart Rates (beats per min)	0-30s	153.20±6.90	153.75±7.61	0.596
	61-90s	148.22±6.71	148.25±7.40	0.487
	121-150s	145.62±6.18	145.87±6.81	0.570
	181-210s	143.47±6.37	143.75±6.20	0.372
	241-270s	141.69±6.14	142.13±6.17	0.433
	301-330s	139.84±6.10	140.36±5.92	0.404
Minimal Oxygen saturation (%)	0-30s	95.21±1.20	95.28±1.24	0.439
	61-90s	96.10±1.14	96.16±1.14	0.383
	121-150s	96.29±1.15	96.35±1.14	0.357
	181-210s	96.98±1.13	96.54±1.16	0.352
	241-270s	96.64±1.14	96.73±1.09	0.383
	301-330s	96.84±1.15	96.88±1.07	0.286
SW		**Term**	**Preterm**	**p-value**
Maximum Heart Rates (beats per min)	0-30s	154.31±8.90	154.44±6.21	0.439
	61-90s	149.40±8.30	149.40±8.30	0.451
	121-150s	147.17±7.98	147.33±5.70	0.433
	181-210s	145.38±7.58	145.22±5.97	0.377
	241-270s	143.45±7.63	143.22±7.33	0.336
	301-330s	141.76±7.33	141.33±5.68	0.336
Minimal Oxygen saturation (%)	0-30s	94.77±1.20	94.80±1.00	0.574
	61-90s	95.56±1.13	95.53±1.03	0.440
	121-150s	95.75±1.12	95.73±1.06	0.393
	181-210s	95.94±1.11	95.96±1.03	0.410
	241-270s	96.14±1.10	96.16±1.01	0.374
	301-330s	96.37±1.10	96.37±0.97	0.296

[Table/Fig-7]: Comparison of outcome variables based on gestational groups.
Where, 25D: 25% Dextrose; EBM: Expressed breast milk; SW: sterile water; Term: neonates ≥37weeks gestation; Preterm: neonates <37 weeks gestation; Values represent Mean±SD; A p-value less than 0.05 was as significant

DISCUSSION

In the current study, both EBM and 25D were found to decrease neonatal pain scores during venipuncture. The efficacy of 25D was significantly more than EBM. A larger dose of EBM was inferior to 25D in relieving pain, decreasing cry times and the controlling physiological response to pain in both term and preterm neonates.

Painful or stressful procedures are very common in neonatal intensive care units. One large study reported that neonates underwent a median of 113 painful procedures during their NICU stay. Preterm and sick neonates may need even more procedures [19,20]. It is thus rather worrisome that only 13-20% of such procedures are done under analgesic coverage [5,19]. On the other hand, early life exposure to both opioid and non steroidal antiinflammatory drugs is associated with a myriad of neurodevelopmental disorders [21].

The efficacy of glucose as an analgesic was studied and it was confirmed to be a helpful agent to decrease pain during venipuncture. Stronger dextrose solutions are known to be better than lower concentrations for analgesia in neonates [22]. EBM on the other hand has been reported to be as effective as lower (10%) strengths of glucose solution while stronger glucose solutions (25% or 50%) provide better analgesia [23]. The mechanism of analgesia in oral agents like 25D and EBM are related to the sweetness of the solutions or due to naturally occurring endorphins in EBM [24,25].

The choice of non pharmacologic agents in our study was dictated by the easy availability and inexpensive nature of both agents. There is some evidence to suggest that larger volumes (5 mL) of EBM may be more effective than a 2 mL dose [16].

Both 25D and EBM significantly reduced pain after venipuncture. Similar results have been reported by Bueno M et al., who compared EBM and 25% glucose for pain relief in infants, finding 25% glucose superior [26]. Skogsdal Y et al., also found similar results [14]. Haouari N et al., on the other, hand had found no significant differences between changes in heart rate for infants given sucrose (dose range 0.5g to 0.6g), which has properties similar to dextrose, compared to placebo [26]. Lower concentration of sucrose used as the study agent may explain this lack of analgesic effect.

Two previous papers using protocols very similar to the current study, compared the effect of 2 mL each of 25D and EBM in providing analgesia during venipuncture or heel lancing in neonates [29,30]. Cry times and PIPP scores were least with 25D, higher with EBM and highest with placebo in both these studies. Numerically, the PIPP scores were substantially lower in the present study suggesting a more robust analgesic effect of 25D in this report.

With a painful exposure, the initial response is a rise in the HR and a fall in SpO_2. The initial changes were significantly controlled only by 25D in both studies as well as in our study. Even with the use of 5 mL EBM, EBM didn't perform better than placebo.

The recovery of MHR was fastest in the 25D group. Significant difference persisted until 5 minutes between 25D and EBM. Complete recovery was seen in both these intervention groups. Similarly, SpO_2 recovered rapidly in 25D group. Interestingly, EBM performed significantly better than placebo after the initial one minute. Although a formal comparison was not presented by previous authors, the heart rate and SpO_2 didn't return to baseline in any of the intervention groups in the study by Sahoo JP et al., [27]. Thus, 5 mL EBM performed better than 2 mL EBM with regard to the recovery of SpO_2.

There were no significant differences in PIPP score, change in heart rate, SpO_2, and cry time between term and preterm infants between the intervention groups. Previous studies have reported episodes of vomiting, transient bradycardia with 25D [27,28]. No adverse events were noticed in the preterm babies in the present study, while Wills DM et al., found increased frequency of necrotising enterocolitis in preterm when administered glucose as the pain-relieving intervention [29]. No episode of hyperglycaemia was recorded in the present study.

The strength of the study was use of PIPP score which is an objective and validated tool as well as use of 25D and EBM which are easily available in NICU.

The study design is the main strength of this current paper. Very limited literature exists on the use of larger than 2 mL dose of EBM for procedural pain relief.

Limitation(s)

The limitation of study includes the cross-sectional design (cross over design may have been more suitable) and that the issue of long-term effect of these interventions was not addressed. Further studies are required to establish the effectiveness, side-effects and long-term outcomes.

CONCLUSION(S)

Neonatal pain, once a neglected issue, has been gaining importance in view of its impact on long-term neurodevelopmental outcome of a newborn. In reducing pain, 25D was found to be significantly effective as assessed by PIPP scores, changes in heart rate and SpO_2. EBM also reduced the pain scores but it was less effective on various counts as compared to 25D. Even with use of 5 mL EBM, analgesic effect was inferior. It is also worth mentioning that breastfeeding is known to have a definite calming effect and contributes to pain relief above and beyond breast milk alone. Further studies should evaluate the effect of breast milk in the context of breastfeeding in the relief of similar procedural pain.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Jul 26, 2022
- Manual Googling: Oct 31, 2022
- iThenticate Software: Nov 02, 2022 (8%)

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 26, 2022**
Date of Peer Review: **Sep 10, 2022**
Date of Acceptance: **Nov 15, 2022**
Date of Publishing: **Jun 30, 2023**