Original Article

Effect of Expressed Breast Milk versus Swaddling versus Oral Sucrose Administration on Pain Associated with Suctioning in Preterm Neonates on Assisted Ventilation: A Randomized Controlled Trial

Saumil Desai, Ruchi Nimish Nanavati, Rohit Nathani, Nandkishor Kabra

Department of Neonatology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India

Abstract

Objective: The objective of our study was to assess the pain associated with suctioning in preterm neonates on assisted ventilation and comparing the use of expressed breast milk (EBM), sucrose, and swaddling to alleviate pain. **Methods:** Study design: A randomized controlled clinical trial. **Inclusion Criteria:** Preterm neonates on assisted ventilation. **Exclusion Criteria:** Major congenital anomalies and severe encephalopathy. **Study Duration and Site:** 6 months in level III neonatal Intensive Care Unit. In the first phase, we used premature infant pain profile (PIPP) score to assess pain associated with suctioning in preterm neonates on assisted ventilation. In the second phase, the effect of EBM, swaddling, and sucrose on pain relief during suctioning in neonates on assisted ventilation was assessed. **Results:** There was a significant increase in pain associated with suctioning in preterm neonates on assisted ventilation (preprocedure PIPP score 7.90 ± 2.50; procedural PIPP score 13.63 ± 2.57; $P < 0.05$). The postintervention mean procedural PIPP score was not significantly different between the EBM, swaddling, and sucrose groups ($P = 0.24$). **Conclusions:** Suctioning is painful for preterm neonates on assisted ventilation. There was no difference between EBM, swaddling, and sucrose in relieving pain associated with suctioning.

Keywords: Expressed breast milk, neonates, pain, sucrose, suctioning, swaddling

Introduction

Pain is an unpleasant sensation experienced by neonates during routine procedures carried out in the neonatal Intensive Care Unit (NICU). Hospitalized neonates experience on an average of 14 painful procedures during the first 2 weeks of life.[1] It is known that respiratory support and related procedures, such as endotracheal suctioning in neonates, provoke pain. Research has shown that preterm neonates respond intensively to pain as compared with term neonates.[1] Procedural pain in neonates can be controlled by nonpharmacological and pharmacological methods. Nonpharmacological methods used to relieve procedural pain have short-term impact and are easily tolerated.[1] Although nonpharmacologic interventions have given promising results in various routine procedures, their role in relieving the pain associated with suctioning in ventilated preterm neonates is still under scrutiny. To control procedural pain, medications such as fentanyl and morphine are being used; however, the use of drugs is not without risk and may cause symptoms such as respiratory depression, nausea, seizures, and physiological dependence.[2] These side effects may deter the clinician from using them routinely for procedural pain relief.[3] Hence, this study was conducted to compare the efficacy of various nonpharmacologic (Expressed breast milk [EBM], swaddling, and sucrose) means to relieve the procedural pain associated with suctioning in preterm neonates on assisted ventilation.

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Address for correspondence: Dr. Saumil Desai, Department of Neonatology, 10th Floor, Multi Storey Building, KEM Hospital, Parel, Mumbai - 400 012, Maharashtra, India.
E-mail: drsaumildesai@gmail.com

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Methods

Ethics

This study was carried out from March to August 2016 after obtaining approval from the Institutional Ethics Committee. Informed consent from parents before enrollment was procured.

Study design

This study was a randomized controlled trial.

Study subjects

- Inclusion criteria: Preterm neonates on assisted ventilation requiring suctioning
- Exclusion criteria: Neonates with major congenital anomalies and severe encephalopathy
- Study duration: 6 months
- Study site: Level III NICU in a public hospital
- Primary outcome: To compare the efficacy of EBM versus swaddling versus oral sucrose administration on alleviating the pain associated with suctioning in preterm neonates on assisted ventilation
- Secondary outcome: To compare the efficacy of EBM versus swaddling versus oral sucrose administration on alleviating the pain associated with suctioning in preterm neonates on invasive and noninvasive ventilation.

Methodology

We conducted the study in two phases. In the first phase of the study, we assessed whether suctioning in preterm neonates on assisted ventilation was a painful procedure. After demonstrating that suctioning was associated with pain, in the second phase of the study, we evaluated the comparative efficacy of EBM, swaddling, and sucrose in alleviating pain during suctioning in preterm neonates on assisted ventilation.

Preterm neonates on assisted ventilation requiring suctioning were enrolled for the study. Pain assessment was performed using the premature infant pain profile (PIPP) score.[4,5] Before commencement of phase 1 of the study, all senior residents were trained to assess need for suctioning and pain evaluation using the PIPP score, in preterm neonates on assisted ventilation. All senior residents were certified for competency in the above by the senior faculty.

The components of PIPP score include gestational age, behavioral state, vital parameters (heart rate, oxygen saturation), and facial characteristics as described in Annexure 1. The weight was recorded on an electronic infant weighing scale with an accuracy of ±1 g. Gestational age was calculated using the date of last menstrual period and first trimester ultrasonography. In case of discrepancy, New Ballard Score was considered definitive for gestational age assessment. The behavioral state of the neonate was assessed by observing the neonate's activity, status of eyes (open or closed), and facial movements. The heart rate and oxygen saturation were recorded using the Masimo pulse oximeter (model radical 7) with signal extraction technology. Facial characteristics were assessed using video recording (Panasonic high-definition camcorder, model HDC-HS9, Osaka, Japan) done during the procedure of suctioning. For all age groups, a total score <6 indicates minimal/no pain while a score ≥12 indicates moderate to severe pain. The suctioning was performed by two senior residents and simultaneous video recording was done by the investigator.

In the second phase of the study, the effect of EBM, swaddling, and sucrose on pain relief during suctioning in preterm neonates on assisted ventilation was assessed. A trained senior resident assessed the need to do suctioning in preterm neonates on assisted ventilation as per unit protocol. The procedure of suctioning was carried out only when needed by the neonate and no procedure was done only for the purpose of the study.

The suctioning episodes in neonates on assisted ventilation were randomized to receive either EBM (Group 1) or swaddling (Group 2) or sucrose (Group 3) by a computer-generated randomization sequence. Randomization was done in variable random blocks of three or six. Treatment allocations were inserted in sequentially numbered opaque envelopes and were sealed. Just before suctioning, a senior resident opened the sequentially numbered envelope and allocated the group. An eligible neonate requiring suctioning could be enrolled more than once and each individual suctioning episode was randomized. In Group 1, 2cc EBM was administered to the neonate 2 min before suctioning. In Group 2, the neonate was swaddled for 10–15 min before suctioning while in Group 3, 2cc sucrose was administered to the neonate for 2 min before suctioning. After demonstrating that suctioning is indeed a very painful procedure in phase 1 of the study, it was deemed ethically unacceptable to include a no-intervention control group based on the evidence that exposure of preterm infants to pain procedures without treatment is harmful. The suctioning was performed by two senior residents and simultaneous video recording using Panasonic high-definition camcorder (model HDC-HS9, Osaka, Japan) was done by the investigator.

Sample size calculations

Sample size for the first phase of the study was calculated using formula for hypothesis of one sample mean. Hypothesizing a preprocedure score of 5 and postprocedure pain score of 7 with allowable difference of 0.1 and expected variance of 0.01 (α error of 0.05 and β error of 0.10 and power of 90%), the estimated sample size was 11 episodes of suctioning.

Sample size for the second phase of the study was calculated using the simplified formula for hypothesis of three parallel sample means. The formula is $22\ s^2/d^2 + 1$. Allowable difference of 0.08 (8%) and expected variance of 0.01 (α error of 0.05 and β error of 0.20 and power of 80%), the estimated sample size is 36 episodes of suctioning in each group.

Statistical analysis

The mean and standard deviation (SD) of the total pain score as well as that of each of the indicator of the PIPP score were calculated. In the first phase of the study, PIPP score results were analyzed using two-tailed paired *t*-test. In the

second phase of the study, baseline characteristics of enrolled neonates were compared by Chi-square test for categorical variables and unpaired *t*-test or Mann–Whitney U-test for continuous variables as appropriate. In the second phase of the study, procedural PIPP score and its components were compared by two-tailed unpaired *t*-test or Mann–Whitney U-test as appropriate. Statistical significance was accepted for values $P < 0.05$. All the statistical tests were performed using the Minitab (version 15, Minitab Inc, Pennsylvania State University) statistical software for Windows.

Results

In the first phase of the study, 11 episodes of suctioning done in preterm neonates on assisted ventilation were enrolled (birth weight in grams, mean ± SD, 1156.67 ± 130.43; gestational age in weeks, mean ± SD, 31.33 ± 1.28). As depicted in Table 1, there was a significant increase in PIPP score with suctioning in preterm neonates on assisted ventilation. Mean preprocedure PIPP score was 7.90 ± 2.50, and procedural mean PIPP score was 13.63 ± 2.57 ($P = 0.003$) as shown in Figure 1.

In the second phase of the study, 138 neonates were assessed for eligibility, of which twenty were excluded for various reasons as depicted in the flow diagram of the recruitment and randomization process [Figure 2]. A total of 118 eligible neonates with a total of 130 suctioning episodes were selected, with 12 neonates being enrolled for 2 suctioning episodes. Of the total 130 suctioning episodes, 108 suctioning episodes were randomized as depicted in Figure 2. A total of 36 episodes of suctioning were allocated to each group of EBM, swaddling, and sucrose. All the randomized suctioning episodes were analyzed without any loss to follow-up and none were excluded from the final analysis.

The baseline characteristics of neonates in three groups are shown in Table 2. As shown in Table 3, the postintervention mean procedural PIPP score for EBM (Group 1), swaddling (Group 2), and sucrose (Group 3) were 12.88 ± 3.59, 11.47 ± 3.23, and 12.11 ± 3.87, respectively. The box plot [Figure 3] shows that there was no statistically significant difference among three groups ($P = 0.24$). These mean PIPP score during suctioning in all the three groups during phase 2 were lower than those observed during the first phase of the study; however, there was no difference statistically. Table 4 depicts that these interventions were not effective for relieving pain during suctioning in mechanical ventilation with a $P = 0.44$, whereas they were effective for pain relief during suctioning in noninvasive ventilation ($P = 0.005$).

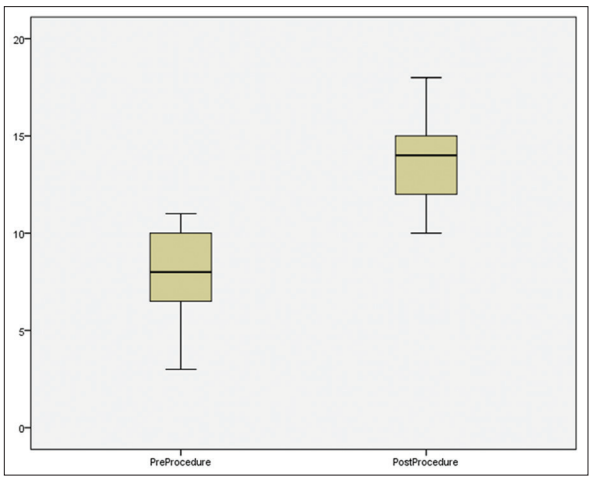

Figure 1: Comparison of premature infant pain profile score before and during the suctioning procedure (Phase 1)

Table 1: Change in various parameters during suctioning (*n*=11) (Phase 1)

Variable	Preprocedure score (*n*=11)	Procedural score (*n*=11)	Mean difference (95% CI), *P*
PIPP score	7.90±2.50	13.63±2.57	−5.72 (−7.14-−4.32), <0.001

PIPP: Premature infant pain profile, CI: Confidence interval

Table 2: Baseline characteristics of the neonates enrolled in the second phase of the study (Phase 2)

	Group 1 EBM (*n*=36)	Group 2 Swaddling (*n*=36)	Group 3 Sucrose (*n*=36)
Weight in grams (mean±SD)	1358.52±573.93	1516.75±750.17	1430.50±648.89
Gestational age in weeks (mean±SD)	32.76±3.96	33.17±4.86	32.91±3.45
Endotracheal suctioning episodes	21	19	25
Oronasal suctioning episodes	15	17	11

EBM: Expressed breast milk, SD: Standard deviation

Table 3: Preprocedural and procedural premature infant pain profile score in expressed breast milk, swaddling, and sucrose group (Phase 2)

PIPP score	Group 1 (EBM)	Group 2 (swaddling)	Group 3 (sucrose)	*P*
Preprocedure	7.75±3.45	6.27±2.68	7.88±2.98	0.051
Procedural	12.88±3.59	11.47±3.23	12.11±3.87	0.247
Difference	5.13±2.78	5.19±2.61	4.22±3.05	0.265

PIPP: Premature infant pain profile, EBM: Expressed breast milk

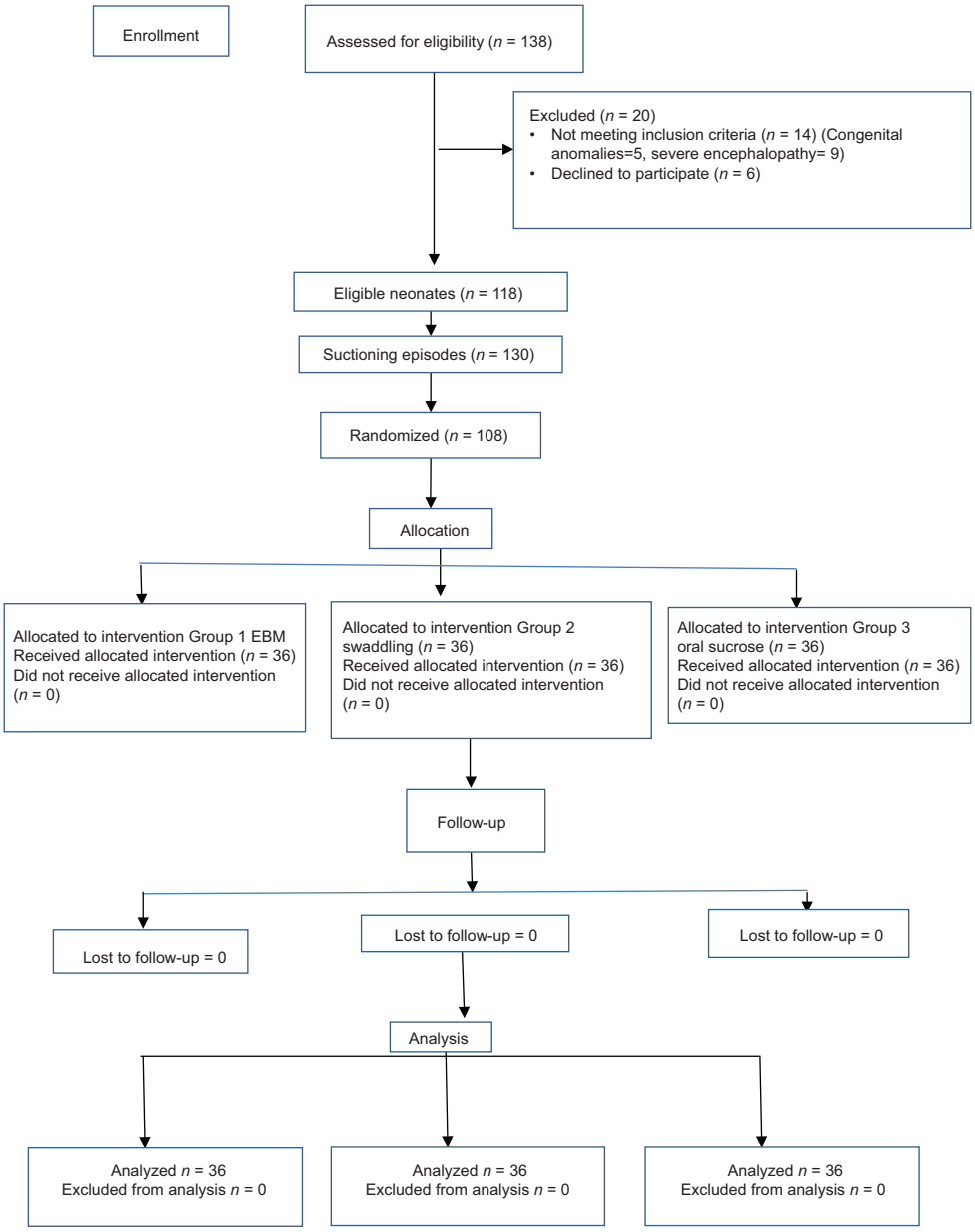

Figure 2: Flow diagram of the recruitment and randomization process

Table 4: Subgroup analysis: Comparative efficacy of expressed breast milk, swaddling, and sucrose for pain relief during suctioning according to the mode of ventilation

Mode of ventilation	Mechanical	Noninvasive
P	0.44	0.005

Discussion

Our study highlights the fact that the preterm neonates on assisted ventilation experience pain even without any procedure being performed as suggested by preprocedural PIPP score of 7.90 also demonstrated by Hummel *et al*.[7] There was statistically significant increase in PIPP score during the suctioning procedure (13.63; $P < 0.001$). The PIPP scores during suctioning were suggestive of severe pain. However, the pain associated with suctioning in preterm neonates on assisted ventilation is underestimated and neglected.[6] There is a paucity of data in literature assessing the pain during suctioning in preterm neonates on assisted ventilation.

The present study assessed the efficacy of EBM, swaddling, and sucrose on pain relief during suctioning in preterm neonates on assisted ventilation. None of these interventions were effective in relieving the pain associated with suctioning. The subgroup analysis showed efficacy of these interventions to relieve pain in neonates on noninvasive ventilation ($P = -0.005$); however, the same was not true for mechanical ventilation ($P = -0.44$). These findings should be interpreted with caution as the sample size for subgroup analysis was inadequate and the study was not powered to conclude the efficacy in subgroups.

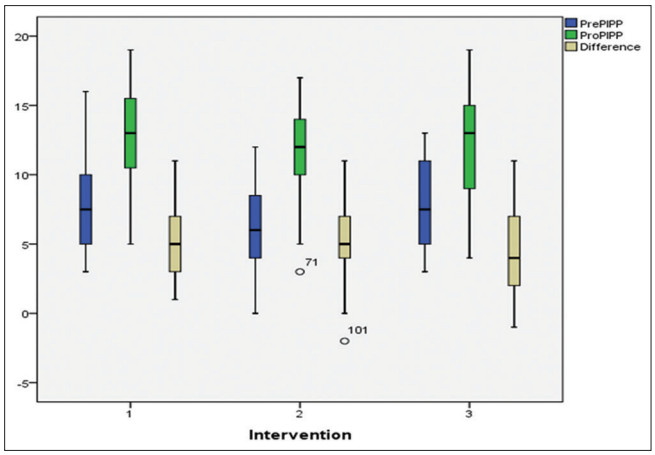

Figure 3: Premature infant pain profile score comparison of expressed breast milk (Group 1) versus swaddling (Group 2) versus sucrose (Group 3) preprocedure, procedural, and difference (Phase 2)

There is enough literature to describe the efficacy of nonpharmacological means such as breastfeeding, administration of EBM, swaddling, Kangaroo Mother Care, facilitated tucking as well as pharmacological interventions such as administration of fentanyl and morphine during various procedures performed in NICU such as heel prick, intravenous cannulation, and removal of adhesives.[8,9] Recently published studies demonstrated the effectiveness of EBM in providing pain relief during heel lancing and venipuncture.[10,11] In a Cochrane review that assessed the impact of breastfeeding or breast milk for procedural pain, it was noted that neonates in the breastfeeding group had statistically significant less increase in the heart rate, reduced duration of crying during procedure compared to swaddled group, or pacifier group.[12] Swaddling as an effective nonpharmacological measure to alleviate pain during heel lancing is also well studied; however, evidence for its effectiveness as a pain-relieving measure during suctioning is lacking.[13,14] Simonse *et al*. demonstrated that the efficacy of sucrose in reducing pain in neonates associated with heel lancing.[15] However, there is scarcity of data for interventions to relieve the pain associated with suctioning.[16-18] A recent study evaluated the effect of facilitated tucking on pain relief during endotracheal suctioning in preterm neonates using the PIPP score. They found that around 38% of neonates experienced pain during suctioning without the intervention while the same reduced to 8.8% with intervention.[17] The present study depicted that reduction in pain was significant in noninvasive ventilation group as compared to those on invasive ventilation.

Strengths of our study were robust randomized controlled trial design, sufficient sample size with adequate power to detect a difference if there was one, and use of PIPP score for assessment of pain.

Limitations of our study are lack of blinding of outcome measures. Additional limitations of our study were that we have only assessed short-term outcomes and the inability to blind the interventions. The lack of subgroup analysis (invasive and noninvasive) during phase 1 of the study was also a drawback.

Conclusions

This study shows that the preterm neonates on assisted ventilation experience pain even in the absence of additional interventions. This study also demonstrates that suctioning in these neonates causes moderate to severe pain. Findings from this study show that administration of EBM, sucrose, and swaddling is ineffective for pain management associated with suctioning in preterm neonates on assisted ventilation.

Future directions

The inability of pharmacologic means (e.g., morphine) and nonpharmacologic means (e.g., EBM, swaddling) to alleviate the pain associated with suctioning in ventilated preterm neonates warrants further research on the use of a combination of these means to alleviate the same.[16,17]

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Annexure

Overview: The premature infant pain profile is a behavioral measure of pain for premature infants. It was developed at the Universities of Toronto and McGill in Canada.

Indicators:

1. Gestational age
2. Behavioral state before painful stimulus
3. Change in heart rate during painful stimulus
4. Change in oxygen saturation during painful stimulus
5. Brow bulge during painful stimulus
6. Eye squeeze during painful stimulus
7. Nasolabial furrow during painful stimulus

Annexure 1: Premature infant pain profile

Indicator	Finding	Points
Gestational age	≥36 weeks	0
	32-35 weeks 6 days	1
	28-31 weeks 6 days	2
	<28 weeks	3
Behavioral state	Active/awake eyes open facial movements	0
	Quiet/awake eyes open no facial movements	1
	Active/sleep eyes closed facial movements	2
	Quiet/sleep eyes closed no facial movements	3
Heart rate change	0-4 beats/min increase	0
	5-14 beats/min increase	1
	15-24 beats/min increase	2
	≥25 beats/min increase	3
Oxygen saturation minimum	0%-2.4% decrease	0
	2.5%-4.9% decrease	1
	5.0%-7.4% decrease	2
	7.5% decrease or more	3
Brow bulge	<9% of time	0
	10%-39% of time	1
	40%-69% of time	2
	>70% of time	3
Eye squeeze	<9% of time	0
	10%-39% of time	1
	40%-69% of time	2
	>70% of time	3
Nasolabial furrow	<9% of time	0
	10%-39% of time	1
	40%-69% of time	2
	>70% of time	3

Interpretation: Minimum score: 0; Moderate pain: ≥6; Maximum score: 21