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ORIGINAL ARTICLE

Role of Sucrose in Reducing Painful Response to Orogastric Tube Insertion in Preterm Neonates

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Abstract
Objectives To study whether orogastric tube (OGT) insertion elicits a painful response in preterm neonates, and the role of oral sucrose in reducing this pain.
Methods This double blinded, randomized control trial was conducted in the neonatal intensive care units of Kalawati Saran Children's Hospital. Clinically stable preterms within the first 7 postnatal days, who had not received painful stimulus 30 min prior to intervention, and who required routine OGT insertion were included. Lingual 24 % sucrose or distilled water (1 ml) was administered 2 min before OGT insertion. The primary outcome was painful response assessed by Premature Infant Pain Profile scale (PIPP), while the secondary outcomes were heart rate and SpO_2 changes. The trial is registered with ClinicalTrials.gov (Registration number: NCT 00949104)
Results Sixty preterms were randomized in each group. Final analysis was carried out on 52 subjects in the placebo group and 53 in the sucrose group. The mean intra-procedure PIPP scores were significantly higher than the mean pre-procedure PIPP scores, in the gestational age groups of more than 34 wk, and 32 wk to 33 wk, 6 d, in both the placebo (7.25 *vs.* 3, and 8.14 *vs.* 3.14, respectively) and sucrose arm (8.06 *vs.* 3.21, and 7.18 *vs.* 4.18, respectively). The mean PIPP scores assessed at 30 s post procedure in the sucrose group were significantly lower than the placebo group (4.32 *vs.* 5.6, $p=0.014$). No significant adverse events were seen.
Conclusions OGT insertion causes pain in preterms and single dose lingual 24 % sucrose may alleviate this pain.

Keywords Orogastric tube · Premature Infant Pain Profile · Preterm neonates · Sucrose

Abbreviations

OGT	Orogastric Tube Insertion
PIPP	Premature Infant Pain Profile
Trial registration number	NCT 00949104

Introduction

Neonatal pain is a subject of intense interest. The analgesic effects of sucrose have been reported in term and pre-term newborn infants [1]. There is a gap in the existing knowledge regarding the pain associated with orogastric tube (OGT) insertion and whether oral sucrose can alleviate the pain associated with this procedure. The present study was therefore planned and conducted with a hypothesis that OGT insertion elicits a painful response in preterm neonates and orally administered sucrose given 2 min prior to the procedure of OGT insertion reduces the pain associated with the procedure.

Material and Methods

The study was conducted in the neonatal units of Kalawati Saran Children's Hospital, Lady Hardinge Medical College, New Delhi and Department of Pharmacology, Lady Hardinge Medical College, New Delhi, India. The study included pre-term neonates (<37 wk of gestational age) within the

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first 7 postnatal days (<168 h). They were clinically stable and had not received any painful stimulus at least 30 min prior to the intervention. Only the first attempt in putting OGT was evaluated. The neonates who required ventilator support or oxygen supplementation, had any facial congenital anomalies received opiates or were born to mothers receiving opiates, to whom muscle relaxants, sedatives or analgesics had been administered, with grade 3 or 4 intraventricular hemorrhage, with major congenital anomalies, with any history of birth trauma especially involving face or scalp (including cephalhematoma/ subgaleal bleed), with face presentation or those with 5 min Apgar score <7 were excluded from the study.

There were two groups in the study. The neonates were randomly assigned to each group. Block randomization using computer generated random sequences was used with a block size of four. Allocation concealment was done by the hospital pharmacy which packed 2 ml of the sucrose and the double distilled water (control/ placebo) into syringes and opaque sealed envelopes sequentially labelled according to randomization code available with the consultant of Department of Pharmacology, unrelated to the study. Randomization sequence was generated by a senior consultant in the Department of Pharmacology unrelated to the study. The investigator assessing the painful response was blinded to the group assignment. Randomization codes and allocation concealment codes were broken only after the statistical analysis was finished.

The patients were enrolled into the study only after an informed written consent had been obtained from either of the parent/ caregiver. The enrolled neonates were not given anything orally at least 30 min before the procedure and were administered either a sterile solution of 24 % sucrose or double distilled water orally depending on their randomization code. The sucrose solution was prepared by the hospital pharmacy which freshly prepared 24 % sucrose solution daily with all aseptic precautions by mixing 2.4 g of sucrose in 10 ml distilled water. Out of this prepared solution, 2 ml was packed in 2 ml sterile syringes. This was further covered with opaque sealed envelopes bearing serially numbered patient codes. The composition of these packets was decided by a senior consultant in the department of Pharmacology who had access to the randomization sequence allocation codes. Fresh solutions were prepared daily and unused solutions were discarded at the end of the day to be replaced with identically numbered solutions from the pharmacy the next time they were required. All study solutions were stored in the refrigerator at 2-8 °C and were brought to the room temperature before administration. Two min prior to the procedure, 1 ml of the solution marked with patient's serial number was administered orally to the patient by a health care provider (who was blinded to the contents of the solution). Two min after administering the solution, a 6 Fr. OGT was inserted in neonate by the same doctor in all the study subjects. The time taken in the OGT insertion was monitored using a stopwatch and the procedure was rated as easy, difficult or very difficult. The whole procedure (beginning 2 min before OGT insertion and continuing till 4 min after it was inserted) was video recorded on a fixed camera focussing on the face of the patient. A non- invasive vital sign monitor ['Recorders and Medicare systems- Phoebus P511'] recorded the continuous heart rate and SpO_2 changes during the intervention. The highest heart rate and lowest SpO_2 obtained during the procedure till 2 min post procedure was recorded.

The present study utilized the Premature Infant Pain Profile (PIPP) scale which has been specifically designed to assess acute pain in neonates [2, 3]. It is a 7-indicator composite measure that includes gestation age, behavior state, heart rate, oxygen saturation, brow bulge, eye squeeze and nasolabial furrow. Each indicator is rated on a 4 point scale for a possible score of 0–21 and has been validated in several studies to have good intra and inter-rater reliability [4].

A consultant of the unit, who was unrelated to the study and was blinded to the study methodology, evaluated the video- recordings and assigned the PIPP scores. The pain response to the procedure according to the PIPP scale was evaluated at pre-procedure, intra procedure, post 30 s, post 1 min and post 2 min.

The primary outcome measured was the painful response as assessed by the PIPP scale and the secondary outcome was the maximum heart rate and minimum oxygen saturation recorded during the procedure.

The population was analyzed in the following three gestational subgroups:

Subgroup 1: 34 wk to 36 wk and 6 d
Subgroup 2: 32 wk to 33 wk and 6 d
Subgroup 3: 28 wk to 31 wk and 6 d

As there was no previously published data on neonatal pain during OGT insertion, hence the range of PIPP responses was unknown. Therefore, a power calculation for the study could not be performed. A convenient sample of 60 in both the limbs, *i.e.*, a total of 120 neonates were enrolled.

All the results were analysed using a window SPSS software version 17. Descriptive statistics (mean and standard deviation) were calculated. For comparison of means between different groups and means of two sets of readings in the same group, unpaired and paired student's *t* test were used respectively. For comparisons of proportions, Chi square test was used. The study was approved by the Institutional Ethical Committee.

Results

A total of 186 preterm neonates (Fig. 1) were assessed for eligibility, out of which 66 were excluded. The final analysis was carried out on 52 subjects in the placebo group with 8 exclusions (in 3 subjects, the OGT was displaced before the 2 min post procedure PIPP scores could be assigned and the monitor malfunctioned in 5 subjects) and 53 subjects in the sucrose group with 7 exclusions (6 subjects were excluded as the monitor malfunctioned). One subject in the sucrose group went into sudden cardio respiratory arrest and had to be excluded. No neonate below 28 wk was enrolled as it could not meet the inclusion criteria.

There was no statistically significant difference in the baseline characteristics (Table 1) between the two study groups. The mean PIPP scores at 30 s post procedure were significantly lower in sucrose group as compared to the placebo group (Table 2).

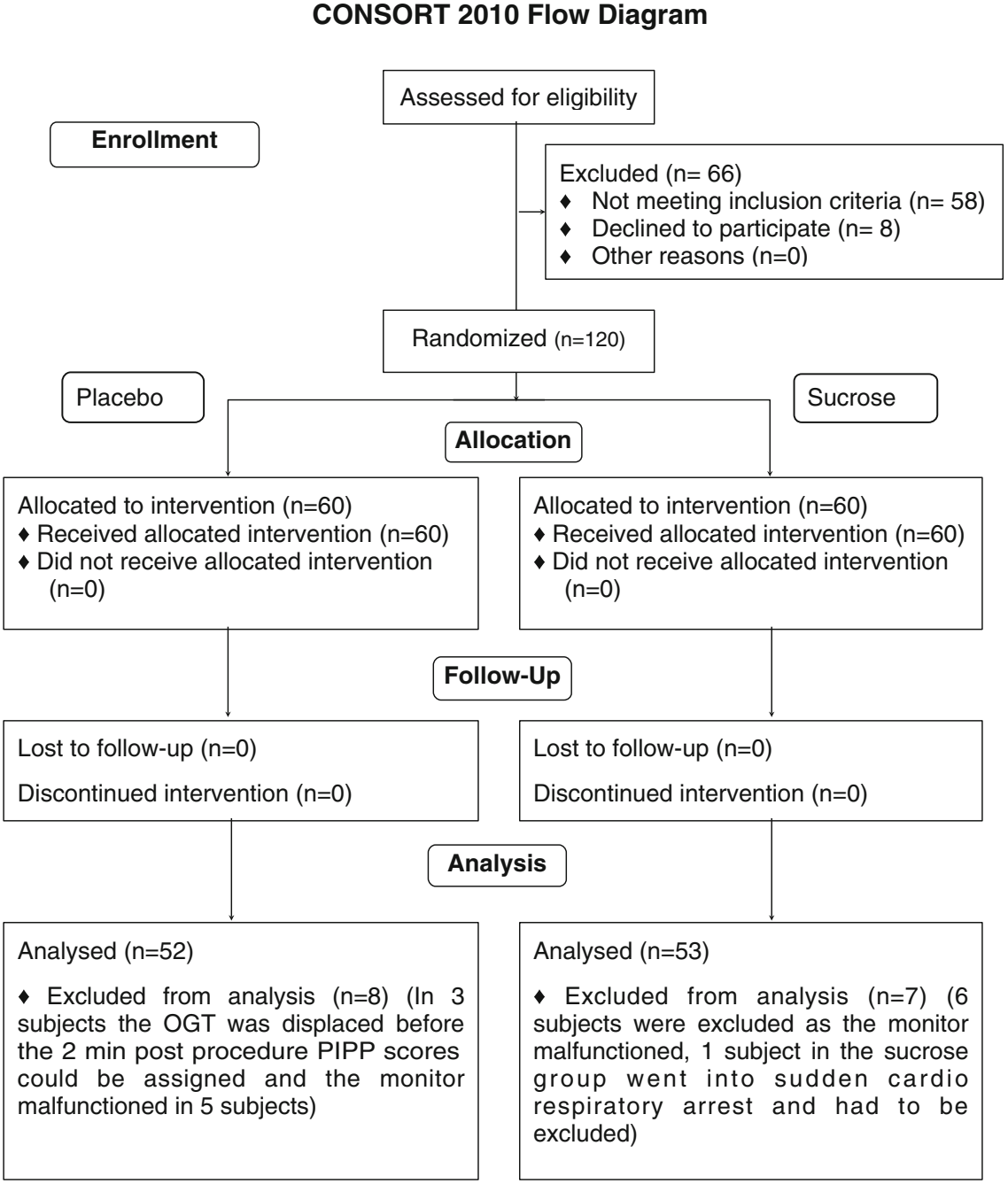

Fig. 1 CONSORT flow diagram

Table 1 Baseline characteristics of the subjects enrolled between the two study groups

	Placebo (n=52)	24 % Sucrose (n=53)	p value
Age (h), (mean, S.D.)	60.9 (42.0)	72.8 (45.3)	0.169
Duration of admission (h) at enrolment, (mean, S.D.)	59.1 (42.0)	67.4 (44.7)	0.332
Birth weight (g), (mean, S.D.)	1605.3 (339.6)	1643.8 (403.5)	0.598
Baseline heart rate (beats per min), (mean, S.D.)	134.6 (21.9)	131.1 (25.7)	0.459
Baseline SpO_2 (%), (mean, S.D.)	94.0 (3.8)	93.4 (6.8)	0.639
Baseline respiratory rate (per min), (mean, S.D.)	52.1 (7.6)	51.4 (3.9)	0.533
Baseline temperature (deg Celsius), (mean, S.D.)	37.3 (2.2)	36.8 (1.4)	0.171
Gestational age, (mean, S.D.)	33.3 (2.0)	33.7 (1.3)	0.091
The difficulty level of OGT insertion (n, %)			
Easy	36 (69.2 %)	38 (71.1 %)	0.846
Difficult	11 (21.2 %)	9 (17 %)	
Very difficult	5 (9.6 %)	6 (11.3 %)	
Number of painful procedures from birth till the time of enrolment (n, %)			
0	5 (9.6 %)	3 (5.7 %)	0.613
1–5	34 (65.4 %)	33 (62.3 %)	
6–10	8 (15.4 %)	13 (24.5 %)	
>10	5 (9.6 %)	4 (7.5 %)	

In the subgroup analysis, in subgroup one (late preterms) which comprised of neonates between 34 wk to 36 wk and 6 d, it was observed that insertion of OGT elicits a significant painful response in both the placebo and the sucrose group [placebo group: pre-procedure PIPP (mean±SD) as 3±1.39 *vs.* intra-procedure PIPP as 7.25±3.01 (p=0.00); sucrose group: pre-procedure PIPP as 3.21±1.76 *vs.* intra-procedure PIPP as 8.06±2.44 (p=0.00)]. The painful response could be demonstrated till one min post procedure in the placebo group where the PIPP scores were found to be significantly higher at 30-s and one min post procedure in comparison to the pre-procedural scores. The PIPP scores in the sucrose group in contrast were not significantly elevated at 30 s and one min post procedure (Fig. 2). The composite PIPP scores, when analysed, comparing the two study arms in subgroup1, did not reveal any significant difference in PIPP scores across the two study limbs.

Table 2 Composite PIPP scores across the gestation subgroups: Mean (S.D.)

	Placebo (n=52)	24 % Sucrose (n=53)	p value
Pre-procedure PIPP	3.7 (2.4)	3.4 (1.7)	0.582
Intra-procedure PIPP	7.9 (2.8)	7.6 (2.6)	0.646
Post 30 s PIPP	5.6 (3.0)	4.3 (2.2)	0.014*
Post 1 min PIPP	4.6 (2.8)	4.1 (1.8)	0.286
Post 2 min PIPP	3.9 (2.8)	3.9 (1.9)	0.965

*Statistically significant p<0.05

In subgroup 2 which comprised of neonates between 32 wk to 33 wk and 6 d, it was seen that insertion of OGT elicitates a painful response in both the placebo and the sucrose group [placebo group: pre-procedure PIPP (mean±SD) as 3.14±1.70 *vs.* intra-procedure PIPP as 8.14±2.98 (p=0.00); sucrose group: pre-procedure PIPP as 4.18±1.33 *vs.* intra-procedure PIPP as 7.18±2.85 (p=0.00)]. The painful response could be demonstrated till 30 s post procedure in the placebo group where the PIPP scores were found to be significantly higher in comparison to the pre-procedural scores. The PIPP scores in the sucrose group in contrast were not significantly elevated at 30 s post procedure (Fig. 2). The composite PIPP scores, when analysed, comparing the two study arms in subgroup 2, again did not reveal any significant difference in PIPP scores across the two study limbs.

The mean PIPP scores in the third subgroup did not reveal any significant difference across the study arms when compared with the pre-procedural PIPP scores.

No significant difference was observed between the baseline and maximum heart rate, and between baseline and lowest SpO_2, across the two study groups. However, there was a significant increase in mean heart rate from baseline in both the study groups during the procedure to 2 min post procedure (19.44 beats per minutes in placebo group *vs.* 22.5 beats per min in sucrose group).

Discussion

The present study evaluated pain response to OGT insertion in preterm neonates and whether oral sucrose alleviated this pain.

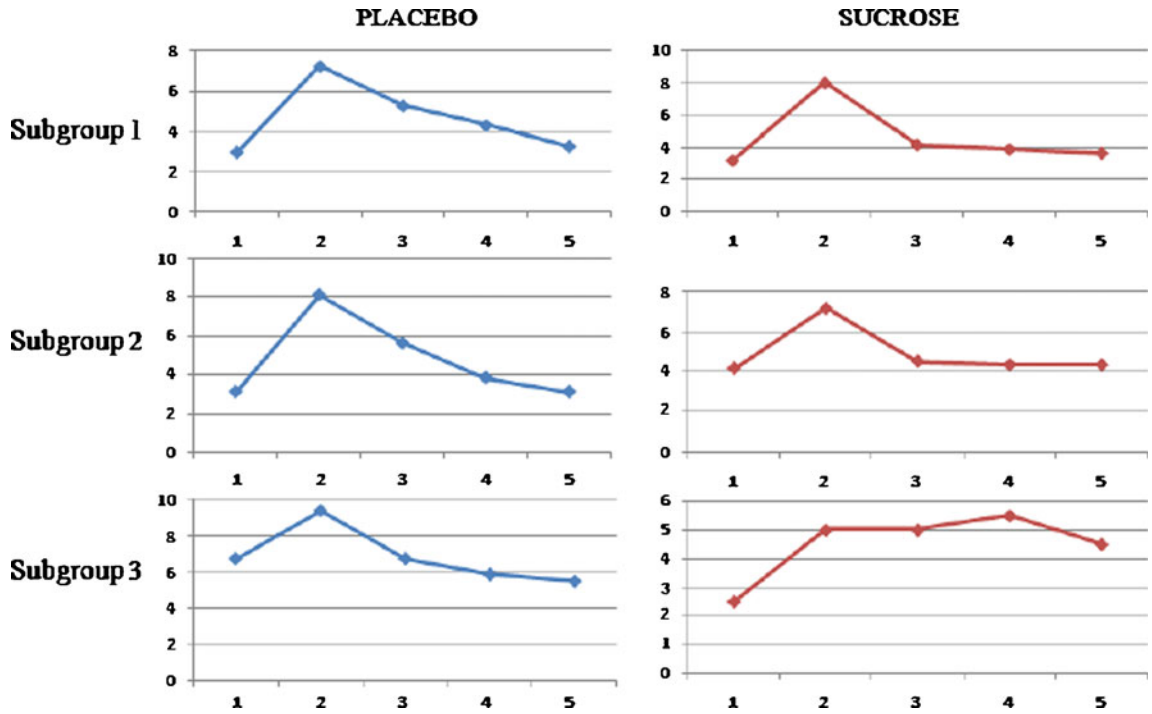

Fig. 2 Mean PIPP scores in subgroups of study across the two study arms. The X-axis shows study time-frames (1: pre-procedure; 2: intra-procedure; 3: post-30 s; 4: post 1-min; 5: post 2-min) and the Y-axis represents the mean PIPP scores

It has been seen that preterm neonates across gestational age subgroups have different pain responses with smallest showing least response [5–7]. With these facts in mind, a gestational age specific analysis of the study population was carried out (Fig. 2). The present study has demonstrated that is near term neonates who can mount a significant response to procedural pain, OGT insertion is a significantaly painful procedure. The criteria used to define pain has been previously validated in a study conducted by Peter Gal et al., where pain has been defined as an increase in PIPP score≥4 points from baseline [8]. Also it was observed that extremely preterm neonates do not mount an effective multidimensional response to pain.

Oral sucrose has been found to decrease pain from heel lances and venepuncture in neonates. Considering the ease of availability, cost and ease of administration, sucrose has been chosen as an analgesic of choice for the present study. The dose of 0.24 g or greater has been found to be most effective in pain relief in neonates [9]. Hence, a concentration of 24 % sucrose solution was administered to the study population. Different concentrations of sucrose administered at varying times have been evaluated and it has been found that the greater analgesic effect is produced when sucrose is administered approximately 2 min prior to the painful stimulus [10–13]. This led the authors to fix 2 min as the duration of time required between the administration of sucrose and initiation of OGT insertion in the present study.

A study by McCullough et al. suggested that the Nasogastric Tube (NGT) insertion in stable preterm infants elicits a measurable pain response [14]. This is similar in magnitude to the pain observed during heel lancing. Lingual 24 % sucrose was effective in reducing this pain response to NGT insertion. The present study indicated that 24 % sucrose provided analgesia to the study subjects in comparison to the placebo where a higher mean PIPP score was observed (Table 2). Similar observations have also been reported by McCullough et al. who observed a statistically lower Neonatal Facial Coding Score (NFCS) during NGT passage compared to the placebo group (Median 1 *vs.* 3, p=0.004) [14].

In the present study in subgroup 1, which comprised of relatively mature neonates, the pain perception was observed across both the study arms till 1 min post procedure. However, in the relatively immature neonates who comprised subgroup 2, this difference was only appreciable till 30 s post procedure. In subgroup 3, which had the most immature neonates, no painful response could be detected to the painful stimuli. This trend leads us to hypothesise that the pain pathways develop with advancing gestational age and the most vulnerable micro preemies are unable to mount a significant detectable response to pain. Other workers have also reported similar findings [5–7]. When pain scores (PIPP) were pooled across 3 studies, they were significantly reduced in infants who were given sucrose (dose range 0.012 g to 0.12 g) compared to the control group, at 30 and 60 s after heel lancing [11, 13, 15]. The present study did not reveal any difference in the PIPP scores across the two arms at and beyond 30 s post procedure. This observation needs to be interpreted with caution as it may be attributed to the small sample size and inadequate power to detect such a difference across all study timelines.

Changes similar to present study in the heart rate were observed in other studies, where no significant difference was seen between the changes in heart rate across the study groups [12, 16–19]. On the contrary, a trend towards reduced heart rate during nasogastric tube passage was observed in the sucrose group when compared with the placebo group by McCullough et al. [14]. It is difficult to explain why there was no significant reduction in heart rate during the process of OGT insertion in sucrose group in the present study. In a study which compared oral *vs.* nasal route for placing feeding tubes, no procedure related bradycardia was documented [20]. No significant changes were observed in the baseline and the lowest SpO_2 recordings between the two study arms in other studies [14, 18, 21, 22].

Recently, Slater et al. have suggested that oral sucrose does not significantly affect activity in neonatal brain or spinal cord nociceptive circuits on the basis of pain specific brain activity evoked by one time-locked heel lance, recorded with electroencephalography; and therefore might not be an effective analgesic drug and that the ability of sucrose to reduce clinical observational scores after noxious events in newborn infants should not be interpreted as pain relief [23]. However it remains to be seen whether nociceptive specific cortical evoked responses serve as an adequate measure of peripheral noxious stimuli, and whether these findings may be replicated in a larger study as this was an underpowered study with a small sample size.

A total of 6 adverse events were noticed during the procedure (5 in placebo and 1 in sucrose group), all of which consisted of vomiting. All neonates recovered spontaneously. The common adverse events reported with the use of sucrose in preterm neonates are desaturation and choking seen more frequently in extremely premature neonates. Four studies evaluated adverse events [11, 24–26], and only one study reported these in 6 infants [11]. As of now the single use of oral sucrose appears to be safe in the population studied.

A limitation of the present study was inability to calculate the power for the study. This could have led to an underestimation of the effect of sucrose on intra- and post-procedural PIPP scores.

Conclusions

In the present study, OGT insertion in preterm neonates is found to be associated with significant pain perception. The use of a single dose of 24 % sucrose solution prior to the insertion of orogastric tube provided transient analgesia in the study population. However, this needs to be viewed with caution and, at this point of time, the study results do not support or refute the effectiveness of oral sucrose in alleviating the pain response during OGT insertion. It is recommended to perform further adequately powered randomized trials to establish the role of 24 % sucrose in reducing pain associated with OGT insertion in preterm neonates.

Contributions MP: Design, acquisition of data, drafting the article, day to day clinical management of the patient and final approval of the version to be published; VD: Design, drafting the article, revising it critically for important intellectual content and final approval and guarantor of the version to be published; HSR: Design, acquisition of data.

Conflict of Interest None.

Role of Funding Source None.

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