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Oral sucrose solution as a pre-immunization analgesic: A randomized controlled study

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***Abstract*---**Introduction: Painful procedures without adequate analgesia cause pain and suffering. The administration of oral sucrose is the most frequently studied behavioural and environmental intervention for the relief of procedural pain in newborn. Breast feeding is also an intervention studied frequently. Material and methods: The present study was a randomized controlled study conducted to assess and compare the analgesic effect of orally administered sucrose with that of breast feeding and controls during immunization in healthy infants using a validated behavioural acute pain rating scale. Approval was taken from institutional ethics committee prior to commencement of the study. 100 infants who met the inclusion criteria were included as study participants. They were randomly allocated into three groups, A (sucrose) and B (breast feeding) and C (control) [no intervention] of 33 to 34 infants each. Infants in group A (sucrose) receiving Inj Pentavac were given 2.0 ml of 24% oral sucrose 2 mins prior to vaccination and the infants behavior before and after the injection was observed and scored on

FLACC Pain rating scale. Infants in group B (breast feeding) were breast fed 10 minutes prior to receiving vaccination and were also observed and scored on FLACC Pain rating scale. The analgesic effect of oral sucrose in children of group A was compared with that of breast feeding in children in group B and with no intervention in group C infants. Data was statistically analyzed using MS Excel and Statistical Package for Social Sciences SPSS 23.0. Results: The Three study groups (A, B & C) were observed to be comparable in terms of their age, gender, weight, height, head circumference, heart rate, body temperature and respiratory rate. Difference in the mean FLACC scale scores of the three study groups was found to be highly significant statistically. (P<0.001) The administration of sucrose solution 2 minutes prior to vaccination in group A infants was found to be significantly more effective compared to both ; breastfeeding prior to vaccination in group B infants and to no intervention in group C (control group) infants. (P<0.001) Breastfeeding prior to vaccination in group B infants was found to be significantly more effective compared to no intervention in group C (control group) infants. (P<0.001). Conclusion: The findings of the present study showed that administration of oral sucrose solution was more effective in reducing pain and crying time in neonates immediately after the vaccination as compared to breast feeding and can be recommended as routine standard of care during immunization

***Keywords*---**oral sucrose, FLACC scale, Breast feeding, Pentavac, Analgesia.

Introduction

International clinical guidelines recommend that procedural pain in newborns can be relieved by giving oral sucrose as preanalgesic. Neonates cannot verbalize their pain, they depend on others to recognize, assess and manage their pain. Health care professionals can diagnose neonatal pain only by recognizing the neonate's associated behavioural and physiological responses [1].Treating pain in the newborn is essential for ethical reasons and because pain can lead to decreased oxygenation, haemodynamic instability, or increased intracranial pressure and increased levels of plasma cortisol, aldosterone, growth hormone, catecholamine's and glucagon.[2]Physical and psychological stress increases the opportunity for infection through generalized depression of immune system. During normal development, pain transmission and pain modulation undergo rapid growth beginning at 22 weeks gestation; attaining maturity at 2 months of age.[2,3] Noxious stimuli during this vulnerable period of neuronal plasticity may trigger long-term epigenetic changes, which affects the neurodevelopment, pain modulation, and pain reactivity into adulthood.[3-5]

Extensive preclinical trials have established the physiological impact of early exposure to noxious stimuli on the developing nervous system [6,7] .Hence It is essential to find a simple, acceptable, and well tolerated methods to reduce pain in these infants. [8] Although vaccine injection creates a short period of pain,

studies show that this short-term pain distresses the infants, parents and vaccinators during the injection.[9] Studies have reported that simple and benign interventions—such as oral sugar solutions,[10] milk,[11] or sucking a pacifier reduces pain in neonates during procedures. The analgesic effects of sucrose and non sucrose have been reported in term and preterm newborn infants.[12,13] .Sucrose is a nonpharmacological treatment option in neonatal pain management. The proposed hypothesis is that glucose (and its alternative forms, such as sucrose) causes endogenous opioid release, through an unknown mechanism. [14] Evaluation of pain in newborns is difficult and reactions such as changes in behaviour, modification in physiological variables, or release of stress hormones to infer pain have to be relied on.

Reliably determining levels of pain in neonates is remarkably difficult and complexities of such assessment in this population are clearly demonstrated by the fact that there are more than 50 currently used pain scales. Assessment instruments used must be practical, reliable, valid, and appropriate for the child's developmental stage. Commonly used methods of self-report are the visual analog scale (VAS) and faces scales, FLACC (face, legs, activity, crying, and consolability),DAN pain scale, Premature Infant pain profile, Neonatal facial coding system (NFCS); neonatal pain, agitation, and sedation scale (N-PASS); cry, required oxygen, increased vital signs, expression, COMFORT Scale are the other scales used. The FLACC (face, legs, activity, crying, and consolability), is a measurement used to assess pain for 2 months to 7 years children who are unable to communicate their pain. The scale is scored in a range of 0 to 10 with 0 representing no pain.(Table 1) The present study aimed to assess and compare the analgesic effect of orally administered sucrose with that of breast feeding and controls during immunization in healthy infants using FLACC scale. [15]

Table 1: FLACC SCALE

Categories	Scoring		
	0	1	2
Face	No particular expression or smile: disinterested	Occasional grimace or frown, withdrawn	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry, awake or asleep	Moans whimpers occasional complaint	Crying steadily screams, sobs frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching hugging or being talked to, distractable	Difficult to console or comfort
Each of the five categories face, leg, activity, cry, consolability is scored from 0 to 2, which results in total score between 0 to 10.			

Materials and Methods

It is a Randomised controlled study done in vaccination room of Bhaskar General hospital, yenkapally. Computer based randomization was done. It was double blinded study. The present study was conducted among 100 infants receiving routine primary immunization. The study was conducted from NOVEMBER 2016 To APRIL 2018 Approval was taken from the Institutional Ethical Committee before commencing the study. The participants were informed regarding the purpose, procedures, risks and benefits of the study. Written and Informed Consent was obtained from all participants.

Inclusion criteria:

1. Infants between 2 to 4 months old receiving single Pentavac.
2. Healthy babies weighing 2.5 kgs or more at birth and appropriate for gestational age (AGA).
3. Parents consenting for the inclusion of their baby in the study.

Exclusion criteria:

1. Infants with concurrent illness (congenital conditions that can alter the response to pain).
2. Pre-term infants.
3. Low birth weight infants.
4. Babies not on any type of analgesics or mothers on analgesics.
5. Those for whom written parental consent not obtained.

Methodology

100 infants who met the inclusion criteria were included as study participants. Computer generated randomisation code was used to allocate into three groups 33 to 34 infants each in A (sucrose) and B (breast feeding) and C (control) groups with no intervention. Demographic characteristics like age, sex, weight, length, head circumference were noted by the nurse in vaccination room. Infants in group A (sucrose) receiving Pentavac were given 2.0 ml of 24% oral sucrose 2mins prior to vaccination and the infant's behavior 1 min after the injection was observed and scored on FLACC scale. Infants in group B (breast feeding) were breastfed 10 minutes prior to receiving vaccination and were also observed and scored onFLACC scale 1 min after the injection. Infants in group C were not given any intervention and FLACC scale was noted 1 min after vaccination. Babies were given intervention like oral sucrose with spoon by trained nurse. Interventions like oral sucrose, breast feeding, or no intervention are done in a separate room. Vaccination is done by another nurse in the vaccination room and video was recorded 2 min before to 7 min after vaccination. Also vital parameters like heart rate, respiratory rate, temperature were noted by the paediatrician before (baseline) and 5 min after vaccination and highest value is noted sitting on another side without interrupting the video taken by the nurse. The Pediatrician is also blinded about the intervention done to each infant. All the videos were mixed before sending to the principal investigator. The principal investigator was also blinded to treatment given when videos were given for analysis. Videos were absorbed by the principal investigator and scoring was done based on FLACC scale. The data was statistically analyzed using MS Excel and Statistical Package

for Social Sciences SPSS 23.0. Categorical variables were analyzed using Chi square or Fischer's exact test. The significance of difference between mean scores of the three groups on FLACC scale was analyzed using ANNOVA and unpaired students t test. A value of $p<0.05$ was considered as significant.

Results

The present study assessed and compared the analgesic effect of orally administered sucrose with breast feeding and control group during immunization in healthy infants using a validated behavioural acute pain rating FLACC scale. The infants comprising of the study group were randomly divided into 3 groups: 1) Group A (sucrose) [N=34] 2) Group B (Breast feeding) [N=33] and 3) Group C (control) [N=33]

Demographic and baseline clinical Characteristics:

In the present study, in Group A (sucrose) the mean age was observed to be 2.68(+-0.74) months, was comprised of 13 (38.24 %) males and 21(61.76%) females; mean weight was 5.01(+-0.19) kg; mean height was 58.82 (+-4.97) cm; mean head circumference was 38.94(+-2.00) cm. The mean heart rate was 116.50(+-7.48), mean body temperature was 98.31(+-0.41) ^{0}F and mean respiratory rate was 34.12(+-0.53) per minute.

In Group B: (Breast feeding) the mean age in was observed to be 2.68(+-0.89); was comprised of 21(63.64%) males and 12 (36.36 %) females; mean weight in was 5.14 (+-0.08) kg mean height in was be 58.48 (+-3.83) cm; mean head circumference was 38.84(+-2.11) cm. The mean heart rate was 118.18(+-9.49) bpm; mean body temperature was 98.37(+-0.45)^{0}F and mean respiratory rate was 98.37(+-0.45) per minute.

In Group C: (control), the mean age in was observed to be 2.89(+-0.85) months; was comprised of 19(57.58%) males and 14 (42.42 %) females; mean weight in was 5.16 (+-0.20) kg. mean height in was 58.88(+-4.68) cm; mean head circumference was 39.02(+-2.20) cm. The mean heart rate was 117.21(+-7.75) bpm; mean body temperature was 98.36(+-0.39) ^{0}F and the mean respiratory rate was 98.36 (+-0.39) per minute. In 68 (68.00%)

The mean (+-standard deviation) with respect to demographic characteristics like age, gender, weight, height, head circumference was observed in all the Groups A,B,C. The difference in the mean of all the above parameters of the three groups under study was not found to be statistically significant. ($P>0.05$) The three study groups were observed to be comparable in terms of the above parameters as shown in Table 2.

Table 2: Demographic Characteristics of the Three Groups under Study:

	Group A (sucrose) N=34	Group B (Breast feeding) N=33	Group C (control) N=33	P value
Age (months)	2.68(+-0.74)	2.68(+-0.89)	2.89(+-0.85)	>0.05
Gender (M/F)	(13/21) (38.24%/61.76 %)	(21/12) (63.64%/36.36%)	(19/14)(57.58% /42.42%)	>0.05
Weight (kgs)	5.01(+-0.19)	5.14(+-0.08)	5.16(+-0.20)	>0.05
Length(cm)	58.82(+-4.97)	58.48 (+-3.83)	58.88(+-4.68)	>0.05
Head circumference (cm)	38.94(+-2.00)	38.84(+-2.11)	39.02(+-2.20)	>0.05

The mean (+-standard deviation) of vital parameters like heart rate, respiratory rate, temperature was observed and noted in all the three groups. Difference in the mean heart rate, respiratory rate and temperature of the three study groups was not found to be statistically significant. (P>0.05) (Table 3)

Table 3: Vital parameters in the three groups under study

VITAL PARAMETRES	Group A (sucrose) N=34	Group B (Breast feeding) N=33	Group C (control) N=33	P value
Heart rate (/min)	116.50(+-7.48)	118.18(+-9.49)	117.21(+-7.75)	>0.05
Respiratory rate (/min)	34.12(+-0.53)	33.79(+-0.54)	35.27(+-0.51)	>0.05
Temperature (^{0}F)	98.31(+-0.41)	98.37(+-0.45)	98.36(+-0.39)	>0.05

The mean (+-standard deviation) FLACC scale score in Group A (sucrose) was assessed to be 1.59 (+-0.22); in Group B (Breast feeding) the mean (+-standard deviation)FLACC scale scores was assessed to be 2.73 (+-0.17); and in group C (control) the mean FLACC scale scores was assessed to be at 9.09 (+-0.21). Difference in the mean FLACC scale scores of the three study groups was found to be highly significant statistically. (P<0.001) Thus the administration of sucrose solution 2 minutes prior to vaccination in group A infants was found to be significantly more effective compared to both ; breastfeeding prior to vaccination in group B infants and to no intervention in group C (control group) infants. (P<0.001) Breastfeeding prior to vaccination in group B infants was found to be significantly more effective compared to no intervention in group C (control group) infants. (P<0.001)

In the present study thus, both interventions i.e. administration of sucrose solution and breastfeeding prior to vaccination were found to be significantly effective in inducing analgesia post immunization. But, sucrose (group A) was found to be significantly more effective in inducing analgesia as compared to group B (breast feeding) and control group. (P<0.001)(Table 4)

Table 4: Comparison of effectiveness of analgesia in the three study groups

FLACC Scale	Group A (sucrose) N=34	Group B (Breast feeding) N=33	Group C (control) N=33	P value
	1.59 (+-0.22)	2.73(+-0.17)	9.09(+-0.21)	<0.001**

P<0.001** highly significant

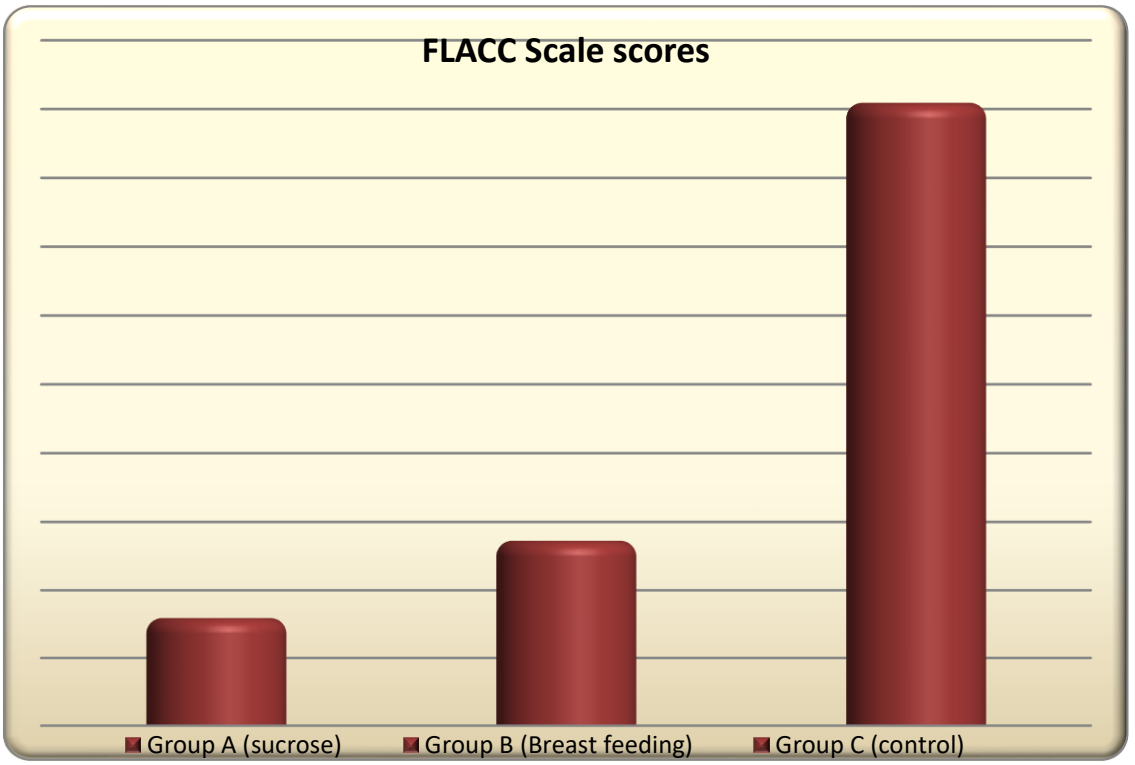

Fig 3: Comparison of effectiveness of analgesia in the three study groups (A, B & C)

Discussion

More than 150 published studies relating to sweet-taste-induced calming and analgesia in human infants have been identified, of which 100 (65%) include sucrose. Sucrose has been widely recommended for routine use during painful procedures in newborn and young infants, yet these recommendations have not been translated into consistent use in clinical practice. Notably, the mechanism of sweet-taste-induced analgesia is still not precisely understood, which has implications for using research evidence in practice.

Several studies about the impact of breastfeeding on pain relief in infants observed that this was a physiological, accessible, practical and safe method which is easily accepted by the parents and health care providers. The present study was conducted on 100 infants randomly divided into three groups (A, B and C) to assess and compare the analgesic effect of sucrose compared with that of

breast feeding along and control group during immunization in healthy infants using a validated behavioural acute pain rating scale. Thus, the three study groups were observed to be comparable in terms of their age, gender, weight, height, head circumference, heart rate, body temperature and respiratory rate. In the present study administration of oral sucrose solution was found to be the most effective intervention followed by breast feeding when compared to control group (without intervention) as assessed by FLACC Scale similar to studies by Curtis SJ et al. [15], Elserafy FA et al. [16), Sahebihag MH et al. [17].

Oral sucrose administration has been associated with calming effects and reductions in observed pain behaviours in preterm, term, and postnatal infants(18) as observed in the present study. In their systematic review; Hatfield LA et al. [18] evaluated the efficacy and safety of oral sucrose as a preprocedural intervention for mild to moderate procedural pain in infants.46 RCTs were critically reviewed. Studies indicated that oral sucrose is an effective, safe, convenient, and immediate-acting analgesic for reducing crying time and significantly decreases biobehavioral pain response following painful procedures with infants.

In Stevens et al. meta-analysis[19], patients receiving sucrose were found to have significant reductions in behavioral and physiologic indicators of pain, as well as improvements on several different validated pain scores . Specifically, measures of physiologic response, such as changes in heart rate, oxygen saturation, and vagal tone, were dampened when compared to placebo . The use of sucrose in neonates, when compared to breast milk or pacifier use, has also been associated with a reduction in behavioral indicators of pain, such as crying and grimacing during painful procedures [19]. Thus, combined interventions (sucrose + physical interventions) are potential areas for further research for studying the synergistic effects of the combined interventions.

One must consider the dose of sucrose used. Doses up to 0.5 g have been studied and determined to be safe for use in the neonatal period [19] and immunization studies have used doses as high as 2.5 g for older infants [9] without adverse events. Stevens et al. [20] found that 2 mL of 12% to 24% sucrose, in the range of 0.24 g or 0.50 g, is effective in reducing pain responses in preterm and term infants. So,we used 2ml of 24% sucrose in our study.

The findings of the present study were also in accordance with the findings of Efe&Savasar [21],Carbajal et al[22], in which crying time was shorter in oral sucrose group and breastfeeding group in comparison with the control group. The findings of Bauer et al, [23], Butcher H et al showed that oral glucose significantly decreased the pain.

Finally, the findings of the present study showed that administration of oral sucrose solution more effectively (significantly) caused reduction in pain and crying time in neonates immediately after the vaccine injection as compared to breast feeding and can be recommended as routine standard of care during immunization. Further study with larger sample sizes and perhaps using stronger concentrations of sucrose would be required to determine the upper age limit for the effectiveness of sucrose. Breast-feeding also caused significant reduction in

pain and crying time in neonates immediately after the vaccine injection as compared to controls.

Limitation of the present study

The present study was conducted to assess and compare sucrose analgesia during immunization only and did not include a variety of procedural pain relief.The study was done using smaller sample size. Different doses of oral sucrose and timing for administration and studies in higher age groups, with more sample size and preterm infants are the identified areas of potential future research.

Conclusions

In the present study, administration of sucrose solution along with breastfeeding prior to vaccination can be recommended for analgesia post immunization.

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