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ORIGINAL RESEARCH

Effectiveness of Sucrose Analgesia in Term Neonates for Procedural Pain - A Randomised Controlled Trial

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Abstract

Background: We know little about the effects of oral sucrose on the overall physiological and behavioural stability of newborns during painful procedures, although infant pain is a multidimensional phenomenon. In the current study, we compared pre and post-test stress response between a routine procedure with placebo and orally administered sucrose solution by observing biochemical (salivary cortisol) and behavioural (NIPS score and total cry time) changes.

Materials and methods: We conducted the study at Kasturba Hospital, Manipal, Karnataka between October 2012 and September 2013. We collected data during heel lance and venipuncture. We performed statistical analyses using SPSS for Windows. We analyzed comparison of demographic factors using the mean, standard deviation, frequency, independent t-test for continuous data and chi-square test for categorical data.

Results: There were no significant differences between the means of salivary cortisol before and after procedure in between 24% sucrose and 10% dextrose for heel lance and venipuncture. The total cry time was very less in the sucrose group (median 10 sec) when compared to dextrose group (median 37.5 sec). However, statistically, there was no significant difference.

Conclusion: There was a reduction in the median total cry time in the 24% sucrose group. 24% Sucrose reduced pain to a considerable level (NIPS < 4) in neonates for heel lance and venipuncture. Hence, we can conclude that clinically 24% sucrose is a better analgesic than 10% dextrose for procedural pain in term neonates.

CTRI trial registration was done.

Keywords

Oral sucrose, Oral dextrose, Venipuncture, Heel lance, Salivary cortisol

Introduction

All neonates will experience iatrogenic pain in the first days of life, beginning with vitamin K injection and blood collection for sugars, bilirubin or lately metabolic screening before discharge from the hospital. Recognition that both premature and full-term infants experience pain [1] has led to increasing appreciation of the prevalent problem of under-treatment of accentuate and pain of infants hospitalised in the newborn intensive care unit. Both humanitarian considerations and scientific principles favour improved management strategies to prevent pain and stress and, when discomfort is unavoidable, to provide prompt and treatment. Neonates admitted to presenting day neonatal intensive care units (NICU) are constantly exposed to pain, discomfort or noxious stimuli of variable intensities for various reasons. These include major and minor surgical procedures, needle pricks for blood drawing, and insertion of IV cannulas. The experience of pain is always subjective. Hence, verbalisation of nociceptive sensation is the gold standard for the assessment of pain.

Since neonates cannot express their pain, the recognition and management of pain in newborn babies is still suboptimal in NICUs. Studies have documented that babies born at less than 32 weeks of gestation are exposed to 10-15 painful procedures each day during the first few weeks of life, and in almost 80% no treatment for pain relief is offered [2].

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Pain recommends that the combination of a variety of pharmacological and behavioural interventions during painful procedures has synergistic effects [2]. Recent studies have shown that the combination of oral sucrose and a pacifier was the most clinically safe and effective method for the management of painful procedures in neonates. The salivary cortisol level is a reasonable reflection of the hypothalamic-pituitary-adrenal axis function. We have measured salivary cortisol in infants subjected to major stressful situations, such as painful procedures, making it a useful alternative to blood sampling. However, other studies did not show the effects of oral sucrose on salivary cortisol changes during painful procedures in newborn infants. So, more explanative studies concerning the effects of sucrose on newborn infants by identifying salivary cortisol changes are needed. We know little about the effects of oral sucrose on the overall physiological and behavioural stability of newborns during painful procedures, although infant pain is a multidimensional phenomenon.

In a study by Kyoung, et al. [3], 24% sucrose was found to be effective in reducing NIPS score and salivary cortisol. This is the only study which has taken NIPS score and salivary cortisol for evaluation of stress because of painful procedures in term neonates. The control group did not receive any treatment in this study. There are no studies which used NIPS score and salivary cortisol for venipuncture procedure. Our study is the first one to use these two parameters in term neonates for both venipuncture and heel prick.

In the current study, we compared pre and post-test stress response between a routine procedure with placebo and orally administered sucrose solution by observing biochemical (salivary cortisol) and behavioural (NIPS score and total cry time) changes.

Aims and Objectives

A. To find the effectiveness of sucrose as an analgesic agent for the following procedures in term (> 37 weeks of gestational age) neonates.

1. Venipuncture done for estimation of bilirubin and thyroid function tests

2. Heel lance done for estimation of glucose

B. Feasibility of noninvasive assessment of neonatal procedural stress based on salivary cortisol estimation.

Materials and Methods

Study design

A double blinded randomised controlled trial

Target population: Term neonates who were admitted in postnatal ward under Neonatology division, Dept. of Paediatrics at Kasturba Hospital, Manipal.

Study period

October 2012 and September 2014.

Sample size

64 controls and 64 test samples, 128.

Sampling method

Random sampling method using computer-generated random numbers.

Inclusion criteria:

1. Term neonates (gestational age > 37 weeks).
2. Clinically stable and requiring investigations for clinical evaluation.

Exclusion criteria:

1. Neonates with gross congenital malformations and neurological symptoms
2. Neonates delivered under maternal general anaesthesia within the last 48 hours
3. Neonates receiving analgesics or sedatives
4. Neonates who were asphyxiated or depressed at birth
5. Neonates with transient metabolic problems like hypoglycaemia or hypocalcaemia
6. Inadequate salivary sample collection.

Sample size calculation

We calculated the sample size for each arm with 5 per cent level of significance and 80 per cent power for an effect size of 0.5 and the value was 63 for each arm. For the sake of uniformity, we took the four subgroups of 128 samples with 64 in each arm.

We conducted the study at Kasturba Hospital, Manipal, Karnataka between October 2012 and September 2013. The Institutional Ethics Committee of Kasturba Hospital, Manipal reviewed and approved the study. CTRI registration was done. Subjects were assessed for eligibility and informed consent from the parents was got in 128 term neonates. 128 neonates (control group n = 64; experimental group n = 64) were evaluated. All neonates were healthy and had no congenital malformations.

Data collection

Physiological and behavioural pain indicators were examined to maximise the validity of pain assessment in newborn infants. Data were collected during heel lance and venipuncture performed as part of routine clinical care for the estimation of glucose and bilirubin, thyroid function tests, respectively. The infants in the control group (n = 64) received 10% dextrose. In the experimental group, 24% sucrose solution was used.

Statistical analysis

We performed Statistical analyzes using the statistical package SPSS for Windows (version 16.0, SPSS Inc, Chicago, IL, USA). We analyzed comparison of demographic factors using the mean, standard deviation, frequency, independent t-test for continuous data, and χ^2 test for categorical data. We calculated the percentage differences salivary cortisol per procedure, at 1 minute and 3 minutes during the procedure. These values were compared between the two groups by using the Mann-Whitney U test. Crying time and NIPS Score between the two groups were compared with the Mann-Whitney U test. I divided the samples in to two categories based on NIPS score, whether it was less than 4 and greater than or equal to 4, as a score of 4 shows clinically significant pain. These values at 1 minute and 3 minutes post-procedure were calculated, and we compared proportions using the Fisher exact test.

Results

The experimental group and the control group did not differ significantly in any of the demographic variables (Table 1).

When compared to 10% dextrose, no. of babies who received sucrose and fall into NIPS score < 4 category at 1 min and 3 min during the procedure were more. Hence, 24% sucrose has a better analgesic effect than 10% dextrose. However, statistically, when Fischer exact test was applied between the groups, there were no significant differences between 24% sucrose and 10% dextrose (Table 2).

Heel lance: There were no significant differences between the means of salivary cortisol before and after procedure in between 24% sucrose and 10% dextrose for heel lance. We have taken the percentage differences between the salivary cortisol before the procedure and after the procedure and applied Mann-Whitney U test. Statistically, there were no significant differences between 24% sucrose and 10% dextrose regarding salivary cortisol for the heel lance procedure (Table 3).

Venipuncture: There were no significant differences between the means of salivary cortisol before and after procedure in between 24% sucrose and 10% dextrose for venipuncture. We have taken the percentage differences between the salivary cortisol before the procedure and after the procedure and applied Mann-Whitney U test. Statistically, there were no significant differences between 24% sucrose and 10% dextrose regarding SPO_2 for the heel lance procedure (Table 3).

Heel lance: The total cry time was very less in the sucrose group (median 10 sec) when compared to dextrose group (median 37.5 sec). However, statistically, there was no significant difference (Figure 1).

Venipuncture: The total cry time was very less in the sucrose group (median 22.5 sec) when compared to dextrose group (median 130 sec). However, statistically, there was no significant difference (Figure 2).

Discussion

The number of neonates randomised was 128, with 64 in each group. The physiological parameters

Table 1: Demographic characteristics.

Variable	10% Dextrose (n = 64)	24% Sucrose (n = 64)	p value*
Gender (male/female)	32/32	33/31	0.860
Birth weight (gm)	2955 ± 435	2826 ± 514	0.213
Gestational age (weeks)	38.2 ± 1.0	38.1 ± 1.0	0.732
Postnatal age (hours)	69.0 ± 46.5	68.4 ± 38.5	0.105
Mode of delivery (VD/LSCS)	17/47	23/41	0.253
Apgar score at 5 min	9	9	

We express data as a number or mean ± SD (standard deviation); *p value corresponds to results of independent t-test for continuous data and χ^2 test for categorical data.

Table 2: Comparison of the no. of neonates with NIPS score < 4 at 1 minute and 3 minutes after the procedure between 10% Dextrose and 24% Sucrose groups.

	NIPS score < 4 at t = 1 min			NIPS score < 4 at t = 3 min		
Procedure	10% Dextrose (n = 32)	24% Sucrose (n = 32)	*p value	10% Dextrose (n = 32)	24% Sucrose (n = 32)	*p value
Heel lance (n = 32)	9	12	0.595	24	28	0.337
Venipuncture (n = 32)	5	12	0.088	14	21	0.131

*p value corresponds to the Fischer Exact test.

Table 3: Comparison of salivary cortisol before and after the procedures between the groups.

Procedure	Solution received	Salivary cortisol before procedure Mean ± SD	Salivary cortisol after procedure Mean ± SD	*p value
Heel lance (n = 40)	10% Dextrose (n = 20)	18.1 ± 9.0	20.1 ± 8.3	0.820
	24% Sucrose (n = 20)	14.1 ± 8.6	17.3 ± 9.8	
Venipuncture (n = 38)	10% Dextrose (n = 20)	16.4 ± 8.4	17.9 ± 7.4	0.593
	24% Sucrose (n = 18)	14.1 ± 9.2	15.5 ± 9.6	

*p value corresponds to the Mann-Whitney U test

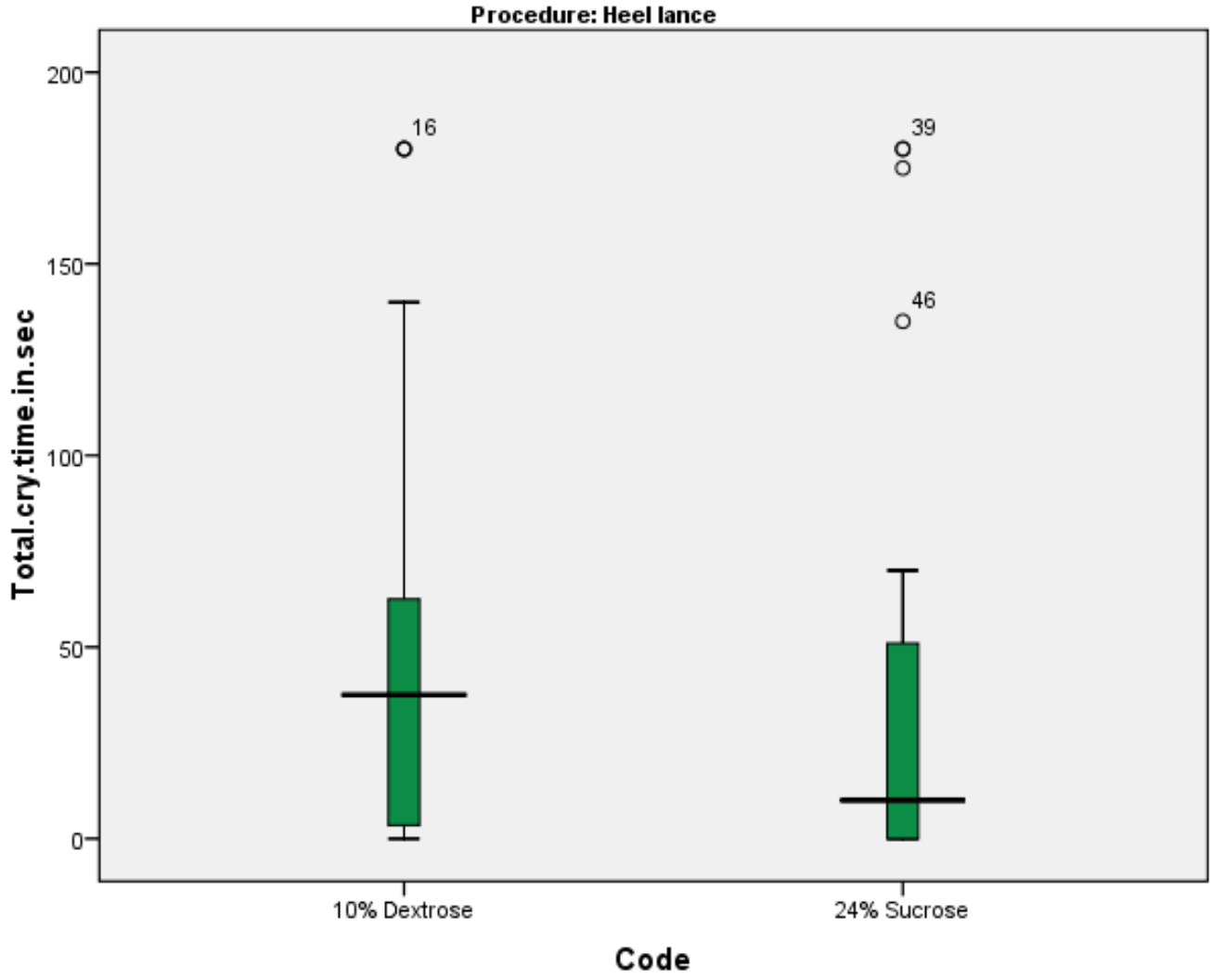

Figure 1: Box plot showing Median Total cry time for both the groups for heel lance procedure.

heart rate, oxygen saturation and total cry time and the pain assessment by NIPS score was done in all 128 neonates. However, salivary cortisol was analysed only for 78 neonates, as the samples were not sufficient. The results and discussion are as follows (Figure 3).

We consider the underlying mechanism of the analgesic effects of sweet solutions to be an orally mediated release of endogenous opioids. Calming effects were sweet taste, not the volume dependent, as small volumes of 0.2 ml sucrose were similarly as effective as larger volumes of 0.6 ml and 1 ml. The effects of sweet taste peak at two minutes following administration, and persist for around five to eight

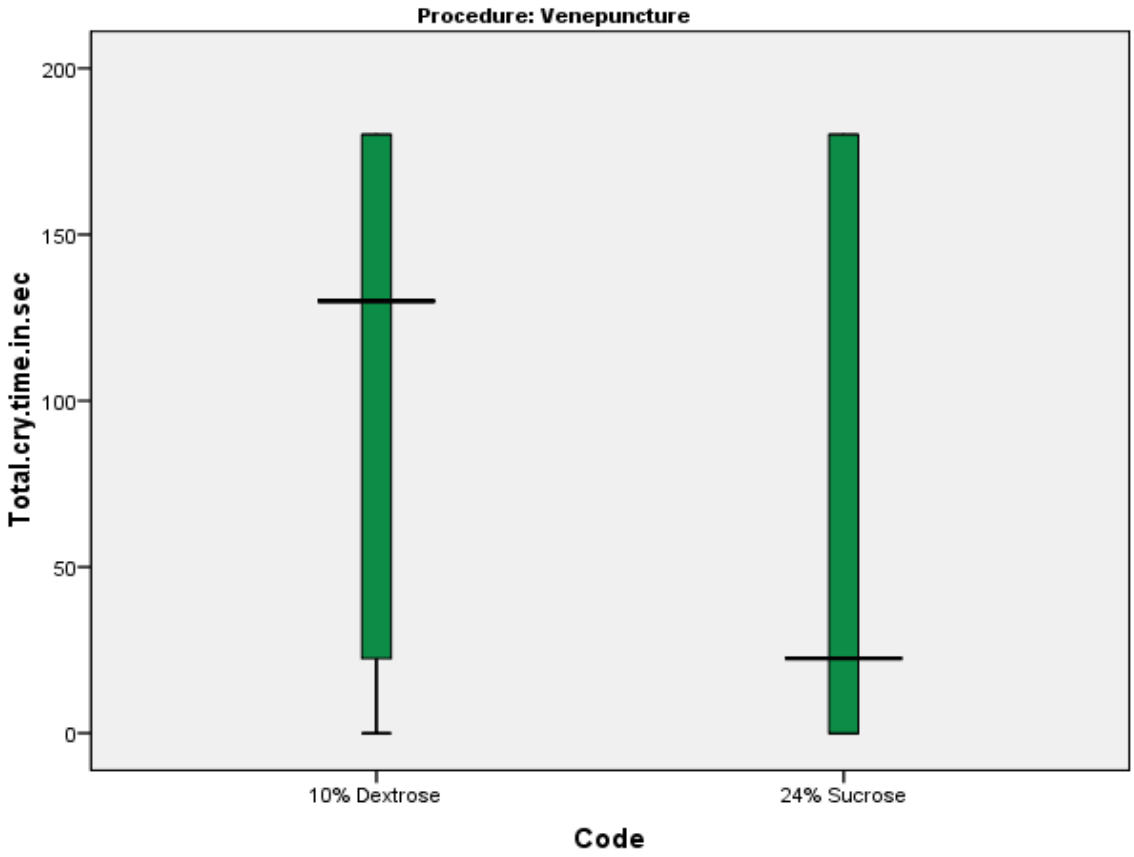

Figure 2: Box plot showing Median Total cry time for both the groups for venipuncture procedure.

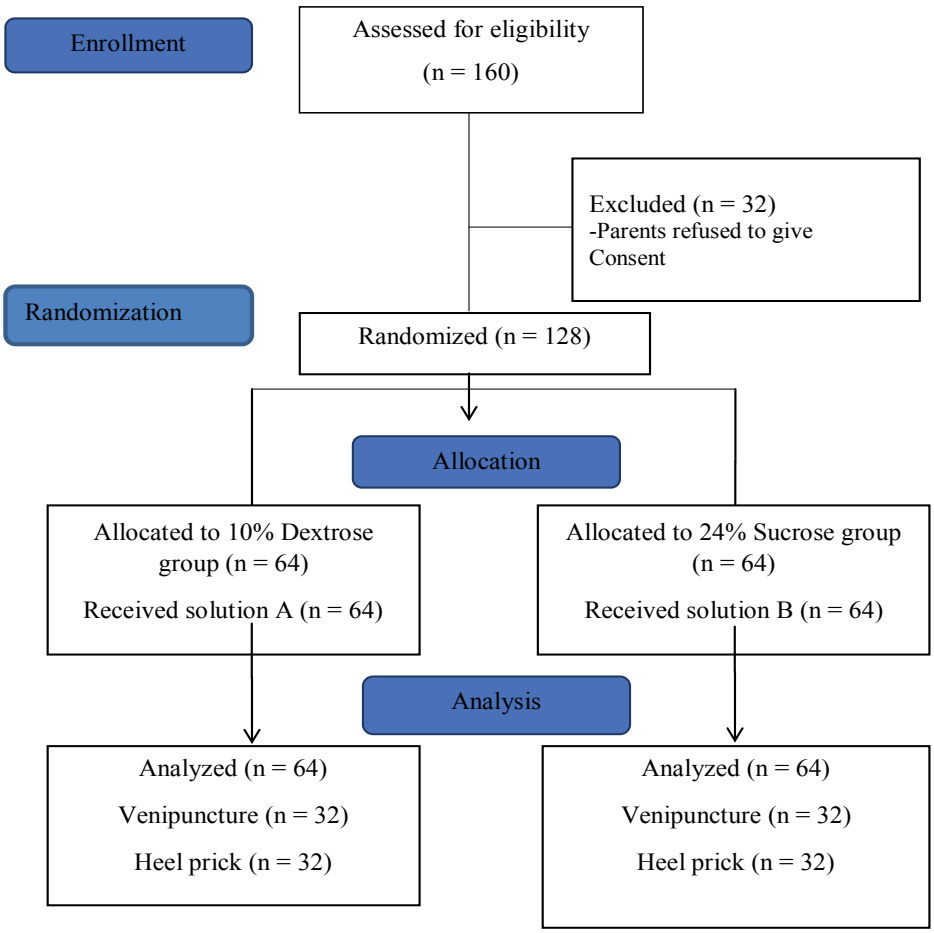

Figure 3: Consort flow diagram.

minutes [4] and depend on contact with the tongue, and not ingestion directly via a nasogastric tube [5]. Despite many studies, the mechanism of sweet taste and pain protection is unclear.

Statistically, there were no significant differences between 24% sucrose and 10% dextrose regarding salivary cortisol for the heel lance procedure. In a study by Kyoung, et al. [3] there was no significant differences between the two groups. There were no studies which have shown significant differences regarding salivary cortisol between sucrose and the control group using 10% dextrose for heel lance.

There were no significant differences between the means of salivary cortisol before and after procedure in between 24% sucrose and 10% dextrose for venipuncture. There were no studies which reported salivary cortisol for venipuncture.

Elevated cortisol, a measure of stress reactivity, has been found to detrimentally affect brain development [6], whereas decreased stress reactivity increases infant learning and memory [7]. To counteract negative outcomes, maternal/caregiver behaviour (talking, touching, eye-to-eye contact, and rocking) facilitates infant self-regulation and soothes infants, especially during times of stress [8]. Because we have validated cortisol assays as a noninvasive measure of stress reactivity with infants, this assay has been used to explore the potential use of various behavioural interventions for stress reduction during painful and other stressful procedures [8].

Salivary cortisol is a useful noninvasive measure of the neonate's immediate stress reactivity response to both physical stimuli [9]. In normal full-term infants, we correlate behavioural responses to stressors with elevated cortisol levels [10,11]. Measurement of cortisol via whole saliva (saliva got from the parotid, submandibular, and sublingual glands) [12] is a simple and noninvasive measure that has facilitated the evaluation of the interactions among the hypothalamic-pituitary-adrenal axis, environmental events, and behaviour within the context of research on health and development [13]. The circadian rhythm of cortisol becomes established in term infants between 8 and 12 postnatal weeks [14].

The total cry time in heel lance was very less in the sucrose group (median 10 sec) when compared to dextrose group (median 37.5 sec). However, statistically, there was no significant difference. In studies by Kyoung, et al. [3], Isik U, et al. [15], Bucher HU, et al. [16], Ramenghi LA, et al. [5], and Ors R, et al. [17] sucrose reduced total crying time when compared to the control group. In different studies by Harrison, et al. [18], Mathai, et al. [19] and Ogawa, et al. [20] there was no significant reduction in cry time for the sucrose group compared to the control group.

The total cry time in venepuncture was very less in the sucrose group (median 22.5 sec) when compared to dextrose group (median 130 sec). However, statistically, there was no significant difference. In studies by Abad, et al. [21] and Acharya, et al. [22], sucrose reduced crying time. In a study by Ogawa, et al. [20], there was no significant reduction in cry time for the sucrose group compared to the control groups.

We studied sucrose as an analgesic agent in different studies with different strengths of solutions for different procedures. According to a systematic review by Stevens, et al. [2] sucrose was effective in reducing crying behaviours, grimacing, and vagal tone, and unidimensional, multidimensional and composite pain scores during heel lance in volumes and concentrations ranging from 0.5 to 2 mL of 12% to 50% solutions. Some effectiveness of sucrose administration was clear during venipuncture regarding reducing heart rate, unidimensional and multidimensional composite pain scores.

Although sucrose has been extensively used in clinical and animal studies, there are a few studies that have investigated the anti-nociceptive effect of dextrose. In a study by Jagadeesh, et al. [23] it was shown showed that 25% dextrose is effective in reducing pain in neonates when compared to expressed breast milk and sterile water. The pain score used here was PIPP score.

In another study by Manizheh Mostafa Gharehbaghi, et al. [24] we showed that oral 20% dextrose solution is a useful, non-expensive, non-pharmacologic method for managing pain of venipuncture in neonates; the pain score used was CRIES score. In a study by Aurimery Gomes, Chermont, et al. [25] the combination of oral 25% dextrose treatment and skin-to-skin contact acted synergistically to decrease acute pain in healthy neonates. However, dextrose is not palatable as opposed to sucrose, which is very sweet and may decrease the pain more effectively.

Conclusion

There was a reduction in the median total cry time in the 24% sucrose group when compared to 10% dextrose group for both procedures. 24% Sucrose reduced pain to a considerable level (NIPS < 4) in neonates at 1 min and at 3 minutes when compared to 10% dextrose for heel lance. Similarly, 24% Sucrose reduced pain to a considerable level (NIPS < 4) in 37.5% neonates at 1 min and 65.6% neonates at 3 min when compared to 10% dextrose, which reduced only 15.6% and 43.8% respectively for venipuncture. Hence, we can conclude that clinically 24% sucrose is a better analgesic than 10% dextrose for procedural pain in term neonates.

Funding

Nil.

Conflicts of Interest

Nil.

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