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The Effectiveness of Sucrose as a Pain Reducing Substance during Procedures in NICU

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Abstract:- The medical community has long been aware of infant distress, which typically happens in a hospital context. It has become clear that many newborns admitted to the neonatal critical care unit are not receiving enough therapy for stress and discomfort because both premature and full-term infants experience pain. The use of enhanced management techniques to decrease stress and pain whenever possible and to offer fast and effective treatment when suffering cannot be avoided is supported by both scientific and humanitarian reasons. At Kasturba Hospital in Manipal, Karnataka, between October 2012 and September 2013, parents of 128 term newborns who had been evaluated for eligibility took part in the study after giving their informed consent. The infants were all congenitally healthy and free of abnormalities.

According to this study, 24% sucrose performs better than 10% dextrose as an analgesic for procedural pain in term neonates. The physiological parameters of all 128 neonates were recorded, including heart rate, oxygen saturation, total cry time, and pain evaluation using the NIPS score. Only 78 newborns' salivary cortisol levels were investigated. The following criteria revealed no discernible differences between the 24% sucrose and 10% dextrose in terms of reducing babies' procedural pain. The median total cry duration for both operations was shorter in the 24% sucrose group than in the 10% dextrose group.

For heel lancing, 24% sucrose significantly decreased discomfort in 37.5% of infants at 1 minute, 87.5% of neonates at 3 minutes, and 22.5 seconds vs. 130 seconds for venipuncture, compared to 10% dextrose. This implies that 24% sucrose, as opposed to 10% dextrose, works better as an analgesic for procedural pain in term babies.

Keywords:- *New Borns, Salivary Cortisol, Sucrose, Dextrose, Pain.*

I. INTRODUCTION

The length of time it took the medical establishment to acknowledge that infants experience pain is astounding.

Everyone has the fundamental right to be pain-free, regardless of their size or age. Pain in newborn infants is a common occurrence. In the hospital setting, infants as young as newborns frequently have uncomfortable procedures. Every infant will experience iatrogenic pain in the first few days of life, beginning with the vitamin K injection and blood testing for glucose, bilirubin, and more recently, metabolic screening before being released from the hospital. The realisation that both premature and full-term infants experience pain has brought to light the widespread problem of newborns hospitalised in the neonatal critical care unit being undertreated for stress and pain1. Improved management techniques are encouraged by both scientific and humanitarian principles in order to reduce stress and pain whenever possible and to give timely and effective treatment when discomfort cannot be avoided. Present-day neonates admitted to NICUs are frequently subjected to noxious stimuli of varying intensities, including pain, discomfort, and discomfort. These include both major and small surgical operations, blood draw techniques, and IV cannula insertion. Pain is always a subjective experience. The gold standard for evaluating pain is hence verbalization of nociceptive sensation2.The detection and management of pain in newborn newborns in NICUs is currently subpar since neonates cannot verbalise their suffering. In the first few weeks of life, infants born at fewer than 32 weeks of gestation are subjected to 10 to 15 unpleasant procedures daily, and in approximately 80% of cases, no pain medication is provided3.

As in the case of protracted mechanical ventilation and necrotizing enterocolitis, discomfort may be short-term or long-term. Even seemingly unimportant carer duties like diaper changes, daily weighed, and tape removal provide uncomfortable stimulation. All of these events have a detrimental effect on long-term neurologic outcomes, somatization disorders, and pain sensitivity, especially in preterm neonates. Both scientific and humanitarian considerations support the use of improved management approaches to lessen stress and pain whenever possible and to provide prompt and effective treatment when suffering cannot be avoided.

Treating pain in infants is essential for a number of reasons, including decreased oxygenation, hemodynamic instability, and increased intracranial pressure4.For the greatest benefit during unpleasant procedures, the International Evidence-Based Group for Neonatal Pain suggests combining pharmaceutical and behavioural therapies5. The combination of oral sucrose and a dummy has been shown to be the best clinically secure and effective technique for the management of painful operations in neonates. Salivary cortisol is a good predictor of the health of the hypothalamic-pituitary-adrenal axis. Salivary cortisol has been evaluated in babies subjected to substantial stressful events, such as painful procedures, and is a useful alternative to blood collection. However, other studies fell short of demonstrating how oral sucrose altered changes in salivary cortisol after painful operations in newborn infants.

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Therefore, more studies that pinpoint variations in salivary cortisol are needed to explain how sucrose affects newborn babies. Little is known about how oral sucrose impacts the overall physiological and behavioural stability of infants undergoing traumatic procedures, despite the fact that baby pain is a complex issue. In the current investigation, we examined physiological (heart rate, oxygen saturation, and salivary cortisol) and behavioural (NIPS score and total cry time) alterations to evaluate pre and post test stress responses between a normal procedure with placebo and orally administered sucrose solution.

II. MATERIALS AND METHODS

The study was conducted at Kasturba Hospital in Manipal, Karnataka, between October 2012 and September 2013. The study was reviewed and approved by the institutional ethics committee at Manipal's Kasturba Hospital. It had CTRI registration. Parents of 128 term neonates were examined for eligibility and provided their informed permission. In total, 128 neonates were evaluated (64 in the control group and 64 in the experimental group). The infants were all congenitally healthy and free of abnormalities.

III. DATA COLLECTION

The validity of pain assessment in newborn infants was improved by examining physiological and behavioural pain indicators. Data were collected during heel lancing and venipuncture procedures carried out as part of regular clinical treatment for the calculation of glucose and bilirubin, as well as for thyroid function tests, respectively. The newborns in the control group (n=64) received 10% dextrose. A 24% sucrose solution was used by the experimental group.

- **Randomization:** The hospital pharmacy provided the NICU with the test solution (24% sucrose) and the placebo solution (10% dextrose) during the trial in identical bottles without labels but with the codes A and B. Only after the study's conclusion were the codes made public. By adopting computer-generated blocked randomization, it was possible to conceal allocation while keeping observers' eyes open.The investigator used randomization to determine the solution to be administered to a certain neonate right before performing the surgery.
- **Procedure:** All operations were carried out as needed when there was a clinical need because cortisol doesn't have a diurnal rhythm throughout the neonatal period. Everything was done one hour after the meal. The neonate's wrist was attached to a pulse oxymeter (Philips vital signs MP 20) monitor to record the pulse rate and oxygen saturation with the least amount of disruption to the baby's routine. A cellphone camera (Nokia Lumia 520) was used to record the entire process. Salivary cortisol was taken before and after the procedure, which is covered in more detail in the next section. Two minutes before the procedure, a 2ml syringe containing 1ml of the solution (A or B) chosen at randomization was injected directly onto the anterior surface of the tongue. Infants consumed the entire amount of sugar or dextrose solution in 45–60 seconds. Venipuncture was performed using a 22G needle on the hand's dorsum, and a heel lance was performed using a 26G needle on the heel's posterolateral surface. The NICU's trained neonatal staff nurses performed heel lancing, while the NICU's trained residents performed venipuncture. Prior to, one and three minutes into, and following the procedure, it was calculated what the hear rate, oxygen saturation, and NIPS score would be. Before and after the surgery, the total cry time was calculated. The investigator and a neonatal staff member independently evaluated each procedure's NIPS score.The face expression (0, 1), cry (0-2), breathing patterns (0, 1), arms (0, 1), legs (0, 1), and level of arousal (0, 1) all contribute to the NIPS score. The overall score is between 0 and 7. A score higher than three denotes pain that is clinically serious. To assess consistency among the raters, an inter rater reliability analysis utilising the Kappa statistic was carried out. It was discovered that the raters' inter-rater reliability was Kappa = 0.584 (p 0.05), 95% CI (0.485, 0.685). This suggests that the two observers are in moderate agreement. For the final analysis, the investigator's NIPS score was used.
- **Saliva collection for cortisol estimation:** A cotton swab that is rolled at one end and measures 10 cm in length. It is sterilised by autoclaving in CSSD and delivered in sterile packets (Figs. 3 and 4). To prevent unintentional choking, the neonate's cotton swab was held underneath the tongue for 20 minutes while being closely watched. Each neonate had two samples taken: one baseline sample before the surgery and the other sample thereafter, which was taken at the peak cortisol release time of 20 minutes.No baby cried or displayed any signs of pain during the saliva collection because it was done in a quiet setting. After saliva collection, a sterile medical blade was used to cut the cotton swab away from the wooden shaft. Using a syringe technique, saliva from the cotton swab was collected and placed in a simple (red) micro vacutainer (Figs. 5 and 6). The samples were kept in the biochemistry lab's cold storage at -70 degrees Celsius. In the biochemistry lab, salivary cortisol was determined in all of the samples using an ELISA kit (DRG Salivary cortisol HS ELISA kit, SLV-4635, Germany). The amount of cortisol in the saliva was measured in ng/ml. The normal reference range for salivary cortisol is 3.4–23.45 ng/ml, with a mean and standard deviation of 10.71–6.58 ng/ml75.

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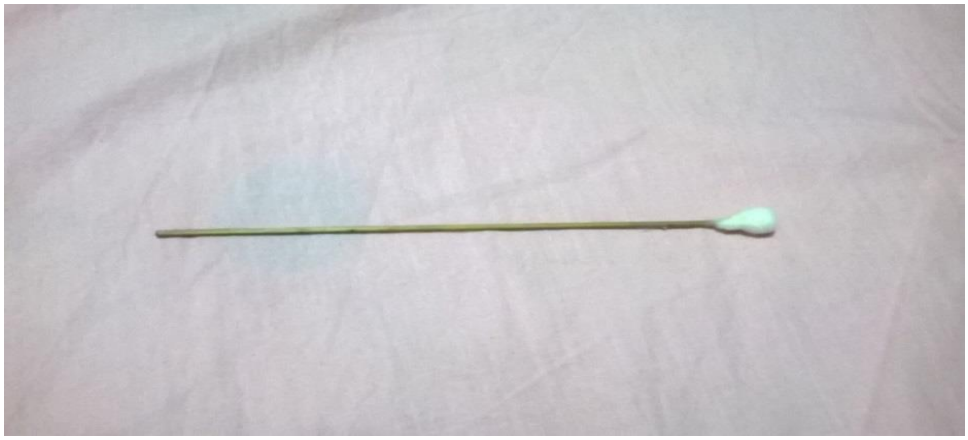

Fig. 1: Sterile cotton swab rolled on a thin wooden stick

Fig. 2: sterile cotton swabs in a sterile packet

Fig. 3: saliva extraction step 1

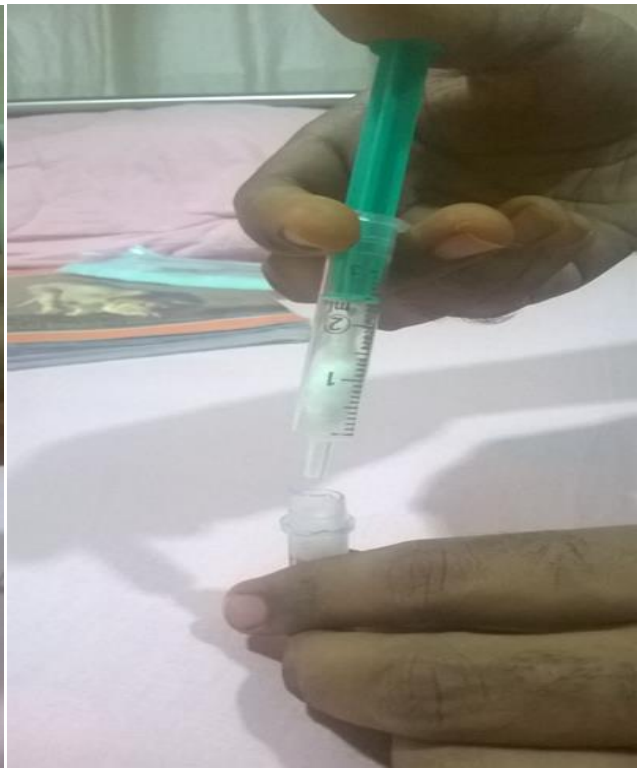

Fig 4: saliva extraction step 2

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- **Statistical Analysis:** The statistical analyses were carried out using SPSS for Windows (version 16.0, SPSS Inc, Chicago, IL, USA). To compare demographic traits, the mean, standard deviation, frequency, independent t-test for continuous data, and 2 test for categorical data were all employed. The differences in heart rate, oxygen saturation, and salivary cortisol % were assessed before the procedure, after it started, and three minutes afterwards. The Mann-Whitney U test was used to compare these numbers between the two groups. Cry length and NIPS Score were compared between the two groups using the Mann-Whitney U test. Based on NIPS scores, the samples were divided into two groups: less than 4 and greater than or equal to 4 because a score of 4 denotes clinically severe pain. The proportions of these values at 1 and 3 minutes following surgery were compared using the Fisher exact test.
- **Codes are revealed:** The principal chemist released the codes following the investigation and analysis.

✓ Code A = 10% Dextrose
✓ Code B = 24% Sucrose

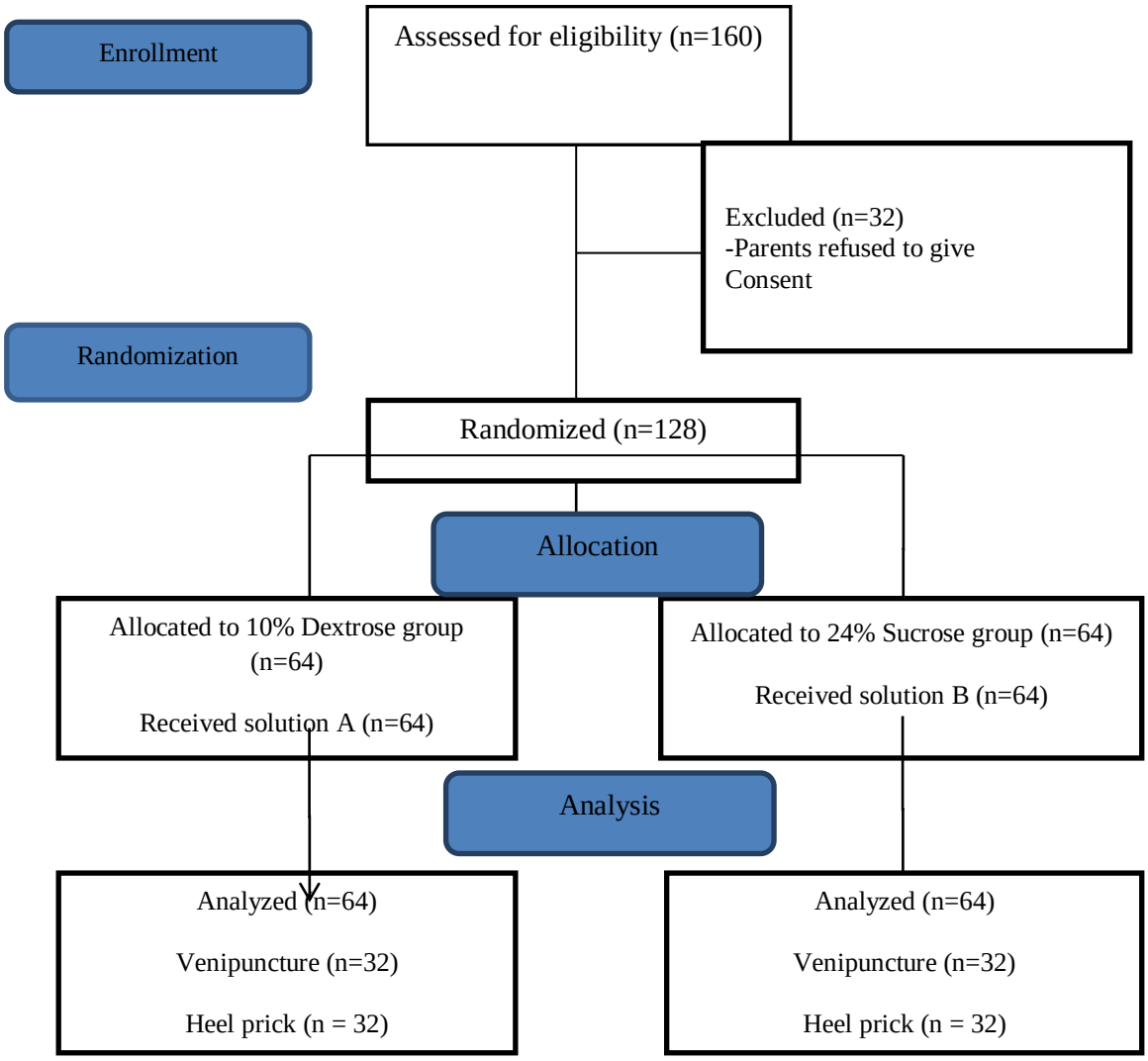

Fig. 5: Consort flow diagram

IV. RESULTS AND DISCUSSION

The results were interpreted between the experimental and control groups with the following parameters.

- Demographic characteristics
- Physiological parameters:

✓ Heart rate
✓ Oxygen saturation

- Biochemical parameters:

✓ Salivary cortisol

- Pain Assessment:

✓ NIPS score

- Crying behavior:

✓ Total cry time

There were 128 neonates randomly assigned, 64 to each group. All 128 neonates had their physiological measurements taken, including heart rate, oxygen saturation, total cry time, and pain assessment using the NIPS score. However, because there were insufficient samples, salivary cortisol was only examined in 78 neonates. The findings and discussion are listed below.

A. DEMOGRAPHIC CHARACTERISTICS

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	

Data are expressed as 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.

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

B. PHYSIOLOGICAL PARAMETERS

➢ *HEART RATE(HR) BEFORE AND DURING THE PROCEDURE:*

Table 2: Comparison of heart ratebefore and during the procedures between the groups

Procedure	Solution received	HR before procedureMean ± SD	HR at t=1minMean ± SD	*p value	HR att=3minMean ± SD	*p value
Heel lance (n=64)	10% Dextrose (n=32)	138 ± 14	142 ± 17	0.327	137 ± 19	0.626
	24% Sucrose (n=32)	140 ± 12	148 ± 16		138 ± 23	
Venipuncture (n=64)	10% Dextrose(n=32)	133 ± 13	146 ± 22	0.340	148 ± 26	0.155
	24% Sucrose(n=32)	133 ± 15	149 ± 18		139 ± 28	

*p value corresponds to Mann-Whitney U test Heart rate expressed as beats per minute.

- **Heel lance:** The mean heart rate rose in both groups one minute after the heel lance procedure, but it fell three minutes later. The heel lance's exceptionally quick-acting discomfort, which for most babies lasts between 30 and a minute, is the cause of this disparity. The heart rates were similar in both groups. The percentage differences between the heart rates prior to surgery and at 1 and 3 minutes following it were calculated using the Mann-Whitney U test. There were no statistically significant differences in heart rate between 24% sucrose and 10% dextrose for the heel lance procedure.

There were no discernible variations in heart rate between the sucrose group and the control group (sterile water or no treatment) in the trials conducted by Kyounget al. and Isik U et al.

Succrose considerably decreased heart rate as compared to the control group (sterile water) in numerous previous experiments conducted by Bucher HU et al.80, Ramenghi LA et al., and Ors R et al.

- **Venipuncture:** At one minute after the procedure, the mean heart rate in both groups increased during the venipuncture technique. However, the heart rate in the 24% sucrose group is lower after 3 minutes after the surgery, while it is higher in the 10% dextrose group. This discrepancy results from the pain, which lasts for two to three minutes. It is likely that sucrose reduced the pain and, as a result, the heart rate three minutes after the treatment. We used the Mann-Whitney U test to calculate the percentage differences between the heart rates before the procedure and at 1 and 3 minutes after it. According to statistics, there were no appreciable variations in heart rate

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during venipuncture between 24% sucrose and 10% dextrose.

In studies by Abad et al, Acharya et al, sucrose significantly reduced heart rate compared to control group.

➢ *OXYGEN SATURATION (SpO2) BEFORE AND DURING THE PROCEDURE:*

Table 3: Comparison of oxygen saturation before and during the procedures between the groups.

Procedure	Solution received	SpO2 before procedureMean ± SD	SpO2 at t=1minMean ± SD	* p value	SpO2 att=3 minMean ± SD	*P value
Heel lance(n=64)	10% Dextrose(n=32)	98.3 ± 2	95.4 ± 4.3	0.543	95.5±5.3	0.253
	24% Sucrose(n=32)	97.8± 2.3	95.6 ± 4.1		96.2±4.4	
Venipuncture(n=64)	10% Dextrose(n=32)	97.7± 2.2	93.0± 7.0	0.727	93.0±6.0	0.535
	24% Sucrose(n=32)	98.0 ± 1.8	94.0± 7.2		94.3±8.3	

*P value Mann-Whitney U test

- **Heel lance:** For heel lance, there were no appreciable changes in the means of oxygen saturation between 24% sucrose and 10% dextrose. We used the Mann-Whitney U test to calculate the percentage differences between the SpO2 levels prior to the surgery and at 1 and 3 minutes after it. In terms of SPO2 for the heel lance operation, there were no statistically significant changes between 24% sucrose and 10% dextrose.

There were no appreciable variations in SpO2 between the sucrose group and the control groups in the investigations by Overgaard C et al., Harrison D et al, Mathai S, and Okan F.

There was a considerable drop in SpO2 in the sucrose group compared to breast feeding group, according to a study by Codipeitro et al.11.

- **Venipuncture:** For venipuncture, there were no appreciable variations in oxygen saturation between 24% sucrose and 10% dextrose. We used the Mann-Whitney U test to calculate the percentage differences between the SpO2 levels prior to the surgery and at 1 and 3 minutes after it. Statistics revealed no significant variations in SpO2 during venipuncture between 24% sucrose and 10% dextrose.

There were no discernible variations in SpO2 between the sucrose and control groups in the research by Rush et al. (1992), Yilmaz F et al. (1993), and Ogawa S et al. (1994).

There are no studies that demonstrate appreciable variations in oxygen saturation between the sucrose group and the control group during venipuncture.

C. BIOCHEMICAL PARAMETERS

➢ *SALIVARY CORTISOL BEFORE AND AFTER THE PROCEDURE*

Table 4: 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 Mann-Whitney U test

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- **Heel lance:** There were no discernible differences between the salivary cortisol levels assessed before and after the heel lance operation using 24% sucrose and 10% dextrose. The percentage differences in salivary cortisol levels before and after the operation were calculated using the Mann-Whitney U test. For the heel lance method, there were no statistically significant differences in salivary cortisol levels between 24% sucrose and 10% dextrose.

In two studies by Kyoung et al.56 and Greenberg et al.95, there were no observable differences between the two groups.

Studies that evaluated the salivary cortisol levels between the sucrose group and the control group using 10% dextrose for the heel lance found no discernible differences.

Salivary cortisol levels before and after venipuncture in the presence of 24% sucrose and 10% dextrose did not differ substantially. The percentage differences in salivary cortisol levels before and after the operation were calculated using the Mann-Whitney U test. There were no statistically significant differences between 24% sucrose and 10% dextrose in terms of SPO2 for the heel lance procedure. Salivary cortisol levels during venipuncture have not been studied.

D. PAIN ASSESSMENT

➢ *NIPS SCORES BEFORE AND DURING THE PROCEDURES*

Table 5: Comparison of NIPS score at 1 min and 3 min after procedure between the groups

Procedure	**Solution received**	**NIPS at t=1 min Median(Q1,Q3)**	***p value**	**NIPS at t=3min Median(Q1,Q3)**	***p value**
Heel lance(n=64)	10% Dextrose (n=32)	7(3,7)	0.814	0(0,3.7)	0.059
	24% Sucrose (n=32)	7(2,7)		0(0,0)	
Venipuncture (n=64)	10% Dextrose (n=32)	7(5,7)	0.102	6(0,7)	0.190
	24% Sucrose (n=32)	7(2,7)		1(0,7)	

*p value corresponds to Mann – Whitney U test

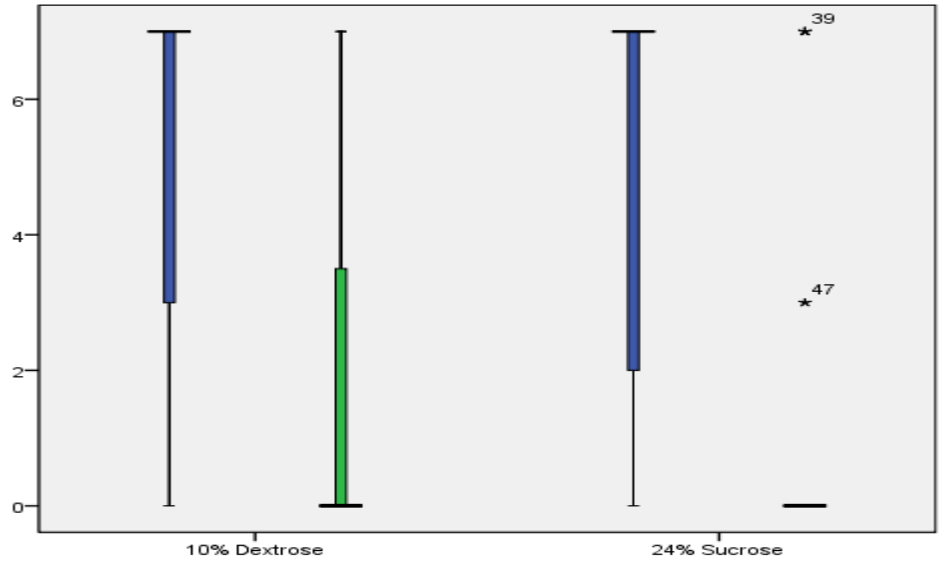

Fig. 6: Box plot showing Median NIPS scores at 1 min and at 3 min for Heel lance. The line inside the box represents the median NIPS score and the colored area represents the inter quartile range

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X axis: Solution received ; Y axis: NIPS score, Procedure: Heel lance

Blue: NIPS score at 3 minutes post procedure
Green:NIPS score at 3 minutes post procedure

- **Heel lance:** The 24% sucrose and 10% dextrose groups did not significantly vary in NIPS scores at 1 or 3 minutes.

There was a substantial decline in NIPS scores for the sucrose group in studies by Kyong et al.16, Overgaard et al.27, and Yilmaz et al.33 as compared to the control group.

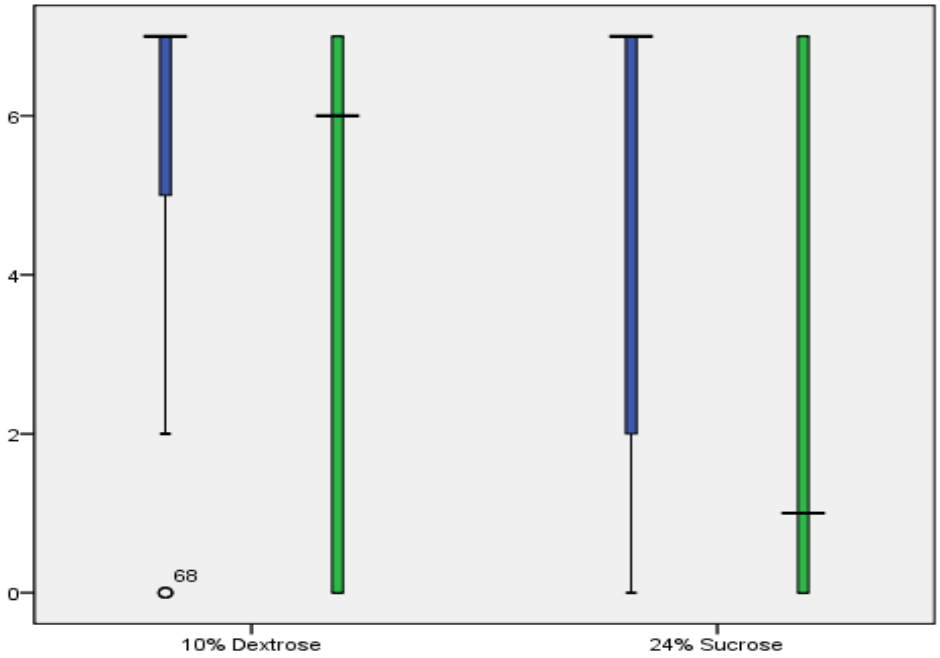

Fig. 7: Box plot showing Median NIPS scores at 1 min and at 3 min for venipuncture. The line inside the box represents the median NIPS score and the colored area represents the inter quartile range

X axis: Solution received ; Y axis: NIPS score, Procedure: Heel lance

Blue: NIPS score at 3 minutes post procedure

Green:NIPS score at 3 minutes post procedure

- **Venipuncture:** While the median NIPS scores at 1 and 3 minutes were similar for both groups, the median NIPS score at 3 minutes for the 10% dextrose group was 6 and the median NIPS score for the 24% sucrose group was 1. This shows that 3 minutes after the surgery, 24% sucrose is effective in reducing discomfort. The groups did not, however, vary statistically significantly. No studies employing the NIPS score for venipuncture have been published.

Table 6: Comparison between the 10% Dextrose and 24% Sucrose groups for the number of newborns with an NIPS score of 4 at 1 minute and 3 minutes following the procedure.

	NIPS score<4 at t=1min			**NIPS score<4 at t=3min**		
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 Fischer Exact test.

At 1 and 3 minutes into the procedure, there were more infants who received sucrose and received an NIPS score of 4 than there were when 10% dextrose was utilised. Therefore, 24% sucrose has a better analgesic impact than 10% dextrose. However, when the Fischer exact test was employed to compare the groups, there were no statistically significant differences between 24% sucrose and 10% dextrose.

E. CRYING BEHAVIOR

➢ *TOTAL CRY TIME DURING THE PROCEDURE:*

Table 7: Comparison of Total cry time during procedure between 10% Dextrose and 24% Sucrose groups

Procedure	Total Cry Time during procedure (in seconds)		*p value
	10% Dextrose (n=64) Median(Q1Q3)	24% Sucrose (n=64) Median(Q1Q3)	
Heel lance(n=64)	37.5(2.7,63.7)	10(0,54)	0.16
Venipuncture (n=64)	130(18.7,180)	22.5(0,180)	0.11

*p value corresponds to Mann-Whitney U test.

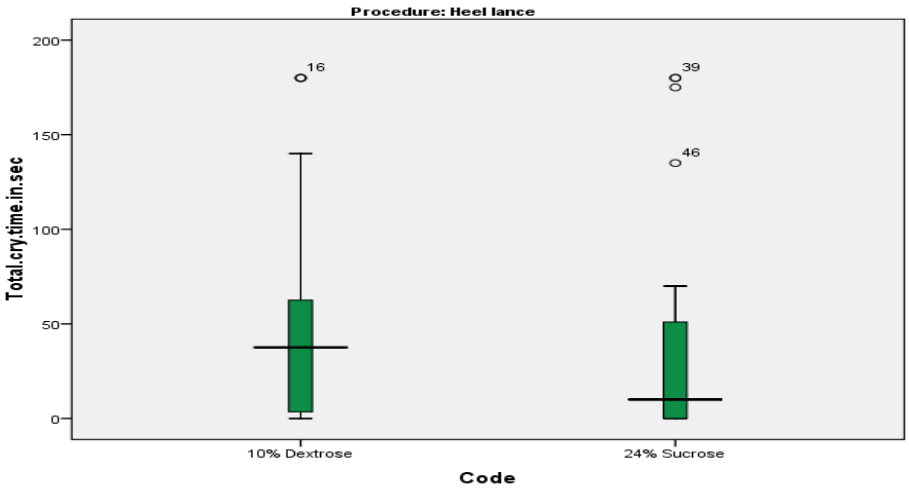

Fig. 8: Box plot showing Median Total cry time for both the groups for heel lance procedure

- **Heel lance:** When compared to the dextrose group, the sucrose group's total cry time was much lower (median 10 sec). However, statistically speaking, there was no change.

Researchers Kyoung et al.16, Isik U et al.19, Bucher HU et al.80, Ramenghi LA et al.11, and Ors R et al.12 found that sucrose reduced the amount of time babies spent crying overall compared to the control group. In other investigations by Harrison et al.88, Mathai et al.29, and Ogawa et al.34, the sucrose group's cry time was not significantly shorter than that of the control group.

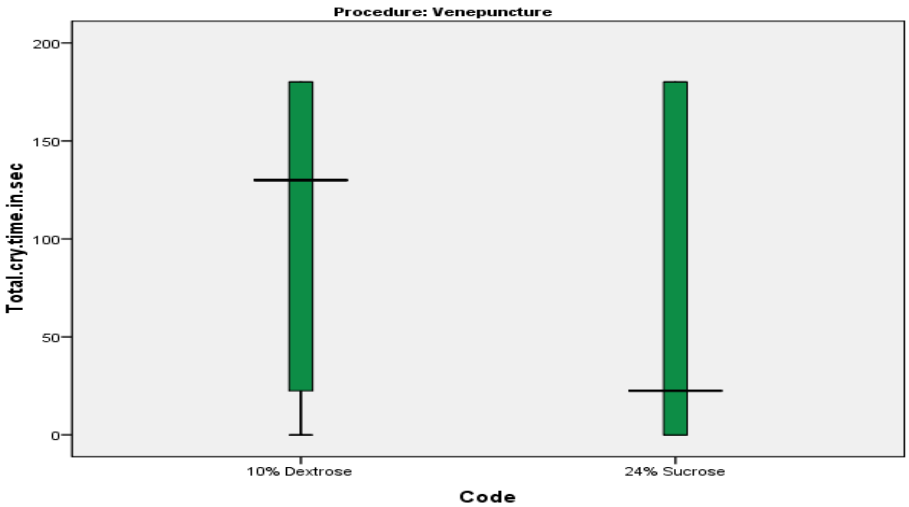

Fig. 9: Box plot showing Median Total cry time for both the groups for venipuncture procedure

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- **Venipuncture:** When compared to the dextrose group (median 130 sec), the sucrose group's total cry time was significantly lower (22.5 sec on average). However, statistically speaking, there was no change.

In investigations by Acharya et al.26 and Abad et al.25, sucrose decreased the amount of sobbing. In a study by Ogawa et al. (1994), the sucrose group's cry time was not significantly shorter than that of the control groups.

V. CONCLUSION

- When it came to reducing neonates' procedural discomfort, there were no discernible differences between the 24% sucrose and 10% dextrose treatments, according to the following criteria.
- Included are heart rate, SpO2, total cry time, NIPS score, and salivary cortisol.
- For both procedures, the median total cry duration was shorter in the 24% sucrose group compared to the 10% dextrose group (10 seconds for heel lancing and 22.5 seconds for venipuncture, respectively).
- Compared to 10% dextrose, which only marginally (NIPS4) decreased pain in 37.5% of infants at 1 minute and 87.5% of neonates at 3 minutes for heel lance, 24% sucrose markedly (NIPS4) decreased pain in these neonates.
- Neonates' pain was greatly reduced by 24% sucrose (NIPS4) compared to 10% dextrose, which had only a minor (15.6%) and significant (43.8%) pain reduction for venipuncture in 37.5% newborns at 1 min and 65.6% neonates at 3 min.
- As a result, we may conclude that in clinical praxis, 24% sucrose performs better than 10% dextrose as an analgesic for procedural pain in term babies.
- Salivary cortisol can be used to quantify neonatal stress non-invasively, and the method used in this investigation to collect saliva resulted in an adequate number of samples that were equivalent to those from other studies.

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