RESEARCH PAPER

Oral Sucrose for Pain in Neonates During Echocardiography: *A Randomized Controlled Trial*

NIRAV T POTANA, ASHISH R DONGARA, SOMASHEKHAR M NIMBALKAR, DIPEN V PATEL, *ARCHANA S NIMBALKAR AND #AJAY PHATAK

*From Departments of Pediatrics and *Physiology, Pramukhswami Medical College; and #Central Research Services, Charutar Arogya Mandal; Karamsad, Gujarat, India.*

Correspondence to: Prof Somashekhar Nimbalkar, Professor of Pediatrics, Department of Pediatrics, Pramukhswami Medical College, Karamsad-Anand, Gujarat 388 325. somu_somu@yahoo.com

Received: June 30, 2014; Initial review: September 01, 2014; Accepted: March 12, 2015.

Objectives: To test the efficacy of oral sucrose in reducing pain/stress during echocardiography as estimated by Premature Infant Pain Profile score.

Design: Double-blind, parallel-group, randomized control trial.

Setting: Tertiary-care neonatal care unit located in Western India.

Participants: Neonates with established enteral feeding, not on any respiratory support and with gestational age between 32 and 42 weeks requiring echocardiography.

Interventions: Neonates in intervention group received oral sucrose prior to echocardiography.

Main outcome measures: Assessment was done using Premature Infant Pain Profile score.

Results: There were 104 examinations; 52 in each group. Baseline characteristics like mean gestational age (37.6 *vs*. 37.1), birth weight (2.20 *vs*. 2.08), and feeding status (Breastfeeding- 59.6% *vs*. 44.2%, paladai feeding- 13.5% *vs*. 13.5%, and gavage feeding- 26.9% *vs*. 42.3%) were comparable. The mean (SD) premature infant pain profile score was significantly higher in control group [(7.4 (3.78) *vs*. 5.2 (1.92), *P* <0.001].

Conclusion: Oral sucrose significantly reduces pain, and is safe to administer to neonates.

Keywords: *Echocardiography, Pain, Sucrose*.

Inadequately managed pain in the neonatal period can have multiple adverse effects [1,2]. Pharmacological agents, due to their side-effects, are usually reserved for procedures causing severe pain [3]. These interventions are not suited for mild or moderate painful interventions. These factors possibly prevent health care providers from addressing pain/stress while performing such procedures. Another barrier for treating pain could be insensitivity/lack of knowledge regarding minor procedural pain and its effects [4]. Non-pharmacological methods have also been shown to be effective for treating and preventing mild to moderate procedural pain [5-11].

Functional echocardiography has, over the years, become a part of routine Neonatal intensive care unit (NICU) care [12]. Due to some controversy regarding the categorization of painful procedures, many guidelines even fail to recognize echocardiography as a painful procedure [13,14]. Various available non-pharmacological methods (swaddling, Kangaroo mother care, breast feeding etc.) might not be feasible during echocardiography. Hence we considered using oral sucrose for reducing pain during echocardiography. The factors favoring its use were feasibility, rapid onset of action, adequate duration of action and low incidence of adverse effects [8,15]. Our objective was to determine the effectiveness of sucrose in decreasing pain/discomfort caused by echocardiography.

METHODS

This double blinded, prospective, parallel group randomized controlled trial was carried out from August 2013 to November 2013, at a level III NICU in Gujarat, India. Written informed consent was obtained from the child's parent/legal guardian. The study was approved by the institutional Human Research Ethics Committee. Neonates on tube feeding, spoon feeding, or breast feeding with gestational age between 32-42 weeks, who were admitted in the NICU/Neonatal intermediate care unit (NIMC)/Neonatal ward, not on any type of respiratory support and subjected to echocardiography were included. Neonates who were nil by mouth, having poor neurological status, and those who were paralyzed or sedated with pharmacological agents were excluded.

Based on pilot data of 15 patients (not included in the study) it was found that the standard deviation (SD) of PIPP was 3.7. Taking SD as 3.7 and clinically significant difference as 2 on the PIPP score and considering 5%

level of significance with a power of 80%, a sample size of 50 in each condition was required, Considering a 5% drop out rate the estimated sample size was 52. Balanced randomization of the participant neonates was done into the two groups using GraphPad software. Sealed opaque envelopes containing the randomization code were opened just before the procedure by the person who was responsible for giving oral sucrose and recording videos.

Newborns in the Intervention group received oral sucrose (Arbineo 24% w/v oral solution, dose: 1mL for 32-40 weeks, 2mL for >40 weeks) 2 minutes prior to echocardiography by a dropper, whereas newborns in the control group did not receive any medication/placebo. Investigators performing echocardiography were unaware of the status of the neonate. Echocardiography involved all regular views done during targeted neonatal echocardiography and did not involve removal of electrodes from the chest in any neonate. Echocardiography in the present study was conducted by neonatal fellows, trained in targeted neonatal echocardiography. During echocardiography, saturation of oxygen (SPO_2) and pulse rate monitoring was done using Philips IntelliVue MP 20 monitor, and video recording was performed using smart phones (Micromax A110Q, Sony Xperia SP-C5302 and Samsung Galaxy SIII). The videos were then transferred to a hard disc and erased from the recording instrument. The investigators performing the video analysis were blinded to the group allocation. Baseline recording of behavioral state, heart rate and SPO_2 was done for 15 seconds prior to initiating echocardiography in both the groups. Gestational age was calculated using Naegel's formula.

Premature infant pain profile (PIPP) scale was used for assessment of pain during echocardiography [16]. PIPP has good inter-rater reliability and can also be applied for term neonates [17]. No specific PIPP scores were done for different views. The lowest reading of SPO_2, highest reading for heart rate and the maximum facial expression irrespective of time, during the procedure of echocardiography were utilized for scoring. Video analysis was done by three experienced researchers in a group, and PIPP scores were assigned to the videos after reaching a consensus. Monitoring of the neonate was done for one hour after the administration of sucrose to look for regurgitation or other side effects. Blood sugar was done after one hour to determine hyperglycemia. A week later, a follow up interview of the caretakers was done to determine if any complications like necrotizing enterocolitis (NEC), feed intolerance etc. had occurred.

Statistical analysis: Data was entered into Microsoft Excel. Analysis of the data was performed using SPSS 14.0. Independent sample *t*-test and descriptive statistics were used for analysis. Bonferroni's correction was applied to determine the significance of various domains of PIPP score. There are seven domains in the PIPP score and the significance value was redefined by dividing the conventional *P* value of 0.05 by 7. Thus a *P* value < 0.007 was considered statistically significant.

RESULTS

A total of 104 echocardiography examinations of 76 neonates were included in the study (52 examinations in each group) (***Fig.* 1**). The baseline characteristics of both the groups were comparable (***Table* I**). The mean (SD) time for which echocardiography was performed in the intervention group was 6.1 (3.05) minutes, and for the control group was 4.9 (2.18) minutes. (*P*=0.024).

The mean (SD) PIPP score of intervention group was 5.2 (1.92) as compared to 7.4 (3.78) in control group (***Fig.* 2**). The mean difference in the PIPP score of both the groups was 2.15 (*P*<0.001) (***Table* II**). Thirty (57.7%) of the neonates belonging to the control group experienced pain while doing echocardiography (PIPP score ≥7). Of these neonates, 24 (46.1%) experienced mild-moderate pain (PIPP score = 7-12), while others

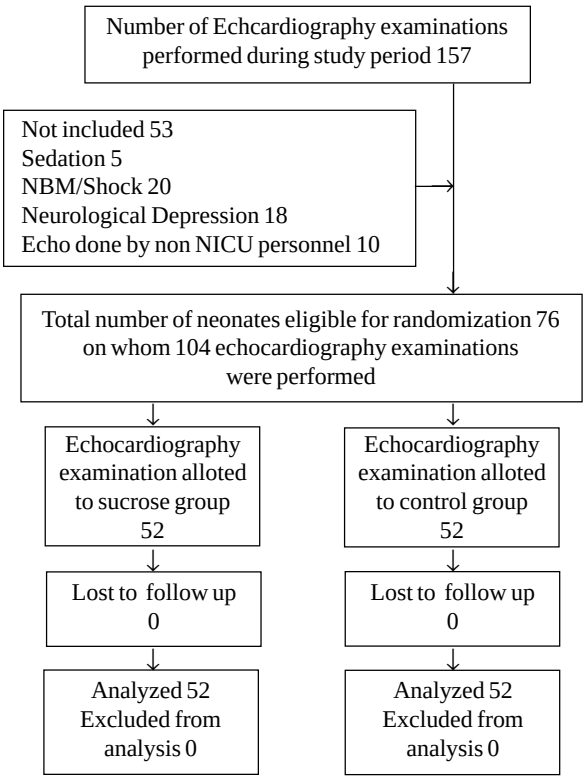

FIG. 1 *Participant CONSORT flow diagram.*

TABLE I COMPARISON OF BASAL CHARACTERISTICS OF THE GROUPS

Characteristics	*Intervention group (n = 52)*	*Control group (n = 52)*
Gest. age, Mean (SD), wk	37.1 (2.3)	37.6 (2.4)
B. weight, Mean (SD), kg	2.1 (0.7)	2.2 (0.6)
SGA	36 (69.2%)	34 (65.4 %)
AGA	16 (30.7%)	18 (34.6 %)
Male gender	30 (57.6%)	26 (50 %)
Feeding characteristics		
BF	23 (44.2%)	31 (59.6 %)
KS Feed	7 (13.4%)	7 (13.4 %)
RT Feed	22 (42.3%)	14 (26.9 %)
SpO_2, Mean (SD)	96.3 (2.9)	97.2 (2.9)
Heart rate, Mean (SD)	147 (21)	138 (19)

SGA – small for gestational age, AGA – appropriate for gestational age, BF – breastfeeding, KS – katori spoon feeding, RT – ryle's tube.

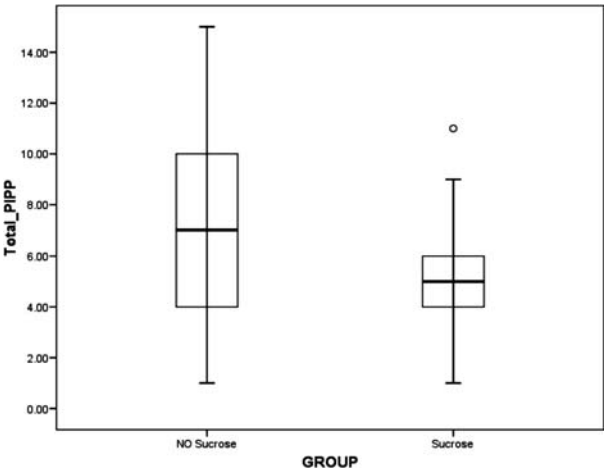

FIG. 2 *Box plot showing mean PIPP score of both the groups.*

experienced severe pain (PIPP score >12). In the intervention (sucrose) group, 42 (80.8%) neonates experienced no pain as indicated by a PIPP score <7, 10 (19.2%) neonates experienced mild-moderate pain (PIPP score = 7-12). No neonate in the sucrose experienced severe pain (PIPP score >12). Four (7.6%) neonates spitted the sucrose solution after administration. No episode of hyperglycemia, necrotizing enterocolitis, or feed intolerance was reported after sucrose administration.

DISCUSSION

A total of 52 echocardiography examinations in each group were included in the study. Both of the study limbs were comparable in terms of their demographic profile. Mean (SD) PIPP score of intervention group was 5.25 (1.92) as compared to 7.40 (3.78) in control group. Forty six percent neonates experienced mild-moderate pain, and 12% neonates experienced severe pain in control group, while in intervention (sucrose) group, nineteen percent neonates experienced mild-moderate pain with no neonate experiencing severe pain.

TABLE II DETAILS OF THE PIPP SCORE OF THE GROUPS

	Intervention (Sucrose) Group (n=52)	*Control (No sucrose) Group (n=52)*
Baseline parameters	1.9 (1.10)	1.61 (1.08)
Change in Heart rate	1.2 (1.02)	1.57 (1.09)
Change in SPO_2	1.09 (1.20)	1.48 (1.33)
*Duration of Brow bulge	0.23 (0.43)	0.81 (0.92)
*Duration of Eye squeeze	0.23 (0.43)	0.84 (0.91)
*Duration of Naso-labial furrow	0.23 (0.43)	0.81 (0.93)
*PIPP score	5.25 (1.92)	7.40 (3.78)

**P <0.001*

The present study included neonates with established enteral feeding, and many neonates on respiratory support, having critical CHD or profound shock were excluded. Hence majority of neonates who needed frequent and longer echocardiography were excluded. Another aspect to be considered is the duration of action of sucrose, which varies from 2 to 5 minutes, extending unto 45 minutes [15]. This duration of action may sometimes be shorter than the duration of echocardiography, necessitating repeat dosing of sucrose. In the present study, no repeat dosing was given, as the personnel performing echocardiography were blinded and duration of echocardiography was short. Oral placebo was not utilized in the present study. Difference in the intervention time can have its independent influence on the PIPP score, but in spite of longer echocardiography time in intervention group they had lower PIPP scores, thereby showing effectiveness of oral sucrose.

In present study, we included neonates with gestational age of 32-42 weeks because in a study by Johnston, *et al.* [18,19], it was reported that preterm infants <31 weeks who had received >10 doses of sucrose per day in the first week of life had poor neurologic outcome. As shown in previous Cochrane analyses, there are wide variations in the inclusion criteria of various studies [6,8]. Probable cause for this difference in spectrum of patients enrolled might be the different clinical practices and socio-economic scenario world over.

WHAT IS ALREADY KNOWN?

- Pain is caused by various procedures that the neonates are subjected to in the neonatal intensive care unit.

WHAT THIS STUDY ADDS?

- Echocardiography is stressful and can cause moderate pain.
- This pain can be effectively reduced by oral sucrose two minutes prior to the procedure.

It is evident that sucrose is effective in lowering mean PIPP score and the behavioral components of the PIPP score but has no/little effect on the physiological components of the PIPP scale (heart rate and SpO2 variability). A study by Slater, *et al*. [20] showed no significant effect of sucrose administered orally in reducing brain activity specific to pain, identified by EEG, in spite of significant change in PIPP score. These observations indicate that measuring pain is a complex process, and measuring only parts of the PIPP score may often be misleading and the whole score in total should be interpreted [21]. The present study also provides indirect evidence, as to why a scale which combines both the physiological and behavioral parameters should be used and not a scale which focuses only on one aspect, as there was no statistically and clinically significant difference in the mean change in heart rate and SPO_2 during echocardiography between both the groups, but there was significant change in behavioral parameters. There was a clinically and statistically significant difference in PIPP score in intervention group 5.25 (1.92) *vs.* control group 7.4 (3.78), $P<0.001$. This was significant even after Bonferroni's correction. This finding is similar to other studies [8, 22].

We found no significant side effects of oral sucrose administration in the intervention group. No hyperglycemia, necrotizing enterocolitis, or feeding intolerance was noted. The incidence of spitting/ regurgitation of sucrose were similar to those noted by other studies [8].

Seemingly harmless procedures like echocardiography also produce pain in neonates. Majority of neonates in the control group experienced pain while performing echocardiography. This pain was of mild to moderate nature, with some neonates even experiencing severe pain. Oral sucrose effectively addressed this pain with almost 80% of the neonates in the intervention (sucrose) group experienced no pain during echocardiography. Thereby we can conclude that oral sucrose is effective in addressing moderate-severe pain during echocardiography. No major adverse effects were found during or after administration of oral sucrose.

Contributors: NP: designed the study, collected the data, wrote the paper, and approved the final manuscript; AD: collected the data, wrote the paper, and approved the final manuscript; SN: conceived the study, designed the study, gave critical inputs to the paper, and approved the final manuscript: DP: analyzed the data, drafted the paper, and approved the final manuscript: AN: conceived the study, analyzed the study and revised it critically for important intellectual content and script and approved the final manuscript; AP: analyzed and interpreted the data and wrote the paper and approved the final manuscript; SN: will be the guarantor for the paper.

Funding: None; *Competing interest*: None stated.

REFERENCES

1. Taddio A, Shah V, Gilbert-MacLeod C, Katz J. Conditioning and hyperalgesia in new-borns exposed to repeated heel lances. JAMA. 2002;288:857-61.
2. Grunau RE. Neonatal pain in very preterm infants: long-term effects on brain, neurodevelopment and pain reactivity. Rambam Maimonides Med J. 2013;4:e0025.
3. Walter-Nicolet E, Annequin D, Biran V, Mitanchez D, Tourniaire B. Pain management in newborns: from prevention to treatment. Paediatr Drugs. 2010;12:353-65.
4. Nimbalkar AS, Dongara AR, Ganjiwale JD, Nimbalkar SM. Pain in children: knowledge and perceptions of the nursing staff at a rural tertiary care teaching hospital in India. Indian J Pediatr. 2013;80:470-5.
5. Ou-Yang MC, Chen IL, Chen CC, Chung MY, Chen FS, Huang HC. Expressed breast milk for procedural pain in preterm neonates: a randomized, double-blind, placebo-controlled trial. Acta Paediatr. 2013;102:15-21.
6. Shah PS, Herbozo C, Aliwalas LL, Shah VS. Breastfeeding or breast milk for procedural pain in neonates. Cochrane Database Syst Rev. 2012;12:CD004950.
7. Nimbalkar S, Sinojia A, and Dongara A. Reduction of neonatal pain following administration of 25% lingual dextrose: a randomized control trial. J Trop Pediatr. 2013;59:223-5.
8. Stevens B, Yamada J, Lee GY, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database Syst Rev. 2013;1: CD001069.
9. Nimbalkar SM, Chaudhary NS, Gadhavi KV, Phatak AG. Kangaroo Mother Care in reducing pain in preterm neonates on heel prick. Indian J Pediatr. 2013;80:6-10.
10. Hartling L, Shaik MS, Tjosvold L, Leicht R, Liang Y, Kumar M. Music for medical indications in the neonatal period: a systematic review of randomized controlled trials.

Arch Dis Child Fetal Neonatal Ed. 2009;94:349-54.
11. Pillai Riddell RR, Racine NM, Turcotte K, Uman LS, Horton RE, Din Osmun L, *et al*. Non-pharmacological management of infant and young child procedural pain. Cochrane Database Syst Rev. 2011;10:CD006275.
12. Jain A, McNamara PJ, Ng E, El-Khuffash A. The use of targeted neonatal echocardiography to confirm placement of peripherally inserted central catheters in neonates. Am J Perinatol. 2012;29:101-6.
13. Cignacco E, Hamers JP, Stoffel L, van Lingen RA, Schütz N, Müller R, et al. Routine procedures in NICUs: factors influencing pain assessment and ranking by pain intensity. Swiss Med Wkly. 2008 Aug 23;138(33-34):484-91.
14. Vani SN, Thakre R, Nimbalkar S. Assessment and management of pain in the newborn. NNF Clinical Practice Guidelines. 2010:199-215.
15. Taddio A, Shah V, Katz J. Reduced infant response to a routine care procedure after sucrose analgesia. Pediatrics. 2009;123:425-9.
16. Stevens B, Johnston C, Petryshen P, Taddio A. Premature Infant Pain Profile: development and initial validation. Clin J Pain. 1996;12:13-22.
17. Ballantyne M1, Stevens B, McAllister M, Dionne K, Jack A. Validation of the premature infant pain profile in the clinical setting. Clin J Pain. 1999;15:297-303.
18. Johnston CC, Filion F, Snider L, Limperopoulos C, Majnemer A, Pelausa E, *et al*. How much sucrose is too much sucrose? Pediatrics. 2007;119:226.
19. Johnston CC, Filion F, Snider L, Majnemer A, Limperopoulos C, Walker CD, *et al*. Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks' postconceptional age. Pediatrics. 2002;110:523-8
20. Slater R, Cornelissen L, Fabrizi L, Patten D, Yoxen J, Worley A, *et al*. Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial. Lancet. 2010;376:1225-32.
21. Stevens B, Johnston C, Taddio A, Gibbins S, Yamada J. The premature infant pain profile: evaluation 13 years after development. Clin J Pain. 2010;26:813-30.
22. Harrison D, Beggs S, Stevens B. Sucrose for procedural pain management in infants. Pediatrics. 2012;130:918-25.