IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

Open Access
Original Article

Comparison of Breast Milk and Sucrose in Neonatal Pain Relief and Coping with Stress of ROP Examination Using ALPS-Neo

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ABSTRACT

Background: Examination for retinopathy of prematurity (ROP) is one of the procedures that can be stressful for neonates admitted to a neonatal intensive care unit. This study compared breast milk and sucrose in pain relief and coping with the stress of ROP examination using the Astrid Lindgren and Lund Children's Hospital Pain and Stress Assessment Scale for Preterm and Sick Newborn Infants (ALPS-Neo).

Methods: The present study was carried out on a total of 63 preterm infants (including breast milk group [n=21], sucrose group [n=21], and distilled water group [n=21]). The neonates were given 0.5 ml/kg of breast milk, sucrose, or distilled water 2 min before the examination. The ROP eye examinations were video recorded from 5 min before to 15 min after the examination, and infants' pain and stress levels were assessed using the ALPS-Neo by two blinded evaluators 5 min before, during, and 5, 10, and 15 min after the examination.

Results: No statistically significant differences were observed during the examinations in the mean scores of the ALPS-Neo among the three groups ($P>0.05$). However, there were statistically significant differences among the three groups after the examinations ($P<0.05$) and in the mean duration of stress adaptation ($P<0.05$). The duration of stress adaptation in the breast milk group was 11.4 min on average which was lower than that reported for the other groups.

Conclusion: Breast milk was more effective in the reduction of pain and stress after ROP examinations, compared to sucrose or distilled water.

Keywords: Breast milk, Pain, Premature neonate, Retinopathy of prematurity, Sucrose

Introduction

Advances in medical care for preterm neonates have improved survival rates (1). However, the central nervous system has been designed to develop in the protected intrauterine environment for 40 weeks. Moreover, the development is disrupted in preterm infants and affected by developmentally unexpected stimuli, such as pain (2). Pain is an unpleasant perception and experience which is caused by an actual or potential injury (3, 4). Pain control is considered an important part of neonatal intensive care unit (NICU) care. Indeed, the International Association for the Study of Pain has defined the term pain as the fifth vital sign aiming to emphasize its importance and raise the awareness of health care team members regarding pain control (4, 5).

Repeated invasive procedures routinely occur in neonates who are hospitalized in NICUs, causing pain at a time when it is developmentally unexpected (6). Untreated pain has many negative effects on neonates (7). These negative effects include decreased oxygenation, hemodynamic

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Please cite this paper as:
Mirlashari J, Holsti L, Begjani J, Roohipoor R, Kasaeian A, Safaiee Fakhr A. Comparison of Breast Milk and Sucrose in Neonatal Pain Relief and Coping with Stress of ROP Examination Using ALPS-Neo. Iranian Journal of Neonatology. 2021 Apr: 12(2). DOI: 10.22038/ijn.2021.49621.1866

instability, and increased intracranial pressure during each painful procedure. Due to the types of procedures these infants should undergo to save their lives, pain is one of the main causes of stress in neonates. For these reasons, both pain and stress need to be evaluated and treated effectively (8).

The ability of neonates to self-regulate and adapt to stressors is very important (9). Premature infants try to cope with stress and pain using self-regulatory techniques, such as hand-to-mouth, change in position, grasping, sucking, and hand clasping (10). Limiting the duration of pain-induced stress adaptation in infants is important for the promotion of optimal neurodevelopment and function of the neonatal brain (11).

With early birth comes an increased risk for chronic lung diseases, intraventricular hemorrhage, and retinopathy of prematurity (ROP) (12). The ROP is one of the causes of vision loss in childhood and a condition that can be prevented by appropriate screening (13). However, one of the stressful procedures performed on preterm infants is ROP examination. The American Academy of Pediatrics, American Academy of Ophthalmology, and American Association of Pediatric Ophthalmology and Strabismus have issued a joint statement on the importance of routine ROP examinations for premature neonates with a birth weight of < 1,500 g or gestational age of 32 weeks or less (14). The examination procedure involves the fixation of the head and opening of the eyelid, often using an eye speculum and a light beam. Despite its importance for the diagnosis of visual deficits, ROP examination is associated with pain, discomfort, and stress for infants (14). Therefore, finding safe and effective methods to reduce the pain and stress of this procedure in premature neonates is very important (13).

Different pharmacological and nonpharmacological methods are used to control pain in preterm infants during painful invasive procedures. The use of medications for pain management is necessary for highly invasive events, such as surgery; however, due to the short- and long-term side effects of the medications, they are not typically used for shorter procedures, such as eye examinations (15, 16). As alternatives to medications, nonpharmacological pain management techniques, especially for mild to moderate pain, are safe and important interventions used in NICUs. Swaddling, kangaroo care, breastfeeding, massage, and pacifier use with or without sucrose are examples of nonpharmacological pain management methods (17).

Sucrose is a sweet disaccharide (glucose-fructose), that in animal models, releases endorphins and alleviates pain by influencing the taste receptor at the tip of the tongue (18). Breast milk is also a natural and safe pain mitigator containing high concentrations of tryptophan. Tryptophan is a precursor to melatonin which increases the concentration of endorphins, thereby relieving pain (19). Various studies have been published showing inconsistent results comparing the effectiveness of breast milk and sucrose. In addition, most of the studies did not include measures for coping with neonatal stress. For example, Taplak and Erdem (2017) compared the effectiveness of breast milk and sucrose in relieving pain during ROP examination in preterm infants in a double-blind randomized controlled trial. They observed that neonates in the breast milk group recovered and returned to their initial values more quickly after ROP examination than the infants in the sucrose group (14).

In another study, Benzer et al. (2017) evaluated sucrose treatment for ROP examination in preterm neonates and observed that sucrose was effective in pain reduction during ROP examination (20). Rosali et al. (2014) studied the impact of breast milk on relieving pain during ROP examination and observed that breast milk significantly reduced pain during and after ROP examinations (21). Ribeiro et al. (2013) studied the effect of human milk on neonatal pain relief during ophthalmoscopy in a pilot study with a quasi-experimental design and concluded no differences between sucrose and breast milk either during or after the eye examination (22).

Given varied results regarding the effectiveness of sucrose and breast milk in relieving pain during painful procedures (3, 14, 23, 24), a field study was conducted by a research team in an ROP unit in an ophthalmology hospital which is an advanced referral hospital in Iran. Currently, there is no specific protocol for controlling pain in ROP examination in most NICUs in Iran, and existing pain relief methods are implemented according to the routine of each hospital and based on physicians' opinions. In the majority of cases, 0.5% tetracaine drops are used to control pain during ROP examinations appearing to have a small treatment effect on pain during ROP examination. It is recommended to use other pain control methods, along with ophthalmic anesthetics (25, 26). Therefore, given the importance of finding effective pain management strategies for use during ROP

examinations, the aim of this study was to compare the use of sucrose and breast milk during ROP examinations in preterm neonates for pain and more broadly stress management.

Methods

Research setting

This double-blind randomized controlled clinical trial was conducted within June to September 2018. The study was registered in the Iranian Registry of Clinical Trials (IRCT201807 18040523N1). The study population consisted of preterm infants admitted to the ROP unit in an ophthalmology hospital in Iran. The inclusion criteria were preterm neonates with a gestational age of ≤ 32 weeks and birth weight of ≤ 2,000 g (27). The exclusion criterion was the neonatal need for cardiopulmonary resuscitation during ROP examinations.

Sample size

The study included 63 preterm neonates assigned to the breast milk group (n=21), sucrose group (n=21), and distilled water group (n=21) after meeting the inclusion criteria. The sample size was estimated using Power Analysis and Sample Size (PASS) software (version 13) and statistical data of a study by Taplak et al. (14). This study also supported an estimated standard deviation of 2.54, yielding a target sample size of 21 subjects per group. A confidence interval of 95% with a power of 90% was used to detect significant differences among the three groups.

Study design

After obtaining the approval of the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran, the research method and objectives and process of video recordings were explained to the ophthalmologist, head nurse, nurses, and parents in the research setting. One of the unit nurses assisted during the procedure as a volunteer. On the days of the ROP examination, the researcher was present in the unit, chose the neonates who were eligible for inclusion, and explained the procedure and goals of the study to the parents. Then, the parents completed the informed consent form and the neonatal demographic information form was also completed by the researcher (Table 1).

A total of 0.5 ml/kg of breast milk was provided by the mother in a syringe. All of the mothers had recently given birth and they had enough milk to be included in the study. Randomization was performed using closed letters. Accordingly, one of the letters was randomly selected and the infants were assigned to one of the three groups, namely breast milk, sucrose, or distilled water. The neonates were randomized just before ROP examination.

In accordance with the hospital routine, for preparing the infant's eyes for retinal examination, each infant's eye was dilated by falling drops in the neonate's eye every 15 min, an hour before the examination. The eye drops contained 0.5% tetracaine (for pain relief), 1% tropicamide, and 2.5% phenylephrine. It should be noted that no analgesic methods were typically used at this center except tetracaine drops. Each neonate was then placed in a special bed to be examined by the ophthalmologist, and each infant's vital signs were monitored (Saadat vital signs monitor [Saadat Co., Iran] used as an advanced monitor measuring continuous heart rate, oxygen saturation (SpO_2), temperature, and blood pressure parameters) every 5 min.

Outcome measures

The Astrid Lindgren and Lund Children's Hospital Pain and Stress Assessment Scale for Preterm and Sick Newborn Infants (ALPS-Neo) was used for the assessment of pain and stress.

Table 1. Characteristics of neonates (n=63)

		Breast milk group (n=21)	Sucrose group (n=21)	Distilled water (n=21)	P-value
Gender (male)		9	9	12	*0.165
Mean birth weight (g)		1416±58	1535±71	1587±54	#0.141
Mean gestational age at birth (week)		30.3±0.3	30.2±0.3	30.8±0.2	#0.459
Mean age on the eye examination day (day)		35±1.1	34±1.3	33±0.8	#0.473
Apnea (n)	Yes	1	1	2	^0.999
	No	20	20	19	
Need for oxygen (n)	Yes	2	3	5	^0.575
	no	19	18	16	

*: Chi-square test
#: One-way analysis of variance
^: Fisher's exact test

This scale was specifically chosen because it can be utilized for the evaluation of stress. The ALPS-Neo has five parts estimating facial expression, pattern of respiration, tone of the organs, activity of the hands and feet, and levels of activity, pain, and stress. Each item is scored within the range of 0 to 2. The psychometric properties of the ALPS-Neo, including the intraclass correlation coefficient, were evaluated to determine inter-rater reliability, and the internal consistency was assessed using Cronbach's alpha. The inter-rater reliability was assessed as good and varied within the range of 0.62 to 0.81 for the five items, and the total score was reported as 0.91. Cronbach's alpha was 0.95 for the total score.

Procedures

The pain was measured using the ALPS-Neo, and coping with stress in this study was considered over when the physical stress of ROP examination had ended and the neonates achieved a score of 3 or lower (28). As per the recommendations of the test developers, the ALPS-Neo evaluation was completed every 5 min and the vital signs were recorded every 5 min. The researcher started the bedside video recording of the infant 5 min before the examination and continued recording until 15 min after the examination (14). The first pain and stress assessment was performed 5 min before using a speculum and then a baseline period of at least 3 min was recorded from the neonate without any intervention.

After the baseline, while recording was in progress, the researcher-assistant opened the randomization letter and provided 0.5 ml/kg of breast milk and 24% sucrose or distilled water for the infant with a syringe. Using soother was not routine in the hospital. The syringe was masked so that the color of the breast milk, 24% sucrose, or distilled water could not be detected in the video to ensure blind evaluation by the video coders.

Two minutes (i.e., the peak effect of sucrose [29]) after providing breast milk, 24% sucrose, or distilled water for the neonates, the ophthalmologist inserted the eye speculum in the infant's eyes to facilitate the examination and began the neonatal eye examination. This time was considered the zero moment and the second pain and stress assessment was performed at this time (followed by the evaluation of the pain and stress of the infants every 5 min for 15 min). The mean duration of ROP examination was approximately 3 min (14). After the completion of the testing for 63 neonates, the videos were collected and given to two independent evaluators. The coders scored the pain and stress using the ALPS-Neo every 5 min and the required time of coping with stress was considered achieving scores of 3 or less based on the ALPS-Neo (28). Reliability for the coders was obtained based on scoring 25 samples. The correlation between their scoring method was examined using the Kappa coefficient and observed to be high (90.48%).

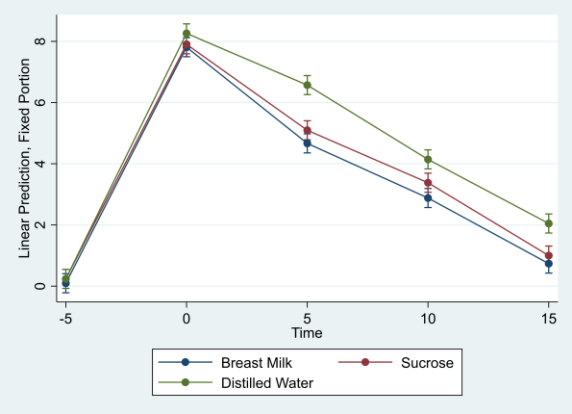

Figure 1. Comparison of mean pain scores among breast milk, sucrose, and distilled water groups
A: breast milk; B: sucrose; C: distilled water

Statistical methods

After the evaluation of the videos by the evaluators, the raw data were entered into Stata software (version 11.2). In the present study, one-way analysis of variance (ANOVA) and Chi-square test were used to examine demographic variables in three groups. In addition, one-way ANOVA was employed to compare the mean scores of pain and stress in the three groups and mean pain scores of the neonates before the examination, during the examination, and in the follow-ups. Furthermore, the repeated-measures ANOVA with a 95% confidence was utilized (Figure 1). To compare the duration of adaptation among the three groups, the mean time of coping with stress based on the ALPS-Neo was calculated and compared using ANOVA and Scheffé's test.

Results

Table 1 tabulates the characteristics of the three groups. The results of ANOVA and Chi-square test showed that no significant differences were observed among the breast milk, sucrose, and distilled water groups with respect to the neonates' gender, birth weight, gestational age at

Table 2. Mean scores of pain in three groups of breast milk, sucrose, and distilled water at different times

Time	M±SD CI Breast milk group	M±SD CI Sucrose group	M±SD CI Distilled water group	Analysis of variance and Scheffé''s test
5 min before examination	0.09±0.3 (-0.05-0.24)	0.23±0.4 (0.06-0.41)	0.23±0.4 (0.03-0.44)	(P=0.4269)
During examination	7.80±0.8 (7.45-8.16)	7.90±0.9 (7.51-8.30)	8.26±0.4 (8.06-8.46)	(P=0.1293)
5 min after examination	4.66±0.6 (4.37-4.96)	5.09±0.9 (4.69-5.49)	6.57±0.4 (6.36-6.78)	(P<0.0001)
10 min after examination	2.88±0.6 (2.58-3.18)	3.38±1.0 (2.91-3.85)	4.14±1.0 (3.69-4.59)	(P=0.0003)
15 min after examination	0.73±0.7 (0.43-1.04)	1.00±0.8 (0.63-1.37)	2.04±0.5 (1.81-2.28)	(P<0.0001)
Result of analysis of variance with repeated measures	Time effect (P<0.0001) Interaction between time and group (P<0.0001)		Group effect (P<0.0001)	

M: Mean; SD: Standard deviation; CI: Confidence interval

birth, age on the eye examination day, apnea, and need for oxygen (P>0.05; Table 1). In addition, according to the results of Table 2 and comparing the mean scores of pain in the three groups and during the follow-ups using ANOVA with repeated measures, the effect of the groups was significant (P<0.001) and the effect of time showed significant differences (P<0.001).

Figure 1 depicts the trend of mean changes in the three groups and in the follow-ups. The Scheffé's test was also used and its results did not reveal a significant difference in the mean scores of neonatal pain before and during the examinations (P>0.05); however, it was indicated that there was a significant difference in the means of the compared groups (P<0.05).

Five minutes before the examination, no statistically significant differences were observed between the mean scores on the ALPS-Neo in the three groups (P=0.43). The same result was observed during the examination (i.e., the insertion of the eye speculum) (P=0.13; Table 2). However, there were statistically significant differences among the mean pain scores of the ALPS-Neo at 5, 10, and 15 min after the insertion of the eye speculum (P=0.01). The ALPS-Neo scores in the breast milk group were lower than those reported for the infants in the other two groups (Table 2; Figure 1). Using ANOVA, statistically significant differences were observed among the three groups in the mean duration of coping with stress (P=0.04). The Scheffé's test also showed that the duration of stress adaptation was on average 11.4 min faster in the breast milk group, compared to that reported for the infants in the other two groups (Table 3).

All the vital signs, including heart rate, SpO_2, and respiratory rate, were evaluated using ANOVA. Moreover, there was no significant difference between the mean SpO_2 and respiratory rate in the three groups (P>0.05; figures 2 and 3); however, the mean heart rate was significantly lower in the breast milk group in comparison to those reported for the other two groups (P<0.05; Figure 4).

Table 3. Mean comparison of stress adaptation duration in three groups of breast milk, sucrose, and distilled water in preterm neonates

Stress adaptation duration (min)	Mean (CI)		Statistical test (p-value)
Breast milk group	11.42	(10.42-12.44)	Analysis of variance (P=0.0441)
Sucrose group	12.61	(11.50-13.73)	
Distilled water group	13.33	(12.28-14.39)	

CI: Confidence interval

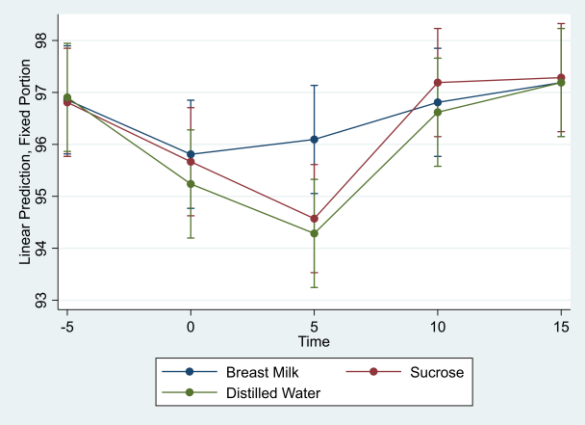

Figure 2. Comparison of mean oxygen saturation among breast milk, sucrose, and distilled water groups
A: breast milk; B: sucrose; C: distilled water

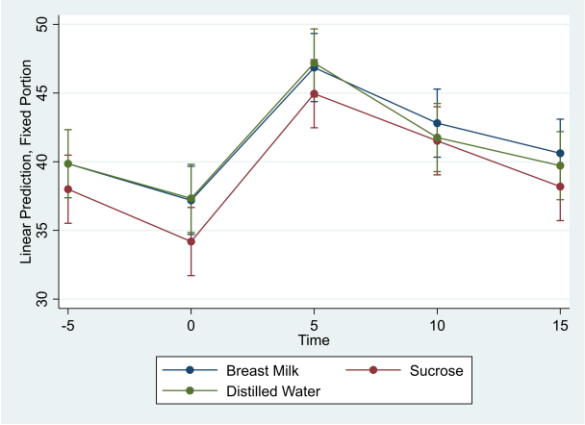

Figure 3. Comparison of mean respiratory rates among breast milk, sucrose, and distilled water groups
A: breast milk; B: sucrose; C: distilled water

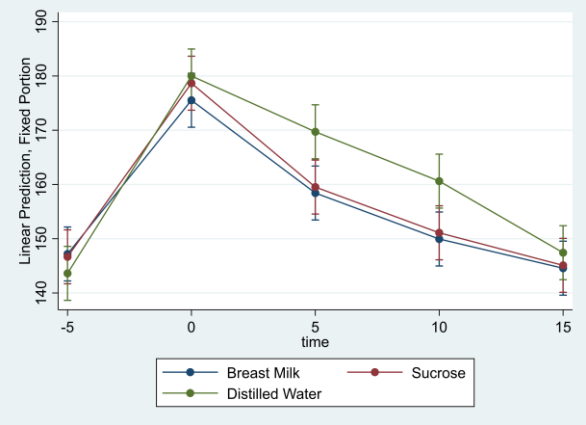

Figure 4. Comparison of mean heart rates among breast milk, sucrose, and distilled water groups
A: breast milk; B: sucrose; C: distilled water

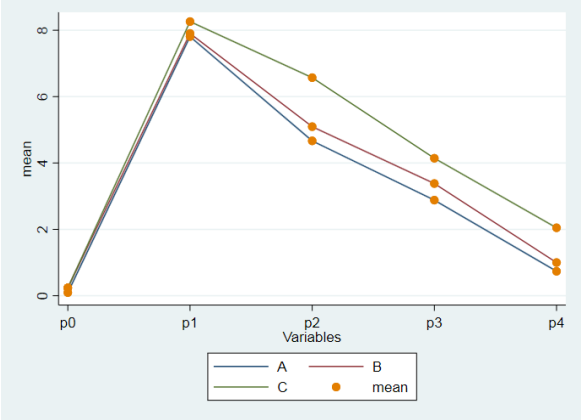

Figure 5. Profile plot for repeated-measures analysis of variance
A: breast milk; B: sucrose; C: distilled water

Discussion

The results of the current study confirmed that using breast milk and sucrose was effective in the reduction of the pain/stress after the procedure. The neonates in the three groups of breast milk, sucrose, and distilled water were equivalent in gender, birth weight, diet, gestational age, age of the examination day, apnea, and need for oxygen. The different results in the three groups after the procedure can be attributed to the different effects of the two solutions (Table 1). Nonpharmacological methods of pain control, such as breast milk, sucrose, and distilled water administration, were not shown to control the pain and stress during the insertion of the eye speculum during ROP examination (Table 2). Nevertheless, it was observed that coping with stress in infants in the breast milk group was better. Overall, breast milk was more effective in pain control than either sucrose and distilled water (Table 3).

Disher et al. (2018) carried out a meta-analysis of treatments for ROP and concluded that no nonpharmaceutical method completely relieves the pain during ROP examination. They suggested that the pain of ROP examination is so high that it can not be controlled by nonpharmacological pain relief methods (30). The results of the current study support the aforementioned findings. Other published reviews consistently emphasize that pain and stress resulting from ROP examinations can be limited, but not completely eliminated, and recommend using clinical guidelines to control the pain of ROP screening (31).

Gómez et al. (2018), in a randomized crossover trial, demonstrated that using breast milk or sucrose provided the same analgesic effect on preterm neonates of at least 28 weeks. The aforementioned multicentre randomized noninferiority crossover trial included infants from five neonatal university units in Madrid, Spain. They

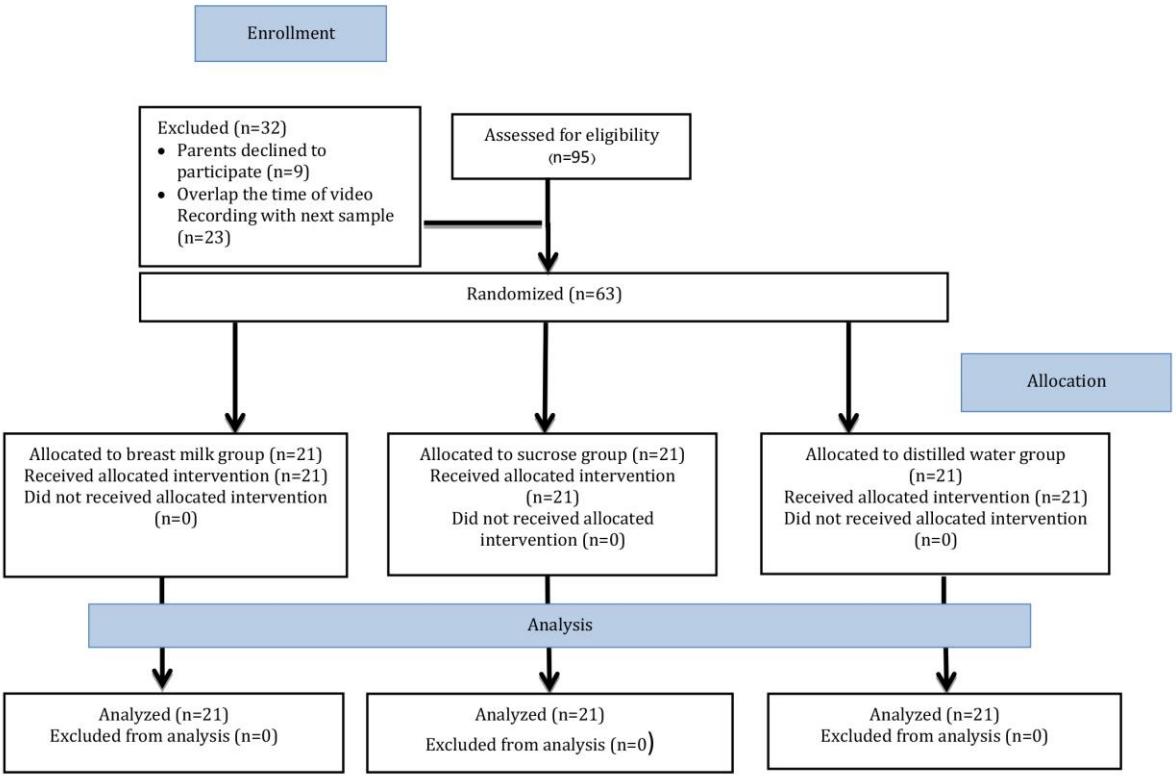

Figure 6. Patient flow diagram

included 66 preterm neonates born at less than 37 weeks and randomly assigned the infants into two groups. The infants received either breast milk or sucrose 2 min before venepuncture, together with nonnutritive sucking and swaddling, and then the opposite procedure at a later point. The pain was measured with the premature infant pain profile (PIPP) and crying. They observed that breast milk and 24% sucrose had the same analgesic effect during venipuncture in most preterm neonates; nonetheless, sucrose was more effective in extremely preterm neonates (32).

In the current study, it was also observed that both sucrose and breast milk can reduce pain and stress of ROP examination but only after the placement of the speculum. Unique to the present study is that coping with stress was better when infants received breast milk. The levels of pain and stress created by ROP examination are much higher than those reported for venepuncture, and it is recommended to carry out randomized crossover trials on ROP examination. Accordingly, the data could be combined in a meta-analysis in order to provide more conclusive recommendations.

Benzer et al. (2017) conducted a randomized controlled trial and evaluated neonatal pain at baseline before the examination, immediately after the administration of local anesthetic drops (i.e., 30 sec before ROP examination), 30 sec, 60 sec, and 2 min after the placement of the speculum for both eyes, and after 4 min for the right eye (the left eye firstly examined followed by the right eye) using PIPP. In the aforementioned study, 64 preterm infants were divided into three groups, with 0.2 ml distilled water given 2 min before, during, and after the procedure with 2-minute intervals (n=21; group 1), 0.2 ml sucrose 24% given 2 min before, during, and after the procedure with 2-minute intervals (n=22; group 2), and 0.6 ml sucrose 24% given by mouth using a syringe 2 min before the procedure and applied empty syringe during and after the procedure with 2-minute intervals (n=21; group 3). Benzer et al. observed that sucrose could reduce infant's crying and pain scores in the first eye; nevertheless, sucrose did not have a similar effect on the next eye (33).

The results of the current study showed that although sucrose or breast milk did not relieve pain during ROP examination, both reduced pain and stress after the placement of the speculum. The reason for the difference between the results of the present study and those of Benzer et al. could be that they evaluated the pain 30 sec after

the examination, not during the examination. Another reason for this difference could be related to the lower amount of sucrose that they used.

Suksumek et al. (2017) studied the effect of oral sucrose and placebo on relieving pain during ROP examination. They demonstrated that sucrose was effective for pain reduction during ROP examination. The reason for the difference in the results of the aforementioned study and those of the present study may be no measurement of the pain when the examiner was inserting the eye speculum at the beginning of the examination, which according to studies, is the most painful time in ROP examination. In addition, the infants were swaddled before the examination. Swaddling is one method of pain control in infants that may work synergistically with sucrose to mitigate pain. Finally, the pain was assessed using a different outcome measure, the Neonatal Pain, Agitation, and Sedation Scale (20).

The findings of the current study regarding pain relief after ROP examination are supported by the results of a study conducted by Rosali et al. (2014) who observed that breast milk significantly reduced pain during and after ROP examinations. In the aforementioned double-blinded randomized controlled trial, Rosali et al. evaluated pain reactivity in 40 preterm neonates with a gestational age of lower than 35 weeks and birth weight of less than 2,000 g at baseline (i.e., before starting the procedure), during the procedure, and at 1 and 5 min after ROP examination using the PIPP (21). The difference between the results of the present study and those of the aforementioned study during the examination may be that they used a nest, swaddling, and a soother (which was the standard practice in their unit), along with breast milk. However, both studies support the effect of breast milk in calming infants after ROP examination.

Ribeiro et al. (2013) investigated the impact of breast milk on neonatal pain relief during ophthalmoscopy. They assessed pain at 5 min before, during, and 5 min after the examination in a comparison between breast milk and 25% sucrose. They demonstrated no differences between sucrose and breast milk either during or after the eye examination. However, the results of the aforementioned study should be interpreted with caution as Ribeiro et al. investigated only 14 infants, with 9 in the sucrose group and 5 in the breast milk group (22).

Finally, the results of the current study are in line with the findings of a study carried out by Taplak et al. (2017) who compared the effectiveness of breast milk and sucrose in relieving pain during ROP examination. The aforementioned study was carried out on 60 preterm neonates who were lower than 32 weeks of gestation with a birth weight of ≤ 1,500 g. The infants were given 1 mL of breast milk, sucrose, and distilled water before the ROP examination. The pain was assessed using the PIPP 5 min before, during, and 5 min after ROP examination. The PIPP scores of the preterm neonates in the three groups were higher during the ROP examination and were not significantly different; nevertheless, the infants in the breast milk group recovered and returned to their initial values more quickly after ROP examination than the neonates in the sucrose group (14). Consequently, both studies indicate an effective role of breast milk in more rapid adaptation of the infants to pain-induced stress. The aforementioned similar findings may arise as a result of using similar methods; however, in the current study, 0.5 ml/kg of oral solutions were used and pain and stress were assessed using the ALPS-Neo that is suitable for the evaluation of both pain and coping with stress.

Limitations

Sucrose %24 was not available in Iran, and a domestic pharmaceutical company accepted to produce sucrose 24% following the efforts of the research team. As a result, since that time, sucrose %24 has been available in the Iranian market.

Conclusion

The ROP examination is one of the stressful procedures performed on preterm neonates. In this study, breast milk and sucrose were compared in the reduction of pain and stress of ROP examination. Based on the results, it was concluded that there is no difference between breast milk and sucrose in decreasing pain during ROP examination, but after the examination. In addition, in coping with stress, breast milk is more effective than sucrose.

Acknowledgments

The authors would like to appreciate all the nursing managers, supervisors, and nurses in the studied hospitals who cooperated in the implementation of the project.

Funding

This project was funded by the School of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran.

Conflicts of interest

The authors declare that there is no conflict of interest in this study.

Ethical issues

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.FNM.REC.1397.052) on July 10 in 2018. Ethical considerations included obtaining consent from the parents, assuring them of the confidentiality of all the information, and showing willingness to participate or withdraw from the study at any stage.

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