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Comparison of the analgesic effect of oral sucrose and/or music in preterm neonates: A double-blind randomized clinical trial

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ABSTRACT

Objective: To compare the analgesic effects of sucrose, music, and their combination on venipuncture's pain in preterm neonates.
Methodology: A double-blinded randomized control trial conducted at a Neonatal Intensive Care Unit (NICU) affiliated to Tehran University of Medical Sciences (TUMS) in Tehran, Iran. One hundred and twenty preterm neonates were randomly allocated into three experimental (sucrose, music and combination of sucrose and music) and one control groups (n = 30 for each group). Two minutes before the venipuncture, 0.5 ml of oral 24% sucrose was provided for the sucrose and combination groups. The combination group additionally received lullaby music as same as the music group. The control group had headphones without playing music and received sterile water. Blinded assessment of the Premature Infant Pain Profile (PIPP) was performed before and during venipuncture, as well as 30 s and 10 min and 10 min after its completion.
Results: The pain scores during venipuncture in the sucrose and combination groups were significantly lower than the control group ($p = .003$, $p < .001$, respectively) but not in the music group. Thirty seconds after the end of the venipuncture, the pain score in the three intervention groups was significantly lower than the control group (sucrose, music and, combination group, $p < .001$, $p = .009$, $p < .001$, respectively). Ten min after the venipuncture, there was no significant difference in pain scores among the four groups.
Conclusion: Music could relief pain 30 s after the venipuncture completion but not during the venipuncture. A more prolonged period of playing music is recommended to evaluate the analgesic effects of music in preterm neonates in future studies.

1. Introduction

Preterm neonates with the highest rate of admission in Neonatal Intensive Care Unit (NICU) endure several minor painful procedures daily as part of their routine care, which may last from a few weeks to a few months.[1–3] Painful procedures can adversely impact neonates' physiological indexes (plasma cortisol level, oxygen saturation, heart rate, and respiratory rate) as well as the behavioral parameters (facial grimacing, crying and body movements). [4] Also, it could have long-term effects on the neurological and behavioral development of preterm neonates such as increased anxiety/stress and attention-deficit disorders. Neurologically immature preterm neonates are the most susceptible to the long-term effects of pain that highlight the importance of pain management in the neonatal period.[5–7]

Different non-pharmacological methods have been reported to exert an analgesic effect on preterm neonates during painful procedures.[2] One of the widely recommended pain management methods is using oral sucrose.[2,8–11] In an integrated review, oral sucrose has been introduced as an effective, safe, and immediate-acting analgesic that can decrease the behavioral pain responses in infants during painful stimuli.[12] However, some evidence showed that sucrose in combination with other non-pharmacological interventions was more effective than

Abbreviations: NICU, neonatal intensive care unit; PIPP, premature infant pain profile

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sucrose alone.[13] Music, as an evolving research area is increasingly being used in neonatal units to manage pain and improve behavioral and physiological outcomes.[14–17] Nevertheless, lack of heterogeneity among studies' population (e.g. difference in gestational and postnatal age), intervention (e.g. duration of playing music and type of music), as well as targeted outcomes (physiological and behavioral), indicated needs for further research to preclude definitive conclusions about the analgesic effects of music application.[14,18]

Combination of two or more non-pharmacological interventions may be more effective than using one method in reducing pain.[19] The theory behind its efficacy is rooted in sensorial saturation. In other words, multisensorial stimulation of neonate via different non-pharmacological methods could provide enhanced pain relief. [20] However, research regarding the confirmation of this theory is contradicting.[21–26] Some studies compared the effectiveness of the combination of sucrose or music with other non-pharmacological interventions to relieve pain in neonates,[25–29] while limited studies assessed if the combination of music and sucrose can provide similar or better analgesia compared to oral sucrose or music alone. [26] In one crossover clinical trial, the combination of sucrose and music was more effective in decreasing pain than using music or sucrose solely in preterm infants. [30] According to limited studies regarding the efficacy of combination therapy and the need to evaluate effectiveness of music, the present study aimed to assess the analgesic effect of sucrose, music, and combination of sucrose and music in stable preterm infants during venipuncture as a painful procedure. We hypothesized that using combination of music and sucrose could involve multisensorial stimulation including auditory and taste stimulation and therefore, it would have a more significant impact on pain management in comparison to using sucrose or music alone.

2. Materials and methods

2.1. Study design

The present double-blinded clinical trial was conducted from October 2012 to February 2013 at the NICU of a referral and teaching hospital affiliated to Tehran University of Medical Sciences (TUMS) in Tehran, Iran.

2.2. Sample size

Considering that the main outcome of the present study was pain relief during venipuncture, it was estimated that a study with a sample size of 27 in each group would have 80% power at 0.05 significance level to detect 30% decrease in pain between groups.[2,9,29] As such considering attritions, 30 infants for each group was thought and 120 preterm neonates hospitalized in the NICU were randomized into four groups (sucrose, music, combination of sucrose and music, and control groups) (Fig. 1).

2.3. Randomization and blinding

The allocation of the neonates to each group was randomly assigned by using eight-block size. A nurse who was blind to the order of group assignment did the drawing of blocks. All neonates were randomly allocated to one of the four groups until the completion of the sampling. A research assistant who was aware of the group allocation sequence, prepared and serially labeled the intervention package including headphone (with or without playing lullaby music) and solution (24 % sucrose or sterile water) and applied intervention. A nurse who performed the venipuncture as well as a trained assessor nurse who analyzed the recorded videos were blind to the group allocation.

2.4. Study population

The study population included all preterm neonates who were admitted to the NICU and met the study prerequisites. Inclusion criteria were neonates with a gestational age of 32–35 weeks (according to the sonography in the first trimester of pregnancy), birth weight ≥ 1500 g, Apgar scores ≥ 7 at 5 min of birth, postnatal age ≥ 48 h, a non-substance-abusing mother, absence of using caffeine or any sedative medications for newborn during the last 48 h before venipuncture, no evidence of congenital anomaly or neonatal diseases such as apnea, asphyxia, or infectious diseases, and confirmation of hearing by Otoacoustic Emission (OAE) device. Exclusion criteria included unwillingness of the parents to complete the study, abnormal physiologic responses such as heart rate above 200 beats or lower than 80 beats per minute, deceleration of oxygen saturation less than 80 % during intervention, any problems in recording physiological and behavioral responses, any medical and nursing handling during the intervention, lack of success in performing venipuncture at the first attempt and/or any blood draw which lasts more than 30 s.

2.5. Intervention

First, the researcher identified preterm neonates, who met the inclusion criteria using the medical records. Then, the aim of the study was explained to the mothers and the informed consent was obtained. The research assistant, who was aware about group allocation, placed the neonate in an assigned sampling area at least 30 min after the last feeding. Two video cameras (a SONY model CX110 and a Canon model ZR 800) were set up by the researcher to record the neonates' faces, as well as the monitor that displayed heart rate and oxygen saturation. For maintaining the double-blind procedure of the study, the research assistant put headphone (with or without playing music) and administered 0.5 ml solution (sucrose or sterile water) via syringe on the anterior portion of all neonates in four groups before the venipuncture. A trained nurse who was blind to the randomization code performed the venipuncture by swiping the blood sampling area via an alcohol pad. The duration of the venipuncture was assumed from the insertion of the needle until its removal which last less than 30 s. Video cameras simultaneously recorded the neonates' faces, and the monitor from 2 min before the venipuncture until 10 min after its completion. All venipunctures were performed by one nurse in the morning shift. It is worth mentioning that pain management is not routine care in NICUs in Iran.

2.6. Study groups

2.6.1. Sucrose

In the sucrose group, 2 min before the venipuncture, 0.5 ml oral 24 % sucrose was administered on the anterior portion of the neonate's tongue. For blinding the study, all neonates in this group had headphones without playing music.

2.6.2. Music

In the music group, 2 min before the venipuncture, Braham's lullaby music with 40 − 50 dB was played for 10 min via a headphone. The decibel level was regulated with a sound level meter, and the headphone volume level was adjusted to avoid unsafe levels for the volume by an audiometrist. The neonates in the music group received 0.5 ml sterile water via syringe on the anterior portion of their tongue for blinding the study.

2.6.3. Combination of sucrose and music

In the combination of sucrose and music group, simultaneously 0.5 ml 24 % of oral sucrose was administered with a syringe on the anterior portion of the tongue, and the lullaby music with 40 − 50 dB was played 2 min before the venipuncture for 10 min via headphone. The decibel level was regulated with a sound level meter, and the headphone volume level was adjusted to avoid unsafe levels for the volume by an audiometrist.

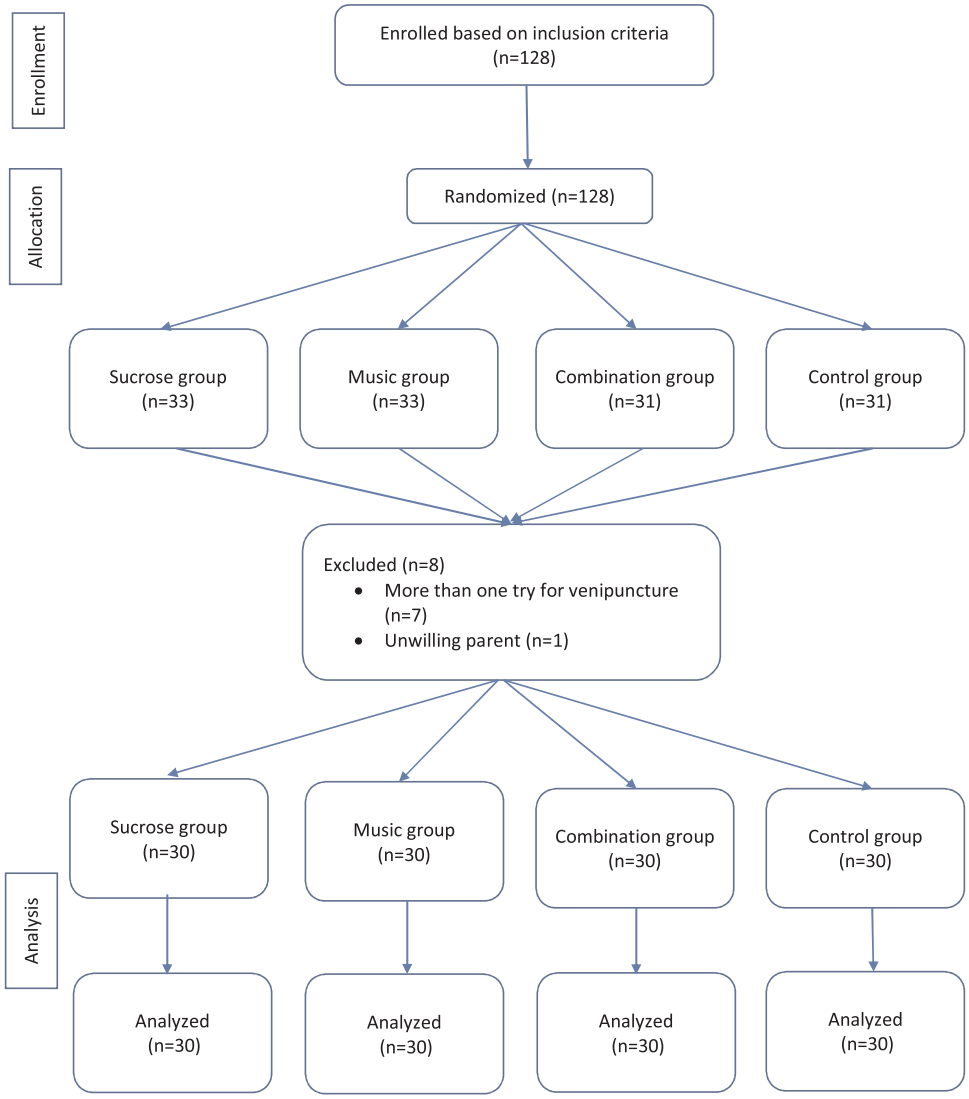

Fig. 1. Consort flow diagram.

2.6.4. Control

Neonates in the control group had headphones without music, and they received 0.5 ml sterile water via syringe on the anterior portion of their tongues 2 min before the venipuncture.

2.7. Instrument and calculation of pain score

The Premature Infant Pain Profile (PIPP) was used for the neonates' pain evaluation. The PIPP scale has been widely evaluated and validated for acute pain assessment in preterm neonates.[31,32] This tool consists of two background factors (gestational age and mode of behavior), two physiological parameters (heart rate and oxygen saturation), and three facial actions (eye squeeze, nasolabial furrowing, and brow bulge). Each of the seven items in this tool is scored from 0 to 3. The possible maximum score for the PIPP is 21.

For analyzing the data, the researcher assigned A, B, C and D codes for the recorded videos in each group (sucrose, music, combination and control groups respectively). The trained assessor nurse who was blind to the coding system, analyzed the recorded videos. The assessor nurse calculated the pain score for four phases: 2 min before the start of the venipuncture, during the venipuncture, as well as 30 s and 10 min after its completion. For physiologic data, any changes in heart rate and oxygen saturation were scored based on the PIPP scale. For instance, score of 3 was given to a neonate if the heart rate increased ≥ 25 beats per minute, and the same score was given if the oxygen saturation fell down by ≥ 7.5 % after 30 s of observation. For scoring the behavioral data, the time of each facial expression including brow bulge, eye squeeze, and naso-labial furrowing, was recorded, and the score was given based on the time of observation. For example, if the facial expression took ≥ 70 % of the monitoring period, the pain score of 3 was assigned.

2.8. Statistical methods

The data were analyzed using SPSS version 17. Descriptive and analytical statistical tests were performed to explore the data. The Kolmogorov–Smirnov test (KS Sample) was used to assess the normality of the data. To compare pain scores among four groups, one-way analysis of variance (ANOVA) for normally distributed data and Kruskal–Wallis test for non-normally distributed data was performed. For tracking the effective group in reducing pain, Bonferroni, as a post hoc test was used. Significant levels in this study were considered to be 0.05.

3. Results

From a total of 128 neonates screened in this study, 120 neonates were recruited into one of the four different study groups: sucrose,

Table 1
Comparison of demographic data and behavioral state among the four groups.

	Sucrose Group (n = 30)	Music Group (n = 30)	Combination Group (n = 30)	Control group (n = 30)	P-Value
Sex (% female)	(11) %36.7	(16) %53.3	(14) %46.7	43.3 % (13)	.62
Gestational age (weeks)	34.2 ± 1.24	34 ± 1.41	33.83 ± 1.34	33.86 ± 1.35	.76
Postnatal age (days)	6.03 ± 3.31	5.23 ± 3.15	4.96 ± 2.53	5.13 ± 2.96	.55
Apgar in 5th min	9.02 ± 0.55	8.93 ± 0.63	9.06 ± 0.63	9.03 ± 0.55	.38
Birth weight (g)	2129.83 ± 315.01	1987 ± 367.86	1932 ± 314.03	2012 ± 352.83	.14
Behavioral state	1.83 ± 1.14	2.03 ± 1.09	1.66 ± 1.26	1.56 ± 1.22	.44

P, statistical significance < .05, One Way ANNOVA.

music, combination of sucrose and music, and the control group. Two neonates in the sucrose group, three neonates in the music group, two neonates in the combination and the control groups (one neonate in each group) were excluded due to more than one attempt to perform the venipuncture. One neonate in the sucrose group had been excluded due to the parent's unwillingness to continue with the study. There were no significant differences in demographic characteristics and neonatal behavioral status among the study groups (Table 1).

At the baseline, pain scores were similar in all groups. The pain scores were significantly different among the four groups during venipuncture and 30 s after its completion ($p < .001$). The Bonferroni post hoc analysis showed that during venipuncture, the pain scores in the sucrose and the combination groups were significantly less than the control group ($p = .003$, $p < .001$, respectively) but not in the music group. Thirty seconds after the end of the venipuncture, based on the Bonferroni post hoc test, the pain scores were significantly lower in all intervention groups compared to the control group (sucrose, music and combination of music and sucrose: $p < .001$, $p = .009$, $p < .001$, respectively). Also, there was no significant difference in the pain scores among the four groups at 10 min following completion of the venipuncture (Table 2).

4. Discussion

The present study is one of the few studies that compare the effectiveness of a combination of sucrose and music on pain relief in preterm infants. The results of the current study revealed that sucrose and a combination of sucrose and music had analgesic effects during and 30 s after the end of the venipuncture, however music decreased pain just after the end of the venipuncture.

Our results revealed that administration of sucrose either alone or in combination with music reduced pain score during the venipuncture. Similar to our findings, numerous studies reported the positive effect of using sucrose alone as a method for pain relief through its influence on endogenous opioid release [9,11,33–35] Also, in a recent meta-analysis, sucrose administration was introduced as a safe method for the reduction of pain in premature newborns. [13]

In our results, despite of ineffectiveness of playing music alone on pain relief, sucrose and combination of sucrose and music had a similar impact on pain score during venipuncture. Perhaps the key factor in pain reduction can be attributed to the analgesic effects of sucrose. In a comparable study, Shah et al. showed that the combination of sucrose and music therapy for 20 min before the heel prick, provided better pain relief during the painful procedure than applying sucrose or music lonely. They also indicated that using sucrose and music alone had a similar impact on pain score [30] which we did not observe such an effect for music application solely. For clarifying the reason, we have discussed studies which evaluated the application of music on pain relief lonely. In one study pain reduction occurred with 10 min and in another with 5 min of music playing before painful procedure in premature infants [17,36] It seems that the duration of playing music before the painful stimuli plays a key role in reducing pain. In our study, the playing music was limited to 2 min before the venipuncture at the same time as sucrose administration to follow the standard protocol of sucrose application (2 min before the venipuncture). Lack of standard time in the onset of music before a painful procedure is one of the gaps for music application in NICUs. Moreover, results of a systematic review revealed no absolute conclusion about the benefits of music on pain reduction due to applying music with different dB ranges, types and durations.[18] Thus, more research is required to evaluate the effectiveness of music on pain relief.

The analgesic effects of music can be explained by releasing of endorphins from the brain and, consequently, reducing the sympathetic system response.[37] This mechanism may elucidate why playing music for longer duration before painful procedure could have a better impact on pain reduction. In our study, the effect of music on pain relief after painful procedure probably was due to the duration of playing music. Therefore, further research is required to determine the effectiveness of playing music with a longer period before a painful procedure.

5. Conclusions

The results of the present study showed the benefits of using sucrose and combination of sucrose and music on pain relief in premature neonates. Also, playing music had an impact on pain reduction just after the end of the venipuncture which highlights the importance of long-term music playing before the start of a painful procedure. Thus, future studies are required to focus on the efficacy of playing music with a longer period on pain relief in preterm neonates.

6. Limitations

The current study had some limitations which need to be considered during the interpretation of the results. The sample was limited with a narrow gestational age range, and the results cannot be generalized to all premature neonates. Further studies should include different gestational age to determine the efficacy of music for pain relief. The authors of this study restricted their population to premature neonates who

Table 2
Mean of pain score at different phases of the study (mean ± SD).

	Sucrose Group (n = 30)	Music Group (n = 30)	Combination Group (n = 30)	Control group (n = 30)	P-Value	F
Before venipuncture	3.06 ± 1.11	3.26 ± 1.28	2.93 ± 1.31	2.90 ± 1.56	.70	.47
30 seconds after start of venipuncture	9.80 ± 3.19	11.56 ± 3.20	9.26 ± 3.22	12.56 ± 2.28	< .001	7.8
30 seconds after end of venipuncture	8.26 ± 2.94	10.20 ± 3.61	7.20 ± 2.92	12.83 ± 2.84	< .001	19.17
10 minutes after venipuncture	3.60 ± 1.63	3.56 ± 1.83	2.90 ± 1.42	3.33 ± 2.05	.38	1.01

P, statistical significance < .05, One Way ANNOVA.

were without any brain disease and severe illness to minimize any risks from auditory stimulation; therefore, future studies should include neonates who are more compromised if feasible.

Contributions of authors

Zahra Amirkhanzadeh Barandouzi and Maryam Keshavarz participated in the design of the study, acquisition and analysis of the data and writing of the manuscript. Ali Montazeri participated in the design of the study, analysis and interpretation of data. Hassan Ashayeri and Zahra Rajaei contributed in study as consultants. All authors read and approved the final version of the submitted manuscript.

Ethics

This study was approved by the Medical Research Ethics Committee of Tehran University of Medical Sciences (TUMS). Written informed consent was obtained from every neonate's parent. The study has been registered at Iranian Registry of Clinical Trials (IRCT) with code number 201101052324N7.

Compliance with ethical standards

All procedures performed in this study involving human participants were in accordance with ethical standards of Ethical Committee of TUMS. Written informed consent was obtained from all parents who participated in this study. Also, this study was funded by the Research Committee of TUMS.

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Declaration of Competing Interest

There is no conflict of interest to declare.

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