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ORIGINAL ARTICLES

Trial of Music, Sucrose, and Combination Therapy for Pain Relief during Heel Prick Procedures in Neonates

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Objective To compare the effectiveness of music, oral sucrose, and combination therapy for pain relief in neonates undergoing a heel prick procedure.

Study design This randomized, controlled, blinded crossover clinical trial included stable neonates >32 weeks of postmenstrual age. Each neonate crossed over to all 3 interventions in random order during consecutive heel pricks. A video camera on mute mode recorded facial expressions, starting 2 minutes before until 7 minutes after the heel prick. The videos were later analyzed using the Premature Infant Pain Profile—Revised (PIPP-R) scale once per minute by 2 independent assessors, blinded to the intervention. The PIPP-R scores were compared between treatment groups using Friedman test.

Results For the 35 participants, the postmenstrual age was 35 weeks (SD, 2.3) with an average weight of 2210 g (SD, 710). The overall median PIPP-R scores following heel prick over 6 minutes were 4 (IQR 0-6), 3 (IQR 0-6), and 1 (IQR 0-3) for the music, sucrose, and combination therapy interventions, respectively. The PIPP-R scores were significantly lower at all time points after combination therapy compared with the groups given music or sucrose alone. There was no difference in PIPP-R scores between the music and sucrose groups.

Conclusions In relatively stable and mature neonates, the combination of music therapy with sucrose provided better pain relief during heel prick than when sucrose or music was used alone. Recorded music in isolation had a similar effect to the current gold standard of oral sucrose. *(J Pediatr 2017;190:153-8).*

Trial registration www.anzctr.org.au ACTRN12615000271505.

Although survival for preterm neonates has improved over the past 5 decades,[1] neonates regularly encounter a number of painful procedures, including blood sampling.[2-6] Heel prick is one of the most commonly performed painful procedures in the neonatal intensive care unit (NICU)[7] and pain relief is often provided using oral sucrose.[8-10] A recent Cochrane review deemed sucrose as safe and effective for procedural pain from a single event, but further research on pain management is warranted. Sucrose has not been shown to prevent the development of remote hyperalgesia.[11] There is uncertainty about the effect of repeated dosages and the effects in combination with other nonpharmacologic and pharmacologic interventions.[10,12,13] A few recent studies have raised concerns about the use of sucrose for pain relief in neonates and questioned its effectiveness as an analgesic.[14-17]

Music therapy can be used as a "structured intervention delivering music with the purpose of achieving specific therapeutic goals."[18] Music may modulate pain perception, cause distraction, and block pain pathways by causing sensorial saturation.[19] There is building evidence that carefully selected music in consultation with a trained music therapist may be beneficial in relieving procedural pain in both full-term and physiologically mature late preterm infants.[20,21] One of the major drawbacks of the studies conducted so far is comparison of music therapy with a control group of no pain relief and the lack of direct assessment with the current gold standard of sucrose. It is not known if music therapy and the combination of music therapy with sucrose can provide similar or better analgesia compared with oral sucrose.

The primary objective of the present study was to compare the effectiveness of sucrose with recorded music therapy (selected in consultation with a trained music therapist) and combination therapy for pain relief during heel prick. The secondary objective was to compare the effect of the 3 interventions on heart rate and oxygen saturation.

Methods

This randomized, controlled, blinded, crossover clinical trial was conducted in a level III perinatal center in Australia, caring for high-risk preterm and term neonates requiring intensive care. The NICU does not care for neonates undergoing surgery other than laser therapy for the treatment of retinopathy of prematurity.

NICU	Neonatal intensive care unit
PIPP-R	Premature Infant Pain Profile—Revised

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Heel pricks are performed by registered nurses trained in the procedure. They are used for minor blood collections up to 0.5 mL, using a spring-loaded device (BD Quickheel Preemie lancet; Becton, Dickinson and Company, East Rutherford, NJ). Sucrose is used for pain relief during heel prick, as a nurse-initiated medication.

A physiologically mature group of neonates was the primary target of the current study. Neonates admitted to the NICU were included if they were >32 weeks postmenstrual age at recruitment, not needing invasive ventilation, positive pressure or high-flow support, and were receiving a minimum of 60 mL/kg/day of feeds with an anticipated need for repeat heel pricks. Exclusion criteria were the presence of a major congenital abnormality, proven or suspected sepsis, necrotizing enterocolitis, major intraventricular hemorrhage (grade III or IV), seizures, and encephalopathy.

The study was approved by the ethics committee of the Local Health District. No changes to the trial methods, inclusion and exclusion criterion, or outcomes were made after study commencement. Informed written consent was obtained by the investigators before recruitment from parents or guardians. The study was prospectively registered with Australian New Zealand Clinical Trials Registry (ANZCTR), www.anzctr.org.au (Trial Id: ACTRN12615000271505).

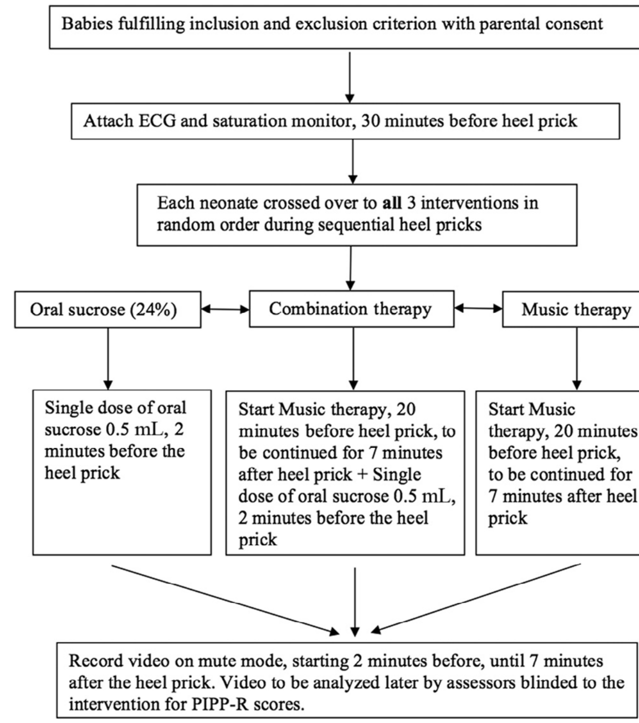

Figure 1. Study flow diagram. *ECG*, Electrocardiograph.

Interventions

Each eligible neonate was crossed over to all 3 interventions in random order, using a computer-generated sequence, during consecutive heel pricks as clinically indicated. The computer allocation of intervention sequence was carried out immediately before the heel prick, by a research nurse. The interventions were administered by the trained medical officers and bedside nurse. There was a minimum 30 minutes of 'wash-out' period between successive interventions (Figure 1).

Intervention I: Recorded Music. In the music intervention, neonates were exposed to recorded music with sounds up to 60 A-weighted decibels,[22] starting 20 minutes before the heel prick, continuing for 7 minutes after the procedure. Music was administered using the "Deep Sleep" track from "Bedtime Mozart: Classical Lullabies for Babies" (2011), an instrumental lullaby music track chosen after discussion with a music therapist for stability, repeatability, and presence of minor tones. The piece of music was presented as a loop and was played back from a sound source using 2 high-quality portable speakers, placed equidistant from the head on each side. The sound levels at both ears were checked after speaker placement and the sound was gradually scaled up to the study limit of 60 A-weighted decibels. To maintain resemblance to a real-life scenario, the ambient noise was not modulated. However, the total auditory exposure was checked to ensure that it remained within the recommended limits at the ear level.[22]

Intervention II: Oral Sucrose Therapy. In the sucrose intervention, neonates received 0.5 mL of oral sucrose (24%) 2 minutes before the heel prick.

Intervention III: Combination Therapy. In the music-sucrose intervention the neonate received both recorded music and oral sucrose during heel prick as a combination of the previous 2 interventions.

All infants received similar standard nonpharmacologic methods of pain relief such as swaddling and comforting throughout the heel prick and blood collection procedure. Pacifiers were avoided to maintain consistency between the groups.

A Masimo Rad 5 pulse Oximeter (Masimo Corporation, Irvine, CA) was attached to the right wrist approximately 30 minutes before the heel prick to obtain readings of heart rate and oxygen saturation every 2 seconds. The monitor probe remained attached for 7 minutes after the procedure. The monitor data were downloaded immediately after the intervention.

A video camera on mute mode recorded facial expressions, starting 2 minutes before and continued until 7 minutes after the heel prick. No forms of patient identifiers were recorded and the videos were labelled with an allocated study number. Recorded facial expressions in the videos were later scored independently by 2 assessors, who were blinded to the intervention sequence, using the Premature Infant Pain Profile—Revised scale (PIPP-R).

The PIPP-R is a 7-item multidimensional (composite) measure of pain widely used to assess acute pain in preterm neonates. The scores obtained for the 7 items are summed to obtain a total pain intensity score. The maximum attainable PIPP score is 21 for preterm infants <28 weeks GA and 18 for full-term infants.[23,24] PIPP-R has been evaluated and validated for acute pain assessment in preterm neonates.[23,24]

Statistical Analyses

The PIPP-R scores at baseline and at 1-minute intervals were evaluated for a total of 6 minutes after the heel prick. An average of the 2 assessors' pain scores was used for comparison between 3 groups. A reduction of 2 points in the PIPP-R score was considered clinically significant. Based on studies evaluating PIPP-R scores in sucrose treated neonates[10] and using a 2-tailed test with a standard deviation of 3.5, an alpha of 0.05 and a power of 80%, the sample size required to detect a reduction of 2 points in PIPP-R scores for a cross over design was 30 neonates. $P < .05$ was set as significant.

The trend in heart rate and oxygen saturation was plotted graphically. The mean heart rate and oxygen saturation was calculated for each of the 1-minute intervals and analyzed for statistical significance between all 3 interventions starting 20 minutes before until 7 minutes after the heel prick, using a 2-tailed paired *t*-test for dependent samples. Statistical analysis was performed using SPSS version 19.0 for Windows (SPSS, Inc, Chicago, IL) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria), with the "coin" and "multcomp" packages, performing the post hoc tests of Wilcoxon-Nemenyi-McDonald-Thompson and Hollander and Wolfe (1999), using the code of "Tal Galili," published on r-statistics.com (https://www.r-statistics.com/tag/friedman-test/).[25]

Results

The study was conducted over a period of 6 months from August 2015 to January 2016. Thirty-nine families of eligible neonates were approached. Four families declined to participate in the study. One family had concerns if music alone would be adequate to provide pain relief. One refused on religious grounds and 2 other families refused as they had already participated in other studies of the unit (**Figure 2**; available at www.jpeds.com). Thirty-five neonates were crossed over to all 3 interventions in random order. All neonates received the allocated treatment and were analyzed for the outcome in the same allocated group.

The mean gestation of the neonates was $34^{2/7} \pm 2^{3/7}$ weeks at birth, and the postmenstrual age was 35 ± 2.3 weeks (range, 32-41) at the time of study entry. At inclusion, infants were 4 ± 6 days of age, with a median weight of 1970 g (IQR, 1740-2480). Sixty percent of the infants were boys. Common indications for repeat heel pricks were blood sugar monitoring (69%) and bilirubin levels (29%). Each included neonate received all 3 heel pricks for the same indication, needing approximately a similar time for blood collection. The time interval between consecutive heel pricks varied from 4 to 24 hours, with an average of 10 hours. None of the neonates required surgery, including laser therapy, in the previous 2 weeks and were not receiving sedative or opioid medications in the previous four weeks. None of the neonates had a blood glucose level <44 mg/dL.

The primary objective was evaluation of the difference in PIPP-R scores between the 3 interventions. The interrater reliability between 2 the assessors was evaluated using 2 tailed Spearman rank correlation coefficients. There was a high correlation for pain scores at most time points. We compared the pain scores at each time point between 3 groups. As the data of PIPP-R scores at each time point were not normally distributed, the differences between groups were compared using the Friedman test with post hoc analysis using the Bonferroni correction.

The baseline pain scores before the heel pricks were similar in all groups. The pain score comparisons using the Friedman test were statistically significant at all time points (**Table I**). In the post hoc analysis, pain scores in response to heel prick stimulus were not different between the music and sucrose groups at all time points post heel prick. The pain scores remained significantly lower in the combination treatment group compared with music or sucrose used alone.

The average values of oxygen saturation and heart rate were compared between the 3 interventions at 1-minute intervals. The graphical trend in oxygen saturations and heart rate is presented in **Figure 3**. The oxygen saturations were tightly distributed amongst the 3 interventions with a range between 96% and 98%. There was variable significance at different time points (**Table II**; available at www.jpeds.com), with a trend for lower saturations in the combination therapy group before and after the heel prick. The heart rate before the heel prick was lower in the music therapy group compared with other 2 groups, but the trend did not persist after heel prick with variable levels of significance (**Table III**; available at www.jpeds.com). There were no unintended side effects of coughing or gagging

Table I. Comparison of PIPP-R scores

Times (min)	PIPP-R music (n = 35), median (IQR)	PIPP-R sucrose (n = 35), median (IQR)	PIPP-R music + sucrose (n = 35), median (IQR)	Friedman test (*P* value)	Post hoc analysis music vs sucrose (*P* value)	Post hoc analysis music + sucrose vs sucrose (*P* value)	Post hoc analysis music + sucrose vs music (*P* value)
Baseline	0 (0-3)	0 (0-2)	0 (0-1)	.48	.87	1.00	.79
1	6 (3-11)	5 (3-10)	3 (0-4)	<.001†	1.00	<.001†	<.001†
2	6 (0-9)	4 (0-12)	0 (0-3)	<.001†	.54	.01†	<.001†
3	4 (0-6)	4 (0-8)	0 (0-2)	<.001†	.96	.002†	<.001†
4	4 (0-6)	0 (0-5)	0 (0-3)	.002†	.23	.20	.002†
5	4 (0-5)	0 (0-4)	0 (0-0)	<.001†	.14	.01†	<.001†
6	3 (0-5)	0 (0-4)	0 (0-0)	.002†	.58	.04*	.002†

*$P < .05$.
†$P \leq .01$.

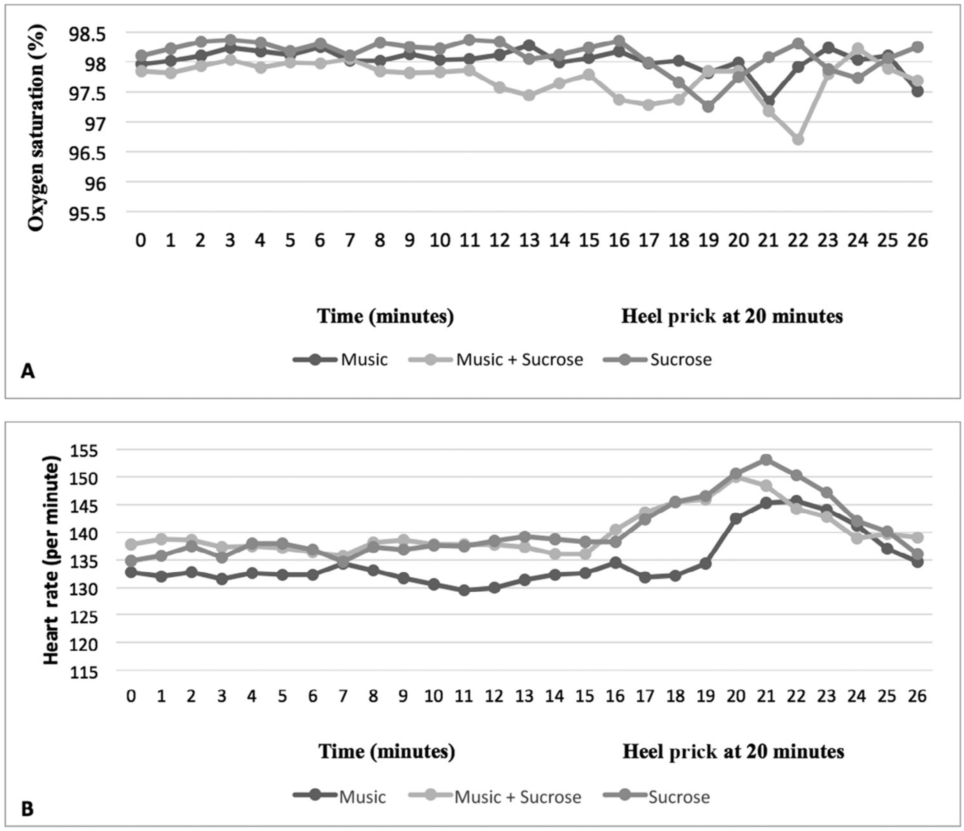

Figure 3. Continuous trend in oxygen saturations and heart rate. Changes in **A,** oxygen saturations and **B,** heart rate, respectively.

associated with significant desaturations and/or bradycardias needing intervention in any of the newborns.

Discussion

This study demonstrated a significant reduction in pain scores by adding music to the current standard of sucrose. Combining music therapy with oral sucrose was beneficial for acute pain relief during heel prick. The significance remained consistent throughout the analyzed time period and supports the inclusion of music therapy as an adjunct modality for pain relief.

Music is increasingly being used in neonatal units to improve behavioral or physiological outcomes. Reported benefits of music are a calmer infant and parent dyad, stable physiological measures, higher oxygen saturation, faster weight gain, shorter duration of hospital stay, and greater milk output in mothers.[19,26-32] In our study, pain scores in the music therapy and sucrose-treated groups were not different. This finding suggests comparable effectiveness of the 2 interventions during heel prick procedure, adding to the list of benefits of music therapy. The reduced pain scores in the combined intervention group point toward a synergistic benefit. More important, the combination did not cause paradoxical agitation or worsening of pain scores. The finding has a practical implication in terms of the potential for reducing the number of required sucrose doses by the addition of music therapy.

A meta-analysis of 30 studies showed significant benefits of music therapy as a supplement to standard medical treatment.[33] The author meta-analysis also noted that live music therapy provided by a board-certified music therapist was more effective than recorded music.[33] There are 2 main limitations in using live music therapy services for heel prick procedures. First, there is paucity of full-time music therapy services worldwide. The use of music therapy has evolved in the US, with the existence of formalized NICU-music therapy training programs; however, similar training programs are nonexistent in most countries. There are too many premature infants undergoing heel prick procedures for their needs to be fully met by the limited number of music therapists.[34] Second, heel pricks are conducted in NICU at variable time points based on neonatal care routines and clinical needs, including at night. The variable timings of these procedures make the use of live music by a music therapist more difficult. We are hopeful that these limitations will be improved in time with development of more music therapy training programs and the availability of funding for a full-time music therapy services in more NICUs, but the current shortfall necessitates the exploration of the use of music in recorded format for the stable neonatal group.

A few studies have evaluated the role of music therapy for heel prick in neonates and have noted beneficial effects. However, there are no blinded studies comparing the use of music with sucrose for heel prick in neonates. Cavaiuolo et al[20] studied the effect of carefully selected recorded Mozart music in preterm neonates undergoing heel prick procedure with a control group of no music. They noted lower pain scores and a significantly lower stress response with favorable effects on heart rate and oxygen saturation. Similarly, Butt et al[21] compared recorded vocal and instrumental versions of Brahm's Lullaby, which had been designed specifically for neonates in consultation with a professional vocalist, versus no music during heel prick in a small crossover trial. These investigators demonstrated that music modulates both physiological (heart rate) and behavioral (state of arousal, facial expressions of pain) responses of preterm infants >31 weeks of age after a heel prick. The findings from our study support implication of music therapy as a synergistic modality with sucrose.

We selected a group of stable late preterm and early term neonates in the interactive/discharge planning phase. Late preterm and early term neonates present a unique group at higher risk of morbidity,[35] and there remains a concern about overstimulation with inappropriate use of music.[34] In a position paper on NICU music therapy practices, Standley[34] has warned against inadvertent use of music without consultation or involvement of an appropriately trained music therapist. The use of music in fragile preterm neonates can cause harm if not carefully coordinated with fetal developmental milestones and cues. Music therapy has a well-established role in pediatrics,[36,37] but is still in the initial stages of development for neonates. There is uncertainty about the effectiveness of various delivery methods such as live versus recorded music and type of music to be used. In the interim, clinicians should use caution in using nontested measures such as radio station broadcasted music or toys that generate music as "music therapy" for newborns.[38]

In the current study, the mean heart rate in the music group was consistently lower compared with the other 2 interventions. The magnitude of the effect was between 2 and 13 beats per minute, which is clinically important, but surprisingly the same effect on the heart rate was not seen in the combined intervention group. The possible explanation is small sample size, which was not powered adequately for this secondary objective. Similarly, oxygen saturation in the combination group (music-sucrose) group was frequently lower, although the magnitude of effect was very small and clinically insignificant.

The strengths of the current study were reliable blinding of the assessor to the intervention and the comparison of music with the current gold standard of sucrose for pain relief during heel prick. One of the major limitations was that we examined the effects of music on a very specific short-term outcome, with no data on long-term neurodevelopmental outcome measures. The crossover study model precluded the ability to evaluate long-term effects. Because we had a small sample size, stratification by gestational age at inclusion and by birth gestation was not possible. Also, the information about the effects of the burden of exposure to prior painful procedures, previous neonatal surgeries, and use of opioid medications, which might modulate pain perception and pain response,[39] could not be derived from the included group of neonates. We evaluated the music effectiveness in a relatively mature and stable neonatal group with a broad gestational age range at the time of study (32-41 weeks of postmenstrual age). This group includes late preterm, early term, and term neonates.[40] Combining term with late preterm neonates in the same group imparts some limitations about the generalizability of the study findings to the group of late preterm and extremely preterm neonates.

The results from the current study showed a consistent and clinically relevant reduction in pain scores by combining recorded music with sucrose. The recorded music was selected carefully in consultation with an accredited music therapist for pain relief during heel prick procedures in the stable late preterm and term neonate population. The results of the study are relevant for hospitals without the availability of music therapy services or when painful procedures are performed at times when a music therapist is not available. Although music therapy has an evolving research base and evidence showing benefits for premature infants, it is not yet a standard of medical care in the US and around the world.[34] Larger, well-designed interventional trials are needed to promote effective pain relief strategies involving music therapy in neonatal care. ■

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References

1. Manley BJ, Doyle LW, Davies MW, Davis PG. Fifty years in neonatology. J Paediatr Child Health 2015;51:118-21.
2. Carbajal R, Rousset A, Danan C, Coquery S, Nolent P, Ducrocq S, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. JAMA 2008;300:60-70.
3. Chen M, Shi X, Chen Y, Cao Z, Cheng R, Xu Y, et al. A prospective study of pain experience in a neonatal intensive care unit of China. Clin J Pain 2012;28:700-4.
4. Simons SH, van Dijk M, Anand KS, Roofthooft D, van Lingen RA, Tibboel D. Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. Arch Pediatr Adolesc Med 2003;157:1058-64.
5. Cruz MD, Fernandes AM, Oliveira CR. Epidemiology of painful procedures performed in neonates: a systematic review of observational studies. Eur J Pain 2016;20:489-98.
6. Batton DG, Barrington KJ, Wallman C. Prevention and management of pain in the neonate: an update. Pediatrics 2006;118:2231-41.

7. Barker DP, Rutter N. Exposure to invasive procedures in neonatal intensive care unit admissions. Arch Dis Child Fetal Neonatal Ed 1995;72:F47-8.
8. Carbajal R, Lenclen R, Gajdos V, Jugie M, Paupe A. Crossover trial of analgesic efficacy of glucose and pacifier in very preterm neonates during subcutaneous injections. Pediatrics 2002;110:389-93.
9. Overgaard C, Knudsen A. Pain-relieving effect of sucrose in newborns during heel prick. Biol Neonate 1999;75:279-84.
10. Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database Syst Rev 2016;(7):CD001069.
11. Taddio A, Shah V, Atenafu E, Katz J. Influence of repeated painful procedures and sucrose analgesia on the development of hyperalgesia in newborn infants. Pain 2009;144:43-8.
12. Stevens B, Yamada J, Lee GY, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database Syst Rev 2013;(1):CD001069.
13. Lefrak L, Burch K, Caravantes R, Knoerlein K, DeNolf N, Duncan J, et al. Sucrose analgesia: identifying potentially better practices. Pediatrics 2006;118(Suppl 2):S197-202.
14. Holsti L, Grunau RE. Considerations for using sucrose to reduce procedural pain in preterm infants. Pediatrics 2010;125:1042-7.
15. Wilkinson DJ, Savulescu J, Slater R. Sugaring the pill: ethics and uncertainties in the use of sucrose for newborn infants. Arch Pediatr Adolesc Med 2012;166:629-33.
16. 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.
17. van Dijk M, Tibboel D, Simons S. Oral sucrose for acute pain studied in more than 7000 neonates, but many questions remain. Arch Dis Child Fetal Neonatal Ed 2017;102:F373.
18. Stouffer JW, Shirk BJ, Polomano RC. Practice guidelines for music interventions with hospitalized pediatric patients. J Pediatr Nurs 2007;22:448-56.
19. Standley J. Music therapy research in the NICU: an updated meta-analysis. Neonatal Netw 2012;31:311-6.
20. Cavaiuolo C, Casani A, Di Manso G, Orfeo L. Effect of Mozart music on heel prick pain in preterm infants: a pilot randomized controlled trial. J Pediatr Neonat Individual Med 2015;4:e040109.
21. Butt ML, Kisilevsky BS. Music modulates behaviour of premature infants following heel lance. Can J Nurs Res 2000;31:17-39.
22. Etzel R, Balk S, Bearer C, Miller M, Shea K, Simon P, et al. Noise: a hazard for the fetus and newborn. Pediatrics 1997;100:724-7.
23. Gibbins S, Stevens BJ, Yamada J, Dionne K, Campbell-Yeo M, Lee G, et al. Validation of the Premature Infant Pain Profile-Revised (PIPP-R). Early Hum Dev 2014;90:189-93.
24. Stevens BJ, Gibbins S, Yamada J, Dionne K, Lee G, Johnston C, et al. The Premature Infant Pain Profile-Revised (PIPP-R): initial validation and feasibility. Clin J Pain 2014;30:238-43.
25. R Development Core Team. R: A Language and environment for statistical computing. Vienna: 2011 Version 3.2.2. AhwR-po.
26. Ak J, Lakshmanagowda PB, G CMP, Goturu J. Impact of music therapy on breast milk secretion in mothers of premature newborns. J Clin Diagn Res 2015;9:CC4-6.
27. Caine J. The effects of music on the selected stress behaviors, weight, caloric and formula intake, and length of hospital stay of premature and low birth weight neonates in a newborn intensive care unit. J Music Ther 1991;28:180-92.
28. Cevasco AM. The effects of mothers' singing on full-term and preterm infants and maternal emotional responses. J Music Ther 2008;45:273-306.
29. Cevasco AM, Grant RE. Effects of the pacifier activated lullaby on weight gain of premature infants. J Music Ther 2005;42:123-39.
30. Whipple J. The effect of parent training in music and multimodal stimulation on parent-neonate interactions in the neonatal intensive care unit. J Music Ther 2000;37:250-68.
31. Yildiz A, Arikan D. The effects of giving pacifiers to premature infants and making them listen to lullabies on their transition period for total oral feeding and sucking success. J Clin Nurs 2012;21:644-56.
32. Vianna MN, Barbosa AP, Carvalhaes AS, Cunha AJ. Music therapy may increase breastfeeding rates among mothers of premature newborns: a randomized controlled trial. J Pediatr (Rio J) 2011;87:206-12.
33. Standley JM. Efficacy of music therapy for premature infants in the neonatal intensive care unit: a meta-analysis. Arch Dis Child Fetal Neonatal Ed 2011;96:Fa52.
34. Standley JM. Premature infants: perspectives on NICU-MT practice. Voices: A World Forum for Music Therapy [S.I.] 2015;14. doi:10.15845/voices.v14i2.767.
35. Raju TN, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics 2006;118:1207-14.
36. Ghetti CM. The future of medical music therapy for children and adolescents. In: Dileo C, ed. Envisioning the future of music therapy. Temple University's Arts and Quality of Life Research Center; 2016. p. 62-70 [Chapter 7] http://www.temple.edu/musictherapy.
37. National Guideline Clearinghouse. Best evidence statement (BESt). The effects of music therapy on well-being in pediatric inpatients. Rockville MD: Agency for Healthcare Research and Quality (AHRQ); 2012. https://www.guideline.gov/summaries/summary/36088/best-evidence-statement-best-the-effects-of-music-therapy-on-wellbeing-in-pediatric-inpatients. Accessed June 30, 2017.
38. Arnon S. Music therapy intervention in the neonatal intensive care unit environment. J Pediatr (Rio J) 2011;87:183-5.
39. Gokulu G, Bilgen H, Ozdemir H, Sarioz A, Memisoglu A, Gucuyener K, et al. Comparative heel stick study showed that newborn infants who had undergone repeated painful procedures showed increased short-term pain responses. Acta Paediatr 2016;105:e520-5.
40. Raju TN. The "late preterm" birth-ten years later. Pediatrics 2017;139.

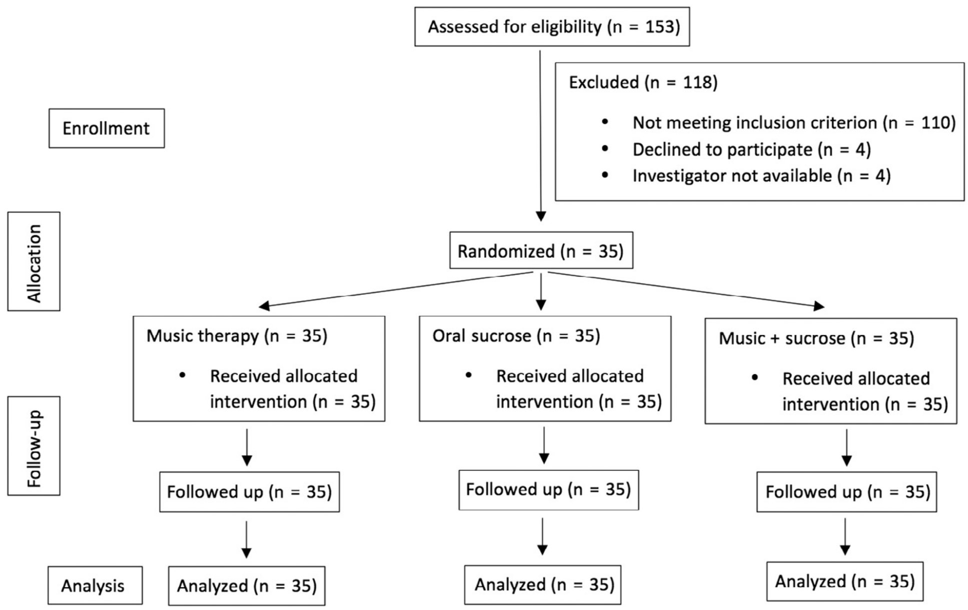

Figure 2. CONSORT flow diagram.

Table II. Comparison of mean oxygen saturations

Times in relation to heel prick (min)	Music	Music + sucrose	Sucrose	Music vs sucrose (*P* value)*	Music vs music + sucrose (*P* value)*	Sucrose vs music + sucrose (*P* value)*
Before heel prick						
Baseline	98.0 (2.7)	97.9 (2.2)	98.1 (2.5)	.06	.23	**.004**
1	98.0 (2.4)	97.8 (2.3)	98.2 (2.1)	.008	.008	**<.001**
2	98.1 (2.1)	97.9 (2.2)	98.3 (1.8)	.001	.02	**<.001**
3	98.2 (2.1)	98.0 (2.0)	98.4 (1.9)	.04	.005	**<.001**
4	98.2 (2.3)	97.9 (2.0)	98.3 (1.9)	.02	**<.001**	**<.001**
5	98.1 (2.2)	98.0 (2.0)	98.2 (2.0)	.37	.02	**.004**
6	98.3 (2.4)	98.0 (2.2)	98.3 (1.9)	.39	**<.001**	**<.001**
7	98.0 (2.5)	98.1 (2.0)	98.1 (2.1)	.22	.67	.41
8	98.0 (2.5)	97.8 (2.3)	98.3 (2.0)	**<.001**	.02	**<.001**
9	98.1 (2.2)	97.8 (2.4)	98.3 (2.1)	.09	**<.001**	**<.001**
10	98.0 (2.3)	97.8 (2.2)	98.2 (2.1)	.01	.02	**<.001**
11	98.0 (2.1)	97.9 (2.0)	98.4 (2.0)	**<.001**	.02	**<.001**
12	98.1 (2.2)	97.6 (2.5)	98.3 (1.8)	.002	**<.001**	**<.001**
13	98.3 (1.9)	97.5 (3.4)	98.1 (1.9)	.001	**<.001**	**<.001**
14	98.0 (2.7)	97.6 (2.9)	98.1 (2.3)	.19	.002	**<.001**
15	98.1 (2.5)	97.8 (2.3)	98.2 (2.6)	.09	.003	**<.001**
16	98.2 (2.2)	97.4 (2.6)	98.4 (1.9)	.008	**<.001**	**<.001**
17	98.0 (2.4)	97.3 (4.0)	98.0 (2.6)	.90	**<.001**	**<.001**
18	98.0 (2.7)	97.4 (3.4)	97.7 (3.4)	.002	**<.001**	**.004**
19	97.8 (2.8)	97.9 (2.3)	97.3 (4.1)	**<.001**	.83	**<.001**
Heel prick						
20	98.0 (2.1)	97.8 (2.1)	97.8 (2.8)	.005	.05	.31
21	97.4 (3.9)	97.2 (4.7)	98.1 (2.5)	**<.001**	.40	**<.001**
22	97.9 (2.8)	96.7 (6.4)	98.3 (2.2)	**<.001**	**<.001**	**<.001**
23	98.2 (2.2)	97.8 (3.1)	97.9 (2.8)	**<.001**	**<.001**	.53
24	98.0 (2.2)	98.2 (1.8)	97.7 (2.8)	.001	.005	**<.001**
25	98.1 (2.2)	97.9 (2.0)	98.1 (2.2)	.53	.004	**.008**
26	97.5 (3.6)	97.7 (2.1)	98.3 (2.1)	**<.001**	.12	**<.001**

Values are mean (SD). Highly significant values are marked as bold.
*Two-tailed *P* value.

Table III. Comparison of average heart rates

Times in relation to heel prick (min)	Music	Music + sucrose	Sucrose	Music vs sucrose (*P* value)*	Music vs music + sucrose (*P* value)*	Sucrose vs music + sucrose (*P* value)*
Before heel prick						
0	133 (16)	138 (18)	135 (19)	**<.001**	**<.001**	**<.001**
1	132 (14)	139 (20)	136 (20)	**<.001**	**<.001**	**<.001**
2	133 (14)	139 (20)	137 (22)	**<.001**	**<.001**	.03
3	132 (14)	137 (20)	135 (19)	**<.001**	**<.001**	**<.001**
4	133 (13)	138 (19)	138 (20)	**<.001**	**<.001**	.48
5	132 (14)	137 (18)	138 (19)	**<.001**	**<.001**	.14
6	132 (15)	136 (17)	137 (19)	**<.001**	**<.001**	.33
7	134 (16)	136 (16)	135 (16)	.51	**.004**	.02
8	133 (15)	138 (19)	137 (18)	**<.001**	**<.001**	.08
9	132 (16)	139 (18)	137 (19)	**<.001**	**<.001**	.003
10	131 (15)	138 (17)	138 (20)	**<.001**	**<.001**	.92
11	130 (16)	138 (19)	138 (18)	**<.001**	**<.001**	.59
12	130 (15)	138 (19)	138 (20)	**<.001**	**<.001**	.30
13	131 (14)	137 (18)	139 (22)	**<.001**	**<.001**	.003
14	132 (16)	136 (17)	139 (19)	**<.001**	**<.001**	**<.001**
15	133 (17)	136 (16)	138 (19)	**<.001**	**<.001**	**<.001**
16	134 (17)	140 (18)	138 (18)	**<.001**	**<.001**	**<.001**
17	132 (15)	144 (16)	142 (18)	**<.001**	**<.001**	.02
18	132 (16)	146 (17)	146 (18)	**<.001**	**<.001**	.97
19	134 (16)	146 (17)	147 (17)	**<.001**	**<.001**	.13
Heel prick						
20	143 (18)	150 (18)	151 (18)	**<.001**	**<.001**	.25
21	145 (21)	149 (19)	153 (22)	**<.001**	**<.001**	**<.001**
22	146 (22)	144 (19)	150 (22)	**<.001**	**.04**	**<.001**
23	144 (24)	143 (21)	147 (23)	**<.001**	.09	**<.001**
24	141 (25)	139 (19)	142 (19)	.28	**.001**	**<.001**
25	137 (22)	140 (19)	140 (19)	**<.001**	**<.001**	.42
26	135 (22)	139 (17)	136 (19)	.05	**<.001**	**<.001**

Values are average (SD). Highly significant values are marked as bold.
*Two-tailed *P* value.