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Effects of Music on Physiological and Behavioral Indices of Acute Pain and Stress in Premature Infants: Clinical Trial and Literature Review

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Abstract

Infants in intensive care units often undergo medically necessary heel-stick procedures. Because the risks of administering analgesics and anesthetics are often thought to outweigh the benefits, there remain no proven means of ameliorating the pain and stress these infants suffer, particularly during procedures. This study examined the controlled use of recorded vocal music to attenuate physiological and behavioral responses to heel stick in 13 premature infants via an experimental design. In both instances, infants exposed to music and infants in the control group, heart rate, and respiration rate increased during the heel-stick procedure (P's $= .02$) and nearly all infants cried. During a 10-minute recovery following the heel stick, heart rate, and crying significantly decreased in infants exposed to music ($P = .02$) but not in unexposed infants. Controlled music stimulation appears to be a safe and effective way to ameliorate pain and stress in premature infants following heel sticks.

Keywords

NICU music, infant, heart rate, pain, heel stick, premature

Introduction

Ample empirical evidence indicates that music stimulates cognitive, emotional, and sensorimotor processing across widely distributed brain regions.[1,2] The strong physiological and emotional effects of music on many listeners[3,4] and the wealth of qualitative and quantitative findings provided by music therapy[5-8] motivate the development of standardized protocols for the use of music in a wide range of clinical settings. Prospective, randomized-controlled clinical trials are needed in order to elucidate how music's effects can be harnessed to ameliorate suffering and, possibly, decrease morbidity and mortality independent of, and additive to, benefits related to therapist skills.[5,6] Two recent Cochrane Database reviews have examined the use of music for pain relief[9] and end-of-life care.[10]

Neonates, especially premature infants, constitute a needy population of patients who might benefit from the implementation of standardized protocols incorporating music for analgesia, stress reduction, and auditory enrichment.[9,11-13] The human cochlea is anatomically developed by 24 weeks gestational age,[14] and auditory evoked responses have been recorded in premature infants as early as 26 weeks gestational age.[15,16] The results of many recent studies of the fetus and infant are consistent with the notion that perceptual competence develops prenatally.[17,18] Fetuses from 27 to 35 weeks gestational age demonstrate behavioral habituation to auditory stimuli.[19] Heart rate (HR) changes in response to music have been observed in fetuses of 28 to 38 weeks gestational age.[20] Functional Magnetic Resonance Imaging (fMRI) studies indicate left temporal lobe activation to sound in fetuses at 33 weeks gestational age.[21] Newborns demonstrate ERP sensitivity to 10% deviations in tonal frequency.[22] Approximately, 12% of the US births are premature (ie, before 37 weeks)[23]; about half of these require immediate hospital admission and many need long-term care. Neurological complications of premature birth include learning disorders in as many as 2 in 5 school-age

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children,[24] a 2.6 relative risk for attention deficit hyperactivity disorder (ADHD),[25] and a significant risk of hypothalamic-pituitary dysfunction.[26] Developmentally, sensitive care that incorporates noise management as well as human contact and other "positive" stimuli appear to improve clinical outcome and decrease costs associated with inpatient care for premature infants.[27-32]

The acoustic environment in which many premature infants spend their first days-to-months of life—hospital neonatal intensive care units (NICUs) and special care units (SCUs)—is at once impoverished and chaotic.[33] Whether lying in a bassinet or enclosed in a temperature-controlled isolette on mechanical-assisted ventilation, hospitalized infants are exposed to little in the way of speech, music, and other ethologically relevant sounds important for normal language and social development. Even worse, the sound environment is filled with unpredictable, sometimes loud acoustic stimuli (eg, alarms indicating a potentially dangerous change in a physiological measure).[34] The ambient sound level in an NICU can reach intensities as high as 90 dB SPL, several-fold louder than the ambient intrauterine intensities the infant had been accustomed to (50 dB SPL).[35,36] Moreover, NICU sounds contain high as well as low frequencies, whereas the intrauterine environment only allows low-frequency sounds (less than 250 Hz) to reach the infant. Infants born before 36 weeks may be especially sensitive, and thus vulnerable, to the effects of an impoverished, chaotic auditory environment because their auditory discrimination capabilities are immature,[37] and they remain unable to visually identify the sources of sound and have limited exposure to faces and visual scenes in general. The infant's heightened auditory sensitivity requires that physicians and nurses determine the type, dose, and dose interval of acoustic stimuli empirically. What the optimal auditory conditions are, and how they could be provided in the NICU environment, remain unknown. The American Academy of Pediatrics[38] and the National Association of Neonatal Nurses[39] have proposed a number of procedural and technical strategies to reduce ambient noise. One study of 30 premature infants showed that wearing earmuffs significantly increased quiet sleep time.[40] Another study of 24 very low birthweight neonates found that wearing silicone earplugs significantly increased weight gain.[41] However, there remains the possibility that quiet is suboptimal because stimulation with music or other natural sounds would promote development while avoiding the potential deleterious consequences of decreasing auditory and multimodal stimulation (for reviews see Philbin[42] and Aucott et al[43]). Several researchers have explored the potential benefits of auditory stimulation with music in the NICU environment.[6,5,44] In their recent review, Hartling et al[5] found that the researchers have used a variety of musical types (eg, vocal vs instrumental, folk vs classical), presentation methods (recorded vs live), and acoustic environments (eg, music alone vs with intrauterine sounds) in the NICU.[5] Methodological consideration, as the authors point out, preclude a straight forward interpretation of how the type of music and its presentation affect physiological and behavioral responses. Auditory stimulation, controlled with respect to music type, intensity, presentation, dose, and dose-interval, could counter the effects on unpredictable noise in the NICU environment and promote normal auditory and cognitive development via exposure to the language and music of the infant's culture.

Acutely painful stimuli typically cause increases in HR, respiration rate, blood pressure, plasma cortisol levels, facial grimacing, crying and body movements, and decreases in oxygen saturation (O_2-sat).[45,46] These responses, which could reflect an internal state of stress, can be difficult to appreciate in the most vulnerable premature infants because their immature central nervous system precludes their ability to generate all the components of a stress response.[47,48] Even routine procedures administered to hospitalized infants have been shown to elicit a stress response.[49,50] A recent study of 430 infants admitted to NICUs in Paris found that on average, each infant received 12 painful procedures daily during their first 2 weeks in the NICU.[51] In another study, 54 infants admitted to a NICU over a 3-month period experienced 3283 invasive procedures.[52] The majority (56%) involved the "heel-stick" (aka "heel lance," "heel prick") procedure, a painful method of obtaining blood for serologic analyses in which the infant's heel is pierced with a sterile needle and squeezed repeatedly to express blood through the puncture site. The high metabolic demands of these repeated stressors could decrease energy stores available for growth. Moreover, adrenocortical responses to repeated stressful stimuli might weaken the infant's immune system and increase the risk of illness.[53,54] Grunau[55] has hypothesized that infants who receive frequent medical interventions without "positive" or soothing stimuli may develop a low pain threshold or become hypersensitive to touch. Recent evidence shows that 3- to 18-month preterm babies have abnormal basal cortisol levels[56] and that 4-month-old infants have abnormal cortisol responses during pain associated with immunizations.[57] Abnormal cortisol levels may be one mechanism by which early pain exposure could compromise brain development.[55] This, in turn, could contribute to learning, attentional, and behavioral problems later in childhood.[58]

Although infants undergo many painful procedures and may perceive pain more acutely than do adults, pain management for this population is less than optimal.[51,59-61] There is wide variation in the use of pharmacological analgesics in NICUs,[62] which increase fluid retention and bilirubin levels and routinely raise concerns about CNS depressant effects, including respiratory depression. Standardized protocols for nonpharmacological analgesia are lacking, and NICU personnel may not be adequately trained in pain assessment, management, and prevention.[63] A better understanding of nonpharmacological treatments is needed to advance the development of protocols to alleviate pain and stress without the risks of potential medication side effects.[33] As a noninvasive, analgesic, and anxiolytic intervention, controlled auditory stimulation with music may provide a treatment with a high benefit:risk ratio. The present study tests the hypothesis that music attenuates physiological and behavioral responses to heel stick.

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Table 1. Age, Sex, Weight, and Apgar Scores of Participants

Infant	Sex	Age (days)	Birth weight (g)	GA at birth (weeks: days)	1 m Apgar	5 m Apgar
1C	Male	28	1200	30:6	—	—
2C	Male	28	1260	30:6	7	8
3C	Male	4	1790	34:0	8	9
5C	Male	4	2305	34:3	8	9
6C	Female	1	1780	34:0	8	9
7C	Female	11	1900	31:5	7	7
1T	Male	16	1960	32:4	5	9
2T	Male	35	1260	30:6	7	8
3T	Female	4	2195	34:0	8	9
4T	Female	4	2160	34:0	7	8
5T	Female	4	2175	34:3	4	9
6T	Male	1	2600	34:0	9	9
7T	Male	10	1800	32:4	8	8

Abbreviations: C, control; T, treatment.

Methods

The study protocol was approved by the Institutional Review Boards of the hospital and university where the study was conducted.

Participants

All participants were premature infants in the hospital SCU. All admission logs and medical charts were reviewed soon after patients were admitted to the unit. We identified infants who met the following selection criteria for inclusion: (1) gestational age less than 36 weeks and birth weight no more than 2600 g, (2) not on a ventilator or receiving oxygen inhalation therapy for respiratory illness, and (3) no neurological disease. Individual cases were reviewed with nurses caring for each infant. Parents/guardians received a recruitment letter detailing the study; they were given one week to decide about participation and were offered a video of their infant on DVD as a reward for participation at the conclusion of the study. Parents/guardians and nurses were instructed not to play music to the infant from the time of enrollment to the experimental procedure.

Written consent was obtained from the parents of 14 infants. Participants were pseudorandomized into the treatment group (N = 7 [4 males]) and control group (N =7 [5 males]) irrespective of sex and ethnicity. In total, 6 participants were from 3 fraternal twin pairs and 2 participants were from fraternal triplets; in these cases, one sibling was assigned to the treatment group and the other to the control group. Data for one male infant in the Control Group were excluded from the analysis because of a protocol violation: a parent played recorded music to him several hours a day. Each infant was tested individually in her/his isolette.

The age, sex, birthweight, gestational age, and Apgar scores of each participant are listed in Table 1. The median gestational age for the control group was 33 weeks, one day; for the Treatment Group, the median gestational age was 34 weeks. The median postdelivery age at the time of study was 7.5 days for the control group and 4 days for the treatment group. All infants had 5-minute Apgar scores of 7 or greater. There were no significant differences between groups for any of these background variables. The parents of all infants were English-speaking.

Special Care Unit Environment and Routine Care

All infants were admitted to the SCU under the care of an attending perinatologist, pediatrician, or nurse practitioner. Infants were housed in closed or open isolettes. The standard SCU protocol called for serologic testing every Sunday night or Monday morning. Heel sticks typically occurred between the hours of 9 and 11 PM or between 4 and 6 AM, just before night time or morning feeding, respectively. Standard approaches to developmentally sensitive care were implemented throughout the infants' SCU stays (eg, swaddling, covering incubators to limit bright light exposure, limiting loud conversation).

We measured the ambient sound level in the SCU on multiple occasions. A Quest Technologies Impulse Sound Level Meter Model 2700 was held at the head of an empty, open isolette. During daytime hours, the ambient sound level was approximately 62 dBA; at night, 56 dBA.

Auditory Stimulation

We listened to several commercially available CDs of lullabies sung by females in English. We selected one (SRT Music Group[64]) in which the lullabies were performed with simple accompaniment at moderate tempo.

For each patient, the total music stimulation time was 10 minutes. We avoided starting the music shortly before and during the heel stick because we did not want the patient to associate music with the painful stimulus. We used a 10-minute window of observation because this provided a sufficient time window for normalization or near-normalization of pain-induced changes in outcome variables.

Recordings of 3 complete songs and part of a 4th were presented in the 10-minute music stimulation window: (1) "Row Row Row Your Boat" (duration = 3 minutes, 9 seconds), (2) "Baa Baa Black Sheep" (3:00), (3) "Are You Sleeping" (2:23), and (4) the first 1:28 of "Rock a Bye Baby" (original song length of 3:06). Each song began with a short instrumental introduction (range = 6-26 seconds) followed by a sung melody whose pitches ranged from E3 to C5# on the equal-tempered scale (fundamental frequencies = 164.8-554.4Hz, A4 = 440 Hz) and a moderate tempo of 84 to 88 beats per minute in 4/4 or 3/4 meter. Each recording contained only 3 to 4 instrumental voices with timbres varying among electric piano, electric organ, glockenspiel, and synthetic sounds. We chose traditional Western lullabies sung in English by a female because we thought they would have the highest probability of achieving a beneficial effect for our Western, English-speaking population, and because a female voice (ie, mother's voice) is the one most frequently heard prenatally in the womb. Moreover, lullabies include both music and speech sounds, have cross-cultural significance in parent-infant communication, and have been shown to improve longer-term endpoints, such as weight gain in hospitalized infants.[65]

Each CD track was converted to a monophonic mp3 file and uploaded onto an Apple iPod. Stimuli were presented at an intensity of approximately 70 dBA using one JBL Duet speaker placed in the sagittal midline at the foot of the infant's isolette, approximately 50 cm from her/his head, outside the field of the heel-stick procedure. The advantages of using a single speaker playing a monophonic recording (less space, fewer wires) outweighed the advantages of using 2 speakers playing a stereo recording, in our opinion, because we did not hypothesize that this difference in the spatial mix of the music would influence the results. The iPod was placed on a small dock at the bedside.

Physiological Responses

For each infant, HR, respiratory rate (RR), and O_2-sat were continuously monitored before, during, and after the heel-stick procedure using a GE Medical Clinical Information Center Pro system. During 1 to 2 minutes before the heel-stick procedure, throughout the procedure, and during the first 4 minutes postprocedure, a trained observer (ML or CV) recorded at least 4 measurements of each of the 3 dependent variables per minute. At the beginning of the study, data were recorded every 15 seconds online in real time by reading the output of the HR, RR, and O_2-sat monitors. About halfway through the study, we were able to analyze the output of the monitors offline, which recorded data every 2 seconds, after data collection was finished. Finally, during the last half of the post heel stick epoch, data were sampled at 3 points: 5, 7, and 10 minutes postprocedure. For the purpose of population data analyses, data collected preprocedure, during the procedure, and $\leq$4 minutes postprocedure were calculated using a bin width of 15 seconds. We checked that there were no significant differences between the means calculated from 15 seconds sample points and 2 seconds sample points for each dependent variable.

Behavioral Responses

Behavioral responses were recorded before, during, and after the heel-stick procedure with a Samsung SCD-23 digital video camera. At the start of the procedure, the camera was mounted on a tripod at the foot of the isolette; after the nurse completed the heel-stick procedure, the camera was moved closer to the infant alongside of the isolette. Digital videos were converted to QuickTime movie files for offline analysis. We initially aimed to code whether or not each of the following behaviors occurred before, during, and after the heel-stick procedure: (1) eye-opening, (2) head movements, and (3) crying. However, we were unable to reliably code eye-opening and head movements. Behavioral data could not be collected during blood collection for 3 babies because the nurse blocked the camera's view; in general, reswaddling of infants following heel stick compromised the observations of changes in behavior. Behavioral data from one infant was lost due to equipment malfunction.

Experimental Procedure

Figure 1 depicts the timeline of the heel-stick procedure, auditory stimulation (for the treatment group), and data collection. The heel-stick procedure was performed by Registered Nurses caring for the SCU patients. Stimuli were presented and data collected by 1 of the 2 investigators (ML or CV), who were trained in experimental psychology, acoustic calibration, and music.

First, with the infant at rest, undisturbed in her/his isolette, we recorded baseline HR, RR, and O_2-sat data and started the video. Second, during the prepuncture handling period, a nurse prepared the infant's heel with a warm pad followed by an alcohol swab. There were differences among nurses with respect to preparation routine and pre and post heel-stick swaddling. In all, 2 infants in the control group and 2 in the treatment group were swaddled at baseline and remained so throughout the heel-stick procedure and recovery period. One infant in the control group and 2 in the treatment group were not swaddled at baseline and remained unswaddled throughout the heel-stick procedure and recovery period. One infant in the Control Group was swaddled at baseline, unswaddled during handling and blood collection, and remained unswaddled during the recovery period. One infant in the control group was not swaddled at baseline, remained unswaddled during handling and blood collection, and then swaddled during postpuncture handling and the recovery period. A total of 3 infants in the treatment group were swaddled at baseline, unswaddled during handling and blood collection, and reswaddled during postpuncture handling and the recovery period. Four infants in the control group and 4 in the treatment group were given a pacifier during prepuncture handling; 2 of the pacifiers given to the control group and all 4 given to the treatment were sweetened

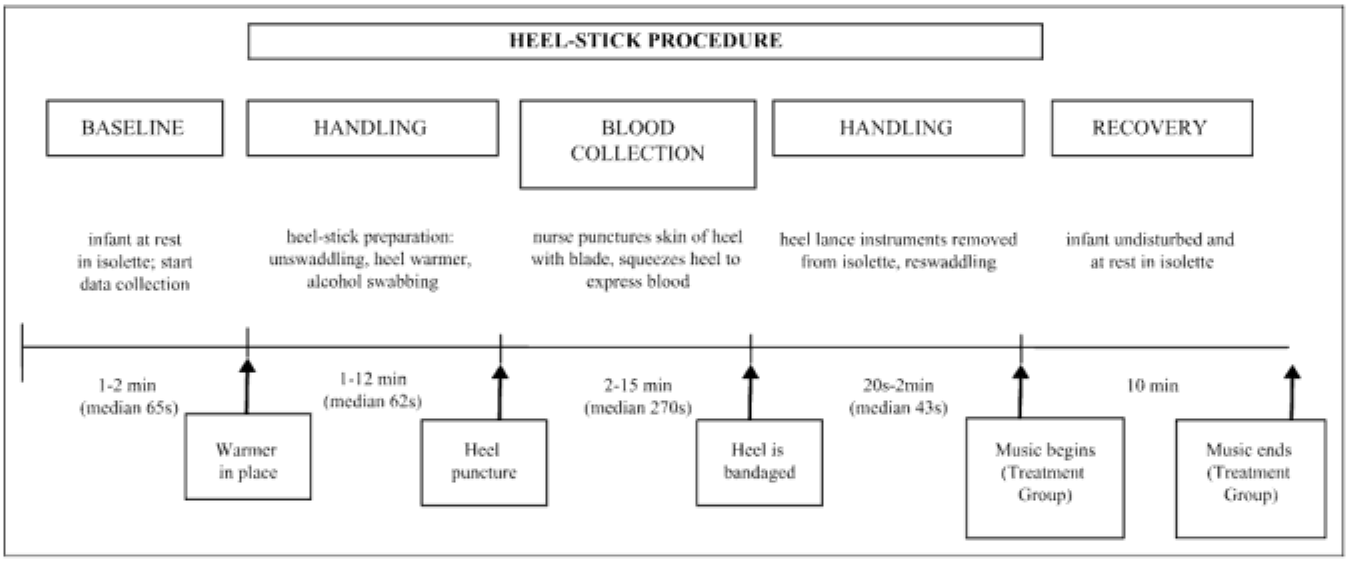

Figure 1. Experimental procedure.

with sucrose. Blood collection began with the nurse puncturing the skin of the prepped heel using a sterile, spring-loaded blade; squeezing of the heel to collect blood into a tube followed. Following blood collection and subsequent handling, including bandaging of the puncture site, the infants in the treatment group were stimulated with music for 10 minutes.

Statistical Analysis

After collecting data from 13 infants over 8 months, we examined our data using nonparametric statistics (Wilcoxon Signed-Rank Test) to compare the physiological-dependent variables before, during, and following the heel-stick procedure. Persistence or cessation of crying from the heel-stick to the recovery period was compared between the treatment and control groups using Pearson χ^2 test. Given that we had tested our working hypothesis at this juncture, we ceased enrollment of additional infants.

Results

Physiological Results

Figure 2A-C illustrates HR, RR, and O_2-sat population data, respectively, collected before and during heel stick and blood collection. There was a significant increase in HR from baseline to blood collection (Wilcoxon Signed-Rank Test [WSRT], $Z = -2.36$, $P = .02$); on average, HR increased 19%. All infants showed an HR increase of at least 5 beats per minute (bpm); in 8 (62%), HR went above normal limits (>160 bpm). There was no significant increase in HR coefficient of variation (CV) across the 2 epochs (WSRT, $Z = -0.53$, $P = .60$).

There was a significant increase in RR from baseline to blood collection (WSRT, $Z = -2.24$, $P = .02$]; on average, RR increased 39%. All infants showed an increase of at least 5 inspirations per minute (ipm); in 10 (77%), RR went above 40 ipm. There was also a significant increase in RR CV (WSRT $Z = -2.37$, $P = .02$).

There was no significant change in O_2-sat from baseline to blood collection (WSRT, $Z = -0.14$, $P = .89$). The nadir O_2-sat fell below 90% for only 3 infants. There was no significant change in O_2-sat CV (WSRT, $Z = -1.07$, $P = .29$).

Figure 3A-C illustrates HR, RR, and O_2-sat population data, respectively, collected during blood collection and the 10-minute recovery period (Figure 3). In the treatment group, there was a significant decrease in HR across the 2 epochs (WSRT $Z = -2.37$, $P = .02$). On average, HR decreased 17%. In 6 of the 7 infants (86%) in the treatment group, HR decreased by 10 bpm or more. In the control group, there was no significant change in HR (WSRT $Z = -1.15$, $P = .25$), average HR decreased only 6%, and only 3 of the 6 infants (50%) showed an HR decrease of 10 bpm or more. No significant change in HR variability during recovery versus blood collection was found for either the treatment group (WRST $Z = -0.68$, $P = .50$) or the control group (WSRT $Z = -1.07$, $P = .29$). There was no significant change in RR or RR CV from blood collection to recovery in either the treatment group (respectively, WSRT $Z = -0.34$, $P = .74$; $Z = -0.08$, $P = .93$) or the control group ($Z = -1.36$, $P = .17$; $Z = -0.94$, $P = .35$).

There was no significant change in O_2-sat or O_2-sat CV from blood collection to recovery in either the treatment group (respectively, WSRT $Z = -0.17$, $P = .86$; $Z = -0.81$, $P = .42$) or the control group ($Z = -0.21$, $P = .83$; $Z = -0.37$, $P = .71$).

To further depict the time course of HR, RR, and O_2-sat data across the various epochs of data collection, we present the results from a single premature infant in the treatment group (Figure 4). These are representative of data collected: (1) before and during heel stick and blood collection for the entire study population of 13 infants and (2) after blood collection for the population of 7 infants in the treatment group, who received controlled auditory stimulation with vocal music during the 10-minute recovery period. This patient was a 2.6-kg male twin born at 34 weeks gestation with 1-min and 5-min Apgar scores of 9. He was admitted to the SCU after delivery with a

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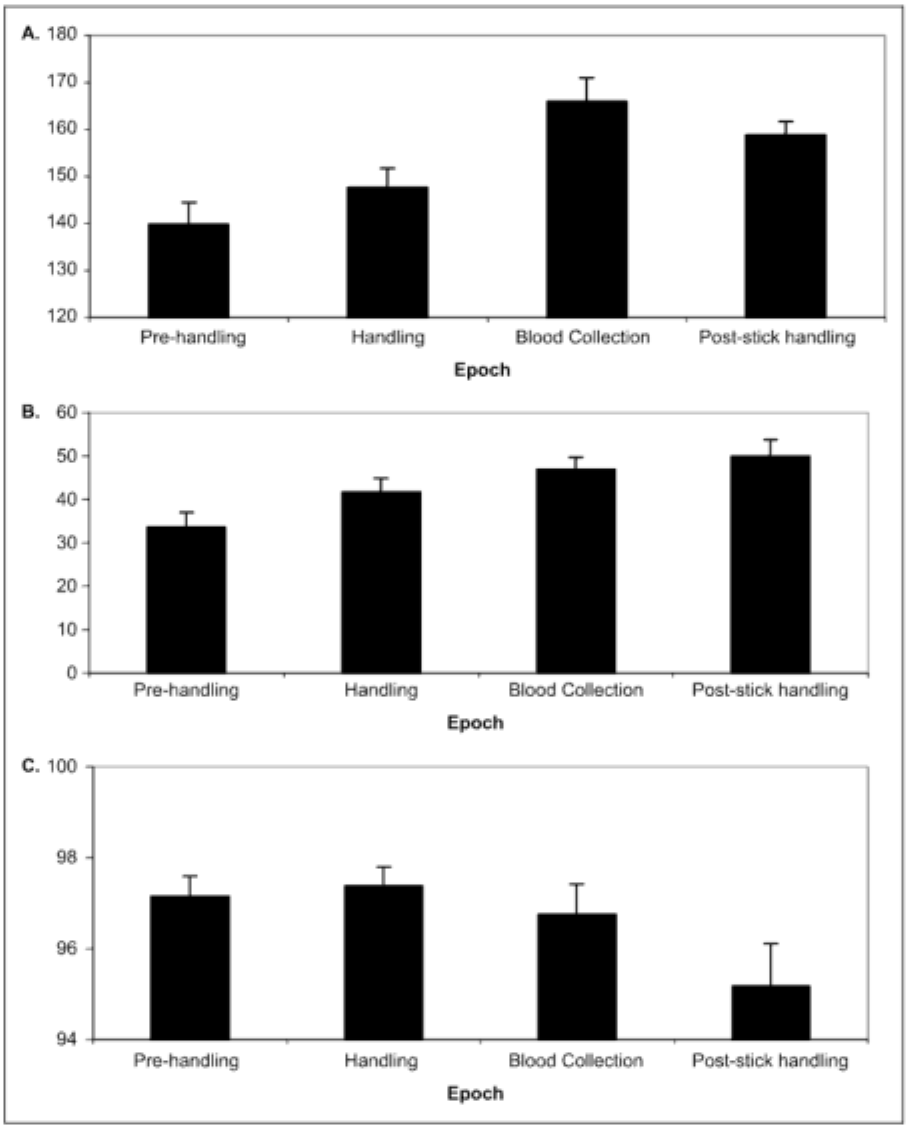

Figure 2. Population data collected before and during heel-stick procedure. Error bars represent ± 1 standard error from the mean.

diagnosis of prematurity. The heel-stick procedure was performed during postnatal day one to check bilirubin levels. Ten minutes before skin puncture, his foot was unswaddled and prepped with a warming pad. In the minutes before skin puncture, the patient was lying quietly with his eyes closed and no head movements; the HR ranged from 118 to 132 bpm (mean = 121 bpm; CV = 17%). During the 33 seconds of handling prior to skin puncture, HR rose to 141 bpm; he remained quiet and still with eyes closed. Immediately upon skin puncture, he began to cry; by 10 seconds postpuncture, HR was 153 bpm, by 30 seconds it was above the normal limit of 160 bpm (161 bpm), and by one minute it was 178 bpm (47% above the baseline mean). During blood collection, mean HR was 175 bpm, and the CV rose to approximately 5 times what it was at baseline; the peak HR was 192 bpm (59% above baseline) at 150 seconds postpuncture. The infant cried for more than 3 minutes, until he was given a pacifier; his eyes remained closed, and no head movements were discernable. Heart rate began to decline after blood collection when the heel was bandaged. The heel remained unswaddled throughout the postpuncture-handling period and recovery period. During the 10 minutes of auditory stimulation with vocal music, HR continued to decline until approximately 100 seconds posthandling, when it reached a plateau of 125 bpm, near the baseline mean of 121 bpm. He remained quiet with his eyes closed, and he made a total of only 5 brief head movements.

Changes in RR paralleled those of HR (Figure 4B). At baseline, mean RR was 24.5 ipm with a CV of 4.5%. During prepuncture handling, RR rose slightly, but immediately after skin puncture, when the infant began to cry, RR rose precipitously and became highly variable. During blood collection, RR peaked at 83 ipm approximately 100 seconds postpuncture, and mean RR rose to 46.3 ipm, 89% above baseline, with a 31% increase in CV. Within 100 seconds after initiation of auditory stimulation, RR decreased, though its mean and variance remained elevated relative to baseline.

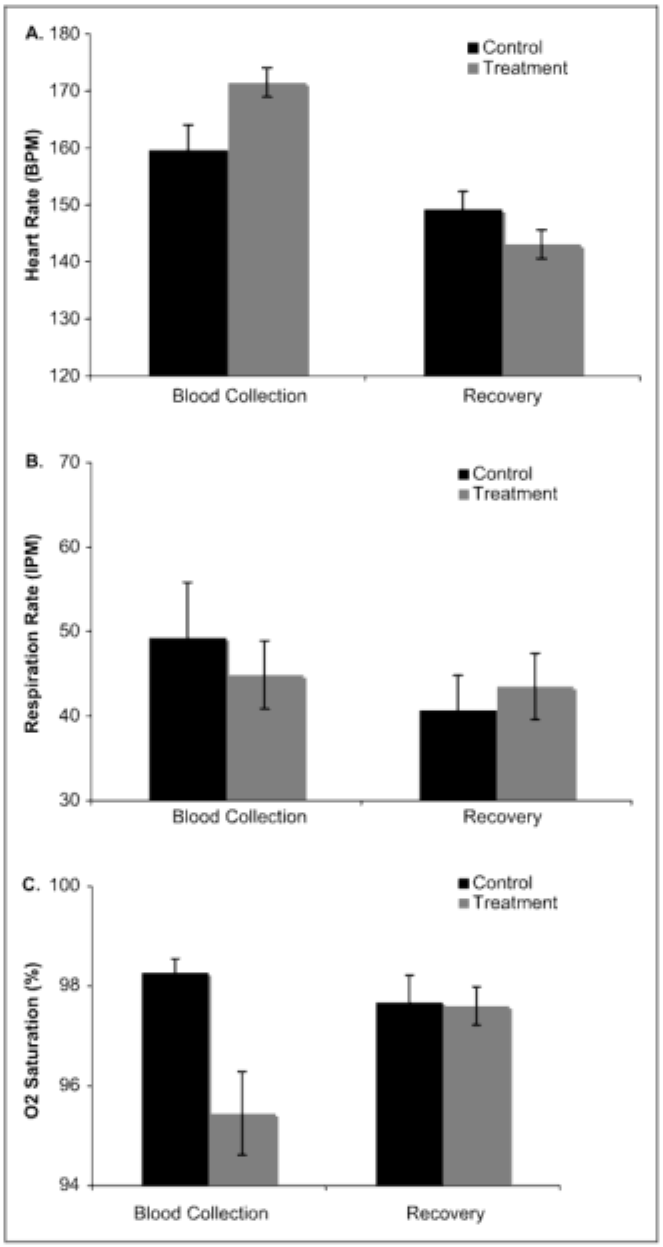

Figure 3. Population data collected during blood collection and recovery.

Oxygen saturation data for this infant are shown in Figure 4C. Immediately after skin puncture and initiation of crying, O_2-sat declined and its variance increased. With auditory stimulation, O_2-sat immediately began to rise and its variance decreased. Oxygen saturation reached a plateau of approximately 98.5% within 100 seconds.

Behavioral Results

Behavioral data could be reliably recorded in 9 infants: 4 in the Treatment Group, 5 in the Control Group. During the heel-stick procedure, 8 out of the 9 cried. Crying ceased in all 4 infants who received auditory stimulation with vocal music during the recovery period, whereas 2 of the 4 infants in the Control Group continued to cry during the recovery period. There was a trend for a significant χ^2-test comparing cessation vs continuation of crying in the Treatment vs Control group ($\chi^2 = 2.667$, $P = .10$) though the small sample size renders the significance test questionable. We were unable to reliably code eye opening and head movements owing to logistical problems (ie, view blocked by nurse, variability among nurses in swaddling and pacifier use [as described previously]).

Discussion

The heel-stick procedure is routinely used to obtain blood for serologic analyses in small babies who lack peripheral venous access. The results from our study population of 13 premature infants demonstrate that the procedure precipitates sudden increases in HR, RR, and crying that peak within seconds and are sustained for several minutes after delivery of the acutely painful stimulus. We tested our working hypothesis that controlled auditory stimulation with vocal music attenuates physiological and behavioral signs of stress evoked by heel stick.

We chose traditional Western lullabies as our auditory stimulus because we thought they might have the highest probability of achieving a beneficial effect. Lullabies include both music and human vocal sounds, including words, and are ethologically and ethnologically relevant owing to their rich cross-cultural history in parent-infant communication. In the previous clinical studies, lullabies have been shown to accelerate weight gain in hospitalized infants.[65]

The results show a significant decrease in mean HR over the 10-minute postprocedure period in the treatment group (17% mean HR decrease) but not the control group (6% mean HR decrease). There were no effects of vocal music on RR or O_2-sat. Qualitative differences between the treatment and control groups were also observed for crying. We found no significant difference between the treatment and the control groups with respect to procedure length, so it is unlikely that it contributed to the observed effects on HR and behavior.

Several limitations of our study may hamper its applicability to the general population of premature infants undergoing heel stick. Our population size was small. We studied the effects of music on a single heel stick; our study does not address the potential benefits of repeated music stimulation for the patients in NICU undergoing frequent heel sticks. There was variability across the clinicians with respect to swaddling, pacifier use, and sucrose use. Our results may have been influenced by the fact that a higher proportion of infants in the treatment group (57% vs 33% in the control group) received sucrose before and during the heel-stick procedure. However, the response to the heel stick was equally robust in both groups, and HR increased as much in the treatment group as in the control group during the heel-stick procedure. Our behavioral analyses were limited to crying due to logistical difficulties with video recording in the SCU. Future studies would benefit from using multiple cameras from different angles or a mobile camera to improve the behavioral data collection. With only one small SCU

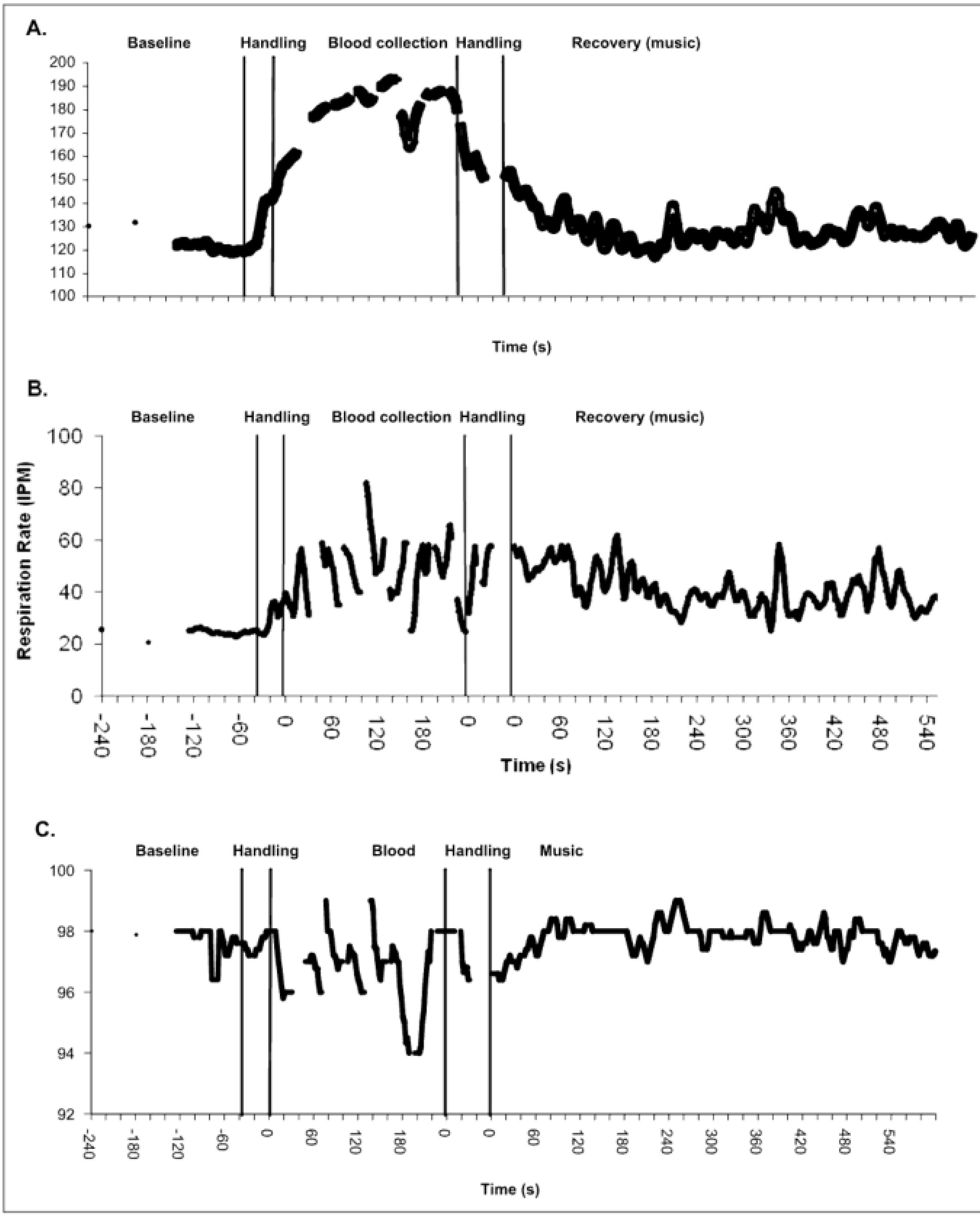

Figure 4. Single-neonate data collected before, during, and after heel-stick procedure.

participating, there were limited numbers of patients available for enrolment. A multisite study would be beneficial to increase the population size and examine reproducibility of results across different centers.

Future studies with larger samples of babies born to English-speaking parents—no less infants from other cultures[66,67]—are needed to corroborate our findings and to ascertain whether different types of music, other auditory stimuli, or other types of ecologically and ethnologically relevant stimuli have more or less of an effect on physiological and behavioral indices of pain and stress. It is possible that live music may have an even greater effect on physiological recovery from heel stick, as a previous study demonstrated a decrease in HR in infants at rest after stimulation with live music, but not with recorded music or no music.[68]

Neural mechanisms mediating the effects of controlled auditory stimulation with music on HR and other aspects of autonomic function have not been fully elucidated. The results of experiments with chicks and rats indicate they are not specific to humans. For example, Sutoo and Akiyama[69] played the Adagio by Mozart (K. 205) repeatedly to spontaneously hypertensive rats for 2 hours on 3 consecutive nights at 65 to 75 dB SPL. The rats' blood pressure as well as their behavioral activity decreased during the music, and the effect persisted for about 30 minutes after the music stopped. Compared to a control group that did not receive music stimulation, treated rats exhibited increased dopamine levels in the neostriatum. Moreover, pretreatment with a D2 receptor antagonist, but not a D1 receptor antagonist, blocked the blood pressure response. These results indicate that music induced the activation of D2 receptors in the neostriatum, which in turn, decreased sympathetic tone.

We restricted the recruitment of participants to premature infants who were free of brain disease and serious illness in order to minimize any risks from auditory stimulation. No complications were observed. Extending the research to include infants who are more compromised is feasible. In general, the younger the neonate at birth, the greater the risk of illness, the greater the number of procedures she/he undergoes, and consequently, the greater the risk of recurrent pain and stress.[52] Further study is needed to determine the age groups and medical conditions of infant populations that benefit from controlled auditory stimulation.

Previous Studies

In general, clinical research on the potential benefits of auditory stimulation with music in premature infants has looked at the endpoints indexing effects of pervasive stress (eg, cardiopulmonary events and weight gain). Relatively little work has focused on specific physiological and behavioral responses to sudden, noxious stimuli, such as those delivered during medical procedures.[70] Recordings of the mother talking soothingly to her baby, digitally filtered to simulate what they would sound like in the womb, failed to attenuate physiological and behavioral responses to heel stick in one study.[71] Whipple found decreased behavioral, but not physiological, indices of pain and stress following heel stick using a music-reinforced, nonnutritive sucking paradigm that employed sung lullabies.[72]

Butt and Kisilevsky[53] investigated the effects of music on physiological and behavioral responses to the heel-stick procedure using a randomized-controlled, single-crossover design with 14 premature infants in levels I, II, and III nurseries. Infants were exposed to both a control and a music condition in 2 separate heel sticks (time lapse between heel sticks unknown). The music stimuli was either an instrumental version of Brahms's Lullaby (Op. 49, No. 4) performed on piano or a vocal version of the same excerpt, performed a capella. The absolute sound intensity, 76 dBA on average, was similar to ours, but the relative stimulus intensity was only about 4 dB (potentially lower for infants receiving mechanical support), compared to about 10 dB in our study. Consequently, the softest portions of the music may have not been audible, thereby rendering music discontinuous. The duration range of heel-stick procedure in their study overlapped with ours, and similar to our study, various aspects of developmentally sensitive care were "neither consistent nor universal." Setting aside reservations about the use of a parametric statistic and multiple post hoc analyses with multiple factors in a small, clinically diverse patient population, and acknowledging differences in statistical and other methods, we note results are paralleling those of this study. First, a 3-way ANOVA carried out on data collected during the heel-stick procedure found an increase in HR, a decrease in O_2-sat, an increase in behavioral arousal score, and an increase in the facial pain expression score over time for all babies. Second, a 3-way ANOVA comparing data collected during the last half of the 10-minute postprocedure recovery period found smaller changes in HR and facial expression scores when the infants were played music. No clearcut differences in the efficacy of instrumental vs a capella music were discernable.

Bo and Callaghan[73] investigated the effects of music, a pacifier, or both on physiological and behavioral responses during and after the heel-stick procedure in 27 Chinese pre- and full-term neonates. Their crossover design required infants to have a minimum of 4 heel sticks and the order of the 3 treatment conditions and no-treatment condition was pseudorandomized. The duration of the heel sticks, time lag between heel sticks, and characteristics of the developmentally sensitive care were not provided. The authors characterized the music stimuli as "soothing," but the specific music used, its intensity, the intensity of ambient room noise, and the amount of daily exposure to music were not specified. One-way and multivariate ANOVAs, the designs of which were not detailed, were reported to show the significant effects of treatment on HR, blood oxygenation, and Neonatal Infant Pain Scale (NIPS) scores. A Scheffe test analyzing all possible comparisons of the different treatment conditions at each data collection time showed that treatment with music was associated with the lowest HR, highest oxygenation, and lowest NIPS scores at multiple time points during and after treatment. At other times, treatment with music plus a pacifier was associated with these minima and maxima, but at no time did treatment with a pacifier alone produce this result. Acknowledging methodological differences with our study, most notably the timing of auditory stimulation, we interpret the findings of Bo and Callaghan as broadly consistent with ours.

Beneficial effects of controlled auditory stimulation on acute pain and stress have been observed in the setting of other medical procedures. In a randomized trial of 58 healthy male neonates undergoing circumcision, Marchette et al[74] reported that they were less likely to have tachycardia toward the end of the procedure (tightening the clamp, waiting for hemostasis, and cutting foreskin) if recorded "classical music for neonates"[(p209)] was played. Burke et al[75] found that synthesized female vocals and womb sounds stabilized HR and behavioral agitation in 4 neonates following endotracheal suctioning, which is frequently performed in critically ill, intubated infants on mechanical ventilation. Chou et al,[76] using the same auditory stimuli of Burke et al, reported that the musical stimuli improved O_2-sat during endotracheal suctioning and may have hastened its return to baseline levels after suctioning in 30 infants.

We explored the use of music to reduce stress caused by cranial ultrasound in a set of fraternal twins. One twin was played lullabies following the procedure and was found to have a lower mean HR, and unlike the unstimulated twin, did not cry. These anecdotal observations raise the possibility that music might decrease stress caused by cranial ultrasound, a procedure that is commonly performed on premature infants.

Concluding Remarks

There is growing awareness of the need for better management of pain and stress in hospitalized infants who undergo many medical procedures, standardized approaches to managing procedure-induced pain remain lacking.[59-61,63,77] Whereas the risk: benefit ratio of treatment with opioids and sedatives is high, owing to steep dose-response curves and the potentially devastating consequences of respiratory depression, nonpharmacological interventions such as controlled auditory stimulation with music carry little or no risk to the infant. The amount, timing, and type of controlled auditory stimulation that maximize its amelioration of procedure-induced distress remain unclear, and they may not be easy to predict. Future investigations aimed at optimizing and standardizing the use of music, other auditory stimuli, and multimodal treatment incorporating auditory stimuli are needed to advance the efforts to alleviate pain and stress in this needy patient population.

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