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Recorded Maternal Voice for Preterm Neonates Undergoing Heel Lance

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ABSTRACT

PURPOSE: To determine if a recording of a mother's voice talking soothingly to her baby is useful in diminishing pain in newborns born between 32 and 36 weeks' gestational age (GA) during routine painful procedures.

BACKGROUND: While maternal skin-to-skin contact has been proven efficacious for diminishing procedural pain in both full-term and preterm neonates, it is often not possible for mothers to be present during a painful procedure. Because auditory development occurs before the third trimester of gestation, it was hypothesized that maternal voice could substitute for maternal presence and be effective in diminishing pain response.

SUBJECTS: Preterm infants between 32 and 36 weeks' GA (n = 20) in the first 10 days of life admitted to 2 urban university-affiliated neonatal intensive care units.

DESIGN AND METHODS: Crossover design with random ordering of condition. Following informed consent, an audio recording of the mother talking soothingly to her baby was filtered to simulate the mother's voice traveling through amniotic fluid. A final 10-minute recording of repetition of mothers' talking was recorded with maximum peaks of 70 decibels (dB) and played at levels ranging between 60 and 70 ambient decibels (dbA), selected above recommendations of the American Academy of Pediatrics in order to be heard over high ambient noise in the settings. This was played to her infant by a portable cassette tape player 3 times daily during a 48-hour period after feedings (gavage, bottle, or breast). At the end of 48 hours when blood work was required for clinical purposes, using a crossover design, the infant underwent the heel lancing with or without the recording being played. The order of condition was randomized, and the second condition was within 10 days. The Premature Infant Pain Profile (PIPP) was used as primary outcome. This is a composite measure using heart rate, oxygen saturation, 3 facial actions, behavioral state, and gestational age. This measure has demonstrated reliability and validity indexes.

RESULTS: There were no significant differences between groups on the PIPP or any of the individual components of the PIPP except a lower oxygen saturation level in the voice condition following the procedure. The second condition, regardless of whether it was voice or control, had higher heart rate scores and lower oxygen saturation scores even in the prelance baseline and warming phases. Order did not affect PIPP scores or facial actions.

CONCLUSIONS: Different modalities of maternal presence would appear to be necessary to blunt pain response in infants, and recorded maternal voice alone is not sufficient. The loudness of the recording may have obliterated the infant's ability to discern the mother's voice and may even have been aversive, reflected in decreased oxygen saturation levels in the voice condition. Preterm neonates of 32 to 36 weeks' gestation may become sensitized to painful experiences and show anticipatory physiological response.

KEY WORDS: auditory stimulation, maternal voice, newborn learning, pain

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It is now well documented that preterm neonates in the neonatal intensive care unit (NICU) undergo numerous painful procedures without benefit of analgesia.[1,2] The repetition of the pain of these procedures is also now known to have deleterious effects.[3]

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However, the evidence supporting the use of pharmacologic analgesia for procedures in this population is sometimes questioned because they are not always efficacious[4,5] or they present negative sequelae themselves.[6] Nonpharmacologic methods need to be tested. There are several well-conducted studies on the efficacy of sucrose for single procedures,[7] but there remain some questions about using it repetitively.[8]

Recent attention has turned toward maternal contact as a source of comfort. In full-term infants, breastfeeding has been shown to be analgesic,[9] but it may not be the breast milk per se that is analgesic, but rather being held.[10] Three studies in which mothers held their infant skin-to-skin in kangaroo care reported a significant effect in diminishing the pain response to heel lance, one with full-term neonates[11] and the others with preterm neonates.[12,13] There are several components of kangaroo care and breastfeeding, including the powerful effect of touch,[14,15] the warmth and rhythmicity of the mother's heartbeat and breathing, oragustatory stimulation in breastfeeding, and the mother's voice. In one study, it was the holding component of breastfeeding that made the difference in pain response.[10] In a more recent study on full-term breastfed infants, comparisons were made of the mother breastfeeding, the mother offering a pacifier, and a nonrelated female offering a pacifier; the study found that comforting by the mother was effective regardless of breastfeeding or pacifier modality.[16] However, often mothers of preterm neonates are unavailable. They may be ill, or they may have other responsibilities, such as young children at home. Although there would be many components missing in selecting a unisensory representation of the mother, there are data to support the notion that infants have memory of their mother via olfactory[17-19] as well as auditory senses. For convenience concerning the production of the mother's voice as opposed to scent, we selected auditory representation of the mother for our study.

Review of the Literature

The human fetus is thought to be capable of auditory perception by 29 weeks, with anatomical structures in place 2 weeks earlier.[20,21] DeCasper and Fifer[22] examined newborns within 3 days of life and found that they learned to recognize their mother's voice more times than a female stranger's voice; the researchers noted the infants had varying sucking intensities on a nonnutritive nipple. In addition, the newborn, up to 8 months in age, can discriminate and show preference for the mother's voice compared with a female stranger's voice.[23] Fifer and Moon found that newborns suck a nonnutritive nipple significantly more often when syllables are paired with the maternal voice than when syllables are paired with another woman's voice or silence.[24] When presented with a choice of hearing their own mother's voice in speech or a filtered version in such a way as to mimic womb-like sounds, newborns chose to suck more often to the signal predicting the "in utero" versions of their own mother's voice.

During the third trimester (27 weeks gestational age) fetuses are able to hear and respond behaviorally to sound and auditory stimuli.[22,25] DeCasper and Spence[26] studied pregnant women at 7½ months gestation who recited a target story aloud to their fetuses twice daily until birth, at which time the target story had greater reinforcing value (measured by sucking bursts) to a novel story and was independent of who recited the story. In another study, pregnant women at 33 weeks' gestation recited a target rhyme 3 times daily for a succession of 4 weeks, after which the fetuses differentially responded with a brief decrease in fetal heart rate.[27]

These studies exemplify the neonate's ability for auditory processing, not just perception. This ability may have the potential to be used to help the infant in coping with pain. The maternal voice and music have been used throughout time as an intervention to interact with infants in many situations, including soothing infants during distress and discomfort. Lullabies are musically simple songs with lower pitch and slower tempo that are used and recognized across cultures.[28] They are musical structures that infants can clearly differentiate.[29,30] While heart rate accelerations are a component of a defensive response typically associated with loud sounds, decelerations are indicative of an orienting or attentional response corresponding with low intensity stimuli, such as a mother's voice in lullaby or singsong voice.[24,31] Lowered stress levels and physiologic indicators such as positive effects on heart rate, respiratory rate, and oxygen saturation occur in response to lullabies sung by a female.[32,33] Increased oxygen saturation in preterm neonates during an agitated (fussy) state has been found to occur in response to womb sounds and simulations of a mother's in utero voice.[34] Sedative music compared with stimulative music produces less variability in mean systolic blood pressure and heart rate.[35] Increased sleep or quiet awake states in agitated preterm infants have improved with the use of music.[34] A study on full-term infants confirmed that maternal voice recordings produced a decrease in heart rate and respiratory rate; however, after the playing of recordings ceased, these measures increased.[25] Lullabies sung by a female or speaking by the preterm infant's mother had an immediate positive affect on oxygen saturation, which dropped after termination of the stimulus.[23,36] Thus, there would appear to be substantial theoretical and empirical data to support the easily observable and generally held belief that the mother's voice singing or speaking softly in a singsong way has a soothing effect on infants.

The purpose of this study was to determine the efficacy of the sound of mother's prerecorded voice to decrease pain response in preterm neonates undergoing heel lance for blood procurement for clinical purposes. The recording of the mother's voice was filtered to mimic voice traveling through amniotic fluid.

METHODS

Study Design

A crossover design with random order of condition was selected to decrease interinfant variability. A washout period of at least 24 hours lessened the possibility of a cumulative effect from one condition to the next. Because it was a crossover design, it was not intent to treat. A computer-generated list of random ordering for the 2 conditions of 20 infants was produced for each site before recruitment began. At the time of enrollment, that is at the moment the mother gave consent, the infant was assigned the next sequenced study number on the list, which then determined the first session. The primary hypothesis was that infants undergoing heel lance in the mother's voice condition would have lower pain scores according to the Premature Infant Pain Profile (PIPP) than in the control condition.

Sample and Settings

Two university-affiliated NICUs were the sites for this study. Both were level 3 NICUs. All infants were in-born.

Infants were born between 32 weeks 0 days and 35 weeks 6 days gestational age (GA) according to ultrasound or last menstrual period, with no congenital anomalies. All infants had Apgar scores at 5 minutes greater than 3. The infants had no intraventricular hemorrhage (IVH) greater than a grade 2, and no infants had periventricular leukomalacia (PVL). No infant required surgery, and infants receiving analgesic therapy were not eligible. Sample size estimates based on previous studies with differences in PIPP scores of 2 points and a standard deviation of 2 points, setting alpha at .05 and a power of .80, indicated 44 infants would be needed for separate groups, 22 for a repeated measures design; for facial actions of 22% and standard deviation of 30%, a sample size of 46 infants in a randomized control trial but only 20 in a repeated measures design would be indicated.[37,38] Using heart rate differences of 15 with standard deviation of 17 to 20 (from previous studies), a sample size of 27 was needed for a repeated measures design. Thus, a conservative sample of 27 was sought, allowing for 20% loss.

Procedure

Following ethical approval by local ethical review boards, the research nurse determined eligibility and consulted the staff before requesting permission from mothers to discuss protocol with them. Mothers who agreed to participate signed an informed consent. The research nurse then discussed with the mother the importance of talking or singing rhythmically to her infant for purposes of the study.

During the next 24 hours, the research nurse convened a time with the mother to make a recording of her voice talking to her baby, either singing, saying nursery rhymes, or talking "baby talk" in a singsong voice. This recording was then filtered through a music editing software program (CoolEdit, Adobe Systems Inc., San Jose, Calif.), in which it was low-pass filtered with an attenuation of –96 decibels (dB)/octave above the normal cutoff frequency of 500 Hz that emulated the effect of the mother's voice traveling through amniotic fluid. This filtered talk was made into a recording, which was repeated to constitute 10 minutes' duration. This recording was then played to the infant on a small cassette player with small speakers (Sony WM-FS420 in one site and older version WM-FS398 in other site) placed in the isolette. The sound was set to never go above a maximum volume of 70 ambient decibels (dbA) or A-weighted decibels with the sound pressure scale adjusted to conform with the frequency response of the human ear. A sound level meter that measures A-weighted decibels has an electrical circuit that allows the meter to have the same sensitivity to sound at different frequencies as the average human ear. It was generally played between 60 and 65 db 3 times per day during quiet periods for 48 hours. Although this level was at the maximum for recommendations at the time the study was being conducted, it was selected to be above the relatively loud ambient noise of the NICU, which at the time of the study was always above 55 db during daytime hours. Sound levels were determined by a Quest Technology (model 2500) sonometer (Oconomowoc, Wis) measured inside the isolette.

After the 48 hours, the next instance in which the infant required blood sampling via heel lance for clinical purposes was done according to the predetermined random assignment. With at least 24 hours between sessions, the subsequent heel lance was done again according to the random assignment.

The heel lance procedure was divided into 4 phases: baseline, warming (1 minute) heel lance (30 seconds), heel squeezing (30 second blocks until heel is wiped and bandage applied), and return to baseline. Continuous recordings of heart rate and transcutaneous oxygen saturation were made using a Datex Ohmeda Radical (Masimo) pulse oximeter with an infrared lead (GE HealthCare, Toronto, Ontario) on the infant's unaffected foot and fed into a Compumedics E-series integrated data acquisition system (El Paso, Tex). A Panasonic GP-KS 162CVD camera (Secaucus, NJ) was focused on the infant's face. The camera and pulse oximeter data were fed into the data acquisition system and were time stamped with event markings (phase to phase) by the research nurse. Following each session, other relevant data were collected from the infant's medical record.

Voice Condition

At the time of the heel lance, the recording was started and played for 1 minute before the procedure began and throughout until heart rate and oxygen saturation returned to baseline. In the control condition, the infant underwent the procedure with no intervention, which was the standard care in both units at the time the study was being conducted.

Outcomes and Measures

The primary outcome was the Premature Infant Pain Profile (PIPP).[39] The PIPP is a composite measure of pain, including physiological and behavioral indicators that was originally developed using 4 data sets of preterm infants in a pain/no-pain situation but since has been used to distinguish pain states. The components are heart rate, oxygen saturation, 3 facial actions, neurobehavioral state, and gestational age. Increases in heart rate are measured in incremental blocks of 5 beats per minute (bpm) ranging from 0 (0-4 bpm) to 3 (15+ bpm). Decreases in oxygen saturation are measured in increments of 2%, ranging from 0 (<2% change) to 3 (6%+ change). Each facial action is scored in increments of a third of the time the action is seen, from 0 (less than 1/3 of the time) to 3 (all the time). Weights are added for being young (<28 weeks gets a score of 3) and state (quiet sleep gets a score of 3). The PIPP has been extensively tested and shown to have reliability, validity, and clinical utility in this population.[40-43] The individual components of the PIPP were also examined because in some studies facial action, but not physiological data, have been sensitive to pain intervention strategies.[44,45]

Faces were scored by research assistants who did not know the purpose of the study. Facial actions were scored according to the Neonatal Facial Coding System that provides a detailed, anatomically based, and objective description of newborns' reactions to the heel stick.[46] The selected facial actions were scored on a second-to-second basis in real time on a Panasonic AG-1970 with stop-frame capability and clock to the fourth decimal place. Each recording session was scored 3 times, once for each of the facial actions, using software developed in our laboratory, and a final score based on percentage of time the action was present was calculated for the block time of interest. The neurobehavioral state component was determined according to Prechtl's[47] categories of quiet sleep or quiet awake or active sleep or active awake during the baseline. Age (GA) was taken from the chart.

Severity of illness was determined by the Score for Neonatal Acute Physiology (SNAP-II) for the 12-hour

RESEARCH TUTORIAL#1: Crossover Design

What does the author mean when she writes "because it was a crossover design, it was not intent to treat"?

The intent-to-treat analysis concept suggests that all subjects randomly assigned to a study group should be analyzed together with that study/treatment group irrespective of the treatment they actually received. This approach is of most value in the randomized clinical trial when it is critical to maintain the balance of randomization.[1] If the subject crossed over to another group, the analysis would include that individual in the original group. It is for this reason that in this crossover study design an intent-to-treat analysis is not considered feasible. The crossover is a violation of the principles in an intent-to-treat analysis.

Why would this author use a crossover design?

The crossover design as used in this study is often advocated because it decreases intersubject (interinfant) variability. In the crossover design, there is not a separate comparison group. Each subject serves as his/her own control, receiving both treatments or both conditions, thus reducing error variance. As done in this study, randomization of group order (treatment versus control) is a powerful method of ensuring the equivalence of groups.[2]

Another benefit to the crossover design is sample size. The required sample size for a crossover design is substantially smaller than that for comparable parallel designs.[2]

One important issue with the crossover design is the carryover effect. This is seen when one treatment influences all subsequent treatments or conditions. Allowing for a washout period between treatments or conditions aids in minimizing the effects of the first treatment or condition.[2,3] The washout period is the time lapsed between the two treatments or conditions (intervention vs control). The washout period length may be difficult to determine. It should be chosen based on the length of the effect of the treatment. This information is often not available.

Statistical tests to determine carryover effects can be employed. However, this does increase the required sample size. The sample size would need to be sufficiently large to detect carryover effects.

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period after birth, and for the 24 hours before the procedure, the SNAP–Perinatal Extension (SNAPII-PE) was used.[48-50] The elements for this score can be found in the medical record and include hemodynamic, respiratory, hematologic, metabolic, electrolytic, and neurologic parameters.

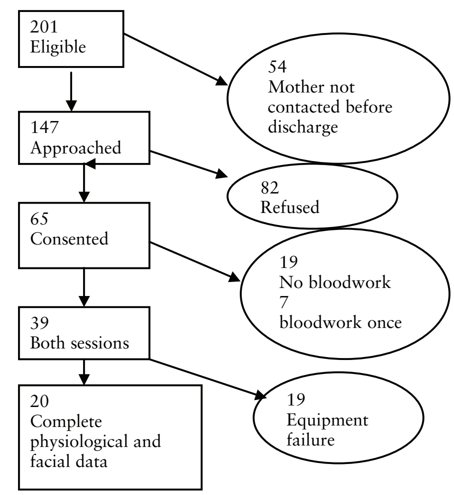
Demographic variables of interest included Apgar scores at 5 minutes, age at birth, time since last painful procedure, number of painful procedures since admission (eg heel lances, intravenous catheter placements), and whether or not the infant was on stimulants (caffeine, theophylline) or received indomethacin in the past 12 hours. All of these variables might affect pain response, and all were documented in the medical record.

FINDINGS

The final sample for study was 20 (Figure 1). The reason for missing eligible infants was that the mother was not able to be contacted twice in order to explain the study on the first visit and obtain consent on second. Reasons for refusal were not given by 32 mothers; 11 mothers felt too tired or sick to record their voice; 10 felt it was too much for the baby; 9 wanted the baby to be in no research of any kind; 4 believed they would be going home before there would be time for the study to be completed; 2 mothers were angry that their baby was premature; 2 were too busy; 1 ultimately felt that her language skills were not adequate to understand the study; 1 father refused after the mother had consented; and 1 did not want the baby to associate her voice with pain. Of the babies with consent, 19 had no blood work ordered and another 7 did not have a second session in the time they were eligible to actually participate in the study before being discharged from the NICU. Of the 7 with one session, 3 had voice first and 4 had control first. There was equipment failure with either the camera or the pulse oximeter for 19, leaving a final sample of 20 with completed data sets at 2 points in time.

These infants ranged in age from 32 weeks 0 days to 34 weeks 5 days, with a mean of 33 weeks GA. Their average birth weight was 1930.9 g, with a standard deviation of 326 g (Table 1).

FIGURE 1.



Eligible infants and study participants.

For analysis of physiological data, all infants with physiological data (n = 36) and similarly for faces (n = 30) were analyzed for PIPP scores, for which complete physiological and facial data were needed. The analyses were based on 20 infants. Factors that were examined for an effect on pain outcome scores were GA at birth, Apgar score at 5 minutes, severity of illness score during the 12 hours before the procedure, number of painful procedures, whether or not the infant was receiving stimulants (caffeine or theophylline), and order of condition. Since GA at birth, and severity of illness 12 hours prior to the procedure were significantly correlated (Pearson's $r = +0.585$), the Apgar score at 5 minutes as an indicator of health status was added as a covariate in the analysis because it was significantly correlated with pain outcomes across more time points than either GA or severity of illness. Order of condition was the only other significant factor and was included in the analysis. Thus, the main analysis was repeated measures analysis of covariance (RM-ANCOVA) that included condition (voice or isolette) as the independent variable, PIPP scores as the

TABLE 1. Means and Standard Deviations of Study Participants

Gestational Age at Birth (SD)	Weight at Birth (SD)	Apgar Score at 5 Minutes (SD)	Postnatal Age* Voice (SD)	Postnatal Age* Control (SD)	Male (%)
33.1 weeks (.89)	1985 g (312)	8.5 (1.1)	6.9 days (3.1)	6.6 days (2.5)	57

SD, standard deviations.

*Chronological age on first day of study.

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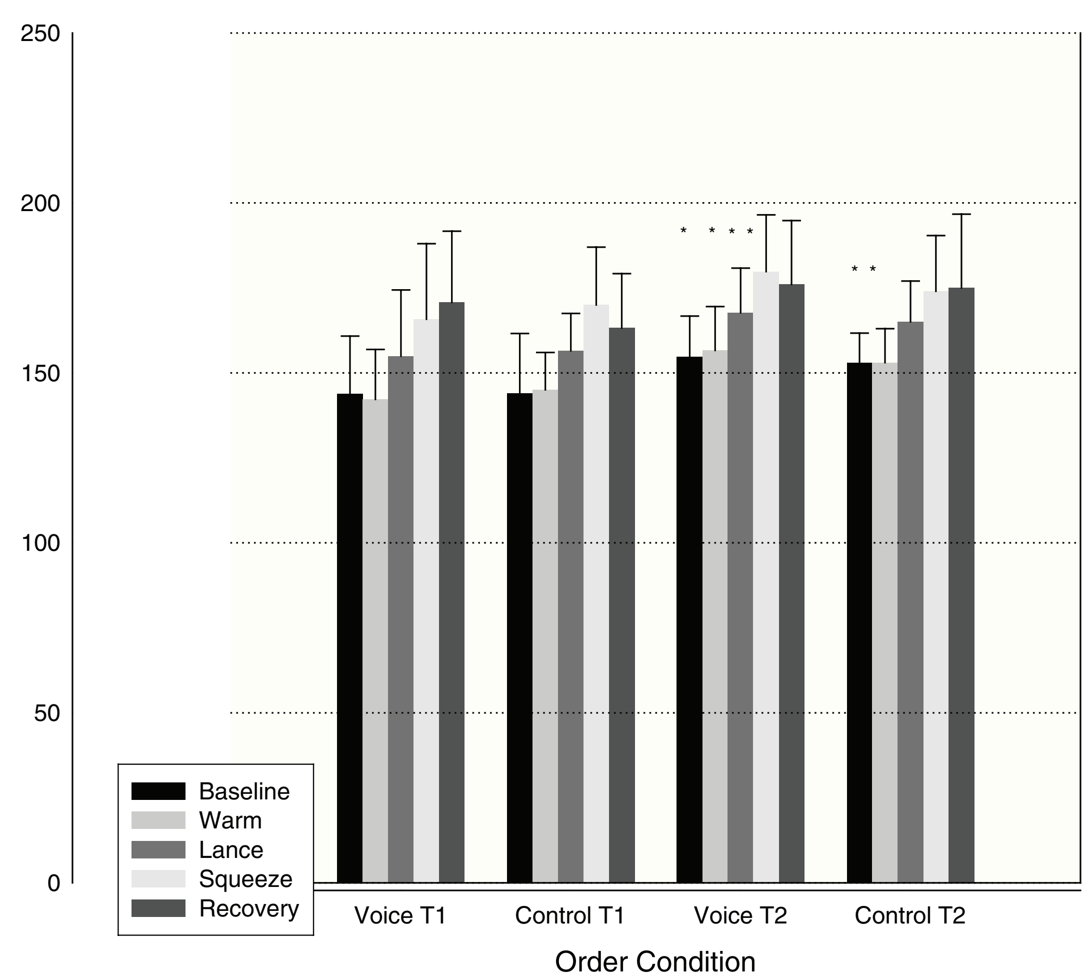
dependent variable, and order of condition as the covariate. Since each baby was in both conditions, the repeated measures analysis accounted for the dependence of the observations. Separate RM-ANCOVAs were also conducted for the separate physiological components of heart rate and oxygen saturation and facial actions at each phase.

There were no differences between the 2 conditions of voice or control on the composite score of the PIPP (Pillais' F = 0.841, $P = .371$) or of its individual components at any point in time, other than there was a lower oxygen saturation in the voice condition during the final phase after the heel lance before return to baseline (94.1 vs 96.2, $P < .01$). The means were almost identical, for example PIPP scores at 30 seconds following lance were 10.15 for voice and 10.95 for control, facial actions at the 30 seconds from heel lance were 52% for voice condition and 56% for control condition, and mean heart rate was 159 bpm for the control condition and 162 bpm for the voice condition. The Apgar score at 5 minutes was a significant covariate for oxygen saturation levels, with babies with higher Apgar scores having higher oxygen saturation levels during all phases and across both conditions, with Pearson correlations ranging from 0.485 to 0.584.

During the second session, be it voice or control, heart rate scores were higher and oxygen saturation levels were lower (Figures 2 and 3) for many phases of the procedure. That is, there was no interaction between condition and order, but there was a main effect of order. The oxygen saturation level differences were not always consistent, but in the instances in which there were significant differences, it was in the second session. For heart rate, the differences were

FIGURE 2.



T1=Time 1, T2=Time 2. * $P < .05$ between T1 and T2.

Heart Rate by Order Condition.

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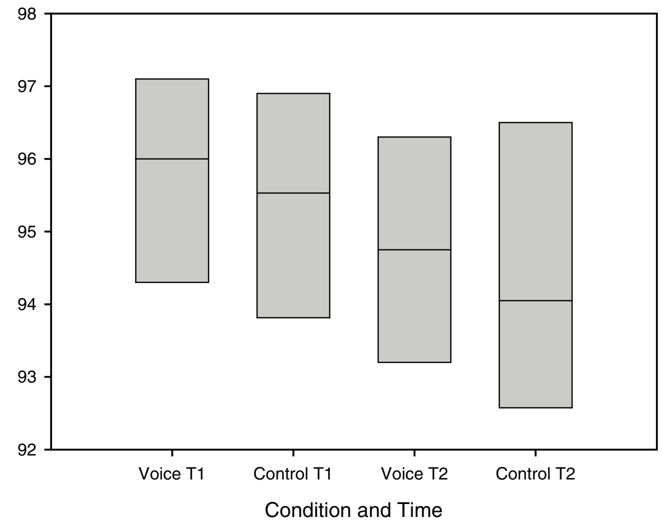
FIGURE 3.



Oxygen saturation levels by order of Condition.

consistent in that in the second session there were significantly higher heart rate levels across many phases, including baseline and warming. There was no order effect for faces or the composite measure of the PIPP. The number of days between sessions was significant only for heart rate during baseline and warming phase: if control was first, then during voice in second session heart rate was higher if there was more than 1 day between sessions (11 bpm in baseline, $P < .05$; 9 bpm difference in warming phase, $P < .05$).

DISCUSSION

Despite a solid rationale for hypothesizing that maternal voice would have a comforting effect during a painful procedure in preterm neonates, there was no evidence to support such a hypothesis from this study. In fact, after the procedure, heart rate was higher and oxygen saturation was lower in the voice condition than in the control condition.

The most likely explanation for the results is that the sound level, going up to 70 db, was too high for the infant. It could have actually been aversive and even if not actually aversive, might have been too loud to allow the infant to discern that it was in fact the mother's soothing voice that was being heard. As mentioned, that sound level was chosen for the recording to be heard above the ambient noise in the NICU. If this study were to be replicated, the NICU would need to have lower ambient noise levels, and the recordings could be played at a more acceptable level. Although the measurements of intensity were taken near the infant's head, the effect of the sound in a closed incubator may have had a negative effect over and above the sound, that is, there may have been physical vibrations that were noxious.

The effectiveness of kangaroo care is a result of multimodal sensory stimulation: tactile, olfactory, auditory, vestibular, and thermal, and it could very well be that a single modality is not sufficient.[12,13] In terms of human development, we know that the tactile sensory system develops sooner than the auditory system,[51,52] so that we may have been testing a modality that the infants between 32 and 36 weeks were not able to use, whereas kangaroo care is accessing the earlier developing tactile and vestibular systems.

Thirty-two weeks may also have been too young an age for infants to have actual cortical memory of their mother's voice. The earlier studies on infant auditory memory tested full-term neonates, not preterm neonates.[22,23,25] Although auditory perception is developed by 32 weeks, the memory of auditory stimuli may just be beginning at that time.[24]

Furthermore, infants prefer their mothers' "real" voice, as opposed to a recorded voice so that any soothing effect could have been lost in the artificialness of the recording.[20,21] It could also be that filtering the voice to sound as though it was going through fluid did not mimic maternal voice in utero and thus was not familiar. An earlier report with infants of the same age[53] found a more rapid return to baseline in the group who heard unvoiced music following heel lance, which is in contrast to our study that found no difference in time to recovery and more response during the time just prior to recovery in the voice condition. The differences could be explained by unvoiced music being more soothing than voiced music, although this has not been tested. It could also be that the study had

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a small sample (n = 14) with even fewer in the older age group so that their finding could be due to type 1 error.

As important is the finding that during the second session, regardless of condition, infants showed greater physiologic arousal, even during the baseline. It could simply be that they were older for the second session, but the time between the sessions was only 1 day for 27 of the 46 infants, and the number of days between sessions was important only for heart rate in the baseline and warming phase during the second session when control was the first condition. The other possible explanation is that the infants became sensitized to the painful condition and showed this through greater physiological response. This notion can be supported by reports in full-term neonates in which males showed increased behavioral and physiological arousal to 2-month immunization if they had been circumcised near birth[54] or had repeated blood testing during the first few days of life[55] or preterm infants who showed peripheral hypersensitivity following repeated heel stick.[56] In an experimental study with preterm neonates between 28 and 32 weeks' gestation in which the heel was held for 10 seconds before the lancing, researchers found that by the fifth heel lance, infants showed increased physiological arousal.[57] Those findings are similar to those in the current study, except that in our study it was in the subsequent lancing that "anticipatory memory" was observed. It has been reported that if preterm neonates were handled prior to a painful event, they showed greater response to the painful event[57] and that pain increases physiological response to routine caregiving procedures. In our earlier study on the analgesic effect of maternal kangaroo care, there was no order effect.[12] However, in that study maternal kangaroo care was analgesic, whereas in the current study, recorded maternal voice was not. The efficacy of kangaroo care may have overridden the effect of order on physiological arousal.

LIMITATIONS

There are several limitations to the study. The low participation rate is likely an indication that this is not a strategy mothers would like to use and if there had been results, the ability to generalize would be in question. Equipment failure was also problematic, and although there was likely no selection bias, this cannot be ruled out. The biggest limitation was the noise level selected. As mentioned, there were reasons underlying the level, but nevertheless, the noise level possibly obscured the possible positive effects of the mother's voice.

IMPLICATIONS

Future research should address if the mother's unfiltered voice played at a lower sound level is effective. This could also be tested in conjunction with maternal olfactory stimuli. The purpose would be to determine if some facsimile of the mother would have a blunting effect on response or enhancement effect on recovery in instances when the mother is unavailable because other studies have demonstrated that maternal kangaroo care is effective. Sensitization to repeated heel lance in preterm neonates should also be a primary focus of future research because other studies to date have examined this only in full terms or only in the periphery.

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