Nonpharmacological Techniques to Reduce Pain in Preterm Infants Who Receive Heel-Lance Procedure: A Randomized Controlled Trial

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Introduction: The heel-lance (HL) method for blood collection from the newborn is controversial for the pain it causes. This is the first randomized controlled trial on the management and reduction of pain using the music of Wolfgang Amadeus Mozart ("Sonata K. 448") in premature infants hospitalized in a neonatal intensive care unit (NICU). This study has compared nonpharmacological techniques with standard procedure for reducing pain during HL procedure. **Methods:** Thirty-five premature infants were enrolled, each for 3 HL procedures, of which each was randomized to 1 of the 3 study arms. Arms were then compared in terms of the Premature Infant Pain Profile (PIPP) changes by analysis of variance (ANOVA). **Results:** One hundred five HL procedures were available for analysis (35 standard procedure, 35 music, 35 glucose). Median baseline PIPP was 3, and median PIPP after the HL procedure was 5. PIPP scale change was +3 in the control arm, +1 in the glucose arm, +2 in the music arm ($p = .008$). **Discussion:** Both glucose and music were safe and effective in limiting pain increase when compared to standard procedure in HL procedures in preterm infants.

Keywords: pain; music; glucose; infant premature

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The heel-lance (HL) method for blood collection from the newborn is controversial for the pain it causes and an increased risk of skin lesions, such as bruising of the puncture site and inflammation (Vertanen, Fellman, Brommels, & Viinikka, 2001). Venipuncture is preferred because it is less painful and more effective (Lago et al., 2009; Morrow, Hidinger, & Wilkinson-Faulk, 2010), but HL is often the only viable option for a blood collection in the care of preterm infants. Preterm infants have the capacity to feel pain at birth, and this can have adverse short- and long-term effects from pain (Fitzgerald, 1991; Johnston, Fernandes, & Campbell-Yeo, 2011). The pain related with heel lancing is closely associated with squeezing of the heel rather than breaking of the skin via the heel prick (Morrow et al., 2010). Squeezing is itself a cause of pointless pain (Lago et al., 2009); moreover, the development of the nervous system is extremely vulnerable to peripheral lesions (Fitzgerald, 1991). The existing guidelines for the management of pain in newborns (Lago et al., 2009; Spence et al., 2010; Vani, 2011) suggest several strategies to reduce pain in this setting, including environmental, pharmacological, and nonpharmacological measures.

NONPHARMACOLOGICAL INTERVENTIONS TO REDUCE PAIN IN PRETERM INFANTS DURING HEEL LANCE

The use of nonpharmacological techniques for pain control was poor in all European countries, although it showed a routine use of pacifiers and sucrose solutions in most European neonatal intensive care units (NICUs) except in Spain and the United Kingdom; positioning and wraps are used primarily in Scandinavia, the Netherlands, and Belgium. Procedures not specifically recommended by the guidelines are often used; for example, warming of the heel (often in Denmark and Spain) and the use of local anesthetics (lidocaine 2.5% and prilocaine 2.5%), and eutectic mixture of local anestetics cream (in France and Italy; Losacco et al., 2011). So, despite the tools provided by the scientific literature, there are significant differences in the clinical practice of various NICU, the ability to prevent and treat neonatal pain has not improved along with the ability to recognize and measure it.

Focusing on nonpharmacological measures, the use of oral sucrose and nonnutritive sucking (NNS) or human milk is suggested or, alternatively, glucose use (Lago et al., 2009; Okan, Coban, Ince, Yapici, & Can, 2007). Multiple doses of glucose/sucrose (2 min immediately before and 2 min after the HL) appear more effective than a single dose (Lago et al., 2009). NNS seems to have a synergistic effect with the sweet taste, and it is recommended whenever possible (Lago et al., 2009).

The Use of Music

Another nonpharmacological intervention used to reduce pain in premature infants is listening to music. The human fetus can hear from 29 weeks of gestation and has the ability to understand and remember auditory stimuli already in the womb (Johnston et al., 2011). According to neurophysiological studies, infants perceive

simple and repetitive sounds composed of individual sounds (De Battistini, 2011; Rocchi, 2007) and are tuned to consonant patterns, melodic as well as harmonic, and to metric rhythms (Trehub, 2001). Live music can distract the infant/child during painful procedures and significantly reduce pain and stress (Kemper & Danhauer, 2005). A meta-analysis of nine randomized trials has shown that music can have a significant clinical benefit for preterm infants in the NICUs (Olson, 1998; Standley, 2011), although studies with more rigorous approach could provide further confirmation (Johnston et al., 2011). The music works by decreasing the state of arousal and behavioral response (the facial expressions of pain) during painful procedures (Cignacco et al., 2007). It has been proven that music has positive effects in the long-term variables such as weight gain related to the reduction of energy use at rest and reduction in hospitalization (Ancora, 2010). A study by Kemper and Danhauer (2005), who recognized that the music plays a vital role in all cultures and has a direct or indirect role in the physiology and clinical symptoms, notes that, after having been carefully selected, it can reduce stress and offers distraction from the pain. The result is the improvement of clinical performance.

The music was in fact able to reduce the heart rate, salivary cortisol levels, and the behavior of distress, and to improve the oxygen saturation, NNS, and the increase in body weight by reducing the duration of hospitalization (Arnon, 2011; Arnon et al., 2006). The same studies have examined the short-term effect of music (in particular live music) therapy on variables such as heart rate, respiratory rate, blood pressure, oxygenation, and pain behavioral status on preterm infants (Arnon, 2011; Arnon et al., 2006).

"Sonata in D Major for Two Pianos (K. 448)" by Wolfgang Amadeus Mozart. In the 1990s, some studies discussed (Chabris, 1999; McLachlan, 1993; Rauscher, Shaw, & Ky, 1993; Steele et al., 1999) and other used (Nantais & Schellenberg, 1999; Newman et al., 1995) the "Sonata in D Major for Two Pianos (K. 448)" by Wolfgang Amadeus Mozart and the relatively well-known "Mozart effect"; in particular, one study showed that exposure to Mozart's music significantly reduced energy consumption at rest in stable preterm infants (Lubetzky et al., 2010). The Mozart effect refers to an enhancement of performance or change in neurophysiological activity associated with listening to Mozart's musical auditory stimulation (Valenti et al., 2012). The selection of music was based on studies that showed the Mozart effect efficient in reducing stress, pain, depression, and anxiety (da Silva, Cação, Silva, Marques, & Merey, 2013; Lubetzky et al., 2010; Pignatta, 2012). The infant hospitalized in the NICU may be routinely exposed to noise between 55 and 70 dB (Arnon, 2011) up to a maximum of 75 dB (Gooding, 2010). One study by Lubetzky et al. (2010) has tested the music of Mozart present on compact disc (CD), making listen from 65 to 70 dB, according to the American Academy of Pediatrics recommendations, which not to exceed volume of 75 dB (Lubetzky et al., 2010).

Strong evidence about the type of music to be used is lacking; in fact, the choice of the type of music was a difficult issue in the design phase. Several studies have examined the effects of different forms of music including instrumental and vocal music (Evans, 2002; Hartling et al., 2009; Hodges, 2010). Regardless of the type of music, a positive effect on pain response was recorded, but direct comparison of types of music is difficult (Standley, 2002).

Importantly, some precautions should be used when using music as a pain-prevention measure in the NICU. First, it is important to consider the level of maturity of the child, the health, and individuality of their responses to stimuli (Evans, 2002; Giuliani, Poluzzi, Bellisario, & Bitetti, 2005). In addition, the music should be heard for no more than 20 min to avoid sensory overload (Cassidy, 2009; Gooding, 2010).

AIMS OF THIS STUDY

We designed this study to assess, in our context, the use of music as a nonpharmacological technique in comparison with the use of glucose or standard procedure. Furthermore, we aimed to compare the time required to conclude the procedure for collection of blood by HL procedure and assess potential differences in response according to gestational age, gender, environmental noise, and provenance of the baby.

METHODS

The Scientific Institute for Research, Hospitalization and Health Care (IRCCS) Policlinico San Matteo Foundation of Pavia, Italy, is a tertiary-care, teaching hospital NICU that hosts an average of 25–30 neonates each day. The main reasons for admittance are prematurity and respiratory distress. It is organized into eight bays: two NICU bays, one baby septic isolation in NICU bays, two intermediate care/minimal therapy bays, and three isolation for infectious diseases bays. The hospital ethical committee was obtained before study entry. We have received formal approval from the institutional review board (IRB) on April 1, 2011 (protocol number: 1571).

Eligibility Criteria

The trial included neonates admitted to the NICU in the period May to July 2011. Eligibility criteria were the following:

- Age ≥30 weeks gestational
- Age ≥48 hr of life
- Written consent of both parents
- The absence of drug therapy for pain relief
- Ability to suck and swallow present
- Expected duration of admission at least 5 days
- Absence of brain lesions impairing swallowing, sedation and intubation, and acute sepsis at the time of treatment.

Study Design

A randomized block study design was used (block = infant, unit of analysis: LH; Bo & Callaghan, 2000). Each infant was randomized to receive, in three consecutive HL procedures, glucose suckling (10% solution), music, or standard procedure. Each of the 35 patients completed the three study procedures ($35 \times 3 = 105$ procedures).

Sample Size, Randomization, and Primary End-Point Measure

Sample size calculations were made with an *F* test for repeated measures, aiming at detecting (with 80% power and alpha error 5%), a 4-point difference in Premature Infant Pain Profile (PIPP) between either glucose or music and no treatment (with standard deviation of 3 points). This required 35 infants all undergoing three HL, each time with a different treatment; the *sequence* of treatments within each infant was randomized.

The PIPP scale has demonstrated moderate internal consistency (0.59–0.76 item-total correlations), high interrater (α = 0.95–0.97) and intrarater (α = 0.89–0.91) reliability, and construct validity (Gibbins et al., 2006). The PIPP scale was developed and validated for premature infant pain assessment in 1996 (Stevens, Johnston, Petryshen, & Taddio, 1996), has been used at the study site since January 2000 (Gibbins et al., 2006), and continues to be a reliable and valid measure (American Academy of Pediatrics Committee on Fetus and Newborn et al., 2006; Stevens, Johnston, Taddio, Gibbins, & Yamada, 2010).

We used the PIPP scale translated into Italian that includes seven indicators: three behavioral indicators (brow bulge, eye squeeze, nasolabial furrow), two clinical indicators (heart rate and oxygen saturation), and two context indicators (sleep–wake rhythm, facial expression, eyes open and closed). To each indicator, a score from 0 to 3 was given; individual scores were then summed up. A final score PIPP ≤6 indicated low or no pain. A final score PIPP >12 indicated a moderate or high pain (Santullo, 2009).

Statistical Methods

Descriptive statistics were produced for demographic, clinical, and laboratory characteristics of cases. Mean and standard deviation (*SD*) are presented for normally distributed variables, and median and interquartile range (IQR) for non-normally distributed variables. The three treatments were compared using analysis of variance (ANOVA) in terms of PIPP scale changes (PIPP after HL minus PIPP before HL) and of time required to conclude the procedure. Multivariate analyses were performed with linear regression.

PIPP score has also been described (without formal statistical testing) in the following categories:

- Gestational age (≥36 weeks, 32–35 weeks, 28–31 weeks; <28 weeks)
- Gender
- Environmental noise, especially impulse sounds (presence/absence)
- Department of origin (NICU/neonatology/home/other).

STUDY PROCEDURES

Every day, nurses screened eligible infants and proposed participation to the parents. During an interview, the study aims and procedures were detailed to both parents, and an information leaflet was left for them to read. In a second interview, written consent was requested from both parents. After obtaining consent, the infant

crib was marked with the study symbol (an image representing three infants with headphones, with the sentence: Pain?! No thank you!). The randomization list with reference to each enrolled child was hung in the nurse coordinator room, so that each nurse on duty could check which treatment each child should receive for each of the three HL procedures for the study and mark it after the procedure.

In our hospital, nursing staff routinely alternate right and left heel for HL, and in our study HL was performed with an automatic lancet of the Tenderfoot variety rather than a manual lancet, without squeezing the heel (Lago et al., 2009; Shepherd, Glenesk, Niven, & Mackenzie, 2006; Vertanen et al., 2001). Tenderfoot is available in four sizes according to body weight or age. The HL blood drawing technique was made with a standardized technique by experienced nurses (Ometto, 2010). Immediately before starting the HL procedure (with the material ready, and before touching the heel, in the range from 0 to 2 min) and immediately after (when the heel was released after the HL procedure, in the range from 0 to 2 min), pain in the infant was rated with the PIPP scale. Assessments were made by researchers blind to study treatment, except in the case of music therapy; in this case, pain was rated twice by two different operators and the average was used.

During the procedure, regardless of the running form of treatment, precautions were taken to reduce background noise, as standard practice to avoid the negative effects of stress, and sounds and noises higher than 70 dB were completely avoided (setting the alarm ringtones to a standard level, setting the standard ringtone of mobile, low level of voices of operators and parents; Gooding, 2010).

The baby could exit this study if discharged, transferred to NICU, parents' wish, or any other condition which in the opinion of the investigator would compromise the health of the newborn in case of continuation of this study. None of the enrolled preterm infants dropped out of this study.

Procedure With Glucose

- The nurse delivered 10% glucose 1–2 ml 2 min before starting the procedure, in small doses over a period of a maximum of 2 min; if the preterm infant prior to sampling was suckling the pacifier, this was allowed to continue.
- The nurse identified the point of the heel (avoiding the puncture if already injured, scarred, or bruised), disinfected, grabbed the heel holding it without squeezing, pricked with a manual needle, and dried the first drop with gauze.
- The nurse filled the capillaries necessary by making an intermittent pressure around the tip area.
- At the end of the procedure, the nurse administered glucose 1–2 ml in small doses for a maximum of 2 min.
- A second nurse rated pain with the PIPP scale, 2 min before starting and 2 min at the end of the procedure.

Procedure With Music

- From 5 min prior of HL to 5 min after the drawing and for not longer than 20 min, the baby was made listen to "Sonata in D Major for Two Pianos (K. 448)" by Wolfgang Amadeus Mozart (the second movement, andante), The Sonata, lasting

about 8 min, was repeatedly played for a maximum time of 18 min. The speakers were positioned in the same room with the cradle/crib of the newborn; the sound intensity in the proximity to the newborn was not allowed to exceed 65–70 dB.

- The nurse identified the point of the heel (avoiding the puncture if already injured, scarred, or bruised), disinfected, grabbed the heel holding it without squeezing, pricked with a manual needle, and dried the first drop with gauze.
- The nurse filled the capillaries necessary by making an intermittent pressure around the tip area.
- A second nurse rated pain with the PIPP scale, 2 min before starting and 2 min at the end of the procedure.

Standard Procedure

- The nurse identified the point of the heel (avoiding the puncture if already injured, scarred, or bruised), disinfected, grabbed the heel holding it without squeezing, pricked with a manual needle, and dried the first drop with gauze.
- The nurse filled the capillaries necessary by making an intermittent pressure around the tip area.
- A second nurse rated pain with the PIPP scale, 2 min before starting and 2 minutes at the end of the procedure.

RESULTS

Thirty-five infants were enrolled; 24 (68.5%) were males, 14 (40%) were from the same hospital neonatology, 1 came from home, and 20 were from other hospitals, from the delivery room, or from the pediatric emergency room of the hospital. The acceptance diagnosis were respiratory distress (9, 25.0%), prematurity and respiratory distress (14, 40.0%), respiratory distress (3, 2.6%), biliary atresia (2, 5.75%), clef palate (2, 5.75%), bronchiolitis (2, 5.75%), suspected sepsis (1, 2.82%), low birth weight (1, 2.82%), and hematochezia (1, 2.82%). The median gestational age at birth was 34 weeks (IQR 32–37, min–max range 25–41), median gestational age at study entry was 37 weeks (IQR 34.4–38.0, min–max range 30–45), and median duration of hospital stay was 10 days (IQR 5.5–25.0, min–max range 2–90).

Therefore, 105 HL were available for analysis (35 standard procedure, 35 music, 35 glucose), 63 (60%) on the right heel. Forty-two (40%) HL procedures were carried out with background noise (mostly monitors and in some cases human voices).

Median baseline PIPP was 3 (IQR 2–3, min–max range 0–8), and median PIPP after the HL procedure was 5 (IQR 4–6, min–max range 0–14). Comparison of PIPP scale changes in the three study arms is reported in Figure 1: Median increase in PIPP was 3 points (IQR 2–6) in the control group, 1 point (IQR 0–2) in the glucose group, and 2 points (IQR 1–4) in the music group ($p = .008$).

Even after adjusting for variables potentially influencing PIPP changes (particularly baseline PIPP), the differences retained statistical significance.

The median time to complete the procedure was 2 min (IQR 2–4, min–max range 1–15) with no significant differences between groups. During this study, there were no adverse events.

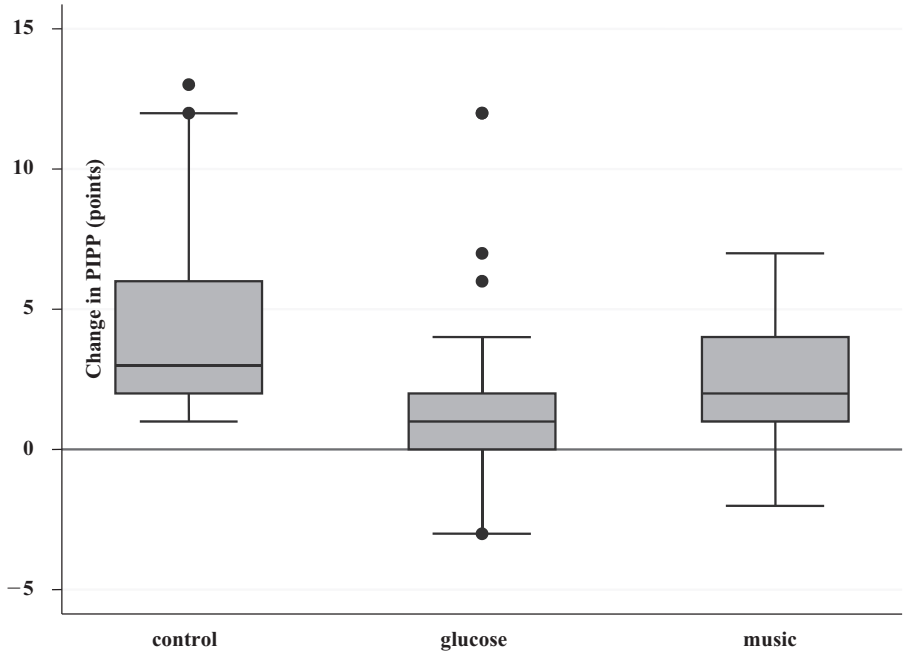

Figure 1. Premature Infant Pain Profile (PIPP) variation between baseline and after heel puncture in 35 newborns treated with three different pain control treatments. Central line = median; box = interquartile range (25 and 75 percentile); whiskers = range; dots = outliers; grey horizontal line = no change (i.e., change = 0). Overall, p value = 0.008. Post-hoc comparisons: glucose vs. standard <0.001; music vs. standard = 0.002; glucose vs. music = 0.09.

DISCUSSION

Despite the recommendations of the existing guidelines, the use of nonpharmacological techniques of pain relief during procedures such as HL is not uniform (Losacco et al., 2011). The use of automatic incision devices has been demonstrated to be less traumatic than manual lance (Shepherd et al., 2006; Vertanen et al., 2001).

To our knowledge, this is the first randomized controlled trial on the management and reduction of pain using the music of Mozart in premature infants hospitalized in the NICU. Our results confirm that one simple nonpharmacological treatment limits pain in neonates during HL procedures, even after taking into account age, background noise, and baseline pain, with no adverse events and at a low cost (Table 1). Variability in the PIPP change was small and within the range of clinically important difference; therefore, we conclude we can be confident in our results.

A Cochrane review (2010) shows that sucrose is safe and effective for reducing procedural pain from single events, but an optimal dose could not be identified because of inconsistency in effective sucrose dosage among studies (Stevens, Yamada, & Ohlsson, 2010). In some studies, the concentration of glucose have ranged between 10% and 30%, with an administered volume between 0.05 and 2 ml (Bonetto et al.,

TABLE 1. Multivariate Analysis of Factors Determining Premature Infant Pain Profile (PIPP) Variation After Heel Puncture in 35 Newborns

Variable	Difference of Change of PIPP	95% CI	*p* Value
Glucose vs. control	−2.57	−3.60/−1.53	<.001
Music vs. control	−1.90	−2.9/20.90	<.001
PIPP at baseline (per each point)	−0.70	−1.07/0.34	<.001
Background noise vs. no noise	0.24	−0.69/1.10	.60
Heel left vs. heel right	−0.74	−1.62/0.14	.10
Ga-weekly	0.04	−0.10/0.19	.56

Note. CI = confidence interval; Ga = gestational age.

2008; Dilen & Elseviers, 2009; Işik, Ozek, Bilgen, & Cebeci, 2000; Marcatto, Tavares, & Silva, 2011; Stevens, Yamada, et al., 2010). A study by Guala et al. (2001) has evaluated the effect of different oral glucose or sucrose solutions (namely, 5%, 33%, and 50%) on the pain response to HL in newborns (gestational age 38–41 weeks), concluding that sweet solutions may be an easy, useful, safe, and cheap analgesic for minor invasive procedures in newborns (Guala et al., 2001).

The use of glucose, or sweetener associated with NNS, often encounters resistance from the parents because of prior beliefs that artificial sweeteners can damage children's teeth in the future (Harrison, 2008). In our experience, parents have shown more interest in music than in glucose, although they easily accepted glucose treatment; in fact, these myths have been refuted at least for short-term glucose use (Cignacco et al., 2007; Golianu, Krane, Seybold, Almgren, & Anand, 2007; Harrison, 2008; Harrison, Johnston, & Loughnan, 2003).

"Sonata in D Major for Two Pianos (K. 448)" has simple melodic elements and rare dissonances that fuel a perceived simplicity (Cacciafesta et al., 2010). The simple elements in the music of Mozart are a result of the influences of *Galante Style* (Pignatta, 2012), a movement from which the classical style evolved as a reaction to the complexity of late baroque music. Mozart's mature style is clearly rooted in the tendencies of this style, and one of the most recognizable features of Mozart's work is a sequence of harmonies or modes that usually leads to a cadence in the dominant or tonal key (Bourdon, 2010; Carter, 2008). Some results indicate that the neural architecture underlying music processing in newborns is sensitive to changes in tonal key as well as to differences in consonance and dissonance (Perani et al., 2010). Furthermore, Mozart repeats his melodic line far more frequently than other well-known composers (Hughes, 2001a, 2001b, 2002; Lubetzky et al., 2010); this periodicity is the same which characterizes brain and bodily function (Hughes, 2001a). A study reported that nurses prefer the presence of recorded music in the NICU to live music; they believe that it can benefit preterm infants, parents, and the whole staff (Pölkki, Korhonen, & Laukkala, 2012).

Our study had several strengths: (a) It was randomized and block balanced, with a control group; (b) preterms were randomized consecutively; (c) a range of diseases/health problems were represented in the sample; (d) no additional therapy for pain was given, and the effect may be solely attributed to the study treatment; and (e) well-defined eligibility criteria.

Some limitations need to be acknowledged. First, the music arm could not be blinded, and, although in these cases PIPP was ascertained by two independent investigators and then averaged, it is possible that individual beliefs on music efficacy may have influenced judgment. Secondly, enrolled children were aged >30 weeks and results could not be extended to younger children. In addition, children with no ability to suckle were excluded. Importantly, the limited sample size determined a low capacity to detect differences in secondary analyses (e.g., difference between glucose and music). Besides, pacifiers were equally used during the three treatments, and (although it would not qualify as confounder), if suckling is effective against pain, it would rather contribute to reduce differences between groups.

Finally, we chose not to compare nonpharmacological techniques to the standard procedure arm in terms of variation of individual PIPP parameters because the variations of individual parameters seem to be related to the squeezing of the heel and to an incorrect execution of the procedure.

CONCLUSIONS

This is the first randomized controlled trial in the management and reduction of pain using the music of Mozart in preterm infants hospitalized in the NICU, and confirms that the use of nonpharmacological techniques, in particular music and glucose, for pain control in preterm infants is safe and effective. These measures meet the criteria of good clinical practice and ethical needs of the NICU. The result of this study gives direction for future studies on the topic area, including investigation of sensory overload and sensory adaptation in response to continuous exposure to music (which may reduce its effectiveness in the medium long–term), on the effects of prolonged use of repeated doses of glucose, and on parents' beliefs about glucose use.

Finally, great care is needed in daily practice, as opposed to within-research protocols, to enforce good practices among health care workers, raise awareness on pain detection and management in preterm infants, and improve quality of care for young patients.

What Is Known About This Topic?

The use of nonpharmacological techniques for pain control in preterm infants is safe and effective, but randomized controlled trials using the music of Mozart ("Sonata K. 448") as intervention for the management and reduction of pain in preterm infants hospitalized in a NICU during HL procedure were not available.

What This Article Adds

The music of Mozart ("Sonata K. 448") is effective in decreasing pain behavior when compared to standard procedure.

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