Efficacy and safety of Maternal voice for Preterm Neonatal Pain: a Systematic Literature Review

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KEYWORDS
Preterm Neonatal Pain, Cortisol level, Maternal voice, recorded maternal voice, maternal heartbeat

ABSTRACT
Purpose: Pain in neonates, especially in preterm neonates has short effects and long effects. A mother’s voice can stabilize the physiological state, support feeding, reduce pain, and promote growth and development. aimed to analyze the effect and safety of maternal voice for preterm neonatal pain, to provide scientific evidence.

Design: The research design used in this study is the systematic literature review. The identification of the study uses a PRISMA flow diagram, and quality assessment uses critical appraisal tools from the Centre for Evidence-Based Medicine. The analyzed data related to the population, intervention, and outcomes (PIO components).

Findings: Ten studies were included in this study, ranging from 2018 to 2023. Seven studies showed the significant efficacy of maternal voice in reducing preterm neonatal pain, and three studies no significance. Five studies show maternal voice can reduce pain significantly more than routine care, and two studies use a combination of maternal voice and other non-pharmacological management, including breast milk, taste, Non-nutritive sucking, heartbeat sounds mother voice, and mother touch therapy. Pain parameters use the Pain Scale and serum and salivary cortisol level.

Implications: Maternal voice; both live or recorded, voice or heartbeat, was effective and safe in reducing pain sensation in preterm neonates.

K E Y W O R D S
Preterm Neonatal, Pain, Cortisol level, Maternal voice, recorded maternal voice, maternal heartbeat

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I. INTRODUCTION

Prematurity until now is still the largest contributor to Indonesian neonatal deaths, about 15% (Rohsiswanto, 2021). According to the World Health Organization (WHO), in 2015 Indonesia ranked 5th in the number of premature births, amounting to 15 in every 100 live births, and was the first cause of neonatal death (35.5%) (McCormick et al., 2011; Haksari, 2019; Gomella, Eyal and Bany-Mohammed, 2020; Tsikouras et al., 2021). Prematurity is also related to the risk of treatment in a hospital, which relates to a risk of pain either due to clinical conditions or due to treatment procedures. On average number of daily acute painful events for hospitalized preterm neonate reach up to 26 and the cumulative time is 57.61 hours (Shen et al., 2022).

Pain in neonates, especially in preterm neonates has short effects and long effects, for example: neurodevelopmental outcome disorder, and behavioral and learning disorder (Gomella, Eyal and Bany-Mohammed, 2020). Preterm neonatal had a risk for cerebral palsy 5 – 10%, fine motor disorders at 40%, and social and cognitive disorders at 60% (Cong et al., 2017). Several managements for neonatal pain, both pharmacological and non-pharmacological. These Non-pharmacological management are recommended as a first-line treatment for preterm neonatal such as Non-nutritive sucking (NNS), sweet solution, breastfeeding, kangaroo mother care (KMC), and music or voice therapy (Shen et al., 2022). Maternal voice stimulation in preterm neonatal care has received attention in recent years, Previous research has shown that a mother’s voice can stabilize the physiological state, support the feeding process, reduce pain, and promote growth and development (Wu, Yin, et al., 2020; Jin et al., 2023). The research about the effect of maternal voice on preterm neonatal pain is still controversial, with small samples. Therefore, this study aimed to analyze the effect and safety of maternal voice for preterm neonatal pain, to provide scientific evidence.

II. METHODS

Study Design and Literature Search strategy

The research design used in this study is the systematic literature review. The literature search strategy and selection criteria used: (“premature newborn” OR “premature neonate” OR “premature infant” OR “preterm newborn” OR "preterm neonate" OR "preterm infant") and (“voice” OR “mother voice” OR “maternal voice” OR "speech" OR "mother speech" OR "maternal speech") and (“pain”) and ("experimental study" OR “Randomized Control Trial”). The researchers searched from several search sites: including Science Direct, Proquest, Nature Journal, National Institute of Health (.go), and Research Gate, Willey Online Library.

Selection Criteria, Screening, and Quality Evaluation

Filtering data from researcher search by following provisions: (1) article from the last five years (2018 – 2023); (2) the study population were preterm neonatal who did not receive sedative or analgesic for 24 hours before procedure; (3) the stimulus can be either mother’s voice or recorded maternal voice including the mother’s heart-bate, storytelling, song singing and speaking during procedure; (4) assessment of pain use pain scale for examples: premature infant pain profile, neonatal infants pain scale or biochemical parameter (salivary cortisol or plasma cortisol level; (5) from reputable international journals; (6) accessible full text; (7) experimental study and randomized control trial study. The identification of the study uses PRISMA flow diagram (figure 1) (Page et al., 2021). Quality assessment uses critical appraisal tools from the Centre for Evidence-Based Medicine. The analyzed data related to the population, intervention, and outcomes (PIO components) (Sackett and Haynes, 2016).
**Figure 1. Flowchart of the selection process of included systematic literature review**

**Data Synthesis**
A descriptive analysis was used to evaluate the efficacy and safety of mother voice for preterm neonatal pain, including a characteristic study.

**Ethical Considerations**
Ethical approval was obtained from the Health Research Ethics Committee Faculty of Medicine Universitas Brawijaya.

### III. RESULT

**General Information of Study**
Based on a review 10 Journal that included in qualitative synthesis, most journal was published in 2021 (table 1)

<table>
<thead>
<tr>
<th>Table 1. General Characteristics of Study</th>
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<tbody>
<tr>
<td><strong>Category</strong></td>
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<td><strong>Year of Publish</strong></td>
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<tr>
<td>2018</td>
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<td>2019</td>
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<td>2020</td>
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<td>2021</td>
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<td>2022</td>
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<td>2023</td>
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<tr>
<td><strong>Total</strong></td>
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<td><strong>Instrument for pain</strong></td>
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<tr>
<td>Premature Infant Pain Profile (PIPP)</td>
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<td>Premature Infants Comfort Scale (PICS)</td>
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<tr>
<td>Crying duration</td>
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<td>Behavioral stress</td>
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<td>Salivary cortisol level</td>
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<td>Saliva oxytocin level</td>
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<td>plasma cortisol level</td>
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<tr>
<td>Neonatal Infants Pain Scale (NIPS)</td>
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<td>Generalized estimating equation (GEF)</td>
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<td>Neonatal Infant Acute Assessment Scale (NIAPAS)</td>
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<tr>
<th><strong>Result</strong></th>
<th><strong>N</strong></th>
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<tbody>
<tr>
<td>Significant</td>
<td>7</td>
</tr>
<tr>
<td>Not Significant</td>
<td>3</td>
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<tr>
<td><strong>Total</strong></td>
<td>10</td>
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Result of Data Analysis
The analysis of all studies that included critical appraisal is shown in Table 2

<table>
<thead>
<tr>
<th>No</th>
<th>Years. Journal</th>
<th>Title</th>
<th>Methods</th>
<th>Result</th>
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<tbody>
<tr>
<td>1</td>
<td>2018 Aplied Nursing Research (Alemdar, 2018)</td>
<td>Effect of recorded maternal voice, breast milk odor, and incubator cover on pain and comfort during peripheral cannulation in preterm infants</td>
<td></td>
<td>Significant difference in the PIPP score of the control and intervention groups before the peripheral cannulation procedure and after peripheral cannulation (p&lt;0.05). In terms of difference, the infants in the incubator cover group were followed in the breast milk odor, maternal voice, and control group.</td>
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<tr>
<td>Year</td>
<td>Journal</td>
<td>Study Title</td>
<td>Participants</td>
<td>Settings</td>
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<tr>
<td>2018</td>
<td>Japan Journal of Nursing Science</td>
<td>Effects of maternal heart sounds on pain and comfort during aspiration in preterm infants</td>
<td>62 infants</td>
<td>During and after the procedure.</td>
</tr>
<tr>
<td>2018</td>
<td>Japan Journal of Nursing Science</td>
<td>Clinical effect of maternal voice stimulation in alleviating procedural pain in hospitalized neonates</td>
<td>72 neonates</td>
<td>During and after the procedure.</td>
</tr>
<tr>
<td>2020</td>
<td>Journal of Nursing Scholarship</td>
<td>Effects of combined use of mother’s breast milk, heartbeat sounds, and non-nutritive sucking on preterm infant’s behavioral stress during venipuncture: A Randomized controlled trial</td>
<td>138 preterm infants</td>
<td>During and after the procedure.</td>
</tr>
</tbody>
</table>
d. Breast milk odor and taste (BM-OT) + heartbeat sounds (HBs) + Non nutritive sucking (NNS).
   - Duration crying recorded from the time puncture (the infant started crying) to the recovery period (the infant stopped crying).
   - Behavioral stress was recorded using a video recorder.

5. 2021 International Journal of Nursing Studies (Liao et al., 2021)

Mother’s voices and white noise on premature infant’s physiological reactions in a neonatal intensive care unit: A multi-arm randomized controlled trial

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- 103 neonates
  a. Routine care group
  b. Mother voice groups. Premature infant receives 20 min sessions three times a day of mother’s voice (the Chinese version of a lullaby for about 5 min in a quiet environment).
  c. White noise group, premature infants received white noise

- Routine care
  - Haaring mother’s voice
  - Hearing white noise

- Sleep-wake patterns
  - Pain
  - Heart rate
  - Oxygen saturation

- Sleep-wake patterns
  - Salivary cortisol level
  - Heart rate
  - Oxygen saturation

A significant difference between the pre-test and post-test evaluation in sleep efficiency (p=0.002).

No significant differences were found in the salivary cortisol levels, heart rate and oxygen saturation levels among the three groups (p>0.005).

Non-significant decreases in the salivary cortisol levels at post test were noted in all the three groups.
in 20-minutes sessions 3 times a day on 4 consecutive days on the basic of routine care by the researchers.

- Sleep-wake patterns, salivary cortisol level, and weight were measured every five minutes at 11am, 2pm, and 5pm for four consecutive days.

| 6. | 2021 La Pediatria Medica e Chirurgica (Efendi et al., 2021). | Comparison of mother’s therapeutic touch and voice stimulus in reduce pain in premature infants undergoing invasive procedure | 63 preterm infants  
- Invasive procedure:  
  1. Endotracheal suction  
  2. Heel prick  
  3. Vein puncture  
  a. Routine care  
  b. Mother touch therapy (MTT).  
  c. Mother’s voice stimulus (MVS)  
  d. Combination of MTT and MVS.  
- Intervention allocated time of 25 minutes.  
- Video recording the infant’s response | Routine care  
- Mother touch therapy (MTT).  
- Mother’s voice stimulus (MVS) | Pain score |  
- Neonatal Infants Pain Scale (NIPS)  
- Generalized estimating equation (GEF) | The MTT + MVS interventions show a decrease in pain scores by a factor of 7.  
Compared to the control group, the MVS group experienced a significant reduction pain score of 0.82 at 8th minute (p=<0.05), MTT reduced the pain score 0.76 at 9th minute (p=<0.05); 1.07 at 21st minute (p=<0.05).  
Compared to the control group, MTT + MVS significantly reduced pain score 1.49 at 8th minutes (p<0.05); 1.58 at 10th minutes (p=<0.05). |
<table>
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<tr>
<th>No.</th>
<th>Year</th>
<th>Journal</th>
<th>Study Title</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>7.</td>
<td>2021</td>
<td>Pain Management Nursing (Chen et al., 2021)</td>
<td>The effect of maternal voice on venipuncture induced pain in neonates: A Randomized Study</td>
<td>One hundred and sixteen (116) preterm infants</td>
<td>Venipuncture (peripheral and femoral) Routine care Maternal voice: Received recorded maternal voice before, during and after venipuncture.</td>
<td>Routine care Maternal voice</td>
<td>Pain Neonatal Infant Acute Assessment Scale (NIAPAS). The NIAPAS scores, behavioral indicator, and physiological indicator in the maternal voice group were significantly lower compare with routine groups (p=0.001).</td>
</tr>
<tr>
<td>8.</td>
<td>2021</td>
<td>Scientific Reports (Filippa et al., 2021)</td>
<td>Maternal speech decreases pain score and increases oxytocin level in preterm infants during painful procedures</td>
<td>Twenty preterm infants Heel stick procedure procedure a. Standard care b. Mother’s live voice (speaking or singing)</td>
<td></td>
<td></td>
<td>Live mother voice (speaking and singing) reduced PIPP score significantly (p=0.028), no effect on plasma cortisol level.</td>
</tr>
<tr>
<td>9.</td>
<td>2022</td>
<td>Journal of Pediatrics Nursing (Yu et al., 2022)</td>
<td>Effects of Maternal voice on pain and mother-infant bonding in premature infants in Taiwan: A randomized controlled trial</td>
<td>64 preterm infants Heel stick procedure procedure a. Control groups b. Maternal voice: recorded mother reading a children’s book, was played starting at 3 min before procedure until the</td>
<td>Control group Hearing maternal voice</td>
<td>Heart rate Respiratory rate Oxygen saturation Pain</td>
<td>Heart rate Respiratory rate Oxygen saturation Neonatal Infants Pain Scale (NIPS). At 1 minutes after the procedure, the maternal voice group had a lower heart rate (p&lt;0.001) and pain score (NIPS) (p&lt;0.001) than control groups.</td>
</tr>
</tbody>
</table>
### 10. Journal of Pediatrics Nursing (Apaydin Cirik et al., 2023)

The effect of using maternal voice, white noise, and holding combination interventions on the heel stick sampling

- 178 infants
- Heel stick procedure.
  - Control groups
  - White noise group
  - Maternal voice group
  - Holding group
  - White noise+holding group
  - Maternal voice+holding group
- All interventions were done 5 min before heel stick procedure and 5 min after the procedure was done.
- Pain scales were evaluated one minute before, during, and one minute after the procedure.
- Control care
  - White noise
  - Holding
  - Maternal voice
- Pain
  - Heart rate
  - Oxygen saturation
- Neonatal Infant Pain Scale (NIPS)
- Premature Infant Pain Profile (PIPP).

White noise and white noise+holding were found to have the lowest mean NIPS and PIPS score (p<0.001).
IV. DISCUSSION

The improved life expectancy and management for preterm infants, make the increased procedure for preterm neonatal procedures, especially in the hospital or Neonatal Intensive Care. This condition increases the risk of suffering pain, which can come from the underlying disease or condition, including from the procedure, whether routine, diagnostic, or therapeutic procedure. Preterm infants in the neonatal intensive care unit (NICU) undergo numerous and frequent painful procedures, an average of more than 700 procedures during treatment, and 93 needle punctures (heel pricks) over 2 weeks that can cause pain (Newnham, Inder and Milgrom, 2009; Williams and Lascelles, 2020; Febriani, 2021).

The number of painful and distressing events can influence the physiological changes, including heart rate, and oxygen saturation (Küçük Alemdar and Güdücü Tüfekcİ, 2018; Apaydin Cirik et al., 2023) changes in the brain; reduced white matter, subcortical grey matter (Brummelte et al., 2012), and long-outcome including neurodevelopmental disorders, and behavioral and cognitive disorders (Vinall and Grunau, 2014; Cong et al., 2017; Gomella, Eyal and Bany-Mohammed, 2020).

Recently, the study for the management of neonatal pain focused on non-pharmacological analgesia methods to prevent pain, including breastfeeding, the mother-kangaroo methods or skin contact, oral sucrose of glucose, non-nutritive sucking, family odor, acoustic/music/mother voice, massage, acupuncture, holding and family odor, which have emerged to prevent the side effects the drugs for preterm infants. Non-pharmacological methods is preferred not only because it is ethical but also because of their high benefit-risk ratio (Kawaljeet., 2012; Asmarani et al., 2020; Gomella, Eyal and Bany-Mohammed, 2020; Rad et al., 2021; García-Valdivieso et al., 2023).

The human auditory system is unique, unlike the visual system where the actual visual experience begins after birth at term, the auditory system requires auditory experience with voice, language, and meaningful environmental sounds during the last 10 to 12 weeks of fetal life (18 – 30 week’s gestational age) (Graven and Browne, 2008; Partanen et al., 2013). Live and recorded music/voice have a measurable short-term physiological and behavioral impact on hospitalized preterm and term infants and their parents. With reduced infant stress responses and crying, reduced parental stress and anxiety, and improved parent-infant interaction and bonding (Arnon et al., 2014; Bieleninik, Ghetti and Gold, 2016; Ullsten, Eriksson and Kla, 2018). Recorded maternal voices and recorded lullabies have been shown the positive effects on infants’ behavioral pain indicators (Graven and Browne, 2008; Arnon et al., 2014; Rand and Lahav, 2014; Chirico et al., 2017).

In this systematic literature review, 10 types of research from 2018 until 2023: seven types of study showing effectiveness and safety using maternal voice both maternal voice or heart rate to reduce preterm infant’s pain. Five studies show maternal voice can reduce pain significantly more than routine care, using the Premature Infant Pain Scale (PIPP) (Küçük Alemdar and Güdücü Tüfekcİ, 2018; Chen, Tan and Zhou, 2019; Filippa et al., 2021), Neonatal Infant Acute Assessment Scale (NIAPAS) (Chen et al., 2021), and Neonatal Infants Pain Scale (NIPS) (Yu et al., 2022). One study use a combination of breast milk, taste, Non-nutritive sucking and heartbeat sounds (Wu, Yang, et al., 2020), and the result that effective in shooting crying and shortening crying duration. One study used mother voice and mother touch therapy (Efendi et al., 2021) showing that mother voice stimulation decreased pain scale significantly.

Pain is a severe stressor that activates the hypothalamic-pituitary-adrenal-thyroid-gonadal (HPATG) system, which functions as the major stress control mechanism of the body. Pain will influence the hormone system for many control functions, such as thyroid, cortisol, or testosterone for protection and regeneration of injured tissue, immunologic activity and metabolic controls. The critical pain-control hormones that are produced in glands are cortisol,
pregnenolone, dehydroepiandrosterone (DHEA), progesterone, testosterone, estrogen, and thyroid (Tennant, 2013). Cortisol is the main hormone for pain response, and the receptors are distributed almost around the body (Pourkaviani et al., 2020). Cortisol circadian rhythm is the fluctuating cortisol level, the highest when waking up in the morning, then decreases until the lowest level before sleeping time (Jones and Gwenin, 2021). Cortisol circadian rhythm perfectly occurs from 1 month in term infants (Ivars et al., 2015) and at 1 month corrected age in preterm infants (Ivars et al., 2017). Biologically active free cortisol enters cells by passive diffusion and can measured in all bodily fluids. Salivary cortisol reflects levels of free cortisol in blood. Exiting studies result increases in cortisol level during pain procedure, and decreases following pain management in preterm infant (Kim et al., 2020; Pourkaviani et al., 2020; Tasci and Kuzlu Ayyildiz, 2020).

Pain in preterm infants increases cortisol levels, especially salivary cortisol levels. Salivary cortisol reactivity is the difference in saliva cortisol level between pain and baseline condition. Some procedures including diagnostic or therapy procedures cause an increase in salivary cortisol in preterm infants (Mörelius, He and Shorey, 2016; Stoye et al., 2022). The difference results in 2021 that no significant difference in the salivary cortisol level in the preterm infants who listened to their mother's voice during Neonatal Intensive Care Unit hospitalizes and routine care without mother's voice (Liao et al., 2021).

Listening to maternal voice or music would increase autonomy system response, support a comfortable environment, and decrease pain sensation in preterm infants (Dorn et al., 2014; Rand and Lahav, 2014). The maternal voice and bonding increased endogen neuropeptides and endogen opioids to reduce pain (Ullsten, Eriksson and Kla, 2018), stimulate the emotional center at the limbic system, and then influence pain responses (Graven and Browne, 2008).

Implications for practice the use of maternal voice in preterm neonatal pain: (1) playing recordings of maternal voice during the time or pain procedure when the mother is unable to visit, (2) modulating the external environment and observing the infant’s cues and behavioral changes, to avoid adding neonatal stress; (3) modulating the volume of the recording or the other or environment noise (average 45 dB) (Williamson and McGrath, 2019; Almadhoob and Ohlsson, 2020).

V. CONCLUSION

This overview investigated the efficacy and safety of maternal voice for preterm neonatal pain, and concluded that maternal voice, both of live or recorded, voice or heartbeat were effective and safe to reduce pain sensation in preterm infant. Many non-pharmacological management for preterm neonatal pain, which had many mechanism, need more studies to evaluated the combination of more than one management.

REFERENCES


Apaydin Cirik, V. et al. (2023) ‘The effect of using maternal voice, white noise, and holding combination interventions on the heel stick sampling’, Journal of Pediatric Nursing, 70,


BIOGRAPHY

Ni Luh Putu Herli Mastuti. The author was born in Ponorogo, East Java on February 1975. Completed Elementary school at Grobogan, Madiun 1 Elementary School in 1986, Junior high school in SMP 2 Madiun, in 1990, Senior High School in SMA 2 Madiun in 1993. Completed general practitioner in 2000, Pediatrician in 2011 in Medical Faculty, Universitas Brawijaya, and Neonatologist in 2023 in Airlangga University. Currently a lecturer at the Midwifery Department, Faculty of Medicine Universitas Brawijaya and a Neonatologist in Brawijaya University hospital. Award for best poster presentation in 14th PICU NICU Update in 2023 and third best oral presentation in 9th Indonesian Pediatric Endocrinology (PEDENDO) 2023.