

Article

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

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A B S T R A C T

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.

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).

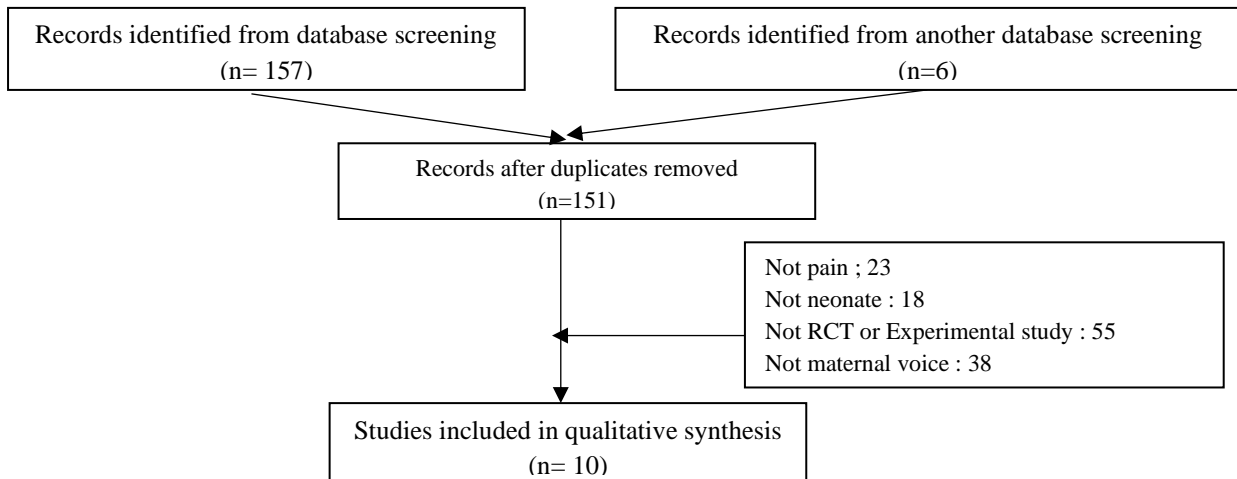


Figure 1. Flowchart of the selection process of included systematic literature review

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 1. General Characteristics of Study

Category	N
Year of Publish	
2018	2
2019	1
2020	1
2021	4
2022	1
2023	1
Total	10
Instrument for pain	
Premature Infant Pain Profile (PIPP)	4
Premature Infants Comfort Scale (PICS)	3
Crying duration	1
Behavioral stress	1
Salivary cortisol level	1
Saliva oxytocin level	1
plasma cortisol level	1
Neonatal Infants Pain Scale (NIPS).	1
Generalized estimating equation (GEF).	1
Neonatal Infant Acute Assessment Scale (NIAPAS)	1
Result	
Significant	7
Not Significant	3
Total	10

Result of Data Analysis

The analysis of all studies that included critical appraisal is shown in Table 2

Table 2. The characteristics and analysis of included studies

No	Years. Journal	Title	Methods			Result	
			Sample/Interventions	Variabel			Instrumen/Parameter
				Dependent	Independent		
1.	2018 Applied Nursing Research (Alemdar, 2018)	Effect of recorded maternal voice, breast milk odor, and incubator cover on pain and comfort during peripheral cannulation in preterm infants	<ul style="list-style-type: none"> - 136 preterm neonates - Peripheral cannulation a. Standard care b. maternal voice group. The mother voice recording was set to 45 dB and played for 15 min before procedure until 15 min after the procedure. c. Breast milk odor group, A total 5 ml breastmilk was poured in the sterile sponge 15 min before the procedure until 15 min after the procedure, and placed 5 cm away from the infant. d. Incubator cover group. The incubator were covered before, 	<ul style="list-style-type: none"> - Hearing maternal voice - breast milk odor - Incubator cover 	Pain	<ul style="list-style-type: none"> - Premature Infant Pain Profile (PIPP) - Premature Infants Comfort Scale (PICS) 	<p>Significant difference in the PIPP score of the control and intervention groups before the peripheral cannulation procedure and after peripheral cannulation (p<0.05).</p> <p>In terms of difference, the infants in the incubator cover group were followed in the breast milk odor, maternal voice, and control group.</p>

			during and after the procedure.				
2.	2018 Japan Journal of Nursing Science (Küçük Alemdar and Güdücü Tüfekçi, 2018)	Effects of maternal heart sounds on pain and comfort during aspiration in preterm infants	<ul style="list-style-type: none"> - 62 infants - Aspiration after the intubation process a. Routine care group b. Maternal heart sound, was conducted for 1 minute before the aspiration and continued 1 minute after the aspiration. 	<ul style="list-style-type: none"> - Routine care - Hearing maternal heart sound 	Pain	<ul style="list-style-type: none"> - Premature Infant Pain Profile (PIPP) - Premature Infants Comfort Scale (PICS) 	A significant difference in PIPP score between the routine group and maternal heart sound during aspiration ($p < 0,05$).
3.	2019 Chin J Contemp Pediatr (Chen, Tan and Zhou, 2019)	Clinical effect of maternal voice stimulation in alleviating procedural pain in hospitalized neonates	<ul style="list-style-type: none"> - 72 neonates - Heel blood collection a. Routine care. b. Mother voice; listening to mother's voice from 1 minute before heel blood collection to the end of the procedure. 	<ul style="list-style-type: none"> - Routine care - Hearing mother's voice 	<ul style="list-style-type: none"> - Pain - Incident of crying - Vital sign 	Premature Infant Pain Profile-Revised (PIPP-R) score	A significant decrease Pain score in maternal voice groups ($p < 0.05$).
4.	2020 Journal of Nursing Scholarship (Wu, Yang, et al., 2020).	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	<ul style="list-style-type: none"> - 138 preterm infants. - Venipuncture procedure. a. Routine care b. Breast milk odor and taste (BM-OT) c. Breast milk odor and taste (BM-OT) + heartbeat sounds (HBs). 	<ul style="list-style-type: none"> - Routine care - Breast milk odor and taste (BM-OT) - Heartbeat sounds (HBs) - Non nutritive sucking (NNS) 	<ul style="list-style-type: none"> - Crying duration - Behavioral stress (Infant Fascial actions and body movements). 	<ul style="list-style-type: none"> - Crying duration - Behavioral stress 	Breast milk odor and taste (BM-OT) + heartbeat sounds (HBs) and Breast milk odor and taste (BM-OT) + heartbeat sounds (HBs)+Non nutritive sucking (NNS) effective in soothing crying and shortening crying duration ($p < 0.001$), and reduced the occurrence of

			<p>d. Breast milk odor and taste (BM-OT) + heartbeat sounds (HBs)+Non nutritive sucking (NNS).</p> <p>– Duration crying recorded from the time puncture (the infant started crying) to the recovery period (the infant stopped crying).</p> <p>– Behavioral stress was recorded using a video recorder.</p>				<p>facial actions and body movements after venipuncture.</p>
5.	<p>2021 International Journal of Nursing Studies (Liao <i>et al.</i>, 2021)</p>	<p>Mother's voices and white noise on premature infant's physiological reactions in a neonatal intensive care unit: A multi-arm randomized controlled trial</p>	<p>– 103 neonates</p> <p>a. Routine care group</p> <p>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).</p> <p>c. White noise group, premature infants received white noise</p>	<p>– Routine care</p> <p>– Hearing mother's voice</p> <p>– Hearing white noise</p>	<p>– Sleep-wake patterns</p> <p>– Pain</p> <p>– heart rate</p> <p>– Oxygen saturation</p>	<p>– Sleep-wake patterns</p> <p>– Salivary cortisol level</p> <p>– Heart rate</p> <p>– Oxygen saturation</p>	<p>A significant difference between the pre-test and post-test evaluation in sleep efficiency (p=0.002).</p> <p>No significant differences were found in the salivary cortisol levels, heart rate and oxygen saturation levels among the three groups (p>0.005).</p> <p>Non-significant decreases in the salivary cortisol levels at post test were noted in all the three groups.</p>

			<p>in 20-minutes sessions 3 times a day on 4 consecutive days on the basic of routine care by the researchers.</p> <ul style="list-style-type: none"> – 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 <i>et al.</i> , 2021).	Comparison of mother's therapeutic touch and voice stimulus in reduce pain in premature infants undergoing invasive procedure	<ul style="list-style-type: none"> – 63 preterm infants – Invasive procedure: <ol style="list-style-type: none"> 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 	<ul style="list-style-type: none"> – Routine care – Mother touch therapy (MTT). – Mother's voice stimulus (MVS) 	Pain score	<ul style="list-style-type: none"> – Neonatal Infants Pain Scale (NIPS) – Generalized estimating equation (GEF). 	<p>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 ($p<0.05$).</p> <p>Compared to the control group, MTT + MVS significantly reduced pain score 1.49 at 8th minutes ($p<0.05$); 1.58 at 10th minutes ($p<0.05$).</p>

			from head during invasive procedure.				
7.	2021 Pain Management Nursing (Chen <i>et al.</i> , 2021).	The effect of maternal voice on venipuncture Induced Pain in Neonates ; A Randomized Study	One hundred and sixteen (116) preterm infants Venipuncture (peripheral and femoral) Routine care Maternal voice : Received recorded maternal voice before, during and after venipuncture.	– Routine care – Maternal voice	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).
8.	2021 Scientific Reports (Filippa <i>et al.</i> , 2021)	Maternal speech decreases pain score and increases oxytocin level in preterm infants during painful procedures	– Twenty preterm infants – Heel stick procedure procedure a. Standard care b. Mother's live voice (speaking or singing)	– Standard care – Mother live voice	Pain	– Premature infant Pain Profile (PIPP) – Saliva oxytocin level – plasma cortisol level	Live mother voice (speaking and singing) reduced PIPP score significantly (p=0.028), no effect on plasma cortisol level.
9.	2022 Journal of Pediatrics Nursing (Yu <i>et al.</i> , 2022).	Effects of Maternal voice on pain and mother-infant bonding in premature infants in Taiwan: A randomized controlled trial	– 64 preterm infants – Heel stick procedure a. Control groups b. Maternal voice: recorded mother reading a children's book, was played starting at 3 min before procedure until the	– Control group – Hearing maternal voice	– Heart rate – Respiratory rate – oxygen saturation – Pain	– 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<0.001) and pain score (NIPS) (p<0.001) than control groups.

			procedure completion.				
10.	2023 Journal of Pediatrics Nursing (Apaydin Cirik <i>et al.</i> , 2023).	The effect of using maternal voice, white noise, and holding combination interventions on the heel stick sampling	<ul style="list-style-type: none"> - 178 infants - Heel stick procedure. <ul style="list-style-type: none"> a. Control groups b. White noise group c. Maternal voice group d. Holding group e. White noise+holding group f. 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. 	<ul style="list-style-type: none"> - Control care - White noise - Holding - Maternal voice 	<ul style="list-style-type: none"> - Pain - Heart rate - Oxygen saturation 	<ul style="list-style-type: none"> - 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 Tüfekçi, 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 Tüfekçi, 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,

pregenolone, 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 be measured in all bodily fluids. Salivary cortisol reflects levels of free cortisol in blood. Existing studies result in 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 (Mörelus, 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 endogenous neuropeptides and endogenous 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 mechanisms, need more studies to evaluate the combination of more than one management.

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