Journal Of Health Science Vol X. No. 1 2025 | 18-31

Journal of Health Science
(Jurnal Ilmu Kesehatan)
https://www.ejournalwiraraja.com/index.php/JIK
2356-5284 (print) | 2356-5543 (online)

Effectiveness Of Non-Nutritive Sucking and Murottal In Reducing Neonates' Pain Response To Needle-Related Medical Procedures

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Article Information

Article History

Received: 10-04-25
Revised: 03-05-25
Accepted:16-05-25

Keywords:

Non-Nutritive Sucking
Murottal
Neonatepain response
medical procedures
needle

ABSTRACT

Neonates are newborns up to 28 days old who are highly vulnerable to infections and organ system disorders, often requiring medical intervention. One of the most common medical procedures performed on neonates is needle-related invasive procedures, such as intravenous catheter insertion and blood sampling, which can cause pain. Neonatal pain management generally avoids the use of pharmacological analgesics due to their various side effects. Therefore, effective non-pharmacological methods, such as Non-Nutritive Sucking (NNS) and Murottal therapy, are needed. This study aims to determine the effects of NNS, Murottal therapy, and their combination on reducing neonatal pain responses during needle-related medical procedures, using a quasi-experimental post-test only control group design. This study was conducted at Lamaddukelleng District General Hospital, Wajo Regency, South Sulawesi, specifically in the perinatology ward from August to October 2024 with a sample size of 92 people. The results indicate that the combination of NNS and Murottal therapy is the most effective in reducing neonatal pain responses during needle-related medical procedures, with an average pain response of 3.78 and a significance value of P > 0.001, compared to neonates who received a single intervention (either NNS or Murottal) or those in the control group.

Introduction

Neonates refer to newborns up to 28 days of age. In this neonatal period, babies are very vulnerable to pathogenic infections and organ system disorders due to the body's immunity that has not been fully formed, and also still needs adaptation to life outside the womb after birth. This is a factor that greatly affects the Infant Mortality Rate (IMR) globally and nationally. According to data from the *World Bank*, the infant mortality rate worldwide in 2019 reached 28.2 per 1000 live births (*The World Bank*, 2020). Meanwhile, based on the results of the 2017 Indonesian Demographic and Health Survey (IDHS), the neonatal mortality rate (IMR) in Indonesia was 15 per 1000 live births and the infant mortality rate (IMR) was 24 per 1000 live births (Indonesian Health Profile, 2018). As for infant mortality cases in South Sulawesi province, based on data from the South Sulawesi Health Office in 2019, there was a decrease in the number of cases from 2015 of 917 cases, which is equivalent to 6.12 per 1,000 live births, to 799 cases or 5.3 per 1,000 live births in 2018.[1,2]

The WHO revealed that most neonatal deaths (75%) occur within the first week of life, with approximately 1 million neonates dying within the first 24 hours. These neonatal deaths are caused by various factors such as premature birth, complications related to the delivery process (such as asphyxia or failure to breathe at birth), and infections with birth defects. These factors were also the main causes of neonatal deaths in 2017 (WHO, 2020). To minimize these events, in general, babies who after birth have health risks will be treated in the Perinatology room. The Perinatology room is a place that serves to facilitate various medical interventions while monitoring the development of neonates, and of the various medical procedures, one of the most frequently performed is needle-related actions, including infusion, blood collection, drug injection, and other invasive procedures.[3,4]

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain management in neonates is still not given much attention, mostly because babies cannot interpret the pain they experience verbally so it tends to be underestimated. Especially neonates who are often exposed to acute, recurrent, and chronic pain due to medical procedures, surgeries, and disease processes. Preterm neonates, especially those born before 30 weeks of gestation, are exposed to 10-15 painful procedures daily at a time when the experience of pain is developmentally unexpected. Pain in the neonatal period is often undetected and poorly managed. In infants born extremely preterm (≤29 weeks gestation), procedural pain has been associated with impaired early neurodevelopment, altered brain development, delayed postnatal growth and higher cortical activation. Acute pain can also lead to increased pulse rate, blood pressure, intracranial pressure and decreased oxygen saturation, potentially leading to further complications.[5,6]

Avoiding the side effects of oral or intravenous analgesics, there are several alternatives that can be done to manage procedural pain in neonates. *Non-nutritive sucking* is one of the non-pharmacological therapies by placing objects (such as pacifiers, pacifiers) into the baby's mouth during medical procedures to distract the baby's attention to the pain stimuli it receives. When a pacifier is placed in the infant's mouth, the sucking reflex is activated

through non-opioid mechanisms, which in turn activates tactile sensitivity, mechanical receptors, and endogenous analgesic pathways, resulting in the reduction of acute pain due to medical procedures.[6,7]

Another non-pharmacological therapy that researchers would like to observe is the effectiveness of murottal. The recitation of the Qur'an, which is audio as a human voice, is an amazing healing instrument. In a study conducted by Wahida et al, it was proven that murottal can increase *β-Endorphin* levels in reducing pain intensity, and cause feelings of relaxation (Wahida, 2015). Murottal chanting is also proven to reduce the frequency of pulse and breathing in LBW. Based on the background that has been stated, researchers are interested in seeing the effectiveness of *non-nutritive sucking* combined with murottal in handling neonate pain response during needle insertion medical procedures.[6,7,8]

Method

This study was an experimental study with a quasi-experimental post-test only control group design conducted from August to October 2024 in the perinatology ward of Lamaddukelleng Hospital, Wajo Regency, South Sulawesi. The study population included all neonates who underwent needle-related invasive procedures at the hospital, with *consecutive sampling* method to determine samples based on inclusion and exclusion criteria. This study used a consecutive sampling method, where the samples taken were those that met the inclusion and exclusion criteria. The samples given treatment were neonates who met the research criteria until the specified sample size was reached.

The inclusion criteria for this study sample included 1) Healthy neonates aged less than 28 days at Lamaddukelleng District Hospital, Wajo Regency. 2). Gestational age of more than 37 weeks. 3). Neonates with nutritional status appropriate for their gestational age. 4). Neonates with good sucking reflexes. 5). Neonates in a calm condition before the procedure.

The exclusion criteria for this study sample included 1) Neonates with serious health problems such as infection, asphyxia, dehydration, and malnutrition. 2) Parents or guardians who refuse the procedure. 3) Neonates with congenital abnormalities that may hinder the examiner in observing the neonate's body response. 4) Neonates who have received sedatives, opioids, and steroids within 12 hours before the infusion was administered. 5) Neonates undergoing oxygen therapy.

In determining the sample size, the Lemeshow formula was used with the following calculation:

$$n = \frac{Z^2 \mathrm{p}(1-\mathrm{p})}{d^2}$$

$$n = \frac{1{,}96^2 . 0{,}5(1-0{,}5)}{0{,}05^2}$$

$$n = \frac{3.8416 \cdot 0.25}{0{,}0025}$$

$$n = \frac{0.9604}{0{,}0025} = 384{,}16$$

Sample Size Correction for Limited Populations (n'):

$$n' = \frac{\mathrm{n}}{1 + (\frac{n-1}{N})}$$

$$n' = \frac{384{,}16}{1 + (\frac{384{,}16 - 1}{120})}$$

$$n' = \frac{384{,}16}{1+3{,}192} = 91{,}56 \rightarrow 92 \text{ people}$$

The preparatory stage of this study began with obtaining a research permit

after receiving approval from the Research Ethics Committee of the Faculty of Medicine, University of Muslim Indonesia (FK UMI). The research permit application was submitted to the Director of Lamaddukelleng General Hospital. After obtaining approval from the Director of the hospital, the Head of the Service Division, and the Head of the Nursing Section, the researcher proceeded to request permission from the Head of the Functional Service Unit (KaUPF) and the head of the perinatology ward to introduce the objectives and purpose of the research to the care team. Before data collection, neonatal nurses were provided with an update on the assessment of neonatal pain response

using the N-PASS scale. Respondents were selected based on predefined inclusion criteria using a specific sampling technique. The researcher will collect data by assessing neonatal pain response using the N-PASS scale two minutes after invasive procedures involving needles are performed.

For the control group (Ko), the procedure began by obtaining consent from the parents or guardians of neonates who met the inclusion criteria and asking them to sign an informed consent form voluntarily. Following this, the equipment and materials are prepared, and the neonate is placed under a radiant warmer wearing only a diaper and a clean pad, with a temperature of approximately 35°C. The neonate is fitted with monitors for temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation prior to the procedure. Ensure the infant is calm and not crying before the invasive procedure is performed by the nurse or doctor. The entire process is recorded, and after the procedure is completed, the neonate is returned to its bed. Research data is stored securely, and pain assessment is conducted two minutes after the procedure by reviewing the video recording 2–3 times to ensure the accuracy of the response.

In the first intervention group (K1) receiving non-nutritive sucking (NNS), the procedure is similar to the control group, but with the addition of providing a sterile silicone pacifier for the neonate to suck on for 50–60 seconds before the invasive procedure is performed. The process is still recorded, and pain assessment is also conducted two minutes after the procedure by reviewing the video 2–3 times.

For the second intervention group (K2) that received murottal, in addition to the standard procedures like the other groups, the neonates were played murottal from a recorder placed approximately five inches from the baby for about 50 seconds before the invasive procedure was performed. After the procedure, pain assessment was also conducted as before through video recording.

The third intervention group (K3) was a combination of NNS and murottal. The procedure began with the playback of murottal and the provision of a silicone pacifier for the neonate to suck on. After approximately 50–60 seconds, the medical procedure involving the needle was performed by medical staff. The entire process was recorded, and pain response assessment was conducted two minutes after the procedure using the N-PASS scale through the replay of the video 2–3 times. All research data were properly stored and kept confidential. Data were analyzed univariately to describe the characteristics of respondents and

neonate pain scoring, and multivariately to compare the effect of interventions between groups using SPSS 29.0 software. Kolmogorov-Smirnov normality test was used to determine data distribution, followed by ANOVA test if the data were normally distributed or Kruskal-Wallis test if not. Further analysis was performed with LSD post-hoc test for normal data and *Non-Parametric Pairwise Comparison Test* for non-normal data to determine the most effective intervention in reducing procedural pain in neonates.

Results and Discussion

Univariate Analysis

Table 1. Frequency Distribution of Respondents Based on Gestational Age in the Perinatology Room at La Maddukelleng Hospital

Chronological Age	Frequency (n)	Presentation (%)
37 weeks	22	23.9
38 weeks	10	10.9
39 weeks	23	25.0
40 weeks	15	16.3
41 weeks	13	14.1
42 weeks	9	9.8
Total	92	100

Based on table 1, it can be seen that *most of the* respondents had a gestational age of 39 weeks, namely 23 people (25%).

Table 2. Frequency Distribution of Respondents Based on Chronological Age in the Perinatology Room of La Maddukelleng Hospital

Chronological Age	Frequency (n)	Percentage (%)
2 days	32	34.8
3 days	60	65.2
Total	92	100.0

Based on table 2, it can be seen that most respondents have a chronological age of 3 days, namely 60 people (65%).

Table 3. Frequency Distribution of Respondents Based on Gender in the Perinatology Room at La Maddukelleng Hospital

Gender	Frequency (n)	Percentage (%)
Male	43	46.7
Female	49	53.3
Total	92	100.0

Based on table 3, it can be seen that most of the respondents are female, namely 49 people (53%).

Table 4. Average Total Score of Neonate Pain Response Based on Group in Perinatology Room of La Maddukelleng Hospital

Average Total Neonate Pain Response		
Group	Average	**Number of Neonates**
K0 (Control)	7.17	**23**
K1 (NNS only)	4.43	**23**
K2 (Murottal only)	5.17	**23**
K3 (NNS and Murottal)	3.78	**23**
Total	5.14	**92**

Based on table 4, The K0 control group had the highest mean pain score (7), while the K3 group (NNS + Murottal) had the lowest (4). The following is a chart that visually shows the average pain response of respondents in each group based on the N-PASS pain scoring criteria, namely Vital Signs (TTV), Crying irritability, behavioral status, facial expressions, and extremities.

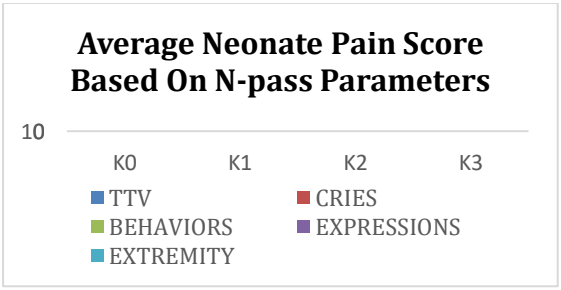

Figure 1. Average Neonate Pain Response Score per Criteria N-PASS in the Perinatology room of La Maddukelleng Hospital

Multivariate Analysis

Table 5. Normality Test of Pain Response with *Kolmogorov-Smirnov* Method

Normality Test

Pain Response	KLP	Kolmogorov-Smirnov[a]		
		Statistic	df	Sig.
	K0 (Control)	0.148	23	**0.200***
	K1 (NNS only)	0.211	23	**0.009**
	K2 (Murottal only)	0.190	23	**0.030**
	K3 (NNS and Murottal)	0.337	23	**<0,001**

Based on table 5, it can be seen that in the normality test, the data of group K1 (given NNS alone) obtained a value of P = 0.009; group K2 (given Murottal alone) obtained a value of P = 0.03; and group K3 (given NNS and Murottal) obtained a value of P < 0.001. Apart from K0 which has a value of P = 0.200, the other three groups have a value of P < 0.05 so it is said that these data are not normally distributed, so for statistical analysis in this study will use the *Kruskal-Wallis* method.

Table 6. Statistical Analysis with Non-Parametric Kruskal-Wallis Test

Test Statistics Kruskal-Wallis[a,b]

	Pain Response
Kruskal-Wallis H	**47.125**
df	**3**
Asymp. Sig.	**<0,001**
a. Kruskal Wallis Test	
b. Grouping Variable: Group (K0,K1,K2,K3)	

Based on table 6, it can be seen that the *Asym. Sig* or P value <0.001 which means it is smaller than the Kruskal-Wallis testing criteria (<0.05), so it can be said that there is a significant difference between the group given NNS, Murottal, or a combination of both with the group of respondents who were not given anything.

Table 7. Hypothesis Test of variables with Non-Parametric Kruskal-Wallis Test

Hypothesis Test Summary

Null Hypothesis	Test	Sig.[a,b]	Decision
Distribution of pain response was similar across groups / NNS and Murottal did not affect neonate pain response	Independent-Samples Kruskal-Wallis Test	<0,001	**Rejecting the null hypothesis**

a. The significance level is 0.050.

b. Asymptotic significance is displayed.

Based on table 7, it can be seen that the *Asym. Sig* or P value <0.001 which means it is smaller than the Kruskal-Wallis testing criteria (<0.05), so it can be said that the null hypothesis (H_0) which says that there is no difference in pain response across groups can be rejected, and the alternative hypothesis (H_a) which states that NNS and Murottal affect the pain response of neoates in each group is accepted.

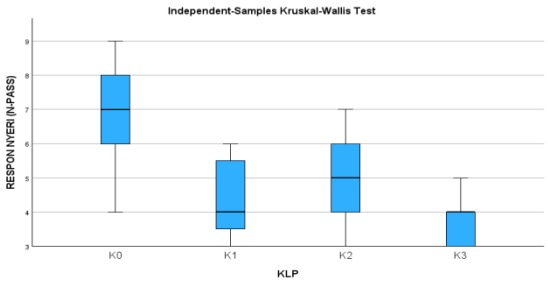

Figure 2. Distribution Chart of Neonate Pain Response Score to All Neonate Groups in the Perinatology Room La Maddukelleng Hospital

Table 8. Pairwise Comparison Test between Groups with Non-Parametric Pairwise Comparison Test

Pairwise Comparison between Groups.					
Group	**Test Statistic**	**Std. Error**	**Std. Test Statistic**	**Sig.**	**Adj. Sig.[a]**
K3-K1	11.804	7.701	1.533	0.125	**0.752**
K3-K2	25.130	7.701	3.263	0.001	**0.007**
K3-K0	50.283	7.701	6.529	<0,001	**0.000**
K1-K2	-13.326	7.701	-1.730	0.084	**0.501**
K1-K0	38.478	7.701	4.996	<0,001	**0.000**
K2-K0	25.152	7.701	3.266	0.001	**0.007**

Based on Table 8, pairwise comparisons showed significant differences between K3 and K0, and between K3 and K2, but not between K3 and K1. Thus, there is insufficient evidence to conclude a difference between these two groups. The comparison between K3 and K2 groups showed a statistically significant difference, with an *Adjusted Significance* value of 0.007 (smaller than 0.05). This means that there is a significant difference between the K3 and K2 groups. The comparison between the K3 and K0 groups showed a highly statistically significant difference, with an *Adjusted Significance* value of 0.000 (much smaller than 0.05). This indicates that there is a highly significant difference between the K3 and K0 groups.

A comparison between groups K1 and K2 showed that the difference was not statistically significant, with an *Adjusted Significance* value of 0.501 (greater than 0.05). Therefore, there is insufficient evidence to conclude a difference between groups K1 and K2. The comparison between groups K1 and K0 showed a highly statistically significant difference, with an *Adjusted Significance* value of 0.000 (much smaller than 0.05). This indicates a highly significant difference between groups K1 and K0. Finally, the comparison between groups K2 and K0 showed a statistically significant difference, with an *Adjusted Significance* value of 0.007 (much smaller than 0.05). This indicates that there is a significant difference between groups K2 and K0.

To make it easier to conclude the magnitude of the relationship between groups, the data will be presented in the form of a kite graph in Figure 3.

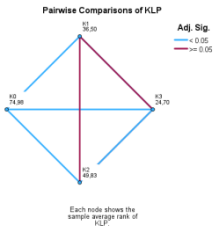

Figure 3. Kite Graphs Showing the Relationship Between Research Groups

From the results of this comparison test, it can be concluded that there are significant differences between the K3-K2, K3-K0, K1-K0, and K2-K0 group pairs, where the K3 group (given NNS and Murottal) has the greatest effect on K0 (control group). Meanwhile, the differences between the K3-K1 and K1-K2 group pairs were not statistically significant

Relationship between Chronological Age and Pain Response of Neonates after Congenital Hypothyroid Screening

To determine whether chronological age affects the pain response of neonates, the Spearman correlation test was conducted because both the dependent and independent variables are numerical data.

Spearman Correlation Test between Chronological Age and Neonate Pain Response

Spearman Correlation		
	Pain Respon	**Chronological**

			se	age
Spearman's rho	Response Pain	Correlation Coefficient (ρ)	1.000	**-0.040**
		P	.	**0.708**
		N	92	**92**
	Chronological age	Correlation Coefficient (ρ)	-0.040	**1.000**
		P	0.708	**.**
		N	92	**92**

From table 9, the results of the analysis show that the relationship between chronological age and pain response has a very weak correlation strength, namely ρ = (-0.040), with a negative relationship direction indicating a tendency for pain response to decrease slightly with increasing chronological age, but this relationship is not statistically significant (p> 0.05).

Relationship between gestational age and neonate pain response after congenital hypothyroid screening

To determine whether gestational age has an effect on neonate pain response, Spearman correlation test was conducted because both dependent and independent variables are numerical data.

Table 10. Spearman Correlation Test between Gestational Age and Neonate Pain Response

Spearman Correlation

			Pain Response	Gestational Age
Spearman's rho	Response Pain	Correlation Coefficient (ρ)	1.000	**0.066**
		P	.	**0.535**
		N	92	**92**
	Gestational Age	Correlation Coefficient (ρ)	0.066	**1.000**
		P	0.535	.
		N	92	**92**

The correlation value ρ = 0.066 indicates a very weak and positive relationship between gestational age and pain response, which means that pain response increases slightly with gestational age, but this correlation is too small to be of practical significance (p > 0.05).

Relationship between Gender and Neonate Pain Response after Congenital Hypothyroid Screening

To determine whether gestational age affects the pain response of neonates, the *Mann-Whitney U* test was conducted because the dependent variable is numerical data while the independent variable is categorical data.

Mann-Whitney U test between gender and neonate pain response

Test Statistics[a]

	Pain Response
Mann-Whitney U	**853.500**
Wilcoxon W	**2078.500**
Z	**-1.600**
Asymp. Sig. (2-tailed) / p	**0.110**
a. Grouping Variable: Gender	

The p value = 0.110 which is greater than 0.05 indicates that H_0 fails to be rejected, so there is no significant difference in N-PASS (pain response) scores between the male and female groups.

Discussion

Pain Response Characteristics of Neonates Receiving *Non-Nutritive Sucking* During Needle-Related Medical Procedures.

Nociceptive pain results from damage to body tissues and serves as the body's mechanism for detecting harmful stimuli. This pain is often felt as a sharp sensation, dull ache, or throbbing. Pain receptors, known as nociceptors, are located in peripheral areas such as the skin, mucosa, and cornea. When activated, nociceptors transmit pain stimuli through spinothalamic pathways.[9]

Until the early 1990s, the medical community had not fully recognized that neonates could experience this type of pain. Previously, it was believed that an

infant's nervous system was not fully developed and that they were incapable of remembering pain sensations. As a result, invasive procedures were often performed without sedation or anesthesia. Today, it is known that nociceptors begin to develop at 7 weeks of gestation and reach maturity at 20 weeks. The application of adequate analgesia is crucial during invasive procedures, as pain stimulation in infants can lead to increased intracranial pressure and decreased oxygen saturation, posing a risk of both short-term and long-term brain damage.[10]

In this study, it was found that the average score of pain response in the group that was only given NNS (K1) was the second lowest after the Murottal & NNS group, which was 4.43. Proven again by the *Pairwise Comparasion* analysis test where there is a very significant difference between K1 and K0 (control) seen from p of <0.001 (much smaller than 0.05), indicating a real effect of NNS on reducing the pain response of neonates undergoing needle procedures. This mechanism occurs in the Substantia gelatinosa in the *dorsal horn of* the spinal cord, where interneurons regulate whether pain signals will be forwarded to the brain or not. These fibers are activated by non-painful stimulus such as light touch, pressure, or massage. When A-β fibers are activated, interneurons produce an inhibitory response that closes the pain gate, so pain signals are not relayed to the brain. In contrast**,** A-δ fibers, which are thinly myelinated and small in diameter, and C fibers**,** which are unmyelinated and small in diameter, are activated by pain stimuli such as cuts from sharp objects, extreme temperatures, or burning sensations. Activation of these fibers opens the pain gate, allowing signals to be passed to the brain and pain to be felt. Activation of A-β fibers can inhibit signal transmission from A-δ and C fibers, which is why light touch, pressure, or massage can provide pain relief. Thus, this pain gating mechanism serves as a natural modulator system that regulates pain intensity based on the activity of the involved nerve fibers. *Non-Nutritive Sucking* stimulates A-β nerve fibers through the sucking reflex. This stimulation sends signals to the brain faster than the impulses carried by the fibers that send pain signals. As a result, NNS can help close the gate on pain stimuli experienced by neonates during medical procedures[11,26]

The effectiveness of Non-Nutritive Sucking (NNS) in reducing infants' pain responses has been widely studied. Research conducted by Nengrum et al. on 56 neonates in the perinatology unit of Hospital X Malang in 2022, who underwent immunization, found that the average pain response in the control group was higher than in the intervention group (15.50 > 7.89). Similarly, Vu-Ngoc et al. (2020) examined the pain response of 42 full-term infants undergoing heel prick screening using the N-PASS scale. The results showed a significant difference between the intervention and control groups, with rho Z values of 0.643, 0.775, 0.810, and 0.819 ($p < 0.001$). Additionally, Pramesti & Suryaningsih (2021) studied the effect of NNS on the pain response of 36 neonates during invasive procedures such as venipuncture. Their findings indicated that the pain response in the NNS group was lower than in the non-intervention group, with a significant difference of $p < 0.001$.[6,7,12]

Pain Response Characteristics of Neonates who received Murottal therapy during needle-related medical procedures.

Murottal is a slow rhythmic recitation of the Qur'an. Murottal therapy is similar to the use of music interventions to soothe neonates and is effective in helping to stabilize oxygen saturation without causing negative effects. Neonates with sufficiently mature gestational age can respond to surrounding sounds. Therefore, rhythmic recitations can be perceived even by neonates, suggesting that auditory access may play a crucial role in pain reduction. Additionally, Murottal provides rhythm, melody, and harmony that can help ease emotions and induce relaxation.[13,14]

In this study, 23 neonates were exposed to Murottal during a heel prick procedure (K2), while another 23 neonates were given both Murottal and Non-Nutritive Sucking (NNS) (K3). The results showed that the average pain response in the K2 group was lower than in the control group (5:7). A pairwise comparison test between the K2 and K0 groups revealed a statistically significant difference, with an Adjusted Significance value of 0.007 (less than 0.05). This indicates that Murottal has an effect in reducing neonatal pain response. These findings align with research conducted by Majidipour et al. (2018) on the impact of Qur'anic therapy on the physiological responses of 56 preterm infants in the NICU. Their study showed that the heart rate in the intervention group was significantly lower than in the control group ($p < 0.005$) across six evaluation sessions. Majidipour et al. also examined the physiological response of preterm infants during and after phlebotomy procedures. The study found a significant difference in respiratory rate 20 minutes after the intervention ($p = 0.039$). Additionally, oxygen saturation in the intervention group was significantly higher than in the control group ($p < 0.05$), indicating that Qur'anic therapy can enhance oxygenation in preterm infants.[14,15]

Auditory Murottal therapy provided to infants sends signals to the hypothalamus, stimulating a response in the adrenal medulla. This process suppresses the release of epinephrine and norepinephrine, or catecholamines, into constricted blood vessels. As a result, catecholamine concentration in the bloodstream decreases, leading to a reduction in heart rate and oxygen consumption, ultimately stabilizing respiratory frequency. Sound stimulation interventions with calming frequencies have been proven effective in maintaining infants' physiological responses. This stimulation can reduce infant stress, as reflected in changes in SpO_2, heart rate, and respiration.[16,17]

There is no research that can explain why Murottal therapy is not as effective as NNS in reducing neonate pain response, but through some literature, researchers found that this could be due to differences in pain suppression mechanisms between NNS and Murottal therapy. It has been previously explained that stimulation in the form of NNS can inhibit the perception of pain to be transmitted to the central nervous system by activating the *gate-control* mechanism through A-β nerve fibers, preventing nociceptive nerve fibers from transmitting pain, especially those that are rapid and localized, resulting in a significant reduction in the level of pain felt during acute episodes.[18]

As for music/murottal therapy itself, it emphasizes pain reduction through increased production of β-endorphin. In the peripheral nervous system, β-endorphin exerts analgesic effects by binding to opioid receptors, especially the *mu* subtype, which are present in pre- and post-synaptic nerve terminals. The analgesic effect mainly occurs through binding to presynaptic

terminals. Once bound, a series of interactions occur that inhibit the release of tachykinins, particularly substance P, which is a major protein in pain transmission. Substance P has an important role in the transition from acute to chronic pain. The persistent release of substance P can lead to changes in neuronal plasticity and increased sensitivity, which favors the continuation of chronic pain conditions.
In summary, both mechanisms are effective for reducing acute as well as chronic pain, the difference being that the *gate-control* mechanism emphasizes more on the diversion of acute pain, while the β-endorphin mechanism is more effective for relieving systemic or chronic pain due to its longer effect. That is why the pain response of heel prick treated with NNS is smaller than murottal therapy.[15,19,20]

Pain response characteristics of neonates receiving combined NNS and murottal therapy during needle-related medical procedures various non-pharmacological treatment methods, such as *Non-Nutritive Sucking* with or without sucrose, kangaroo care, music therapy, and multisensory stimulation, are known to help reduce pain in preterm neonates. This is because these methods are able to attract the infant's attention, divert their focus from the pain, thus changing the perception of pain. Low frequency sound therapy in particular can reduce procedural pain in preterm and term infants by providing auditory stimulation that helps modulate pain perception, thereby avoiding or reducing the need for medication.[21]

In this study, the results obtained in the neonate group given the combination of NNS and Murottal (K3) had the smallest average pain of the four groups which was 3.78, and when compared to the K0 (Control) group there was a difference in pain response as indicated by a P value of 0.000 (much smaller than 0.05). So far, there is no study that examines the effectiveness of the combination of NNS and music therapy (Murottal) on neonate pain response, but there are other trials involving a combination of non-pharmacological treatments of music and *Sucrose Nutritive-Sucking.* In a study conducted by Swapnil R Shah et al involving 35 neonates with an average gestational age of 35 weeks and an average body weight of 2210 grams, it was found that pain response after heel prick for 6 minutes differed between intervention groups. The median PIPP-R score was 4 for music therapy, 3 for sucrose, and 1 for the combination of music therapy and *Sucrose Nutritive-Sucking*. The PIPP-R scores were significantly lower in the combination group compared to the music therapy or sucrose groups separately. These results suggest that in stable and moderately mature neonates, the combination of music therapy with *Sucrose Nutritive-Sucking* provides a better analgesic effect than the use of music therapy or sucrose alone.[22]

In addition, there are trials that test the effectiveness of the combination of music and touch therapy (*CMT; Combination of Music and Touch).* A study conducted in the NICU of Nanjing Medical Children's Hospital in 2012 tested the pain response of 74 neonates who underwent procedural pain while in the ward (including intravenous blood draw, tracheal aspiration, finger prick, heel prick, adhesive removal). The

results showed that the average pain response of the group of neonates who were given an intervention in the form of CMT administration was lower than the group who were not given any intervention when experiencing procedural pain, namely 10.5 *vs* 13.[21]

Relationship between chronological age and neonate pain response

In this study, it was found that chronological age had no significant association with the pain response of neonates undergoing needle medical procedures. In theory, with age, the central nervous system undergoes significant development, which affects the way infants process and respond to pain. Younger infants may show a more generalized response to painful stimuli, whereas older infants may show a more specific and localized reaction. Pain thresholds may change with age. Younger infants often show increased sensitivity to pain (hyperalgesia) due to their immature neural circuitry. Conversely, with age, some people may develop a higher tolerance to pain (hypoalgesia), although this can vary greatly between individuals.[23,24]

Relationship between gestational age and neonate pain response

In this study, it was found that gestational age did not have a significant relationship with the pain response of neonates undergoing needle medical procedures. This is because all neonates who became respondents were born with full-term gestational age (>37 weeks). A prospective cross-sectional study conducted in a neonatal intensive care unit (NICU) in South India assessed the frequency of painful procedures among neonates during the first 14 days of hospital admission. The study included 101 neonates with a mean gestational age of 35.11 weeks. The findings highlighted significant differences in pain experience based on gestational age: Frequency of Painful Procedures: Each neonate underwent an average of 8.09 ± 5.53 painful procedures per day, totaling 68.32 ± 64.78 procedures during hospitalization. The most common painful procedure was heel prick (30%). Impact of Gestational Age: Preterm infants (≤32 weeks gestation) experienced significantly more painful procedures than infants born at more than 32 weeks gestation, with an average of 10.3 ± 5.4 vs. 7.4 ± 5.3 painful procedures per day ($p = 0.029$). In addition, preterm infants had more intrusions daily compared to term infants (18.1 ± 5.8 vs. 15.7 ± 5.2 times per day, $p = 0.035$)[25,26].

Relationship between gender and neonate pain response

In this study, it was found that gender did not have a significant relationship with the pain response of neonates undergoing needle medical procedures. The study conducted by Selvanathan et al was a prospective cohort study involving 193 very preterm infants (gestational age <32 weeks) recruited from two neonatal intensive care units in Toronto, Canada. Structural connectivity data were analyzed in 150 infants, and neurodevelopmental outcomes were assessed in 123 infants. The study found that greater exposure to painful procedures early in life was associated with slower maturation of neonatal structural connectivity, particularly in female infants.[22]

In female infants, there was a significant interaction between early-life pain exposure and postmenstrual age (PMA) at the time of MRI scanning, indicating that as PMA increased, the negative impact of pain exposure on global efficiency (a measure of tissue integration) became more pronounced

(P = 0.002). In contrast, male infants showed no significant interaction

between pain early in life and PMA (P = 0.90), although greater pain exposure was still associated with decreased global efficiency.[22]

Conclusion

The administration of *Non-Nutritive Sucking* is proven to be effective in reducing the pain response of neonates during needle medical procedures at La Maddukelleng Hospital, Wajo Regency compared to neonates who are not given any intervention. Giving Murottal therapy proved to be slightly more effective in reducing neonates' pain response during needle medical procedure at La Maddukelleng Hospital, Wajo Regency than neonates who were not given any intervention. Giving the combination of *Non-Nutritive Sucking* and Murottal therapy proved to be the most effective in reducing the pain response of neonates during undergoing needle medical procedures at La Maddukelleng District Hospital Wajo compared to neonates who were not given any intervention or who were given a single intervention in the form of NNS or Murottal alone.

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