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ASSOCIATION BETWEEN THE NEONATAL PAIN SCALE AND SALIVARY CORTISOL LEVELS IN PRETERM NEONATES USING MECHANICAL VENTILATOR

Syahrurrahman[1], Andi Dwi Bahagia Febriani[2*], Ema Alasiry[2], Aidah Juliaty A. Baso[2], Nadirah Rasyid Ridha[2]

[1] Pediatric Specialist Study Program, Department of Pediatrics, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

[2] Department of Pediatrics, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
DR Wahidin Sudirohusoso Hospital, Makassar, Indonesia
*Corresponding author e-mail: bahagiadwi@med.unhas.ac.id

ABSTRACT

Background: Preterm neonates have an increased risk of respiratory distress syndrome requiring mechanical ventilation. This medical procedure causes pain which increases the risk of stress and impaired brain development. Several studies have reported that serum cortisol increases in response to pain in neonates. Several methods can be used to assess pain including Neonatal Infant Pain Scale (NIPS) and the Premature Infant Pain Profile (PIPP). This study aims to determine the association of neonate pain scale with salivary cortisol levels of preterm neonates who use mechanical ventilators.

Methods: This one-group pretest-posttest study was conducted from June 2022 to May 2023 at Dr. Wahidin Sudirohusodo Hospital, Indonesia. NIPS, PIPP, and salivary cortisol were assessed before intubation and 60 minutes after mechanical ventilator installation.

Results: A total 28 subject was analyzed in this study. After 60 minutes of ventilator installation, the saliva cortisol value in the NIPS assessment of the non-pain group (n=29) was 1.349 (0.028-9.641) ng/dL and moderate pain (n=1) was 3.742 ng/dL with p>0.05 and the PIPP assessment of the non-pain group (n=25) was 1.349 (0.028-9.641) ng/dL and moderate pain (n=3) was 1.651 (1.324-3.742) ng/dL with p>0.05.

Conclusion: There is no association NIPS or PIPP assessment and salivary cortisol levels in the use of mechanical ventilator. However, pain scales should be assessed to guide management and reduce morbidity.

Keywords: salivary cortisol, mechanical ventilator, preterm neonates.

INTRODUCTION

Respiratory distress in newborns is an important problem because it causes morbidity and mortality of 4-6% in the world. The main causes of newborn death in the first week (0-6 days) are asphyxia and low birth weight (LBW)/prematurity (36% vs. 32%).[1,2] Based on the medical records of the Perinatology Unit of the Paediatrics Department, Cipto Mangunkusumo Hospital, there are approximately 750 cases of preterm infant birth per year, 38% were neonates with respiratory distress.[3] While in Dr Wahidin Sudirohusodo Hospital, the number of preterm neonates admitted to the neonatal intensive care unit (NICU) last year was 127; 33% of these were neonates with respiratory distress.

Respiratory problems are common in preterm neonates, especially very preterm neonates (<28 weeks gestation), and most of these neonates require ventilatory support.[4] Preterm neonates are also at greater risk of experiencing medical events or procedures that can result in pain and stress during the first week of life including the use of mechanical ventilators.[5,6] Newborns who experience stress will show behavioral changes and physiological changes that can be assessed by pain scales. This increases the risk of impaired brain development and maturation due to stress and pain which can manifest as an increased risk of cerebral palsy, cognitive deficits and psychiatric disorders, such as attention deficit hyperactivity disorder or autism spectrum disorder.[7]

Several studies reported serum cortisol increases in response to stress in newborns. The presence of both physical and psychological stressors will stimulate hormonal changes through the hypothalamus which triggers the release of cortisol.[8,9] The pain scales often recommended for the assessment of acute pain in newborns are the Neonatal Infant Pain Scale (NIPS) and the Premature Infant Pain Profile (PIPP).[9,10,11] Although pain scales in newborns have been widely studied, data linking pain scales with stress hormones such as cortisol and invasive procedures such as mechanical ventilators are still lacking.

The accuracy of salivary cortisol testing has been established, and serum and salivary cortisol levels have been shown to be well correlated.[12] Salivary cortisol examination over some advantages: noninvasive, stress-free, and easy to perform anywhere.[13,14,15]

Based on the description above, the objective of this study is to determine whether the use of mechanical ventilators in preterm neonates will cause acute stress characterized by increased salivary cortisol levels and pain scale (NIPS and PIPP).

METHOD

Study area and design

This study was conducted from June 2022 to May 2023 at Dr. Wahidin Sudirohusodo Hospital, Indonesia. This study used a one group pretest posttest design to assess the association of NIPS and PIPP with salivary cortisol levels in preterm neonates with respiratory distress before and after 60 minutes of mechanical ventilator installation. Ethical approval was obtained from the Ethics Committee for Biomedical Research in Humans, Faculty of Medicine, Hasanuddin University. All parents/guardians of the participants have signed written consent to participate in this study.

Subject

Inclusion criteria were neonates with gestational age ranging from 28 weeks to 36 weeks and 6 days with respiratory distress indicating the use of mechanical ventilators, with a birth weight greater than 1000 grams. Exclusion criteria were newborns with major congenital abnormalities, severe birth trauma, neonates with apgar at 5 minutes less than 3, hypoglycemia, shock, postoperative neonates, neonates born with eclamptic mothers, HELLP syndrome, mothers with long-term opioid or steroid consumption, and using CPAP for more than 48 hours.

Procedure

divided into three categories: no pain (PIPP score 0-5,) mild pain (PIPP score >5) and severe pain (PIPP score >12). [17–19]

Data Analysis

Statistical analyses were completed by using IBM SPSS Statistic version 26. The data were expressed as mean values with standar deviation or medians with maximum and minimum values for continous variables. Changes in salivary cortisol value were determined by paired T test. Changes in NIPS and PIPP before and after mechanical ventilator installation were determined by McNemar. The significant results marked with $p \leq 0.05$.

Eligible subjects were assessed for NIPS, PIPP and saliva sampling for cortisol levels. Name, gestational age, sex, birth weight, birth length, head circumference, vital signs, birth method, diagnosis, history of antenatal steroid therapy, maternal diagnosis, and blood sugar were recorded. Saliva collection was performed with equipment kit in small saliva sample (10-50µl) before premedication of intubation (sample I), and after 60 minutes of ventilator installation (sample II). The kit was placed under the tongue for approximately 60 seconds until it was noticeably moistened. Saliva specimens were stored at -10°C to -80°C in the HUMRC laboratory until analysis. premedication before intubation using fentanyl at a dose of 1 mcg/kilogram of body weight/intravenous. The NIPS and PIPP was assesed by video recording.

Saliva samples were tested using the enzyme-linked immunosorbent assay technique with the DBC Saliva Cortisol Kit (DBC-Diagnostics Biochem Canada, Ontario, Canada) at the HUMRC laboratory of Hasanuddin University Medical Research Center, Faculty of Medicine. Cortisol concentration was measured in ng/mL.

The NIPS evaluates six variables to assess procedural pain: five behavioral variables (facial expression, crying, state of arousal, arm and leg position) and one physiological variable (breathing pattern). Each indicator is assigned a value of 0 or 1, with the exception of crying, which is assigned a value ranging between 0 to 2, resulting in a total score between 0 to 7 for the minimum and maximum levels. The pain scale was divided into three categories: no pain (NIPS score 0-2), mild pain (NIPS score 3-4) and severe pain (NIPS score >4).[16]

PIPP evaluates seven variables to assess pain consisting of gestational age, behavioral state, heart rate, oxygen saturation, brow bump, eye squeeze, and nasolabial groove when experiencing a painful stimulus. The minimum PIPP score was 0 and the maximum score was 21. The pain scale was

RESULT

The subjects consisted of 30 preterm neonates, and 2 were excluded due to shock and some medical procedure before mechanical ventilator installation. Males were 2.1 times more than females. Sectio cesarean delivery was more common than vaginal delivery, as well as very low birth weight to low birth weight. Most of the sample did not receive antenatal steroids. There was no difference between moderate to late preterm vs. very preterm gestational age. The characteristics of the study subjects can be seen in table 1.

Table 1. Characteristics of preterm neonates

No	Characteristics of subjects	Neonates on mechanical ventilators (n = 30)
1	Gender	
	• Male	19 (67.9%)
	• Female	9 (32.1%)
2	Birth method	
	• Vaginal birth	11 (39.3%)
	• *Sectio cesarea*	17 (60.7%)
3	Birth weight	
	• Low birth weight	10 (35.7%)
	• very low birth weight	18 (64.3%)
4	Gestational age	
	• Moderate to late preterm	14 (50%)
	• Very preterm	14 (50%)
5	Antenatal Steroids	
	• Given	5 (17.9%)
	• Not given	23 (82.1%)

Analysis of salivary cortisol, NIPS, PIPP, heart rate, and SpO_2 before and after mechanical ventilator installation can be seen in table 2. In this study, there were significant differences between salivary cortisol, NIPS, PIPP, and SpO_2 before vs. after mechanical ventilation installation (p < 0.05).

In the salivary cortisol assessment, there were 3.584 vs. 2.457 ng/dl of salivary cortisol level with p 0.021. The distribution of salivary cortisol levels can be seen in Figure 1.

In the NIPS assessment, there was differences in the non-pain group 46.4% vs. 96.4% and moderate pain group 62.5% vs. 3.6% with p 0.001. Similarly in the PIPP, the non-pain group 35.72% vs. 89.28% and moderate pain group 64.28% vs. 10.72% with p 0.007. SpO_2 was also improves 89.29% vs. 95.82% with p 0.000.

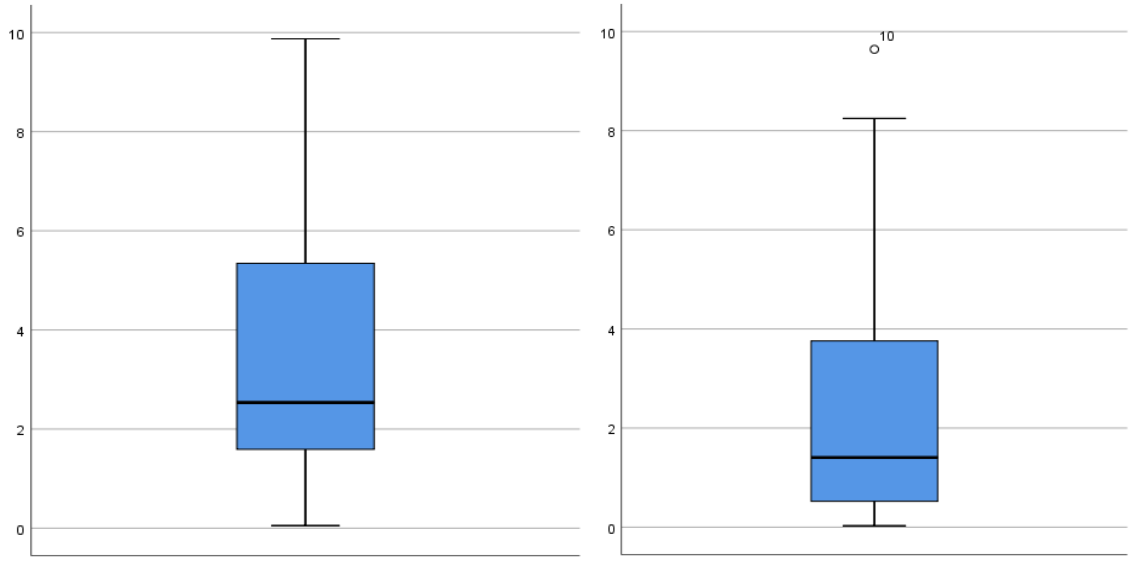

Figure 1. Salivary cortisol levels before and after mechanical ventilator installation

In the assessment of associations between NIPS and salivary cortisol levels, there was no significant difference in cortisol levels between the non-pain group and the moderate-pain group before and after mechanical ventilator installation (*p* 0.120 and *p* 0.210). Similarly, in the PIPP, there was no significant difference in cortisol levels between the non-pain group and the moderate pain group before and after mechanical ventilator installation (*p* 0.082 and *p* 0.311) (tables 3 and 4).

Table 2. Salivary cortisol, NIPS, PIPP, heart rate, and SpO_2 before and after mechanical ventilator installation

Variable	Before installation mechanical ventilator (n=28)	After installation mechanical ventilator (n=28)	*P*
Cortisol value (SD)	3.584 (2.81)	2.457 (2.66)	0.021 *
NIPS			
Non-pain (%)	13 (46.5)	27 (96.4)	0.001#
Moderate pain (%)	15 (62.5)	1 (3.6)	
PIPP			
Non-pain (%)	10 (35.72)	25 (89.28)	0.007 #
Moderate pain (%)	18 (64.28)	3 (10.72)	
Heart Rate (min-max)	150 (84-213)	149.5 (120-197)	0.964 †
SpO_2 (SD)	89.29 (5.199)	95.82(3.486)	0.000 *

**Paired T test*

#*McNemar test*

†*Wilcoxon test*

Table 3. Association NIPS and salivary cortisol levels before and after mechanical ventilator installation.

Before mechanical ventilator	Cortisol value (min-max)	*p*	After mechanical ventilator	Cortisol value (min-max)	*p*
NIPS (n=28)			**NIPS (n=28)**		
Non-pain (n=13)	4.322 (0.341-9.872)	0.120¥	Non-pain (n=29)	1.349 (0.028-9.641)	0.210¥
Moderate pain (n=15)	2,372 (0.051- 9.160)		Moderate pain (n=1)	3.742 (-)	

Table 4. Association PIPP and salivary cortisol levels before and after mechanical ventilator installation.

Before mechanical ventilator	Cortisol value (min-max)	*p*	After mechanical ventilator	Cortisol value (min-max)	*p*
PIPP (n=28)			**PIPP (n=28)**		
Non-pain (n=10)	3.840 (0.341-9.872)	0.082¥	Non-pain (n=25)	1.349 (0.028-9.641)	0.311¥
Moderate pain (n=18)	2.151 (0.051- 9.160)		Moderate pain (n=3)	1.651 (1.324- 3.742)	

¥Mann Whitney test

DISCUSSION

Preterm infants are at high risk of developing respiratory distress syndrome (RDS). Some preterm infants may only require oxygen in response to RDS, while others may require intubation and mechanical ventilation for severe respiratory distress. Infants on mechanical ventilators may experience pain and discomfort in the form of agitation and sleep disturbance, leading to infant stress. Stressed infants show behavioural, physiological, and hormonal changes. The presence of both physical and psychological stressors will trigger the release of cortisol.[8,9,20] Jalaluddin S et al. reported in their research that serum cortisol in newborns can be used as an accurate method to assess stress in newborns.[20]

The objective of this study is to determine whether the use of mechanical ventilators in preterm neonates will cause acute stress characterized by increased salivary cortisol levels and pain scale (NIPS and PIPP). This study found that there was no increasing of salivary cortisol and pain scales (NIPS and PIPP) after 60 minutes mechanical ventilator installation (table 2). There were significant differences between the non-pain and moderate-pain groups, both NIPS and PIPP, with decrease in the number of subjects in the moderate pain group before vs. after mechanical ventilator installation (table 2). In addition, there were also significant differences before and after mechanical ventilator installation in salivary cortisol values (3.584 Vs. 2.457) and SpO2 values (89.29 Vs. 95.82) (table 2). However, there was no difference in salivary cortisol values between the non-pain and moderate pain (NIPS and PIPP) before and after mechanical ventilator installation (table 3 and 4).

Gunes et al reported 79 preterm neonates (gestational age 31-36 weeks) with respiratory distress, cortisol levels increased in all three groups (control group, not using mechanical ventilators, and using mechanical ventilators). Cortisol was assessed from blood serum on day 1 (8 hours of age) and day 3. The cortisol levels of neonates with mechanical ventilation were found to be higher than the other groups. Neonates with respiratory distress release more cortisol than normal preterm neonates due to poor lung function.[21]

Arafa et al, in 90 preterm neonates (gestational age 28-34 weeks), serum cortisol was tested at 1 day of age for all subject, found a relationship between the serum cortisol levels of preterm neonates and the severity of respiratory distress in neonates who use breathing equipment (CPAP and mechanical ventilator) with average value of cortisol levels was 39.22 mg/dL in neonates with mechanical ventilators, and CPAP was lower with an average value of 28.96 mg/dL (p 0.001) and head box 25.88 mg/dl. [15] In contrast in our study, salivary cortisol examination was carried out regardless of age in all subjects indicated to receive mechanical ventilators, before and after 60 minutes after mechanical ventilator installation.

The improvement in NIPS and PIPP criteria and salivary cortisol levels in all subjects may result from improved oxygenation and lung function after mechanical ventilation with improvement of SpO_2 before and after mechanical ventilatilator installation (table 2). Another possible cause is the effect of fentanyl. In this study, the assessment of salivary cortisol levels was not associated to the NIPS or PIPP and therefore could not be used for stress assessment. However, the NIPS or PIPP should still be used to assess infant pain caused by medical procedures.

Some literature has mentioned that fentanyl has a rapid onset of action of 2-5 minutes with a duration of action of 30-60 minutes if given intravenously.[22] Pacifici et al in premature infants stated that the duration of action of fentanyl was 60 minutes.[23] However, there were other studies reporting the onset of action of fentanyl 4.5-8 minutes with a duration of action of 60-120 minutes.[24] The fentanyl given in this study was 1 mcg per kilograms of body weight which was given before intubation.

The limitation of this study is that fentanyl levels were not measured. Therefore, there was no parameter for when the effects of fentanyl wear off to avoid affecting cortisol levels. Routine care, such as infusion and suctioning, cannot be done the same way for all neonates because of their different conditions. However, developmental care is still given.

CONCLUSION

In this study there was no association between NIPS and PIPP assessment and salivary cortisol levels in the use of mechanical ventilator. However, the pain scales should be assessed to guide management and reduce morbidity.

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