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Differences between vitamin D levels in premature neonates with respiratory Distress and without respiratory distress

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ABSTRACT

Respiratory distress is associated with lung maturation and vitamin D which is explained by the mechanism of production and secretion of phospholipids (surfactants) on the surface of type II alveolar cells (ATII). To determine the differences between in vitamin D levels in premature neonates with respiratory distress in premature neonates and without respiratory distress. Analytical analyses with a case-control study in premature neonates who experienced respiratory distress at the H. Adam Malik Medan General Hospital from September 2021 to March 2022. To assess the difference among variables with t-independent test, Mann-Whitney test, and Kruskal Wallis test. A total of 25 patients with respiratory distress samples and 25 controls were analyzed. Differences between the classification of vitamin D levels in children with respiratory distress and without respiratory distress had a significant (p=0.014) with vitamin D level with respiratory distress of 14.72. The difference between Downe Score and APGAR Score in children with respiratory distress and without respiratory distress also had significance (p=0.001) with a mean of Downe Score of 4.68 and APGAR Score of 5.96 for the first 7.16 for the fifth, and 7.6 for the tenth minutes. The differences between Downe Score and vitamin D levels in the group of infants with respiratory distress did not have a significant (p=0.742). There are significant differences among the classification of vitamin D levels, Downe Score and APGAR Score in neonates with respiratory distress and without respiratory distress. However, there was no significant differences between Downe Score and vitamin D levels.

1. Introduction

Respiratory distress is characterized by inflammation of the airways experienced by premature neonates. Previous studies have shown that genetic, age, social and other factors have an important role in determining someone who can have difficulty breathing [1]. One example of respiratory distress in neonates is respiratory distress syndrome (RDS) which is also a major cause of death in premature infants [2]. The prevalence of respiratory distress in RDS is about 60,000 – 70,000 cases reported annually in the United States, with a mortality rate of about 20% of all neonatal deaths [1], [2].

Symptoms of respiratory distress experienced by premature neonates or low birth weight infants are the main causes of neonatal death in Indonesia based on the mortality trend from 2001-2007 [3]. A study conducted at Cipto Mangunkusumo General Hospital (RSCM) reported that over a 10 month period (October 2015 – August 2016) there were 101 patients diagnosed with RDS [4].

Vitamin D is a fat-soluble vitamin that functions to regulate calcium and phosphorus as bone mineralization [5]. In addition, vitamin D also plays an important role in the immune system [6]. Neonates begin to get vitamin D since the mother's womb through the placental circulation. The level of vitamin D in the mother's serum greatly affects the level of vitamin D in the fetus [7]. Several studies on vitamin D have explained the role of vitamin D in lung development and regulation of lung maturation in the fetus. In addition, vitamin D also plays a role in the process of embryogenesis, the process of cell growth and differentiation [8]. The relationship between lung maturation and vitamin D was explained through the mechanism of production and secretion of phospholipids (surfactants) on the surface of type II alveolar cells (ATII) [9].

Epidemiological studies have described an association between maternal vitamin D and the development of early childhood respiratory infections and asthma [10]. Currently, other studies are also being carried out to determine the impact of vitamin D on early lung development and maturation and lung disease that occurs in early life [11]. Another study also describes the administration of vitamin D supplementation with the right dose which is beneficial for respiratory disorders. Because basically vitamin D plays a role in reducing the risk of respiratory distress syndrome, improving quality of life, and is relatively effective for lung maturation in premature neonates [10]. Based on these data, the researcher intends to assess the relationship between vitamin D levels and respiratory distress in premature infants.

2. Method

This study is a case control study conducted at H. Adam Malik (HAM) Medan General Hospital, which will be held from September 2021 to March 2022. This study included 50 premature neonates with the inclusion criteria of neonates born spontaneously (vaginally) or by cesarean section (SC) with gestational age ranging from below 28-36 weeks and based on the New Ballard score below 28-36 weeks at the H. Adam Malik (HAM) Medan General Hospital. Parents agreed to carry out the procedure and examination, and signed the informed consent form. Exclusion criteria were neonates born at term, premature neonates with congenital physical abnormalities and suspicion of congenital anomalies.

3. Statistical Analysis

Data were analyzed using SPSS version 23. program. The data is presented in the form of frequency and

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percentage as categorical data, while the mean and standard deviation are for numerical data. To determine the difference between vitamin D levels, Downe's score and APGAR score in the group, independent t-test / Mann Whitney and Kruskal Wallis tests were used. The level of significance and the confidence interval used were P<0.05 and 95%.

4. Results

This study included 50 premature neonates born at the H. Adam Malik hospital in Medan which were divided into two groups with a total of 25 samples in each group, namely the group of neonates with respiratory distress and without respiratory distress. Subject characteristics are shown in table 1.

Subjects in the two groups were mostly male, 18 (72%) neonates with respiratory distress and 15 (60%) neonates without respiratory distress. The mean gestational age in the group of neonates with respiratory distress was 31 months (SD = 2 months) and in the group without respiratory distress was 32.84 months (SD = 1.72 months). The mean birth weight in the group of neonates with respiratory distress was 1545.4 grams (SD = 376.61 grams) and in the group without respiratory distress was 2100 grams (SD = 302.46 grams). The mean birth length in the group of neonates with respiratory distress was 45.88 cm (SD = 0.97 cm) and in the group without respiratory distress was 45.46 cm (SD = 4.96 cm). The majority of neonates in both groups were delivered by cesarean section, approximately 23 (92%) in neonates with respiratory distress and 22 (88%) in neonates without respiratory distress.

Table 1. Subjects Characteristics

Characteristics	Respiratory Distress (n=25)	No Respiratory Distress (n=25)
Sex, n (%)		
Man	18 (72)	15 (60)
Woman	7 (28)	10 (40)
Gestational age, Month		
Mean (SD)	31 (2,2)	32,84 (1,72)
Median (Min – Max)	31 (27 – 35)	33 (28 – 35)
Birth Weight, gram		
Mean (SD)	1545,4 (376,61)	2100 (302,46)
Median (Min – Max)	1450 (850-2200)	2100 (1520-2650)
Length, cm		
Rerata (SD)	45,88 (0,97)	45,44 (4,96)
Median (Min – Max)	46 (44 – 48)	47 (31 – 49)
Birth History, n (%)		
PSP	2 (8)	3 (12)
SC	23 (92)	22 (88)
Mother Age, years		
Rerata (SD)	29,08 (4,15)	28,72 (4,73)
Median (Min – Max)	28 (22 – 36)	28 (18 – 37)
Mother Education, n (%)		
Junior High School	1 (4)	4 (16)
Senior High School	16 (64)	17 (68)
College	8 (32)	4 (16)
History of ANC, n (%)		
Blood spots	3 (12)	0
Hypertension	1 (4)	0
Vaginal discharge	5 (20)	3 (12)
Fever	0	3 (12)
No abnormalities	16 (64)	19 (76)
Mothers' Job, n (%)		
House wife	14 (56)	18 (72)

Employee private	7 (28)	4 (16)
Civil Servant	2 (8)	2 (8)
Self Employee	2 (8)	1 (4)
Breathing apparatus, n (%)		
CPAP	13 (52)	0
Nasal canule	5 (20)	0
Ventilator	7 (28)	0
No	0	25 (100)

Table 2 shows vitamin D levels in the two study groups, the mean vitamin D level in the group of premature neonates with respiratory distress was 14.72 ng/mL and in the group without respiratory distress the mean was 15.63 ng/mL. The Mann Whitney test that has been carried out showed a significant difference in vitamin D levels between the group of preterm neonates with respiratory distress and without respiratory distress (p = 0.014). By categorizing vitamin D levels, it was found that most of the two groups including deficiency were 21 premature neonates (84%) in the group of premature neonates with respiratory distress and 19 neonates (76%) in the group of premature neonates without respiratory distress. As many as 49 of 50 premature neonates (98%) showed low levels of vitamin D.

Table 2. Differences between Vitamin D Levels in Premature Neonates with and without Respiratory Distress

Variables	**Respiratory Distress**		**p**
	Yes (n=25)	**No (n=25)**	
Vitamine D, ng/mL			
Means (SD)	14,72 (21,42)	15,63 (5,53)	0,014[a]
Median (Min – Max)	10,8 (0,3-113)	16,1 (5,5-23,7)	
Cathegory of Vitamin D, n (%)			
Severe Deficiency	4(16)	0	
Deficiency	17 (68)	19 (76)	
Insuficiency	3 (12)	6 (24)	
Normal	1 (4)	0	

[a]*Mann Whitney*

Table 3 shows the Downe score and APGAR score in the two study groups, the mean Downe score in the group of premature neonates with respiratory distress was 4.68 and in the group without respiratory distress was 0. Using the Mann Whitney test showed a significant difference in Downe's score between the groups of preterm neonates with respiratory distress and without respiratory distress (p < 0.001). The results of the APGAR score examination at the first, fifth and tenth minutes showed a lower value in the group of premature neonates with respiratory distress than the group without respiratory distress.

Table 4 shows the results of the analysis of differences in Downe scores with vitamin D in the group of premature neonates with respiratory distress, the highest mean Downe score is shown in the group of premature neonates with vitamin D deficiency category with a mean of 5.67 (SD = 1.53) and the lowest Downe score. found in the group of neonates with normal vitamin D category with a mean of 4. Using the Kruskal Wallis test, there was no difference between Downe scores and vitamin D levels in the group of neonates with respiratory distress (p =0.742).

Table 3. Differences in Downe Score and APGAR Score in Premature Neonates with and without Respiratory Distress

Variable	**Respiratory Distress**	**p**

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	Yes (n=25)	No (n=25)	
Downe Score			
Mean (SD)	4,68 (1,89)	0	<0,001[a]
Median (Min – Max)	5 (1 – 7)	0	
APGAR Score			
First Minute			
Mean (SD)	5,96 (0,89)	7,64 (0,7)	<0,001[a]
Median (Min – Max)	6 (4 – 7)	8 (6 – 9)	
Fifth Minute			
Mean (SD)	7,16 (0,75)	8,44 (0,58)	<0,001[a]
Median (Min – Max)	7 (5 – 9)	8 (7 – 9)	
Tenth Minute			
Mean (SD)	7,6 (0,82)	9,36 (0,64)	<0,001[a]
Median (Min – Max)	7 (6 – 9)	9 (8 – 10)	

[a]*Mann Whitney*

Table 4. Differences in Downes Score with Vitamin D Levels in the Group of Premature Neonates with Respiratory Distress

Vitamin D	n	Downe Score		p
		Mean (SD)	Median (Min – ax)	
Severe Deficiency	4	5 (0,82)	5 (4 – 6)	0,742*
Deficiency	17	4,47 (2,15)	5 (1 – 7)	
Insuficiency	3	5,67 (1,53)	6 (4 – 7)	
Normal	1	4		

*Kruskal Wallis

5. Discussion

Vitamin D is a fat-soluble vitamin that has a major role in calcium and phosphorus homeostasis and bone metabolism [12]. In addition, vitamin D also plays a role in cell development and embryogenesis and helps in the maturation of the fetal lungs [13]. The fetus does not produce vitamin D but receives vitamin D from the mother. Neonates born with very low weight (< 1,500 g) and with a short delivery age lead to a lack of fetal vitamin D levels received from the mother. Therefore, vitamin D deficiency often causes morbidity and mortality in neonates [12].

One of the main problems that often occur in premature neonates is respiratory distress syndrome (RDS) and surfactant deficiency and lung immaturity are important factors in the pathogenesis [13]. A study conducted by [14] reported about 56.9% of neonates who had vitamin D deficiency with a mean birth weight of 1,380 g and of 174 neonates who were admitted to the NICU with respiratory distress around 99 neonates who received a breathing apparatus with vitamin D deficiency and about 75 neonates who received a breathing apparatus with normal vitamin D levels. Studi lain oleh [13] melaporkan sekitar 72 neonatus prematur yang mengalami RDS dengan defisiensi vitamin D sebanyak 49 neonatus, dengan jenis kelamin neonatus RDS terbanyak ialah perempuan sekitar 72,2%.

In this study we reported approximately 50 preterm neonates, who experienced respiratory distress and impaired vitamin D levels of approximately 24 premature neonates. Male premature neonates who experienced respiratory distress were reported as 18 neonates (72%) more than women, the mean maternal gestational age was 31 weeks, the mean birth weight was 1545 g, as many as 92% were born with Sectio caesarea and neonates who were born with Sectio Caesarea. requires a 52% CPAP breathing apparatus, 20% nasal cannula and 28% ventilator.

A study describes vitamin D in humans and animals found to have an important role in the development and

maturation of the fetal lungs [14]. Vitamin D has also been reported to be an important regulator of lung growth in utero affecting alveolar epithelial-mesenchymal interactions, the relationship between maternal vitamin D intake during pregnancy and 25-hydroxy vitamin D (25-OHD) levels [15]. The study conducted by [13] reported that there was a significant relationship between vitamin D levels and the incidence of RDS with a p value of 0.04, but this study showed no significant relationship between the differences (classification) of vitamin D levels and RDS with a p value of 0.06.

Another study by [15] regarding the relationship of neonatal vitamin D deficiency to risk factors for bronchopulmonary dysplasia (BPD) in premature neonates reported that there was a significant relationship between neonatal vitamin D levels and BPD with $p < 0.001$. Another study by [16] reported a significant relationship between vitamin D levels and the incidence of RDS in premature neonates. The study conducted by Dogan and Centinkaya showed similar results in our study, where there was a significant difference between vitamin D and RDS levels but no significant difference between the proportions of vitamin D and RDS classifications. In contrast to the study conducted by Hamed which reported a significant difference between the levels of vitamin D and RDS. This difference is due to the study by Ahmed that maternal vitamin D levels were known, the mean difference in birth weight in Ahmed's study was 2,000 grams, whereas in our study the mean value was 1,500 grams and the study intervened in the administration of vitamin D supplementation to neonates.

Assessment of the APGAR score in newborns is very important as a method of immediately after birth for neonates and assessing the need for immediate intervention to stimulate breathing. or the second 5 minutes. The APGAR score varies according to gestational age, birth weight, history of drug consumption in the mother, and congenital anomalies. The greater the APGAR score, the better the condition of the neonate [17]. Studies conducted by [16] reported that there was no significance between the first minute and second minute APGAR scores with the incidence of RDS in patients. Another study by [15] reported a significant relationship between first and fifth minute APGAR scores and the incidence of BPD.

The study by Cetinkaya is similar to ours, but not to the study by Hamed. In our study it was reported that there was a significant relationship between the first and fifth minute APGAR scores and the incidence of respiratory distress. The explanation for this difference in results is thought to be because the study sample by Ahmed in the RDS group had received intervention on respiratory distress and external vitamin D treatment.

Assessment of the severity of respiratory distress is done by calculating the Downe score. It is known that the Downe score is more comprehensive and can be applied to all ages and conditions of pregnancy, and can be used as a clinical diagnostic tool to assess hypoxia in neonates with clinical respiratory distress.51 The study conducted by [18] reported that there was a significant relationship between Downe's score and the etiology of respiratory distress, Likewise, a study by [19] reported a significant relationship between Downe's score and severity of respiratory distress according to etiology. The results of these two studies are similar to the results in our study of the association of Downe's score with the incidence of respiratory distress. Our study still has limitations, namely not being able to explain the etiology of respiratory distress, unknown maternal vitamin D levels and not providing vitamin D intervention to samples with deficiency.

6. Conclusion

There was a significant difference in vitamin D levels between the group of premature neonates with respiratory distress and without respiratory distress who were treated at H. Adam Malik (HAM) Medan General Hospital. There was no significant difference between vitamin D classification and respiratory

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distress in premature neonates. there was a significant difference in Downe's score between the groups of preterm neonates with respiratory distress and without respiratory distress. There was a significant difference in APGAR scores between the groups of neonates with respiratory distress and without respiratory distress in the first minute, fifth minute and tenth minute. There was no correlation between Downe's score and vitamin D levels in the group of neonates with respiratory distress.

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