The Relationship between Vitamin D Levels and Clinical Outcomes of Neonatal Sepsis in Haji Adam Malik Hospital Medan, Indonesia

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Abstract

BACKGROUND: Vitamin D deficiency in neonates is associated with neonatal sepsis incidence. It is also significantly correlated to the increased risk in the outcomes of sepsis, such as mortality, length of hospital stay, and use of ventilatory support.

AIM: The aim of the study is to observe the relationship between Vitamin D levels and clinical outcomes of sepsis in the neonatal unit.

METHODS: An analytical cross-sectional study was conducted to neonates in neonatology Haji Adam Malik hospital from June 2019 to February 2020. A Chi-square test was carried out to observe the relationship between Vitamin D levels and sepsis outcomes, and a Mann-Whitney test was done to assess the significance between Vitamin D levels and length of hospital stay.

RESULTS: Among 41 full-term and pre-term neonates, there were 75.6% (31/41) neonates with Vitamin D deficiency, while 24.4% (10/41) had normal Vitamin D levels and did not suffer from deficiency. The relationship of Vitamin D levels with mortality, use of ventilatory support, length of stay, and blood culture was p = 0.660 (95% confidence interval [CI] = 0.810–1.677), p = 0.013 (median 21 days), and p =0.712 (95% CI = 0.623–1.353), respectively.

CONCLUSION: Vitamin D deficiency had a significant relationship with ventilatory support requirement as one of the sepsis outcomes in neonates.

Introduction

Neonatal sepsis is an invasive bloodstream infection, with or without bacteremia, that occurs in neonates within the 1st month of life. It is an important cause of neonatal morbidity and mortality. In addition, other clinical outcomes, such as respiratory support requirement, length of hospital stay, and respiratory distress, can be caused by neonatal sepsis. The study done by Levit et al., (2014) in the United States reported that the need of intubation or breathing aid was associated with mortality in neonatal sepsis [1]. In 2015, Haji Adam Malik Hospital, Medan recorded 154 (25.6%) sepsis patients, with 79 (51.3%) early-onset sepsis and 75 (48.7%) late-onset sepsis cases among 626 neonates admitted [2].

Bacteria removal is the main option in the management of neonatal sepsis. Therefore, neonatal sepsis patients need to be treated as early as possible to prevent the unwanted outcomes, which can be longer hospital stay, respiratory problems including respiratory distress, ventilatory support requirements, and even death [1]. The deficiency in Vitamin D is correlated with the incidence of upper and lower respiratory tract infections by various causes, especially viruses and sepsis. Hasan et al., (2017) in their study in Iran reported a significant relationship between Vitamin D levels and respiratory distress syndrome in neonates [3].

Vitamin D is one of the fat-soluble Vitamins. It regulates calcium and phosphor in the bone mineralization process [4]. Besides the classic functions, Vitamin D also plays an important role in the immunity system [5]. Casecontrol study by Kanth et al., (2016) in India on pre-term and full-term neonates with early-onset sepsis found that these babies had significantly lower levels of 25(OH)2-D that control group (14.69 ± 4.45 ng/ml and 28.46 ± 22.01 ng/ml; p < 0.01) [6]. A prospective study in Dublin by Onwuneme et al., (2015) done to 94 pre-term neonates with<32 weeks gestational age and <1500 g birth weight reported 92% neonates with ≤20 ng/mL Vitamin D levels. Meanwhile, 64% neonates with <12 ng/mL Vitamin D levels showed significant increases in supplemental oxygen use (p = 0.008), mechanical ventilation requirement and duration (p = 0.013 and p = 0.032 respectively) [7]. Neonates begin receiving Vitamin D in the womb through the placenta. Vitamin D levels in maternal serum greatly affect the levels in the fetus. Low Vitamin D levels in mothers have a negative impact on the children’s growth and development [8], as well as the immunity...
Vitamin D and neonatal sepsis clinical outcomes

Methods

This research was an analytical study with a cross-sectional approach to assess the relationship between Vitamin D levels and the outcomes of neonatal sepsis in neonatology Haji Adam Malik Hospital, Medan from June 2019 to February 2020. Research samples were neonates admitted to neonatology Haji Adam Malik Hospital during the study period and met the inclusion and exclusion criteria. Inclusion criteria were neonates with sepsis, either proven or probable sepsis, and the parents or guardians were willing to give their consent to join the research. Exclusion criteria were neonates with multiple congenital anomalies, suspected or proven pulmonary embolism from chest X-ray, and signs of deep vein thrombosis such as swelling in the extremities. This research has received approval from the Health Research Ethics Committee of Medical Faculty, Universitas Sumatera Utara (No. 538/TGL/KEPK FK USU-RSUP HAM/2019) and Haji Adam Malik Hospital, Medan (DP.02.01/V/2.2.1/1826/2020).

Before the study was started, parents and guardians of the research subjects were given explanation about the research and they signed informed consent. Interviews and data collected from the medical record were done to obtain demographic data of the neonates. Laboratory test was done to all new patients with suspected sepsis when they were treated in the neonatology for the first time, following the laboratory standard in Haji Adam Malik Hospital for total Liaison® 25-OH Vitamin D and blood culture tests.

Results

Research subject demographic characteristics

There were 41 full and pre-term neonates who met the inclusion and exclusion criteria during the research period. From all research patients, 46.3% (19/41) were male and 53.7% (22/41) were female. There were 60.9% (25/41) neonates with gestational age <36 weeks. Based on the birth weight, 17% (7/41) had very low birth weight, 43.9% (18/41) had low birth weight, and 39% (16/41) had normal birth weight. From blood culture test, there were 34.1% (14/41) neonates with positive culture, while the rest 65.9% (27/41) had negative culture. Vitamin D deficiency was observed in 75.6% (31/41) neonates, and only 24.4% (10/41) neonates with normal Vitamin D levels were recorded. The average length of hospital stay was 21 days (ranging from 4 to 80 days). Death involved during the study was 17% (7/41), whereas 82.9% (34/41) neonates were discharged after treatment. Most neonates used CPAP (46.3%, 19/41) and followed by ventilator uses (34.1%, 14/41), whereas 19.5% (8/41) did not require respiratory support. The demographic characteristics of research subject are presented in Table 1.

The relationship between Vitamin D levels and neonatal sepsis outcomes

Vitamin D level data were divided into two groups, such as normal (31/41) and the deficiency (10/41) in Vitamin D. The outcomes of neonatal sepsis assessed were mortality, the requirement of respiratory support, length of stay, and blood culture. The
relationships between Vitamin D levels and neonatal sepsis outcomes were presented in Table 2.

Table 2: Vitamin D levels and neonatal sepsis outcomes

| Characteristic | Vitamin D deficiency | p |
|----------------|----------------------|---|
| Mortality, n (%) | Yes (n = 31) | No (n = 10) |
| Death | 6 (19.4) | 1 (10) | 0.069a |
| Alive | 25 (80.6) | 9 (90) |
| Respiratory suppport, n (%) | | |
| Ventilator | 13 (41.9) | 1 (10) | 0.013** |
| CPAP | 15 (48.4) | 4 (40) |
| No support required | 3 (9.7) | 2 (20) |
| Length of stay, median (range) | 21 (5–80) | 22.5 (4–63) | 0.940 |
| Blood culture, n (%) | | |
| Positive | 10 (32.3) | 4 (40) | 0.712 |
| Negative | 21 (67.7) | 6 (60) |

*Fisher exact test, Pearson Chi-square, Mann-whitney, significant value is p <0.05. Respiratory support at p = 0.05 is significant.

The mortality rates in Vitamin D deficiency group was 19.4% (6/31) and only one death was recorded in the normal group (1/10). Whereas, patients who lived and discharged after completion of treatment were 80.6% (25/31) and 90% (9/10) in Vitamin D deficiency and normal groups, respectively. Statistical test result analysis gave p = 0.660 (95% CI = 0.810–1.677). There was no correlation between Vitamin D level and mortality in this study for neonatal sepsis.

The need of respiratory support was divided into three groups as follows: ventilator, CPAP, and no requirement. In Vitamin D deficiency group, 41.9% (13/31) neonates used ventilator, 48.4% (15/31) used CPAP tool and 9.7% (3/31) did not require breathing support. While in normal Vitamin D group, 10% (1/10) used ventilator, 40% (4/10) needed CPAP, and 50% (5/10) did not require breathing support during treatment. Statistical test result obtained was 0.013 (p < 0.05), therefore, Vitamin D levels were correlated to the need of respiratory support.

Another outcome assessed was the length of hospital stay. The median duration of hospital stay was 21 days (5–80 day range) and 22.5 (4–63 day) in Vitamin D deficiency and normal groups respectively. Statistical test showed p = 0.940, which can be concluded that there was no relationship between Vitamin D levels and the length of hospital stay.

In blood culture assessment, 32.3% (10/31) positive blood cultures came from the deficiency Vitamin D group, while 40% (4/10) were from normal Vitamin D level group. Statistical test showed p = 0.712 (95% CI = 0.623–1.353). Therefore, the relationship between Vitamin D levels and blood culture was insignificant.

Discussion

The roles of Vitamin D in immune system have triggered more research about Vitamin D levels and the relationship with neonatal sepsis incidence. Premature babies are at risk of Vitamin D deficiency compared to full-term babies [10]. The study done by Park et al., (2015) in Korea to 278 premature babies reported 98.9% were deficient in Vitamin D and 51.1% were severely deficient [10]. In 2014, Heather et al., (2014) conducted their study in Boston and reported lower rates of Vitamin D deficiency in premature babies [11]. In this study, however, 25(OH)-D serum levels in full and pre-term babies were not separately recorded. The concentration of 25(OH)-D serum levels in neonates is positively correlated with maternal 25(OH)-D serum concentration during pregnancy. Park et al., (2015) in their study in Korea reported lower 25(OH)-D concentration in babies (10 ng/mL) than in Northern European Countries [10], including Norway (12.2 ± 5.5 ng/mL) [12], and Finlandia (11.7 ± 4.7 ng/mL) [13]. This could happen as maternal Vitamin D levels were affected by race, regions, genetics, and season changes [13]. Vitamin D levels also affected gestational age and birth weight of neonates [6,14]. In this study, 60.9% (25/41) of neonates with sepsis was at <36 weeks gestation, and 43.9% (18/41) were born with low birth weight (>1500–2500 g).

Vitamin D deficiency in neonates was correlated with neonatal sepsis incidence [15]. In several pediatrics studies, significant relationships were reported between Vitamin D deficiency and sepsis [16]. Kanth et al., (2016) reported the majority of neonates (64.1%) with neonatal sepsis were suffering from Vitamin D deficiency, and Vitamin D was statistically significant to neonatal sepsis (p = 0.05) [6]. Vitamin D roles in neonatal sepsis refer to clinical and bacteremia-related signs and symptoms that occur in the 1st month of life; the occurrence is related to Vitamin D receptors in the cellular immune system. The regulation of pathogenic microbes and TLRs by Vitamin D were expressed by signaling proteins, hence triggering monocytes, macrophages and neutrophils, and increasing...
chemotaxis, phagocytes, and bactericidal activities in the innate immune system. Another important role of Vitamin D is also to induce cathelicidin – an important anti-microbial peptide that can directly inhibit the growth of Gram-positive and Gram-negative bacteria [17].

A casecontrol study done by Sarwade et al., (2019) in India to 60 Vitamin D deficient neonates with sepsis reported 66% positive culture blood test (p ≤ 0.001) [18]. The study done in Turkey by Terek et al., (2018) to 394 neonates showed positive and negative gram cultures were not significantly correlated to Vitamin D levels [14]. This result was aligned with this study, where blood culture was not significantly correlated to Vitamin D level, with p > 0.05. Another study by Hollick et al., (2011) to 117 neonates also reported insignificant difference between Vitamin D levels and neonatal sepsis from blood culture result [19]. Diagnosis of neonatal sepsis can be enforced only by looking at clinical condition, and with or without bacteremia.

The incidence rate of sepsis in developing countries is pretty high at 1.8–18/1000 live births, with 12–68% mortality rate. Meanwhile, industrialized countries reported 3 sepsis cases per 1000 live births and 10.3% mortality rate. In Indonesia, the mortality rate of neonatal sepsis reached 14% in the year 2013 [20]. A cohort study by Braun et al., (2011) in Boston stated that death occurred when Vitamin D level was <32 nmol/L, and no death was recorded when Vitamin D level was higher than 65 nmol/L [21]. The Institute of Medicine (US) Committee reported an inverse J-form relationship between 25(OH)-D and all causes of mortality. This showed that too high of Vitamin D levels would be toxic to neonates, while too low would lead to unwanted outcomes. 25(OH)-D serum at 50–60 nmol/L had low risk of mortality [22]. A meta-analysis study done by Mukhopadhyay and Puopolo (2012) in Boston reported similar result, where Vitamin D level below 50 nmol/L increased mortality risk [23]. However, mortality and Vitamin D levels were not correlated in this study, with p > 0.05. This is because the neonates with >36 weeks gestation were not excluded. While, low birth weight and a history of severe asphyxia risk factors, which facilitate infections with cell injuries from hypoxia and trigger inflammation to deaths, are not found in neonates with >36 weeks gestation.

The effect of Vitamin D on lung development is an important issue that has been much researched about recently. A few studies reported different results, where the studies done by Ozdemir et al., (2018) [24] in Turkey and Onwuneme et al., (2015) [7] in Dublin reported no correlation between Vitamin D and neonatal sepsis or respiratory distress, NEC, intraventricular bleeding and death. However, the study done by Lykkeøegn et al., (2015) in Denmark stated that deficiency in Vitamin D in pregnant mothers affected fetal growth and development and led to low birth weight and premature births; in which all of them may have impact on respiratory distress and increase in bronchopulmonary dysplasia [25]. Moreover, the prospective study done by Catinkaya et al., (2015) in Turkey to 81 pre-term neonates showed significant relationship between Vitamin D levels below 15 ng/mL and increased risk of respiratory disorders, including respiratory distress [9]. The deficiency in Vitamin D is related with risk of bad fetal growth, in which Vitamin D affect fetal development and growth during pregnancy and the deficiency is a risk factor in developmental disorders of many organs in neonates [7].

The need of respiratory support, both invasive or non-invasive, often becomes the risk factor for neonatal sepsis [9]. The study by Onwuneme et al., (2015) to 94 neonates reported 25(OH)-D concentration <30 nmol/L (12 ng/mL) in newborns increases the need of oxygen (p = 0.008), as well as the increase of mechanical ventilator and the length of use (p = 0.013) [7]. Similarly, our study showed correlation between Vitamin D levels and the use of respiratory support as one of the outcomes of neonatal sepsis. A retrospective study done by Shah et al., (2015) to 7509 neonates found babies with late onset sepsis significantly increased the length of stay and requirement of breathing support [26].

Vitamin D deficiency also inhibits the maturation of macrophages, therefore, reducing the production of lysozyme and H2O2 that have antimicrobial effects. Moraes et al., (2015) in their study in Sao Paolo reported the correlation of Vitamin D deficiency with the increase in length of stay, mechanical ventilation needs, and fluid and inotropic resuscitation in sepsis patients [27]. However, this report was not align with the cross-sectional analytical research in Padang, Indonesia by Nice and Indra (2017) done to 56 critically ill children reported no significant differences between Vitamin D with the length of hospital stay, although there were differences of the length of stay in the group that survived [28]. In this research, using the Mann-Whitney test, no significant relationship was observed between Vitamin D and length of hospital stay.

The status of Vitamin D in neonates is due to many factors, one of them because of the mothers as the source of Vitamin D in neonates. When a mother was Vitamin D deficient, it would affect not only the mother but also the neonate she was carrying [29]. The Institute of Medicine has pointed out the need of at least 400–600 IU/day Vitamin D intake in pregnant women. In Turkey, 50–94% of pregnant women were reported to suffer from Vitamin D deficiency, therefore, they were given 1200 IU/day Vitamin D supplementation [24]. The study done by Ozdemir et al., (2018) in Turkey reported only 14.4% of pregnant women took 1000–1200 IU/day of Vitamin D. When the mother groups were evaluated in terms of risk factors, there were significant differences in daily vitamin intake and clothing style. Whereas, only 27% of neonates with Vitamin D deficiency were born from mothers who received Vitamin D supplements during pregnancy (p < 0.001 and p < 0.001,
respectively) [24]. Similar results were also reported by the study done by Cizmeci et al., (2014) in Turkey [30]. In this study, however, maternal Vitamin D levels were not assessed because not all neonates involved in the study were born in Haji Adam Malik hospital.

**Conclusion**

The results of this study showed that Vitamin D levels were positively correlated to the requirement and use of ventilatory support. Whereas, other outcomes such as mortality, length of hospital stay, and blood culture did not have a significant relationship with Vitamin D levels.

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