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ORIGINAL ARTICLE

Evaluation of the Relationship Between Vitamin D Deficiency and Early-Onset Neonatal Sepsis in Neonates: A Cross-Sectional Analytical Study

PARDEEP KUMAR[1], BAKHTIAR AHMED BHANBHRO[2], ASIF ALI KHUHRO[3], IFTIKHAR HAIDER[4], MUMTAZ ALI BHARO[5], UBEDULLAH BAHALKANI[6]

[1]Assistant Professor Paediatric, Pir Abdul Qadir Shah Jilani Institute of Medical Science Gambat Khairpur Pakistan
[2]Associate Professor Paediatric, Pir Abdul Qadir Shah Jilani Institute of Medical Science Gambat Khairpur Pakistan
[3]Assistant Professor Paediatric Medicine, Pir Abdul Qadir Shah Jilani Institute of Medical Science Gambat Khairpur Pakistan
[4]Senior Registrar Paediatrics, Pir Abdul Qadir Shah Jilani Institute of Medical Science Gambat Khairpur Pakistan
[5]Assistant Professor Paediatric Medicine, Ghulam Muhammad Mahar Medical College Sukkur Pakistan
[6]Assistant Professor Paediatrics, Khairpur Medical College Khairpur Mirs Pakistan
Corresponding author: Pardeep Kumar, Email: Pardeep79thadhani@gmail.com

ABSTRACT

Aims: To evaluate the relationship between vitamin D deficiency and early-onset neonatal sepsis in neonates

Study design: A cross-sectional analytical study

Place and duration: This study was conducted at Pir Abdul Qadir Shah Jilani Institute of Medical Science Gambat Khairpur Pakistan from March 2020 to March 2021

Methodology: Samples were taken from the neonatal department that met the inclusion criteria. All neonates with proven or suspected sepsis were included. We used the Chi-square test to identify the relationship between vitamin D levels and neonate sepsis. However, Fisher exact test was applied where Chi-square was not fitted well. Mann Whitney analysis was also performed.

Results: We recruited 41 cases of preterm and full-term neonates with sepsis. Out of these 41 cases, 46.3% (19/41) were male and 53.7% (22/41) were females. An insignificant correlation was observed between mortality, length of hospital stay, and blood culture with Vitamin D levels. However, we observed a positive correlation between Vitamin D levels and the need for respiratory support.

Conclusion: Our study concluded that vitamin D deficiency is associated with the need for respiratory support in neonates with sepsis. However, no correlation with other outcomes was observed in the current study.

Keywords: Neonatal sepsis, Vitamin D deficiency, outcome, respiratory support

INTRODUCTION

Neonatal sepsis is a bacterial or nonbacteremic bloodstream infection that occurred within the 1st month of life. Other than bacteremia, respiratory distress and prolonged hospital stay after sepsis are also challenging factors that required early management to avoid any circumstances which lead to ventilatory support or even death.[1] Morbidity and mortality of neonatal sepsis are high in the ratio in some parts of the world. The study reported 25.6% neonatal sepsis in Indonesia of which 51.3% were diagnosed as early-onset sepsis and 48.7% as late-onset sepsis.[2] Vitamin D deficiency has a high association with respiratory tract infections, especially with viruses and sepsis. In 2017 study found a positive association of vitamin D deficiency with respiratory distress syndrome in neonates.[3] The basic function of vitamin D is to regulate phosphor and calcium in the bone mineralization process.[4] However, this fat-soluble vitamin also plays an important role in boosting the immune system.[5] In 2016 a case-control study by Kenth et al discovered low vitamin D levels in cases. In the case of the group, he reported 14.69 ± 4.45 ng/m however the participants in the control group had 26.46 ± 22.01 ng/m 25(OH) 2-D levels. Both groups reported significant differences ($p < 0.01$).[6] A prospective study conducted in 2015 observed that 92% of neonates had vitamin D levels less than 20 ng/mL who were born in <32 weeks with <1500 g birth weight. The requirement for supplemental oxygen and ventilator significantly increased due to low serum concentrations ($p = 0.008$).[7] Placenta provides vitamin D to neonates in the uterus.[8]. Low vitamin D levels in mothers also affect the fetus's immunity.[8, 5] At the time of birth, the transition occurred in the immunity system, and full development of the adaptive immune system is completed. At that period neonates are highly dependent on the immune system which protected them from pathogenic microbe invasion.[9] The levels of vitamin D are highly associated with the production of LL-37 which protects neonates from infections.[6] In the past, limited studies had been published to explore the association of vitamin D levels with neonatal sepsis. We designed this study to evaluate the relationship between vitamin D levels and neonatal sepsis along with examining the other outcomes such as duration of hospital stay and respiratory support requirements and mortality ratio.

METHODOLOGY

This cross-sectional analytical study was conducted at Pir Abdul Qadir Shah Jilani Institute of Medical Science Gambat Khairpur Pakistan from March 2020 to March 2021. Permission was taken from the ethical review committee of the institute. The basic concern of this study was to evaluate the relationship between vitamin D deficiency and neonatal sepsis. Samples were taken from the neonatal department of the hospital. We assured that all neonates with proven or suspected sepsis were included. All the cases of multiple congenital anomalies, probable cases of deep vein thrombosis were excluded. We also excluded all the suspected or confirmed cases of pulmonary embolism

on the basis of the chest X-ray. Complete protocol of Helsinki declarations was followed. We assured parents or guardians were well informed about the research objectives and consequences. All the doubts of parents were cleared at the initial stage. Volunteer participation was encouraged. Suspected cases of sepsis underwent laboratory examination for a blood culture test and total level of 25-OH Vitamin D assay.[10]

We used SPSS 23.0 version for data processing and analysis. Bivariate analysis was used to describe the characteristics of the sample. A single tail test was applied with a confidence interval of 95%. We used the Chi-square test to identify the relationship between vitamin D and neonate sepsis. However, Fisher exact test was applied where Chi-square was not fitted well. Mann Whitney test was used to describe the relationship between vitamin D levels and length of hospital stay. We set a 0.05 p-value to describe the statistical significance.

RESULTS

We recruited 41 cases of full-term neonates with sepsis. Out of these 41 cases, 46.3% (19/41) were male and 53.7% (22/41) were females. We reported 60.9% cases with gestational age less than 36 while 39.1% cases were born after 36 weeks of gestation. C-section was the process of delivery in 75.6% of cases. Out of these 41 cases we reported that 43.9% had low birth weight, while only 39% cases reported normal birth weight (As shown in Table 1). A total of 65.9% of cases had negative blood cultures. Vitamin D deficiency was reported in 31 cases (75.6%). CRP level was observed below 1 mg in 56.1% of cases. Meanwhile, the death rate was comparatively low than those who were discharged after treatment (17.1% vs 82.9%). A total of 46.3% of cases required CPAP, 34.1% required ventilator support, and only 19.5% does not require any respiratory support. The median length of hospital stay is shown in Table 2). In table 3 comparison was drawn between groups. We divided neonate sepsis into two major groups; those having deficiency and those who had normal vitamin D levels. Our results reported no significant difference between the two groups in terms of mortality outcomes, blood culture, and length of hospital stay. However, we observed a positive correlation between Vitamin D levels and the need for respiratory support.

Table 1: Demographic information of study participants

Characteristics	Frequency of neonatal sepsis N= 41
Gender	
Female	22 (53.7%)
Male	19 (46.3%)
Gestational age	
>36 weeks	16 (39.1%)
<36 weeks	25 (60.9%)
Delivery process	
Cesarean Section	31 (75.6%)
Spontaneous vaginal	10 (24.4%)
Birth weight in grams	
>2500	16 (39%)
>1500–2500	18 (43.9%)
1000–1500	7 (17.1%)
<1000	0 (0%)

Table 2: Clinical outcomes of recruited patients

Variables	Frequency N=41
Blood culture	
Negative	27 (65.9%)
Positive	14 (34.1%)
Vitamin D deficiency	
No	10 (24.4%)
Yes	31 (75.6%)
CRP value	
>1 mg	18 (43.9%)
<1 mg	23 (56.1%)
The median length of hospital stay	21 (4–80)
Respiratory support	
Ventilator	14 (34.1%)
No support required	8 (19.5%)
CPAP	19 (46.3%)
Outcomes	
Death	7 (17.1%)
Alive	34 (82.9%)

Table 3: Comparison of neonatal sepsis outcomes with vitamin D deficiency

Neonatal sepsis outcomes N= 41	Vitamin D deficiency		P-value
	No (N=10)	Yes (N= 31)	
Blood culture			0.712 (Fisher exact test)
Negative	6 (60)	21 (67.7)	
Positive	4 (40)	10 (32.3)	
Mortality			0.660 (Fisher exact test)
Alive	9 (90%)	25 (80.6%)	
Death	1 (10%)	6 (19.4%)	
The median length of stay	22.5 (4–63)	21 (5–80)	0.940 (Mann Whitney test)
Respiratory support			0.013 (Pearson and Chi-square test)
CPAP	4 (40%)	15 (48.4%)	
Ventilator	1 (10%)	13 (41.9%)	
No support required	5 (50%)	3 (9.7%)	

DISCUSSION

Recent study reported that premature babies had a high probability of low vitamin D levels than full-term babies.[11] In 2015 Korean[11] study reported 98.9% of premature babies with low vitamin D levels however, 51.1% of them were severely deficient. Similar results had been observed in the Bostan study regarding vitamin D deficiency in premature neonates.[12] However, in our study, we did not separately report the vitamin D levels in premature and full-term neonates. In 2015 Korean study observed a low concentration of 25(OH)-D than Northern European Countries. A study revealed Korean[11] babies had a 10 ng/mL concentration of 25(OH)-D whereas Norwegian babies[13] had a 12.2 ± 5.5 ng/m concentration. In Finland, [14] researchers reported variation in serum vitamin D levels in neonates due to maternal race, environment, regions, and genetics.[14] Gestational age and neonate birth weight are also affected by vitamin D levels.[6,15]

The deficiency of vitamin D is highly associated with neonatal sepsis. In the past several pediatric studies

explore the correlation of low levels of vitamin D with sepsis.[16-18] In 2016 study of Kenth reported 64.1% cases of neonatal sepsis with low vitamin D levels. He observed a positive correlation between both variables (p-value = 0.05).[6] In 2019 a case-control study conducted in India reported 66% positive culture blood in 60 vitamin D deficient babies.[19] However, a study conducted in Turkey revealed no significant correlation between vitamin D levels and positive or negative gram cultures.[15] Another study also reported an insignificant correlation between blood culture and Vitamin D concentrations among 117 neonates.[20]

In developing countries, the incidence rate of sepsis is quite high. Almost 18 out of 1000 cases reported sepsis at the time of birth with a 12-68% mortality ratio. However, in developed countries, only 3 cases were reported out of 1000 with a 10.3% mortality ratio.[2] In 2013, the Indonesian region reported a 14% mortality ratio.[21] A cohort study by Braun et al revealed that vitamin D <32 nmol/L causes mortality among neonates.[22] On the other hand, inverse J forms a relationship between 25(OH)-D and mortality. [20] Another study revealed that 50–60 nmol/L 25 (OH) D had a low probability of mortality.[23] One meta-analysis suggested that vitamin D serum level less than 50 nmol/L enhanced the mortality ratio.[24] However, in our study, we did not find any relation between vitamin D and mortality ratio (p > 0.05). These results may be happened due to the inclusion of cases with >36 week gestation period. In our study, we did not observe any case of severe asphyxia risk factors and low birth weight which enhances infection and triggered inflammation in cases >36 weeks gestation resulting in death. A study conducted in Turkey[25] and Dublin[7] reported a positive correlation between vitamin D levels and respiratory distress or neonatal sepsis. On the other hand, a study conducted in Denmark observed the effect of vitamin D on fetus growth and development. They revealed that pregnant women with low vitamin D levels had a high chance of premature births of low weighted babies with impact on respiratory distress and enhanced bronchopulmonary dysplasia.[26] Development disorders are also observed in neonates due to low vitamin D levels during pregnancy.[7]

Both invasive and noninvasive need of respiratory support become a risk factor for neonatal sepsis.[9] In our study, we explored the correlation between vitamin D levels and respiratory support as one of the outcomes of neonate sepsis. These results are consistent with the previous study of Shah et al., [27] which claimed that babies with late-onset sepsis demand breathing support and prolonged hospital stay. The deficiency of Vitamin C reduces the lysozyme and H_2O_2 production that have antimicrobial effects. A 2015 study revealed the need for mechanical ventilation, inotropic resuscitation, and fluids in sepsis patients with vitamin D deficiency.[28] On the contrary cross, sectional analytical research in Indonesia did not reveal any significant difference with deficiency of vitamin D and prolonged hospital stay.[29] These results are in line with our results in which we observed no significant relationship between Vitamin D deficiency and prolonged hospital stay in the Mann Whitney test.

Researchers observed that pregnant women required 400–600 IU vitamin per day.[30] Studies by Cizmeci et al., [31] reported 27% vitamin D deficiency among neonates whose mothers intake vitamin C during pregnancy. However, maternal vitamin D levels were not accessed in our study because not all neonates were born in our hospital.

CONCLUSION

Our study concluded that vitamin D deficiency is associated with the need for respiratory support in neonates with sepsis. However, no correlation with other outcomes was observed in the current study.

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Conflict of interest: None

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