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Research Article

Association of Vitamin D Deficiency with Late Onset Neonatal Sepsis

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Abstract

Background: Neonatal sepsis is a critical condition and one of the important causes of neonatal mortality and morbidity. Late onset neonatal sepsis is an important type of neonatal sepsis. Vitamin D has important immune modulatory effects. Vitamin D deficiency is widespread among pregnant women and neonates. The association of vitamin D deficiency with neonatal sepsis has recently been an area of intense scientific research.

Objectives: This study aimed to determine the association of vitamin D deficiency with late onset neonatal sepsis.

Methods: This cross-sectional observational study was conducted in a neonatal intensive care unit of a tertiary care hospital. A total of 82 near term and term neonates of postnatal age 72 hours to 7 days were included in the study. Among them, 41 neonates with late onset sepsis were in the septic group and 41 babies without sepsis were in non septic group. Vitamin D level was measured in both groups. Baseline maternal and neonatal demographic data, clinical examination findings and relevant investigation reports were recorded. The difference between the mean vitamin D level of the septic and non-septic group was calculated. The percentage of vitamin D in both groups of neonates was ascertained. The association of vitamin D deficiency with late onset neonatal sepsis was determined by multivariate logistic regression analysis. P value 0.05 was considered statistically significant.

Results: Total of 82 neonates was included in the study. Among them 45 neonates were term and 40 neonates were with normal birth weights. Of the total study population, 41 neonates were in the septic group and 41 were in non-septic group. In the septic group, 56% were near term with a mean gestational age of 36.20 ± 2.07 weeks and 61% of neonates were low birth weight with a mean birth weight of 2176.33 gm ± 976.76 gm. In the non-septic group 41% of neonates were near term with a mean gestational age of 36.60 gm ± 1.759 gm and 41% were low birth weight with a mean birth weight of 2456.22 gm ± 572.96 gm. The mean vitamin D level in the septic group (18.27 ng/ml ± 7.05 ng/ml) was significantly lower than in the non-septic group (21.47 n/ml ± 6.98 n/ml); p value 0.026. About 87.9% of neonates in the septic group and 78% of neonates in non-septic group had vitamin D deficiency (p value 0.042). On the multivariate regression analysis, vitamin D deficiency was found to be significantly associated with late onset neonatal sepsis (OR=4.3, 95% CI 1.122-16.513, p value 0.033).

Study implication: Vitamin D deficiency may be a risk factor for late onset neonatal sepsis. Vitamin D may have an adjuvant therapeutic role in late onset neonatal sepsis.

Conclusion: This study shows that vitamin D is significantly lower in septic group neonates than in nonseptic group neonates. Low vitamin D level is independently associated with late onset neonatal sepsis. Further studies are needed to determine the direction of this association.

Keywords: Neonates; Vitamin D; Sepsis; Late onset neonatal sepsis

Introduction

High neonatal mortality is a major global health issue, contributing to 47% of fewer than 5 mortalities [1]. The rate of neonatal mortality per thousand live births is 19 worldwide [2]. In Bangladesh, neonatal mortality is high accounting for 30 per 1000 live births and 66.66% of all under 5 deaths [3]. An important cause of neonatal death is neonatal sepsis. It is the third most common cause of death among neonates, accounting for 22,5000 deaths globally every year [1]. The incidence of neonatal sepsis varies from 1 to 8 neonates per 1000 live births [4]. Globally, sepsis increased neonatal mortality by 1% to 5% and severe sepsis by 9% to 20% [1]. The burden of neonatal mortality due to neonatal sepsis is even higher in developing countries, accounting for 30% to 50% of total deaths per year [5]. In Bangladesh, neonatal sepsis contributes 19.9% to neonatal mortality [6]. Late Onset Neonatal Sepsis (LONS) refers to sepsis from 72 hours to 3 months of age [7]. It is clearly distinct from early onset neonatal disease in terms of the spectrum of causative pathogens and risk factors. LONS is associated with the postnatal nosocomial or community environment [8]. Apart from prematurity and low birth weight, other risk factors

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for LONS include the long-term use of invasive interventions, such as mechanical ventilation and intravascular catheterization, the failure of early enteral feeding with breast milk, prolonged duration of parenteral nutrition, hospitalization, surgery and underlying respiratory and cardiovascular diseases. The genetic polymorphism in immunity-associated genes may also be implicated in neonatal susceptibility to LONS [9]. In contrast to the decreasing incidence of early onset neonatal sepsis over the last few decades, the morbidity and mortality related to late-onset sepsis (LONS) is increasing due to improved survival of preterm infants and prolonged hospital stay [7,10]. Hospital-acquired LOS represents 62% of all neonatal sepsis episodes [11]. In our country, 91.1% of culture-proven septic cases have late onset neonatal sepsis with mortality as high as 94.1% [12]. Management of neonatal sepsis is still challenging due to subtle and confusing clinical presentation, lack of specific biomarkers, need for starting empirical and high-cost antibiotics and emergence of antibiotic resistance. So preventive approaches including the identification of risk factors and adjuvant therapies have become newer research avenues in the battle against neonatal sepsis. The immature immune system is mainly responsible for increased vulnerability of neonates to infection [13]. So, successful modulation of the neonatal immune system has promising role in reducing the incidence of sepsis, sepsis-related morbidity and mortality [14]. Vitamin D, commonly known as a fat-soluble vitamin with predominant skeletal effects has now been proven to have many extraosseous and immunological effects [15]. Vitamin D exerts its immunological effects mainly by binding with the vitamin D receptor on the cells of the key innate immune cells such as monocytes, macrophages, and neutrophils leading to enhanced chemotactic, phagocytic and bactericidal activities [16]. It activates Toll-like Receptor-4 (TLR-4) which induces antimicrobial proteins such as P-defensin and cathelicidin, maintains the integrity of epithelial cells, enhances Th2 cell differentiation and inhibits Th1 cell activation [17]. Unfortunately, suboptimal vitamin D level has recently appeared as a concerning issue in people around the globe, including pregnant mothers and newborn babies. It has been estimated that approximately 30% and 60% of children and adults worldwide are vitamin D deficient and insufficient respectively [18]. Widespread vitamin D deficiency is also prevalent in pregnant women and newborn babies [19]. Vitamin D deficiency among newborn population ranges from 73% to 94% [20]. The newly established immune modulator role of vitamin D and the global pandemic of vitamin D deficiency have led to the speculation of a possible association of vitamin D deficiency with neonatal sepsis [15]. With this backdrop, recently few studies have shown the association of vitamin-D deficiency with EONS in and acute lower respiratory infection in neonates [21-23]. However, there is a lack of sufficient data defining the role of vitamin D in late onset neonatal sepsis. Given the significant prevalence of late onset neonatal sepsis in late preterm and term neonates, more studies are warranted to elucidate the association of vitamin D deficiency with late onset neonatal sepsis in these neonates. This study has been planned to find the association of vitamin D deficiency with LONS in late preterm and term neonates who are comparable in terms of disease severity and risk factors of late onset neonatal sepsis.

Materials and Methods

This observational study was conducted from October 2021 to September 2022 in the neonatal intensive care unit (NICU) of Bangabondhu Sheikh Mujib Medical University, a tertiary care teaching institution in Bangladesh. Prior approval from the institutional ethical committee was obtained. Term and late preterm neonates of 3 to 7 days of postnatal age were the study population. Neonates of this age group with septic screen positive late onset neonatal sepsis were included as cases. Non septic term and near-term neonates of 3 to 7 days post-natal age were in control group. Any major congenital anomaly, history of early onset sepsis, need for resuscitation at birth, maternal history of chronic kidney disease and parental refusal to participate in the study were exclusion criteria. Estimated sample size with a 5% level of significance and 80% power was 41 in each group.

Forty-one babies from those who developed septic screen positive late onset neonatal sepsis were included into septic group by convenient sampling. Similarly, forty-one babies of same age range with morbidities other than late onset neonatal sepsis were grouped into non septic group. A written informed consent was obtained from parents or guardians before enrollment of each baby in the study. Among the babies in septic group, blood was drawn for vitamin D analysis as early as possible after septic screen report was available. Regarding neonates in non-septic group, informed consent was taken to do septic screen in order to ensure septic free condition at postnatal age 72 hours. Sample for vitamin D assay was sent after as soon as septic screen report was available.

For sending septic work up, cleansing of the skin site was done with 70% isopropyl alcohol for 30 seconds followed by povidone-iodine and isopropyl alcohol again [24]. A total of 3.5 ml venous blood was taken at a time for investigation purpose for suspected septic positive baby, 1.5 ml blood drawn for CBC with PBF while 1 ml for blood C/S and 1 ml for CRP were collected. Only 2 ml blood for Septic screen was taken from non-septic baby.

Blood for CBC and PBF was sent in EDTA tube to the Department of Laboratory medicine where Test is done by, BSMMU, by XT-4000I (Japan) or XN-2000 (Japan). For C Reactive Protein (CRP) estimation blood was sent in a clot activator tube in Biochemistry Department. Quantitative assay for the estimation of C-Reactive Protein (CRP) levels was done on an automated Biochemistry analyser (Beckman Coulter, USA) by using a commercially available particle enhanced turbidimetric assay. Blood culture sample was sent to Department of Microbiology and Immunology, BSMMU. The sample was inoculated in the BD BACTEC Peds Plus/F Culture bottle containing 40 ml broth and culture was done by BD BACTEC FX40 (USA) fully automated system. For measurement of vitamin D, 0.5 to 1 ml of venous blood was collected from each baby with proper asepsis in a clot activator tube. Each sample was left to stand for 30 minutes to clot and then centrifuged at 4000 rpm for 10 minutes. Samples were then analyzed by Liason 25 OH Vitamin D total assay using a Chemiluminescent Immunoassay (CLIA) system attached to an ultraviolet detector. The results were expressed as ng/ml. Vitamin D levels were considered 'deficient', 'insufficient', and 'optimum' when serum 25(OH) vitamin D levels were <20, 20 to 30, and >30 ng/ml respectively, as per the U.S. Endocrine Society classification [25].

A detailed natal and postnatal history of all the neonates including gestational age, gender, mode, and place of delivery was obtained. Clinical features of septic babies were noted. The maternal data including maternal age, parity, educational status, socio-economic status, residence, any chronic illness or pregnancy associated complications, antenatal checkup, and vitamin D supplementation during pregnancy were obtained from the mother/legal guardians of the baby and from the medical records of the mother. Septic screen reports of all neonates and blood culture reports of septic

babies were documented. All data were documented in a pre-formed data collection form. Management of all the neonates was ensured according to NICU protocol.

Gestational age was calculated from the first day of Last Menstrual Period (LMP) or early obstetric ultrasonography or New Ballard Score. Birth weight was recorded immediately after delivery using an electronic scale having a sensitivity of 5 grams in case of inborn babies. For outborn babies birth weight was determined from previous documents. Lubchenco intrauterine growth chart was used for classification as AGA/SGA/LGA.

Statistical Analysis

Data was entered into a personal computer and was edited, analyzed and plotted in graphs and tables. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 21. Continuous variables have been displayed as mean ± SD. Categorical variables have been presented as frequencies and percentages. The independent sample t-test was used for comparing vitamin D levels in two groups. Categorical data between the groups were compared using the Chi-square test or Fisher's exact test as appropriate. The association of vitamin D deficiency with late onset sepsis was determined by logistic regression analysis and expressed as odds ratio. P value <0.05 was considered statistically significant.

Results

A total of 312 late preterm and term neonates of postnatal age 1 to 7 days were admitted in NICU during the study period. Out of them, 40 babies were excluded initially according to exclusion criteria. Among the remaining 272 neonates, 124 neonates developed features of late-onset neonatal sepsis of which 101 neonates had positive septic screen. From these neonates, 41 neonates were taken into septic group by convenient sampling. The neonates of same age range with morbidities other than sepsis were included in non-septic group by same sampling method (Figure 1).

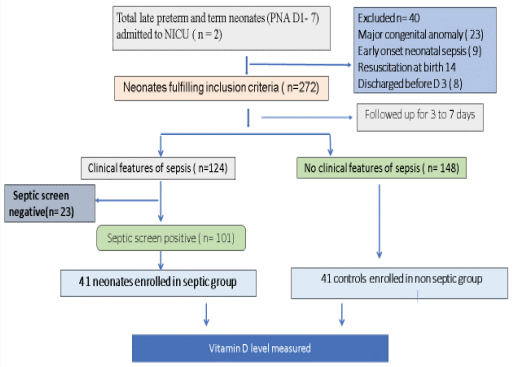

Figure 1: Flow chart of study procedure

The baseline demographic and perinatal characteristics of the studied neonates were presented in Table 1. The mean gestational age of the case and control were 36.20 ± 2.07 weeks and 36.61 ± 1.76 weeks respectively with no significant difference. The mean birth weight of the case and control were 2176.33 gm ± 976.76. gm and 2456.22 gm ± 572.96 gm respectively. 61% of neonates in septic group and 41% of infants in non-septic group had low birth weight. Though there was a slight preponderance of male gender in the total study population (56% in septic and 53.7% in non-septic group), variation is not significant in two groups. There was a statistically significant difference (p value 0.020) in the mean age at the time of collection of a sample of the case (4.66 ± 1.1 days) and the control (5.44 ± 1.11 days).

Regarding demographic characteristics of the mothers (Table 2), Most of the mothers belong to 20 to 29 years of age with mean age 26.23 ± 4.32 years and 26.63 ± 4.80 years in the case and control group respectively. There was no significant difference in the distribution of mothers according to parity with multiparous mothers being slightly more in both groups. Two-thirds of the mothers (75.6%) responded positively regarding antenatal vitamin D intake. There was no statistically significant difference in antenatal vitamin D intake among mothers of septic (71%) and non-septic babies (51%). The consistency and compliance regarding vitamin intake and adequacy of dose and duration could not be verified due to recall bias and in some cases unavailability of mothers. Twenty four percent of babies of mothers taking antenatal vitamin D and 5% of babies with no maternal history of antenatal vitamin D had optimum vitamin D level. However, this difference is not statistically significant.

Total 62 mothers (75%) had history of vitamin D intake. Among the babies of these mothers, 15 neonates had optimum vitamin D levels. Out of 20 mothers who did not take antenatal vitamin D, 19 neonates (95%) neonates were deficient in vitamin D. However, this relation in this study is not statistically significant (Table 3).

Table 4 shows comparison of the septic and non-septic group according to vitamin D level. The overall mean vitamin D level was 19.81 ng/ml ± 7.16 ng/ml. The mean vitamin D level in the case was 21.47 ng/ml ± 6.98 ng/ml which was significantly lower than in the control (18.14 ng/ml ± 7.07 ng/ml) with a p-value of 0.035. Only 14 out of 82 study population (17%) had sufficient Vitamin D (>30 ng/ml). The percentage of vitamin D deficient neonates was also significantly higher in the septic group (88%) than in non-septic group (78%) with p value 0.042. Sub group analysis into deficient and insufficient vitamin D level among two groups has failed to show statistically significant difference due to small sample size (Figure 2).

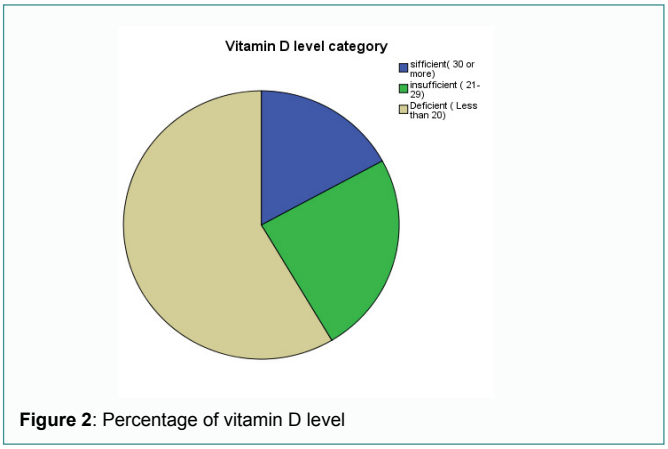

Figure 2: Percentage of vitamin D level

Among all variables other than vitamin D, postnatal age was found to be significantly associated with LONS. After adjustment with multivariate logistic regression analysis (Table 5), the risk of late onset neonatal sepsis was shown to be four times higher in vitamin D deficient neonates (OR=4.3, 95% CI 1.122–16.513, p value 0.033).

Discussion

This study aimed to determine the association of vitamin D deficiency with late onset neonatal sepsis in term and late preterm neonates. We excluded neonates with gestational age less than 34

Table 1: Baseline characteristics of neonates in studied groups (N=82).

Characteristics	Septic group (n=41)	Non-septic group (n=41)	Total	P value
Gestational age in weeks Mean ± SD	36.20 ± 2.07	36.60 ± 1.759	19.81 ± 7.16	0.507^{ns}
Gestational age category				
Late preterm	23 (56.09%)	17 (41.46%)	40 (49%)	0.675^{ns}
Term	18 (43.90%)	24 (58.53%)	42 (51%)	
Birth weight (gm) Mean ± SD	2176.33 ± 976.76	2456.22 ± 572.96	2316.26 ± 749.26	0.09^{ns}
Fetal growth category				
SGA	26 (63.41%)	18 (43.90)	44 (53.6%)	0.65^{ns}
AGA	15 (36.58%)	23 (56.09)	38 (46.4%)	
Gender, n (%)				
Male	23 (56.1)	22 (53.7)	45 (54.8%)	0.824^{ns}
Female	18 (43.9)	19 (46.3)	37 (45.2%)	
Mode of delivery				
LUCS	34(82.92)	37 (90.24)	71 (86.6%)	0.082^{ns}
NVD	7(17.07)	4 (9.75)	11 (13.4%)	
Place of delivery				
Inborn	39 (95)	38(93%)	77 (94%)	0.885^{ns}
Out born	2 (5%)	3 (7%)	5 (6%)	
Age at enrollment (days) Mean ± SD	5.44 ± 1.119	4.66 ± 1.109	5.05 ± 1.17	0.020^{s}

Table 2: Demographic characteristics of mothers in studied groups (N=82).

Characteristics	Septic group (n=41)	Non-septic group (n =41)	Total (N = 82)	P value
Age in years Mean ± SD	26.23 ± 4.32	26.63 ± 4.80	26.43 ± 5.47	0.69^{ns}
Age category				
<20 years	2 (4.9%)	4 (9.8%)	6 (7.3%)	
20-29 years	26 (63.4%)	27 (65.9%)	53 (64.3%)	0.584^{ns}
30-39 years	13 (31.7%)	10 (24.4%)	23 (28.4%)	
Parity				
Primi	15 (36.6%)	12 (29.3%)	27 (33%)	0.481^{ns}
Multi	26 (63.4%)	29 (70.7%)	55 (67%)	
Residence				
Urban	19 (53.7)	26 (63.4)	45 (54.8%)	0.120^{ns}
Rural	22 (46.3)	15 (36.6)	37 (45.2%)	
Antenatal vitamin D intake				
Yes				
No	29 (70.7)	33 (80.5)	62 (75.6%)	0.304^{ns}
	12 (29.3)	8 (19.5)	20 (24.4%)	
Educational level				
Less than high school	5 (12%)	6 (14.6%)	11 (13.4%)	0.056^{ns}
SSC	18 (44%)	21 (51.2%)	39 (47.5%)	
HSC and above	18 (44%)	14 (34.2%)	32 (39.0%)	

S: significant; ^{ns}: not significant; SD: Standard Deviation

Table 3: Relation of antenatal vitamin D intake with neonatal vitamin D level.

Vitamin D Level	Antenatal vitamin D intake		
	Yes	No	P value
<30 ng/ml	47	19	
≥ 30ng/ml	15	1	0.060^{ns}

weeks and also early onset sepsis to rule out the role of maternal and perinatal factors to establish the independent association of vitamin D level with sepsis. The finding of the significantly lower level of vitamin D in septic neonates compared to non-septic neonates and a higher percentage of vitamin D deficient neonates in septic group suggest an association of low vitamin D levels with late onset neonatal sepsis. The immune regulatory role and antimicrobial implications of vitamin D have been supported by a mount of evidence [26]. Vitamin D ligation to vitamin D receptors in the immune cells induces the production of antimicrobial peptides namely p defensin and cathelicidin that inhibit the growth of gram positive and gram-negative bacteria [27], By encoding the proteins, needed for tight junction, vitamin D maintains the integrity of epithelial cells, thereby enhancing first line barrier to infection. In addition, the activity of Toll-Like Receptor-4 (TLR-4), which is responsible for igniting the immune response to specific pathogens, is induced by vitamin D [28]. It also exerts an anti-inflammatory effect by inhibiting activation and differentiation of Th 1 cells [29], thus limiting excessive production of proinflammatory 25 cytokines like tumor necrosis factor-alpha (TNF alpha) and interleukin 12. So, Vitamin D has the potential to reduce infection susceptibility as well as severity. Though the active form of vitamin D is 1.25(OH)2D3, its shorter half-life and very low level in circulation confer technical difficulty in assessment [30]. Serum or plasma concentration of 25(OH)D is the best indicator of vitamin D status, owing to its long half-life in the body (15 days), relative stability and higher concentration in the blood [30]. Vitamin D status varies in different countries due to differences in geographical location, skin complexion, and exposure to sunlight, dietary intake of vitamin D, ethnicities and cultural factors, and genetic predisposition [31]. In theory, thresholds for vitamin D adequacy may vary by age, body composition and lifestyle. For example, a 25(OH)D threshold that is deemed sufficient for a healthy adult may be inadequate for the growing age of an infant or adolescent. Considering all these issues, experts suggest that Vitamin D level should be interpreted in the context of individualized factors and a single threshold for deficiency is unlikely to be valid in all situations [32]. However, there are currently insufficient data to provide a strong basis for setting different 25(OH)D cutoffs to define deficiency in different life stages or on the basis of other individual factors. 25(OH)D level may vary significantly from hour to hour during inflammation and stress. So, the assessment of single time point levels may fail to portray the actual picture [33]. Despite ongoing debates, to date 30 ng/ml is proposed as a cutoff for deficiency to be used across all populations and population subgroups [25]. First important study of vitamin D in neonates was undertaken by Cizmeci and colleagues [24], where the association of hypovitaminosis D with early onset neonatal sepsis was evident by significantly lower vitamin D level (median 12.6 ng/mL (3.1-78.9) in the septic neonates than in non-septic counterparts (median 21 ng/

Table 4: Comparison of septic and non-septic group according to vitamin D level.

Parameter	Septic group	Non-septic group	Total	P value
Vitamin D level (ng/ml) mean(SD)	18.27 (7.05)	21.47 (6.98)	19.81(7.16)	0.026[s]
Vitamin D status n (%)				
< 30 ng/ml	36 (87.8)	32 (78)	68 (83%))	0.042[s]
≥ 30 ng/ml	5 (12.2)	9 (22)	14 (17%)	
Vitamin D status according to 3 categories n (%)				
Sufficient	9 (22)	5 (12)	14(17%)	0.35[ns]
Insufficient	11(27)	9 (22)	20 (24%)	
Deficient	21 (51)	27(66)	48 (59%)	

Table 5: Multivariate logistic regression analysis showing the association of LONS with other variables.

Model	OR	95% CI	P value
Gestational age	0.515	0.119-2.242	0.377 [ns]
Gender	1.056	0.402-2.776	0.912 [ns]
Birth weight	3.06	0.735-12.780	0.125 [ns]
Parity	0.606	0.217-1.693	0.339 [ns]
Post natal age	1.76	1.138-2.723	0.01 [ns]
Vitamin D deficiency	4.304	1.112-16.513	0.033 [ns]

S: Significant; [ns]: not significant

ml (5-118); p value 0.038. Later on, most of the studies conformed with this finding [21,34]. The study by Behera et al. suggested possible risk of sepsis in neonates with lower vitamin D [35]. Few studies have investigated Vitamin D as a risk factor of late onset neonatal sepsis. In a study by Dhandai and colleagues [36], the case group had significantly lower mean (SD) vitamin D levels [15.37 ng/ml (10.0)] than the control group [21.37 ng/ml (9.53)] (p=0.001). These values are in line with the findings of our study where the case and control group had vitamin D 18.27 (7.05) ng/ml and 21.47 (6.98) ng/ml respectively. But vitamin D level was much lower in a study by Agrawal et al. 14.88+7.2 ng/ml and 12.28+6.11 ng/ml in case and control group respectively [37]. A comparatively lower level of vitamin D was also found in a study in preterm neonates with LONS [38]. Significantly higher percentage (88%) of septic babies in our study had vitamin D deficiency (<30 ng/ml) than non-septic group (78%); p value 0.042. This result parallels with that of study by Agrawal et al. [37] where 86% of cases and 74% of control group had vitamin D deficiency (p=0.0003) whereas in the study by Dhandai et al. [36], 63% of study group and 50% in control group had vitamin D deficiency (p-value 0.01). Moreover, 20.57% in the case group and 7% of the control group were identified with severe vitamin D deficiency in the study by Agrawal et al. However, none of the babies in our study had severe vitamin D deficiency (<5 ng/ml). The small sample size and the same economic background might be the cause of the absence of severe vitamin D deficient neonates in our study. A larger multi-center study including all socioeconomic background is needed to determine the magnitude of severe vitamin D deficiency in our country. A wide variation in vitamin D levels in different studies in neonates was also evident in a meta-analysis [20]. In this study vitamin D deficiency among neonates with neonatal sepsis ranged from 50% to 98.8%, whereas vitamin D deficiency among the controls ranged from 2% to 86.7%. The possible explanation for the discrepancies could be associated with sample size differences, geospatial and seasonal variations, and differences in the study setting of the original studies. Positive correlations with maternal and neonatal vitamin D levels have been found in studies on EONS [39] and LONS [36]. As maternal vitamin D is the only source of vitamin D in fetal and immediate neonatal life, this correlation is well anticipated. We did not assess maternal vitamin D status due to financial problems. However, the establishment of relation between maternal and neonatal vitamin D levels would have been helpful to establish causal association between Vitamin D deficiency LONS. Our study had some limitations. Due to small sample size, we could not determine the association of vitamin D level with the severity of sepsis. Inclusion of septic screen positive neonates irrespective of blood culture positivity might pose the risk of selection bias. Causal association of vitamin D deficiency with sepsis could not be established by single time point measurement of vitamin D level after the onset of sepsis.

Conclusion

Our study demonstrated the association of vitamin D deficiency with late onset neonatal sepsis in late preterm and term neonates in the first 7 days of life. Considering the severity of neonatal sepsis, establishment of causal association between vitamin D deficiency and late onset sepsis may pave the way for its new preventive and therapeutic approach. Large multicenter studies with randomized clinical trial with vitamin D are warranted to determine its therapeutic potential in the management of neonatal sepsis.

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