ORIGINAL ARTICLE

ASSOCIATION OF VITAMIN D WITH EARLY ONSET SEPSIS IN TERM NEONATES

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ABSTRACT

Background: Vitamin D deficiency has been associated with increased viral respiratory infections and early-onset sepsis in neonates. Newborns are more susceptible to infections as both innate and adaptive immune systems are not entirely developed. Neonatal sepsis is a frequent and important cause of neonatal morbidity and mortality worldwide. The aim of the study is to determine the association of vitamin D deficiency with early onset of sepsis among term neonates.

Methods: This study was conducted at Neonatal Intensive Care Unit, Ziauddin Hospital Karachi. A total of 100 neonates, with early onset sepsis (n=50) and with no sepsis (n=50as controls) were included. Blood was drawn for CBC, CRP and Vitamin D levels with levels <20ng/ml considered as vitamin D deficiency. Descriptive statistics were calculated. Chi square test was applied to see the association of vitamin D deficiency with study groups. Odd ratio >1 was considered as significant.

Results: There were 64% male and 36% female among neonates with sepsis and 54% male and 46% female among controls. Mean time of onset of infection was 2.08±0.82 days among cases. The mean serum vitamin D level was 10.56±5.83 ng/mL and 22.18±4.44 ng/mL among cases and controls respectively. Vitamin D deficiency was observed among 88% patients with early sepsis and among 20% non-sepsis controls and association was found significant with an odds ratio of 29.33.

Conclusion: Vitamin D level in neonates with early sepsis was significantly lower than non-sepsis patients. Hence, it may be a risk factor for early onset of sepsis in term neonates.

Keywords: Early-Onset Sepsis; Neonates; Vitamin D Deficiency.

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INTRODUCTION

Septicemia still by far remains one of the most frequent causes of neonatal mortality and morbidity worldwide[1]. World Health Organization estimated about 5 million neonatal deaths a year, with 98% occurring in developing countries[2]. It is an important and common cause of morbidity and mortality in full term as well as preterm neonates[3].

The incidence of neonatal sepsis in developed countries has reduced approximately three folds as compared to the developing countries[4]. Neonatal sepsis is defined as the presence of infection in a neonate due to bacteria documented via positive blood culture in the first 4-weeks of life[5]. Neonatal sepsis is divided into two groups; one is early-onset sepsis, which occurs within 7-days of life, and second one is late-onset sepsis, which occurs between day7 to day28 of neonatal life[6].

There is a wide array of bacterial micro-organisms that may result in neonatal sepsis. They vary according to the geographiclocation, socioeconomic conditions, seasonal variation and prevalent use of various antibiotics. Klebsiella, Staphylococcus aureus, and E coli are the most common bacterial organisms responsible for neonatal sepsis (early onset) in developing countries like Bangladesh, India, and Pakistan[7]. Blood culture remains a gold standard for the diagnosis of neonatal sepsis and thus the identification of the causative bacteria. The present automated blood culture system, namely BACTEC examines each bottle after an interval of few minutes and thus helps in earlier detection of bacterial growth[5].

Vitamin D has been reported to carry immunomod-

ulatory effects due to its hypothesized role in the induction of antimicrobial peptides in epithelial cells, neutrophils and macrophages and thus strengthening the innate immune system[8,9]. Due to underdeveloped immune systems i.e., innate and adaptive immunity, newborns are more prone to infections. The association between vitamin D deficiency and susceptibility to infections in children and newborns has been studied extensively[10].

A study reported an increased incidence of development of respiratory syncytial virus infection in healthy infants who had decreased 25-OHD levels in cord blood[11]. This study was aimed to determine the association of vitamin D deficiency with early onset of sepsis among term neonates. The results of this study will help in establishing frequency of deficiency for Vitamin-D in critically ill children suspicious of neonatal sepsis.

MATERIAL AND METHOD

This study was conducted at NICU of Ziauddin University Hospital, Karachi, from February to August 2017. The sample size was calculated using WHO sample size calculator. Total 100 newborns, who were delivered between 37 to 42 gestation weeks of either gender, were included.

Diagnosis of sepsis was made when any two conditions were present i.e., Temperature <36°C at the time of examination /Temperature>37°C at the time of examination /Refusal to feeding for more than 12 hours /Vomiting more than 3 in 24 hours /Respiratory rate >60 breaths/min / Pulse >160 beat/min / Pulse <100 beat/min /Prolonged capillary filling time >3 sec. Early onset of sepsis was considered when it occurred within 72 hours after birth and serial C-reactive protein level ≥5mg/L with either Platelets <100×109/l or Leukocytes count (<5×109/l or 20×109/l)12.

Exclusion criteria included preterm neonates (gestational age <37 weeks) and patients admitted with congenital anomalies. Cases were the group neonates with early onset of sepsis. The group not having early onset of sepsis was considered as Controls.

Blood was drawn for CBC, CRP, and vitamin D level. CRP level was obtained on 2nd day and the cutoff value ≥5 mg/L was considered as early-onset neonatal sepsis. After receiving laboratory results, diagnosis for early-onset neonatal sepsis was made and vitamin D levels were sent to evaluate the deficiency. For controls, vitamin D level was sent along with other investigations required for the particular disease.

Data were compiled and analyzed through SPSS. Descriptive statistics were calculated. Chi square test was applied to see the association of vitamin D deficiency with the two study groups. Odds ratio >1 and p-value ≤0.05 were considered as significant in all analysis.

RESULTS

The results showed that mean birth weight was 2.68±0.55 Kg in cases and 2.53±0.47 Kg in controls. The mean CRP level was 17.9±12 mg/L in cases and 1.48±1.25 mg/L in controls. The mean platelets count in cases was 113.42±51.03 x109/l and in controls the mean platelet count was 214.96±62.65 x109/l. The mean leukocyte count was 22.18±12.28 x109/L in cases and in controls it was 9.97±4.6 x109/L. The mean time of onset of sepsis in cases was 2.1±0.83 days. The mean serum vitamin D level was 10.56±5.83 ng/mL in cases and 22.18±4.44 ng/mL in controls. The detailed results about descriptive statistics are presented in Table 1.

There were 64% male and 36% female neonates in cases and 54% males and 46% females in controls. Results showed that among cases, 58% were vaginal deliveries (36% spontaneous and 22% instrumental), and 42% were delivered through Cesarean sections. Among controls, 50% deliveries were vaginal (32% spontaneous and 18% instrumental) and an equal number of neonates (50%) were delivered through Cesarean sections. The birth weight, gestational age and parity were further stratified into groups.

Vitamin D deficiency was observed in 88% cases and 20% controls. The deficiency was significantly associated with early onset of sepsis with an odd ratio of 29.33 and p< 0.01. Vitamin-D deficiency was evaluated for association with cases and controls according to gender, gestational age, parity, birth weight, and mode of delivery. The detailed results of associations are presented in Table 2.

Table 1: Descriptive statistics of cases and controls.

		Mean±SD	Median	Minimum	Maximum	Range
CASES (n=50)	Birth Weight (Kg)	2.68±0.55	2.70	1.50	4.60	3.10
	Gestational Age (weeks)	37.42±0.57	37.0	37.0	39.0	2.0
	Parity	2.52±1.51	2.0	0	6	6
	CRP Level (mg/L)	17.90±12.00	13.60	5.5	65.0	59.5

	Platelet Count (x109/l)	113.42±51.03	120.00	10.0	250.0	240.0
	Leukocyte Count (x109/L)	22.18±12.28	20.25	1.50	46.32	44.82
	Time of Onset (days)	2.10±0.83	2.00	1.0	3.0	2.0
	Serum Vitamin D (ng/mL)	10.56±5.83	9.04	3.26	23.61	20.36
CONTROLS (n=50)	Weight (Kg)	2.53±0.47	2.55	1.40	3.90	2.50
	Gestational Age (weeks)	37.52±0.73	37.0	37.0	39.0	2.0
	Parity	2.40±1.32	2.0	0	5	5
	CRP Level (mg/L)	1.48±1.25	0.95	0.1	4.5	4.4
	Platelet Count (x109/l)	214.96±62.65	200.00	115.0	450.0	335.0
	Leukocyte Count(x109/L)	9.97±4.60	9.00	4.0	25.0	21.0
	Serum Vitamin D (ng/mL)	22.18±4.44	22.50	13.68	31.22	17.55

Table 2: Comparison of Vitamin D deficiency among cases and controls.

TOTAL (n=150)		**VITAMIN D DEFICIENCY**				**Total**
		YES		**NO**		
		n	**%**	**n**	**%**	
OVERALL	Cases	44	88.0	6	12.0	50
	Controls	10	20.0	40	80.0	50
	ODD Ratio	**29.33**				
	p value	**0.000***				
MALE GENDER	Cases	28	87.5	4	12.5	32
	Controls	8	29.6	19	70.4	27
	ODD Ratio	**16.62**				
	p value	**0.000***				
BIRTH WEIGHT < 2.5 KG	Cases	16	88.9	2	11.1	18
	Controls	2	8.7	21	91.3	23
	ODD Ratio	**84.00**				
	p value	**0.000***				
BIRTH WEIGHT > 2.5 KG	Cases	21	95.5	1	4.5	22
	Controls	6	24.0	19	76.0	25
	ODD Ratio	**66.50**				
	p value	**0.000***				
BIRTH WEIGHT < 38 KG	Cases	23	82.1	5	17.9	28
	Controls	4	16.0	21	84.0	25
	ODD Ratio	**24.15**				
	p value	**0.000***				
BIRTH WEIGHT > 38 KG	Cases	27	87.1	4	12.9	31
	Controls	6	18.2	27	81.8	33
	ODD Ratio	**30.37**				
	p value	**0.000***				
GESTATIONAL AGE > 38 WEEKS	Cases	17	89.5	2	10.5	19
	Controls	4	23.5	13	76.5	17
	ODD Ratio	**27.62**				

DISCUSSION

Early onset of sepsis (EOS) is one of the most important diseases affecting the newborn's health. With reference to the national population few studies have been conducted to evaluate the association between neonatal vitamin D level and early-onset sepsis. In a study carried out in Niger delta region of Nigeria, 18.7% of the neonates were preterm, while 3.7% were post term witha male to female ratio of 1.6:1. In addition, there were 17.2% low birth weight neonates. Most of the neonates were admitted after 24 hours of life with a mean age at admission of 5.7±5.9 days13. In our study, males were 64% in case group and 54% in control group. The females were 36% in case group and 46% in control group. The birth weight of cases was 2.68±0.55 kg and it was 2.53±0.47 kg in controls.

In another study carried out in Turkey, a significant difference was observed in vitamin D levels between the two groups i.e., 8.6±3.1 ng/ml in cases and19.0±4.8 ng/ml in controls (p-value <0.001). It was also observed that the neonatal sepsis observed in 84% infants were also those who were severely Vitamin D deficient i.e., <11 ng/ml12. The present study concluded that the Vitamin D level in case group was 10.56±5.83ng/mL in comparison to the control group which had levels of 22.18±4.44ng/mL (p-value <0.001).

Advancement in obstetrical as well as neonatal care over the years has led to a decrease in the incidence of EOS, but still approximately 2.0 to 3.0% of full-term infants died with this disease[14,15]. Vitamin D has been reported to carry antibiotic effect due to its ability to induce antimicrobial peptides[16,17]. It has also been found in literature that by decreasing the growth of and/or killing strains of K. pneumonia, S. pyogenes, Staphylococcus aureus, and E. coli, Vitamin-D also serves the purpose of increasing eradication of the invading organisms at certain sites[18]. A study reported an increased incidence of respiratory tract infection in infants up to 3-months of age and wheezing in early childhood in infants who had low cord blood levels of 25-OHD[19,20]. Few other studies reported increased incidence of vitamin D deficiency amongst critically ill children[21-24].

There are some limitations in our study. The lack of measurement of maternal serum 25-hydroxyvitamin D level in this study was a limitation. Therefore, it cannot prove lower Vitamin D level may be due to lower maternal serum 25-hydroxyvitamin D level. Further, this study was a single hospital-based study with a small sample size, and conducted in urban environment, therefore, the results might not be generalizable to larger populations.

CONCLUSION

The results showed that Vitamin D level was significantly lower in case group as compared to the control group. With these findings it can be concluded that low serum vitamin D levels is a risk factor for early onset of sepsis in term neonates.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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