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Original Research Article

Association of vitamin D deficiency with early onset sepsis in term neonates

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ABSTRACT

Background: Vitamin D is a fat-soluble steroid hormone. Vitamin D also has immunomodulatory effects on immune function. Early onset sepsis (EOS) is characterized by signs and symptoms of infection with or without accompanying bacteremia in the first three days of life. The objective of the study was to determine the possible association between neonatal vitamin D levels and EOS in term neonates.
Methods: 100 term neonates with clinical and laboratory findings of EOS (study group) and 100 healthy infants with no signs of clinical/laboratory infection (control group) were enrolled. Sera was drawn during first 3 postnatal days of life in both groups for measurement of 25-hydroxyvitamin D (25-OHD) levels.
Results: Neonatal 25-OHD levels (17.4ng/dL) in the study group were significantly lower than those of the control group (26.8 ng/dL) (p=0.001). In present study negative correlation was found between vitamin D level and CRP.
Conclusions: Lower neonatal 25-OHD levels are associated with EOS. Adequate vitamin D supplementation during pregnancy may be helpful to prevent EOS in term neonates.

Keywords: 25-OH vitamin D, Early onset sepsis, Term neonates

INTRODUCTION

Neonatal sepsis is still one of the major causes of the neonatal morbidity and mortality.[1,2] Overall incidence of neonatal sepsis varies between 1 and 8 neonates per 1000 live births. It is broadly defined as a systemic inflammatory response occurring in the first 4 weeks of life as a result of a suspected or proven infection. Early onset sepsis is defined as bloodstream infection at less than or equal to 72h of age. It is generally associated with the acquisition of microorganisms from the mother and usually presents with respiratory distress and pneumonia.[1] The warning signs and symptoms are often subtle and non-specific and thus makes it difficult to establish an early clinical diagnosis. Vitamin D is a fat-soluble steroid hormone that contributes to the maintenance of normal calcium homeostasis and skeletal mineralization.[3]

Vitamin D also has immunomodulatory effects on immune function.[4] It was suggested that it might have a role in the optimal functioning of the innate immune system by inducing antimicrobial peptides, cathelicidin (LL-37) in epithelial cells, neutrophils and macrophages.[4,5] Newborns are more susceptible to infections as both innate and adaptive immune systems are not entirely developed. The relationship between vitamin D deficiency and infections, especially lower respiratory tract infections (RTIs), has been demonstrated in children and newborns.[6-8] The objective of this prospective study was to determine the possible

association between neonatal vitamin D deficiency and development of early onset sepsis in term neonates.

METHODS

This prospective observational study was conducted in the NICU of Sri Guru Ran Das Institute of Medical Sciences and Research, Sri Amritsar from December 2015 till December 2017. This study was conducted on 200 term neonates after seeking approval from the ethical committee of the institute and taking informed consent from the parents of patients. The study group consisted of 100 term neonates with clinical and laboratory findings suggestive of early onset sepsis infection admitted to NICU within the first three postnatal days of life who were >37 weeks of gestation. The control group consisted of 100 neonates with no signs of clinical and laboratory infection. Sera of all the neonates was subjected to testing for 25-OHD levels by Enzyme Linked Immune Sorbent Assay. Recent guidelines have defined vitamin d status as-US Endocrine Society classification: deficiency <20ng/ml (50nmol/l), insufficiency 21-29ng/ml (52.5-72.5nmol/l), sufficiency >30ng/ml (75nmol/l) and toxicity >150 ng/ml (to convert ng/ml into nmol/l a conversion factor of 2.5 needs to be multiplied with ng/ml (ng/ml x 2.5=nmol/l)).[9] A septic screen including total leukocyte count, absolute neutrophil count, blood smear evaluation, blood cultures and C-reactive protein (CRP) were performed in all neonates with suspected sepsis to corroborate EOS diagnosis. Gestational age, birth weight, sex, mode of delivery and birth season of all infants were also recorded.

Inclusion criteria

- The sepsis criteria used in the study defined by Gitto et al.[10] a) highly probable sepsis: at least three sepsis related clinical signs, CRP>5mg/dl, at least two other altered parameters in addition to CRP, blood cultures; positive or negative. b) probable sepsis: less than 3 sepsis-related clinical signs, CRP>5mg/dl, at least two other altered parameters in addition to CRP, blood cultures; negative. c) possible sepsis: less than 3 sepsis-related clinical signs, CRP<5mg/dl, less than 2 other altered parameters, blood culture; negative. d) nosepsis: CRP<5mg/dl, no altered parameters, blood cultures; negative.
- Sepsis related clinical signs: temperature instability, apnea, need for supplemented oxygen, need for ventilation, tachycardia/ bradycardia, hypotension, feeding intolerance, abdominal distension, necrotizing enterocolitis and seizures.
- Parameters: CRP, Other Than CRP: white blood cell count, absolute neutrophil count, platelet count and blood cultures.

Exclusion criteria

- Outborn admitted after 72hrs of life, major congenital abnormality, maternal clinical chorioamnionitis and premature rupture of membranes.

Statistical analysis

The data were statistically analyzed using the SPSS software, version 16. Comparative studies were done using a Student t-test and chi-square test (p-value <0.05 was considered significant).

RESULTS

In present study the control group consisted of 100 healthy, full term newborns. A total of 68 neonates (68%) were male and 32 (32%) were females in the control group (Table 1), with mean gestational age of 38.24±0.77 weeks and mean birth weight of 2.98±0.35kg. The study group consisted of 100 neonates with clinical and laboratory findings suggestive of early onset sepsis. In the study group, 62 (62%) were males and 38 (38%) were females (Table 1), with mean gestational age of 38.06±0.87 weeks and mean birth weight of 2.88±0.29kg.

Table 1: Gender wise distribution.

Gender	Cases		Control	
	No.	%	No.	%
Male	62	62.0	68	68.0
Female	38	38.0	32	32.0
Total	100	100.0	100	100.0

Out of total 100 cases with EOS, 78 (78.0%) cases belonged to rural and 22 (22.0%) to urban area. Out of total 100 controls, 77 (77.0%) control belonged to rural background and 23 (23.0%) to urban area (Table 2).

Table 2: Distribution according to rural/ urban background.

Rural/ urban	Cases		Control	
	No.	%	No.	%
Rural	78	78.0	77	77.0
Urban	22	22.0	23	23.0
Total	100	100.0	100	100.0

Out of total 100 cases with EOS, 31 neonates (31.0%) were born by NVD and 69 (69.0%) were delivered by LSCS. Out of total 100 healthy controls, 32 neonates (32.0%) were born by NVD and 68 (68.0%) were delivered by LSCS (Table 3). No significant difference was found between the two groups in terms of sex, birth weight, gestational age, rural/urban background and mode of delivery.

In present study it was found that out of total 100 neonates with EOS, 77 (77.0%) neonates had vitamin D deficiency (levels below 20ng/dL), 23 (23.0%) had insufficiency (levels between 20 and 30ng/dL) and none had sufficient (above 30ng/dL) levels.

Table 3: Distribution according to mode of delivery.

Mode of delivery	Cases		Control	
	No.	%	No.	%
NVD	31	31.0	32	32.0
LSCS	69	69.0	68	68.0
Total	100	100.0	100	100.0

Out of total 100 healthy controls, 41 (41.0%) had vitamin D deficiency, 28 (28.0%) had insufficient levels and 31 (31.0%) had sufficient (above 30ng/dL) levels. Mean serum vitamin D levels were significantly lower among cases (neonates with EOS) than controls (healthy neonates) (Table 4). The study also showed that the mean serum vitamin D levels in study group was lower than those of the control group (17.4ng/dL vs 26.8ng/dL; p=0.001). In present study authors found negative correlation between vitamin D level and CRP (r=-0.198, p=0.005).

Table 4: Distribution of vitamin D levels.

Vitamin D (ng/dL)	Cases		Control	
	No.	%	No.	%
Deficiency (<20)	77	77.0	41	41.0
Insufficiency (20-30)	23	23.0	28	28.0
Sufficiency (>30)	0	0	31	31.0
Total	100	100.0	100	100.0

DISCUSSION

Vitamin D deficiency has emerged as a significant health problem throughout the world. Even in Indian context, it has been reported to be present in majority of children in spite of wide availability of sunlight. In recent years, emerging evidence supports the immuno-modulatory effects of vitamin D on immune function as studied by Grant et al in 2009, Lee at al in 2009, and Braun et al in 2011.[11-13] Vitamin D was reported to have a complex effect on immune functions as it enhanced innate immunity while it also down regulated the acquired immune response. In addition to systemic inflammatory response modulation, vitamin D also has effects on the local control of pathogens. Vitamin D was reported to inhibit the growth of and/or killed strains of *Staphylococcus aureus*, *S. pyogenes*, *K. pneumoniae*, and *E. coli* as studied by Youssef et al in 2011.[14] Vitamin D also prevents direct invasion of pathogenic bacteria by enhancing the clearance of these invading organisms at sites such as respiratory tract as studied by Camargo et al.in 2011.[15]

In present study the control group consisted of 100 healthy, full term newborns. A total of 68 neonates (68%) were male and 32 (32%) were females in the control group, with mean gestational age of 38.24±0.77 weeks and mean birth weight of 2.98±0.35 kg. The study group consisted of 100 neonates with clinical and laboratory findings suggestive of early onset sepsis. In the study group, 62 (62%) were males and 38 (38%) were females, with mean gestational age of 38.06±0.87 weeks and mean birth weight of 2.88±0.29 kg. No significant difference was found between the two groups in terms of sex, birth weight and gestational age.

In present study it was found that out of total 100 neonates with EOS, 77 (77.0%) neonates had vitamin D deficiency (levels below 20ng/dL), 23 (23.0%) had insufficiency (levels between 20 and 30ng/dL) and none had sufficient (above 30ng/dL) levels. Out of total 100 healthy controls, 41 (41.0%) had vitamin D deficiency, 28 (28.0%) had insufficient levels and 31 (31.0%) had sufficient (above 30ng/dL) levels. Mean serum vitamin D levels were significantly lower among cases (neonates with EOS) than controls (healthy neonates). The study also showed that the mean serum vitamin D levels in study group was lower than those of the control group (17.4ng/dL vs 26.8ng/dL; p=0.001). Cetinkya et al in 2014 found a positive correlation between vitamin D deficiency and early onset sepsis.[16] Seliem et al in 2016 concluded that low neonatal vitamin D level was associated with EOS. The best cut off value of neonatal vitamin D for risk of sepsis was 14.4ng/dl.[17] Kanth et al in 2016 found that 25(OH)D levels in the study group were significantly lower compared with those in the control group. The majority (64.1%) of infants in the sepsis group had a mean 25(OH)D level >12ng/ml, which was statistically significant (p<0.05).[18] Gamal et al in 2017 found cut off values <20ng/dl for neonatal 25-OH vitamin D for detection of neonatal sepsis.[19] In two studies by Madden et al and McNally et al investigating the prevalence of vitamin D deficiency in critically ill children admitted to the pediatric intensive care unit, a high rate of vitamin D deficiency was present among critically ill children and was associated with greater severity of critical illness.[20,21] In contrary to present results, Aydemir et al reported that high serum 25-OH vitamin D levels are associated with pediatric sepsis, and this difference may be due to the age group and the different sample size.[22] In addition, Ratzinger et al reported that 1,25-OH D but not 25-OH D can predict bacteraemia and both of them failed to predict sepsis and mortality in a prospective cohort study, but this difference between present results and Ratzinger's may be attributed to the age group of patients, as all of Ratzinger's patients were above 41 years old, the different types of infections recruited in his study (respiratory, gastrointestinal (GIT), urological and central nervous system (CNS) infections), and, lastly, the methodology and the time for assay of vitamin D levels.[23]

In the present study, negative correlation was found between vitamin D level and CRP (r=-0.198; p=0.005). This is in agreement with the studies by Tao et al and Chen et al, who showed that vitamin D supplementation significantly decreased the circulating CRP levels. Liefaard et al also confirmed that serum vitamin D was inversely associated with CRP, but Grzanka et al did not observe any significant association between concentrations of 25(OH)D and CRP.[24-27] This may be

due to the small sample size and single assessment of 25(OH)D concentrations performed in the summer.

One of the limitations of study was that maternal vitamin D status during pregnancy was not included so authors could not assess the correlation among maternal and neonatal vitamin D status.

CONCLUSION

This study report significantly lower neonatal vitamin D levels in term infants with EOS compared to the healthy control who did not have sepsis. The current picture of vitamin D and sepsis in neonates is one of a research field early in its course with many important links that provide fertile ground for further investigation. Such investigation is warranted as vitamin D is inexpensive and safe to administer and even incremental benefits in the outcomes of sepsis may be enacted on a scale to produce a significant public health impact.

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