RESEARCH PAPER

Association of Early-Onset Sepsis and Vitamin D Deficiency in Term Neonates

POONAM SINGH AND VAISHALI CHAUDHARI

From Department of Pediatrics, Surat Municipal Institute of Medical Education and Research, Surat, India.

Correspondence to: Dr Vaishali Chaudhari, Department of Pediatrics, Surat Municipal Institute of Medical Education and Research, Surat, India. chaudharivaishali400@gmail.com
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Objective: To determine if vitamin D status is affected in term neonates with early onset sepsis and its association with outcome. **Methods:** Study was done at a level 3 neonatal unit on 140 neonates. Term neonates with early onset sepsis (study group, 70 patients) and without sepsis (control group, 70 patients) were enrolled. **Results:** Mean neonatal vitamin D level in the study group was 16.00 (10.49) ng/mL and in the control group, was 29.07(8.36) ng/mL (*P* =0.061). In the study group 80% (*n*=56) babies had low vitamin D levels (<32 ng/mL) among whom 51.7% (*n*=29) had severe vitamin D deficiency (<11ng/mL). In the control group, 58.5% (*n*=41) had low vitamin D levels of whom, 9.8% (*n*=4) had severe vitamin D deficiency (*P*<0.001 and *P*<0.001, respectively). Mortality and highly probable sepsis were more common with vitamin D levels <11ng/mL in the study group (*P*= 0.005 and *P*=0.006, respectively). **Conclusion:** Vitamin D is deficient in neonates with early onset sepsis and is associated with increased sepsis severity and mortality.

Keywords: *25-OHD, Deficiency state, Sepsis severity*.

Neonatal sepsis is an important cause of morbidity and mortality. It has been suggested that vitamin D might have a role in the optimal functioning of the innate immune system by inducing antimicrobial peptides in epithelial cells, neutrophils and macrophages [1,2]. Some studies suggest that vitamin D concentration in cord blood is associated with increased susceptibility to infections in newborns [3,4]. Some studies report a link between vitamin D deficiency and neonatal sepsis in term infants [5-8]. The present study was designed to assess the association of vitamin D deficiency and early onset sepsis in term babies.

METHODS

This prospective study was carried out in the NICU of a tertiary-care hospital between October, 2015 and September, 2016. Term neonates presenting within first 3 days of life with one or more of the following clinical features suggestive of sepsis were eligible for inclusion temperature instability, apnea, need for supplemented oxygen, need for ventilation, tachycardia/bradycardia, hypotension, feeding intolerance, abdominal distension, and necrotizing enterocolitis. Neonates with history of maternal clinical chorioamnionitis, premature rupture of membranes, and major congenital abnormalities were excluded. In all enrolled neonates, serum C-reactive protein (CRP), white blood cell count, absolute neutrophil count, platelet count and blood culture were done. Highly probable sepsis was defined as at least three sepsis-related clinical signs, CRP >1mg/dL, alteration in at least two other blood tests listed above, irrespective of any isolates in blood culture. Probable sepsis was defined as less than 3 sepsis-related clinical signs, CRP>1 mg/dL, at least two other altered serum parameters in addition to CRP, and blood culture negative. Possible sepsis was defined as less than 3 sepsis-related clinical signs, CRP <1 mg/dL, alteration in less than two blood tests listed earlier and no isolates in blood culture. Neonates not fulfilling any of the above criteria were considered as no sepsis (Control group). Informed consent was obtained from the parents/guardians prior to enrolment. All data was recorded in pre-designed structured proforma. The study was approved by the institutional ethics committee. Blood samples were also taken for measurement of 25-hydroxyvitamin D (25-OHD) levels. Blood samples were separated and stored at -80 ºC. Levels of 25-OHD were determined using ECLIA 411 Model with chemiluminescence system attached with ultraviolet detector. Vitamin D status was classified into three groups: Serum 25-OHD level <11ng/mL was severe deficiency, 11-32 ng/mL was insufficiency, and >32-100 ng/mL was adequate [10]. Complete blood count was performed using an automatic counter Sysmax. CRP was determined by CRP Kit by latex slide method with a detection limit of 0.6 mg/dL.

Statistical analysis: Data were analysed using . (SPSS,

WHAT THIS STUDY ADDS?

- Low vitamin D levels were found in term babies with early onset sepsis.
- Vitamin D-deficiency was associated with higher mortality in neonates with early onset sepsis.

version 20.0). The differences between groups were evaluated using chi-square test for qualitative data and t-test for independent sample for continuous data with normal distribution. ANOVA and Post Hoc test were other tests used. Values of P <0.05 were considered statistically significant.

RESULTS

During the study period, 1431 neonates were admitted to the neonatal care unit, the final study group had 70 with sepsis, while 70 neonates without sepsis formed the control group. The baseline neonatal profile, mean weight, gender and Apgar scores were comparable in both groups. Neonatal vitamin D level was lower in all seasons (winter, summer and monsoon) in the study group (P=0.02, 0.03 and 0.04, respectively). This level was lowest in monsoon season. In the study group, 56 (80%) babies had low vitamin D levels (<32ng/mL) and in the control group only 41 (58.5%) had low vitamin D levels (P<0.001) (***Table* I**). In the study group, mortality was higher in babies with vitamin D deficiency 15 (51.7%) as compared to babies with adequate level 1 (7%) (P=0.005) (***Table* II**). Most common pathogens found in blood culture of patients with neonatal sepsis were Coagulase negative Staphylococcus Aureus (21.42%), Klebsiella (12.86%), and Acinetobacter (10%).

DISCUSSION

This observational study showed that neonatal vitamin D (25-OHD) levels were significantly lower in term infants with early onset sepsis in comparison to babies without sepsis. Severity of vitamin D deficiency was also associated with increased mortality and degree of sepsis. An important limitation of the study was that the maternal vitamin D status was not evaluated.

In our study, mean vitamin D levels were lower in the sepsis group as compared to the control group. Cetinkaya, *et al*. [6] and Kanth, *et al*. [7] also found low vitamin D levels in neonates with sepsis. Some other studies also support the observation that lower maternal and neonatal vitamin D levels are associated with early onset sepsis [6-8]. Similar to our results, Cetinkaya, *et al*. [6] found larger proportion of neonates in sepsis group having severe deficiency as compared to the control group [7]. As reported by previous researchers [6,7], we found that severe neonatal vitamin D deficiency was associated with higher severity of sepsis, higher mortality and culture positivity.

We conclude that vitamin D is deficient in neonates with early onset sepsis and is associated with increased sepsis severity and mortality.

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Contributors; PS: conceived the study, conceptualized study design, supervised data collection and analysis, and reviewed the intellectual outcome: drafted and critically revised the manuscript; VC: prepared study design, carried out the study, enrolled patients, collected

Table I Profile of Neonates in the Study

Variables	*Study group (n=70)*	*Control group (n=70)*
Birthweight, g *	2640 (480)	2580 (370)
Male, n (%)	43 (61)	40 (57)
Apgar 1min #	9 (9-10)	9 (9-10)
Apgar 5 min #	9 (9-10)	10 (9-10)
Vitamin D level (ng/mL)*	16.0 (10.5)	29.07 (8.4)
#Vitamin D‡		
<32 ng/mL, *n* (%)	56 (80)	41 (58.5)
<11 ng/mL, *n* (%)	29 (51.7)	4 (9.8)

**mean (SD), # median (IQR); ‡P<0.001.*

Table II Association Between Vitamin D Status and Outcome Among Neonates in the Study Group (*N*=70)

Variable	*Deficiency n =29 (%)*	*Insufficiency n=27 (%)*	*Adequate n=14 (%)*
*Death	15 (51.7)	1 (3.7)	1 (07)
Culture positive	19 (65.5)	8 (29.6)	5 (35.7)
**Sepsis*			
Possible	07 (24.1)	10 (37)	7 (50)
Probable	04 (13.8)	12 (44.4)	3 (21.4)
Highly probable	18 (62.1)	5 (18.6)	4 (28.6)

***P<0.01; All values in No. (%); deficiency and insufficiency defined as serum vitamin D levels <11 ng/mL and 11-32 ng/mL, respectively.*

data and prepared result: collected data, data analysis and drafted the manuscript. All authors have reviewed and approved of the final draft of the paper. Dr Poonam Singh will act as guarantor for the paper.

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