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Original article

Impact of serum level of vitamin D on term neonates with early onset sepsis

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Background: Neonatal sepsis a major health challenge associated with major morbidity and mortality. Neonatal care improved recently. However, different challenges regarding management still exist. Vitamin D deficiencies was proposed as a predictor of neonatal sepsis.

Objective: To highlight the impact of vitamin D levels on early onset sepsis in full term neonates.

Methodology: This is a case control which carried out at the neonatal intensive care unit of Al-Azhar university hospital (Damietta), from March to April 2019. It included 50 full-term neonates with probable sepsis and 50 healthy controls of matched age and sex with no signs of sepsis.

Results: vitamin D level showed significant negative correlation with sepsis, C-reactive protein (CRP), positive blood cultures; and significant positive correlations with Apgar score, hemoglobin concentration and platelets count. Regression analysis revealed that, higher CRP and lower vitamin D were associated risks of neonatal sepsis in univariate analysis. Multivariable regression analysis revealed that only lower vitamin D level is the predictor for early neonatal sepsis.

Conclusions: Vitamin D levels were significantly lower in septic neonates with high sensitivity and specificity. Vitamin D supplementation to mothers during pregnancy could prevent early onset neonatal sepsis.

Keywords: Vitamin D; Neonates; Sepsis; Full term; Neonatal sepsis.

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Introduction

Neonatal sepsis is a clinical syndrome affecting neonates in their first month of life with characteristic signs and symptoms of infection with or without bacteremia^[1]. Early onset neonatal sepsis (EOS) is a characteristic subtype of neonatal sepsis defined according to disease onset, with bacteremia or bacterial meningitis occurring at ≤ 72 hours in preterm neonates admitted to neonatal intensive care unit (NICU), and in term neonates in must be occurred before 7 days^[2]. Sepsis is still one of the responsible etiologies of neonatal morbidity and mortality all over the world in spite of technological developments in neonatal health care units^[3]. In Egypt, the incidence of neonatal sepsis in South Sinai Governorate hospitals was 8.6% in the NICUs and mortality rate among septic neonates (sepsis fatality rate) was about 25%^[4]. The discovery of vitamin D receptors (VDR) in different immune cells (e.g., B cells, neutrophils, T cells, macrophages and dendritic cells) was associated with elucidation of the important role of vitamin D in the human health. These cells are responsible for both innate and adaptive immune responses to pathogens^[5]. Optimal vitamin D supplementation for pregnant mothers is usually associated with protective effects against neonatal and maternal morbidities^[1]. In addition, reduced maternal and neonatal vitamin D values are usually associated with early neonatal sepsis. These data proposed that optimal vitamin D supplementation for pregnant mothers may be helpful in prevention of early neonatal sepsis in full-term neonate^[6].

Aim of the study

To highlight the impact of vitamin D level on early onset sepsis in term neonates.

Patients and Methods

The study is a case control which carried out at the neonatal intensive care unit of Al-Azhar university hospital (Damiatta), starting from March to April 2019. The study included 50 term neonates with high probable or probable sepsis and 50 healthy controls of matched age and sex with no signs of sepsis according to Gitto *et al.*^[7]. Inclusion criteria included; full-term neonates with manifestations of neonatal sepsis, of both genders, during the first 72 hours, with perinatal history of premature rupture of membranes (PROM), pre-eclampsia and eclampsia. Neonates with multiple congenital anomalies, other cause of decreased vitamin-D levels such as infant of diabetic mother (IDM), and neonates need resuscitation were excluded from the study. The aim

of the study was explained to the guardians and an informed consent was taken. In addition, privacy of all data was assured. All the newborns in the study were subjected to full history taking, complete clinical examination, laboratory investigations (complete blood count, CRP, arterial blood gases (ABGs), blood culture, measurement of serum level of vitamin-D by ELISA. Levels < 12 ng/ml was deficient, 12-20 ng/ml are insufficient and 21-150ng/ml are sufficient.

Statistical analysis: Data were prepared, documented and analyzed by the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Arithmetic mean and standard deviation (SD) were calculated for numerical variables, while frequency and percentages were calculated for qualitative variables. Student (t) test was used to compare between two means, while Chi-square (χ^2) test of significance was used in order to compare proportions between two qualitative variables. The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant if (P-value < 0.05).

Results

The study was conducted on 50 full term neonates admitted with sepsis. Their mean age was 2.2 days. They were 17 males (34%) and 33 females (66%). In addition, 50 healthy control group of matched age and gender were included as well. Feeding by breast and mixed feeding routes were statistically significant associated with healthy neonates, while artificial route was statistically significant associated with septic cases. No statistically significant differences were found in weight, length and head circumference between cases and control groups (Table 1). In addition, leukocytosis, thrombocytopenia, high I/T ratio, high CRP, higher ANC were statistically significant associated with septic cases when compared to control groups. Furthermore, there was statistically significant lower frequency of sufficient, statistically significant higher frequency of insufficient and deficient vitamin D status frequency when compared to control groups. Also, vitamin D level was significantly lower in septic cases when compared to control group (table 2).

Comparing insufficient to deficient neonates, deficiency in vitamin D was associated with older age (2.4 ± 0.6 vs 1.9 ± 0.8 in deficient versus insufficient subgroups respectively) and history of mother's vitamin D intake was significantly decreased in deficient when compared to insufficient subgroups (7.7% vs 41.7% respectively).

ROC curve of serum vitamin D was conducted for discrimination between septic and control groups. AUC was 0.907, and at cut off value of 18.75ng/ml, sensitivity was 100%, specificity was 80%, PPV was 83.3%, NPV was 100% and accuracy was 90%. In addition, for differentiation between PRS and HRS, the AUC was 0.881, and at cut off value of 18.3 ng/ml, the sensitivity was 100%, specificity was 66.7%, PPV was 93.2%, NPV was 100% and accuracy was 94% (table 3).

In all studied subjects, vitamin D level showed significant negative correlation with occurrence of sepsis, CRP, positive blood cultures; significant positive correlations with Apgar score, hemoglobin concentration and platelets count. On the other hand, vitamin D level showed significant negative correlation with HPS and age.

Regression analysis was conducted for prediction of sepsis within healthy term neonates, using age, gender, CRP and vitamin D level as covariates. Higher CRP and lower vitamin D were associated risk of neonatal sepsis in univariable analysis. Taking significant risk factors in univariable into multivariable analysis revealed that only lower vitamin D level was bad predictor for early neonatal sepsis (table 4). Regression analysis was conducted for prediction of HPS within septic neonates, using age, gender, CRP and vitamin D level as covariates. Higher CRP and lower vitamin D were associated risk of HPS in univariable analysis. Taking significant risk factors in univariable into multivariable analysis revealed that only lower vitamin D level was bad predictor for HPS within septic neonates (table 5).

Table (1): Comparison between case and control groups regarding socio-demographic data, anthropometric measures.

Variables		Control N=50	Cases N=50	P
Age (days)mean(±SD)		2.2 (±0.7)	2.2(±0.8)	0.893
Gender: Male (N, %)		24(48%)	17 (34%)	0.155
Female (N, %)		26(52%)	33(66%)	
Mean gestation (weeks)		38.2 (±0.9)	38.1(±0.9)	0.404
Mean Weight (kg)		2.9 (±0.3)	2.9 (±0.3)	0.773
Mean Length (cm)		47.2(±1.3)	47.7 (±1.6)	0.064
Mean HC(cm)		34.1(±1.1)	33.9(±1.1)	0.663
Mode of delivery	CS	41(82%)	46 (92%)	0.137
	NVD	9(18%)	4 (8%)	
Exclusive breast		27 (54%)	0 (0%)	<0.001*
Artificial		9 (18%)	49 (98%)	
Mixed feeding		14 (28%)	1(2%)	

NVD= Normal vaginal delivery, CS= caesarian section, HC=Head circumference; * Significant.

Table (2): Comparison of laboratory data between cases and control groups.

Variables N (%)		Control N=50	Cases N=50	P
Hb.	Non Anemic	50 (100%)	28 (56%)	<0.001*
	Anemic	0(0%)	22(44%)	
WBCs	Normal	50(100%)	13 (26%)	<0.001*
	leucopenia	0(0%)	3 (6%)	
	leukocytosis	0(0%)	34 (68%)	
Platelets	Normal	50 (100%)	20(40%)	<0.001*
	Thrombocytopenia	0(0%)	26(52%)	
	Thrombocytosis	0 (0%)	4(8%)	
I/T ratio	<0.2	50 (100%)	47 (94%)	<0.001*
	>0.2	0(0%)	3 (6%)	
CRP	≤ 6	50(100%)	8 (16%)	<0.001*
	>6	0(0%)	42 (84%)	
Absolute neutrophil count mean(±SD)		19.6 (±6.5)	43.4(±12.6)	<0.001*
Vitamin D status	Sufficient	37 (74%)	0 (0%)	<0.001*
	Insufficient	11 (22%)	24 (48%)	
	Deficient	2 (4%)	26 (52%)	
Vitamin D-Levels (ng/ml) (mean±(SD))		25.7 (±8.1)	14.2 (±3.4)	<0.001*

Hb: hemoglobin, WBCs: white blood cells; CRP: C reactive protein; I/T: immature/total neutrophil ratio

Table (3): sensitivity of vitamin D in diagnosis of sepsis and discrimination between probable sepsis (PRS) and high probable sepsis (HRS)

	Sepsis vs control	PRS vs HRS
AUC	0.907	0.881
95% CI	0.846-0.968	0.737-1.00
P	<0.001*	<0.001*
Cut off	18.75	18.3
Sensitivity (%)	100	100
Specificity (%)	80	66.7
PPV (%)	83.3	93.2
NPV (%)	100	100
Accuracy (%)	90	94

AUC: area under ROC curve; PPV, positive predictive value; NPV, negative predictive value.

Table (4): Regression analysis for prediction of sepsis within healthy term neonates.

	Univariable			Multivariable		
	p	OR	95% CI	p	OR	95% CI
Age	0.892	0.977	0.700-1.365			
Gender	0.155	1.440	0.871-2.381			
CRP	0.017	1.007	1.001-1.013	0.255	1.004	0.997-0.011
Vitamin D level	<0.001	0.866	0.822-0.912	0.043	0.977	0.955-0.999

OR, odds ratio; CI, confidence interval; logistic regression test was used.

Table (5): Regression analysis for prediction of HPS within septic neonates.

	Univariable			Multivariable		
	p	OR	95% CI	p	OR	95% CI
Age	0.503	1.192	0.713-1.992			
Gender	0.405	0.679	0.272-1.692			
CRP	0.045	1.028	1.001-1.056	0.148	1.021	0.993-1.051
Vitamin D level	0.005	0.777	0.653-0.925	0.012	0.792	0.661-0.950

OR, odds ratio; CI, confidence interval; logistic regression test was used.

Discussion

During infancy, it had been reported that, lower values of cord blood 25-OH vitamin D had been associated with higher incidence of sepsis in the first year of life and available data proposed that 25-OH vitamin D deficiencies may predict the occurrence of sepsis and/or increased mortality rate in critically ill neonates, and vitamin D deficiency is strongly correlated with positivity of blood culture^[8]. The explanatory mechanism is that disturbances in the function of macrophage and the production of pro-inflammatory cytokines may occur in 25-OH Vitamin D deficiency^[9-11].

The aim of the present work was to highlight the impact of vit D levels on early onset sepsis in term neonates.

In our study there were 17males (34%) and 33 females (66%) with female predominance compared to male: female ratio of 1.1: 1 in study of Aye *et al.*^[12], and 1.32: 1 in Ye *et al.*^[13]. In addition, results of the present work revealed non-significant difference between study and controls as regard to sex distribution and this agrees with Maamouri *et al.*^[14] and Schlapbach *et al.*^[15]. The mean age of neonates in the study group was 2.2 (± 0.8), that agrees with the

Fattah *et al.*^[16] who found that mean (\pm SD) age was 2.6 (± 2.1) days, and results of the present study agree with Rass *et al.*^[17] who found no significant difference between control and sepsis groups regarding postnatal age.

Results of the present study also are comparable to Schlapbach *et al.*^[18] who found that the mean gestational age 39 ± 0.4 weeks (38.1 ± 0.9 weeks in the present one), and agrees with Rass *et al.*^[17] who found out that there was no significant difference between the sepsis and control group regarding the gestational age.

Apgar score was significantly low in sepsis when compared to control groups, which agrees with Schlapbach *et al.*^[15].

The commonest mode of delivery was cesarean section (92%) which higher than the results obtained by Gamal *et al.*^[19] who found that, CS was 72%. However, the results of the current study agree with Aye *et al.*^[12] who found no significant difference between cases and controls regarding mode of delivery. In the contrary, Prashant *et al.*^[20] found out that caesarian section as significantly higher in the control group. Also, Masood *et al.*^[21] found that out of sepsis group, 74% of neonates were delivered normally and 26% were delivered by CS. Masood *et*

al.^[21] explained that, some environmental variables such as polluted environment and inexperienced staff, were accountable for neonatal sepsis in normal vaginal delivery. Wilmsink *et al.*^[22] found a higher percentage of sepsis in elective cesarean section with gestational age less than 39 weeks.

Regarding medical illness (Preeclampsia) there was no significant difference between both groups which agrees with the results of Say *et al.*^[23].

In the current work, less maternal vitamin D intake was statistically significant associated with septic neonates. Cetinkaya *et al.*^[11] has shown that, low maternal and neonatal vitamin D values were associated with early onset neonatal sepsis. Cizmeci *et al.*^[10] emphasized that the maternal and cord blood vitamin D levels were significantly low in the babies who have EOS.

The most common presentation (hypotension and pallor) were significantly higher in cases when compared to controls. El-Din *et al.*^[3] found that the most common causes of admission to NICU were respiratory distress (46.7%) and pneumonia (7.8%), while Abd Elmoutaleb *et al.*^[24] detected that the most presenting signs was respiratory distress (70%).

We found a statistical significant difference in most CBC indices (Hemoglobin, WBCs, and platelets) between cases and controls. Absolute neutrophil count was significantly increased in patients' group. Saleh *et al.*^[25] detected no significant difference between case and control group regarding HB level; but, platelet count was significantly decreased. Rass *et al.*^[17] found a significant difference sepsis and healthy groups regarding RBCs, PLT, WBC, neutrophil and CRP. In addition, Gamal *et al.*^[19] studied 50 neonates with EOS and reported significant decrease of hemoglobin.

CRP was significantly increased in study when compared to control group. This agrees with the study done by Fattah *et al.*^[16]. Some trials proposed that, CRP is still a significant, sensitive, and specific predictor for sepsis. However, it had a low sensitivity during the early phases of sepsis as it needs time for release (about 6 hours). Serial measurements improve its sensitivity and are useful for assessing the response to medical therapy^[26]. Results of the present work also in line with Pessar^[27] and El-Sonbaty *et al.*^[28].

Neonates with sepsis had lower vitamin D than controls. Aye *et al.*^[12] stated that in early onset sepsis group, all 40 cases of serum 25-hydroxyvitamin D levels were deficient compared to 65% of controls, and there was no significant difference between neonates with insufficient and deficient vitamin-D regarding results of culture

growth, as in the present work. In addition, CRP was inversely correlated with Vitamin D as in the study done by Tao *et al.*^[29]. Vitamin D was proposed to impede both Gram-positive and Gram-negative bacterial growth^[30], and induces release of antimicrobial proteins like β -defensin in cells of the innate immune system^[31].

In conclusion, Vitamin-D levels were significantly reduced in septic neonates, and associated with inflammatory markers. Vitamin-D supplementation to pregnant mothers may play a role in prevention of early neonatal sepsis.

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