DOI: 103126/JNPS.V4113

Original Article

Role of Vitamin D Therapy in Recovery from Early Onset Neonatal Sepsis – A Randomized Controlled Trial

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Article History
Received on - 2023 Dec 13
Accepted on - 2024 Sep 29

Keywords:
Early-onset neonatal sepsis; Full term; Vitamin D; 25(OH)D.

Online Access

DOI: https://doi.org/10.60086/jnps1231

Abstract

Introduction: Neonatal sepsis is a major cause of morbidity and mortality in neonates. Significant association has been shown between vitamin D deficiency and sepsis. Our objective is to compare two different regimens (400 IU / day versus 800 IU / day) of oral vitamin D supplementation in full term neonates with early-onset sepsis (EOS).

Methods: A randomized controlled trial comprising of 66 full term neonates with EOS were included. We excluded preterm neonates on NPO, and neonates with maternal risk factors, or with major congenital abnormalities. All patients were assessed according to Newborn Scale of Sepsis. Neonates were randomly assigned into three groups; group A and group B who received oral 400 IU / day, 800 IU / day of vitamin D3 respectively and group C who didn't receive any vitamin D supplementation. Serum concentrations of 25-OH vitamin D were measured at enrolment and on recovery.

Results: The mean serum level of 25-OH vitamin D in all 66 newborns with early onset sepsis included in the study was 18.12 ± 3.6 ng / ml and it was considered insufficient. Of all the enrolled infants, 78.8% were vitamin D-insufficient. The study shows significant relation between the mean of serum vitamin D on recovery and vitamin D supplementation to the newborns. We found significant difference in mean age of recovery between group B and group C.

Conclusions: Vitamin D supplementation has a role in the survival of full term neonates suffering from sepsis and decrease the duration of hospital admission.

Introduction

Sepsis is a deregulated host response to infection leading to life-threatening organ dysfunction.[1] Sepsis is classified according to the infant's age at the onset of symptoms: early and late onset sepsis.[2] Early and late neonatal septicaemia are the most common problems in the newborn stage that causes high morbidity and mortality rate. Early-onset sepsis is defined as the onset of symptoms before seven days of age, although some experts limit the definition to infections occurring within the first 72 hours of life.[3]

Sepsis is responsible for 30 - 50% of neonatal deaths in developing countries, according to WHO estimates.[4] Significant associations have been shown between vitamin D deficiency and respiratory tract infections and sepsis.[5] It has been well established that low levels of circulating 25-OH vitamin D have been shown to be strongly

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associated with infections. Vitamin D has immunomodulatory effects on immune function.[6] Although the mechanism of 25-OH Vitamin D on enhanced immunity is complex, it might have an important role in the optimal functions of the innate immune system by inducing antimicrobial peptides in epithelial cells, neutrophils and macrophages.[6] Vitamin D potentially regulates many other cellular functions.[7] 25-hydroxyvitamin D (25[OH] D) is the major circulating form of Vitamin D.[8] The Vitamin D receptor (VDR) is almost universally expressed in nucleated cells.[7]

The aim of our study is to assess the status of vitamin D levels in full term with EOS, and the role of the vitamin D supplementation in recovery from neonatal sepsis.

Methods

This is a randomized controlled trial (RCT) conducted on 66 full term newborns with clinical and laboratory findings of EOS and admitted to the Neonatal Intensive Care Unit of Children's Hospital, Ain -Shams University and the NICU of El- Ahrar Teaching Hospital in Zagazig from January 2018 to January 2020. Using PASS program, setting alpha error at 5% and power at 80%, we calculated the sample size. Assuming that NICU duration for placebo, 400 IU vitamin D and 800 IU vitamin D respectively is 7 ± 2.5, 5.5 ± 2.5, 4 ± 2.5, based on this, the needed sample is 20 cases per group (total 60). The research has been reviewed and accepted by The REC (Research Ethics committee) of AUS (Ain Shams University) and received a number FMASU MD 438 / 2017 on 13 December 2017. An informed consent was taken from the parents or legal guardian of the newborns before participating in the study. We included full term newborns with clinical and laboratory findings of early onset of sepsis (EOS). Preterm neonates, NPO neonates, infants with maternal risk factors, such as chorioamnionitis, neonates delivered at home, neonates to mothers with premature rupture of membrane, and major congenital abnormalities were excluded. We excluded the cases with mortality only in the recovery sample but they were included in the initial sample as seen in Table 1 (6 cases who died before completion of the study and didn't reach recovery). Detailed history was taken from all the mothers of neonates in the study. The history emphasizing on vitamin D supplementation to the mothers during pregnancy, sun exposure in mothers during pregnancy and dietetic history according to the National Nutrition Institute guidelines were noted.[9] Detailed examination of the study population was done. Subjects were classified into three groups: Group A - (Conventional dose Vitamin D) (21 cases of which one case died) those neonates who received oral Vitamin D of 400 IU , Group B - (Higher dose Vitamin D) (22 cases of which two died) - Oral dose of vitamin D of 800 IU, and Group C (Placebo group) (23 cases of which three neonates died) - who did not receive any vitamin D supplementation. Clinical evaluation of all newborns for signs of neonatal sepsis was done. Any neonate with a total clinical score greater than 10 was considered sick. The duration of hospital admission and recovery age for all were recorded. Venous blood samples were taken for complete blood count (CBC) with differential counts [(Haemoglobin (HB), platelet count, total WBC count, absolute neutrophil count (ANC), Immature : Total neutrophil ratio (I: T) by manual method were noted. C-reactive protein (CRP) was calculated by CRP latex reagent, (Genesis Lab for diagnostic reagents, EGYPT) and blood culture (Spectrum, Egyptian Company for Biotechnology (S.A.E) were done. Serum 25 (OH) vitamin D levels was measured by Human Vitamin D ELISA Kit (Qualpro diagnostics, INDIA) on the first day of sepsis. 25 (OH) vitamin D levels were classified according to the guidelines of the Endocrine Society as sufficient > 20 ng / ml (> 50 nmol / l), insufficient – 12 - 20 ng / ml (30 - 50 nmol / l), deficient < 12 ng / ml (< 30 nmol / l). Re-evaluation of serum vitamin D levels for all patients on recovery (recovery was assessed by Newborn Scale of Sepsis to be less than 10). Serum Ca and P were measured initially for all patients upon diagnosis of EOS, and on discharge or recovery. All patients were initially assessed according to Newborn Scale of Sepsis. A total clinical score less than 10 indicated that the newborn did not have sepsis - a negative predictive value of 97%. Any neonate with a total clinical score greater than 10 was considered ''sick,'' possibly with sepsis. A clinical score greater than 10 is also an indicator of the need for further diagnostic evaluation.[10] Patients were matched regarding sepsis score. All three groups were treated using protocol of sepsis treatment used in Ain- Shams University Neonatal Intensive Care Unit. Statistical analysis was performed using SPSS statistical software (version 20). Parametric continuous variables were expressed as mean ± standard deviation, nonparametric continuous variables were expressed as median (interquartile range), and categorical variables were expressed as number (%). Student t-test or ANOVA test were used to compare continuous parametric variables; Chi-square test was used for categorical variables, when appropriate. Correlation analysis was used to detect the relation between vitamin D and other variables. ROC analysis of vitamin D level was done to predict death. A p-value of < 0.05 was considered to be statistically significant.

Results

The mean serum level of vitamin D in all 66 newborns with early onset sepsis included in our study was 18.12 ± 3.6 ng / ml and it was low and considered insufficient. Comparing the three groups; the mean age of neonates in group A was 4.29 ± 1.8 days, in group B 3.27 ± 1.4 days, while in group C was 4.39 ± 1.8. There was a significant difference between surviving and mortality cases with regards to initial vitamin D level. All mortality cases had insufficient vitamin D level, while 32.3% of surviving cases (14 cases) had sufficient vitamin D and 76.6% had insufficient vitamin D level (46 cases), with a p-value = 0.003. As shown in Table 1, there

was no significant difference in the neonatal scale of sepsis between the three groups; where it was 19.4 ± 2.7 in group A, 19.36 ± 3.8 in group B, and 21.21 ± 3.2 in group C, with a p- value 0.117. Also, there was no significant correlation between maternal vitamin D supplementation and initial vitamin D level in the neonates (p–value = 0.414). There was no significant difference between the three groups regarding initial CBC, I / T ratio, CRP, with a p-value = 0.935, 0.990, 0.727 respectively. But we noticed that the mean ± SD of CRP is higher in neonates with insufficient vitamin D level (Mean ± SD = 28.2 ± 32.4 and 33.2 ± 27.3 with p value 0.727 in sufficient and insufficient vitamin D respectively). As for serum calcium and phosphorus after vitamin D supplementation, there was no significant difference between three groups; p-value = 0.355 and 0.16 respectively. As regards to blood cultures there were 11 (16.6% from total) positive blood cultures, nine (81.8%) of them had insufficient initial serum vitamin D, and two (18.2%) had sufficient initial vitamin D level.

As shown in Table 2, the mean vitamin D level on recovery was significantly higher in Group A and Group B compared to Group C who didn't receive any vitamin D supplementation with p- value = 0.022. The study shows significant relation between the mean serum vitamin D level on recovery and the regimen of oral vitamin D supplementation to the newborns, where 55% of the patients in group A became sufficient on recovery and 75% of the patients of group B became sufficient on recovery, while only 25% of neonates in group C (receiving no vitamin D supplementation) became sufficient in vitamin D on recovery, as shown in Table 3, with p- value = 0.006.

Mean age of recovery in studied neonates in group A, group B and group C was (Mean ± SD) 10.4 ± 3.6, 8.7 ± 3.2 and 11.3 ± 3.8 respectively with significant difference in age of recovery between group B and group C, where recovery occurred at mean age of 8.7 ± 3.2 days in group B while it occurred at mean age of 11.3 ± 3.8 in group C (with p-value 0.024). None of the infants enrolled in the study had signs of vitamin D toxicity or serum levels exceeding 80 - 100 ng / ml upon recovery. Duration of hospital admission in group A, group B and group C was (mean ± SD) 6.1 ± 2.8, 5.5 ± 2.7 and 7.1 ± 3.5 respectively, with a p- value 0.28. However, the shortest duration of hospital stay was in group B. There was significant correlation between initial vitamin D level and neonatal scale of sepsis as shown in Table 4. ROC analysis revealed that vitamin D cut off value of 14.83 was able to detect dead cases with an area under curve of 91.7% sensitivity of 50% specificity and p-value > 0.05 as shown in Figure 1.

Table 1: Initial serum vitamin D levels in the different groups and NSS

Initial Vit D	Group A (400 IU vit D) (N = 21)	Group B (800 IU vit D) (N = 22)	Group C (Placebo) (N = 23)	Total (66)	P- value
Sufficient	6 (28.6%)	7 (31.8%)	1 (4.3%)	14 (21.2%)	0.04
Insufficient	15 (71.4%)	15 (68.2%)	22 (95.7%)	52 (78.8%)	
Mean ± SD	18.76 ± 5.18	18.24 ± 3.41	17.43 ± 1.93		
NSS (Mean ± SD)	19.4 ± 2.7	19.36 ± 3.8	21.21 ± 3.2		0.117

Table 2: Vitamin D on recovery in the three groups among surviving cases

	Group A (400 IU vit D) (N = 20)	Group B (800 IU vit D) (N = 20)	Group C (Placebo) (N = 20)	Total (60)
Mean ± SD	22.08 ± 6.3	22.9 ± 4.5	18.95 ± 1.9	0.022*

Table 3: Comparison between the three groups regarding serum vitamin D levels on recovery

	Group A (400 IU vit D) (N = 20)	Group B (800 IU vit D) (N = 20)	Group C (Placebo) (N = 20)	Total (60)
Sufficient	11 (55%)	15 (75%)	5 (25%)	0.006*
Insufficient	9 (45%)	5 (25%)	15 (75%)	

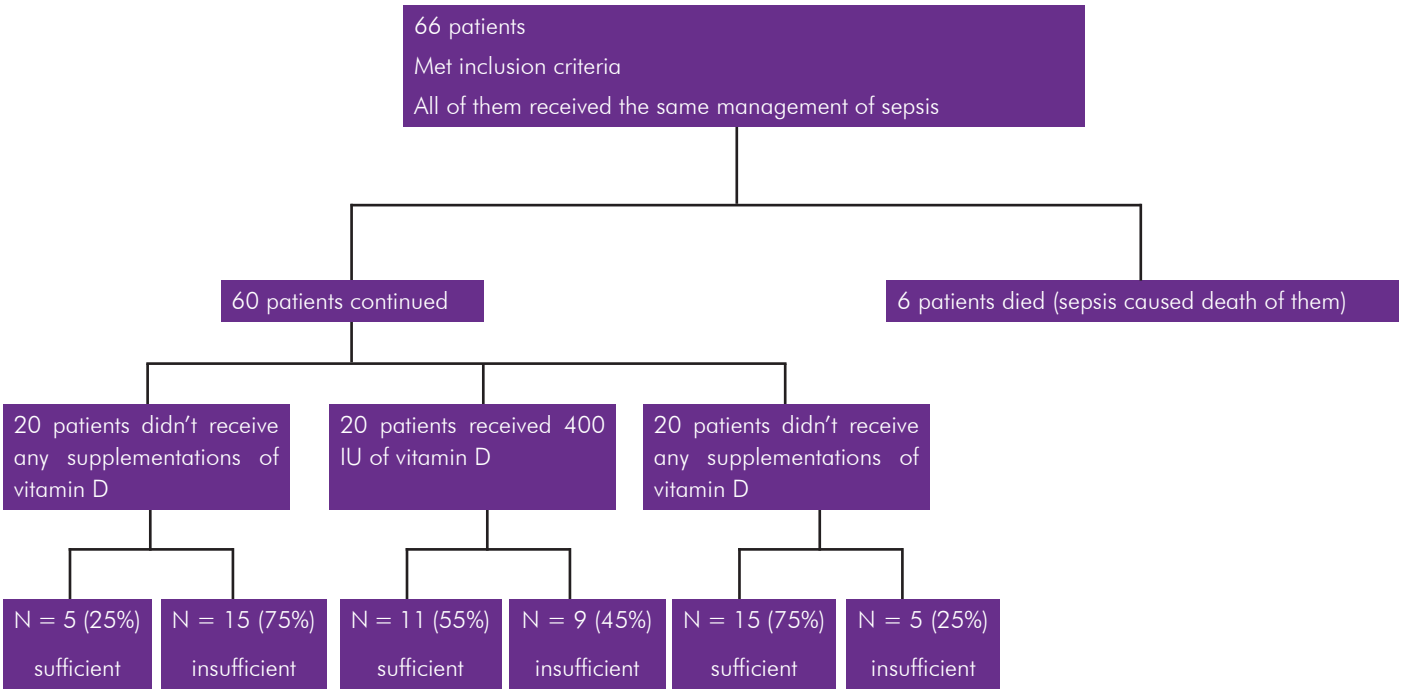

Figure 2: Flow chart of the role of Vitamin D therapy in recovery from EOS

Table 4: ROC analysis of vitamin D level as prediction of mortality

Area	Std. Errora	Asymptotic Sig	Asymptotic 95% Confidence Interval		Cut off	Sensitivity	Specificity
			Lower Bound	Upper Bound			
0.704	0.118	0.101	0.472	0.936	14.83	91.7%	50%

Roc analysis revealed that vitamin D cut off value of 14.83 was able to detect dead cases with an area under curve of 91.7% sensitivity of 50% specificity and p-value > 0.05.

Table 5 : Correlation between initial vitamin D level and other parameters

	R	p
NSS	0.234	0.05*
Duration of hospital admission (Days)	0.048	0.717
Hb (mg / dl)	0.038	0.776
Hct%	0.029	0.818
TLC (10^3 / cmm)	0.212	0.088
Neutrophil count (10^3 / cmm)	0.210	0.091
Platelet count (10^3 / cmm)	0.200	0.107
I/T ratio	0.029	0.819
CRP	-0.035	0.778
Ca (mg / dl)	-0.398	0.001*
Ph (mg / dl)	0.041	0.740
Age (days)	-0.088	0.483
Temp (°C)	-0.009	0.946
Pulse (Beat / min)	0.113	0.367
RR (Respiratory rate)	0.061	0.625
SDS wt	-0.055	0.629
Wt (kg)	-0.034	0.785
Length (cm)	-0.017	0.890
SDS Ht	-0.055	0.659

Discussion

Vitamin D deficiency is considered a worldwide public health problem with a high prevalence in all paediatric age groups. Vitamin D status is evaluated by the level of circulating 25-hydroxy D {25(OH) D} as the best-accepted marker.[10] Various studies have revealed that vitamin D and its

metabolites are related to several illnesses, including cancer, diabetes, asthma and sepsis. Since the innate immune system of neonates are not fully developed, they are more susceptible to various infections.[11] It has been reported that, lower values of cord blood 25-OH vitamin D have been associated with higher incidence of sepsis in the first year of life. 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.[12] Vitamin D also prevents direct invasion of pathogenic bacteria by enhancing the clearance of these invading organisms as studied by Camargo et al.[13]

In a study by Workneh Bitew et al,[14] the pooled prevalence of vitamin D deficiency among all neonates was 61%. The prevalence was significantly higher (79.4%) among neonates with sepsis as compared to neonates without sepsis (43.7%). This finding was relatively lower than a study conducted in India, where the prevalence of vitamin D deficiency among neonates with sepsis was 91.7% and 86.7% in the control group (sepsis-free neonates).[15] The possible elucidation for the discrepancies could be associated with sample size differences, geospatial variations, and differences in the study setting of the original studies. Jeengar et al[16] had published that vitamin D was significantly lower in the neonates with EOS (18.50 ± 7.4 ng / ml). In our study, the mean serum level of vitamin D in all 66 newborns with early onset sepsis was 18.12 ± 3.6 ng / ml, which was considered insufficient. Cetinkaya et al[12] noted that a mean vitamin D level of 8.6 ng / ml in term newborns with EOS, as compared with 19 ng / ml in the control group, and a positive correlation between vitamin D deficiency and EOS. Singh et al reported[17] found that in the study group 80% of babies (N = 56) had low vitamin D levels (< 32 ng / mL) among whom 51.7% (N = 29) had severe vitamin D deficiency (< 11 ng / 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).

Several studies have shown significant positive correlation between maternal and neonatal 25(OH)D levels and positive effect of vitamin D supplementation on neonatal 25(OH)D level.[12,18] Whereas in this study, non-significant correlation was found between maternal vitamin D supplementation and neonatal vitamin D level.

In our study, we observed an increase in the mean CRP level in insufficient vitamin D level cases, in spite of insignificant correlation. After vitamin D supplementation, there was no apparent difference between the three groups in CRP. Gamal et al[19] had noticed significant negative correlations between neonatal 25(OH)D levels and CRP (r = −0.75, P < .001) and Kumar et al[20] found negative correlation between vitamin D levels and CRP (r = -0.198; p = 0.005). Vitamin D has immunomodulatory effects on immune function. 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.[6] This is in agreement with the study by Tao et al[21] who showed that vitamin D supplementation significantly decreased the circulating CRP levels, but Grzanka et al[22] did not observe any significant association between concentrations of 25(OH)D and CRP. This may be due to the small sample size only 35 patients and single assessment of 25(OH)D concentrations.

Cetinkaya et al[12] observed no significant difference in neonatal 25(OH)D level in infants with or without culture proven sepsis among cases (P = 0.25). In our study, 11 (16%) neonates (out from 66 neonates with EOS) had positive blood culture, nine (81%) of them had insufficient serum D level in spite of insignificant correlation between mean vitamin D level and blood culture. In a study by Noah et al,[23] majority of blood cultures were negative (80%). This may be due to the fact that mothers in the majority of the sample had received prenatal preventive antibiotics in addition to the randomized use of antibiotics in our society.[23]

According to Singh et al,[17] Vitamin D is deficient in neonates with EOS and is associated with increased sepsis severity and mortality, especially with vitamin D levels < 11 ng / mL. In our study, there was a significant difference between surviving and mortality cases with regards to initial vitamin D level, as all mortality cases had insufficient vitamin D level, while 32.3% of surviving cases (14 cases) had sufficient vitamin D and 76.6% had insufficient vitamin D level (46 cases), with a p-value = 0.003. Siafarikas et al[24] and Holmlund-Suila et al[25] performed RCTs (randomized controlled trials) to investigate vitamin D status in breastfed, term infants. Siafarikas et al[24] had studied "low doses" of vitamin D supplementation, 250 versus 500 IU / day. Holmlund-Suila et al[25] evaluated the effects of "high doses" of vitamin D supplementation with three dose groups (400, 1200 and 1600 IU / day) to identify the dose that ensures 25(OH) D status of at least 32 ng / ml without evidence of toxicity. In both the studies, no vitamin D toxicity and no difference in markers of calcium homeostasis or bone health were appreciated among doses. Siafarikas et al[24] concluded that 250 IU / day is adequate for breastfed infants and Holmlund-Suila et al[25] concluded that vitamin D supplementation up to 1600 IU / day safely maintains vitamin D sufficiency. Until more conclusive results are available.

In a study by Abdel-Hady et al,[26] 76% percentage of enrolled infants were vitamin D-deficient at enrolment, whereas only one infant in the 400 IU group and none in the 800 IU group remained deficient at 40 week's PMA (Post menstrual age). None of the infants enrolled in the study had signs of vitamin D toxicity. In both the 400 and 800 IU groups, serum 25(OH) D increased significantly at 40 weeks' PMA. The magnitude of change in serum 25(OH)D was greater in the 800 IU compared with the 400 IU group. These data imply that the 400 IU / day dose recommended by the AAP may not be 100% sufficient to correct vitamin D deficiency in preterm infants with

sepsis and would support the ESPGHAN recommendation of 800 IU / day.

A study by Priyadarsh et al,[27] found that a daily dose of 800 IU achieved target serum vitamin D level ≥ 50 nmol / L in more than 90% of infants but is associated with a potential risk of vitamin D toxicity. One of our limitations is that we didn't measure maternal 25(OH)D level and didn't observe the effect of season and clothing on neonatal 25(OH)D level.

Conclusions

Vitamin D supplementation has a role in the survival of full term neonates suffering from sepsis and decrease the duration of hospital admission. Significant correlation between the mean of serum vitamin D level in recovery and vitamin D supplementation for the newborns.

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