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Original Research Article

Vitamin D deficiency and morbidity among preterm infants in a developing country

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ABSTRACT

Background: The association of serum vitamin D levels to clinical outcome in VLBW infants has not been studied. Our objective was to measure the cord blood levels, and the dose response for two doses of vitamin D in preterm infants and correlate the relationship of vitamin D levels to the clinical outcome.
Methods: We prospectively obtained cord blood levels in 80 preterm infants under 34 weeks gestation (mean gestation age 29±2 weeks and BW: 1210±350 gms). Infants were supplemented with 400 IU or 800-1000 IU vitamin D daily. Serun vitamin D levels were obtained at 2 - 3 weeks after supplementation and levels were correlated to clinical outcome.
Results: The mean cord blood vitamin D level was 12±8.5 ng/ml. Babies who developed sepsis and compared to those who did not develop these morbidities, ROP had vitamin D levels: 13.5±6 (ng/ml) versus 30.5±10 (ng/ml) ($p < 0.01$) and 15.7±11 (ng/ml) versus 34±18 (ng/ml) ($p < 0.03$) respectively. Supplementation with 400 IU vitamin D resulted in levels of 17±8.6 (ng/ml) and infants given 800-1000 IU vitamin D had levels 46±17(ng/ml) ($p < 0.001$).
Conclusions: These data suggest that cord blood vitamin D levels are low in preterm infants and 800-1000 IU vitamin D supplementation is advisable to achieve levels >30 ng/ml. Infants with low levels of vitamin D have higher incidence of sepsis, and ROP.

Keywords: Morbidity**,** Preterm Infants, Vitamin D levels

INTRODUCTION

Although there is no consensus on optimum levels of serum vitamin D levels, vitamin D deficiency is defined as a 25-hydroxy vitamin D level of less than 20 ng per millilitre (50 nmol per litre).[1-4] No specific definition exists for preterm infants. With the use of such definitions, it has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency.[5-7] High prevalence of physiologically significant hypovitaminosis D among pregnant women and their term newborns have been reported in India.[8] The active metabolite of vitamin D, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), exerts its bio-logical actions by binding to a nuclear receptor, the vitamin D receptor (VDR) and these are present in almost every organ system in the body. It is speculated that there is a physiologic role for vitamin D and its metabolites in general health.[9,12,13]

The awareness of a role for vitamin D in the regulation of immune responses was triggered by the discovery of VDRs in almost all immune cells of the innate and adaptive immune system.[10] Moreover, immune signals can regulate expression levels of the VDR and the enzymes involved in vitamin D metabolism.[11]

The VDRs and vitamin D metabolizing enzymes have also been identified in both the vasculature and the heart

including cardiac myocytes, vascular smooth muscle cells, and endothelial cells. 1,25(OH)2D3 also inhibits angiogenesis, by inhibiting the proliferation of endothelial cells and/or by repressing the release of angiogenic factors such as TGF-a, epidermal growth factor, and vascular endothelial growth factor (VEGF).[20] The association of vitamin D levels to clinical outcome in VLBW infants has not been well studied. Objectives of the study were to determine the vitamin D levels in the cord blood of preterm infants, supplement vitamin D in two doses 400 IU daily and 800-1000 IU daily to randomly assigned preterm infants and to correlate the serum vitamin D levels to neonatal morbidity and outcome.

METHODS

The study was conducted in the neonatal intensive care unit of a tertiary care hospital in south India. The study was approved by the medical ethics committee. The criterion for enrolment was gestational age of ≤34 weeks. Infants born with severe asphyxia, chromosomal disorders and congenital infections were excluded from enrolment.

Previously we have noticed that several convalescent preterm infants had very low vit. D levels ranging from 3 to 10 ng/ml, although they were receiving 400 IU of vit. D daily. In order to determine vit. D levels at birth, we obtained cord blood levels of 25 hydroxy Vitamin D3 and followed their serum vitamin D levels 2 to 3 weeks after vitamin D supplementation. When infants were getting enteral feedings of 120ml/kg/day, they were randomly assigned to receive vitamin D supplementation of 400 IU (Group 1) or 800-1000 IU (Group 2) orally daily. Vitamin D levels were measured by chemiluminescence assay (Roche Diagnostics Limited, Sussex, UK). The baseline characteristics of these groups before supplementation with vitamin D are given in Table 1.

Table 1: Baseline characteristics of infants in the study group 1 supplemented with 400 IU vitamin D and group 2 supplemented with 800-1000 IU of vitamin D.

	Group 1	Group 2	p
Birthweight (gms)	1350±30	1140±360	0.22
GA (weeks)	30±2.16	29±2.08	0.1
Cord blood vitamin D levels (ng/ml)	13.5±6.3	10.7±8.5	0.2

Statistical differences between groups were analyzed with the Student t-test (two-tailed). P value <0.05 was considered significant.

RESULTS

We studied 80 preterm infants under 34 weeks gestation. The mean GA was 29±2 weeks and BW: 1210±350 gms. There was no mortality in this study group. The mean cord blood vit D levels were 12±8.5 ng/ml. Late onset sepsis was present in 48 infants (60%). Sepsis was defined as either blood culture proven sepsis or culture negative clinical sepsis syndrome. Retinopathy of prematurity was present in 30 infants (37.5%); 16 infants (20%) did not develop ROP and the rest 46 infants (42.5%) had their retinal maturation delayed beyond 40 weeks and were still being followed. Eleven infants with ROP (36.6%) required laser therapy. There was no difference in the highest PO_2 levels and supplemental O_2 administration between the infants in the ROP and non-ROP groups. Infants who developed sepsis had serum vitamin D levels: 13.5±6 ng/ml compared to infants who did not develop sepsis: 30.5±10 ng/ml (P <0.01). Infants who developed ROP had serum vitamin D levels: 15.7±11 ng/ml compared to infants who did not develop ROP: 34±18 ng/ml (P <0.03). Similarly infants whose retinal maturation was delayed beyond 40 weeks had lower vitamin D levels postnatally 12.4±5.5 ng/ml vs 26±6.5 ng/ml who did not have delayed retinal maturation (P <0.02).

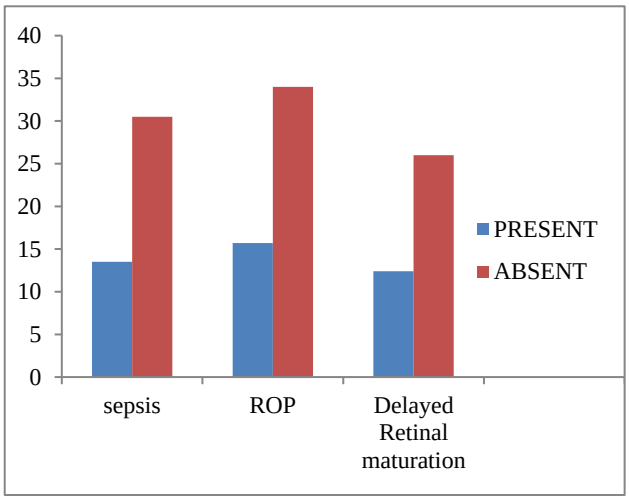

Figure 1: Vitamin D levels and morbidity.

Two infants developed NEC (2.5%), and grade ≥3 IVH was diagnosed in 4 infants (5%) of the total group. There were no cases of BPD. Infants who were supplemented with 400 IU vit. D (Group 1) had mean vitamin D levels of 16±8.6(ng/ml) and infants given 800-1000 IU vit D had vitamin D levels of 46±17 (ng/ml) (p <0.0001). These levels were obtained 3 weeks after supplementation with vit D.

DISCUSSION

To our knowledge this is the first study linking vitamin D levels to morbidity in preterm babies. Our data indicate that babies with low vit. D levels have higher incidence of ROP and late onset sepsis. Retinopathy of prematurity occurs when abnormal new blood vessels develop in response to angiogenic stimuli from hypoxia. The factors that lead to this include HIF 1-α and VEGF. The newly formed blood vessels are fragile and may leak which can

give rise to scarring fibrous tissue resulting in retinal detachment in severe cases. Therefore, there is great interest in the development and identification of agents that can inhibit the growth of new blood vessels. The anti-angiogenic properties of calcitriol (1,25-dihydroxyvitamin D3), has been studied in the mouse model and it has been mentioned as a potent inhibitor of retinal neovascularization and may be of benefit in the treatment of a variety of eye diseases with a neovascular component like ROP.[14,15,21] How calcitriol affects angiogenesis has been unclear.

It was also found that there is an association an association of vitamin D deficiency and late onset sepsis. Vitamin D has a role in regulating inflammation and chemokine production as well as an important role in immunomodulation.[16-18,22] Nearly all cells display a specific vitamin D receptor (VDR), including B and T lymphocytes (both resting and activated), monocytes and dendritic cells.[23] Vitamin D also facilitates neutrophil motility and phagocytic function. A major component of the antimicrobial action of Vitamin D is through the production of peptides which have antimicrobial as well as anti-endotoxin activity. Vitamin D stimulates the expression of potent antimicrobial peptides, such as cathelicidin and β defensin which exist in neutrophils, monocytes, natural killer (NK) cells and epithelial cells lining the respiratory tract.[24,25] Macrophages, lymphocytes and monocytes have VDRs that, with 25(OH)D stimulation, increase the expression of these antimicrobial peptides.[26,27] Jeng et al. noted a positive relationship between vitamin D levels and cathelicidin levels in acutely ill patients.[28] Cathelicidin is effective against gram-positive and gram-negative bacteria, fungi and mycobacteria at a variety of pathogen entry sites, including the skin and the mucosal linings of the respiratory and gastrointestinal sys-tems.[24] Patients with 25(OH) D levels less than 20 ng/mL may be unable to fully express cathelicidin, which could be associated with increased susceptibility to nosocomial infec-tions such as pneumonia, sepsis and central line infections.[28,29] A randomized controlled trial involving Japanese schoolchildren found a relative risk of influenza of 0.36 in those taking 1,200 IU/day compared with those taking 200 IU/day.[30] In-vitro studies have shown that vit-amin D3 has inhibitory activity on strains of *Staphylococcus aureus, Streptococcus pyogenes, Klebsiella pneumoniae, Escherichia coli* (E. coli) and other bacteria. In the presence of 50,000-90,000 IU/mL of vitamin D_3, the organisms were killed or demonstrated marked growth inhibition.[31] The risk of diseases comorbid with septicemia are generally inversely correlated with serum 25(OH)D levels.[32] Grant had reported that vitamin D supplementation of mother and infant can reduce the risk of sepsis in infants and neonates.[33,34]

The results of our study also indicate that the usual recommended dose of 400 IU Vitamin D in preterms is not sufficient to maintain normal physiological levels in our cohort of Indian infants. This has been observed in other Indian studies also.[35-37] It is quite possible that these infants had very low vitamin D levels at birth perhaps due to maternal vitamin D deficiency and required a higher dose of vitamin D supplementation postnatally. Although none of the infants in our study who received 800-1000 IU of vitamin D very high levels of serum vita-min D we recommend that serum vitamin D levels should be monitored at least once within a month of supplementation of this high dose of vitamin D. We did not correlate the cord blood vitamin D levels to postnatal vitamin D requirement. It is quite possible that the mothers of these infants might have low vitamin D levels during pregnancy which might have contributed to low cord blood levels of vitamin D in these infants. Whether if pregnant mothers are adequately supplemented with vitamin D leading to higher cord blood levels of vitamin D may lead to lower requirements of vitamin D postnatally in these infants is not known. We realize that this is not a randomized controlled study and the sample size is rather small but the results are very convincing that a larger multicenter trial may be warranted to confirm these findings.

CONCLUSION

These data suggest that severe vit.D deficiency is common in preterm newborns at birth and postnatally. In infants with low levels of vit D: incidences of late onset sepsis and ROP are significantly higher. Retinal maturation of infants with low levels of vitamin D is delayed perhaps increasing their risk for development of ROP even in the absence of supplemental oxygen administration. AAP guidelines of supplementation with 400 IU is insufficient and most infants require 800-1000 IU vitamin D soon after birth to maintain vitamin D levels ≥ 30 ng/ml in developing countries especially if they are exclusively breast fed. These preliminary results will assist in planning a larger multicenter trial in this field.

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