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A Randomized Controlled Trial to Compare the Efficacy of Single Mega Dose Vitamin D Therapy with Standard Daily Dose Vitamin D Therapy in Vitamin D Deficient Critically Ill Children

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Abstract

Introduction: The prevalence of vitamin D deficiency has been reported to be very high (up to 50%) in critically ill children admitted in Paediatric ICU, and vitamin D deficiency has been associated with increased mortality, increased length of Paediatric ICU and hospital stay. But the impact of supplementation of vitamin D in these children on the clinical outcome is not very clear.

Study Objectives: Primary Objective: To compare the efficacy of single mega dose vitamin D therapy with standard daily dose vitamin D therapy in vitamin D deficient critically ill children.

Secondary Objective: To assess the prevalence of vitamin D deficiency in critically ill children in a tertiary care centre.

Methodology: A study population of 50 children meeting inclusion criteria were enrolled in our study. All the subjects admitted to our Paediatric ICU were subjected to a detailed history and examination. Vitamin D levels were sent at admission and children with vitamin D deficiency (< 20ng/dl) were taken as study subjects and randomized into two groups. One group received single mega dose vitamin D therapy, and the second group received standard daily dose vitamin D therapy. These children were followed up until their Paediatric ICU stay or death. The impact of supplementation was compared among both the groups in terms of length of Paediatric ICU stay and mortality.

Results: The mean length of Paediatric ICU stay among children receiving a single mega dose vitamin D therapy was 5.04 days compared to 3.56 days among children receiving standard-dose vitamin D therapy (p-value 0.337),

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suggesting no significant difference in the length of Paediatric ICU stay among the study subjects of both groups. There was no mortality among these study subjects. The prevalence of vitamin D deficiency in the study group was 55.6%.

Conclusion: Supplementation of a single mega dose of vitamin D compared to the standard dose of vitamin D has no advantage on the clinical outcome of Vitamin D deficient critically ill children in terms of length of Paediatric ICU stay and mortality.

Keywords: Critically ill children, Megadose vitamin D therapy, Vitamin D deficiency

Introduction

Vitamin D is important to facilitate calcium absorption, and it has an essential role in maintaining bone and skeletal health. The human body can obtain vitamin D through exposure to sunlight, diet and dietary supplements. Serum 25-hydroxy vitamin D [25(OH) D] is the measurement variable for vitamin D status [1]. Patients with levels <20 ng/mL are commonly categorized as vitamin D deficient, and treatment is initiated in children to prevent rickets [2]. Vitamin D deficiency is a global problem, and it is known as an essential factor involved in different immune functions besides skeletal and muscle development [3]. A recent study reported that most of the nonspecific aetiologies of common symptoms could result from vitamin D deficiency. However, more studies need to be done to prove that vitamin D deficiency can lead to common symptoms of unknown aetiologies such as headache and fatigue. Another study found that the prevalence of nonspecific muscle pains among the population might result from vitamin D deficiency [3]. Most of the literature reviews have indicated that the severity of vitamin D deficiency in population can lead to serious implications for the growth of future generations and the community's overall health [3]. Vitamin D deficiency has been associated with higher levels of admission illness severity in adult ICU patients [4-6]. The prevalence of vitamin D deficiency and its influence on critical illness severity in children is unknown [7]. So, we aimed to compare the efficacy of single mega dose vitamin D therapy with standard daily dose vitamin D therapy in vitamin D deficient critically ill children. We also assessed the prevalence of vitamin D deficiency in critically ill children in a tertiary care centre.

Materials and Method

A randomized controlled trial to compare the efficacy of single mega dose vitamin D therapy with standard daily dose vitamin D therapy in vitamin D deficient critically ill children was conducted in a tertiary care hospital in India from October 2019 to March 2021.

Sample Size Calculation

Calculated based on the literature, by comparing mean of the outcome of the study (length of ICU stay in days) with group A mean of 23 and group B mean of 15, with standard deviation of 10 considering α error of 5 percent and power of the study as 80 percent, the calculated sample size based on formula mentioned below was 25 in each group.

By using formulae- $n= (Z\alpha+Z\beta)^2 X S^2 X 2/d^2$

Study Population and Source of Data

A sample size of 50 children meeting eligibility criteria, consisting of children between 1 year to 18 years admitted at the Paediatric ICU of a tertiary care centre in India.

Subject Eligibility

Inclusion Criteria: All critically ill children (requiring inotropic support and or fluid resuscitation and or positive pressure ventilation) admitted in Pediatric ICU aged 1 year to 18 years and estimated Pediatric ICU stay of more than 24 hours.

Exclusion Criteria:

- Children who are on calcium supplementation and vitamin D therapy or have taken large doses for rickets.
- Children on steroids for > 10 days before admission.
- Children with chronic kidney disease or past history of renal stones.
- Severely impaired gastrointestinal function (continuous NG tube drainage, strict NPO, malabsorption syndrome, paralytic ileus).

Study Setting and Method of Collection of Data: Informed consent was taken from parents after explaining regarding the study, randomization and supplementation, following which children went through detailed history taking and examination at the time of admission to full fill the inclusion criteria as defined above. Under aseptic precaution, 3 ml of venous blood sample is collected in plain vacutainer at admission, to assess levels of serum 25(OH) vitamin D (calcidiol). 25(OH) vitamin D levels were assayed in the hospital laboratory using ECLIA (Electrochemiluminescence) in the fully automated COBAS 6000 integrated system analyzer.

Children with deficient levels of vitamin D (20ng/ml) were randomly allotted in two groups (25 children in each group) by envelope method. Envelop labelled as A and B were picked up, among which one group received single mega dose vitamin D therapy (10,000 IU/KG with maximum dose of 4 lakh IU) and other group received standard dose of vitamin D therapy (5000 IU/Day for 8 weeks) as per envelope. The children were followed up only until Paediatric ICU stay and advised to continue vitamin D supplementation until the full course was completed. During the hospital stay, children were followed up for the length of Paediatric ICU stay or death of the patient.

Results

Data were analyzed using statistical package for social science (SPSS) version 20.0 after entering the data in excel sheet. All descriptive statistics were presented as percent, frequency, mean and standard deviation and inferential statistics were analyzed using T test, Pearson Chi Square and Fisher Exact Test. A P value of <0.05 was taken as statistically significant.

The study subjects were divided into cases (children with Vitamin D deficiency) and controls (children having vitamin D of >20 ng/dl) groups. It is depicted in the following table 1 below. Among cases and control, most of the subjects were in the age group of 1 to 3 years with 18 children (36%) and 22 children (55%) respectively, then among cases followed by 13 children (26%) above 11 years of age, 24% between 8-11 years and 14% between 4-7 years. Among controls, it was 22.5% between the age group of 4-7 years, 17.5% between 8-11 years and 5% above the age group of 11 years. The age of the study participants ranged from 1 to 16 years.

Table 1: Age-wise distribution of the study subjects

Crosstab					
			Groups		Total
			Case	Control	
Age groups	≤3 years	Count	18	22	40
		% within groups	36.0%	55.0%	44.4%
	4-7 years	Count	7	9	16
		% within groups	14.0%	22.5%	17.8%
	8-11 years	Count	12	7	19
		% within groups	24.0%	17.5%	21.1%
	≥11 years	Count	13	2	15
		% within groups	26.0%	5.0%	16.7%
Total		Count	50	40	90
		% within groups	100.0%	100.0%	100.0%

Among both cases and controls, 50% were male, and 50% were female, i.e. 25 children each among cases and 20 children each among controls.

Among the study subjects taken as cases, the majority were below three years of age, with eight children (44.4%) receiving intervention A and ten

children (55.6%) receiving intervention B, followed by age group 11 years and above with seven children (53.8%) receiving intervention A and six children (46.2%) receiving intervention B, least were between the age group of 4 to 7 years. Both the intervention groups had the comparable number of children in age each group suggested by the p-value of 0.931.

Among children receiving single mega dose vitamin D therapy, 13 children (52%) required fluid resuscitation and for those receiving standard daily dose vitamin D therapy, six children (24%) required fluid resuscitation. The p-value of 0.79 (>0.05) tells that subjects of both groups were comparable in terms of the requirement of fluid resuscitation.

Among children receiving mega dose and standard dose, two children (8%) required inotrope support. A p-value of 1.000, suggests that children among both these groups were comparable in terms of the requirement of inotrope support.

Among children receiving mega-dose vitamin D therapy, 18 children (72%) required respiratory support, and 24 children (96%) needed respiratory support among those receiving the standard dose. There was a statistically significant difference between these two groups in terms of the requirement of respiratory support. (p-value of 0.049).

In our study, the mean length of Paediatric ICU stay among children who received mega-dose vitamin D therapy was 5.04 days compared to 3.56 days among children who received the standard dose of vitamin D therapy. The p value of 0.337 shows no statistically significant difference in length of Paediatric ICU stay among the study subjects receiving intervention A and intervention B. There was zero mortality among the study subjects of 50 children.

Among the total study subjects of 90 children, 50 children (55.6%) had vitamin D deficiency (values <20ng/ml), and 40 children (44.4%) had insufficient or sufficient vitamin D levels (>20ng/ml) (Table 2).

Table 2: Prevalence of vitamin D deficiency

		Frequency	Percent
Vit D	Case	50	55.6
	Control	40	44.4
	Total	90	100.0

Vitamin D therapy was given to children with vitamin D levels ranging from 20 to 30 ng/ml but not included in the interventional study. Mean vitamin D levels among cases were 11.54 ng/dl, compared to 33.925 ng/dl among controls (Table 15).

Discussion

The study was conducted to compare the efficacy of single mega dose vitamin D therapy versus standard-dose vitamin D therapy among vitamin D deficient critically ill children. Now it is a well-known fact that vitamin D has other vital roles in addition to calcium and bone homeostasis [8]. Many surveys have shown a significant prevalence of vitamin D deficiency among critically ill children [9, 10]. This study was conducted to know the outcome of supplementing vitamin D to vitamin D Deficient critically ill children and check the efficiency of single mega-dose vitamin D therapy versus standard-dose vitamin D therapy among Vitamin D deficient critically ill children.

Vitamin D levels in the present study

Total study subjects were 90 children, among which 50 (55.6%) were vitamin D deficient, 19 children (21.1%) had vitamin D insufficiency, and others 21(23.3%) had normal vitamin D levels. Although, the pathophysiology behind vitamin D deficiency in sick children is not clear, the accepted theory is, due to systemic inflammation, there is loss of albumin and protein along with reduced production which in turn will lead to reduced vitamin D binding proteins, which affect the absorption of vitamin D from renal tubules leading to deficiency[11]. This theory helps us correlate vitamin D Deficiency with the severity of critically ill children, so vitamin D Deficiency has been linked with the extended length of ICU stay and death among critically ill children. The present study was done to determine the outcome of vitamin D supplementation among vitamin D Deficient critically ill children.

In the present study, among 50 children with vitamin D deficeincy, we used a single mega dose of vitamin D to raise the vitamin D levels quickly, while the other group received standard vitamin D therapy. Previous studies tell us that a high oral dose is safe and increases the vitamin D levels to normal rapidly;

this will help us compare the outcome between the two groups, i.e. length of hospital stay and mortality [12]. In the present study, 50 children were found to be vitamin D deficient; these children were randomly allocated into two groups (group A and B), among which group A received a single mega dose of vitamin D therapy of (10,000 IU/KG) and group B received a standard dose of vitamin D therapy. Still, in our study, we did not find any advantage of children receiving single mega dose vitamin D therapy over standard-dose treatment on length of Paediatric ICU stay/mortality. Table 3 shows the comparison between the present study and previous studies.

Table 3: Comparison between the present study and previous similar studies

Author	Year	Study subjects	Intervention	Length of hospital stay	Mortality	Other outcomes
Leaf DE et al [13]	2014	Critically ill adult patient with sepsis/ septic shock	Single-dose of calcitriol versus placebo	No effect	No effect	No increase in plasma cathelicidin levels after 24 hours of administration
Amrein K et al [14]	2014	Critically ill adult patients	Single high dose vs placebo	No effect	No effect	No effect on six months mortality
Han JE et al[12]	2016	Mechanically ventilated adult ICU patients	High dose over five days vs placebo	Decreased length of hospital stay	No effect	Increased vitamin D levels safely to sufficient levels
Present study	2021	Critically ill children	Single mega dose versus standard dose	No difference between the two groups	No deaths	Prevalence of vitamin D deficiency was 55.6%

Table 4 provides the details regarding the comparison of prevalence of vitamin D deficiency in critically ill children among different studies.

Table 4: Comparison of prevalence of vitamin D deficiency in critically ill children among different studies

Author	Year	Subjects	Prevalence
Shilpa bansal et al[15]	2020	Crtically ill children	72%
James dayre mcnally et al [16]	2017	Critically ill children	54.8%
Kate madden et al [17]	2012	Critically ill children	40.1%
Present study	2021	Critically ill children	55.6%

Most of the above-mentioned studies have established that supplementation of high dose vitamin D in vitamin D deficient patients, in general, will increase the levels to a sufficient range within days but has not been associated with better clinical outcomes among patients when compared to the placebo group, which complies with our study. Our study showed that administering a single mega dose compared to standard dose vitamin D among vitamin D deficient critically ill children did not change the clinical outcome between the groups.

Conclusion

Our study revealed that among vitamin D deficient critically ill children, supplementation of a single mega-dose of vitamin D therapy did not show any advantage on clinical outcome in terms of length of pediatric ICU stay and mortality compared to supplementing standard-dose therapy. The present study also revealed the prevalence of vitamin D deficiency among critically ill children getting admitted to our pediatric ICU is high (55.6%), i.e. 50 children among the total of 90 children. Thus,

we conclude that early high dose vitamin D therapy has no impact on the clinical outcome of the vitamin D deficient critically ill children compared to the standard dose of vitamin D therapy.

Limitations: The sample size is relatively small in our study, compared to other similar studies where the sample size is more in each group, which might reflect the outcome in a better way. Vitamin D levels after the intervention, i.e. mega dose and standard-dose vitamin D therapy, could not be done due to financial constraints.

Conflict of interest: Nil

Source of funding: None

Ethical clearence: Taken from the Institutional Ethical Committee, JSS Medical College, JSS Academy of Higher Education and Research

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