Effect of Single High Dose Vitamin D Administration in Critically Ill Vitamin D-deficient Pediatric Patients: A Randomized Trial

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Abstract

Objective: Vitamin D deficiency (VDD) has been thought to be a common modifiable risk factor for severity and clinical outcome during critical illness. The primary objective was to evaluate the effect of single high-dose vitamin D supplementation on mortality in critically ill vitamin D-deficient children. The secondary objective was to study the change in vitamin D levels after the intervention.

Design and setting: This study was a randomized controlled trial conducted at the Department of Pediatrics of a Tertiary Care Hospital from May 2019 to March 2020.

Subjects and intervention: Two hundred and fifty vitamin D-deficient children aged 1 month–12 years admitted in pediatric intensive care units (PICU) were randomized into 2 groups (group A received 10,000 U/kg cholecalciferol intramuscularly, group B received no intervention), with 125 in each group.

Measurement: Baseline serum calcium, ionized calcium, serum phosphate, vitamin D and parathyroid hormone (PTH) levels were measured at the time of recruitment. Ionized calcium, and kidney function tests (KFT) were repeated at 24 and 72 hours, while vitamin D and PTH levels were repeated at 72 hours only.

Results: Both the groups were comparable for baseline characteristics. There was no statistically significant difference between mortality ($p = 0.439$), length of PICU stay ($p = 0.57$) need and duration of mechanical ventilation ($p = 0.449$) between 2 groups. The subgroup analysis between severe and less severe VDD had similar results. However, there was a significant increase in levels of vitamin D after intervention in group A at 72 hours ($p = 0$).

Conclusion: Administration of single high dose of vitamin D increases the vitamin D levels but does not convincingly improve the outcomes in vitamin D-deficient critically sick children admitted in PICU.

Keywords: Critically ill, Outcome, Pediatric intensive care units, Vitamin D deficiency.

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Highlights

- Vitamin D plays an integral part in maintaining the hemostasis and vital organ functions.
- Most of the data of its supplementation and its effect on the outcome is extrapolated from the adult studies.
- Vitamin D supplementation does not significantly alter the outcome of critically sick patients.

Introduction

Various studies have reported 30–80% of children to be vitamin D deficient in different pediatric intensive care units (PICU) all over the globe.[1-4] The proper functioning of multiple organs in our body is well postulated to be dependent on vitamin D levels. In addition, it is also an integral part of our body defense mechanism through its immunological and endothelial functions. Vitamin D deficiency (VDD) can cause hypocalcemia, cardiovascular dysfunction and worsen critical illness associated polyneuropathy and muscular weakness.[5]

Vitamin D is a modest, potentially modifiable risk factor for improving the clinical outcomes in intensive care unit (ICU). Vitamin D deficiency predisposes to different neurological, cardiovascular, respiratory and immunological pathologies, and these organ systems are decisive for a good prognosis in sick patients.[6] Studies on adult patients have associated poorer outcomes with vitamin D deficiency, especially those admitted to ICUs.[7–11] Also, it has been seen to be causing greater severity of illness, multiorgan dysfunction syndrome (MODS), higher mortality longer PICU stay and the need for vasopressor support though there is considerable variability in the results of various studies.[3,6–9,12–18]

Numerous observational studies have tried to associate VDD with poorer clinical prognosis in sick children.[6,13,19,20] At present, what remains unclear is whether VDD in critically sick children is because of disease severity and poor nutritional status, or is an independent contributor to the poor outcomes. Unfortunately, this is mainly due to the lack of interventional trials in the pediatric

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population. To generate more prospective data, we planned this clinical trial to investigate whether cholecalciferol administration would improve the outcomes of critically ill children with VDD.

Materials and Methods

Study Design and Participants

It was a randomized controlled trial conducted at a Tertiary Referral Hospital's Pediatric intensive care unit between May 2019 to March 2020. All children of age 1 month–12 years requiring PICU admission who had low serum vitamin D levels, i.e., 25 hydroxycholecalciferol was less than 20 ng/mL, were enrolled.

Children with hypocalcemia, known renal disease, urolithiasis or nephrocalcinosis, parathyroid disease or pituitary dysfunction were excluded.

All procedures were carried out adhering to the ethical standards of the institute and the principles of Helsinki Declaration of 1975, ensuring ethical research practices.

Randomization and Study Drug Administration

All the patients who met the inclusion criteria were evaluated for severity of illness by pediatric risk of mortality (PRISM) III score. A blood sample was withdrawn at the time of admission to assess baseline biochemical parameters like serum calcium, ionized calcium, serum phosphate and vitamin D. Children who were vitamin D deficient were randomized into two groups. A sequence for block randomization with a size of 10 blocks generated through computer. It was being maintained by a person who was not involved in running this trial. Allocation was carried out using sealed opaque envelopes, each sequentially labeled to maintain confidentiality.

Cholecalciferol was supplemented by, 10,000 U/kg I/M to one group (group A), and no intervention was given to the other group (group B) after randomization (i.e., when vitamin D reports were available usually 24 hours after sending the sample).[3,5]

Monitoring

Ionized calcium, kidney function tests (KFT) were repeated at 24 hours for hypercalcemia and after 72 hours of intervention, vitamin D levels, ionized calcium and KFT were repeated. Patients not receiving intervention were given, 10,000 U/kg vitamin D supplementation at the time of discharge.

Sample Analysis

Serum calcium and serum phosphate were analyzed using o-cresolphthalein complexone and phosphomolybdate methods, respectively. The sample for vitamin D was analyzed using electro-chemiluminescence immunoassay method.

Outcome Measurements

The main (primary) outcome evaluated was the difference in PICU mortality after supplementing vitamin D deficient children with a single high dose of vitamin D.

Other outcomes like duration of PICU stay, need for mechanical ventilation, duration of ventilation, MODS and cardiovascular support were also studied as secondary outcomes. Another secondary outcome was the measurement of change in vitamin D levels in vitamin D deficient children after supplementing them with a single high dose of vitamin D. Multiorgan dysfunction syndrome was defined as a simultaneous dysfunction of more than one organ system because of a common underlying pathological mechanism.[21]

The vitamin D deficient group was further divided as severe vitamin D deficient (subgroup I), i.e., 25-hydroxycholecalciferol levels ≤10 ng/mL and less severe vitamin D deficient (subgroup II) i.e. 25-hydroxycholecalciferol levels 10–20 ng/mL respectively.

Sample Size Estimation

When this was planned, there were no similar pediatric data were available. An adult study reported mortality of 28.3% (95% CI, 22.6–34.5%) for vitamin D (intervention group) vs 35.3% (95% CI, 29.2–41.7%) for placebo (control group); $p = 0.18$. After the calculation (with zα 1.96 and zβ 0.84), the sample size was 690 in each group. However, we took a convenient sample size of 125 in intervention and control group.

Statistical Analysis

Microsoft Excel was used for data entry and SPSS software for statistical analysis. Descriptive statistics were used to compare baseline characteristics of both groups. Variables that were categorical were mainly reported as frequency and percentages, while variables that were continuous in nature were expressed as mean, median, standard deviation, and interquartile range. Univariate analysis was done using either Fisher's exact or χ^2 tests, as appropriate. Parametric tests like the student's *t*-test or non-parametric tests like Mann-Whitney *U* test were used to assess differences between the two groups. Analysis of the outcome was done following the intention-to-treat principle. Changes in serum calcium levels were analyzed using a paired *t*-test. A *p*-value of less than 0.05 was taken to be statistically significant.

Results

There were total 296 admissions through our study period in our PICU. Forty patients were excluded due to various reasons, as summarized in Figure 1. Total 256 were sampled, of which 250 were vitamin D deficient (97.65%) and were included in the study. Six patients were vitamin D sufficient, with their vitamin D levels between 20 and 44 ng/mL.

Then, the study participants were randomly assigned to one of the intervention groups. Out of 250 included patients, 125 were in group A (vitamin D given) and 125 were in group B (no vitamin D given). The final analysis included all the study participants, as there was no loss of follow-up.

Table 1 summarizes the demographic and clinical characteristics of the two groups, which were comparable. The mean age was 37.56 months (SD, 41.8), and 62% were males. Almost half of the patients were less than 1 year of age. At admission, vitamin D levels were comparable between the two groups, with no significant differences observed in PRISM III scores ($p = 0.788$).

Outcomes

Primary Outcome

The primary outcome results are summarized in Table 2. Pediatric intensive care unit-stay was for 10 days (IQR 5–18) which was comparable in both the groups; with a median of 10 days (IQR 6–20) in group A and median of 9 days (IQR 5–17) in B. The need for mechanical ventilation and its duration reported no statistically significant difference among the two; 8 days (IQR 3–18) and 10 days (IQR 5–20) in group A and group B, respectively. Overall mortality was 21.6% and it was comparable in both the groups.

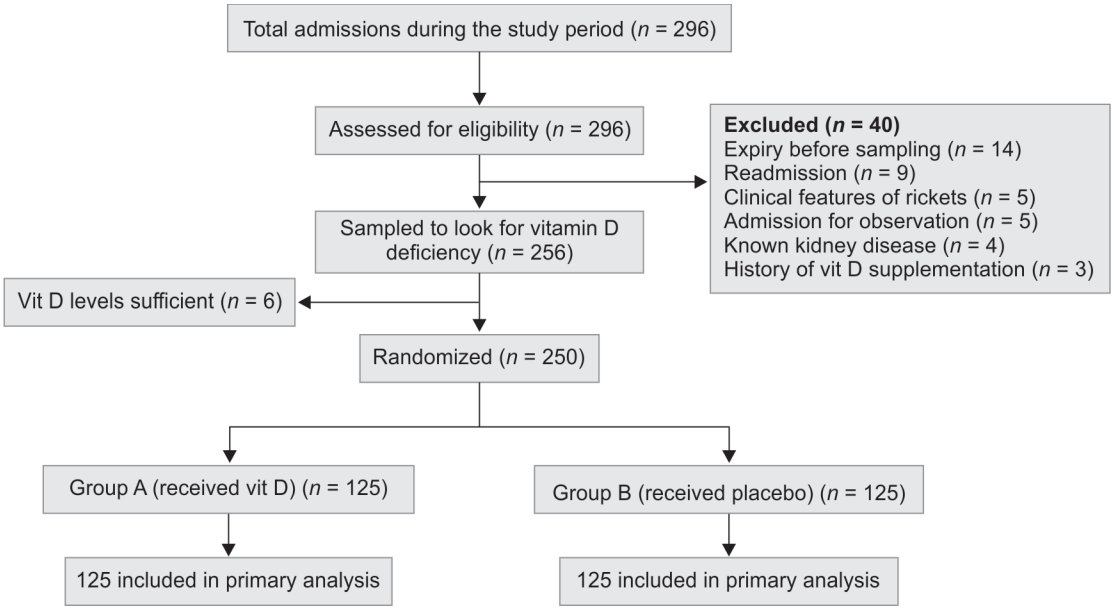

Fig. 1: Flow diagram of the study participant's

Table 1: Demographic and clinical characteristics of both the groups for comparison

Parameter	*Total*	*Group A*	*Group B*	*p-value*
No. of patients	250	125	125	-
Gender (Male), *n* (%)	155 (62)	78 (62.4)	77 (61.6)	*0.896
Age (months) Mean age (SD)	37.56 (41.8)	40.78 (42.01)	34.34 (41.52)	*0.462
Vitamin D at admission (ng/mL) Mean (SD)	9.46 (5.05)	9.83 (5.11)	9.09 (5.0)	**0.237
Vitamin D <10 ng/mL at admission, *n* (%)	138 (55.2)	66 (47.83)	72 (52.17)	*1
Vitamin D 10–20 ng/mL at admission, *n* (%)	112 (44.8)	59 (52.68)	53 (47.32)	*0.571
PRISM score Mean (SD)	4.64 (3.74)	4.83 (3.79)	4.45 (3.68)	**0.788
Mean calcium levels total Mean (SD)	9.86 (0.95)	9.81 (0.91)	9.92 (0.99)	**0.474
Mean calcium levels ionized Mean (SD)	1.0 (0.095)	1.08 (0.1)	1.08 (0.09)	**0.651
Fluid bolus >40 mL/kg in first 24 hours, *n* (%)	92 (36.8%)	49 (39.2%)	43 (34.4%)	*0.256
Diagnosis, *n* (%)				
Respiratory system	97 (38.8)	48 (38.4)	49 (39.2)	
Nervous system	47 (18.8)	21 (16.8)	26 (20.8)	
Gastrointestinal	27 (10.8)	13 (10.4)	14 (11.2)	
Cardiovascular system	24 (9.6)	13 (10.4)	11 (8.8)	
Postoperative	24 (9.6)	13 (10.4)	11 (8.8)	
Infective	17 (6.8)	8 (6.4)	9 (7.2)	
Miscellaneous	10 (4)	5 (4)	5 (4)	
Endocrine system	4 (1.6)	4 (3.2)	0	

*Chi-square; **Mann Whitney

Analysis of Severe and Less-severe VDD Subgroups

There were 138 (55.2%) patients in the subgroup I and 112 (44.8%) in the subgroup II. Within each subgroup, no statistically significant differences in outcomes were observed when comparing group, A and group B (Table 3). The number of patients mechanically ventilated among the patients with baseline vitamin D levels <10 ng/mL and 10–20 ng/mL in both groups A and B was comparable. The number of patients with septic shock and MODS were higher in patients in group B of subgroup1, but without any statistical significance.

The mean calcium level was 9.81 mg/dL (SD 0.91) at baseline and 9.93 mg/dL (SD 0.94) at 24 hours after intervention in group A. This was statistically significant with $p < 0.001$, but

Table 2: Comparison of outcome variables in both the groups

	Group A	*Group B*	*p-value*
Mortality, *n* (%)	26 (20.8%)	28 (22.4%)	*0.439
Duration of PICU stay (days), median (IQR)	10 (6–20)	9 (5–17)	**0.570
Mechanical ventilation, *n* (%)	52 (41.6%)	54 (43.2%)	*0.449
Duration of MV (days), median (IQR)	8 (3–18)	10 (5–20.75)	**0.692
Received inotropes, *n* (%)	43 (34.4%)	40 (32%)	*0.394
Duration of inotropes (days), median (IQR)	3 (3–4.5)	3 (2–5.25)	**0.937
Multiple organ dysfunction syndrome, *n* (%)	13 (10.4%)	18 (14.4%)	*0.222
Septic shock, *n* (%)	43 (34.4%)	43 (34.4%)	*0.553

*Chi-square **Mann Whitney ≈Vitamin D: 25(OH) vitamin D

Table 3: Comparison of outcome variables in prespecified subgroups

	Severe vitamin D deficiency			*Less-severe vitamin D deficiency*		
	Group A	*Group B*	*p-value*	*Group A*	*Group B*	*p-value*
Mortality, *n* (%)	14/66 (21.2)	23/72 (31.9)	*0.181	12/59 (20.3)	5/53 (9.4)	*0.468
Duration of PICU stay (days) Median (IQR)	11 (5.25–26)	9 (5–15)	**0.124	8 (6–13.5)	10 (5–20)	**0.261
Mechanical ventilated, *n* (%)	33/66 (50)	34/72 (47.2)	*0.438	19/59 (32.2)	20/53 (27.7)	*0.445
Duration of MV (days) Median (IQR)	12 (3–25)	8 (4.25–19.25)	**0.538	6 (3.5–12.5)	14 (5.75–23)	**0.249
Received inotropes, *n* (%)	27/66 (40.9)	28/72 (38.8)	0.473	16/59 (27.1)	12/53 (22.6)	0.543
Duration of inotropes (days) Median (IQR)	3 (2.5–5)	3 (2–5.25)	0.932	3 (3–3.25)	2 (2–4.5)	0.687
Multiple organ dysfunction syndrome, *n* (%)	8/66 (12.1)	15/72 (20.8)	0.126	5/59 (8.4)	3/53 (5.6)	0.486
Septic shock, *n* (%)	25/66 (37.8)	31/72 (43.0)	0.328	18/59 (30.5)	12/53 (22.6)	0.539

*Chi-square **Mann Whitney ≈Vitamin D: 25(OH) vitamin D

no patient developed hypercalcemia. The total calcium levels had significantly increased in subgroup I ($p = 0.001$) but not in subgroup II (p-value = 0.055). Also, ionized calcium was low (<1 mmol/L) in 19 (7.6%) patients at baseline and in 1 patient at 24 hours in group A.

The mean serum phosphate levels were normal at baseline, with no significant difference in either of the subgroups. Hypophosphatemia (serum PO_4 <3.7 mg/dL) was noted in 39 out of 250 patients before any intervention.

Secondary Outcome

Postintervention, the serum vitamin D levels had significantly increased in group A at 72 hours ($p = 0$). The mean rise in vitamin D levels was 3.74 ng/mL (SD 3.69) in subgroup I and 6.34 ng/mL (SD 2.74) in subgroup II.

Parathyroid hormone levels were found to be comparable (normal range 15–65 pg/mL) pre- and postintervention. However, on subgroup analysis, the difference in PTH levels pre- and post-intervention in the less severe vitamin D deficient subgroup, was reported to be significant with p-value = 0.015. The change in vitamin D and PTH levels after the intervention has been depicted in Figure 2.

It was observed that in patients with a higher vitamin D level range at 72 hours, there was no difference in mortality, duration of stay and duration of inotropes used, but there was a significant decrease in duration of ventilation ($p = 0.018$), as summarized in Supplementary Table 1.

Discussion

This randomized controlled trial showed no difference in mortality, length of stay, MODS, need and duration of mechanical ventilation, and inotropic support after administration of vitamin D in sick children who were vitamin D deficient at the time of admission.

In our study, 97.6% of eligible patients had 25-hydroxycholecalciferol levels less than 20 ng/dL. A similar percentage of vitamin D-deficient sick children was found in our PICU patients a few years back.[22] This highlights that a large percentage of sick children are vitamin D deficient at the time of admission in different PICUs around the globe. No difference was noted between two patient groups in severe and less-severe vitamin D deficient subgroups. Categorically, patients with septic shock and MODS were more in group B of the severe vitamin D deficient subgroup, but these differences were not significant.

However, the group of patients who achieved higher vitamin D levels 72 hours postintervention had significantly shorter duration of ventilation. This could be attributed to the significant contribution of vitamin D in regulation of our immune system, as well as its involvement in critical illness-related myopathy and neuropathy.

We supplemented critically ill children who were vitamin D deficient with an intramuscular injection of 25-hydroxycholecalciferol at a dose of 10,000 U/kg to rapidly restore serum vitamin D and observe improved PICU outcomes. This was based on meta-

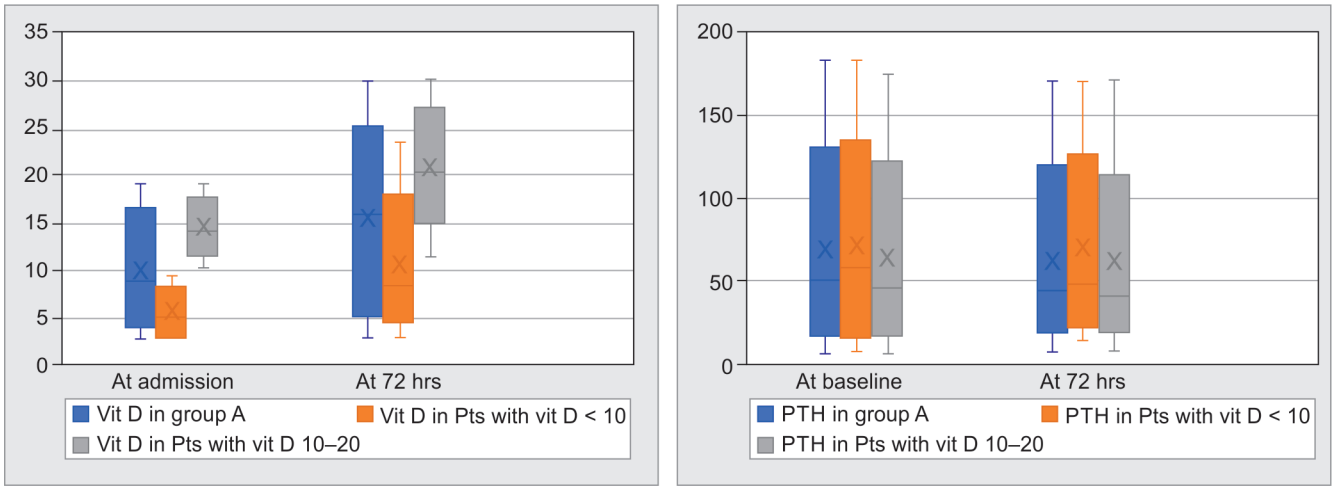

Fig. 2: Vitamin D and PTH levels at baseline and after intervention in group A

regression and a systematic review of supplementing children with high-doses of vitamin D done by McNally et al.[23] They have identified a single enteral dose of 10,000 IU/kg with a maximum dose going up to 400,000 IU to correct the vitamin D levels swiftly. During critical illness, enteral formulations may not be effective because of malabsorption due to gastrointestinal edema and inflammation. Therefore, we planned to administer vitamin D through the intramuscular route. Though smaller doses of vitamin D over months have been extensively studied for the treatment of vitamin D deficiency, but the pace might be too slow to tide over a critical illness.

However, apprehension for the risk of vitamin D toxicity still prevails for the high dose vitamin D supplementation. A meta-analysis[23] found the risk of hypercalcemia increased only after giving more than 400,000 IU of vitamin D. Also, we had not given any other vitamin D supplementation on day-to-day basis to any group. We studied if the given dose of vitamin D is enough to improve vitamin D levels to a sufficient range and whether it produces any toxicity.

There was an increase in mean total calcium levels post-intervention. Though, no hypercalcemia was reported. In VITdAL-PICU study there were also no life-threatening side effects found after giving an enteral high dose of vitamin D (10,000 U/Kg with maximum 400,000 U).[5]

Our study reported single high dose vitamin D (10,000 U/Kg) to be safe. Even after giving high dose vitamin D, mean vitamin D levels were still in deficient range. Highest and lowest recorded vitamin D levels in group A were 19.2 ng/mL and 3 ng/mL before intervention and 30 ng/mL after intervention respectively. No child achieved levels more than 30 ng/mL post-intervention.[24–27]

The effects of critical illness on renal function and drug interactions with the hepatic cytochrome P450 (CYP450) system, which facilitates the 25-hydroxylation of vitamin D3, may explain this phenomenon. In sick patients, there is often an increased demand for vitamin D at the tissue level, causing increased conversion of inactive 25-hydroxycholecalciferol to its active form i.e. 1,25-hydroxycholecalciferol. Furthermore, factors such as differences in kidney hydroxylation, hepatic transport of chylomicrons, and liver-mediated metabolism of 25-hydroxy-cholecalciferol, can all influence the increase in vitamin D levels following supplementation.[11,28]

Few studies have found an increase in vitamin D levels post-intervention on day 7 and day 14.[10,11] We, however, repeated vitamin D levels at 72 hours post intervention and not beyond.

There is a lot of variation in the results of different studies. Few have reported increased severity of disease at presentation, need and duration of inotropes, mechanical ventilation, duration of stay and even mortality while in others no such association could be established.[3,4,6–8,10,16,17,19,23–25]

Variability in the results may be because of the small sample size and non-attainment of sufficient vitamin D levels after intervention. In addition, most of the data is from adult studies, which cannot be implied on children without conducting good randomized pediatric trials.

One of the main strengths, of this study is its prospective nature with randomization. It is also establishing vitamin D levels post-intervention to look for sufficient rise and risk of toxicity. This study has certain limitations. The major limitation was the sample size, which was much less than the calculation. Also, the intervention (vitamin D) did not improve the vitamin D levels in the intervention group. Also, our intervention was not completely blinded, as group A received vitamin D while group B did not receive any placebo. Even though, levels of vitamin D after intervention are an objective parameter. Also, only the nurse who gave the injection of vitamin D and the investigator knew about the allotted group and not the treating PICU team. Also, vitamin D levels could have been estimated at follow-up to look for a gradual rise in vitamin D levels post-resolution of critical illness in both the intervention and non-intervention groups. It was a single-center study with few post-surgical cases and a small sample size. Hence, the results may not be generalized.

Since none of our patients achieved vitamin D levels >30 ng/mL and only 41 (34.75%) attained >20 ng/mL post-intervention; its effect on the outcome may not be relevant. It won't be wrong to say that a higher dose of vitamin D would probably have raised the levels in a sufficient range and the effect on the outcome might have been different from what we observed.

Therefore, there is a need to conduct studies with a higher vitamin D dose to ensure that patients reach a sufficient level at least before effects on various outcome parameters can be studied relevantly.

Also, there are few studies in adults but hardly any data on the improvement in the outcomes of sick children who are

vitamin D deficient after supplementing them with vitamin D. Therefore, further interventional studies with sufficient power to address specific endpoints are needed to determine whether supplementing vitamin D deficient sick children with vitamin D, can bring improvement in their outcomes or not.

Recommendation and Conclusion

Administration of single high-dose vitamin D3 did not improve mortality, hospital length of stay, MODS, need and duration of mechanical ventilation or inotropic support in critically ill vitamin D deficient children. This finding must be further considered for the generation of hypotheses and the conduct of sufficiently powered intervention studies.

Availability of Data and Materials

The data is available with the corresponding author on reasonable request.

Author Contributions

UJ: Conceptualized the study and formulated the strategy. MS: Screening and inclusion of subjects along with sample collection. PP and RS: Results and data extraction. UJ: Any disagreements were resolved after discussion. All authors contributed in drafting of manuscript and approved the final submitted version of manuscript.

Clinical Trial Registry Number

The study was registered with Clinical Trials Registry of India (CTRI/2019/11/022098).

Ethical Approval

The study titled "Effect of vitamin D administration in critically ill vitamin D-deficient patients" was approved by the Institutional ethics committee, MAMC via letter number F.No.17/IEC/MAMC/2018/3 dated 26.10.2018.

Supplementary Materials

The supplementary table 1 is available online on the website www.ijccm.org.

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