



COMPARISON OF EFFICACY OF SINGLE MEGA DOSE VIT D THERAPY VERSUS STANDARD DAILY DOSE VIT D THERAPY IN VIT D DEFICIENT CRITICALLY ILL CHILDREN – A RANDOMIZED CONTROL TRAIL IN A TERTIARY CARE CENTRE.

Paediatric Medicine

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ABSTRACT

Introduction: Vitamin D is very important in calcium and bone homeostasis. The prevalence of VDD has been reported to be very high (upto 50%) in critically ill children admitted in PICU which is associated with increased mortality, increased length of PICU stay. But the impact of supplementation of vitamin D in these children on the clinical outcome is not clear. **Methodology:** A randomized control trial was conducted during the period of October 2019 to march 2021. A study population of 50 children meeting inclusion criteria were enrolled in our study. Vitamin D levels were sent at admission for PICU children if subjects were meeting the inclusion criteria. Children having vitamin D deficiency (<20ng/dl) were randomized into two groups, among which one group received single mega dose vitamin D therapy and second group received standard daily dose vitamin D therapy. These children were followed up until there PICU stay or death. And at the end impact of supplementation was compared among both the groups in terms of length of PICU stay and mortality. **Results:** The mean length of PICU stay among children receiving single mega dose was 5.04 days compared to 3.56 days among children receiving standard dose vitamin D therapy. p value of 0.337 suggesting no significant difference and there was no mortality among these study subjects. Among total of 90 children admitted in PICU fulfilling criteria we found that 50 children had vitamin D deficiency, prevalence being 55.6%. **Conclusion:** The study showed that supplementing single mega dose of vitamin D therapy when compared to standard dose of vitamin D therapy had no advantage on length of PICU stay and mortality.

KEYWORDS

Critically ill children, Mega dose vitamin D therapy, Vitamin D deficiency, Mortality, Clinical outcome.

INTRODUCTION:

Vitamin D is a fat soluble vitamin required for calcium and bone homeostasis vitamin D3 (cholecalciferol) is synthesized in the body from 7-dehydrocholesterol with help of UV light, and later it gets hydroxylated twice to the active form 1,25-dihydroxycholecalciferol in liver and kidney. The human body cannot produce vitamin D2 which has been taken up unlike vitamin D3 which is produced in our body. The prevalence of a lower level of serum vitamin D (<25 nmol/L) is most common in India and other developing countries, darker skin pigmentation, limited sun exposure, higher latitude and lack of foods fortified with vitamin D.⁴

Vitamin D deficiency (VDD) is known to cause hypocalcaemia and skeletal disorders (e.g., rickets).¹ Although, it is very rare to see bone disorders due to severe deficiencies in recent times, many children are in a subclinical VDD state without any classical symptoms but may lead on to causing cardiovascular, respiratory, and immune pathology.

Involvement of these system lead on to severe illness and vitamin D also required for recovery from a critical illness. Vitamin D deficiency is common in critically ill patients.² Vitamin D deficiency is an ongoing pandemic, yet it is one of the most under diagnosed and under-treated nutritional deficiency in the world.³

According to our knowledge there are less studies on relation between VDD and illness severity along with clinical course of the disease. The current study observes the effect of mega dose versus standard dose vit D in VDD sick children admitted in our Paediatric ICU.

Methodology

Materials And Method:

a) **Study Design:** A Randomized Controlled Trial

b) **Study Duration:** 18 months

c) **Sampling technique:**

Type Of Sampling: Simple random sampling

Sample Size: Calculated based on the literature⁹⁷, 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- $n = (Z_{\alpha} + Z_{\beta})^2 \frac{S^2}{X^2} \times \frac{2}{d^2}$

Source of study: Paediatric intensive care unit

D) Study Setting And Method Of Collection Of Data:

After clearance from ethical committee, informed consent was taken from parents after explaining regarding the study, randomization and supplementation, following which children went through

1. Detailed history taking
2. Examination at the time admission to full fill the inclusion criteria as defined above.

Under aseptic precaution 3ml 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 will be assayed in JSS hospital laboratory using ECLIA (Electrochemiluminescence) in the fully automated COBAS 6000 integrated system analyzer.

3. Children with vitamin D levels of 20ng/ml or less were considered as vitamin D deficient and were selected for the study. They were randomly allotted in two groups (25 children in each group) by envelope method. Envelope 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.

With the help of PICU staff, vitamin D deficient children will be allotted into two groups randomly by envelope method.

One group will receive mega dose of vitamin D of 10,000 IU/KG with maximum of 4 lakhs IU as a single oral dose or through NG tube.

Other group will receive vitamin D at 5000 IU/Day for 8 weeks as per standard therapeutic dose, but the children will be followed up only until PICU stay and advised to continue vitamin D supplementation

until the full course is completed.

The outcome of the study were measured in the form of length of Paediatric ICU stay or death of the patient.

Study Population And Source Of Data: A sample size of 50 children meeting inclusion criteria were recruited study, consisting children between 1 year to 18 years admitted at hospital in our PICU, a tertiary care center.

Subject Eligibility:

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

B. Exclusion Criteria:

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

Statistical Analysis:

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.

RESULTS

The study was conducted in children between age group of 1 year to 18 years were enrolled in our study. Among 50 children, 25 children got allotted into group A and received single mega dose and other 25 children allotted in group B received standard daily dose of therapy.

When study subjects receiving intervention A and B were categorized into age groups, both the intervention groups had comparable number of children in age each group suggested by the p value of 0.931.

Table 1 - Distribution Of Study Subjects According To Requirement Of Fluid Resuscitation And Intervention Given

			Intervention given		Total
			A (mega dose)	B (Std dose)	
Fluid resuscitation	Yes	Count	13	6	19
		% within Intervention given	52.0%	24.0%	38.0%
	No	Count	12	19	31
		% within Intervention given	48.0%	76.0%	62.0%
Total		Count	25	25	50
		% within Intervention given	100.0%	100.0%	100.0%

Among children receiving mega dose, 13 (52%) required fluid resuscitation and among children receiving standard dose 6 (24%) required fluid resuscitation.

The p value of 0.79 (>0.05) tells that subjects of both the groups were comparable in terms of requirement of fluid resuscitation.

Table 2 - Distribution of study subjects based on requirement of inotrope support and type of intervention given.

			Intervention given		Total
			A (mega dose)	B (std dose)	
Inotrope support	Yes	Count	2	2	4
		% within Intervention given	8.0%	8.0%	8.0%
	No	Count	23	23	46
		% within Intervention given	92.0%	92.0%	92.0%

Total	Count	25	25	50
	% within Intervention given	100.0%	100.0%	100.0%

Both among children receiving mega dose and standard dose 2 (8%) children required inotrope support.

Table 3 : Showing Comparability Of Inotrope Support Requirement

Chi-Square Tests				
	Value	Df	Asymp. Sig. (2-sided)	p value
Pearson Chi-Square (X^2)	.000	1	1.000	
Fisher's Exact Test				1.000

This table 3 shows a p value of 1.000, suggesting children among both these groups were comparable in terms of requirement of inotrope support.

Table 4 - Distribution Of Study Subjects Based On Requirement Of Respiratory Support And Type Of Intervention Given.

			Intervention given		Total
			A (mega dose)	B (std dose)	
Respiratory support	Yes	Count	18	24	42
		% within Intervention given	72.0%	96.0%	84.0%
	No	Count	7	1	8
		% within Intervention given	28.0%	4.0%	16.0%
Total		Count	25	25	50
		% within Intervention given	100.0%	100.0%	100.0%

Among children receiving mega dose 18 (72%) required respiratory support and 24 (96%) required respiratory support among children receiving standard dose.

The p value of 0.049 tells that statistically significant difference was present between these two groups in terms of requirement of respiratory support.

Table no – 5 Depicting Mean of length of PICU stay among both the groups

	Intervention given	N	Mean	Std. Deviation	Std. Error Mean
Length of PICU	A	25	5.0400	7.43012	1.48602
	B	25	3.5600	1.70978	.34196

Mean of length of PICU stay among children who received mega dose in our study was 5.04 days when compared to 3.56 days among children who received standard dose of vitamin D therapy.

Table 6 : Length of PICU stay among groups

	t	Df	p value	Mean Difference
Length of PICU	.971	48	.337	1.48000

In this table 6 p value of 0.337 tells that there is no statistically significant difference in length of PICU stay among the study subjects receiving intervention A and intervention B. There was zero mortality among the study subjects of 50 children.

Table 7 - Frequencies (Prevalance of vitamin D deficiency)

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

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).

Vitamin D therapy was given to children with vitamin D levels of ranging from 20 to 30ng/ml, but were not included in the interventional study.

Table No 8– Mean Vitamin D Levels Between Cases And Control

	groups	N	Mean	Std. Deviation	Std. Error Mean
Vitamin-D level	Case	50	11.5400	4.97426	.70347
	Control	40	33.9250	18.91870	2.99131

Mean vit D levels among cases were 11.54 ng/dl, when compared to 33.925 ng/dl among controls.

DISCUSSION

The study has been 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.

This study has been conducted between october/2019 to march/2021. vitamin D has other important role in immunity, receptors of vitamin D are present over B and T cells which are important in protecting against infections and recovery from a illness and also plays an important role in autoimmunity¹⁶. Many surveys have shown a large prevalence of vit D deficiency among critically ill children^{14,15} and this study was conducted to know the outcome of supplementing vitamin D to VDD critically ill children and check the efficiency of single mega dose vs std dose vitamin D therapy among VDD critically ill children.

Vitamin D Levels In Present Study

Total study subjects were 90 children among which 50 (55.6%) were vitamin D deficient and 19 (21.1%) had vitamin D insufficiency and others 21(23.3%) had normal vitamin D levels.

Pathophysiology behind vit 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 vit D binding proteins, which affect the absorption of vitamin D from renal tubules leading to deficiency⁶.

This theory helps us correlate VDD with severity of critically ill children, so VDD has been linked with extended length of ICU stay and death among critically ill children.

Present study has been done to determine the outcome of vit D supplementation among VDD critically ill children.

In present study among 50 children with vit D deficiency we used single mega dose vit D keeping in mind to rise the vit D levels quickly, while the other group received standard vit D therapy. Previous studies tell us that high oral dose is safe and is shown to increase the vit D levels to normal rapidly⁷, this will help us to compare the outcome between the two groups i.e length of hospital stay and mortality.

In the present study 50 children were found to be vitamin D deficient, these children were randomly allotted into 2 groups (group A and B), among which group A received single mega dose vit D therapy of (10,000 IU/KG) and group B received standard dose of vitamin D therapy, But in our study we did not find any advantage of children receiving single mega dose vitamin D therapy over standard dose therapy on length of PICU stay / mortality.

Table No 9 - Comparison Between Present Study And Previous Similar Studies

Author	Year	Study subjects	Intervention	Length of hospital stay	Mortality	Other outcomes
Leaf DE ¹⁰	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 ⁹	2014	Critically ill adult patients	Single high dose vs placebo	No effect	No effect	No effect on 6 months mortality
Han JE ⁷	2016	Mechanically ventilated adult ICU patients	High dose over 5 days vs placebo	Decrease d 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 vit D deficiency was 55.6%
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David E leaf⁶ conducted an RCT study with placebo control involving 67 critically ill patient having severe sepsis or shock due to sepsis. Patients got randomized to take single dose of 1,25 (OH)₂ cholecalciferol vs placebo. This study revealed that administration of calcitriol had no effect on plasma cathelicidin levels in these patients and effect on other immunomodulatory markers were varied, calcitriol had no effect on clinical outcomes of the patients when compared to placebo group and observed no side effects with administration of calcitriol.

Amrein K⁹ conducted a RCT study with placebo-controlled, study was done from May of 2010 to September of 2012 at five different ICUs, which consisted 492 critically ill adult white patients admitted under medicine and surgery having vit D deficiency (20 ng/mL). And these patients were assigned to get either placebo (243) vitamin D3 (249). And found out that there was no improvement in length of stay, hospital deaths or 6 months mortality among high dose vit D group in comparison to placebo group, also noticed that a small section of patients showed lower hospital mortality with extreme vit D deficiency, but have suggested that this requires further studies.

Han JE⁷ conducted an RCT which was a pilot study involving patients on MV in adult ICU. Study subjects got randomized into group receiving enteral either 50 thousand IU or 1 lakh IU of vit D 3 consecutively for 5 days and placebo group. The primary outcome for the study was plasma concentration of vitamin D on day 7 and secondary objective were plasma level of cathelicidin, length of hospital stay, SOFA score hospital mortality, duration of mechanical ventilation, mortality at 12 weeks and nosocomial infections.

Supplementing large doses vit D3 safely elevated plasma vit D levels into normal range and also showed decreased length of hospital stay with no alteration in other clinical outcomes compared to placebo group in this pilot study.

Table No 10- Comparison Of Prevalence Of Vitamin D Deficiency In Critically Ill Children Among Different Studies

Author	Year	Subjects	Prevalence
Shilpa bansal et al ¹¹	2020	Critically ill children	72%
James dayremcnally et al ¹²	2017	Critically ill children	54.8%
Kate madden et al ¹³	2012	Critically ill children	40.1%
Present study	2021	Critically ill children	55.6%

And we found that prevalence of vit D deficiency in these children getting admitted to our PICU setup was (55.6%) i.e among 90 children 50 were found to be vitamin D deficient.

Most of the above mentioned studies have established that supplementation of high dose vitamin D in VDD patients in general will increase the levels to sufficient range within days but has not been associated with better clinical outcome .

Our study showed that administration of single mega dose when compared to standard dose vitamin D among VDD critically ill children did not change the clinical outcome.

CONCLUSION

Our study revealed that among vitamin D deficient critically ill children supplementation of single mega dose vit D therapy did not show any advantage on clinical outcome in terms of length of paediatric ICU stay and mortality in comparison to supplementing standard dose therapy.

Present study also revealed the prevalence of vit D deficiency among critically ill children getting admitted to our paediatric ICU is high, (55.6%) i.e 50 children among 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 standard dose of vitamin D therapy.

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