Original Article

The Effects of Vitamin D3 in Pediatric Patients Undergoing Congenital Heart Surgery

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Abstract

Background: To investigate the effects of vitamin D3 on the surgical outcome of pediatric patients undergoing cardiac surgery for congenital heart conditions.

Materials and Methods: Ninety pediatric cardiac surgery patients referred for preoperative evaluation were enrolled. Patients with insufficient vitamin D3 levels received intramuscular vitamin D3 (300,000 IU) three days before the surgery and those with final vitamin D3 level of ≥30 ng/dl were included and divided into 3 groups (Group A: abnormal Vit D levels, no Vit D treatment; Group B: abnormal Vit D levels, Vit D treatment up to normal serum Vit D levels before surgery; Group C: normal baseline Vit D levels, no supplemental Vit D treatment). Interleukin 1, 6, 10, tumor necrosis factor-alpha, vital signs, and arterial blood gas parameters were measured before the surgery and at 6 and 24 hours after cardiopulmonary bypass. Data on total hospital stay, reoperation rates, and inotropes scores were retrieved. Additionally, postoperative measures including hemodynamic factors, blood pressure, heart rate, cardiac output, electrocardiography changes, chest-tube drainage, and ventilation-related factors (i.e. respiratory rate, arterial blood gas, respiratory resistance, intubation time, …) were recorded.

Results: We observed a significant increase in post cardiopulmonary bypass levels of IL-10 and IL-6 in all groups ($p<0.002$) regardless of vitamin D treatment status; however, no significant difference was seen in levels of IL-1 and TNF-alpha. Groups B had more patients with critical levels of VIS scores compared to groups A and C ($p<0.002$). Furthermore, no differences in hemodynamic and metabolic parameters were observed.

Conclusion: No significant difference in the rates of postoperative parameters in patients with normal and those with deficient levels of vitamin D3 was observed.

Keywords: Vitamin D, Congenital heart disease (CHD), Cardiac surgery, Cardiopulmonary bypass, Vitamin D3 supplementation

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Introduction

Twenty-eight percent of all major congenital anomalies consist of heart defects (1). The incidence of congenital heart disease (CHD) has been reported to be approximately 8 in 1000 live births, and 40,000 surgeries are performed in the United States annually to treat this condition (2, 3). The effects of Vitamin D3 deficiency and its contribution to congenital heart disease has long been known and proven (4). Newborns with vitamin D3 deficiency are found to have a greater prevalence of patent foramen ovale (PFO), atrial septal defect (ASD), ventricular septal defect (VSD), and overriding of the great vessels (5, 6). The mechanism of vitamin D3 deficiency leading to these congenital malformations is not well understood to this date. Pediatric patients with vitamin D3 deficiency also experience a more eventful postoperative course, greater mortality, greater postoperative complications, and longer stay in the ICU (2). The literature shows that in children with CHD, preoperative optimization of vitamin D levels improves the postoperative outcomes (7).

Vitamin D3 (1, 25 dihydroxy vitamin D) is a pleiotropic hormone, important for the function of multiple organs. Sufficiency for vitamin D3 is defined as levels above 75-80 ng/dl, a deficiency is defined as levels below 50 ng/dl, and severe deficiency is defined as levels below 30 ng/dl (8).

The best study to date comes from a large prospective observational study published by Zitterman and colleagues, wherein, they demonstrated that compared to normal vitamin D3 levels (75-100 ng/dl) having a value below 50 ng/dl was significantly associated with MACCE risk (i.e., in-hospital death, myocardial infarction, duration of hospitalization, or stroke) (9). The traditional approach to correct vitamin D levels involves oral supplementation over a period of 2 to 3 months (10, 11). Another regimen commonly referred to as Stoss therapy (or mega dose therapy) involves a single oral or intramuscular administration of 50,000 to 600,000 IU (Bordelon, P. Recognition and management of vitamin D deficiency). The efficacy of different vitamin D replenishment regimens to achieve the desired preoperative serum levels can be inferred from several recently completed studies performed on healthy children (12, 13). Early studies of vitamin D and its effects on the immune system demonstrated vitamin D receptor expression in both T and B cells (14). Notably, VDR expression by these cells was only immunologically functional inactive, proliferating cells, suggesting an anti-proliferative role for vitamin D3 in these cells (15). Vitamin D3 targets T helper (Th) cells, and it enforces its effects by suppressing their proliferation and reducing their production of cytokines (16). Activation of naive Th cells by antigens, in turn, leads to the generation of Th cell subgroups with distinct cytokine profiles: Th1 (IL-2, IFN γ, tumor necrosis factor-alpha) and Th2 (IL-3, IL-4, IL-5, IL-10) that respectively support cell-mediated and humoral immunity (17, 18).

Methods

The study was performed after ethical approval from the University Ethics Committee (ethics code: IR.SBMU.RAM.REC.1394.624) and taking informed written consent. A total of 318 consecutive patients were evaluated by the anesthesiology team between April 2016 and April 2018 and assessed for being included in this study. Our inclusion criteria consisted of enrolling patients under the age of 16 with a confirmed diagnosis of congenital heart disease. We excluded patients with insufficient levels of vitamin D who failed to demonstrate a proper level of vitamin D level after intramuscular injection. A total of 179 patients consented to take part in this study. Of the consented patients, 30 were found to have normal serum levels of vitamin D while the remaining 149 were vitamin D deficient. Patients with deficient levels of vitamin D were randomized to either treatment (received intramuscular vitamin D injection) or placebo (did not receive vitamin D). The reception desk at the surgical ward handing the admitting nurse a sealed envelope containing a code representing the group that patients would enter did the randomization. In the vitamin D deficient population, no intervention was undertaken in 30 patients, while another 30 received vitamin D treatment and had adequate levels preoperatively. The remaining 89 patients were excluded from the study because their serum vitamin D levels failed to reach the threshold level set by our study (i.e., 30 ng/dl).

A total of 90 patients were included in our final analysis of data. We divided our patients into three groups as follows. Group A were patients with abnormal levels of vitamin D who did not receive any treatment. Group B consisted of patients who had abnormal levels of vitamin D and received treatment and achieved normal levels before surgery. Group C patients were those with normal baseline levels of vitamin D who did not require treatment with vitamin D.

Our intervention consisted of a single intramuscular injection of 300,000 IU of vitamin D3 three days before the operation in the A group. We also sent blood samples to the lab for evaluating major inflammatory mediators such as interleukins 1, 6, 10 and tissue necrotizing factor-alpha (TNF alpha) before starting the CPB as well six and twenty-four hours after removing patients from CPB. Other items that we measured intraoperatively and postoperatively in the ICU were data on hemodynamic parameters such as blood pressure, Spo2, heart rate, EKG patterns, body temperature, serum electrolytes, arterial blood gas, time spent on the pump, inotropes, amount of blood, and blood products, extubation times, ICU stay, hospital stay, morbidity, and mortality.

Results

Demographics: Ninety consecutive pediatric patients undergoing cardiac surgery were enrolled in this study. The average age was 3.69±1.97 years, while there were 45 males and 45 females who were enrolled in the study. The underlying disease of the patients and their frequencies are demonstrated in Table 1.

In the next step, the patients who were enrolled in the study were then divided into three different groups (A, B & C) each including 30. Patients in ***Group A*** (n=30) had subnormal levels of vitamin D ranging 5-23 nm/ml (mean 12.8 nm/ml, SD ±5.15), this group did not receive any vitamin treatment. ***Group B*** consisted of children with subnormal vitamin D levels ranging 5-29 nm/ml (mean 17.83 nm/ml, SD±6.85) who received a one-time treatment of 300,000 IU intramuscular of vitamin D three day before surgery, in this group the vitamin D levels were checked and those that were above 30 ml were enrolled in the study. ***Group C*** included children with normal vitamin D levels ranging from 30-112 nm/ml (mean 50.71 nm/ml, SD ±20.49) and did not receive any vitamin D treatment before their surgery.

Cytokine levels: Levels of four different cytokines including IL-1, IL-6, IL-10, and TNF-alpha were checked just before surgery, 6 and 12 hours after surgery in all patients, and the change in their levels were documented (Table 2). The levels of IL-1 and TNF-alpha were not significantly different in any of the three different groups preoperatively and after initiating the CPB. On the other hand, levels of IL-10

Table 1- Indicator for patient's level of critical status postoperatively *

	TF	PS	AVC	AS	PVR	VSD	ASD	TGA	Female/Male ratio	Age
Group A	17	1	2	1	0	4	5	0	15/15	3.97±2.2 years (range 4 days-11 years)
Group B	19	0	0	1	1	5	3	1	15/15	2.79±1.9 years (range 5 months-14.0 years)
Group C	12	5	1	0	2	7	2	1	15/15	4.30±1.8 years (range 1.00-11.00 years)
Total	48	6	3	2	3	16	10	2	45/45	3.69±1.97 (4 days-14 years)

* **TF**: Tetralogy of Fallot; **PS**: Pulmonary Stenosis; **AVC**: Atrioventricular Canal; **AS**: Congenital Aortic Stenosis; **PVR**: Pulmonary Valve Replacement; **VSD**: Ventricular Septal Defect; **ASD**: Atrial Septal Defect; **TGA**: Transposition of Great Arteries

Table 2- Cytokine levels in the study groups.

	Group A (n=30)	Group B (n=30)	Group C (n=30)	P value
IL-1				
Before surgery	1.14±0.64	1.00	1.45±2.37	0.638
6 hrs after CPB	1.28±0.80	1.30±1.42	1.59±2.93	0.261
24 hrs after CPB	1.12±0.34	1.00	1.40±2.19	0.185
p-value[1]	0.422	--	0.203	
IL-6				
Before	1.60±2.92	3.59±5.10	4.86±9.21	0.025
6 hrs	31.58±21.68	54.03±51.95	35.75±35.02	0.454
24 hrs	14.22±22.38	19.61±27.10	18.73±25.82	0.104
p-value	<0.001	<0.001	<0.001	
IL-10				
Before	7.00±14.78	20.95±48.68	14.80±26.24	0.414
6 hrs	55.13±44.98	95.42±79.20	86.88±83.85	0.180
24 hrs	25.16±56.33	25.35±48.53	31.14±56.28	0.493
p-value	<0.001	<0.001	<0.001	
TNF-α				
Before	1.05±0.03	1.00	1.02±0.13	0.212
6 hrs	1.05±0.09	1.00	1.32±1.21	0.169
24 hrs	1.10±0.28	1.00	1.40±2.19	0.222
p-value	0.122	--	0.446	

1. Results of Repeated Measures ANOVA

For IL-6 differences between groups A and B (p=0.025) and groups A and C (p=0.007) are significant.

Table 3- Metabolic and fluidic variables in the study groups

	Group A (n=30)	Group B (n=30)	Group C (n=30)	P value
Hematocrit	36.50±6.97	34.87±6.06	34.87±6.06	0.616
Lactate	4.04±2.46	4.31±2.73	4.22±3.20	0.958
Mechanical Ventilation Time	10.74±4.64	17.49±11.56	9.47±5.80	<0.001
Arterial Pressure of CO2 (PaCO2)	37.57±14.12	39.20±12.19	40.93±11.26	0.211
Intravenous fluids	46.17±19.90	43.83±18.23	40.34±21.29	0.325

Hemodynamic changes including Hematocrit, lactate, and CO2 levels were not significantly changed in all groups. Group B patients had a longer ICU stay. The range of hemodynamic changes and secretion in all groups were comparable.

and IL-6 increased significantly in all groups after the initiation of the CPB. Preoperative IL-1 levels were comparable in all three groups but IL-6 levels were significantly higher in group B (3.59±10) and group C (4.86±9). IL-10 had the highest concentration in group B (20.95± 48). The levels of IL-1 were lower than normal in all three groups six hours after initiating CPB (1.78), but levels of IL-6 were significantly higher in group B compared with other groups six hours after the surgery (54.00±51). Levels of IL-10 were higher in both group B (95.42±79) and group C (86.88±83) when compared with group A (55.13±44.98). However, 24 hours after the surgery, levels of IL-1, IL-6, and IL-10 were significantly reduced (Table 2)

Hemodynamic and metabolic measurements: Metabolic measurements including hematocrit level, lactate level, PaCO2, minute ventilation time, and intravenous fluid therapy were measured for all groups and reported (Table 3). Levels of various hemodynamic entities including systolic and diastolic Blood Pressure, heart rate, SpO2, as well as ECG were documented just preoperatively, at the time of the surgery, and postoperatively for all patients, and the

Table 4- Summary of hemodynamic measures.

	Group A (n=30)	Group B (n=30)	Group C (n=30)	P value
Systolic BP	91.27±15.34	99.93±24.41	97.07±19.81	0.437
Diastolic BP	53.00±12.46	58.82±12.47	53.61±12.84	0.166
Heart Rate	128.33±21.01	124.03±17.92	129.87±20.96	0.507
SpO2 §	97.37±4.94	97.87±4.56	96.47±6.08	0.656
Hematocrit	36.50±6.97	34.87±6.06	34.87±6.06	0.616

ICU and hospital stay, as well as IS (Inotrope score) and VIS (Vasoactive Inotropic Score) are shown for all groups. Group B had significantly longer hospital and ICU stay and a longer VIS score
§ Arterial Oxygen Saturation level by Pulse Oxymeter

representative values were selected to obtain an average value for each group (Table 4). No differences in hemodynamic and metabolic parameters were observed amongst the three groups.

Patient morbidity and mortality: Total number of days patients stayed in ICU and hospital were measured for all patients as well as each group separately. Besides, ionotropic score and vasoactive ionotropic score were measured for all patients postoperatively the results of which are summarized in Tables 4 and 5. There were a greater number of patients in the B group (n=23) with critical levels of the vasoactive inotropic score, (defined as a VIS score of 2 or greater) compared to groups A and C (Figure-1).

Statistical Analysis: All continuous variables were presented as mean and standard deviation. The normality of the variables was tested by Kolmogorov Smirnov test and proper graphs. One-way analysis of variance (ANOVA) was employed for comparison of continuous variables among three groups (A, B and C) followed by Tukey post hoc test. For variables that were not normally distributed, nonparametric Kruskal-Wallis test was applied. To evaluate time effects, i.e. before treatment, 6 and 24 hours after treatment, ANOVA method was employed. P-values less than 0.05 were considered as a significant difference.

Discussion

Several interconnected factors may play an important role in outcome of surgery as well as the duration of hospital stay in patients with congenital heart disease; these include elevated levels of pro-inflammatory factors, vitamin D deficiency, and the duration of CPB use during the operation. Ample evidence in the literature points to the fact that elevated levels of interleukins lead to vascular damage resulting in hemodynamic instability and coagulopathy. The main stay of treatment to reduce these factors is the use of high dose systemic corticosteroids as well as

Table 5- Vasoactive inotrope score in various groups.

VIS Group*	Group A (n=30)	Group B (n=30)	Group C (n=30)	P value
0	0 (0.0%)	0(0.0%)	2(6.7%)	<0.001
1	20 (66.7%)	7(23.3%)	18(60.0%)	<0.001
2	7 (23.3%)	11(36.7%)	7(23.3%)	<0.001
3	2 (6.7%)	9(30.0%)	1(3.3%)	<0.001
4	0 (0.0%)	1(3.3%)	1(3.3%)	<0.001
5	1 (3.3%)	2(6.7%)	1(3.3%)	<0.001
Death	1 (3.3%)	0(0.0%)	1(3.3%)	>0.999

* VIS: Vasoactive Inotropic Score; Breakdown of the VIS score is demonstrated for all groups.

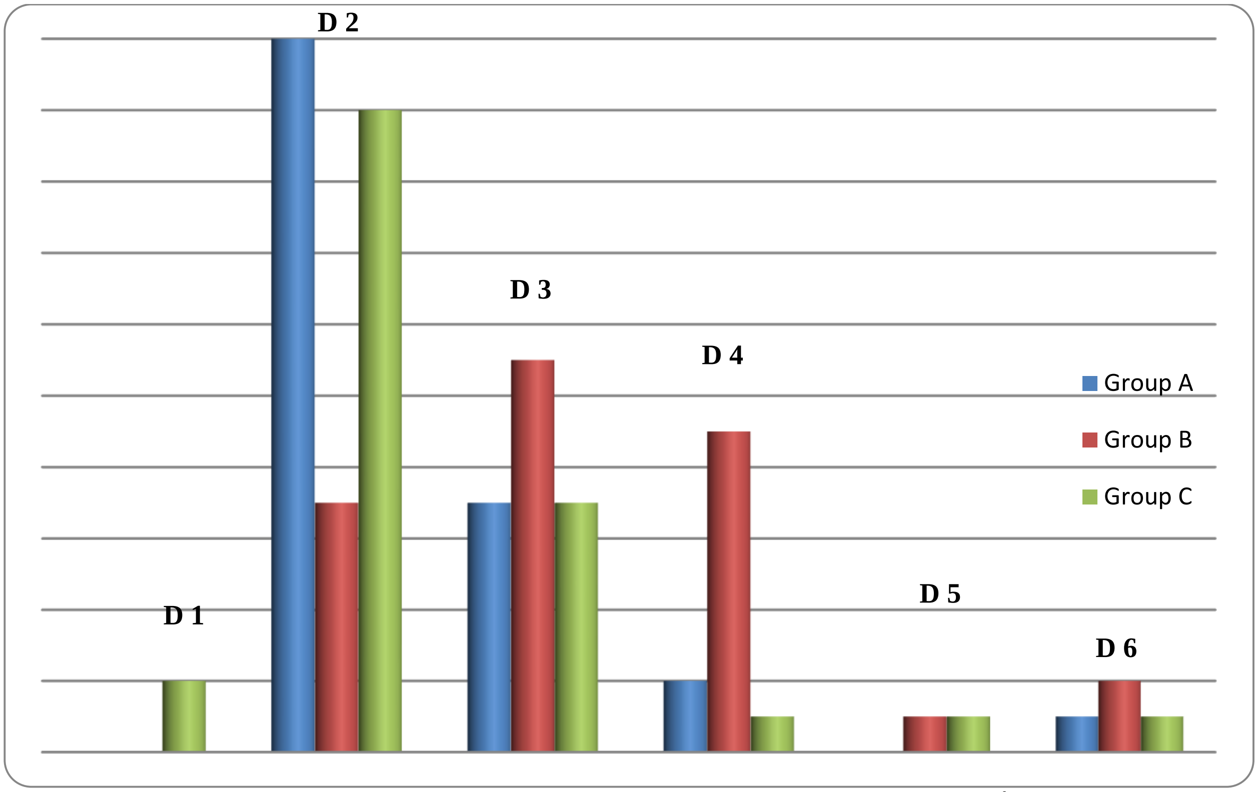

Figure 1. Indicator for patients' postoperative critical status level; **D1**: 1st postoperative day; **D2**: 2nd postoperative day; **D3**: 3rd postoperative day; **D4**: 4th postoperative day; D5: 5th postoperative day; **D6**: 6th postoperative day.

procedures to improve the ventilation status of these patients. However, the treatment modalities mentioned above, aim at reducing already elevated interleukin levels which may have already caused damage. A better option would be taking measures to prevent the interleukins from rising in the first place thus reducing their deleterious effect. We hypothesize based on the current literature that identifying and treating patients with vitamin D deficiency may be effective in this regard. We were able to show that IL 1,6,10 and TNF-alpha increased after placing patients on CPB in all groups regardless of their levels of vitamin D. There has been no evidence, to date, in the literature demonstrating the potential harms or benefits of treating or withholding treatment with vitamin D, in patients with insufficient levels just before the surgery. Therefore, we did not feel that withholding vitamin D therapy in Group A of the study (those with insufficient levels) was detrimental to their health in any known way.

Furthermore, we did not find a meaningful reduction in the levels of aforementioned cytokines in groups of patients who were properly treated for vitamin D deficiency; therefore, demonstrating that correcting vitamin D levels just before surgery (i.e., 3 days before operation) did not improve the surgical outcome, including the time spent in the hospital and ICU postoperatively. However, based on the results of our study, it remains unknown whether identifying patients with vitamin D deficiency and treating them earlier (weeks or months before surgery) would have had any beneficial effects.

One of the prognostic indicators in patients undergoing congenital heart surgery is the use of postoperative inotropes including adrenaline, epinephrine, dopamine, and milrinone. Vitamin D may also play a role in reducing the use of these inotropes postoperatively, therefore, potentially reducing patient morbidity and mortality. In our study, we demonstrated a significant reduction in the amounts of inotropes used in vitamin D deficient patients who were treated with vitamin D before the operation; however, we did not see a significant improvement in the reduction of postoperative complications and hospitalization days, which may be due to our small sample size.

Conclusion

No significant difference in the rates of postoperative parameters in patients with normal and those with deficient levels of vitamin D3 was observed

Acknowledgment

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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