Investigating the Effect of Vitamin D Administration on the Recovery Progress of Infants and Children with Congenital Heart Disease Requiring Reconstructive Heart Surgery

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Abstract

Background

Regular consumption of vitamin D doses can improve heart function in patients with heart failure. The present study aimed to investigate the effect of vitamin D on the recovery process of neonates, infants, and children with Congenital Heart Disease (CHD) following reconstructive cardiac surgery.

Materials and Methods: In this single-blinded clinical trial study, 60 children with CHD requiring reconstructive cardiac surgery, who had been referred to the cardiology department of Razi Hospital affiliated to Birjand University of Medical Sciences, Iran in 2019, were selected and randomly divided to the intervention and control groups. Patients in the intervention group received oral vitamin D before operation (300,000 units of vitamin D) 24 and 48 hours after the operation, patients' hemodynamic conditions were assessed and inotropic drugs were administered accordingly.

Results: The mean vitamin D level was 33.21 ± 4.66 ng/ml in the intervention group (with vitamin D) and 23.55 ± 2.68 ng/ml in the control group (P<0.05). The mean RACH category of the intervention and control groups was 2.33 ± 0.15 and 2.2 ± 0.14 respectively; there was no significant difference between the two groups in this regard. The relationship between vitamin D level with RACH category score, inotrope score, and vasoactive inotrope score was not significant at 24 and 48 hours after the operation in both groups.

Conclusion

According to the results, the administration of vitamin D had no significant effect on the improvement of patients with the congenital cardiac disease after reconstructive heart surgery.

Key Words: Children, Congenital Heart Disease, Infants, Vitamin D.


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1- INTRODUCTION

Congenital heart disorder is a condition that exists from birth and affects the structure of the neonate’s heart as well as its function. These disorders and defects vary from mild to severe (1). Signs and symptoms of congenital heart defect depend on its severity and type; they can be asymptomatic, or they can present with symptoms such as cyanosis, tachypnea, respiratory distress, or tiredness while feeding (1). The cause of congenital heart defects is unknown among most neonates; some of these defects are the reason for genetic or chromosomal changes. These disorders can be created through the combination of genetic and other risk factors such as environmental factors, maternal nutrition, or maternal consumption of specific medicines (1, 2).

The prevalence rate of the congenital heart is about 1% (3). The majority of the patients require one or more reconstructive surgery. During the postoperative period, numerous issues can arise including systemic inflammatory reaction, multi-organ failure, electrolyte disorders, arrhythmias, infection, and endocrine disorders. Some studies have shown that the administration of vitamin D can be an appropriate intervention to improve the results of therapeutic measures in children with congenital heart disease (3, 4).

Recent studies have shown that regular consumption of vitamin D doses empowers heart function in patients with heart failure (5). Researchers have stated that there is an improvement in some patients who took vitamin D, which may reduce their need for an Implantable Cardioverter-Defibrillator (ICD). A cardiac defibrillator is a device that diagnoses dangerous heart rhythm problems and shocks to restore a normal heart rate (5). Vitamin D plays a significant role in health, survival, and fertility of the human. Numerous studies have emphasized its role in the prevention of heart diseases, malignancies, and immune and infectious diseases (6).

Recent studies, raise this matter that vitamin D has a key role in maintaining muscle strength, immune system efficiency, and myocardial health (7). These organs play an important role in restoring the patient’s health after heart surgery. Therefore, vitamin D deficiency can be a modifiable risk factor for postoperative heart issues (8). Vitamin D affects DNA by binding to its receptors in the cell nucleus. Vitamin D also has numerous effects on the immune system of the body and stimulates macrophages, T cells, lymphocytes, activated B cells and regulates Tumor Necrosis Factor (TNF) expression and antibacterial peptides production (9).

It has been identified researches the recent studies that the risk of heart attacks, brain stroke, and cardiovascular failure can be predicted by measuring vitamin D level in the blood (10). Notably, vitamin D could improve exercise tolerance. The response of vitamin D receptors in all tissues, including the cardiovascular system (in presence of sufficient amounts of it) lead to prevent from the sufficient amounts of vitamin D level in blood prevents the irregular proliferation of myocardial cells and the smooth muscles of the vessels wall, and as a result, prevents myocardial hypertrophy and atherosclerosis (11).

Intensive Cares Unit (ICU) patients are at risk of vitamin D deficiency; the underlying cause includes vitamin D deficiency before admission, immobility, insufficient exposure to sunlight, malnutrition, increased conversion of 25 (OH) vitamin D to 1,25 (OH) vitamin D, inflammation, and liver or renal failure (7). Hypocalcemia is a common complication in patients admitted to ICU, and vitamin D deficiency is a key factor. There is a significant relation between hypocalcemia and the incidence of complications in these patients (12). According to recent clinical
studies, a significant number of children with congenital cardiac disorder during the post-operative period suffer from vitamin D deficiency, which is accompanied by an increasing rate of cardiovascular dysfunction. Review articles indicate that vitamin D administration during surgery can accelerate the recovery process and leads to achieving the final results (3, 4). Available data indicate that the current approach to vitamin D prescription is not reliably able to prevent vitamin D deficiency during the post-operative periods (3, 13). Currently, medical personnel responsible for the care of patients with congenital heart defects are recommended to follow the RDA (Recommended Daily Allowance) for vitamin D administration (3, 13).

Designing and conducting clinical trials can help us find alternative strategies for vitamin D administration and improve vitamin D levels during the postoperative period (3). Regarding the lack of studies about the effect of vitamin D administration to infants and children with CHD during the post-operative period, this study was conducted to investigate the effect of vitamin D administration on infants and children with CHD requiring heart reconstruction surgery at Razi Hospital of Birjand city, Iran.

2- MATERIALS AND METHODS

The present study is a single-blinded clinical trial which was conducted in 2019 in Cardiac Surgery of Razi Hospital affiliated to Birjand University of Medical Sciences, Iran. In this study, 46 children with CHD requiring reconstructive cardiac surgery, who had the inclusion criteria to participate in the study were selected and randomly divided to the intervention and control groups.

2-1. Inclusion Criteria

The main inclination criteria were as follow:

- Having congenital heart disease
- The severity of cardiac anomaly (RACH category) less than five
- Lower than or equal to 18 years old
- Serum vitamin D level less than/equal to 150 ng/ml
- Parental or legal guardian consent to participate in the research project and
- Open heart surgery candidate.

2-2. Exclusion Criteria

The main exclusion criteria were as follow:

- Treatment with steroids
- Mechanical ventilation requirement
- Inability to take oral medication due to gastrointestinal problems or worsening heart condition
- Death during surgery or immediately after surgery
- Patients who had undergone cardiopulmonary resuscitation and
- The dissatisfaction of the patient or legal guardian for participating in any phase of the research plan.

2-3. Sample Size

As there were no related studies to determine the sample size; the sample size was determined according to the following equation by considering the first-type error of 0.05 and statistical power of 90% on 30 individuals including 15 individuals of the intervention group, and 15 individuals of the control group. Moreover, to ensure the accuracy of the results, 30 patients were assigned to the intervention group and 30 patients to the control group.

2-4. Method

In this single-blinded clinical trial study, infants and children with CHD requiring reconstructive cardiac surgery were admitted to the cardiac surgery ward of Razi Hospital, who had the inclusion criteria, were randomly assigned into intervention and control groups. After
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approving the design (plan) in the Research Council and getting approvals from the Ethics in Research Committee of the Medical Sciences University of Birjand, patients requiring surgery were investigated in terms of inclusion and exclusion criteria. Initially, a blood sample was taken to determine the serum vitamin D level of the patients and was sent to the hospital laboratory. If the blood vitamin D level of patients were above 150 ng/ml, indicated that the patient was at risk for vitamin D poisoning, therefore must be excluded from the study (4, 5). The severity and complexity of cardiac disorders were also determined using the RACH category scoring system (14).

The RACH category contains six scores (1 to 6) - a higher score indicates a greater risk of morbidity and mortality (14). 300,000 units of vitamin D in the form of six 50,000 unit pearls, which had been softened in water, were orally administered to the patients of the intervention group before the operation, and the patients of the control group received a placebo. Placebo was an oral solution that was similar to the administered vitamin D in terms of appearance and volume; the substance used as the placebo is permitted to be used in the studied age group.

In this study, Cardiac Inotrope Score and Vasoactive Inotrope Score indicators were used as recovery indicators during the 48 hours after surgery. The Inotrope score and the Vasoactive Inotrope Score indicate the patient's need for cardiovascular support with heart stimulant drugs (inotropes) during hospitalization in the cardiac surgery intensive care unit. A higher score is indicative of greater overall morbidity and mortality rate and a worse condition during the post-operative period. These criteria were used to monitor the patients’ response to treatment during the 48 hours after the operation (15). The equations for calculation these two criteria are as follow (15):

Inotrope Score (IS) = Dopamine dose (mcg/kg/min) + Dobutamine dose (mcg/kg/min) + 100 x Epinephrine dose (mcg/kg/min), and

Vasoactive-Inotropic Score (VIS) = IS + 10 x Milrinone dose (mcg/kg/min) + 10,000 x Vasopressin dose (units/kg/min) + 100 x Norepinephrine dose (mcg/kg/min).

The same surgeon carried out all cardiac surgeries. After completing the operation and transferring the patient to the cardiac surgery ICU, within 24 and 48 hours after surgery, the patient's symptoms and signs including heart rate, blood pressure, urinary output, peripheral pulses, arrhythmia, cardiac arrest, heart function status, and other conditions requiring special cares were evaluated by researchers; according to the patient’s conditions, inotropic drugs (milrinone, dopamine, dobutamine, vasopressin, epinephrine, or norepinephrine) were prescribed and the dose was adjusted; using the dose of administered drugs, Inotrope score, and Vasoactive-Inotrope Score was also calculated. Inotrope Score and Vasoactive Inotrope Score were used to calculate the amount of hemodynamic support the patients receive through the administration of different inotropic drugs.

A higher score is indicative of greater morbidity and mortality and also a worse outcome during the post-operative period. Inotrope Score and Vasoactive Inotrope Score were used to assess the patients’ condition and their response to treatment during the 24 hours and 48 hours intervals after the operation.

2-5. Ethical consideration

Parents’ informed consent was obtained before participation in the study. The aim of the present study was also explained to the patient's parents, and participation in this study imposed no costs on patients. This study has the Ethics Code Permission from Birjand University of Medical Sciences (IR.BUMS.REC.1397.301), and
was also registered in the Iranian Registry of Clinical Trials (IRCT20170316033099N6).

### 2-6. Data analysis

Data were analyzed using the SPSS software version 22.0 using the Kolmogorov-Smirnov test to show the normal distribution of data. If there is normal distribution, independent and paired t-tests were performed, otherwise, Mann-Whitney U tests were used. Pearson correlation statistical test was used to investigate the correlation relationships in two groups and the significance level was considered $p < 0.05$. Among the data, only Vasoactive Inotrope Score of the first 24 h had a normal distribution. A $p$-value of less than 0.05 was considered a statically significant difference.

### 3- RESULTS

**Table-1**: Comparison of vitamin D level between the experimental and control groups.

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean± SD</td>
<td>Max</td>
<td>Min</td>
</tr>
<tr>
<td>33.21± 25.55</td>
<td>126</td>
<td>3</td>
</tr>
</tbody>
</table>

SD: Standard deviation.

According to **Table. 2** and after performing the Mann-Whitney U Test, there was no statistically significant difference in Inotrope Score in the first 24 hours period after surgery between the two groups. A similar statistical analysis revealed that there was no statistically significant difference in Inotrope Score in the second 24 hours period after surgery between the two groups. According to the results of the Mann-Whitney U test, there was a statistically significant difference in Inotrope Score during the first and the second 24 hours after the surgery in the intervention group ($P<0.001$). Moreover, there was also a statistically significant difference in Inotrope Score during the first and the second 24 hours after the surgery in the control group ($P=0.037$). It should be noted that vitamin D was prescribed after surgery in the intervention group.

The study was performed on 60 children with congenital heart disease; There were 16 male patients (53.3%) and 14 female patients (44.7%) in each group. The mean age of patients in the intervention group was 46.73 months with a standard deviation of 10.35, and the mean age of patients of the control group was 46.72 months with a standard deviation of 9.48 ($P> 0.05$). According to **Table.1**, the average vitamin D level in the intervention group and the control group was 33.21 ± 4.66 (33.21± 4.66), and 23.55 ± 2.68 ng/ml, respectively. A comparison of average with the Mann-Whitney method showed that there was a significant difference at the level of 5% between the two groups in terms of the vitamin D level ($P = 0.037$).
**Table-2:** Comparison of Inotrope Score in the experimental and control groups between the first and the second 24 hours periods.

<table>
<thead>
<tr>
<th>Study groups</th>
<th>The first 24 hours, Mean± SD</th>
<th>The second 24 hours, Mean± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>9.17± 4.30</td>
<td>4.03± 3.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>7.90+4.68</td>
<td>4.23± 3.11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD: Standard deviation.

According to Table.3 and after performing the Mann-Whitney U Test, there was no statistically significant difference in Vasoactive Inotrope Score in the first 24 hours period after surgery between the two groups. A similar statistical analysis revealed that there was no statistically significant difference in Vasoactive Inotrope Score in the second 24 hours period after surgery between the two groups. According to the results of the Mann-Whitney U test, there was a statistically significant difference in Vasoactive Inotrope Score during the first and the second 24 hours after the surgery in the intervention group (P<0.001). Moreover, there was also a statistically significant difference in Vasoactive Inotrope Score during the first and the second 24 hours postoperatively in the control group (P<0.001). According to Table. 3, Vasoactive Inotrope Score reduction between the first and the second 24 hours period in the intervention group was more significant compared to the control group. However, after analyzing with iterative measuring method, therapy group variable was not significant by considering the effects of time and vitamin D level (P = 0.73), which indicates that Vasoactive Inotrope Score changes during the first and the second 24 periods after surgery are not statistically different between the two groups.

**Table-3:** Comparison of Vasoactive-Inotrope Score in the experimental and control groups between the first and the second 24 hours periods.

<table>
<thead>
<tr>
<th>Study groups</th>
<th>The first 24 hours, Mean± SD</th>
<th>The second 24 hours, Mean± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>11.43±5.36</td>
<td>6.30±4.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>10.67±5.75</td>
<td>6.73±4.21</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD: Standard deviation.

According to Table.4, and after conducting the Mann-Whitney U Test, there was no statistically significant difference in the RACHS category mean between the two groups (P=0.427). There is also no statistically significant difference in the RACHS category first and third quartile between the two groups. Pearson correlation test showed that there is no significant statistical relationship between vitamin D level with the RACH category score, cardiac inotrope score, and vasoactive inotrope score at the first and second 24h in two intervention and control groups (P> 0.05) (Table.5).

**Table-4:** Comparison of RACHS category between the experimental and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Experimental group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean± SD</td>
<td>Mean (first quartile – third quartile)</td>
<td>Mean (first quartile – third quartile)</td>
<td>0.427</td>
</tr>
<tr>
<td>2.33± 0.80</td>
<td>2(2-3)</td>
<td>2.2± 0.76</td>
<td>2(2-3)</td>
</tr>
</tbody>
</table>

SD: Standard deviation.
Table-5: Relationship between VIS, IS and RACH category with vitamin D level among the experimental and control groups in first and the second 24 hours periods.

<table>
<thead>
<tr>
<th>Vitamin D level</th>
<th>Study group</th>
<th>RACHS category</th>
<th>IS in the first 24 hours</th>
<th>IS in the second 24 hours</th>
<th>VIS in the first 24 hours</th>
<th>VIS in the second 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>r</td>
<td>P-value</td>
<td>r</td>
<td>r</td>
<td>P-value</td>
</tr>
<tr>
<td>Experimental</td>
<td></td>
<td>0.147</td>
<td>0.439</td>
<td>0.351</td>
<td>0.057</td>
<td>0.162</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td>0.087</td>
<td>0.649</td>
<td>0.099</td>
<td>0.604</td>
<td>0.022</td>
</tr>
</tbody>
</table>

VIS: Vasoactive-Inotropic Score, IS: Inotrope Score, r: Pearson correlation coefficient.

4- DISCUSSION

This study was performed to investigate the effect of vitamin D prescription on the recovery process of infants and children with CHD requiring reconstructive heart surgery. According to the previous studies and findings of vitamin D deficiency in critically ill patients and postoperative vitamin D level reduction in patients with congenital heart disease, we designed this study to assess the effect of vitamin D administration on the postoperative therapy course of patients with CHD. In our study, 89% of the enrolled patients had moderate, and 51.5% of the patients had severe vitamin D deficiency, which highlighted the importance of vitamin D deficiency modification as a possible risk factor for poor postoperative outcomes. We assessed the postoperative therapy course and outcome by using inotrope score and vasoactive inotrope score during the 48 hours postoperatively in the two groups. The results of this study showed that vitamin D administration had no effect on the outcome. According to the results of the present study, before the intervention, the mean vitamin D level in the intervention group and the control group were normal and below normal, respectively. The mean vitamin D level after consuming vitamin D was 33.4 ± 21.66 ng/ml in the intervention group and 23.2 ± 55.68 ng/ml in the control group. The difference between the blood vitamin D level of the two groups was statistically significant (P = 0.037). Regarding other aspects including age, gender, and RACH category, there was no significant difference between the two groups. According to the study conducted by Kazemi et al. (4) on 67 pregnant mothers who performed normal vaginal delivery in Zanjan city, blood levels of vitamin D in newborns were much lower than the control group. In a study conducted by Abou Zahr et al. (16) on children between 2-17 years, vitamin D level of 20 patients with CHD was measured at three time points, including immediately before surgery, immediately after surgery, and 24 hours after surgery; the mean vitamin D level was 26.8 ± 4.2, 21.5 ± 5.7 and 23.9 ± 4.9 ng/ml, respectively (P <0.001). These findings are extremely similar to the results of our study regarding the control group who had not received vitamin D supplementation, which confirms the hypothesis that predicts cardiopulmonary bypass reduces vitamin D blood level (16). McNally et al. (13) also have reported a 40% reduction in mean vitamin D level of children with CHD after surgery; the mean vitamin D level was 58 nM (23.24 ng/ml) at admission and 34.2 nM (13.70 ng/ml) after surgery. In this study, cardiac Inotrope Score, and Vasoactive Inotrope Score indices were used as criteria of
recovery within 48 hours after surgery. According to the results, the mean IS in the second 24 hours was sharply lower than the first 24 hours in the two groups, and this difference was quite significant (P <0.001). IS reduction between the first and the second 24 hours period in the experimental group was more significant compared to the control group. Nevertheless, after analyzing with the repeated measure method, therapy group variable was not significant by considering the effects of time and vitamin D level (P = 0.73), which indicates that IS changes during the first and the second 24 periods after surgery were not statistically different between the two groups. Graham et al. reported similar results; their study was performed on 70 neonates in which IS was reduced after the first 24 hours period (P=0.008), but mean serum vitamin D level at 24 hours after heart surgery did not change compared to the pre-operative values (17). The different pattern of serum vitamin D level changes in the study conducted by Graham et al. compared to other studies (13, 16, 18) can be due to differences in age, race, and sex of the patients enrolled in these studied; differences in the of priming solutions used, including crystalloid and colloid solutions which contain 25 (OH) D during cardiopulmonary bypass (CPB) (17).

The IS of the intervention group was reduced more significantly during the second 24 hours interval after operation compared to the control group; this difference could be due to the positive effect of vitamin D administration on the therapy course of patients. According to the results of the present study, there was a statistically significant difference in Vasoactive Inotrope Score during the first and the second 24 hours of post-operatively periods in both the intervention and control groups (P<0.001). High VISs indicate a worsening patient's condition and an increased mortality rate (14). VIS reduction between the first and the second 24 hours periods in the intervention group was more significant compared to the control group; but after analyzing with repeated measures, therapy group variable was not significant by considering the effects of time and vitamin D level (P = 0.73), which indicates that VIS changes during the first and the second 24 periods after surgery are not statistically different between the two groups. Davidson et al. found that high VIS at 48 hours after cardiac surgery was strongly associated with increased duration of ventilation, length of ICU stay, and the total length of hospital stay (19). Infants undergoing cardiac surgery, who require CPB, have higher morbidity and mortality rates compared to other groups (20).

According to a study conducted by Gaies et al. (15) on 391 infants, showed that the highest VIS (VIS> 15) was recorded during the first 24 hours period. They found that high VIS was strongly associated with a 30-day mortality rate, cardiac arrest, hemodynamic mechanical support requirements, dialysis, nerve damage, duration of mechanical ventilation, and length of ICU stay (15).

Favia et al. suggest that as Levosimendan is being increasingly used in children with chronic heart failure and post-operative severe left ventricular dysfunction, VIS should also be calculated based on the dosage of this drug, like phosphodiesterase inhibitors (Milrinone, Amrinone) (21). The results of the present study showed that the mean RACH category, which is an indicator of the complexity of congenital heart disease and corrective surgical procedures, was statistically the same in both intervention and control groups (P= 0.427). Regarding the RACH category, both groups were statistically the same, which indicates that the complexity of patients’ congenital heart disease had no confounding effect on our study. Larsen et al. (22) applied the RACH category score
to 957 heart surgeries in Denmark and concluded that it is a good predictor of mortality and length of stay in the hospital. Mattos et al. (23) suggested that age, nutritional status, clinical factors associated with it (lung infection, heart failure, sinusitis, acidosis, infection, genetic syndrome, mechanical ventilation, and long-time hospitalization), and cardiopulmonary bypass time should be evaluated in addition to surgical complexity, and they concluded that these variables could have a direct impact on the result of surgery. The results of the study of Al-Radi et al. (24) also showed that the RACH category method is the best method for predicting infants' mortality.

4-1. Limitations of the study

The limitations of this study are as follow; pre-operative vitamin D level difference between the intervention and control groups could have a confounding effect, which was not measured in this study. We recommend considering this possible confounding effect in future studies. Small sample size and the lack of long term patient follow up are among other limitations. We are aware that this study cannot strongly rule out the role of vitamin D deficiency and vitamin D administration in the postoperative therapy course of CHD patients. We recommend performing similar studies with a larger sample size. We also recommend a more accurate study design in which more possible confounding factors could be eradicated.

5- CONCLUSION

According to the results of this study, vitamin D administration had no significant effect on the recovery process of CHD patients after surgery. In other words, the scores of IS, VIS, and RACH had no significant relationship with post-operative vitamin D levels in these patients. As several other factors might affect the recovery process of congenital cardiac disease and their overall mortality, we suggest further studies with a larger sample size.

6- CONFLICT OF INTEREST

7- REFERENCES


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