Effect of Vitamin D Supplementation on Postoperative Outcomes in Cardiac Surgery Patients: A Systematic Review

Sambhunath Das1 Punyatoya Bej2

1 Department of Cardiac Anaesthesia and Critical Care, AIIMS, New Delhi, India
2 Department of Community Medicine, Rama Medical College and Research Centre, Hapur, Uttar Pradesh, India


Introduction
Vitamin D deficiency (VDD) is highly prevalent worldwide due to the environmental pollution, minimal exposure to sunlight, dietary deficiency, and lifestyle changes of man-kind.1 It is detected in all the age groups. Commonly VDD has been associated with infection, respiratory illness, cardiovascular diseases, cancer, preeclampsia, dental caries, and neurological diseases.1 Greater proportions of people with cardiovascular disease have low vitamin D level compared
with general populations. Patients undergoing cardiac surgery are at risk of arrhythmia, myocardial ischemia, ventricular dysfunction, bleeding, and infections. The risks may be aggravated by VDD. Many patients have low vitamin D levels before and after open heart surgery, but those levels can be restored to normal with supplementation with vitamin D. Vitamin D supplementations taken by patients with chronic heart failure are associated with improved cardiac function. Low blood levels of vitamin D have increased risks of heart disease like stroke, hypertension, and aortic dissection that create problems in postoperative outcome. Low vitamin D level may be a potential risk to respiratory complications in intensive care unit (ICU). Low levels of vitamin D have been linked to high blood pressure. The postoperative ICU stay and complications are higher in pediatric cardiac surgery patients with VDD.

However, a few recent articles have not detected any difference in postoperative outcome of VDD patients related to atrial fibrillation and other parameters. In the hospital setup, perioperative vitamin D therapy is the way forward to normalize the serum level. Hence, the outcome of the therapy needs to be systematically reviewed for clinical recommendation.

In the present systemic review, all the available literatures related to impact of vitamin D therapy on postoperative outcomes in cardiovascular surgical patients over duration of 10 years are analyzed. The efficacy, safety, and public health impact of vitamin D therapy in cardiac surgical patients on postoperative period were assessed.

**Methodology**

**Inclusion criteria:** Only original articles were included. The original papers were from clinical trials, observational, cross-sectional, and cohort studies. The studies were both prospective and retrospective. Studies with all age groups and all types of cardiac surgery were included. The full-text articles with complete data on postoperative outcome were chosen.

**Exclusion criteria:** Review, systematic review, meta-analysis, case report, letter to editor, editorial papers, and stand-alone abstract were excluded. Papers of the patients with emergency surgeries, redo surgeries, transplantation, New York Heart Association class 4, and multisystem illness undergoing cardiac surgery were also excluded.

**Publications search method:** Published full-text studies were searched in PubMed, Embase, Google Scholar, and Cochrane database with the keywords of vitamin D supplementation, VDD, postoperative cardiac outcome, cardiac surgery, cardiac anesthesia, perioperative period, ICU, and hospital stay for 10 years during year 2012 to 2022. One independent person was involved in searching the literatures. The details of literature search are mentioned in Fig. 1.

Data analysis: The data collected from the articles were processed and evaluated to conclude the study. The articles related to the VDD in cardiac surgery patients and the impacts of vitamin D supplementation and therapy on postoperative outcomes were assessed.

**Result**

Total 10,407 articles were retrieved. Out of which eight full-text original studies were found suitable for the systemic review and critical analysis after applying the study protocol and exclusion criteria (Fig. 1). All the eight articles were randomized control trials (RCT). The authors’ name, year of publication, study type, sample size, and outcomes are mentioned in Table 1.

Most of the studies reported a significant fall in vitamin D level in the patients during and after cardiac surgery. Valve and congenital heart surgery patients had maximum fall in vitamin D level. All the RCTs detected restoration of vitamin D level back to normal value after supplementation of vitamin D. Six studies (75%) showed more than or equal to 1 parameter improvement in postoperative outcome after cardiac surgery because of vitamin D supplementation (Table 2). Two studies (25%) reported no significant difference on postoperative outcomes. Three studies (37.5%) detected significant reduction in postoperative atrial fibrillation (POAF) by vitamin D therapy. Two studies (25%) detected significant reduction in inotrope requirement postoperatively compared with control group. One study (12.5%) observed marked reduction in duration of ICU and hospital stay in vitamin D supplementation group compared with control. One study (12.5%) detected small reduction of interleukin–10 in vitamin D supplementation group compared with placebo without any difference in postoperative acute kidney injury. One study (12.5%) observed anti-
<table>
<thead>
<tr>
<th>Authors reference</th>
<th>Study type</th>
<th>Sample size</th>
<th>Outcome of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerit et al&lt;sup&gt;19&lt;/sup&gt; 2018</td>
<td>RCT</td>
<td>136 CABG</td>
<td>The occurrence of POAF was not significantly different among treatment and control groups in patients with vitamin D insufficiency (31 vs. 33%, <em>p</em> = 0.538); however, there was a significant difference between the two groups regarding POAF in patients with vitamin D deficiency (18 vs. 29%, <em>p</em> = 0.02)</td>
</tr>
<tr>
<td>Barker et al&lt;sup&gt;7&lt;/sup&gt; 2021</td>
<td>RCT</td>
<td>150 Adult cardiac surgery</td>
<td>Perioperative vitamin D supplementation protects against the immediate decrease in plasma 25(OH)D induced by open-heart surgery. In patient outcomes and serious adverse events did not differ significantly between vitamin D and placebo-treated groups postoperatively and after 6 months. However, there tended (both <em>p</em> = 0.06) to be fewer heart failure hospitalizations, and other serious adverse events (i.e., atrial fibrillation, pacemaker, cardiomyopathy) in the vitamin D-treated group</td>
</tr>
<tr>
<td>Jelveh-Moghaddam et al&lt;sup&gt;11&lt;/sup&gt; 2020</td>
<td>RCT</td>
<td>318 CHD</td>
<td>A significant increase in post-CPB levels of IL-10 and IL-6 in all groups (<em>p</em> &lt; 0.002) regardless of vitamin D treatment status; however, no significant difference was seen in levels of IL-1 and TNF-α. Groups B (abnormal vitamin D levels, vitamin D treatment up to normal serum vitamin D levels before surgery) had more patients with critical levels of VIS compared with groups A (abnormal vitamin D levels, no vitamin D treatment) and C (normal baseline vitamin D levels, no supplemental vitamin D treatment) (<em>p</em> &lt; 0.002). Furthermore, no differences in hemodynamic and metabolic parameters were observed. A significant reduction in the amounts of inotropes was used in vitamin D deficient patients who were treated with vitamin D before the operation</td>
</tr>
<tr>
<td>Talasaz et al&lt;sup&gt;9&lt;/sup&gt; 2022</td>
<td>RCT</td>
<td>196 CABG</td>
<td>The occurrence of POAF was significantly lower in group B as compared with group A (9.68 vs. 20.39%, <em>p</em> = 0.038). The length of ICU stay and hospital stay was reduced in group B patients (2.21 vs. 3.86 days, <em>p</em> &lt; 0.001 and 7.40 vs. 9.58 days, <em>p</em> = 0.022, respectively). The study demonstrated that vitamin D supplementation reduces the incidence of POAF, duration of ICU, and hospital stay following CABG surgery</td>
</tr>
<tr>
<td>Kara and Yasim&lt;sup&gt;10&lt;/sup&gt; 2019</td>
<td>RCT</td>
<td>116 CABG</td>
<td>The ratio of POAF occurrence found in the treatment and control groups were 12.07 and 27.59%, respectively. Vitamin D treatment was found to reduce the risk of POAF development by 0.24 times (<em>p</em> = 0.034). In this study with sufficient sample size, preoperative short-term high-dose vitamin D supplementation was found to be significantly preventive to the occurrence of POAF in patients with vitamin D insufficiency and deficiency who underwent CABG surgery</td>
</tr>
<tr>
<td>Sahu et al&lt;sup&gt;8&lt;/sup&gt; 2019</td>
<td>RCT</td>
<td>60 CHD</td>
<td>Prevalence of severe vitamin D deficiency was 93.1%. When compared with the control group, study group showed higher serum vitamin D levels in the immediate preoperative period (<em>p</em> = 0.001), postoperative period following CPB (<em>p</em> = 0.012), and on the first postoperative day (<em>p</em> = 0.003). No statistically significant difference was observed in postoperative mechanical ventilation (<em>p</em> = 0.35), ICU stay (<em>p</em> = 0.15), and inotropic duration (<em>p</em> = 0.19). Children with TOF are highly deficient of vitamin D, its level falls further after CPB, and supplementing vitamin D preoperatively does not influence postoperative recovery pattern. Supplementation of vitamin D as “stoss therapy” was useful in raising serum levels before and after cardiac surgery</td>
</tr>
<tr>
<td>McNally et al&lt;sup&gt;25&lt;/sup&gt; 2020</td>
<td>RCT</td>
<td>41 CHD</td>
<td>The high-dose group had higher 25-hydroxyvitamin D concentrations both intraoperatively (mean difference + 25.9 nmol/L; 95% CI: 8.3–43.5) and postoperatively (mean difference + 17.2 nmol/L; 95% CI: 5.5–29.0). Fewer participants receiving high-dose supplementation had postoperative serum 25-hydroxyvitamin D concentrations under 50nmol/L, compared with usual care (RR: 0.31, 95% CI: 0.11–0.87). Postoperative vitamin D status was associated with the treatment arm and the number of doses</td>
</tr>
</tbody>
</table>
inflammatory effect with high-dose supplementation but without any difference in prevention of acute kidney injury both in control and treatment group.\textsuperscript{12} There was an insignificant lesser incidence of adverse cardiac events like pacemaker insertion and cardiomyopathy, POAF, and postoperative heart failure with vitamin D supplementation in one RCT.\textsuperscript{7} All the eight RCT did not found any adverse effects with vitamin D supplementation and detected to be safe in all patients even with high doses.

**Discussion**

The systemic review of the literatures over past 10 years from the peer reviewed journals with 8 RCTs detected that vitamin D supplementation in perioperative period helped to restore the VDD in all patients. The normal level of vitamin D is important to balance the calcium and other vitamin D-dependent activity in cardiac patients after surgery, which was achieved by perioperative administration of vitamin D. Improvement in postoperative outcomes from vitamin D treatment in the form of reduction in POAF, lower requirement of inotropes, reduction in duration of ICU, and hospital stay and less cardiac adverse events were detected by six studies. Two studies did not find any significant difference in postoperative outcomes. Supplementation of vitamin D was found to be safe and without any adverse side effects as proved by all RCT.

Vitamin D is not only a fat-soluble vitamin but also has prohormone property and has pleiotropic action.\textsuperscript{13} Commonly known function of vitamin D is for calcium and phosphorus absorption from intestine and kidney with the help of parathormone (PTH).\textsuperscript{13,14} Hence, it is responsible for bone and muscle growth. It is also responsible for genetic regulation of cardiac myocytes, vascular endothelium, and other tissue cells. It has other important biological activities in the body like modulation of immune system, reduction in cancer risk, and others.

**Table 1** Improvement in postoperative outcomes from vitamin D treatment in the form of reduction in POAF, lower requirement of inotropes, reduction in duration of ICU, and hospital stay and less cardiac adverse events were detected by six studies. Two studies did not find any significant difference in postoperative outcomes. Supplementation of vitamin D was found to be safe and without any adverse side effects as proved by all RCT.

**Table 2** Improvement in postoperative outcomes by vitamin D treatment from studies ($n = 8$)
insulin secretion, inflammation, and cellular functions by binding to vitamin D receptors (► Fig. 2). Vitamin D is classified into five types. The most important are D2 or ergocalciferol and D3 or cholecalciferol. These two forms are produced by ultraviolet light irradiation of calciferol in plant foods to D2 and exposure of epidermis (skin) of human to sun light for D3. Vitamin D is converted to 25, hydroxyl vitamin D (25(OH)D) in liver. 25(OH)D is used to measure vitamin D level and help to detect the deficiency. A value of 25(OH)D less than 20nL/mL is diagnosed as VDD. 25(OH)D is converted to 1,25(OH)2D in kidney. 1,25(OH)2D is the active form for performing all actions but cannot be measured to know the level of vitamin D.

Deficiency of vitamin D is more common after cardiac surgery. Valve surgery patients compared with other adult cardiac surgical cases had significant fall in vitamin D both intra- and postoperative period. The fall is more pronounced in children compared with adult. TekeliKunt et al detected more fall in females compared with male.

POAF: The present systemic review detected three RCTs showing reduction in POAF by vitamin D supplementation. However, Sahu et al did not find any difference. Conflicting results were seen by a prospective cohort study by Ohlrogge et al for POAF with VDD. Many of the studies commented on VDD and POAF, though they have not conducted the studies with supplementation of vitamin D.

Inotropes requirement: Jelveh-Moghaddam et al reported a significant reduction in inotrope requirement in patients after supplementation of vitamin D. The vasoactive inotropic score (VIS) was less compared with placebo treatment. It can be proved by the logic that VDD patients are more dependent on high-dose inotropes, more incidences of vasoplegia, and high VIS. However, Sahu et al observed no difference in days of inotropes requirement by vitamin D supplementation.

Major adverse cardiac and cerebrovascular events (MACCE) and kidney function: In this systematic review, Barker et al reported less MACCE in vitamin D-treated patients. This is supported by Zittermann et al who detected 9.4% incidence of stroke, myocardial infarction, low cardiac output syndrome in postoperative patients of cardiac surgery with VDD compared with normal level. None of the RCTs in this review showed any improvement in kidney function by vitamin D therapy. However, in literature some of the studies reported postoperative deterioration of renal function in the presence of VDD.

ICU and hospital stay: Talasaz et al detected reduced ICU and hospital stay with vitamin D supplementation. This is justified by the study by Ney et al who detected higher incidence of respiratory failure, organ dysfunction, infection, high PTH, neuronal injury, longer ICU, and hospital stay in cardiac surgical patients with low levels of 1,25(OH)2D. However, in another RCT by Sahu et al detected no difference in duration of mechanical ventilation and ICU stay between supplementation and control group.

The present systematic review recommends the perioperative supplementation of vitamin D in cardiac patients. This is supported by six out of eight RCTs. The supplementation will restore the normal level of vitamin D in VDD cardiac surgery patients and it is without any side effects.

**Limitations**

The numbers of prospective studies were only eight in number. More RCTs with large sample size will provide clarity on the effects of routine perioperative vitamin D supplementation.

**Conclusion**

To conclude, VDD is very common after cardiac surgery. Vitamin D supplementation will restore vitamin D level to normal in all patients. The systematic review detected one or more improvement in postoperative outcomes after cardiac surgery from 75% studies. Vitamin D supplementation was found to be safe in clinical practice even with high-dose regime. Further studies, followed by meta-analysis and systematic reviews, will provide more knowledge on the perioperative use of vitamin D supplementation in cardiac surgery patients.

**Funding**

None.

**Conflict of Interest**

None declared.

**References**

Vitamin D Supplementation on Postoperative Outcomes


