ISSN: 0975-3583,0976-2833 VOL13,ISSUE05,2022

Title page

Correlation of Preoperative Vitamin D Levels with Adverse Cardiac and Cerebrovascular Events in Cardiac Surgery.

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Abstract

Objectives

To investigate the association of pre-operative 25-hydroxyvitamin D (25(OH)D) levels with major cardiac and cerebrovascular events (MACCE) in patients undergoing cardiac surgery.

Materials and methods

All patients undergoing cardiac surgery in Department of Cardiothoracic surgery, J.N.M.C.H., Aligarh were included. Prior to day of surgery, fasting sample were withdrawn and sent for measurement of Vitamin D levels in endocrinology laboratory. Estimation of Vitamin D levels were done by Chemo-luminescence Immuno-Assay (CLIA) [BECKMAN COULTER Access 2 Model]. 48 hours after surgery, again fasting blood sample were sent to same lab for evaluation of vitamin D levels. MACCEs were recorded.

Results

Among the seven expired patients in the study , only one had Vitamin D level in the borderline category, while the remaining six had levels in the deficient category. No patient with Vitamin D levels in the sufficient category had in-hospital mortality. The effect of Vitamin D levels on in-hospital mortality is, however, not statistically significant with p-values of 0.287, 0.95 and 0.418 respectively for Gr. I vs Gr. II, Gr. II vs Gr. III and Gr. I vs Gr. III. It is observed that lower the Vitamin D level, the higher is the duration of in-hospital stay. The effect of Vitamin D levels on in-hospital stay is not significant for Gr. II vs Gr. III with p-value of 0.266. It is, however, highly significant for deficient vitamin D levels than borderline or sufficient levels with p-values of 0.001, and 0.000 respectively. Higher the level of Vitamin D, the shorter is the duration of stay in ICU among the patients in the present study. The effect of Vitamin D levels on ICU stay is

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highly significant for all the three groups with p-values of 0.05, 0.006 and 0.000 respectively for Gr. I vs Gr. II, Gr. II vs Gr. III and Gr. I vs Gr. III. Higher the level of Vitamin D, the shorter is the duration of ventilation. The effect of Vitamin D on the duration of ventilation is highly significant only for Gr. I vs Gr. II and Gr. I vs Gr. III with p-values of 0.000 and 0.002 respectively. There were only five patients who had post-operative stroke in our study. All the cases with post-operative stroke belonged to the deficient category (<30 ng/ml) of Vitamin D level.

Conclusion

We recommend that all patients undergoing cardiac surgery should have their serum Vitamin D level checked and if time permits vitamin D level should be corrected by oral / parenteral supplementation to decrease incidence of post-operative MACCE events.

Vitamin D which is a fat soluble vitamin act after binding with a specific nuclear binding receptor and is involved in many metabolic pathways in humans. Adequate vitamin D status is important for optimal function of many organs and tissues throughout the body, including the cardiovascular (CV) system besides involvement in bone health [1]. Many studies have shown that low 25-hydroxyvitamin D levels are associated with coronary risk factors and adverse cardiovascular outcomes. A study of male health professionals showed a 2-fold risk of myocardial infarction (MI) in subjects who were vitamin D deficient compared to those in the sufficient range [2].

It is estimated that approximately 50% of young adults [3] and apparently healthy children [4] are suffering from vit D deficiency. In 1990s, study was done in two human population at high and moderate risk of CV disease and an inverse association was reported between circulating 1,25(OH)2D level and vascular calcification[5]. A study done by Zittermann et al(6) has shown a nonlinear increase of major adverse cardiac and cerebrovascular events (MACCE) until discharge in patients with inadequate and deficient circulating 25(OH)D levels as compared with patients of adequate vitamin D levels.

In a study Vitamin D supplements were given in heart failure patients and are associated with reduced mortality Inverse association of vitamin D supplement with mortality was most pronounced in patient with 25(OH)D levels < 24nmol/L. [7] In another study on cardiovascular patients [8], there was substantial survival benefit among individuals who were on vitamin D supplementation (odds ratio for death 0.39 (95%CI: 0.280.53) compared to vitamin D non-users.

In Framingham Offspring study, a correlation between 25(OH)2D deficiency and subsequent major adverse CV events was found among 1,739 participants who were free of CV disease at baseline[9]. In this prospective observational study, 25(OH)2D levels were measured at baseline and follow up was done for mean of 5.4 years. The rate of a composite CV end point (fatal or nonfatal MI, ischemia, stroke, or heart failure) was 53% to 80% higher in people with low vitamin D levels. The increased CV risk associated with vitamin D deficiency was magnified in the cohort of Framingham offspring with hypertension.

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An understanding of the pathophysiological mechanisms involved in CVDs, as well as their risk factors, is essential for planning of prevention and treatment strategies.In recent years, many studies have shown a relationship between vitamin D deficiency and CVDs, with a direct influence on prognosis. Based on the understanding of this association, the focus of researchers has been in the correction of vitamin deficiency with the aim of preventing diseases and improving the prognosis of established diseases. However, there are still no consistent data to recommend vitamin D replacement in the context of cardiac diseases.

Aims and objective

To investigate the association of pre-operative 25-hydroxyvitamin D (25(OH)D) levels with major cardiac and cerebrovascular events (MACCE) in patients undergoing cardiac surgery.

Materials and Method

This is a Prospective nonrandomized Observational Study between November 2018 to November 2020 conducted at the Department of Cardiothoracic surgery, Jawaharlal Nehru medical College, AMU, Aligarh. All patients undergoing cardiac surgery in Department of Cardiothoracic surgery, J.N.M.C.H., Aligarh were included. Prior to day of surgery, fasting sample were withdrawn and sent for measurement of Vitamin D levels in endocrinology laboratory. Estimation of Vitamin D levels were done by Chemo-luminescence Immuno-Assay (CLIA) [BECKMAN COULTER Access 2 Model]. 48 hours after surgery, again fasting blood sample were sent to same lab for evaluation of vitamin D levels. MACCEs were recorded (defined as in-hospital death, Myocardial infarction, Low cardiac output syndrome, or stroke).

Observation and Results

There were total of 100 patients who were included in this study. There were 55 males and 45 females in this study. The minimum age of patient is 1 year and the maximum age is 82 years (table 1). The mean age was calculated to be 26.62 years. The patients of the current study were diagnosed with seven types of disorders. The maximum number of patients (25%) appeared to be diagnosed with Coronary Artery Disease (CAD) as shown in (table 2). There was only one case each for patients with Total Anomalous Pulmonary Venous Connection (TAPVC) and Lt. Atrial Myxoma.

On the basis of Vitamin D level, patients were divided into three categories, deficient (≤ 30ng/ml), borderline(30 – 74.9 ng/ml) and sufficient (≥ 75 ng/ml).The maximum number of patients were found to have serum Vitamin D level less than 30 ng/ml (54%). The male patients outnumbered the female patients in the first two categories, while the third category had 5 patients each from both the sexes.

Only seven out of the 100 patients had in-hospital mortality during the study period. As shown in (table 3), among the seven expired patients, only one had Vitamin D level in the borderline category (30 ‑ 74.9 ng/ml), while the remaining six had levels in the deficient category (< 30 ng/ml). No patient with Vitamin D levels in the sufficient category had in-hospital mortality. The effect of Vitamin D levels on in-hospital mortality is, however, not statistically significant with p-values of 0.287, 0.95 and 0.418 respectively for
Gr. I vs Gr. II, Gr. II vs Gr. III and Gr. I vs Gr. III

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It is observed that lower the Vitamin D level, the higher is the duration of in-hospital stay. The Minimum duration in all three categories was seven days (table 4) while the maximum duration varied among the three categories. The effect of Vitamin D levels on in-hospital stay is not significant for Gr. II vs Gr. III with p-value of 0.266. It is, however, highly significant for deficient vitamin D levels than borderline or sufficient levels with p-values of 0.001, and 0.000 respectively.

It is apparent from the (table 5) that higher the level of Vitamin D, the shorter is the duration of stay in ICU among the patients in the present study. The effect of Vitamin D levels on ICU stay is highly significant for all the three groups with p-values of 0.05, 0.006 and 0.000 respectively for Gr. I vs Gr. II,
Gr. II vs Gr. III and Gr. I vs Gr. III. It is apparent from the (table 6) that the higher the level of Vitamin D, the shorter is the duration of ventilation. The effect of Vitamin D on the duration of ventilation is highly significant only for Gr. I vs Gr. II and Gr. I vs Gr. III with p-values of 0.000 and 0.002 respectively
There were only five patients who had post-operative stroke in our study. All the cases with post-operative stroke belonged to the deficient category (<30 ng/ml) of Vitamin D level as shown in (table 7). The effect of Vitamin D levels on post-operative stroke is, however, not statistically significant with p- values of 0.120, 0.077 and 0.431 respectively for Gr. I vs Gr. II, Gr. II vs Gr. III and Gr. I vs Gr. III.

Table 1: Mean Age and standard deviation of patients

Minimum Age	Maximum Age	Mean Age	SD	Median Age
1	82	26.62	23.09	17

Table 2. Percentage of patients on the basis of diagnosis

Diagnosis	No. of patients	Percentage
Rheumatic heart disease	23	23%
Coronary artery disease	25	25%
Tetrology of fallot	21	21%
Ventricular septal defect	15	15%
Atrial septal defect	14	14%
TAPVC	1	1%

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Left atrial myxoma	1	1%
Total	100	100%

Table 3 Vitamin D levels and no. of patients with in-hospital mortality

Vitamin D levels	No. of patients	In hospital mortality	Percentage
≤ 30 ng/ml	54	6	11.11
30 - 74.9 ng/ml	36	1	2.77%
≥ 75ng/ml	10	0	0%

Table 4 Minimum and maximum days of in-hospital stay

Vitamin D levels	Minimum days	Maximum days
≤ 30 ng/ml	7	16
30 - 74.9 ng/ml	7	12
≥ 75ng/ml	7	9

Table 5 Minimum and maximum duration of ICU stay

Vitamin D levels	Minimum hrs	Maximum hrs
≤ 30 ng/ml	52	95
30 - 74.9 ng/ml	52	65
≥ 75ng/ml	50	59

Table 6 Minimum and maximum duration of ventilation

Vitamin D levels	Minimum hrs	Maximum hrs
≤ 30 ng/ml	5	85

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30 - 74.9 ng/ml	4	20
≥ 75ng/ml	5	13

Table 7 Vitamin D levels and no. of cases with stroke

VITAMIN D LEVEL	≤ 30 ng / ml	30.01- 74.9 ng / ml	≥ 74.9 ng/ml
NUMBER OF PATIENTS 54 36 10	54	36	10
NUMBER OF PATIENTS THAT HAD STROKE	5	0	0
PERCENTAGE	9.26%	0%	0%

Discussion

Several studies have shown that Vitamin D is of paramount importance for well-being of cardiovascular system. Studies also suggest that vitamin D status is the most relevant predictor of long term outcome and that minimal benefits can be gained by supplementation at the time of surgery or thereafter. Vitamin D has the potential to represent an independent, modifiable risk factor amendable to rapid normalisation through loading dose supplementation. Vitamin D deficiency is associated with an increased risk of mortality, organ dysfunction, infections, prolonged ICU and hospital stay as well as increased duration of mechanical ventilation.

In our study, maximum number of patients belonged to the age class of 0 - 10 years with mean age of 26.61.1 ± 23.09 years. In a similar study by Kunt A. T et al [10] the total number of patients was 360 and the mean age was ≥ 68.2±8.0 years.

In our study 55% patients were males and 45% were females. As opposed to other studies, our study showed higher incidence of vitamin D deficiency in males as compared to female. A study conducted by Kunt et al[10] also reported significantly lower levels of Preoperative mean serum 25-OHD in females than in males (31.0±18.4 nmol/L, 35.6±18.8 nmol/L, respectively p=0.035).

In our study, there was higher mortality in patient with deficient vitamin D level as compared to those who had borderline or sufficient vitamin D level. Similarly, in a study conducted by Kunt et al.[10] some association between pre-operative Vitamin D levels and prediction of post-operative mortality have been reported. In yet another study by Zittermann et al.[6] a highly

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significant association between low Vitamin D levels and high in-hospital mortality has been reported.

In our study the occurrence of post-operative MI, as a result of low Vitamin D levels, is also not statistically significant, though there was more number of post-operative MI cases reported in deficient group as compared to borderline and sufficient group. It appears to be in concordance with the studies conducted by Zittermann et al.[6] ; Ng et al.[11] & Milazzo et al.[12] which hold low Vitamin D levels responsible for a high occurrence of postoperative MI in patients post cardiac surgery.

In our study all the cases of post-operative stroke were reported in patients with deficient vitamin D level, however because of less number of patients, statistically significant association between stroke and pre-operative vitamin D level couldn't be proved. There are some Studies that have reported hypovitaminosis D to be responsible for high chances of post-operative stroke (Pilz et al[13] and Moller et al[14]). However there is a study conducted by Zittermann et al[6] in which no significant association between pre-operative Vitamin D level and occurrence of post-operative stroke.

The effect of hypovitaminosis D on the duration of post operative in-hospital stay is significant in our study. The findings are comparable with the study of Kunt et al[10] . The study conducted by Zittermann et al[6]shows no association between hypovitaminosis D and in-hospital stay.

There is a highly significant association between hypovitaminosis D and the duration of ICU stay in our study. Many other studies have also reported similar negative correlation between Vitamin D level and the duration of ICU stay like Kunt A T et al[10] ; Martucci G et al [15]; Zittermann et al[6]. The mean duration of ICU stay in our study was 60.43 ± 6.05 Hours which is quite lower than that reported by Zittermann et al.[6] (71.8 ± 192.5 hours).

The results of our study indicate that the higher the levels of Vitamin D, the shorter is the duration of ventilation following cardiac surgery which is also observed in other studies. (Martucci G et al)[15]. Zittermann et al.[6]. The mean duration of ventilation in our study was found to be 18.88 ± 13.63 Hours, which is far lower than 23.9 ± 82.0 hours to 42.1+143.8 Hours, as reported by Zittermann et al.[6].

Conclusions

Vitamin D deficiency is highly prevalent in Indian population and males and females are almost equally affected as seen in our study. In our study group most of the patients having Major Cardiac and Cerebrovascular Events (MACCE) had deficient vitamin D level while patients having sufficient serum vitamin D levels had no MACCE event.

Our study also showed an inverse relationship between vitamin D level and duration of ventilation, ICU stay and in hospital stay. So our study stresses upon the fact that the vitamin D is an important variant in overall cardiovascular health of individual and its deficiency can adversely affect post- operative outcome. We recommend that all patients undergoing cardiac surgery should have their serum Vitamin D level checked and if time permits vitamin D level should be corrected by oral / parenteral supplementation to decrease incidence of post-operative MACCE events.

Acknowledgement

I feel extremely honoured to have this opportunity to acknowledge those who provided immense support throughout the period of this study. I take this opportunity to thank my junior residents

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who help me a lot to accomplish this study. I am extremely thankful to Dr. Saif Senior resident department of CTVS for his support during this study. I gratefully acknowledge Dr. Syed Shimayil Rbbani Dr. Mayank Yadav Assistant Professor department of CTVS JNMCH, AMU, Aligarh for their constant guidance and support.

I am obliged to Prof. Mohd Azam Haseen, Department of Cardiothoracic Surgery, JNMCH, AMU for his constant inspiration, timely suggestions, and never ending support in fulfilling the needs of this study. His profound wisdom and unbeatable knowledge deserves highest degree of appreciation. His encouraging guidance and care has made each step easy for me towards the completion of this work.
I extend my acknowledgments to my patients for being a part of the study, and giving me the opportunity to work with them and learn from them in spite of all their pain and suffering.

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