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Vitamin D Levels in Post-Operative Atrial Fibrillation (POAF) after Coronary Artery Bypass Graft Surgery: A Case Control Study

Naseem Ullah, Naser Ali Khan, Muhammad Abdullah, Nadeem Sadiq, Farah Ahmed

ABSTRACT

Objective: To determine if pre-operative vitamin D deficiency is associated with onset of postoperative atrial fibrillation (POAF) following coronary artery bypass graft (CABG) operation.

Study Design & Setting: A Case control study conducted in the Department of Cardiac Surgery, Cardiac Unit PNS Shifa Hospital Karachi, Pakistan from November 2021 to February 2023.

Methodology: Vitamin D levels were estimated pre-operatively upon admission in 48 patients scheduled for isolated, elective CABG surgery. The data obtained from study population comprising both cases (POAF) and controls (NON POAF) was evaluated statistically to know whether vitamin D levels and the development of post-operative atrial fibrillation are correlated.

Results: Those patients with coronary artery disease who were operated for CABG surgery was followed in this study for the effects that vitamin D may have on the POAF onset. The study population included 12(25%) patients with POAF identified in first five days post-operatively were assigned to POAF (YES) group and the remaining 36(75%) in sinus rhythm were in POAF (NO) group. After matching the base line characteristics, the patients in POAF (YES) group revealed significantly lesser vitamin D levels compared to those in the POAF(NO) group (27.62±23.11 & 77.42±29.08 nmol/L, P=0.0001 respectively). In the POAF (YES) group Left atrial dimension and LV diastolic dimension were also higher than in POAF (NO) group.

Conclusion: POAF after CABG surgery was more frequent in patient with deficient or insufficient preoperative vitamin D levels compared to normal levels. Therefore, it may be associated with POAF development in those patients proceeding for CABG operations.

Keywords: Atrial Fibrillation [AF], Coronary Artery Bypass Graft Surgery, Vitamin D deficiency.

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INTRODUCTION:

The most frequent arrhythmia, atrial fibrillation [AF] refers to irregular and often rapid heartbeat arising in the atrial chambers of the heart following coronary artery bypass graft (CABG) surgery is a common complication which affects approximately 15% to 40% patients. Postoperative atrial fibrillation (POAF) is related to increased rates of morbidity and mortality, longer hospital stays, high costs of healthcare and a two-to threefold rise in the incidence of postoperative cerebrovascular accidents. The lack of an organized atrial contraction can result in stagnant blood, especially in the left atrial appendage (LAA), the site of thrombus formation in >90% of cases in non-valvular atrial fibrillation making it a nidus for threatening complications of thromboembolism in central as well as peripheral circulation. The annual risk of stroke in patients with nonvalvular atrial fibrillation when not anticoagulated is 3%–5%, and atrial fibrillation is thought responsible for 15% of all thromboembolic strokes. The risk of POAF is increases with advanced age, obesity, hypertension (HTN), previous AF history, COPD, and congestive heart failure. Most often onset of this arrhythmia is seen, within the first 24-72 hours in the first five days

following surgery.[1] A longer life expectancy and growing risk factors over the coming years are projected to contribute to the current era's significant increase in the prevalence of AF. The processes that generate post-operative AF during recovery are not fully understood. The principles of treatment for postoperative atrial tachyarrhythmias are similar to those for atrial arrhythmias in other circumstances, except that inflammation and increased sympathetic tone have an important etiological role in postoperative arrhythmias. The control of the ventricular rate, anticoagulation, and conversion to sinus rhythm are the goals of therapy. There is discussion of ischemia, inflammation, and electrolyte disturbances as triggers.[2] In addition POAF precipitates the hazard of long-standing AF by 4–5 times.[3] Risk reduction, prediction, and development of preventive strategies depend on understanding of pathophysiology behind AF development.

Vitamin D specifically in active form, cholecalciferol (Vit D3) and ergocalciferol (Vit D2) are fat soluble vitamins with the functions of gastrointestinal absorption of calcium, magnesium and phosphate and various added metabolic and biologic pathways in human body.[4] After activation through Hydroxylation first in liver and then in the kidneys. Active Vit D_3 or calcitriol after synthesis plays important role in regulating body contents of calcium and phosphate to promote healthy growth and remodeling of skeleton. Other functions of calcitriol include reduction of inflammation, immunity building, neuromuscular strength and cellular metabolism.[5] A higher risk of obesity, hypertension (HTN), and cardiovascular disease is linked with insufficient vitamin D levels.[6] Vitamin D has also is reportedto reduceinflammatory processes and has a function in the renin-angiotensin-aldosterone system's (RAAS) suppression. Both contribute to the pathophysiology of atrial fibrillation (AF). Hence, vitamin D possibly could have an effect on the genesis of POAF.[7] Different studies including observational as well as randomized controlled trials (RCTs) failed to confirm a definite association between vitamin D levels and post-CABG AF with resultant mixed data in establishing a correlation between low vitamin D levels and post-CABG AF.[8]

This case-control study's objective was to determine how vitamin D deficiency and insufficiency in preoperative period affected the emergence of POAF, which was identified as an episode of atrial fibrillation documented using continuous telemeter via a cardiac monitor in a setting of cardiac intensive care therapy and confirmed using a 12-lead electrocardiogram (ECG) within the first five days after operation in patients with CABG.

METHODOLGY:

This case control study was designed to enroll participants who were above 18 years in sinus rhythm and hemodynamically stable scheduled for elective, primary on pump isolated CABG surgery at our department of cardiac surgery unit from November 2021 to February 2023. Sample size was calculated keeping in view the mean Vit D levels in participants with POAF group and without POAF. Initial sample size was 42. But we were unable to get the required no of cases of 21 in the POAF (YES) group in the six months that is why the final sample of cases was 12 and they were matched with controls in a ratio of 1:3 so that controls were 36. Sample size was calculated using open EPI technique by using the mean difference calculator and values were taken from reference article reviewed in literature.[9]The sampling for study participants was done using Non-probability purposive technique. Patients for reoperations, concurrent aortic or mitral surgery, heart valve problems or previous valves surgery, documented any supraventricular tachyarrhythmia's in the past, beating heart surgery, chronic kidney failure, hemodialysis patients, chronic hepatic failure, preoperative atrial fibrillation, hypercalcemia, hyperthyroidism, ongoing intake of vitamin D replacement therapy, and use of rhythm control medications other than beta receptors blockers, digitalis, and calcium ion channel blockers were the exclusion criteria.

In Pakistan nmol/L units are used for estimation of Vit D levels. 1ng/ml=2.5nmol/L

Deficiency = <25 nmol/L

Insufficiency = 25 – 75nmol/L

Normal Vit D level = 75 – 250nmol/L.[10]

When the patient were admitted for surgery the evening before the operation, between 8:00 and 9:00 pm, the antecubital vein was selected for blood samples.Di-potassium ethylenediaminetetraacetic acid (EDTA) containing specified tubes were used to keep and store blood at room temperatures. Within 60 minutes after the venipuncture, the pre-operative measurement of vitamin D and assessment of relevant laboratory markers was done at the biochemical laboratory in the hospital. According to Cockcroft- Gault Equation, chronic renal failure is diagnosed by creatinine clearance level up to the limit of less than 30 mL/min. Hyperthyroidism was defined by thyroid stimulating hormone (TSH) level in the blood less than 0.4 mg/dL or already diagnosed patient taking an ant- ithyroid drugs. In this study, moderate hypothermia (32-34°C) was used for all surgeries, which were performed under Cardiopulmonary bypass by the same team of surgeons. Study's participants having mean age of 58.6±8.71 years, included 42 men and 6 women. From the day of surgery to the fifth postoperative day, patients were continuously monitored in cardiac ITC using five lead telemetry.

AF was confirmed by a 12-lead electrocardiogram (ECG), after POAF was identified as any observed incident of AF postoperatively by continuing monitoring. In this study the diagnostic criteria for AF, which included lack of distinct P waves, RR intervals that followed unrepetitive pattern, were described as "irregularly irregular," and ventricular

rates between the range of 100 and 150 beats per minute was used. The participants were assigned into two groups. Those who had any episode of AF in ICU from the first to fifth day post-surgery were assigned in the POAF(YES) group (n=12), on the other hand those participants with absent AF were in the POAF(NO) group (n=36). Prior approval from the ethical committee of the hospital was taken (ERC/2022/CARDIAC SURGERY/02). In addition, written informed consent from patients and their relatives was taken to include them in the research.

Statistical Analysis:

The Windows statistical software SPSS 26 was used to conduct the statistical scrutiny. Qualitative, categorical data displayed as frequency and percentages, whereas mean and standard deviation (SD) was used to display continuous data. Chi-square test analysis was applied for comparison of nominal data, parametric variables analyzed by applying pooled t test and nonparametric constant variables after assessment for normality with Shapiro-wilk test were compared by applying the Mann-Whitney U test.For statistical significance the value of P as below than 0.05 was considered.

RESULTS:

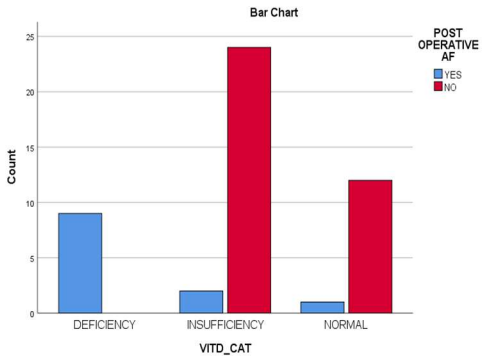
This study included a sample of 48 patients that were proceeded with isolated CABG operation. These patients were assessed for development of POAF.Post operatively 12(25%) patients developed POAF. The study population was categorized in two groups. 12 patients in POAF (yes) group and 36 in POAF (NO) group with mean ages of 56.7 ± 9.06 and 59.2 ± 8.63 respectively. The cases included 10(83.3%) males and 2(16.7%) females. The two groups were compared by taking into account different parameters like preoperative medicines usage, demographic, and clinical conditions, preoperative vitamin D levels, hematological,transthoracic echocardiography indices as well as peroperative and postoperative characteristics.[Table.1].Smoking tendency was high(p=0.067) among in the POAF (YES) group. Comorbidities like DM and COPD were comparable except frequent HTN in POAF positive group (p=0.09) [Table.1].

The pre-operative bio-chemical and hematological parameters of two group revealed no difference such as CRP (15.2 ± 15.8, 16.3 ± 10.8, p=0.780),TSH levels (2.5 ± 1.8, 2.8 ± 2, p=0.649).).Significant difference observed in hemoglobin levels (11.8 ± 1.2, 12.9 ± 12.1, p=0.04) which on further analysis revealed no difference (p=0.095) [Mann-Whitney U). The POAF positive group showed relatively higher LV diastolic dimension (53.6 ± 6.2), than POAF negative group (50.4 ± 7) (p=0.161). Similarly Left atrial dimension was also high (35.5 ± 6.2) in patients with POAF compared to patients without POAF (30.7 ± 10.2) (p=0.198).The ejection fraction (EF %) and other dimensions were similar between the two groups [Table 1].

Regarding per-operative factors such cross clamp time, Cardiopulmonary bypass time, Operating Team, Temperature and post-operative ventilation and ICU stay were comparable between the groups. Both cases and control groups were analyzed in detail for pre-operative levels of vitamin D. Among total 13 patients with normal vit D levels (75-250nmol/L) there was 1 in POAF positive and 12 in the POAF negative group. Similarly, 26 patients had insufficient vit D levels (25-75 nmol/L) with distribution of 2 in POAF and 24 in non POAF group. There were total of 9 patients in deficient (<25nmol/L) in which 9 were in POAF positive group and 0 were in POAF negative group. Vitamin D was statistically highly deficient and insufficient in positive group compared to POAF negative group (p=0.0001) [Table.2], Figure.1. The mean of Vit D was 64.97±5.06, the median was 62.3 (inter quartile range (IQR)=29.9). Upon analysis this data was right skewed. Regarding LA diameter the mean was 32.1±10.48, median was 35 (IQR=20.25). LV dimension measured having mean value of 51.22±6.91, median was 55.5 (IQR=9). For finding the difference in mean pre-operative Vit D levels in nmol/L, very high significant difference was observed between cases and controls. POAF cases found to have a mean of 27.6±SD of 23.1 whereas in the non POAF controls mean was 77.4±29.08 (p=0.0001), Mann-Whitney U test.There was no significant difference when mean of left atrial diameter was compared between cases and controls (p=0.67), Mann Whitney U test.[Table no. 3]. Regarding LV dimension there was also no significant difference between cases and controls (p=0.16), Pooled T.Test.

During post-operative stay there was no mortality among selected patients for study. Two patient required revision of sternal wound for hemopericardium and hemothorax. Two patients from POAF negative group developed superficial sternal wound infection for which daily dressing performed. No any hemodialysis needed for renal dysfunction. One patient required electrical cardioversion for AF.Pharmacological cardioversion with amiodarone and use of beta blocker remained sufficient for rest of POAF patients. Upon discharge patients were in sinus rhythm and hemodynamically stable.

Figure 1:



DISCUSSION:

During the postoperative period after coronary artery bypass grafting multiple related complications can occur and includes respiratory system compromise requiring prolong periods of ventilatory support, low cardiac output heart failure, and postoperative infections such as pneumonitis, urinary tract infections, mediastinitis and superficial and deep sternal wound infections. Among the others are acute renal failure, pericarditis, hemothorax, myocarditis, cerebrovascular accidents (CVAs) and arrhythmias, etc. Among these complications, POAF is one of the most common and can lead to a number of postoperative adverse early and late consequences. It is imperative to note that the specific complications and their severity can vary depending on individual patient factors, the duration and frequency of atrial fibrillation episodes, and the underlying health conditions of the patient. ?

Table 1. POAF(YES) and POAF(NO) group statistics

	POAF(YES)	POAF(NO)	P
Sex (Male) n (%)	10(83.3)	32(88.9)	0.614
Smoking n (%)	6(50)	8(22.2)	0.067
DM n (%)	9(75)	19(52.8)	0.176
HTN n (%)	8(66.7)	14(38.9)	0.094
COPD n (%)	1(8.3)	4(11.1)	0.785
B.blockers use n (%)	7(58.3)	14(38.9)	0.240
Statin use n (%)	6(50)	21(61.8)	0.436
CCB use n (%)	4(33.3)	16(44.4)	0.499
Diuretic use n (%)	7(58.3)	16(44.4)	0.404
Pre-operative C reactive proteins level in mg/l	15.2 ± 15.8	16.3 ± 10.8	0.780
Hemoglobin levels in mg/dl	11.8 ± 1.2	12.9 ± 2.1	0.041(s)
Urea level in mmol/L	5.9 ± 2.2	6.55 ± 5.2	0.709
S. Creatinine in Umol/L	89 ± 28.5	81 ± 23.9	0.356
GFR in ml/min	81.9 ± 34.4	80.9 ± 29.9	0.928
TSH in mlu/ml	2.5 ± 1.8	2.8 ± 2.0	0.649
T. Cholesterol in mmol/L	4.7 ± 1.6	4.8 ± 1.4	0.938
Triglycerides in mmol/L	3.5 ± 1.7	3.09 ± 1.2	0.431
HDL in (mmol/L)	0.9 ± 0.1	0.8 ± 0.1	0.103
LDL in (mmol/L)	3.3 ± 1.0	3.07 ± 1.17	0.419
S. Ca in mmol/L	1.8 ± 0.7	1.9 ± 0.5	0.721
Ejection fraction in %	47.9 ± 11.9	49.6 ± 15.7	0.803
LV diastolic dimension in mm	53.6 ± 6.2	50.4 ± 7.0	0.161
Left atrial diameter in mm	35.5 ± 10.9	30.7 ± 10.2	0.198
Creatine Kinase in U/L	121.8 ± 53.5	121.7 ± 55.3	0.998
CK-MB in u/L	34.8 ± 18.4	31.4 ± 15.04	0.530
Troponin I in ng/ml	0.7 ± 0.9	0.4 ± 0.8	0.419
Interventricular septal thickness in mm	9.9 ± 2.5	9.08 ± 2.1	0.269
FBS in mmol/L	7.7 ± 3.4	6.7 ± 2.5	0.315

Table: 2. Pre-operative Vit D status cases VS control groups.

Vitamin D level	POAF (YES) n(%)	POAF (NO) n(%)	P
Normal Vit D level (75-250nmol/L)	1(8.3)	12(33.3)	0.0001(s)
Insufficient vits level (25-75 nmol/L)	2(16.7)	24(66.7)	
Deficient vit D level (<25nmol/L)	9(75)	0(0)	

Those patients with coronary artery disease who were operated for CABG surgeries were evaluated in this study for the effects that vitamin D may have on the POAF onset. The participants with POAF had predominantly reduced vit D compared to ones with sinus rhythm. Pakistan has huge load of population with low or inadequate vit D, the condition is worse in low income strata and female population. A data audit of larger retrospective analysis of 60937 (30.7% male and 69.3% female) in Pakistan found that 61.1% of subjects had mean vitamin D value of 13.8 ng/mL.[11]

Myocardial contraction results from action potential generation in myocytes due to inward current of, positively charged ions (Na+). Intracellular calcium causes plateau phase of membrane potential desensitization of myocyte to additional impulses during the period. This leads to inhibition of early reactivation and atrial fibrillation triggering. Increasing age is an independent risk related to AF and is up to 26% after the age of 40 years.AF may cause 10% to 15% of all strokes, with an associated resulting increase in 1.9 times of mortality.[12] Atrial fibrillation after cardiac surgery is common complication, previous studies have demonstrated that in 30-60% of cases atrial fibrillation was found to occur in the first seven days after operation.[13] Literature also revealed association of POAF with different risk factors including high size of left atrial diameter, above normal inflammatory markers, hypertension (HTN), Diabetes mellitus, chronic obstructive lung conditions (COPD) and chronic renal insufficiency.[14]

Inflammatory mechanisms are modulated by vit D as well as increase in the activity of interleukin 10 and interleukin-6.[15] Myocardial and vascular effects of vit D occurs through receptor activation in vessels endothelium and myocardial cells as well as renin angiotensin aldosterone system up

Table No. 3: Statistical Analysis for Significance

	POAF(YES) n=12	POAF(NO) n=36	Sum of ranks. YES/NO	U	P
Vitamin D level (Mean Rank)	10.25	29.25	123/1053	45	0.0001(s)
Left Atrial Diameter (Mean Rank)	29.33	22.89	352/824	158	0.16

regulation.[16]The activated RAAS system can precipitates new onset AF.Deficiency of vit D predisposes to the development of AF. Preventive effects of vit D occurs directly through prolongation of action potential during myocyte depolarization resulting in reduced triggers causing POAF generation and also its atrial antiarrhythmic mechanisms.[17]

Contradictory results obtained in some studies negating positive association of effects vit D deficiency and vit D supplementation on POAF development. In one report vit D deficiency was found to cause non valve related AF through its actions to decrease atrial myocardial fibrotic conditions via increase in transforming growth factor (TGF) level.[18] Qayyum et al investigation reported no correlation between vit D deficit and atrial arrhythmias.[19] On the other hand POAF was found to be more prevalent in those subjects with comparatively low pre-operative vit D in serum than with normal quantity.[20] Hematological and laboratory indices of platelets.[21] Red blood cell Distribution Width (R.D.W) and Mean Platelet Volume (M.P.V) and high parathyroid hormone (P.T.H).[22] increases risk of AF.

There is limited and controversial data regarding effects of preoperative vit D deficiency on POAF onset in patients undergoing CABG operation. This study revealed that in addition to other predictive risk factors like HTN, LA diameter and LV dimension sizes POAF was more significantly attributed to vitamin D deficiency therefore correction of serum vitamin D before surgical procedure may be considered. Further randomized trials including clinical studies with adequately large study samples are required to validate ours results.

CONCLUSION:

We found that in this study POAF after CABG surgery was more frequent in patients with deficient or insufficient pre-operative vitamin D level compared to normal levels. Therefore, it may be associated with POAF development in patients undergoing CABG surgery.

Authors Contribution:
Naseem Ullah: Conception, design, analysis data
Naser Ali Khan: revision of work
Muhammad Abdullah: Data ceration
Nadeem Sadiq: Manuscript writing
Farah Ahmed: Expert statistician

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