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Original Article

Effect of preoperative vitamin D levels on the development of atrial fibrillation after cardiac bypass surgery

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Abstract

Aim: Atrial fibrillation is a common complication after coronary bypass surgery. There are various studies aimed at predicting the development of postoperative atrial fibrillation (POAF). Low vitamin D status has been associated with an increased risk of cardiovascular disease. Atrial fibrillation (AF) is the most common cardiac arrhythmia. We purpose to evaluate the effect of serum 25(OH) vitamin D level on the development of POAF after cardiac bypass surgery (CABG).

Material and Methods: Our study is a retrospective chart review which all patients who underwent isolated, elective, on-pump CABG operation between January 2017 and January 2018. POAF was defined as the development of atrial fibrillation after the completion of cardiac surgery, which required intervention.The whole study population divided into two groups: group I, patients who developed POAF and group II, patients who did not.Ejection fraction and left atrium diameter of participants were recorded. 25(OH)D and parathormone values, as well as other demographic and clinical characteristics, were collected.

Results: A total of 78 patients were available for analyses. While 61 patients did not develop POAF, 17 patients developed. The rate of POAF was 22%. The median ages of the patients with and without POAF were significantly different (61(54-72) vs. 69(65-77) years, p=0.012). The left atrial diameter was larger in patients with POAF (p=0.025). Preoperative ejection fractions were not different between the groups. Total bypass time and cross-clamp time were not significantly different. Although the mean value of preoperative 25(OH)D level was slightly higher in patients who did not develop POAF compared to that of patients with POAF, the difference was not statistically different between the groups.

Conclusion: Preoperative 25(OH)D levels were not different between the patients with and without POAF.

Keywords: Coronary artery bypass grafting surgery; postoperative atrial fibrillation; Vitamin D; 25(OH)D

INTRODUCTION

Postoperative atrial fibrillation (POAF) is a common complication. It develops in 30% of patients who undergo cardiac surgery, whereas it is less common among patients undergoing noncardiac surgery (1). POAF is associated with adverse clinical outcomes, longer hospital stay, and increased cost. Several factors have been implicated to be related to the development of POAF, including left atrial diameter, left ventricular function, diabetes mellitus, and obesity, among others. Local and systemic inflammation seems one of the significant underlying mechanisms in the development of POAF (2,3).

Vitamin D is a fat-soluble vitamin principally involved in the regulation of calcium and bone metabolism. On the other hand, the last two decades witnessed a notable increase in other functions that vitamin D is purported to exert. Via its widely distributed vitamin D receptors (VDR), 25(OH)D plays significant roles in regulating the renin-angiotensin-aldosterone system, oxidative system, and inflammation. Some experimental studies revealed that active vitamin D had direct and indirect anti-arrhythmic effects (4). However, many large observational studies failed to show a relationship between 25(OH)D levels and atrial fibrillation (5,6). On the other hand, some other observational studies showed a significant albeit weak association between 25(OH)D levels and atrial fibrillation (7-10).

Since its beneficial effects on inflammation, oxidative stress, and renin-angiotensin system, some authors sought to answer the question that whether 25(OH)D levels might be associated with the development of POAF in cardiac surgery patients. Unfortunately, up till today, the results of the prevailing studies could not answer

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this question satisfactorily. While some studies showed a significant relationship between 25(OH)D level and POAF, others did not (11-15). Thus, we aimed to evaluate the likely association between serum 25(OH)D and the development of POAF in patients undergoing isolated elective coronary artery bypass surgery (CABG) via a retrospective chart review study.

MATERIAL and METHODS

The study was approved by the local ethics committee 11.09.2019 date and 2019\620 number. This is a retrospective chart review study in which all patients who underwent isolated, elective, on-pump coronary artery bypass surgery (CABG) at Kayseri Training and Research Hospital between January 2017 and January 2018 were screened from the prospectively maintained electronic database of the hospital. Overall, we reached the records of 300 patients who underwent CABG. Among these, only patients who had serum 25(OH) vitamin D and parathyroid hormone measurements in the preceding three months were evaluated for eligibility in the study. The primary aim of the present study was to determine whether the occurrence of early postoperative atrial fibrillation was related to preoperative 25(OH)D values. Patients who had emergency surgery, had preexisting persistent or paroxysmal atrial fibrillation, had a concomitant valve or aortic surgery, were already on vitamin D replacement therapy, and had been on antiarrhythmic drugs except for digoxin, beta-blockers and calcium channel blockers were excluded from the study. After exclusion criteria applied, the final analysis involved 78 patients who fulfilled the inclusion criteria in the present study.

We investigated the patient records regarding the occurrence of POAF after the completion of surgery until discharge. POAF was diagnosed with 12-lead electrocardiography tracing. Atrial fibrillation was diagnosed if the ECG tracing of the patient had no discernible P waves and irregularly irregular R-R intervals by a cardiologist. POAF was defined as the development of atrial fibrillation after the completion of cardiac surgery, which required intervention. All patients treated with drug treatment (drug treatment or cardioversion). The whole study population divided into two groups: group I, patients who developed POAF and group II, patients who did not. The duration of atrial fibrillation was recorded.

Reports of preoperative transthoracic echocardiography of all patients were evaluated to extract the data of ejection fraction and left atrium diameter. Echocardiography was performed by the same cardiologist by transthoracic ECO (ClearVue 550, Philips, Netherlands). The Simpson method was utilized to calculate the ejection fraction. The left atrial diameter was measured through the parasternal long-axis view at the end of the left ventricular systole. Complete blood count and biochemical parameters, including cholesterol levels, creatinine level, and prothrombin time were recorded from the latest preoperative laboratory study. Vitamin D and parathormone values that had been studied previously in various outpatient or inpatient clinics of our hospital were collected. Vitamin D and parathormone were measured by LC-MS/MS mass spectrometric technique. The parathormone level was measured using the electrochemiluminescence immunoassay method (Cobas e 602, Roche, Switzerland). Those with a vitamin d value below 20 ug/L were considered to be vitamin D insufficiency and those between 20-30 ug/L were considered to be vitamin D deficiency. Those 30 ugs/L and over were considered normal values. Those below 30 ugs/L were defined as vitamin D deficiency. Patients' demographic data including age and gender, comorbid conditions, and drug use were also collected from the patient charts. Body mass index was calculated as weight (kg) divided by height squared (m2).

All patients underwent on-pump CABG performed by the same surgery team during the study period.

Statistical analysis

In summarization of the data obtained from the study, descriptive statistics for continuous variables were presented as mean + standard deviation or median and interquartile range depending on the distribution of the variables. Categorical variables were expressed as absolute numbers and percentages. The normality check of the numeric variables was performed by the Kolmogorov-Smirnov test. In the comparison of the difference in two independent samples, the Independent Samples t-test and Mann Whitney U test was used when the numerical variables were distributer normally and nonnormally, respectively. In the comparison of the difference between two categorical variables, the Pearson Chi-squared test was used in contingency tables, and Fisher's Exact Test was used in R*C tables. Since the study and the control groups showed a significant difference in terms of age, we adjusted for age using the nonparametric ANCOVA model by R software package "sm.ancova". Jamovi (Jamovi project (2018). Jamovi (Version 1.0.7) [Computer Software]). Retrieved from https://www.jamovi.org) and JASP Team (2018, Version 0.10.2 [Computer Software]) were used to perform the statistical analyses. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 78 patients were available for analyses. While 61 patients did not develop atrial fibrillation after CABG operation, 17 patients did. The rate of postoperative atrial fibrillation was 22%. The median age of the patients with and without POAF was significantly different (61 (54-72) vs. 69 (65-77) years, respectively, p=0.012). The frequency of hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease was not different between the groups. Patients who developed POAF and did not develop POAF were also comparable in terms of various drug uses (Table 1).

When we look at the operative characteristics and preoperative echocardiographic cardiac parameters,

Table 1. Demographic characteristics, comorbid conditions and medication use of patients with and without POAF			
	Postoperative Atrial Fibrillation		p-value
	Absent (n=61)	Present (17)	
Gender			
Male/ Female	44 (72.1) / 17 (27.9)	10 (58.8) / 7 (41.2)	0.451[Ω]
Age (years)	61 [54 – 72]	69 [65 – 77]	**0.012[B]**
Coronary artery disease	61 (100)	17 (100)	-
PTCA and stent placement	7 (11.5)	5 (29.4)	0.121[¥]
Previous CABG	1 (1.6)	0 (0)	0.999[¥]
Diabetes mellitus	33 (54.1)	12 (70.6)	0.348[Ω]
Hypertension	54 (88.5)	15 (88.2)	0.999[¥]
Dyslipidemia	41 (67.2)	7 (41.2)	0.095[Ω]
Smoking	37 (60.7)	9 (52.9)	0.769[Ω]
Metabolic syndrome	11 (18)	2 (11.8)	0.722[¥]
Body mass index	27 [25 – 31]	27 [26 – 29]	0.817[B]
Chronic kidney disease	2 (3.3)	2 (11.8)	0.205[¥]
Warfarin use	1 (1.6)	0 (0)	0.999[¥]
Aspirin use	52 (85.2)	16 (94.1)	0.446[¥]
NSAID use	1 (1.6)	0 (0)	0.999[¥]
Beta Blocker use	36 (59)	11 (64.7)	0.886[Ω]
Digoxin use	1 (1.6)	0 (0)	0.999[¥]
Calcium Channel blocker use	9 (14.8)	2 (11.8)	0.999[¥]
Statin use	33 (54.1)	6 (35.3)	0.273[Ω]
ACE inhibitor use	8 (13.1)	7 (41.2)	**0.016[¥]**
Spironolactone use	2 (3.3)	0 (0)	0.999[¥]
Angiotensin Receptor Antagonist use	5 (8.2)	0 (0)	0.580[¥]
Prosthetic heart valve	1 (1.6)	0 (0)	0.999[¥]

[B]: Mann Whitney U test was used. Descriptive statistics were presented as median [IQR].
[Ω]: Pearson Chi-squared test was used. Descriptive statistics were presented as mean ± SD.
[¥]: Fisher's exact test was used. Descriptive statistics were presented as absolute number and (%).
SD: Standard deviation, IQR: Interquartile Range
p values written in italic were accepted as statistically significant (p<0.05).
[*](Age): Age variable was controlled using nonparametric ANCOVA model with "sm.ancova" software package

Table 2. Preoperative echocardiographic features and operative factors in study groups				
	Postoperative Atrial Fibrillation		p-value	p[*(age)]
	Absent (n=61)	Present (17)		
Number of vessels	3 [2 – 3]	3 [2 – 3]	0.968[B]	
Preoperative ejection fraction	50 [40 – 60]	50 [40 – 55]	0.397[B]	
Left atrial diameter	43 ± 3	45 ± 4	**0.025[Σ]**	**0.004** [**]
Total Bypass time	85 [72 – 100]	91 [65 – 123]	0.342[B]	
Cross-Clamp time	60 [50 – 70]	68 [48 – 78]	0.590[B]	

[Σ]: Independent samples t-test was used and descriptive statistics are presented as mean ± SD.
[β]: Mann Whitney U test was used. Descriptive statistics were presented as median [IQR].
[*(Age)]: Age variable was controlled using nonparametric ANCOVA model with "sm.ancova" software package.
[**]According to the presence of postoperative atrial fibrillation, left atrium diameter and postoperative creatinine values were different, and age also affected these

Table 3. Preoperative 25(OH)D levels along with other laboratory features in study groups

	Postoperative Atrial Fibrillation		p-value	p*(age)
	Absent (n=61)	Present (17)		
Preoperative vitamin D	11.4 [8.3 – 17.3]	10.3 [7.4 – 15.2]	0.439 B	
HDL-Cholesterol	43 ± 9	38 ± 9	**0.037** Σ	0.093
LDL-Cholesterol	134 [116 – 158]	112 [87 – 125]	**0.005** B	0.116
Parathyroid hormone	53.2 [37.8 – 74.3]	66.5 [51 – 79.5]	0.250 B	
Triglycerides	175 [120 – 234]	124 [102 – 156]	**0.036** B	0.635
Preoperative WBC count (/mm^3)	8640 [7140 – 11320]	10490 [8400 – 12190]	0.224 B	
RDW	15.5 [14 – 44.4]	14.7 [13.9 – 43]	0.650 B	
Prothrombine time (INR)	1.1 [1 – 1.1]	1.1 [1 – 1.1]	0.373 B	
Hemoglobin (g/dL)	14.4 [12.5 – 15.7]	13.8 [13.2 – 14.6]	0.121 B	
Hematocrit (%)	43.2 ± 6.1	40.4 ± 6.1	0.094 Σ	
Platelet count (/mm3)	247607 ± 64188	229176 ± 89930	0.343 Σ	
Preoperative creatinine	0.9 [0.7 – 1.1]	0.9 [0.9 – 1.4]	0.283 B	
Postoperative creatinine	0.9 [0.7 – 1.1]	1.1 [0.9 – 1.5]	**0.024** B	**<0.001****

Σ: Independent samples t-test was used and descriptive statistics are presented as mean ± SD.
β: Mann Whitney U test was used. Descriptive statistics were presented as median [IQR].
***(Age): Age variable was controlled using nonparametric ANCOVA model with "sm.ancova" software package.**
****According to the presence of postoperative atrial fibrillation, left atrium diameter and postoperative creatinine values were different, and age also affected these**

the left atrial diameter was larger in patients with POAF (p=0.025). On the other hand, preoperative ejection fractions were not different between the groups.

In a similar vein, the total bypass time and cross-clamp time were not significantly different between the groups (Table 2). In Table 3 we showed laboratory values as well as preoperative vitamin D values in both groups. Although the mean value of preoperative vitamin D was slightly higher in patients who did not develop POAF compared to that of patients with POAF, the difference was not statistically different between the groups. Since the patients were significantly older in POAF group and age is an independent determiner of serum vitamin D level, we controlled age with ANCOVA model. However, the previously observed difference was not affected after this adjustment.

DISCUSSION

The main finding of the present study was that vitamin D deficiency was not different between patients who developed and did not develop POAF. Our results are in line with several of the previous studies that revealed no relationship between serum vitamin D level and POAF development (7-10,15). On the other hand, this result conflicts with other studies that revealed a significant association between vitamin D level and POAF development (5,6). It is important to emphasize the heterogeneity of the patient populations might be responsible for these observed discrepancies. Postoperative AF has many determinants, and all of them should be appropriately controlled to attribute the observed difference to the differences in preoperative serum 25(OH)D levels.

Vitamin D has various additional functions other than simply regulating calcium and bone metabolism. Several experimental and clinical studies unveiled beneficial roles of vitamin D on oxidative stress, inflammation, immune system, and renin-angiotensin system among, others. A retrospective analysis in which approximately 50.000 patients were evaluated; the authors concluded that 25(OH)D deficiency was not associated with atrial fibrillation. On the other hand, the results of the study demonstrated that 25(OH)D deficiency attenuated atrial fibrillation preventing the effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blocker drugs (16). These results support the previous findings that active vitamin D regulates renin gene expression in a negative way (17). Through its multifactorial role in the renin-angiotensin system, 25(OH)D contributes to the regulation of blood pressure and consequently, is helpful in the prevention of atrial wall remodeling and consequent development of atrial fibrillation. These factors, which are modulated by sufficient body vitamin D favorably are at the same time have been suggested as a pathophysiologic mechanism leading to the development of atrial fibrillation. Thus, several experimental and clinical studies attempted to evaluate a possible relationship between 25(OH)D and the occurrence of atrial fibrillation.

There exist conflicting data in the literature regarding the association between the 25(OH)D level and atrial fibrillation. A meta-analysis by Zhang and colleagues concluded that 25(OH)D deficiency is associated with atrial fibrillation (18). However, the authors acknowledged that there were only eight studies included in the analysis, and the included studies were quite heterogeneous in terms of study designs. Moreover, whereas included case-control studies(5,6,19,20) evaluated chronic atrial fibrillation found association between vitamin D level and AF, the other four observational studies (7-10) looked at the development of new-onset atrial fibrillation and did not show an association between 25(OH)D level and AF. Another meta-analysis only included new-onset atrial fibrillation patients did not find a significant association between 25(OH)D levels and AF development (21). Our study also took into account the development of new-onset atrial fibrillation, and vitamin D levels were not different between the groups.

Surgery is an established risk factor for the development of atrial fibrillation that is called postoperative atrial fibrillation (POAF). Moreover, the risk is much higher with cardiac surgery than that of noncardiac surgery (1) The incidence of POAF ranges between 25-36% after cardiac surgery (22). This rate was 22% in our cohort. Several factors have been implicated in the development of POAF after cardiac surgery, among which are advanced age, congestive heart failure, coronary artery disease, left atrial enlargement, chronic kidney disease, obesity, diabetes mellitus, and hyperthyroidism (23). Owing to its putative multilayered effects on the pathophysiology of atrial fibrillation, several authors have studied the association between cardiac surgery and POAF. However, as with the results of the studies investigating the association between vitamin D level and new-onset AF, there is controversy among the results of the studies specifically assessing the association between 25(OH)D levels and POAF after cardiac surgery. Some prospective observational studies revealed a significant association between 25(OH)D levels and the development of POAF (11,12). On the other hand, some other studies did not find a significant association between 25(OH)D and the development of POAF (13-15).

Two studies attempted to evaluate whether preoperative vitamin D supplementation would be protective against the development of POAF after cardiac surgery. Kara and colleagues conducted a randomized controlled, blinded study in which they randomized patients either to vitamin D supplementation (orally 300.000 IU in vitamin D deficiency and 150.000 IU in insufficiency, 48 hours before surgery) or to the control group (24). The authors found that vitamin D supplementation provided a 15% absolute reduction in the incidence of new-onset AF compared with controls in patients undergoing coronary artery bypass surgery. Another randomized controlled study replicated the findings of the latter study only in patients with vitamin D deficiency. The same protective effect was not evident among patients with vitamin D insufficiency (25). From these two studies, it seems that patients with severe vitamin D deficiency benefit most with vitamin D supplementation concerning preventing POAF.

Several limitations of the present study should be mentioned. First, our design is retrospective; thus, we could not control every factor that might have impacted the development of POAF. Since the nature of the retrospective design, the vitamin D levels were not studied just before the operation, rather had been studied sometime before the surgery. Second, the mean ages were different between the groups. Since vitamin D deficiency was more prevalent among the elderly, this might have affected the results of the study. Thus, we adjusted age by ANCOVA model.

CONCLUSION

In conclusion, the results of the present study did not show a difference in terms of preoperative vitamin D levels in patients with and without POAF. Considering the discrepancy of the results of all available studies, a well-designed prospective observational study is needed to settle the current controversy whether vitamin D deficiency leads to the development of POAF.

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