

Preoperative Vitamin Supplemental Therapy might improve Postoperative Outcome of CABG Surgery Patients

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Abstract

Objectives: The effect of preoperative vitamin supplemental therapy (VST) on serum levels of vitamin D (VD), interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP), malonaldehyde (MDA), and superoxide dismutase (SOD), and on outcomes of patients undergoing coronary artery bypass graft (CABG) especially the incidence of postoperative atrial fibrillation (POAF).

Patients & Methods: 124 patients scheduled for elective on-pump isolated CABG surgery were clinically evaluated. Three blood samples (S1-S3); before and after VST and after aortic declamping for estimation of serum levels of 25-hydroxy VD, IL-6, hsCRP, MDA, and SOD. Patients were randomly divided into the Control group (Group C) that did not receive VST and the Study group (Group S) that received VST for four weeks. Study outcomes included POAF incidence, the change of serum levels of estimated variables in S2 and S3 concerning the S1 sample, and the relation between receiving VST and these changes.

Results: Amount of chest tube drainage, the incidence of POAF and the total duration of PO hospital stay were significantly less in Group S than in Group C. VST significantly reduced serum MDA and hsCRP levels with a significantly elevated serum SOD levels in S2 than S1 samples. Preoperative VST is negative, while prolonged cardiopulmonary bypass time, high serum levels of IL-6 and hsCRP, and low serum levels of SOD in the S3 samples as significant positive predictors for POAF development.

Conclusion: Reduced serum inflammatory cytokines' levels with improved levels of SOD by preoperative VST are significant predictors for decreased POAF incidence and improved CABG outcome.

Keywords: POAF, Vitamin supplemental therapy, Hypovitaminosis D, CABG, Interleukin-6

Introduction

Postoperative atrial fibrillation (POAF) was defined as the occurrence of post-cardiac surgery atrial fibrillation or flutter of at least 30 seconds duration and confirmed by the 12-lead ECG ⁽¹⁾. POAF is associated with atrial remodeling that can lead to serious complications ⁽²⁾ with subsequent longer durations of hospital stays, consumption of healthcare resources, and substantial mortality ⁽³⁾.

The incidence of POAF following cardiac surgery varies between 15% and 60% ⁽³⁾, but its actual underlying pathogenesis is not fully understood. However, POAF may be triggered by preoperative, procedure-induced, and postoperative processes especially inflammation, oxidative stress, and autonomic dysfunction

which act on vulnerable atrial tissue and set the stage for arrhythmogenic mechanisms, such as ectopic firing to generate POAF^(4, 5).

The interplay between vitamin D, the renin-angiotensin system, and collagen remodeling is implicated in the pathogenesis of various cardiovascular diseases and may underlie the collagen remodeling process in AF⁽⁶⁾. On the other side, the disturbed immune milieu in the inflammatory direction was correlated with cardiovascular morbidity during cardiac surgery⁽⁷⁾. Further, oxidative stress with the excessive release of reactive oxygen species after ischemia-reperfusion during aortic clamping and extracorporeal circulation might be involved in the structural and functional myocardial impairment and underlie POAF development⁽⁸⁾.

Objectives:

Evaluation of the effect of vitamin supplemental therapy (VST) for four weeks before CABG surgery may ameliorate surgery-induced inflammatory and oxidative stress with a possible reduction of the frequency of POAF

Setting

Departments of Anesthesia and ICU and Medical Biochemistry, Faculty of Medicine, Benha University in conjunction with multiple private centers

Design

A prospective comparative study

Ethical considerations

The study was started after obtaining the preliminarily approval in Jan 2019 by the Local Ethical Committee and the final approval was obtained after the completion of the study by number RC: 1-9-2021.

Patients & Methods

During the study duration since Jun 2019 to Sep 2021, all patients assigned for elective CABG surgery with cardiopulmonary bypass (CPB) were eligible for evaluation.

The study included 124 patients divided into 2 groups after randomization.

Exclusion criteria

Emergency surgery, cardiac surgery requiring CPB for any indication other than CABG, presence of left main coronary artery disease, renal or hepatic dysfunction, hypersensitivity to the studied drugs, chronic obstructive pulmonary, preoperative AF, permanent or temporary pacemaker, any degree of atrioventricular block and maintenance on medication with class I and III antiarrhythmic agents or digoxin.

Inclusion criteria

Patients scheduled for elective on-pump isolated CABG surgery had sinus rhythm and were free of exclusion criteria were enrolled in the study.

Randomization and grouping

Patients were randomly divided using a 1:1 sequencing system into two groups and the sequence was applied as cards carrying the group label that was put in sealed dark envelopes. Patients were allowed to choose a card that specified the group: the Control group (Group C) included patients who did not receive the preoperative vitamin supplemental therapy (VST) and the Study group (Group S) included patients who received the 4-wk VST.

Vitamin Supplemental Therapy (VST)

The applied VST for patients of group S consisted of a vitamin C slow release hard gelatin cap (C-Retard 500 mg cap; Hikma Pharma S.A.E., 6th of October City, Egypt) taken before a meal once daily, vitamin D3 was provided as an oral dose of 5000 IU soft gels (Sunvite Mega Potency Vitamin D3 5000 IU, Puritan's Pride, Inc., Oakdale, NY, USA) to be taken with a meal as a daily dose, which was proved to be safe for correction of VDD⁽⁹⁾ and vitamin E that was provided as once daily 400 IU oral soft gels with a meal (Sundown Naturals, Rexall Sundown, Inc., Bohemia, NY, USA). Then, 1200 mg of vitamin C was injected intravenously after induction of anesthesia, 12-hr later, and every 8-hr till the resumption of oral intake whenever, the oral VST was resumed in the same dose till discharge.

Anesthetic procedure

All patients were pre-medicated with midazolam (0.03–0.05 mg/kg) on arrival at the operating room. A Central venous catheter was inserted in the internal jugular vein and an arterial cannula was inserted in the radial artery under local anesthesia and standard invasive monitors were attached to continuously monitor heart rate (HR), systolic (SBP), and diastolic blood pressure (DBP), and central venous pressure (CVP). Anesthesia was induced by thiopental sodium 3-5 mg/kg with fentanyl 3-5 µg/kg and pancuronium 0.1 mg/kg for muscle relaxation. Controlled mechanical ventilation was applied to keep PaCO₂ in a range of 35-45 mmHg. Anesthesia was maintained by sevoflurane, using a mixture of oxygen/air (1:1), atracurium 5-10 µg/kg/minute, and boluses of fentanyl when needed. The activated clotting time (ACT) was adjusted to be longer than 400 seconds using heparin sulfate (4mg/kg) before the application of the bypass machine (CPB). The CPB machine was established using a membrane oxygenator, roller pump, and non-pulsatile flow at a rate of 2.4 L/min/m². Anesthesia was maintained on CPB by propofol 3-4 mg/kg/hr, and the systemic temperature was maintained in the range of 34-35°C. Blood cardioplegia was provided as a mixture of normal saline and blood (1:1 volume) and composed of potassium chloride 30 mEq/L, Lidocaine 120

mg/L, and sodium bicarbonate 26 mEq/L, was given initially in a dose of 10 ml/kg and followed by 5 ml/kg every 20-30 minutes. Dobutamine was used at 3-5 µg/kg/minute when inotropic support was indicated.

Intraoperative and postoperative data

The durations of aortic clamping, use of the bypass machine, and surgery, PO ICU stay and amount of chest tube drainage were recorded.

Investigations

Three peripheral blood samples (S1-3) were withdrawn from the antecubital vein under complete aseptic conditions; at the time of enrolment, after the end of the 4-wk VST (S2), and just at the time of aortic de-clamping. Blood samples were collected in a plain tube, allowed to clot, centrifuged at 1500×g for 15 min and the serum samples were collected in a clean dry Eppendorf tube to be stored at -70°C until assayed for serum levels of 25-hydroxy vitamin D (25OH-VD), malonaldehyde (MDA), superoxide dismutase (SOD), high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions (Abcam Inc., San Francisco, USA; catalog no. ab213966; ab287797; ab65354; ab260058; ab178013, respectively) and were read using a 96 well microplate ELISA reader (Dynatech. MR 7000)

Diagnosis of POAF

Continuous ECG monitoring was performed for 48-hr using a 5-lead ECG monitor to detect new-onset AF. Thereafter, a 12-lead ECG was performed every 6 h during the ICU stay. The presence of ECG-documented AF for at least 1 min was recorded as POAF.

Study Outcomes

1. The primary outcome was the incidence of POAF after isolated CABG surgery
2. The secondary outcomes included:
 - a. The changes of the estimated lab variables in S2 and S3 concerning the S1 sample.
 - b. The relation between the provision of the 4-wk CDE-VC on the incidence of POAF and changes in lab variables.

Statistical analysis

Statistical analysis was conducted by IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA) for Windows statistical package using paired t-test, One-Way ANOVA and Chi-square tests. Regression and Receiver operating curve analyses were used to determine the sensitivity and positive predictive value (1-specificity) of evaluated parameters as predictors of POAF development. P value <0.05 was considered statistically significant.

Results

The study included 135 patients assigned for elective CABG surgery; 7 patients were excluded for presence of valvular lesions (n=3) and preoperative arrhythmia (n=4) and 4 patients were missed during randomization; these 11 patients were excluded, while 124 patients were randomly divided into two groups (Fig. 1). There were non-significant differences between patients of both groups as regards the inclusion criteria (Table 1).

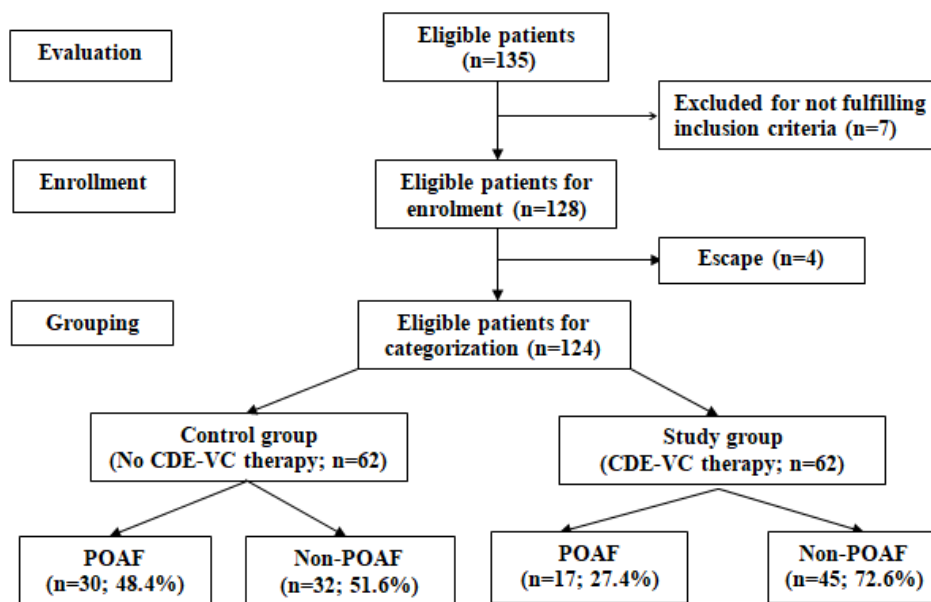


Fig. (1): Study Flow Chart

Table (1): Patients' data

Data	Group	Control (n=62)	Study (n=62)
Age (years)		56.4 (7.2)	57 (5.1)
Body mass index (kg/m ²)		30.5 (1.8)	30.4 (2.2)
Gender; Male: Female		41: 21	46:16 (74.2%)
History of smoking		22 (35.5%)	31 (50%)
Co-morbidities	Hypertension	18 (29%)	21 (33.9%)
	Diabetes mellitus	35 (56.5%)	29 (46.8%)
	Hypercholesterolemia	28 (45.2%)	30 (48.4%)
NYHA functional class (I: II: III)		33:21:8	36:19:7
Left ventricular ejection fraction (%)		50.8 (7.8)	53.6 (8.4)
Number of grafted coronary vessels (1: 2: 3: >3)		4:7:38:13	3:9:40:10
Resting preoperative heart rate (beats/min)		73.2 (3.6)	73.8 (4.1)
Resting systolic blood pressure (mmHg)		119.6 (10.7)	118 (10.5)
Resting diastolic blood pressure (mmHg)		73.9 (9)	72.7 (8.6)
Initial central venous pressure (cmH ₂ O)		9 (1.2)	9.1 (1.1)

Operative and immediate PO data showed non-significant differences between patients of both groups. However, the duration of ICU stay, the amount of chest tube drainage and the total duration of PO hospital stay were significantly

less ($p=0.015$, 0.024 & 0.008 , respectively) in patients of group S in comparison to patients of group C (Table 2).

Table (2): Operative data of patients of both groups

Data	Group	Control (n=62)	Study (n=62)
Aortic cross-clamping time (min)		70.8 (7.1)	72.9 (11.8)
Cardiopulmonary bypass time (min)		80.5 (12.3)	81.4 (7.7)
Frequency of the need for defibrillation		3 (4.8%)	2 (3.2%)
Duration of surgery (min)		360 (42.6)	375 (52.1)
Grafted coronary vessels		1.4 (0.5)	1.3 (0.5)
PO frequency of	Development of new Q wave in ECG	0	0
	Need for inotropic support	5 (8.1%)	3 (4.8%)
	Development of fever	0	0
Duration of mechanical ventilation (h)		12.8 (1.9)	12.6 (2.5)
Duration of ICU stay (h)		80 (15.8)	73.6 (13)*
Amount of chest tube drainage (ml)		590.4 (229)	502 (177.2)*
The total duration of PO hospital stay (days)		8.4 (1.6)	7.6 (1.3)†

*: significance at $p<0.05$; †: significance at $p<0.01$

Serum SOD levels showed a progressive decrease, while serum levels of other variables were increased progressively in S2 and S3 samples of patients of group C compared to S1 samples' levels with a significant difference between S2 and S3 samples. In S2 samples of group S, serum MDA and hsCRP levels were significantly lower with significantly higher serum SOD levels compared to their S1 samples. In S3 samples of group S, serum SOD levels had increased and levels of other variables had decreased in comparison to S1 and S2 samples' levels, with significant differences versus levels estimated in S3 samples of patients of group C. Serum 25-OH VD levels in S2 samples of patients of group S (40.6 ± 16.9 nmol/L) were significantly ($p=0.0005$) higher than levels estimated in their S1 samples (32.3 ± 12.4 nmol/L) and were significantly ($p=0.0045$) higher in comparison to levels estimated in S2 samples of patients of group C (33 ± 11.8 nmol/L), while serum levels of 25-OH VD levels in S2 samples of patients of group C were non-significantly ($p=0.775$) higher in comparison to levels estimated in their S1 (30.8 ± 13.5 nmol/L) samples (Table 3).

Table (3): Laboratory findings of samples obtained from patients of both groups

Parameter	Group C (n=62)			Group S (n=62)		
	S1	S2	S3	S1	S2	S3
Serum Malonaldehyde ($\mu\text{mol/L}$)	0.808 \pm 0.16	0.849 \pm 0.14‡	0.96 \pm 0.17‡	0.788 \pm 0.17	0.655 \pm 0.15‡‡	0.838 \pm 0.14‡‡
Serum Superoxide dismutase (U/ml)	7.25 \pm 1.3	6.7 \pm 1.4‡	6.1 \pm 1.37‡	7.3 \pm 1.2	8 \pm 1.38‡‡	7.55 \pm 1.25‡‡
Serum C-reactive protein (ng/ml)	8.4 \pm 2.07	9.9 \pm 2.43‡	16.3 \pm 3.57‡	7.85 \pm 0.17	8.45 \pm 1.8‡‡	10.5 \pm 2.86‡‡
Serum Interleukin-6 (ng/ml)	9.05 \pm 1.86	9.66 \pm 1.92‡	13.67 \pm 3.37‡	8.88 \pm 1.48	8.43 \pm 1.51‡‡	11.8 \pm 2.58‡‡

‡: significant difference at $P < 0.001$; ‡‡: significant difference between both groups

During the immediate PO period 47 patients (37.9%) developed POAF; 30 patients in group C and 17 patients in group S with significantly ($p=0.016$) lower POAF incidence among patients of group S (Fig. 2).

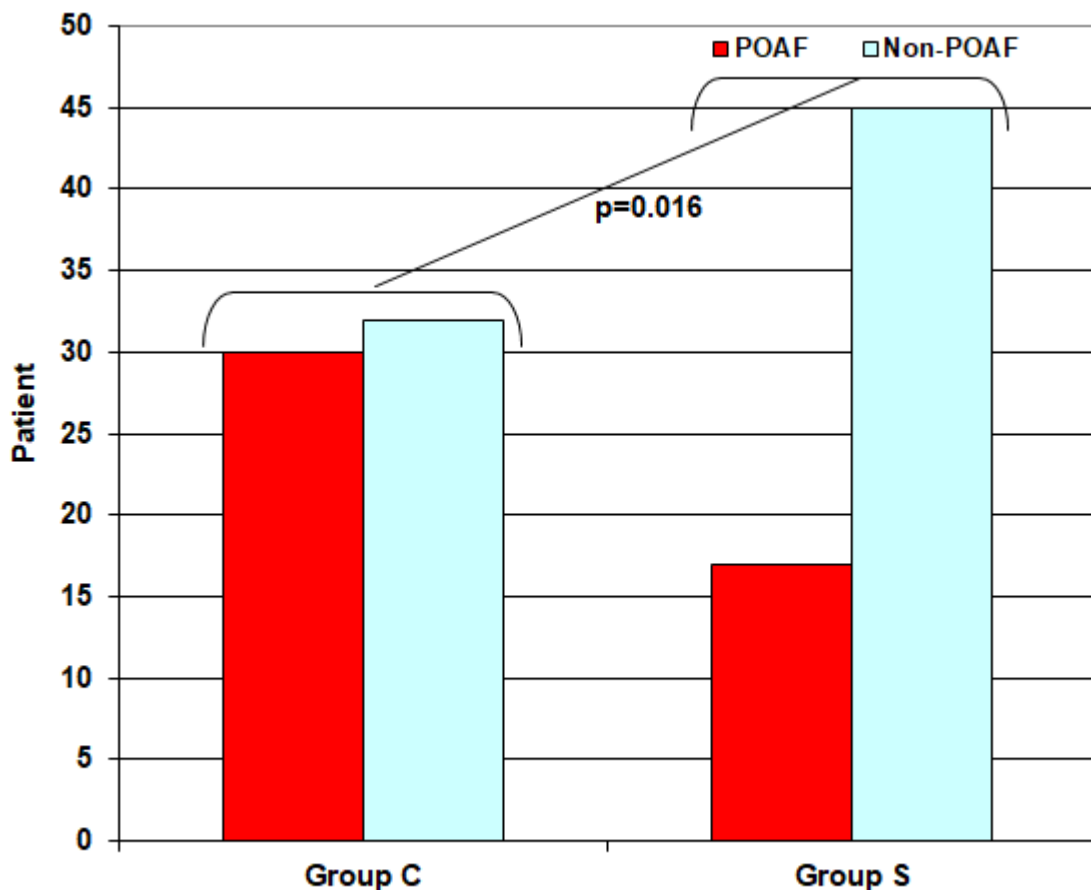


Fig. (2): Number of patients who developed POAF in both groups

The incidence of POAF was negatively correlated with the application of VST and serum SOD, while was positively related to prolonged CBP, aortic clamping and total operative time, and serum levels of other variables. Moreover, prolonged ICU stay and total PO hospital stay were positively correlated with the

development of POAF. Furthermore, serum SOD levels were negatively correlated, while serum levels of other variables were positively correlated with prolonged clamping and CPB times (Table 4).

Table (4): Pearson's correlation between the incidence of POAF and perioperative variables

Variables	POAF		VST		Clamping time		CPB time		Op time	
	"r"	P	"r"	P	"r"	P	"r"	P	"r"	P
POAF			-0.216	0.016	0.335	<0.001	0.515	<0.001	0.247	0.006
Serum MDA	0.645	<0.001	-0.358	<0.001	0.183	0.042	0.320	<0.001	0.196	0.029
Serum SOD	-0.728	<0.001	0.509	<0.001	-0.285	0.001	-0.276	0.002	-0.166	0.065
Serum CRP	0.729	<0.001	-0.670	<0.001	0.193	0.032	0.249	0.005	0.173	0.059
Serum IL-6	0.750	<0.001	-0.298	0.001	0.277	0.002	0.436	<0.001	0.179	0.058
MV time	0.232	0.010	-0.217	0.015						
ICU Stay	0.286	0.001	0.534	0.124						
CT drainage time	0.123	0.173	-0.213	0.018						
Total PO HS	0.233	0.009	-0.237	0.008						

POAF: Postoperative atrial fibrillation; VST: Vitamin supplemental therapy; CPB: Cardiopulmonary bypass; Op time: Operative time; r: Pearson's correlation coefficient; MDA: Malonaldehyde; SOD: Superoxide dismutase; hsCRP: high-sensitivity C-reactive protein; IL-6: Interleukin-6; MV: Mechanical ventilation; CT: Chest tube; PO: Postoperative; HS: Hospital stay; p<0.05: indicates a significant correlation

Regression and ROC curve analyses defined preoperative VST as negative, while prolonged CPB time as positive significant predictors for the development of POAF, and high serum levels of IL-6 and hsCRP and low serum levels of SOD as significant lab findings at the time of de-clamping as predictors for development of POAF (Table 5, Fig. 3)

Table (5): Regression and Receiver operating characteristic (ROC) curve analyses between the incidence of POAF and perioperative variables

Variables	Regression analysis		ROC curve analysis		
	β	P	AUC	P	95% confidence interval
Preoperative vitamin therapy	0.358	<0.001	0.389	0.038	0.286-0.491
Serum superoxide dismutase	-0.321	<0.001	0.065	<0.001	0.016-0.115
Serum C-reactive protein	0.546	<0.001	0.930	<0.001	0.889-0.970
Serum interleukin-6	0.224	0.001	0.938	<0.001	0.887-0.989
Cardiopulmonary bypass time	0.136	0.009	0.813	<0.001	0.732-0.894

Paired-sample area difference of areas under the ROC curves for POAF predictors defined preoperative VST as the sensitive negative predictors for POAF development with significant area difference versus that of SOD (AUC difference: 0.323, p<0.001, 95%CI: 0.235-412) and high serum levels of CRP (AUC difference: 0.116, p=0.018, 95CI: 0.02-0.213) and IL-6 (AUC difference: 0.124, p=0.013, 95% CI: 0.026-0.223) compared to area for prolonged CPB time.

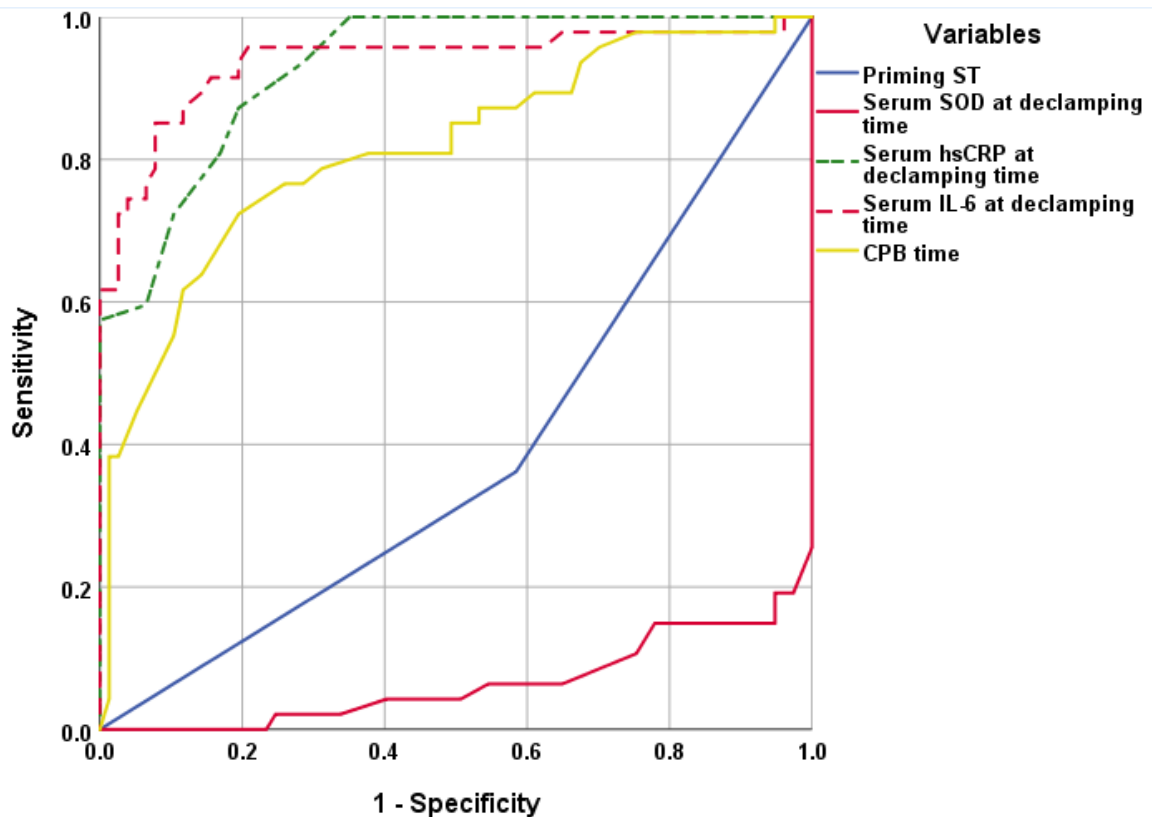


Fig. (3): ROC curve analysis for predictors for POAF after CABG surgery

Discussion

Estimated serum levels of studied parameters showed that all patients assigned for CABG surgery had hypovitaminosis D (HVD) with disturbed redox status and immune milieu in the inflammatory direction. Moreover, these disturbances were progressively deteriorating as shown in the S2 sample of controls. In line with these findings, one study found the amount of activated T-helper cells and regulatory T-lymphocytes were elevated in blood and pericardial fluid samples of CABG patients with higher levels of natural killer cells and IL-6 in pericardial than blood samples⁽¹⁰⁾. Another study detected higher levels of tumor necrosis factor- α and IL-6 with reduced antioxidant levels in preoperative left atrial tissue of POAF than in non-POAF patients after CABG surgery⁽¹¹⁾. Moreover, increased expression and secretion of IL-6 was detected in epicardial than subcutaneous biopsies obtained during CABG with a maximum secretion in severe and extremely severe coronary artery lesions⁽¹²⁾.

Considering the primary outcome of the current study is the incidence of POAF, the applied preoperative VST allowed a significant reduction of the incidence of POAF in comparison to control patients who did not receive the VST. Moreover, statistical analyses defined modulation of serum levels of IL-6, hs-CRP, and SOD with VST are significant predictors for the decreased incidence of POAF.

Unfortunately, the literature review detected no previous article used a similar vitamin cocktail for pre-CABG preparation, however, one study found

oxidative and nitrosative stresses are involved in the development of an arrhythmogenic substrate via their effect on connexins and suggested that prevention of lateralization of connexins 40/43 in atrial tissue by treatment with omega-3 fatty acids and antioxidant vitamins might reduce these stress and likely contribute to POAF prevention⁽¹³⁾. The reported relation between HVD and POAF development and the prophylactic role of vitamin D therapy assured that previously reported by multiple studies which documented that HVD may be one of the reasons for POAF development, the VD level is an independent predictor for this complication^(14, 15) and preoperative VD supplementation was strongly associated with POAF prevention in patients with VD deficiency⁽¹⁶⁾ acting in a dose-response manner⁽¹⁷⁾. Moreover, the reported relation between serum high serum IL-6 and POAF development supported the recently detected that highly elevated levels of IL-6 are excellent predictors for an unfortunate post-cardiac surgery course in ICU⁽¹⁸⁾.

The obtained results and these literature findings point to the importance of preoperative correction of disturbed inflammatory and redox milieu to improve surgical outcomes of CABG surgery patients. In support of this assumption, patients who received preoperative VST for four weeks showed a significant decrease in serum MDA with increased serum levels of SOD in the S2 sample of patients of the study group than controls. Concomitantly, serum levels of hsCRP and IL-6 levels were reduced, thus indicating improvement of inflammatory milieu. Moreover, in support of improving outcomes with the use of VST, the incidence of POAF was significantly lower, the amount of chest tube drainage was significantly lesser, and the total duration of PO hospital stay was significantly shorter with VST.

By the obtained data, meta-analysis studies indicated that preoperative vitamin C supplementation may prevent POAF, and shorten the duration of mechanical ventilation, ICU, and a hospital stay of cardiac surgery patients^(19, 20, 21). Another study documented that preoperative short-term high-dose VD supplementation for patients, with VD insufficiency or deficiency, which underwent CABG surgery significantly, prevents the occurrence of POAF⁽²²⁾.

Injectable vitamin C supplementation was used immediately postoperatively and the VST protocol was resumed when oral intake was allowed, for patient support during the postoperative period. In line with this policy, a meta-analysis detected progressively depleted plasma vitamin C concentration after a different type of surgery with 39% depletion during the first week and further 21% depletion within 2-3 months postoperatively⁽²³⁾.

Conclusion:

Preoperative preparation for correction of hypovitaminosis D and disturbances of inflammatory and/or redox milieu is mandatory before CABG surgery to improve surgical outcomes and reduce complication rates and severity.

Limitation:

No postoperative estimation of serum levels of the studied parameters is the study limitation.

Recommendation:

The preoperative VST of patients undergoing non-cardiac and cardiac surgery other than CABG is recommended to establish its effect on the PO outcome of these patients.

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