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Effect of oral vitamin C on atrial fibrillation development after isolated coronary artery bypass grafting surgery: A prospective randomized clinical trial

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Abstract

Background: *Some evidences have shown the role of antioxidant vitamins in preventing atrial fibrillation (AF) after coronary artery bypass grafting (CABG) surgery. We sought to determine the effect of oral vitamin C on the incidence of postoperative AF in patients undergoing elective isolated on-pump CABG surgery.*

Methods: *One-hundred patients who underwent isolated CABG surgery were prospectively assigned into two groups: Group 1 — 50 patients received 2 g of oral vitamin C before and 500 mg twice daily lasting for 5 days after surgery; Group 2 — 50 patients as the control group did not receive any. All patients were continuously monitored after surgery in the intensive care unit (ICU), and then Holter monitoring was implemented for 72 h.*

Results: *The mean of patients' age was 61.31 ± 6.42 years. Postoperative AF occurred in 16 and 4 patients in control and treatment groups, respectively (32% vs. 8%, $p = 0.003$). The ICU stay was 1.79 ± 0.313 and 2.10 ± 0.61 days for vitamin C and control groups, respectively ($p = 0.002$). The hospital stay was significantly lower in vitamin C group compared with that of the control group (5.32 ± 0.59 vs. 5.74 ± 1.30 days, respectively, $p = 0.041$). Baseline erythrocyte sedimentation rate (OR 1.030, 95% CI 1.003–1.058, $p = 0.030$) and taking vitamin C (OR 8.068, 95% CI 1.783–36.517, $p = 0.007$) were the independent predictors of postoperative AF.*

Conclusions: *Oral vitamin C can be safely used to decrease the incidence of postoperative AF in patients undergoing elective isolated on-pump CABG surgery.* (Cardiol J 2014; 21, 5: 492–499)

Key words: atrial fibrillation, coronary artery bypass grafting, ascorbic acid, vitamin C

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice with the estimated prevalence of 0.4% to 1%, advancing with age [1–4]. The lifetime risk of AF development in both sexes is estimated to be 25%, that is showing the need for further investigation to elucidate preventive strategies, predisposing factors and treatments for this public health problem [5]. AF is indicative of cardiac diseases progression that is associated with increased long-term risk of stroke and mortality. Some factors were found to predispose patients to AF that include advanced age, diabetes mellitus (DM), hypertension, smoking, valvular heart disease, prior myocardial infarction (MI), congestive heart failure (CHF), left ventricular hypertrophy and decreased left ventricular ejection fraction (LVEF) [1, 6].

AF is also the commonest cardiac rhythm disturbance following cardiac surgeries, with the exception of sinus tachycardia [7]. The incidence of postoperative AF differs between cardiac surgeries as it has been found to be about 30% in patients undergoing coronary artery bypass grafting (CABG) surgery alone, and about 60% in those undergoing combined CABG and valve surgeries [7–9]. Postoperative AF is a substantial factor for developing morbidity and mortality following cardiac surgery [8, 10, 11], and it has been shown that it contributes to the increase in the length of hospital stay and intensive care unit (ICU) stay following isolated CABG surgery [12].

The fundamental mechanism involved in developing postoperative AF has been shown to be multifactorial. It has been investigated that inflammation and oxidative stress attributable to ischemia/reperfusion events in the setting of CABG surgery result in electrophysiological remodeling of atrium, and these are the main etiologies for the occurrence of postoperative AF [13]. Given these points in terms of etiologies, few studies have demonstrated the effect of antioxidant agents including vitamins C and E on the incidence of postoperative AF [14]. Hereby, we conducted a randomized clinical trial to evaluate the effect of oral vitamin C on the incidence of AF following elective isolated on-pump CABG surgery, and, also, on the length of hospital and ICU stays after the surgery.

Methods

Patients and protocols

The patients who underwent elective isolated on-pump CABG surgery in our institution, Seyyed-al-Shohada Heart Center, form March 2012 to March 2013, were randomly assigned to receive either oral vitamin C, treatment group, or no agent, control group. This study was approved by our local ethical committee in the Urmia University of Medical Sciences; all patients were informed and given their written consent.

The inclusion criteria were as follows: age > 50 years, without history of CABG surgery, isolated on-pump CABG surgery, and taking beta-blocker agents before and after surgery. Exclusion criteria were as follows: history of any cardiac arrhythmia and/or being under anti-arrhythmic therapy, being under digoxin therapy, having pacemaker, severe CHF and/or LVEF < 30%, renal failure (creatinine ≥ 1.5 mg/dL), severe hepatic failure, chronic obstructive pulmonary disease, no occurrence of intra- or post-operative cardiopulmonary arrest, or any degree of cardiac blockade and/or bradycardia < 50 bpm.

Considering Eslami et al. [15] study showing the incidence of postoperative AF 26% and 4% in the vitamin C and control groups, respectively, and 95% confidence interval (CI) with the power of 80%, our sample size was calculated as approximately 50 patients per group. Consequently, 100 patients who met our study inclusion criteria were allocated into groups. All patients were randomized into two groups in a 1:1 ratio using random-number table. The groups included: Group 1 — 50 patients who were given 2 g of vitamin C tablets before the surgery and 500 mg twice daily for 5 days after the surgery; Group 2 — 50 patients as control group, were not given any drug. All patients also received beta-blockers 1 week before the surgery and continued after the surgery.

Clinical characteristics including age, gender, risk factors history, drugs history, echocardiographic examination, and laboratory measurements were collected. Drug history was defined as those agents which were consumed at least 1 week before the surgery. Hypertension was defined as those who had systolic blood pressure ≥ 140 mm Hg and diastolic blood pressure ≥ 90 mm Hg and/or taking antihypertensive medicines. Hyperlipidemia was defined as those who either had low-density lipoprotein > 100 mg/dL or were under therapy for hyperlipidemia. DM was diagnosed as those who had one of the following criteria; 1) the symptoms of diabetes plus plasma glucose concentration > 200 mg/dL; 2) fasting plasma glucose ≥ 126 mg/dL; 3) 2-h post-loading glucose ≥ 200 mg/dL during an oral glucose tolerance test; and/or 4) consuming anti-diabetic drugs.

Echocardiography was performed by a single echocardiographer and some measurements including LVEF, left atrium diameter, and left ventricular end-systolic and end-diastolic diameters were calculated upon echocardiographic evaluation. Blood samples were collected 6 to 24 h before the surgery to assess hematologic parameters including white blood cell count, hemoglobin, hematocrit and erythrocyte sedimentation rate (ESR). All patients underwent on-pump CABG surgery using standard cardiopulmonary bypass by a single surgical team. CABG-related characteristics including the number of grafts used, the duration of aortic cross-clamp, the duration of pump perfusion and the duration of postoperative ventilation were also recorded.

All patients were continuously monitored after surgery using a wearable health monitoring in the ICU, and then monitored using an electrocardiographic Holter monitoring for 72 h in the ward. Postoperative AF was defined as patients who had an episode of AF lasting more than 10 min. Amiodarone was intravenously used to control fibrillation rhythm and conversion to sinus rhythm (SR) and was continued orally during a 6-week period. Wearable continuous monitoring and electrocardiographic Holter monitoring was assessed by a single cardiac electrophysiologist.

Statistical analysis

Categorical variables were presented as number (percentage) and analyzed using χ^2 or Fisher's exact tests, as appropriate. Continuous variables were evaluated using Student's t-test or Mann-Whitney U test, as appropriate. For identifying the diagnostic value of laboratory, a receiver operating characteristic (ROC) curve was conducted. Multivariate analysis, binary logistic regression, were also used to detect the independent predictors of postoperative AF. In this model, covariates included the variables which proved significant or $p < 0.1$ in the univariate analysis. P values less than 0.05 were considered statistically significant. All analyses were performed by SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

One-hundred (100%) patients completed this study; in each group there were 50 patients, the two groups were the vitamin C group and the control group. The mean age of patients was 61.31 ± ± 6.42 years, and the majority of them (74%) were male. The baseline and CABG-related characteristics of both groups are shown in Table 1. There were no significant differences between the groups regarding measured baseline and CABG-related characteristics (Table 1).

Postoperative AF occurred in 20 (20%) patients; its incidence were 16 and 4 patients in control and treatment groups, respectively (32% vs. 8%, p = 0.003). The mean length of postoperative AF incidence was 2.55 ± 1.15 days, and its mean for the treatment group was 2 ± 0.816 days vs. 2.69 ± 1.195 days for the control group (p = = 0.295). The majority of postoperative AFs were seen at 2nd and 3rd days, however it did not show any significant differences between the groups (Fig. 1). The time needed for converting AF to SR was not significantly different among groups, although its value was considerably lower in the vitamin C compared with the control group (3.37 ± 1.03 vs. 14 ± 28.95 h, p = 0.395) (Table 2).

No significant difference regarding the beginning location of postoperative AF, ICU or ward, was observed (Table 2). The total mean length of ICU stay was 1.95 ± 0.51 days, and this time was 1.79 ± ± 0.313 days for vitamin C and 2.10 ± 0.61 days for control group (p = 0.002). The mean length of hospital stay was 5.53 ± 1.03 days, and it was significantly lower in vitamin C compared with control group (5.32 ± 0.59 vs. 5.74 ± 1.30 days, respectively, p = 0.041). The mean of ICU stay was 1.80 ± 0.30 days in the patients who developed AF postoperatively and 2.56 ± 0.69 days in those who had SR postoperatively (p = 0.001). The mean of hospital stay was 5.25 ± 0.50 vs. 6.65 ± 1.70 days in the patients with AF and SR, respectively (p = 0.001).

The predictors of developing postoperative AF were listed in Tables 3 and 4. Based on univariate analysis, having DM, prolonged ventilation time and increased ESR were the main risk factors for developing postoperative AF. In addition, a trend was observed that patients with AF were older and had lower amount of LVEF than those with SR (Tables 3, 4).

The ROC curve was drawn for detecting ESR diagnostic value (Fig. 2). The area under the curve (AUC) was 0.710 (95% CI 0.574–0.846, p = 0.005). The best cut-off point was 27.5 mm/h with the sensitivity and specificity of 63% and 71%, respectively.

Logistic regression model showed that the baseline ESR value (odd ratio [OR] 1.030, 95% CI 1.003–1.058, p = 0.030) and taking vitamin C (OR 8.068, 95% CI 1.783–36.517, p = 0.007) were the independent predictors of developing postoperative AF (Table 5). Hosmer-Lemeshow test of goodness

Table 1. Baseline and coronary artery bypass grafting-related characteristics of study cohort.

	Total (n = 100)	Vitamin C (n = 50)	Control (n = 50)	P
Age [years]	61.31 ± 6.42	60.52 ± 5.83	62.12 ± 6.93	0.215
Sex (male)	74 (74%)	38 (76%)	36 (72%)	0.648
Hypertension	30 (30%)	14 (28%)	16 (32%)	0.663
Diabetes mellitus	24 (24%)	9 (18%)	15 (30%)	0.160
Hypercholesterolemia	15 (15%)	9 (18%)	6 (12%)	0.401
Smoking	21 (21%)	12 (24%)	9 (18%)	0.461
Myocardial infarction	21 (21%)	11 (22%)	10 (20%)	0.806
Nitrate use before CABG	37 (37%)	17 (34%)	21 (42%)	0.410
Nitrate use after CABG	96 (96%)	47 (94%)	49 (98%)	0.307
Statin use before CABG	16 (16%)	9 (18%)	7 (14%)	0.585
Statin use after CABG	18 (18%)	10 (20%)	8 (16%)	0.603
Left atrial diameter [cm]	19.37 ± 2.60	19.72 ± 2.42	19.02 ± 2.75	0.180
LVEF [%]	43.30 ± 8.17	43.6 ± 8.15	43 ± 8.27	0.716
LVEF < 30%	10 (10%)	4 (8%)	6 (12%)	0.505
LV end-systolic diameter [cm]	3.08 ± 0.65	3.05 ± 0.66	3.10 ± 0.64	0.668
LV end-diastolic diameter [cm]	4.67 ± 0.73	4.55 ± 0.68	4.77 ± 0.77	0.136
Number of grafted vessels	2.79 ± 0.56	2.80 ± 0.57	2.78 ± 0.54	0.858
Aortic cross-clamp time [min]	75.50 ± 23.30	77.44 ± 24.07	73.56 ± 22.58	0.408
Perfusion pump time [min]	116.25 ± 30.13	118.64 ± 29.71	113.86 ± 30.66	0.430
Ventilation time [h]	14.40 ± 10.25	13.38 ± 2.01	15.41 ± 14.35	0.325
Ventilation > 24 h	1 (1%)	0 (0%)	1 (2%)	1
Blood transfusion before CABG [U]	0.92 ± 1.06	0.88 ± 1.06	0.96 ± 1.07	0.708
Blood transfusion after CABG [U]	0.69 ± 1.13	0.66 ± 1.14	0.72 ± 1.14	0.739
Central venous pressure [cm]	5.22 ± 1.77	5.28 ± 1.77	5.16 ± 1.8	0.737
White blood cell ($\times 10^3$)	7.29 ± 2.11	7.33 ± 2.13	7.24 ± 2.09	0.837
Erythrocyte sedimentation rate [mm/h]	26.27 ± 24.07	27.52 ± 25.09	24.96 ± 23.16	0.601
Hemoglobin [mg/dL]	13.08 ± 1.61	12.95 ± 1.72	13.21 ± 1.49	0.431
Hematocrit [%]	39.40 ± 4.55	39.36 ± 4.60	39.43 ± 4.54	0.938

CABG — coronary artery bypass grafting; LV — left ventricular; LVEF — left ventricular ejection fraction

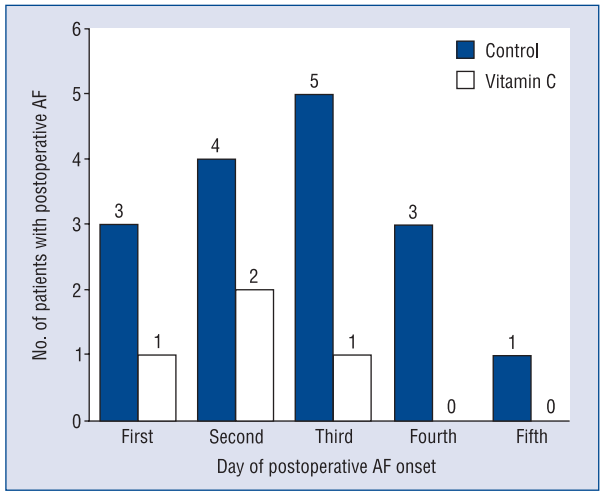

Figure 1. Time of first incidence of postoperative atrial fibrillation (AF) in those who received vitamin C vs. control group.

of fit the model showed high predictive value with p value of 0.993.

Moreover, a case of stroke occurred in one of the control group's patient who had been developing AF at the first day after the CABG surgery (Table 2).

Discussion

In the present investigation, in accordance with previous studies regarding the effect of antioxidants on the occurrence of postoperative AF, we showed that oral vitamin C, as an antioxidant agent, led to decrease in the incidence of postoperative AF and the length of ICU stay and length of hospital stay in the patients who underwent elective isolated on-pump CABG surgery. Univariate analysis showed that DM, increased ventilation time, and increased baseline ESR were the main

Table 2. Measured outcomes of study following coronary artery bypass grafting.

	Total (n = 100)	Vitamin C (n = 50)	Control (n = 50)	P
Postoperative AF	20 (20%)	4 (8%)	16 (32%)	0.003
Day of postoperative AF [days]	2.55 ± 1.15	2 ± 0.816	2.69 ± 1.195	0.295
Location of postoperative AF occurrence:				0.639
ICU	7 (35%)	1 (25%)	6 (37.5%)	
Ward	13 (65%)	3 (75%)	10 (62.5%)	
Duration of rhythm conversion [h]	11.87 ± 26.10	3.37 ± 1.03	14 ± 28.95	0.395
ICU stay [days]	1.95 ± 0.51	1.79 ± 0.313	2.10 ± 0.61	0.002
Hospital stay [days]	5.53 ± 1.03	5.32 ± 0.59	5.74 ± 1.30	0.041
Cerebrovascular events	1 (1%)	0 (0%)	1 (2%)	1

AF — atrial fibrillation; ICU — intensive care unit

Table 3. Univariate analysis of qualitative predictors of postoperative atrial fibrillation (AF).

	AF in variable positive	AF in variable negative	P
Sex (male)	16/74 (21.6%)	4/26 (15.4%)	0.494
Hypertension	7/30 (23.3%)	13/70 (18.6%)	0.585
Diabetes mellitus	10/24 (41.7%)	10/76 (13.2%)	0.002
Hypercholesterolemia	3/15 (20%)	17/85 (20%)	1
Smoking	4/21 (19%)	16/79 (20.3%)	0.902
Myocardial infarction	5/21 (23.8%)	15/79 (19%)	0.623
Nitrate use before CABG	6/38 (15.8%)	14/62 (22.6%)	0.410
Nitrate use after CABG	20/96 (20.8%)	0/4 (0%)	0.307
Statin use before CABG	3/16 (18.8%)	17/84 (20.2%)	0.892
Statin use after CABG	4/18 (22.2%)	16/82 (19.5%)	0.795
LVEF < 30%	4/10 (40%)	16/90 (17.8%)	0.096
Ventilation > 24 h	1/1 (100%)	0/99 (0%)	0.200

CABG — coronary artery bypass grafting; LVEF — left ventricular ejection fraction

Table 4. Univariate analysis of quantitative predictors of postoperative atrial fibrillation.

	Atrial fibrillation	Sinus rhythm	P
Age [years]	63.75 ± 6.24	60.71 ± 6.36	0.058
Left atrial diameter [cm]	19.25 ± 2.86	19.40 ± 2.55	0.819
LVEF [%]	40.25 ± 8.50	44.06 ± 7.95	0.062
LV end-diastolic diameter [cm]	3.04 ± 0.57	3.08 ± 0.67	0.781
LV end-systolic diameter [cm]	4.45 ± 0.74	4.72 ± 0.73	0.142
Number of grafted vessels	2.65 ± 0.74	2.82 ± 0.50	0.210
Aortic cross-clamp time [min]	72.85 ± 17.06	76.16 ± 24.66	0.572
Perfusion pump time [min]	112.95 ± 20.34	117.08 ± 32.17	0.587
Ventilation time [h]	19.36 ± 22.39	13.15 ± 1.80	0.015
Blood transfusion before CABG [U]	0.6 ± 0.68	1 ± 1.025	0.132
Blood transfusion after CABG [U]	1 ± 1.49	0.61 ± 1.025	0.173
Central venous pressure [cm]	5.65 ± 1.56	5.11 ± 1.81	0.227
White blood cell ($\times 10^3$)	7.21 ± 2.03	7.31 ± 2.13	0.858
Erythrocyte sedimentation rate [mm/h]	42.58 ± 29.74	22.34 ± 20.88	0.001
Hemoglobin [mg/dL]	12.78 ± 2.22	13.16 ± 1.42	0.348
Hematocrit [%]	40.08 ± 5.26	39.23 ± 4.37	0.459

CABG – coronary artery bypass grafting; LV — left ventricular; LVEF — left ventricular ejection fraction

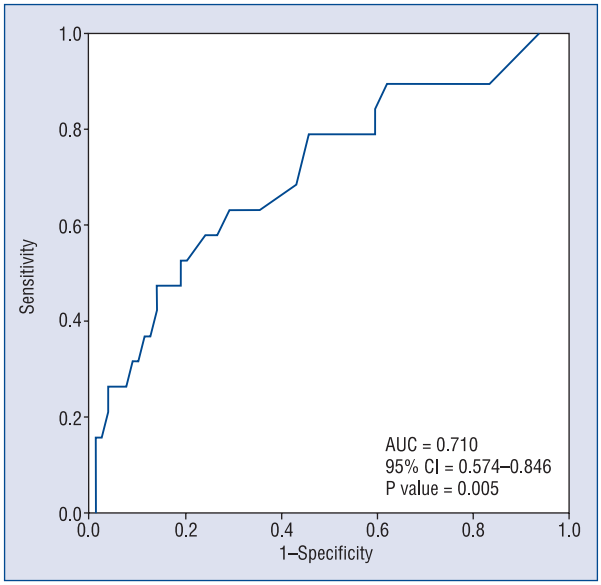

Figure 2. Receiver operating characteristics curve of erythrocyte sedimentation rate for identifying postoperative atrial fibrillation; AUC — area under the curve; CI — confidence interval.

risk factors for postoperative AF. Furthermore, it showed a trend toward a higher incidence of postoperative AF in aging patients and those with decreased LVEF. All baseline and perioperative characteristics were similar between groups and the study cohort was homogenous. Consequently, we may be able to state that these findings are due to the effect of vitamin C, not any other factors which have an impact on the incidence of AF after CABG surgery.

AF as the commonest arrhythmia after cardiac surgery is usually developed during 2 or 3 days postoperatively [8], in our study the most of AF occurred on the 2nd and 3rd days after the surgery (Fig. 1). The recent studies have shown that the postoperative AF correlated with decreased survival and increased in-hospital adverse events during short- and long-term follow-up [16–18]. Despite conducting more investigations regarding postoperative AF pathogenesis, its mechanism has not been identified yet [19]. Increasing evidences exist that have demonstrated the oxidative stress and inflammation as the main etiologies for developing AF after cardiac surgery. It has been previously found that the increased sympathetic tone due to surgical trauma and injury owing to ischemia/reperfusion during CABG surgery resulting in triggering oxidative stress have important role in the electrophysiological remodeling of atrial myocytes and consequent AF genesis [2]. Additionally, the substantial impact of vitamin C may be attributed to decreasing peroxynitrite formation and increase in intracellular ascorbate levels, as well [2]. Hence, we prescribed beta-blockers pre- and post-operatively to all patients to decrease the sympathetic effect on atrial remodeling, and then examined the antioxidant ability of vitamin C in reducing AF by controlling oxidative stress mediated processes.

Eslami et al. [15] have found that adding vitamin C to beta-blocker regimen before and after isolated CABG resulted in decreased postoperative AF in the combination group compared with beta-blocker usage alone (4% vs. 26%, respectively), however it did not reduce the length of ICU and hospital stays. Another study has investigated the role of oral ascorbic acid in the attenuation of postoperative AF in patients who underwent CABG, and interestingly led to decrease in AF occurrence from 34.9% for control to 16.4% for vitamin C group [2]. The study of Papoulidis et al. [20] has indicated that taking vitamin C reduced the rate of AF in comparison with not taking any (44.7% vs. 61.2%). They also found significant decreases in the time of AF conversion to SR (7.3 ± 2.1 h in control vs. 5 ± 1.3 h in vitamin C group), and the length of hospital stay (9.5 ± 2.8 days in control vs. 6.7 ± 1.9 days in treatment group). These findings are consistent with our study showing the efficacy of vitamin C in preventing postoperative AF, however,

Table 5. Logistic regression analysis detecting independent predictors of postoperative atrial fibrillation.

	Exp (B)	95% confidence interval for Exp (B)	P
Age	1.005	0.907–1.114	0.925
Diabetes mellitus	1.613	0.399–6.525	0.503
Ventilation time	1.272	0.893–1.811	0.182
Left ventricular ejection fraction	0.960	0.890–1.036	0.291
Erythrocyte sedimentation rate	1.030	1.003–1.058	0.030
Vitamin C use	8.068	1.783–36.517	0.007

the present study for the first time showed the impact of vitamin C on reducing the length of ICU stay. In contrast, in the latest published placebo-controlled clinical trial, Bjordahl et al. [21] have concluded that there was no difference in postoperative AF incidence among patients who were given supplementation of vitamin C compared with those who were given placebo (30.3% vs. 30.2%, respectively; p = 0.985). It seems that the risk factors involved in the occurrence of postoperative AF and selection bias are the main factors which underlie paradoxical findings.

Considering inflammatory processes involved in postoperative AF, the markers of inflammation may be of importance in diagnosing and/or risk stratification of such patients. Accordingly, Ishida et al. [22] have noted that C-reactive protein (CRP), interleukin-6 (IL-6) and IL-8 increased after off-pump CABG surgery, but IL-6 was only significantly different between patients with and without postoperative AF, and it was an independent predictor of postoperative AF occurrence. Patients with an increased baseline CRP value have also been found to be in higher risk for developing AF after on- and off-pump CABG surgery [23]. White blood cell count is another marker that has been investigated and both pre- and post-operative increased values were the independent predictors of AF incidence following cardiac surgery [24, 25]. ESR is an inexpensive marker for acute phase response accompanied with diagnostic and prognostic values, especially in the rheumatic diseases and newly found non-inflammatory conditions such as stork and coronary artery disease [26, 27]. In our study, for the first time, we showed that increased baseline ESR was a risk factor for AF development, and also based on multivariate analysis it was an independent predictor of postoperative AF, although it had partially low sensitivity and specificity. Moreover, the chronic inflammation due to DM and coronary artery disease in patients may be another causes leading to increased ESR value. Further evaluations regarding ESR change after surgery may be of benefit, however, CRP and other newly developed inflammatory markers are more useful than ESR [28].

DM and decreased LVEF have been proposed to be the predictors of AF development [4, 6], and the need for prolonged ventilation (24 h or more) has also been shown to be an AF independent predictor [29]. In our study, univariate analysis showed that DM and increased ventilation time were the correlates of postoperative AF (p = 0.002, p = 0.015, respectively). Additionally, aging is one of the main predictors of AF development as its prevalence becomes 2-fold with each decade of age advancing, and males have 1.5-fold greater risk for developing AF than women [4]. In the present study, despite no significant differences in terms of age and gender between patients with AF and those with SR, there was a trend toward patients with AF to be older (63.75 ± 6.24 years vs. 60.71 ± 6.36 years, p = 0.058), and also there was a higher incidence of AF in men than women (21.6% vs. 15.4%, p = 0.494). We believe that the sample size of our study may be the main reason for our inability to show more correlates of AF development. Further evaluations will be helpful to clarify these notions.

Limitations of the study

This study has some limitations. First, it was not placebo-controlled trial, and had a relatively small sample size, which resulted in inability to identify postoperative AF correlates, however, we determined the sample size using previous study [15]. Surprisingly, significant results in terms of vitamin C impacts are promising for future preventive protocols. Second, we did not measure laboratory data including white blood cell count, hemoglobin, hematocrit and ESR after surgery, and if we measured postoperatively, we could find more interesting results.

Conclusions

Oral vitamin C can be used safely and efficaciously to decrease the incidence of postoperative AF in patients undergoing elective isolated on-pump CABG surgery. Furthermore, increased baseline ESR and taking vitamin C were the independent predictors of AF development after CABG surgery.

Conflict of interest: None declared

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