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The role of ascorbic acid in the prevention of atrial fibrillation after elective on-pump myocardial revascularization surgery: a single-center experience – a pilot study

Pavlos Papoulidis[a], Olga Ananiadou[a,*], Eleftherios Chalvatzoulis[a], Fotini Ampatzidou[b], Charilaos Koutsogiannidis[a], Theodoros Karaiskos[a], Athanasios Madesis[a], George Drossos[a]

[a]*Department of Cardiothoracic Surgery, General Hospital 'G. PAPANIKOLAOU', Exohi, 57010 Thessaloniki, Greece*
[b]*2nd ICU Department, General Hospital 'G. PAPANIKOLAOU', Thessaloniki, Greece*

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Abstract

Atrial fibrillation (AF) is a common arrhythmia that occurs postoperatively in cardiac surgery. There is evidence for the role of oxidative stress in the etiology of AF. In our study, we examined whether antioxidant ascorbic acid (vitamin C), could help in the reduction of the incidence of postoperative AF. Patients who were scheduled to undergo elective isolated on-pump coronary artery bypass grafting (CABG) were included in our study. One hundred and seventy patients were randomly divided in two groups: Group A ($n=85$) received vitamin C preoperatively and postoperatively whereas Group B ($n=85$) did not receive any (control group). The incidence of AF was 44.7% in the vitamin C group and 61.2% in the control group ($P=0.041$). The hospitalization time, the intensive care unit stay and the time interval for the conversion of AF into sinus rhythm was significantly shorter in the vitamin C group. Patients that developed AF also had longer hospital length of stay (9.5±2.8 days vs. 6.7±1.9, $P=0.034$). Supplementation of vitamin C reduces the incidence of postCABG AF, and decreases the time needed for rhythm restoration and length of hospital stay.

Keywords: PostCABG atrial fibrillation; Oxidative stress; Ascorbic acid; Vitamin C

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and is also a frequent complication that follows cardiac surgery. New onset AF, atrial flutter, and other atrial tachyarrhythmias occur in 15–50% of patients after cardiac surgery [1]. It occurs increasingly with age and it is also an independent risk factor for death with a risk ratio of 1.5 for men and 1.9 for women. The reported incidence varies, also depending on severity of cardiac disease, comorbidity and case complexity. Patients undergoing combined coronary artery bypass grafting (CABG) and valve surgery have a higher incidence of postoperative AF than those undergoing CABG alone [1, 2].

AF, which in the past was considered transient and benign arrhythmia, is a major cause of morbidity and mortality in cardiac surgery. Yet, the management and prevention of postoperative AF poses a significant challenge and remains problematic and controversial. Despite advances in surgery, anesthesia, and postoperative care, the incidence of AF arising de novo after cardiac surgery has not decreased. The onset of AF usually occurs on the second or third postoperative day, in most cases it is self-limited and 80% of patients return to sinus rhythm (SR) within one to three days after initiation of digoxin or amiodarone and β-blocker therapy [1, 2]. Nevertheless, it affects quality of life and importantly, patients who develop postoperatively AF have significantly higher 30-day and six-month mortality rates [3]. In addition, postCABG AF is associated with increased risk of stroke and perioperative myocardial infarction, and also increases the length of stay in the intensive care unit (ICU), as well as total hospitalization time [3, 4].

In view of the great burden of AF on health care resources, interest has been directed towards greater understanding of the associated pathophysiology underlying this common arrhythmia, in an effort to explore new therapeutic options. The traditional view of AF mechanisms is that it results from multiple re-entrant wavelets that move randomly throughout the atria and that atrial tachyarrhythmias alter atrial electrical properties, thus promoting multiple-circuit re-entrant AF [5, 6]. Recent work links inflammation and AF [7, 8] and there is substantial evidence that inflammation augments oxidative stress and vice versa, implicating such interrelation in the pathophysiology of AF [9]. Accordingly, therapeutic approaches that target inflammatory pathways have the potential to reduce the incidence

*Corresponding author. Tel.: +30 2313 307661/6944 465347; fax: +30 2313 307667.
E-mail address: oananiadou@gmail.com (O. Ananiadou).

of AF. Indeed, the development of AF leads to many structural and functional changes within the atria that perpetuates the arrhythmia, a process known as electrical remodelling. Carnes and colleagues show that oxidative stress may play a role in atrial remodelling, and there is preliminary evidence that oral vitamin C (ascorbic acid) may prevent electrical remodelling and postoperative AF [10].

The aim of our study is first to evaluate the efficacy of prophylactic and postoperative administration of ascorbic acid in achieving reduction of the incidence of postCABG AF; second to examine whether supplemental antioxidant has any beneficial effect on time needed for rhythm restoration and third to confirm AF as a source of longer hospitalization.

2. Materials and methods

Patients scheduled to undergo elective isolated CABG from December 2006 to March 2009 were screened to participate in this prospective randomized trial. All patients were NYHA class III and IV and also under β-blocker therapy, which was continued after surgery. Exclusion criteria were: age <65 years, preoperative AF, hyperoxaluria, permanent or temporary pacemaker, severe renal or hepatic failure, medication with class I and III antiarrhythmic agents or digoxin, any degree of atrioventricular block or bradycardia with a heart rate of <50 beats/min and severe pulmonary disease (pneumonia or chronic obstructive pulmonary disease).

The initial random assignment was by flipping a coin but simple randomization led to an imbalance with respect to sample size with a treatment group of 130 patients and control group of 85 patients. In order to have an equal sample size, we reevaluated our randomization protocol and using a random generator, the computer chose 85 out of 130 patients which were initially enrolled in the study group.

Echocardiography was performed before surgery by a single echocardiographer in a blinded fashion. Left ventricular ejection fractions were estimated by study of the apical 2- and 4-chamber views. Left atrium (LA) dimensions were also estimated and patients with enlarged LA (LAD >4.4 cm) were excluded from the study.

Hypertension was defined as a systolic blood pressure of 140 mmHg or a diastolic blood pressure of 90 mmHg, or as a history of treatment for hypertension. Hypercholesterolemia was defined as low-density lipoprotein levels >100 mg/dl. All patients with hypercholesterolemia were prescribed statin (20 mg/day) at least one week before surgery. Cigarette smoking was defined as the consumption of at least three cigarettes per day during the preceding three months. Diabetes mellitus was defined as the presence of fasting blood sugar level of >120 mg/dl on patients without antidiabetic medical therapy, or as the presence of diabetic history, and medication use [11].

Patients were randomly assigned into two groups. Group A (vitamin C group) included patients that received ascorbic acid, whereas Group B (control group) consisted of patients who received placebo (intravenous administration of 0.9% N/S). Vitamin C was administered intravenously. The pattern of administration was 2 g of vitamin C three hours prior the initiation of the cardiopulmonary bypass (CPB) and afterwards, 500 mg twice a day from the first postoperative day and for the next five days.

All patients were operated on by a single surgical team and underwent CABG on standard CPB with myocardial protection provided by the perfusion of blood cardioplegic solution. The total CPB, aortic cross-clamp and also reperfusion time were recorded. Reperfusion time, between aortic declamping and separation from CBP, is of importance as it is the time that the heart starts beating and has a continuous supply of fully oxygenated blood, to wash off all free oxygen radicals. Patients were continuously monitored in intensive care unit and high dependency unit and monitoring was continued after being transferred to the ward with standard 12-lead electrocardiography recorded twice daily. A blood count and biochemical profile was done every day and the potassium level in both groups was maintained approximately at a level of 4 mEq/l.

The detection of an episode of AF lasting >10 min or the requirement for urgent intervention due to AF (AF related profound symptoms or hemodynamic instability) was recorded. Amiodarone was used for rhythm control and after pharmacological intervention the conversion to SR was also recorded.

All patients who were included in the study were informed and gave written consent and our hospital's Ethics Committee approved our study protocol.

2.1. Statistical analysis

Clinical data were evaluated using SPSS version 14.0 statistical software (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean$\pm$S.D. The univariate association between qualitative variables was evaluated by the χ^2-test. Student's *t*-test was used for two-group comparisons of continuous parametric data; the Mann–Whitney test was used for non-parametric two-group comparison. *P* values of <0.05 were considered statistically significant.

3. Results

One hundred and seventy patients participated in this study. The vitamin C group included 85 patients and the control group consisted of 85 patients. The baseline characteristics of patients in the vitamin C and control group appear in Table 1. No significant difference among demographics was observed, and both groups had similar intraoperative characteristics, with no difference in the number of grafts used, the number of arterial conduits, the CPB, myocardial ischemia or the reperfusion time (Table 2).

We observed a significant difference in the overall incidence of postoperative AF between vitamin C and control group (44.7 vs. 61%, respectively, $P=0.041$). The incidence of postCABG AF with respect to gender was 47.4% in males who received vitamin C and 39.3% in females, whereas in the control group 60.3% and 63.6%, respectively (Table 3).

Overall, AF developed at a mean of 2.8 ± 1.5 days after surgery with no difference in time course of onset between the two groups, as presented in Fig. 1. Fig. 2 shows the time needed for conversion into SR in AF patients of both

Table 1. Baseline characteristics of patients

Characteristic	Vitamin C group ($n=85$)	Control group ($n=85$)	*P*-value
Mean age (years)	73.1±7.2	71.3±6.8	0.26
Sex (male)	57/85	63/85	0.65
Hypertension	53	46	0.70
Diabetes mellitus	16	17	0.94
Statin therapy	78	77	0.98
Cigarette smoking	64	55	0.97
LVEF <30%	3	3	0.98
Mean LVEF	0.4±0.2	0.5±0.2	0.89
Mean diameter of LA (cm)	3.5±1.8	3.4±1.8	0.99
ACE inhibitors	7	4	0.88
Nitrates prior surgery	1	0	0.95

Values represent mean±S.D. LVEF, left ventricular ejection fraction; LA, left atrium; ACE, angiotensin-converting enzyme.

groups, and the mean time was 5±1.3 h for vitamin C group vs. 7.3±2.1 h in control group ($P=0.047$, Mann–Whitney test).

The mean ICU stay was 2.2±0.9 days and the overall mean hospital stay after operation was 6.9±1.8 days. As seen in Table 2, the mean hospitalization time was 7.9±2.2 days in vitamin C group and 9.8±3.6 days in control group ($P=0.04$, Mann–Whitney test) and the mean ICU stay was 1.6±0.9 days vs. 2.1±1.1 days, respectively ($P=0.05$, Mann–Whitney test). Also, the mean hospital stay after operation was 9.5±2.8 days in patients who developed AF postoperatively and 6.7±1.9 days in SR patients ($P=0.034$, Mann–Whitney test). Respectively, the mean ICU stay was 2.7±1.3 days in those who experienced AF and 2±1.4 in those who maintained SR ($P=0.08$, Mann–Whitney test).

An adverse cerebral event (transient ischemic attack) occurred in one patient of the control group, who had an episode of AF prior to the stroke.

4. Discussion

In our study, we were able to demonstrate that administration of vitamin C can achieve a significant reduction in the incidence of postCABG AF. The study and the control group were homogenous, as regards the baseline and intraoperative characteristics. There was a statistical significant reduction of AF incidence in the vitamin C group, regardless of patient's sex. The role of ascorbic acid was also studied by Eslami and coworkers in 100 patients undergoing CABG [11]. Consistent with our findings but with lower overall incidence of AF, they found that vitamin C had a clearly beneficial effect with 4% incidence in the group that received both ascorbic acid and β-blocker therapy compared with 26% in the β-blocker usage alone group.

The rationale for β-blocker therapy as prophylaxis is that increased sympathetic tone is speculated to enhance the

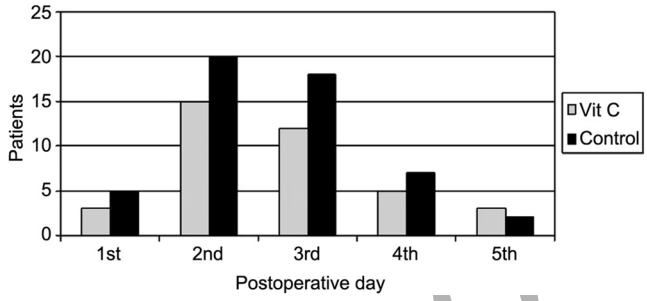

Fig. 1. Day of onset of postoperative atrial fibrillation in vitamin C and control group. Vit C, vitamin C group; Control, control group.

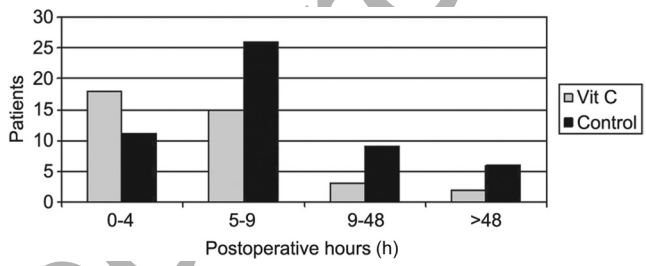

Fig. 2. Time needed for conversion of AF into sinus rhythm in vitamin C and control group. Vit C, vitamin C group; Control, control group; AF, atrial fibrillation.

Table 2. Intraoperative and postoperative characteristics

Characteristic	Vitamin C group ($n=85$)	Control group ($n=85$)	*P*-value
Mean no of grafts	2.8±1.8	2.7±1.6	0.98
Mean no of arterial grafts	1.1±0.8	0.9±0.7	0.89
Mean CPB time (min)	53.8±8.5	51±9.1	0.85
Mean aortic cross-clamp time (min)	43.8±9.7	48.1±8.6	0.75
Mean reperfusion time (min)	12±3.9	14.1±3.9	0.83
Mean ICU stay (days)	1.6±0.9	2.1±1.1	0.05
Mean hospitalization time after surgery (days)	7.9±2.2	9.8±3.6	0.04

Values represent mean±S.D. CPB, cardiopulmonary bypass; ICU, intensive care unit.

Table 3. Univariate analysis of AF incidence with respect to gender

Variable	AF (+) No. of patients (%)	Males No. of patients (%)	Females No. of patients (%)
Ascorbic acid group	38/85 (44.7)	27/57 (47.4)	11/28 (39.3)
Control group	52/85 (61.2)	38/63 (60.3)	14/22 (63.6)
P-value	0.041	0.038	0.049

AF, atrial fibrillation.

susceptibility of patients to dysrhythmias. For that reason, all our patients were under β-blocker therapy preoperatively, which was not discontinued before surgery and was also continued postoperatively. However, recent experimental data have broadened our thinking about AF mechanisms and new supplemental pharmacologic agents alter clinical approaches to prevention. Bruins et al. was the first to propose a direct link between inflammation and AF by observing an increased frequency of AF after CABG surgery, where the peak incidence of AF occurred on the second and third postoperative day, coinciding with the peak elevation of C-reactive protein (CRP) [12].

Sufficient physiological data support the role of inflammation in the genesis of AF after surgery [7, 9]. The heart, which has been subjected to ischemia of variable duration, is exposed to pro-inflammatory cytokines invoked by ischemic and traumatic injury. When exposed to these inflammatory cytokines, oxygen radical signalling is initiated. Surgical trauma also causes a depletion of plasma antioxidants [13]. The inflammatory process affects the electrophysiological properties of atrial myocytes. Ascorbate as an antioxidant and free radical scavenger possibly prevents the effects of the oxidative stress and interestingly Carnes et al. showed in an experimental study that atrial ascorbate levels are reduced after rapid atrial pacing. Treatment with ascorbate attenuated electrical remodelling that resulted from short-term rapid atrial pacing [10]. The beneficial effects of supplemental ascorbic acid are likely attributable to the preservation of intracellular ascorbic acid levels, which minimizes the peroxynitrite mediated injury that is associated with human AF [10, 14]. In another study, oral ascorbic acid reduced early recurrence rates after electrical cardioversion of persistent AF, and a significant reduction was observed in serum inflammatory indices, such as white blood cell count, fibrinogen level and CRP level [15].

Apart from reducing the incidence of postCABG AF, vitamin C may have played a role in decreasing the time for rhythm restoration. Although in our series, there was no difference in time course of onset between the two groups, we report a significant reduction of the time needed for conversion of AF into SR in vitamin C group (Fig. 2). Of note, men are more likely to develop AF after CABG than women [2, 4]. Although the number of female patients that participated in our study was relatively small, univariate analysis in Table 4 showed no significant difference in the incidence of AF between males and females. Patients that received vitamin C had also, significantly shorter ICU and hospital stay. Interestingly enough, AF was a source of longer total hospitalization time but there was no significant difference in ICU stay between patients who developed postoperatively AF and SR patients.

A variety of follow-up studies are underway to further elucidate the mechanisms by which oxidative stress and inflammation are involved in AF, as well as studies to evaluate novel and more effective treatment strategies. The opportunity to use ascorbic acid for AF prophylaxis is attractive because of its low side-effect profile, wide acceptance and low cost, with strong antioxidant properties that might blunt the impact of oxidant signalling, thus affecting the likelihood of inflammation-mediated postoperative AF.

Table 4. Univariate analysis of significant predictors of postoperative AF

Variable	AF in variable (+) No. of patients (%)	AF in variable (−) No. of patients (%)	*P*-value
Sex (male)	65/120 (54.2)	25/50 (50)	0.32
Statin therapy	75/155 (48.4)	15/15 (100)	0.28
Cigarette smoking	45/119 (37.8)	28/51 (54.9)	0.79
History of MI	10/70 (17.9)	21/100 (21)	0.88
LVEF <30%	4/6 (66.7)	75/164 (45.7)	0.34
Ventillation time >24 h	2/5 (40)	28/165 (16.9)	0.22

AF, atrial fibrillation; MI, myocardial infarction; LVEF, left ventricular ejection fraction.

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