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Effect of Vitamin C in Prevention of Atrial Fibrillation after Coronary Artery Bypass Graft: a Double-Blind Randomized Clinical Trial

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Abstract

Background and Objective: Atrial fibrillation is the most common arrhythmia after cardiac surgery. As an antioxidant, vitamin C has a crucial role in reducing the incidence of post-operative atrial fibrillation. The present study was carried out to evaluate the impact of vitamin C administration in reducing the incidence of post-CABG atrial fibrillation.

Methodology: In this double-blind parallel clinical trial, 170 patients with coronary artery disease who underwent CABG were divided into two groups of intervention and control according to the table of random numbers and received vitamin C and placebo, respectively. The groups had no statistically significant difference in terms of demographic and clinical characteristics. The intervention group received 2 g intravenous vitamin C the night before surgery. The medication was continued for 5 days as 500 mg twice a day. After surgery, the groups were evaluated and compared in terms of important outcomes of the study, particularly the occurrence of arrhythmia, length of stay in ICU, and length of stay in hospital.

Findings: A total of 118 men and 52 women with a mean age of 59.1 ± 9.8 years were enrolled in the study in the two groups of vitamin C and placebo (each with 85 patients). The incidence of postoperative atrial fibrillation was 12.9% and 29.4% in the vitamin C and control groups, respectively ($p=0.009$). The length of ICU stay was 2.5 ± 1.4 days in the vitamin C group and 3.0 ± 1.6 days in controls ($p=0.035$), and the length of hospital stay was 6.6 ± 1.5 days in the vitamin C group and 8.2 ± 2.3 days in controls ($p<0.001$).

Conclusion: Vitamin C is a relatively safe, cheap, and well-tolerated treatment with low complication. Since the incidence of post-CABG atrial fibrillation was reduced by 44% in the vitamin C group, the drug can be prescribed as a prophylaxis for prevention of post-CABG atrial fibrillation.

Keywords: atrial fibrillation, coronary artery bypass, vitamin C

Introduction

Atrial fibrillation (AF) is the most common arrhythmia following cardiac surgery. It is a potential factor for prolonged time of hospitalization and occurrence of neurological and renal complications. The incidence of postoperative AF varies from 30% and 40% for coronary bypass and valve surgery alone, respectively, to 50% for simultaneous coronary bypass and valve surgery [1]. The incidence of AF has been reported to range between 12 to 74% in patients undergoing non-cardiac surgery [2]. The time of occurrence of AF is between the second and the fourth day following surgery, with the highest incidence on the second day after surgery. Among patients who develop post-operative AF, it continues until the fourth day in 90% of patients and until the end of the sixth day in 94% of them [3]. Postoperative AF is considered an independent factor for mortality [4]. Given the aforementioned reasons, finding a method for preventing this complication might be effective in reducing the duration of hospitalization and the occurrence of other complications as well as reducing costs. Several factors affect the incidence of postoperative AF, inflammatory and oxidative factors being the most important [5]. Oxidative damage has been shown in the heart tissue of patients with AF by some studies [6], while other studies have shown the elevation of serum levels of myocardial oxidation markers in postoperative AF such as nitrite peroxide and superoxide [7]. Antioxidants including vitamin C, N-acetylcysteine, and statins can decrease the serum levels of oxidants [8, 9]. Since according to studies conducted in other countries, antioxidants were shown to play an important role in reduction of the incidence of postoperative AF, and given the limitations of the previous studies, it seemed necessary to carry out this study.

Methodology

In this parallel double-blind clinical trial, the effect of vitamin C on the incidence of AF and the length of stay at ICU and in the hospital after coronary bypass surgery was evaluated in two groups of intervention and control in Shariati Hospital in Tehran during August 2012-January 2013.

Patients with coronary artery disease (in angiography) who were candidate for coronary artery bypass were included in the study. The exclusion criteria were; 1- age over 80 years; 2-patients with AF before surgery; 3- patients with valvular heart disease, arrhythmia, or cardiac conduction block of any degree; 4- patients using a pacemaker, 5- patients with chronic lung, liver, or kidney disease; 6- patients with other heart surgeries along with coronary bypass graft; 7- history of antiarrhythmic drug consumption; 8- sick sinus syndrome; 9- patients with symptoms or history of urinary calculi; and 10- history of vitamin C consumption during the last three months.

Vitamin C is a well-known antioxidative medicine in the medical literature and can be purchased over the counter (OTC) and has no significant toxicity in the dose prescribed in this study; however, a complete description was provided for the subjects and an informed consent was obtained from them. The study was approved by the ethics committee of the Research Deputy of Tehran University of Medical Sciences. The required data were collected by a nursing master during a period of six months, through attending the bedside of patients who underwent coronary bypass surgery, and using an information form developed for this purpose. The research method was the same for all participants, so that both the intervention and control groups were operated by the same surgical team and received a similar pre- and postoperative ICU care.

The research tool was a data collection form with all the required specifications including the specific code of the patients (assigned to each patient according to the registration form), the file number, the procedure type (off pump/on pump), length of stay at the ICU and in the hospital, incidence of AF, other complications, and the time of discharge.

All relevant information was collected from the admitted patient records (history, surgical procedure, and ICU patients' sheets). The statistical population consisted of patients with coronary artery disease (in angiography) who were candidates for coronary bypass surgery at the cardiology ward of Shariati Hospital. Using the sample size formula, 170 patients were examined in this study. The sample size in this study was determined according to a similar study (Carnes). In the aforementioned study

performed on 86 patients, the incidence of postoperative AF in the control group was 34.9% which decreased to 16.3% after consumption of vitamin C; therefore, to get a similar result with a confidence level of 95% and an accuracy of 100%, and assuming a difference of at least 20% in the intervention and control groups, 116 patients were required. However, by taking the risk of loss, uncertainty, insufficient information, and potential problems at the ICU, 170 patients were studied. They were divided randomly into two groups of intervention and control, each including 85 patients, and were randomly assigned to receive placebo or vitamin C. Parenteral form of vitamin C (ascorbic acid) was used, and each ampoule contained 500 mg vitamin C per 5 mL which was infused intravenously (in 100 mL of normal saline). Since patients were told in the informed consent that they were to receive either vitamin C or placebo (normal saline), they were unaware of their treatment group.

The present study was a double-blind parallel group clinical trial, because neither the patients nor the health care workers were aware of the medications in the infusions (vitamin C or normal saline), except the researcher who was aware according to the code labeled on serum. The intervention group received a total of 7 g intravenous vitamin C as 2 g (four ampoules) 12 hours before the procedure and 500 mg (one ampoule) twice a day for five days after the procedure.

The patients in the control group received placebo (intravenous normal saline). The frequency and duration of administration of the placebo in the controls group was completely the same as the infusion of vitamin C in the intervention group. Depending on surgeon's discretion, the patients were operated in accordance with the standard method of coronary bypass along with myocardial perfusion protection by cardioplegia or the off-pump method. The patients were treated at the ICU after surgery and continuously monitored with ECG under constant surveillance of trained nurses. In case of any arrhythmia, ECG was evaluated by the researchers. ECG was performed on a daily basis after transferring the patients to the ward.

The primary objective of this study was to evaluate the incidence of AF lasting at least 10 minutes or requiring immediate therapeutic intervention due to symptomaticity or hemodynamic instability. Arrhythmias were controlled with amiodarone and all prescriptions were recorded. Data were analyzed with student's *t*-test and χ^2 using SPSS-17, while $p < 0.05$ was considered significant.

Results

A total of 170 patients, including 118 men (69.4%) and 52 women (30.6%) were examined in this study. The age range was between 38 to 78 years with a mean of 59.1 ± 9.8 years. The study groups were matched in terms of demographic and clinical characteristics, and comparisons showed no significant difference between the intervention and control groups in this regard. Therefore, these variables were similarly distributed among the two groups (Table 1).

The length of stay at the ICU had a significant difference (0.49 days) between the intervention and control groups ($p=0.035$), *i.e.* patients in the intervention group who received vitamin C stayed for a shorter duration at the ICU compared to the controls. The difference was 1.53 days for the duration of hospitalization ($p<0.001$). Therefore patients in the intervention group were hospitalized one and a half day less than the placebo group (Table 2).

The relationship between any arrhythmia (VT, PVC, AF) and vitamin C consumption was determined, and a significant relationship was observed according to χ^2 statistics ($p=0.009$). The incidence of AF in vitamin C group was 12.9%, which was significantly lower than in the control group (29.4%). In addition, vitamin C consumption reduced the incidence of PVC (12.9% in the intervention group versus 28.2% in the control group) ($p=0.014$); however, no significant relationship was observed between the decreased incidence of VT and consumption of vitamin C ($p=0.99$) (Table 3).

Table1: Comparison of demographic and clinical characteristics of the intervention and control groups

Variable	Intervention group (n=85)	Control group (n=85)	<i>p</i>
Age (years)*	59.1±10.4	59.1±9.1	0.981*
Gender (male)**	57 (67.1%)	61 (71.8%)	0.506**
Height*	165.6±9.6	165.6±9.1	0.974*
Weight*	72.5±12.2	73.1±13.9	0.779*
Smoking**	21 (24.7%)	29 (34.1%)	0.178**
History of diabetes**	35 (41.2%)	29 (34.1%)	0.342**
Blood creatinine level*	1.09±0.35	1.07±0.20	0.688*
History of hypertension**	47 (55.3%)	44 (51.8%)	0.645**
History of CVS**	2 (2.4%)	2 (2.4%)	1.000**
History of chronic lung disease**	2 (2.4%)	1 (1.2%)	1.000**
Left ventricular ejection fraction*	45.3±7.4	46.9±7.1	0.155*
On-pump surgery**	58 (68.2%)	65 (76.5%)	0.230**
* Values are expressed as mean±SD and Student's <i>t</i> -test			
** Values are expressed as number (percent) and χ^2 ;			
<i>p</i> <0.05 was considered significant			

Table 2: Comparison of the mean length of stay in ICU and hospital in the intervention and control groups

Variable	Intervention group (n=85)	Control group (n=85)	<i>p</i>
Length of stay in ICU (day)	2.5±1.4	3.0±1.6	0.035*
Length of stay in hospital (day)	6.6±1.5	8.2±2.3	<0.001*
* Student's <i>t</i> -test, values are expressed as mean±SD;			
<i>p</i> <0.05 was considered significant			

Table 3: Comparison of the frequency of arrhythmia in heart beat in the intervention and control groups

Variable	Intervention group (n=85)	Control group (n=85)	<i>p</i>
Atrial fibrillation (AF)	11 (12.9%)	25 (29.4%)	0.009*
Premature ventricular contraction (PVC)	11 (12.9%)	24 (28.2%)	0.014**
Ventricular tachycardia (VT)	1 (1.2%)	2 (2.4%)	0.99*
* χ^2 statistical test; values are expressed as number (percent)			

Discussion

The results obtained from this study demonstrated the significant impact of vitamin C in reducing the incidence of AF following coronary bypass surgery. Few studies have been carried out in this regard; however our results are consistent with those obtained by previous studies [9-11].

In a study by Carnes on 11 dogs with pacemaker-induced electrical reconstruction, rapid atrial pacing was shown to lead to increased peroxynitrite, which per se is associated with AF in humans. In addition, atrial ascorbate level decreased following rapid atrial pacing. As an antioxidant, ascorbate is capable of preventing the effects of oxidative stress produced from high activity of atrium (through pacing or increased sympathetic tone, and cardiac surgery-induced ischemia/reperfusion injury). Moreover, the effective refractory period (ERP) was reduced 24 to 48 hours after pacing. They also divided 86 patients who underwent CABG and had sinus rhythm before surgery into two groups of intervention and control. The intervention group received 2 g vitamin C in a single-dose 12 hours before CABG and then 500 mg twice a day for five days. The incidence rate of post-CABG AF was 16.3% and 34.9% in the intervention and control groups, respectively [9]. Korantzopoulos investigated the effect of oral vitamin C on the incidence of AF in 44 patients who developed continuous AF following electrical cardioversion. Patients who received antioxidant agents, except for statins, were excluded. The duration of continuous AF was measured with ECG. The patients were divided into two groups of control and vitamin C (each with 22 patients). The second group received 2 g vitamin C in a single-dose 12 hours before coordinated electric shock followed by 500 mg vitamin C twice a day for seven days. WBC, CRP, and fibrinogen were evaluated at the first, third, and seventh days after treatment. Vitamin C was found to be effective in reducing the recurrence of AF. One week after electrical cardioversion, the prevalence of AF was 4.5% and 36.3% in the intervention and control groups, respectively ($p=0.024\%$). Compared with baseline, consecutive measurements of inflammatory indices did not change considerably in the control group, while they decreased significantly in the intervention group [10]. In a recent study on the effect of vitamin C in reducing the incidence of AF after on-pump myocardial vascular surgery, Papoulidis divided the patients into two groups of control and vitamin C supplementation (each consisting of 85 patients). The incidence of postoperative AF was 44.7% and 61.2% in the intervention and control groups, respectively ($p=0.041\%$) [11].

According to the findings of this study, administration of ascorbic acid before and after bypass surgery is helpful in reducing the incidence of AF and decreases the length of stay at the ICU and in the hospital. These results emphasize the importance of vitamin C administration during CABG surgery. Ascorbic acid is a safe, cheap, and well-tolerated treatment with a low rate of complications. Therefore, interventional programs and protocols for administering ascorbic acid before and after CABG can help preventing AF after coronary bypass surgery.

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