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Original article

Perioperative ascorbic acid supplementation does not reduce the incidence of postoperative atrial fibrillation in on-pump coronary artery bypass graft patients

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ABSTRACT

Background: Atrial fibrillation is the most common arrhythmia following cardiac surgery. It is associated with increased hemodynamic instability, systemic embolization, and complications linked to anticoagulant therapy. Oxidative stress and consequent electrophysiological remodeling have been proposed as a cause of postoperative atrial fibrillation. Ascorbic acid supplementation was suggested as a novel and effective preventive agent. The aim of this study was to evaluate the capability of ascorbic acid to reduce the incidence of postoperative atrial fibrillation in coronary artery bypass grafting (CABG) patients.

Methods: A prospective randomized single-center trial was conducted in patients scheduled for an elective on-pump CABG surgery. Subjects in the ascorbic acid group received 2 g of ascorbic acid 24 h and 2 h before the surgery and 1 g twice a day for five days after the surgery. Postoperatively, the patients were monitored for atrial fibrillation and other complications.

Results: The ascorbic acid group consisted of 52 patients and the control group included 53 patients. The groups were well matched for baseline demographics, preoperative medications, comorbidities, and had similar intraoperative characteristics. The incidence of atrial fibrillation in the ascorbic acid group was 13.5% and 18.9% in the control group ($p = 0.314$). No difference was found between groups in the time of occurrence of atrial fibrillation (3.71 ± 1.89 vs. 2.91 ± 1.58 days after the surgery; $p = 0.342$). There was also no difference in the other observed postoperative complications.

Conclusions: The results of this study do not support the effectiveness of ascorbic acid supplementation in reducing the incidence of postoperative atrial fibrillation in elective on-pump CABG patients.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia following cardiac surgery. The reported postoperative incidence after coronary artery bypass grafting (CABG) varies between 20% and 40%, depending on the severity of heart disease, patient age, history of previous AF, chronic obstructive pulmonary disease, cardiopulmonary bypass time, and aortic cross clamp time [1–4]. It usually occurs between the 2nd and 5th postoperative day and is generally self-limited, with most of the patients converting into the sinus rhythm within 1–3 days after the introduction of an anti-arrhythmic therapy [1,2,5]. However, its occurrence significantly influences the clinical outcome as it is associated with increased hemodynamic instability, systemic embolization, and complications associated with anticoagulant therapy, resulting in higher mortality, morbidity, prolonged in-hospital stay and higher costs [5–7]. Aging of the general population along with the increased recruitment of elderly patients in everyday cardiac surgery practice further increases the incidence of postoperative AF, causing a growing burden on healthcare resources [8,9]. The general prophylactic use of traditional anti-arrhythmic medications has limitations in the perioperative period due to lack of efficacy and possible significant side effects [9,10]. Many efforts have been made to better understand the pathophysiology of this rhythm disturbance with the goal to develop an alternative prophylactic and therapeutic options [10–13]. Previous

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experimental and clinical work has proposed a potential link between postoperative AF and oxidative stress generated during the unavoidable ischemia/reperfusion cycle [13–16]. The production of reactive oxygen species (ROS) may be involved in the electrical remodeling of the myocardium, leading to the establishment of a fertile milieu for genesis and perpetuation of postoperative AF. New pharmacologic strategies have been developed in order to counteract or interfere with initiation of AF at the molecular level. With the identification of ROS as a potential pathophysiologic substrate, antioxidative vitamin ascorbic acid has been proposed as a promising supplement which may reduce the oxidative stress and subsequently the incidence of postoperative arrhythmias [17–21]. However, the results of these studies have so far been contradictory. Furthermore, even with a recent meta-analysis of 5 randomized control trials (RCTs) with a total of 565 patients [22], the data remain largely inconclusive.

The aim of this study was to evaluate the efficacy of perioperative ascorbic acid supplementation on the incidence of the postoperative AF in patents who underwent elective on-pump CABG surgery.

Materials and methods

This randomized prospective trial was conducted in patients scheduled for an elective CABG surgery between March 2013 and June 2014 at the Department of Cardiac Surgery at the University Clinical Center Maribor, Slovenia. The study protocol was approved by the institutional medical ethics committee as well as the National Medical Ethics Committee of the Republic of Slovenia and is in full accordance with the World Medical Association Declaration of Helsinki.

Exclusion criteria included emergency operations, any concomitant valve or other surgery, preoperative history of AF, permanent pacemaker, hyperoxaluria or history of nephrolithiasis, and off-pump surgery. Once a patient was considered eligible for enrolment, he or she was informed about the study protocol and asked to sign a written informed consent. The enrolled patients were then randomly assigned to either the ascorbic acid or control group. Patients in the ascorbic acid group received 2 g of ascorbic acid 24 h and 2 h prior to surgery and 1 g twice a day for five days after the surgery. Ascorbic acid was administered intravenously preoperatively as well as postoperatively. Both groups received the same preoperative medical premedication and underwent the same anesthesia protocol.

Basic demographic, laboratory, and medical data were collected before surgery. A surgical risk profile using the EuroSCORE II system was calculated for every patient.

A team of five cardiac surgeons participated in the study. All patients underwent standard CABG with full sternotomy and cardiopulmonary bypass (CPB) with mild hypothermia (34 °C) and antegrade and retrograde cold blood cardioplegia for cardiac protection. Intraoperatively, surgical data, such as number of grafts, CPB time, and aortic cross-clamp time were recorded. Postoperative troponin I levels were recorded on admission to the intensive care unit (ICU) and 18 h postoperatively. C-reactive protein (CRP) levels were also recorded preoperatively and on a daily basis postoperatively until the 7th postoperative day. Both groups underwent the same routine postoperative ICU and ward care including a continuous heart rhythm monitoring for 7 postoperative days.

The primary endpoints in the present study were an episode of AF or flutter lasting >10 min or the requirement for an urgent intervention due to AF of flutter (e.g. electroconversion) due to profound symptoms or hemodynamic instability.

The sample size estimation was based on the assumption that the incidence of AF after CABG lies at about 25% and that the administration of ascorbic acid would result in a 20% decrease of AF. With a power of 80%, β error of 0.2 and α of 0.05, about 50 patients were required in each group.

Continuous variables were compared using the Student's *t*-test for parametric and Mann–Whitney *U* test for nonparametric data. Categorical variables were analyzed using χ^2 test or Fisher exact test, as appropriate. Additionally, a Kaplan–Meier analysis was conducted in order to allow the estimation of the effect of ascorbic acid administration on postoperative AF over the 7-day postoperative follow-up period.

Subanalyses were conducted for patients older than 65 years and those with CPB time longer than 100 min.

All statistical analyses were performed using the SPSS 22.0 software (IBM Corporation, Armonk, NY, USA).

Results

A total of 105 patients were included in the trial. The ascorbic acid group consisted of 52 patients and the control group included 53 patients. The results are reported as the mean ± standard deviation for continuous data and as frequencies (percentages) for categorical data.

The groups were well matched for baseline demographics, preoperative medications, and comorbidities (Table 1). Likewise, both groups had similar intraoperative characteristics with no significant differences in the number of bypass grafts, CBP time, and aortic cross-clamp time (Table 2).

The data regarding the postoperative course are summarized in Table 3. There was no significant difference in the incidence of postoperative AF between the ascorbic acid group and the control group (13.5% vs. 18.9%; $p = 0.314$). Also, no significant difference was found between groups when comparing the time of occurrence of AF (3.71 ± 1.89 vs. 2.91 ± 1.58 days after surgery; $p = 0.342$). Similarly, no differences between the groups were encountered in the mean duration of AF (11.2 ± 9.7 h vs. 10.4 ± 13.1 h; $p = 0.649$).

The Kaplan–Meier analysis is presented in Fig. 1 and Table 4. Although the control and ascorbic acid curves seem to have a visible separation (Fig. 1), no significant statistical differences between the two curves have been detected in any part of the 7-day follow-up period ($p > 0.05$ in log-rank, Breslow, and Tarone-Ware tests; Table 4).

All patients who developed AF successfully converted to sinus rhythm spontaneously or after pharmacologic intervention. No electroconversions were needed and all patients were discharged from hospital in normal sinus rhythm.

There were no significant statistical differences between the groups regarding the preoperative and postoperative CRP levels (Fig. 2).

No neurologic adverse events (transient ischemic attacks or strokes) were observed in the study. There were also no sternal wound infections or requirements for an intra-aortic balloon insertion.

The groups did not significantly differ in the levels of troponin I 18 h after surgery (3.26 ± 3.26 μg/l vs. 4.81 ± 10.05 μg/l; $p = 0.852$).

As presented in Table 3, when analyzing the ICU length of stay and hospitalization time, no differences were found between groups as well.

Overall, there were two in-hospital deaths in the study. One patient died of a severe respiratory tract infection and the other because of septic/toxic shock due to severe colitis and megacolon caused by a *Clostridium difficile* infection.

Two additional subanalyses were performed to investigate the effect of perioperative supplementation of ascorbic acid on the incidence of postoperative AF in patients older than 65 years and in patients with CBP time longer than 100 min. No beneficial effect of

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