

The Perioperative Effect of Ascorbic Acid on Inflammatory Response in Coronary Artery Bypass Graft Surgery; A Randomized Controlled Trial Coronary Artery Bypass Graft Surgery

Reza Jouybar¹, Hiva Kabgani¹, Hamid Kamalipour^{2*}, Shahrbanoo Shahbazi¹, Elaheh Allahyary¹, Manoocher Rasouli³, Seyd Hedayatallah Akhlagh¹, Masih Shafa¹, Mohammad Ghazinoor¹, Mohammad Taghi Moeinvaziri¹, Saeed Khademi¹

¹Shiraz Anesthesiology and Critical Care Research Center, Shiraz University of Medical Sciences, Shiraz, IR, Iran.

²Laparoscopy Research Center, Shiraz University of Medical Sciences, Shiraz, IR, Iran.

³Immunology and Clinical Microbiology Research center, Shiraz University of Medical Sciences, Shiraz, IR, Iran.

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ABSTRACT

Background: Different pharmacological agents may decrease the inflammatory response during cardiac surgery. The aim of this study was to evaluate the effect of ascorbic acid as an antioxidant on inflammatory markers (interleukins 6 and interleukin 8) released during cardiopulmonary bypass.

Method: Forty patients scheduled for elective coronary artery bypass grafting surgery, were randomly assigned to two groups. The patients in the case group were given 3 grams ascorbic acid 12-18 hours before operation and 3 grams during CPB initiation. The patients in the control group were given the same amounts of normal saline at similar times. Blood samples were collected 6 hours preoperatively and postoperative serum interleukin 6 and 8 were measured using enzyme-linked immunosorbent assay (ELISA).

Result: In both groups CPB caused an increase in IL6 and IL8 plasma concentrations compared with baseline levels, but the pattern of changes at such levels were similar in both groups after receiving ascorbic acid or placebo. Ascorbic acid did not reduce the inflammatory cytokines during CPB. Compared to the placebo, ascorbic acid had no significant effect on hemodynamic parameters such as systolic and diastolic blood pressure, heart rate, arterial blood gases, BUN, Creatinine and WBC and platelet counts.

Conclusion: Ascorbic acid has no effect on the reduction of IL6 and IL8 during CPB. Also, it causes no improvement in hemodynamics, blood gas variables, and the outcomes of patients undergoing CABG.

Implication for health policy/practice/research/medical education:

This Study is intended to reduce inflammatory response due to cardiopulmonary bypass circuit in patients undergoing open cardiac surgery.

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1. Introduction

Cardiothoracic surgery, which is performed on cardiopulmonary bypass circuit, may cause various degrees of undesirable inflammatory reactions, ranging from less severe systemic inflammatory response to more drastic multi-organ dysfunction. These reactions may lead to major complications and increased ICU and hospital stay (1,2).

Contributory factors that cause inflammatory responses include hemodilution, ischemic-reperfusion, surgical trauma, temperature fluctuations, blood products transfusion, and exposure of blood to non-endothelial surfaces. All of these factors may elevate the inflammatory markers(3). Pharmacological strategies for control of inflammation such as using corticosteroids, is controversial in cardiac surgery (4). Reactive oxygen species (ROS), called free radicals, are released by neutrophils(4, 5), cause significant elevation of inflammatory mediators. Patients with postoperative complications have been reported to

* Corresponding author: Hamid Kamalipour, Laparoscopy Research Center, Faghihi Hospital, Zand Ave., Shiraz, IR, Iran. Cell: +989171111112, Fax: 98-711-6284828, Email: kamalih@yahoo.com

have higher levels of inflammatory cytokines (6,7).

Recent reports have supported antioxidant therapy to reduce the endothelial dysfunction and the number of post-myocardial infarctions, as well as improved neurological outcomes (8-10). Pretreatment with C and E vitamins, allopurinol, mannitol, and deferoxamine significantly supported this hypothesis (10). ROS as oxidants can be reduced by antioxidants such as C and E vitamins.

Ascorbic acid is a water soluble and safe antioxidant agent, which depletes the endogenous ROS. Animal studies have shown the efficacy of exogenous antioxidants for attenuating the ROS-mediated damages (4).

This prospective randomized study was performed to evaluate the effect of ascorbic acid on decreasing the inflammatory cytokines; IL₆ and IL₈.

2. Materials and Methods

The present study comprised 44 patients with ASA class I and II who were candidates for elective coronary artery bypass graft surgery, in Nemazee hospital affiliated to Shiraz University of Medical Sciences from 2010 to 2011. The Ethics Committee of the university approved the protocol of the study and written informed consents were obtained from the patients.

The exclusion criteria were pregnancy, systemic/local infection, concomitant malignant disease, positive history of hypersensitivity reaction, hematologic disease or abnormal leukocyte count, diabetes mellitus, major trauma or major surgery less than 6 months before surgery, usage of immunosuppressive drugs such as steroids, ejection fraction less than 35%, renal failure, untreated or uncontrolled arterial hypertension, and recent myocardial infarction in less than 6 months.

Data collected included the demographic variables, blood pressure, heart rate, temperature, serum levels of potassium, BUN, Creatinine, and white blood cell, neutrophil, and platelet count as well as hemoglobin concentration. The patients' baseline serum levels of IL6 and IL8 were also evaluated one day before operation.

The patients were randomly assigned to two groups according to the printed table of random numbers, to either receive 2 doses of 3 gram intravenous ascorbic acid (Vial 500 mg/5ml) (Daroopakhsh Inc., Tehran, IR, Iran) or the same amount of normal saline as placebo. A blinded anesthesiologist who was involved neither in the patients' allocation and management nor in the design of the study and data processing and analysis, generated the randomization list using a computer program. Both ascorbic acid and the placebo were prepared in similar 5 ml syringes to be indistinguishable.

The patients in the study group received the first dose of ascorbic acid 12-18 hours before operation and the second dose just after the induction of anesthesia and before surgery. The patients in the control group received the equal amount of the placebo at the same time as the study group. Ascorbic acid and the placebo were injected intravenously as a single bolus injection by an independent researcher.

All the patients were anesthetized with 0.1 mg/kg midazolam, 8-10 µg/kg fentanyl, 0.1 mg/kg morphine, 2.5

mg/kg sodium thiopental, and 0.12 mg/kg pancuronium as a neuromuscular blocker. Anesthesia was also maintained by isoflurane. Intravenous nitroglycerine, ephedrine or epinephrine was used to control the blood pressure. Moreover, the physician responsible for managing the patients did not participate in the study.

The patients received heparin 300 Unit/kg as an anticoagulant to ensure an activated coagulation time greater than 480 seconds before cardiopulmonary bypass (CPB). All the patients in the two groups underwent CPB with a heparin-coated membrane oxygenator after a midline sternotomy. A cold cardioplegic solution was injected into the coronary arteries to induce cardiac arrest during pump time.

During CPB, a non-pulsatile blood flow of 2.4 to 2.8 L/min/m² was obtained by administration of vasodilators (tri-nitroglycerin and sodium nitroprusside) or vasopressors (phenylephrine, norepinephrine) which maintained a mean blood pressure of 50 to 70 mmHg. Through the CPB period, hematocrit was kept between 21% and 27% and during the surgery, body temperature was kept between 32-34°C. Infusion of regular insulin or 5% dextrose water was considered to achieve the blood glucose concentration in the range of 80 to 120 mg/dL, which was measured hourly by a glucometer. After weaning from the CPB pump, heparin was reversed by protamine sulfate, and after operation the patients were transferred to the cardiac surgery ICU. Having considered the patients' cardiovascular and respiratory status, the weaning from ventilatory support and extubation of trachea was then performed by using common clinical criteria about 6-8 hours after operation.

The blood samples were obtained through the arterial catheters, except the first sample which was obtained from venous puncture. The samples were collected 6 times preoperatively: 12-18 hours before operation just before the administration of the first dose of ascorbic acid or placebo, at the end of CPB, 2 hours after transferring the patients to the ICU, the first day after operation, the second day after cardiac surgery, and the third day after operation.

All the samples were immediately placed in a cold box to stop cytokine release by leukocytes, and within a few

Table 1. Patients' preoperative characteristics, systolic blood pressure (SBP), diastolic blood pressure (DBP), potassium (K), blood urea nitrogen (BUN), and white blood cell (WBC).

Variables	Study group	Control group
Male/female	14/6	12/8
Age (year)	56.9±10.3	61.83±10.45
Weight (Kg)	72.14±10.59	70.54±15.97
Ejection Fraction	51.59±6.21	54.10±7.52
SBP	129.82±21.57	126.67±20.32
DBP	76.27±14.19	72.33±12.31
Serum K	3.14±0.40	3.07±0.42
BUN	16.14±5.50	17.89±6.05
Creatinine	1.08±0.21	1.056±0.28
No of grafts	2.5 ±0.75	3.05 ±0.1
CPB duration	78.09±15.6	69.75±12.80
Hemoglobin	12.08±1.02	11.69±1.35
WBC	7506± 1492	8105±1304
Neutrophil	73.06± 6.98	70.05±4.67

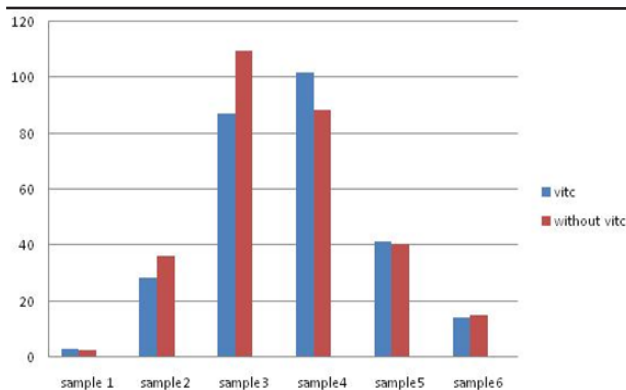


Figure 1. Changes of IL6 concentration at six points: 12-18 hours before operation, at the end of CPB, 2 hours after arrival to ICU, the 1st day after operation, 2nd day after operation, and 3rd day after operation.

minutes, plasma was separated from cells by centrifugation for 5 minutes (2000g). The serum were kept frozen below -40°C until assayed. Serum interleukin 6 and 8 levels were quantified using platinum ELISA BMS213/2TEN (Bender med system, eBioscience). The statistical analysis was done using SPSS for Windows software, version 15.0.

Table 2. Comparison of the intraoperative parameters including packed cell requirements, systolic blood pressure, diastolic blood pressure, blood gas analyses, and cardiopulmonary bypass time between the study and control groups.

	Study group	Control group
Packed cell requirement	72.7%	88.9%
Vasopressor requirement	72.7%	83.3%
Mean PH	7.37±0.06	7.36±0.06
SBP (mmHg)	109.06±18.97	107.48±15.06
DBP (mmHg)	63.86±13.21	61.61±9.17
TM	36.67±0.41	36.44±0.51
PaO ₂	249.45±69.94	250.50±93.32
PaCO ₂	35.68±5.76	34.61±7.31
Base excess	2.48±4.02	1.48±3.64
No of grafts	2.5 ±0.75	3.05 ±0.1
Cardiopulmonary bypass time	78.09±15.6	69.75±12.80

Independent *t* test was used to compare and assess the non-parametric data between the two groups and repeated measurement test was performed for comparison of the parametric data.

3. Results

Of the 44 patients with inclusion criteria, 4 patients were excluded after ascorbic acid administration and the collection of blood samples. Two patients were excluded because CABG was done using the off-pump method, one patient needed post-operative intra-aortic balloon pump (IABP), and the other patient died during operation. Finally 40 patients participated in the study and were equally assigned to two groups.

The two groups did not differ significantly in age, male to female ratio, preoperative systolic and diastolic blood pressure, heart rate, and temperature. As shown in Table 1, the patients had comparable serum potassium, BUN, Creatinine, white blood cell, neutrophil, and platelet count as well as hemoglobin concentration, obtained one day

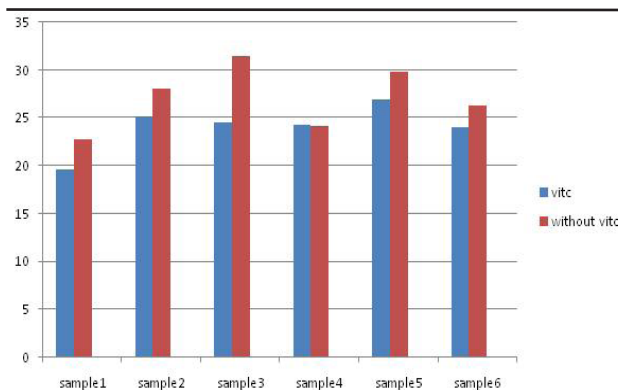


Figure 2. Changes of IL8 concentration at six points: 12-18 hours before operation, at the end of CPB, 2 hours after transfer to ICU, days 1, 2 and 3 after operation.

before operation.

The measurement of baseline levels of IL6 and IL8 did not show significant differences in both groups. Evaluating the ejection fraction, pump time, and number of grafts showed no difference between the two groups. In both groups, serum IL6 and IL8 increased after starting the cardiopulmonary bypass pump compared with the preoperative baseline values ($\alpha=0.01$ and $P=0.014$). The pattern of increase and change in the serum levels of both IL6 and IL8 over time was not significantly different between the groups (Figure 1 and 2). Hemodynamic parameters including SBP (systolic blood pressure), DBP (diastolic blood pressure), and HR (heart rate) were assessed preoperatively using invasive blood pressure monitoring but no significant differences were found between the two groups over time ($P=0.37$).

Analysis of arterial blood gas (ABG) parameters intra-operatively and during the three days after operation did not show significant differences between the groups ($P=0.21$, Table 2). We also compared white blood cell ($P=0.354$), neutrophil, and platelet counts during the three days after operation and did not find any significant differences between the groups. Similar results were found regarding serum potassium, BUN, and creatinine levels. As expected after starting CPB, WBC count increased in both groups ($P=0.006$). Pack cell and vasopressors requirements as well as blood sugar levels were comparable during CPB and operation in both groups (table 2). Regarding the serum levels of IL6 and IL8, no differences were found between the groups when measured at six different times. Reanalysis correctusing repeated measure test showed similar findings (Table 3).

4. Discussion

CPB in all patients evokes an immediate systemic inflammatory response by releasing circulatory cytokines especially in the first hour after CPB (2). Many studies have shown that the inflammatory response in patients undergoing cardiac surgery can be reduced by modification of surgical and perfusion techniques, modification of circuit components, or by using pharmacologic strategies (11). Pro-inflammatory cytokines play a pivotal role in stimulating inflammation especially elevation of plasma levels of IL6, IL8, TNF α , and IL-1 β (12) Extensive

Table 3. IL6 and IL8 concentrations measured at six different times perioperatively in both case and control groups

	Groups	TIME 1	TIME 2	TIME 3	TIME 4	TIME 5	TIME 6
IL6	Case	2.85±1.51	28.70±28.90	87.36±46.34	101.98±83.4	41.36±37.1	14.32±17.36
	Control	2.62±0.51	36.38±47.62	109.56±88.85	88.50±91.31	40.46±35.8	15±12.69
	P Value	0.542	0.533	0.316	0.629	0.939	0.891
IL8	Case	19.65±2.46	25.12±5.32	24.61±6.11	24.31±5.13	26.88±13.98	24.01±9.25
	Control	22.77±8.56	28.05±7.72	31.52±26.76	24.12±6.34	29.89±17.55	26.30±7.51
	P Value	0.111	0.165	0.246	0.918	0.549	0.409

Time 1: before the administration of the first dose of ascorbic acid or placebo, Time 2: at the end of CPB, Time 3: 2 hours after arrival to the ICU, Time 4: the first day after operation, Time 5: the second day after cardiac surgery, and Time 6: the third day after operation.

experimental and clinical studies have been performed to control the inflammatory response during on-pump cardiac surgery. Oxidative stress and genetic predisposing factors are among the possible contributors and may have important roles in these inflammatory cascades which are induced by the CPB circuit (13).

Cytokines have been shown to be responsible for ischemic reperfusion injury. IL6 is pathogenic in vascular wall, endothelial function and tissue metabolism (9). Several pharmacological strategies such as using aprotinin (11) corticosteroids, milrinone, and doxepamine (13), have been shown to attenuate the inflammatory response caused by CPB. Heparin sulfate may also bind to IL8 and inhibit IL8-induced chemotactic response. Also sodium nitroprusside as a vasodilator has recently been reported to be associated with reduction of systemic levels of IL6 and IL8 (13). Allopurinol is an inhibitor of the enzyme xanthine oxidase, a pivotal generator of free radicals, may decrease cytotoxic free radicals.

We aimed to evaluate the effect of ascorbic acid on inflammatory interleukins (IL6 and IL8) in patients scheduled for on-pump CABG. Nader and colleagues found that sevofluran alleviated the ischemic reperfusion injury after CPB by decreasing the levels of IL6, CD11b/CD18, and TNF α , but they found no clinical effect on cytokine balance (14). Mangosh and co-workers evaluated the effect of ascorbic acid as a free radical scavenger on endothelial dependent vasodilation of human arterial conduit for CABG, comparing radial artery and internal thoracic artery. They found that there were no differences in the vasodilation function between the control and the study group for both arteries after an incubation period of 1 hour. But after 72 hours incubation ascorbic acid preserved the endothelial dependent vasodilation function in radial artery. They also found that ascorbic acid had no effect on decreasing the amount of free radicals generated in both arteries (10). In the present study we did not find any clinical effects or modifications on interleukins by ascorbic acid. This finding may result from time or other intermediary inflammatory modulators. Schulze and colleagues showed significant reduction in inflammatory markers and vasopressor requirement with off pump CAB (OPCAB) revascularization procedure without the use of CPB and cardiac arrest compared with conventional CABG (15). They also reported the reduction of systemic pro-inflammatory cytokines; CRP, IL6, IL2-r, TNF α , and TNF specific receptor (RP1, RP2) after OPCAB

versus conventional CABG. In this connection, no single pharmacological or technical intervention will be adequate to entirely inhibit the associated adverse clinical outcomes and inflammatory response. Our disparate results may be due to different surgeons or other surgical reasons.

John Gu Y and co-workers showed the effect of minimally invasive coronary artery bypass (MIDCAB) grafting in reduction of the inflammatory response as well as decrease in postoperative morbidity, mortality, and hospital stay compared with conventional CABG. They measured WBC and platelet count, plasma elastase, and α 1 protease inhibitor using the ELISA test (16). The number of grafts and CPB duration were comparable in our study which failed to evaluate the severity of injuries associated with surgeon's expertise.

Song wan and colleagues showed a similar reduction in cytokines response and myocardial injury with OPCAB and beating heart CABG versus conventional CABG (17) Struber and others also found reductions of IL6, IL8, soluble TNF receptors 1 and 2, complement factor C3a and C1 esterase inhibitor which were advantageous for patients with high grade morbidity undergoing MIDCAB (18) Bodil and colleagues evaluated the effect of temperature on the release of IL6, IL8, IL10, CRP, cortisol, and neutrophil during CPB. They found that the release of these markers were independent of temperature (19). Considering their findings, we kept the temperature identical in both groups in our study. Despite the introduction of minimally invasive cardiac surgeries, OPCAB, and endovascular approaches, the use of CPB is still necessary for many cardiac surgical procedures. Sucu Nehir and colleagues reported the effect of N-acetylcysteine on decreasing the pump induced oxido-inflammatory response during cardiopulmonary bypass (20). Doddakula and co-workers evaluated the effect of anti endotoxin agent, Taurolidine, in CABG patients, and suggested that it could potentially reduce the ischemic reperfusion injury through its metabolite Taurine, especially inducing significant decrease in arrhythmias (21). Barta et al, examined the protective effect of alpha tocopherol and L-ascorbic acid against the ischemic reperfusion injury in patients undergoing open heart surgery. They showed that the most important difference between treated and control groups were in plasma concentration of malondialdehyde; a marker of lipid peroxidation, which was significantly lower in pretreated patients (22). Their findings were different from our results which might be due to the use of alpha tocopherol in their study.

Pronounced inflammatory response to CABG is implicated in the pathogenesis. More specifically, prolonged increases in circulating IL6 are also associated with rising morbidity and mortality after CPB. ACE inhibitors are suggested to be anti-inflammatory and can decrease IL6 leading to improved patients' outcomes (23). High dose vitamin C and vitamin E have been suggested to be effective free radical scavengers, which decrease cell membrane lipid peroxidation and improve hemodynamics leading to shorter ICU and hospital stay. Ascorbic acid is antioxidant with protective effect against oxidative stress and some bacteria and viruses. Mega dose of ascorbic acid, up to 15 grams intravenous is safe. High dose of ascorbic acid was shown to scavenge the free radicals and decrease myocardial injury and cell membrane peroxidation during CPB (13). In our study we did not find any correlation between ascorbic acid and alleviating inflammatory cytokines or any improvement in clinical and laboratory findings. After four months follow-up, clinical outcomes were comparable in both groups. We also found that IL6 and IL8 increased significantly after starting CPB, which suggest that these cytokines are at least involved in ischemic reperfusion injury. During the three days postoperative follow up, IL8 levels, in contrast to IL6, reached its baseline level in both groups..

We did not find any reduction in two inflammatory cytokines IL6 and IL8 in patients receiving intravenous ascorbic acid before and during CPB. Ascorbic acid did not cause any decrease in white blood cell, and neutrophil counts and was not of any benefit to the patients' outcomes. In addition ascorbic acid did not improve kidney function and acid base profiles.

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The authors declare that they have no conflicts of interest.

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