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Combined effects of the implementation of magnesium and ascorbic acid on myocardial ischemia-reperfusion in open heart surgery

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ABSTRACT

Aim: This study aimed to investigate the combined effects of magnesium (Mg) and high dose ascorbic acid on cardiac ischemia-reperfusion (IR) injury.

Material and Method: This study was performed on 45 patients that were scheduled for coronary artery bypass graft (CABG) operations. The patients were divided into three equal groups. Group C received 50 mg/kg ascorbic acid; Group CM received the same dose of ascorbic acid plus 30 mg/kg Mg; Group K received neither ascorbic acid nor Mg. At various times during the operation, the blood levels of malondialdehyde (MDA), serum creatine kinase MB (CK-MB), and lactate dehydrogenase (LDH) levels were analyzed.

Results: There were statistically significant decreases in arrhythmia requiring intervention in Group CM compared to Group K (P=0.026). MDA levels increased in all groups but MDA 2 and MDA 3 levels were found to be statistically significantly lower in Group C and Group CM than in Group K (P=0.009, P=0.012, P=0.009 and P=0.006 respectively). However, inhibition of lipid peroxidation in both Group C and Group CM was not parallel to cardiac enzymes and hemodynamic measurements. There was no significant statistical difference in the cardiac enzyme levels between Group K, Group C, and Group CM (p>0.05).

Conclusion: To reduce the IR, Mg with a high dose of ascorbic acid may be efficacious in patients undergoing cardiac surgery. A larger population group is needed to prove the results of this study.

Keywords: Open heart surgery, ascorbic acid, magnesium, ischemia-reperfusion

INTRODUCTION

Coronary artery bypass graft (CABG) surgery is one of the preferred treatments for ischemic heart disease. Despite advances in anesthesia techniques, myocardial preservation methods, and surgical techniques, myocardial IR injury is still one of the most significant causes of mortality and morbidity in cardiac surgery (1). Cardiopulmonary bypass (CPB) and cardioplegic arrest have some disadvantages, such as, systemic inflammatory response, myocardial damage, neurological damage, and renal and pulmonary insufficiency. Despite these disadvantages, the most important advantage of CPB is the ability to reach the target vessels in the immobile, hollow heart and to perform complete revascularization by working in a bloodless environment (2).

Normalization of myocardial blood flow after CPB, which is ischemic due to coronary artery disease, may result in IR injury. The degree of IR damage depends on the duration of the ischemic period and the degree of oxidative stress that occurs during reperfusion. The physiopathological mechanisms underlying IR injury are completely unknown (3). However, it has been suggested that excessive production of free oxygen radicals (FOR) and intracellular calcium (Ca) overload or redistribution may be the cause (4). IR damage presents clinically as microvascular dysfunction including myocardial stunning, reperfusion arrhythmia, myocyte death, endothelial dysfunction, and inadequate flow (5).

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Different pharmacological treatments have been tried to reduce myocardial IR damage and these can be classified into several categories. However, it is true that the choice of treatment, the method of administration, and the timing, i.e., before ischemia, before reperfusion, immediately after, or hours after reperfusion, is a critical issue (6).

Antioxidants are substances that delay or prevent the oxidation of substrates. Since FOR are constantly formed in normal metabolism, all aerobic cells develop protective mechanisms against their harmful effects. Antioxidants either play a preventive role by removing the FOR precursors from the environment and deactivating the catalysts, or they act by breaking the oxidation reaction chain that has started (7). Ascorbic acid (vitamin C) with its hydrophilic structure is an important antioxidant in both plasma and cytosol (8).

Calcium is an essential cation for normal cell metabolic functions. Calcium and FOR mechanisms are not separate, but two aspects of the same mechanism. While FOR cause membrane dysfunction and Ca redistribution, Ca accumulation may increase the damage initiated by FOR and even facilitate FOR production (9). It has been shown that Ca channel blockers are beneficial with various mechanisms of action in myocardial IR injury. Magnesium (Mg) is a physiological Ca antagonist and cell membrane stabilizer. Together with Ca and phospholipids, Mg plays an important role in the regulation of cell permeability. It replaces Ca competitively in its binding sites and simultaneously inhibits Ca's entry into the cell, while speeding up its exit from the cell (10).

In this study, we aimed to compare the effectiveness of the use of a high dose of ascorbic acid in reducing myocardial IR damage with the effectiveness obtained by adding Mg to ascorbic acid.

MATERIAL AND METHOD

This prospective study was carried out on 45 patients with coronary artery disease who were scheduled to undergo CABG operations at the Department of Cardiovascular Surgery, Faculty of Medicine Osmangazi University. This study was conducted in accordance with the 1964 Declaration of Helsinki and subsequent changes or comparable ethical standards. All the patients participating in the study signed the informed consent form, and the study was carried out with the permission of Scientific Researches Ethics Committee of Osmangazi University Faculty of Medicine (Date: 30.06.2009, Decision No: 60).

Patients whose physical characteristics conformed to class I, II, or III according to the New York Heart Association (NYHA) classification and who were between the ages of 44 and 75 (mean: 63.86±8.59) with an ejection fraction (EF) of 40% or above, were included in the study. Patients who had myocardial infarction in the last six weeks, required emergency surgery and had previous cardiac surgery were excluded from the study. Patients who were known to be using Ca channel blockers or medication known to have antioxidant properties prior to the operation, were not included in the study. These antioxidant drugs are trimetazidine, statins, angiotensin-converting enzyme (ACE) inhibitors, N-acetyl cysteine (NAC), xanthine oxidase inhibitors, vitamins (α-tocopherol (Vit E), β-carotene (Pro-vit A), pyridoxal-5-phosphate), folic acid, nitric oxide donors (L-arginine), endothelin-1 receptor antagonists (bosentan), glucose-insulin-potassium (GIK) solutions, platelet inhibitors and adenosine. The patients were divided into three equal groups of 15 patients. The patients were randomly placed in groups and were not selected in terms of distribution of coronary artery lesions, ventricular function, age, gender, body surface area (BSA), NYHA class, or EF. While one of the groups was followed as the control group (Group K), Group C received 50 mg/kg intravenous (IV) ascorbic acid (Vitabiol C 500 mg ampoule, IE Ulagay, İstanbul, Turkey) after induction. Group CM was given 50 mg/kg IV ascorbic acid and 30 mg/kg IV Mg (Magnesium Sulphate Biofarma 15% Ampoule, Biofarma, Mamak, Ankara) after induction. Preoperative routine tests were performed for the surgery, and none of the patients had undergone CABG surgery before. The same team performed all operations and the operation time, CPB time, cross clamp (CC) time and the number of bypass grafts applied were recorded.

Surgical Technique

Standard premedication and anesthetic methods were used for all patients. Diazepam 10 mg tb was given the night before the operation. When the patients were taken into the operating theatre, electrocardiography (ECG) monitoring was initiated and monitored (Datex-Ohmeda S/5, Datex-Ohmeda Inc., Madison, WI, USA) throughout the operation. At the same time, ECG segment analysis was performed for ischemia monitoring. Anesthesia induction was completed with 8 cg/kg fentanyl, 0.15 mg/kg midazolam, and 0.1 mg/kg pancuronium bromide, after 1 mg/kg IV lidocaine was administered to reduce the hemodynamic response to laryngoscopy and endotracheal intubation at the beginning of induction. Maintenance of anesthesia was accomplished by infusion of 5–10 cg/kg/hour fentanyl and inhalation of 0.2–1.5% isoflurane plus 50% air-oxygen mixture. The neuromuscular blockade was maintained with the addition of 0.05 mg/kg pancuronium bromide to the pump reservoir at the beginning of the CPB, and the termination of the isoflurane inhalation. A median sternotomy was performed on all patients, and heparinization was applied so that the activated coagulation time (ACT) was above 400 seconds before CPB started.

During the operation, arterial cannulation was performed from the ascending aorta, and venous cannulation was performed from the right atrial appendage with a two-stage cannula. All cardioplegia doses were administered antegrade through the cannula placed in the aortic root. CPB was performed on all patients by nonpulsatile perfusion (Terumo® Advanced Perfusion System 1, Terumo Medical Corporation, Ann Arbor, Michigan, USA), with a membrane oxygenator (Capiox SX 18R®, Terumo Medical Corporation, Somerset, NJ, USA). At the onset of CPB, mild systemic hypothermia was applied to all patients until the temperature reached 28°C. Intermittent hyperkalemic cold blood cardioplegia was used for myocardial protection. Before the CC was lifted, 10 ml/kg hot-shot application was applied to provide controlled reperfusion. The presence of arrhythmia was noted at the beginning of the re-contractions of the heart after the removal of the CC. During the operation, no medication known to have an antioxidant effect was administered to the patients. Heparin neutralization was achieved with a 1.3/1 protamine sulfate infusion after CPB was terminated.

To evaluate the hemodynamics of the patients, mean arterial pressure and heart rate were recorded before incision, before CPB, five minutes after protamine infusion and at the postoperative second hour. In addition, patients who needed perioperative inotropes were recorded.

Arterial blood samples taken for an MDA level were taken at the following times: before induction (1), just before the cross clamp was lifted (2), and five minutes after the end of the protamine infusion (3). Plasma MDA determination was performed by applying the Esterbauer method which is based on a spectrophotometric measurement at a wavelength of 532 nm. The color intensity of the complex formed by thiobarbituric acid, one of the degradation products of lipid peroxidation, was measured and results were reported in nmol/g (11).

Venous blood samples were taken preoperatively and two hours after the operation for CK-MB and LDH levels.

Statistical Analysis

All statistics were performed using SPSS (Statistical Package for Social Science) version 15.0 for Windows (IBM Corporation, New York, USA). Data was summarized as mean±standard deviation (mean±std). The compliance of the data to normal distribution was tested with Shapiro-Wilk. ANOVA (analysis of variance) was used to determine the difference in group averages. The Tukey test, one of the POSTHOC tests, was used to determine the means between the different groups. Only the Kruskal–Wallis test was used to compare the NYHA class between the groups, and Fischer's exact test was used to compare the presence of arrhythmia. The $p<0.05$ was considered statistically significant.

RESULTS

There was no statistically significant difference between the three groups in terms of demographic and preoperative data (P>0.05). The data are shown in **Table 1**.

Table 1. Demographic data of patients

	Group K (n=15)	Group C (n=15)	Group CM (n=15)	P value
Age (years)	64.3±8.8	66.7±7.4	60.6±9.5	>0.05
Gender (M / F)	8/3	8/2	8/2	>0.05
BSA(m^2)	1.77±0.16	1.85±0.19	1.84±0.14	>0.05
NYHA(I/II/III)	0/8/2	2/7/1	1/8/1	>0.05
EF (%)	46.5±10.7	49.5±11.5	47.0±4.21	>0.05

BSA: Body surface area; NYHA: New York Heart Association; EF: ejection fraction

There was no statistically significant difference between the three groups in terms of intraoperative data (P>0.05). The data are shown in **Table 2**.

Table 2. Intraoperative parameters of patients

	Group K (n=15) (mean±std)	Group C (n=15) (mean±std)	Group CM (n=15) (mean±std)	P value
Operation time (min)	358.0±55.9	351.0±55.6	315.0±57.2	>0.05
CPB time (min)	127.2±39.4	132.9±32.1	125.6±33.1	>0.05
CC time (min)	70.9±26.9	85.0±28.2	81.4±23.1	>0.05
Bypass grafts count	3.7±0.4	3.8±0.4	3.5±0.8	>0.05

CPB: Cardiopulmonary bypass; CC: cross clamp; std: standard deviation; min: minute.

Preoperative CK-MB (CK-MB1) and postoperative CK-MB (CK-MB 2) levels, preoperative LDH (LDH1) and postoperative LDH (LDH2) levels of the groups are shown in **Table 3**. In all three groups, the levels obtained in the second hour postoperatively for CK-MB and LDH increased significantly compared to preoperative level (P<0.001). There was no significant difference between the groups in preoperative and postoperative CK-MB and LDH levels (P>0.05). However, although not statistically significant, both enzyme levels were found to be lower in Group CM than in Group K and Group C (**Figures 1** and **2**).

Table 3. CK-MB and LDH levels of the groups

	Group K (n=15) (mean±std	Group C (n=15) (mean±std)	Group CM (n=15) (mean±std)	P value
CK-MB 1 (m/l)	16.90±4.05	17.80±6.32	17.30±4.59	>0.05
CK-MB 2 (m/l)	64.00±8.30*	73.10±19.89*	69.32±15.43*	>0.05
LDH 1 (m/l)	418.2±124.3	486.2±114.1	497.8±182.7	>0.05
LDH 2 (m /l)	992.1±225.1*	1013.0±306.9*	1037.2±256.6*	>0.05

std: standard deviation. * P<0.001 compared with the preoperative value.

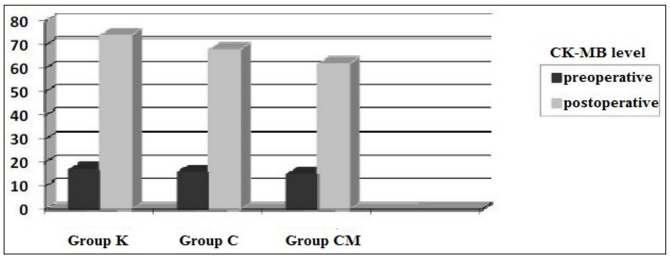

Figure 1. Preoperative and postoperative CK-MB levels in the groups. (When compared with the preoperative values of the postoperative values within the group, P<0.001).

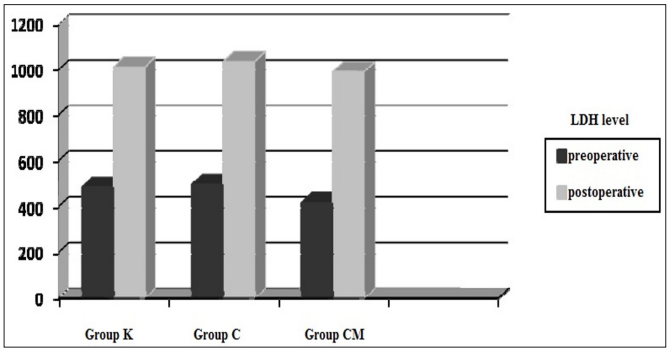

Figure 2. Preoperative and postoperative LDH levels in the groups. (When compared with the preoperative values of the postoperative values within the group. (P<0.001)).

Preoperative and perioperative MDA level are shown in **Table 4** and **Figure 3**. In Group K, MDA 2 and MDA 3 value were statistically significantly higher than the MDA 1 value (P=0.011 and P=0.007). When Group C and Group CM's MDA value were compared within the group, no statistically significant difference was found (p>0.05). MDA 2 and MDA 3 value were found to be statistically significantly lower in Group C and Group CM than in Group K (P=0.009, P=0.012, P=0.009 and P=0.006 respectively)

Table 4. MDA levels of the groups

	Group K (n=15) (mean±std	Group C (n=15) (mean±std)	Group CM (n=15) (mean±std)
MDA 1 (nmol/g)	2.00±0.34	2.16±0.55	2.21±0.96¶
MDA 2 (nmol/g)	3.04±0.88*	2.54±0.74‡	2.55±0.62‡§
MDA 3 (nmol/g)	3.64±0.81*†	2.87±0.61‡	2.62±0.68‡§

MDA: Malondialdehit; std: standard deviation. * P<0.05 compared with MDA 1 value; † P<0.05 compared with MDA 2 value; ‡ P<0.05 compared with Group K; § P>0.05 compared with Group C value; ¶ P>0.05 compared with Group C and Group K.

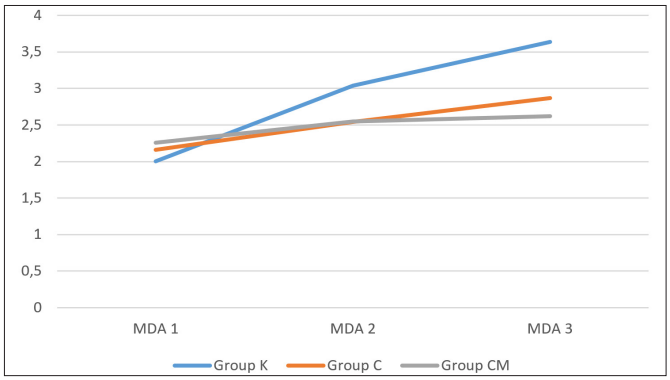

Figure 3. Comparison of MDA (malondialdehit) values in the groups (MDA 1:before induction ; MDA 2: just before cross clamp removal; MDA 3: after protamine infusion).

When the CC was removed, arrhythmia requiring intervention was observed in six patients in Group K, three patients in Group C, and one patient in Group CM. A statistically significant difference was determined only between the K Group and CM Group (P=0.026). The data are shown in **Figure 4**.

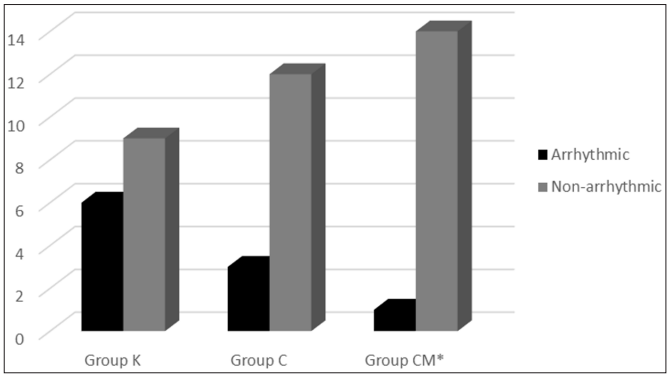

Figure 4. Arrhythmia requiring intervention when the cross clamp is lifted in all three groups (*P=0.026 compared to Group K).

Table 5. Hemodynamic measurements obtained in three groups

	Group K (n=15) (mean±std	Group C (n=15) (mean±std)	Group CM (n=15) (mean±std)
Mean arterial pressure 1 (mmHg)	81.20±19.75	68.30±10.07	72.10±8.86
Mean arterial pressure 2 (mmHg)	73.90±9.31	74.40±11.42	74.30±12.48
Mean arterial pressure 3 (mmHg)	66.40±5.13*	65.80±9.25	68.30±6.73
Mean arterial pressure 4 (mmHg)	78.00±8.68	70.10±6.98	73.70±9.65
Heart rate 1 (beats/min)	70.9±13.8	66.9±16.0	72.6±11.8
Heart rate 2 (beats/min)	81.9±16.6	77.5±15.2	86.2±13.2*
Heart rate 3 (beats/min)	88.1±19.2*	93.0±19.1*†	86.8±10.8*
Heart rate 4 (beats/min)	93.1+18.7*	99.5±16.4*†	100.4±16.4*†‡

std: standard deviation; min: minute. * P<0.05 compared to 1st value; † P<0.05 compared to 2nd value; ‡ P<0.05 compared to 3rd value.

The mean arterial pressure and the heart rate results obtained in the three groups, before incision (1), before CPB (2), five minutes after protamine infusion (3) and at the postoperative second hour (4) are shown in **Table 5**. There was no statistically significant difference between the groups (P>0.05).

The need for inotropes was detected in five patients in Group K, three patients in Group C, and four patients in Group CM. There was no statistically significant difference between the groups (P>0.05).

DISCUSSION

This study demonstrated the efficacy of the combined application of ascorbic acid and Mg in the IR injury caused by CPB in CABG surgery. The main findings of the study were as follows: high-dose ascorbic acid and Mg were shown to prevent lipid peroxidation and arrhythmias requiring intervention.

Despite the advances in pharmacological intervention, surgical methods and CPB system in open heart surgery, ischemia due to CPB and reperfusion injury that develops after the removal of the CC and coronary flow is damaging to the heart. Systemic and local hypothermia, antegrade and retrograde hypothermic crystalloid or blood cardioplegia were used for intraoperative myocardial protection (12). Experimental studies aiming to protect organs against IR damage have been carried out using different surgical, pharmacological, and genetic methods. However, few of the studies that seem successful in the experimental setting have been applied clinically. The reason for this is that IR damage is too complex to be prevented by blocking a single step or mediator (13). The antioxidant system has an important role in protecting damage that could be caused by FOR. There are mechanisms in the antioxidant system for binding transition metal ions, preventing the formation of FOR, collecting or suppressing the formed radicals, breaking radical chain reactions, repairing, or removing damaged target molecules from the environment (14).

Antioxidant and free radical scavenger treatments were created to determine the overproduction of FOR and the role of antioxidant enzymes in the pathogenesis of myocardial damage due to IR (15). For this, pharmacological agents such as calcium channel blockers, antioxidant agents, melatonin, immunosuppressive agents, adenosine, glutamate-aspartate, α-tocopherol, methylprednisolone, ACE inhibitors, trimetazidine, and endothelin-1 receptor antagonists were used (16). Braunwald and Kloner (17) reported that the total antioxidant capacity decreased and oxidant damage occurred during the IR periods during CPB. In addition, it has been shown that the total antioxidant capacity was suppressed, and lipid peroxidation increased for 72 hours after the operation in patients with CPB. During CBP, blood levels of vitamin A, vitamin E and vitamin C were tested. There was a slight decrease in the vitamin A and vitamin E level, and a significant decrease in the vitamin C level during and after the operation (18). The decrease in the ascorbic acid level has been attributed to either a direct reaction with FOR, or its role in the regeneration of other antioxidants. In addition, in studies conducted with ascorbic acid, its inhibitory effect on lipid peroxidation and its protective role of the myocardium from IR damage has been demonstrated (19). In the study conducted by Dingchao et al. (20), it was shown that high-dose ascorbic acid administered intravenously at a dose of 250 mg/kg had a myocardial protective effect.

It is known that reperfusion causes ventricular fibrillation, ventricular tachycardia, idioventricular rhythm, and ventricular premature beats (21). It has been argued that the increase of FOR, which occurs in the early stage of reperfusion, affects the membrane lipids and thus the ion pumps, making the myocardium susceptible to arrhythmia (22). In the study of Seitelberger et al. (23), conducted on 120 patients, it was determined that Ca channel blockers decrease the number of ventricular premature complexes. In another study, it has been shown that ascorbic acid prevents AF (24), and in our study, when the CC was removed, arrhythmia requiring intervention was observed in six patients in Group K, three patients in Group C, and one patient in Group CM. Although the difference between Group K and Group CM is statistically significant, the detection of arrhythmia in a smaller number of patients compared to Group K with high-dose ascorbic acid administration and a further decrease in this number with the addition of Mg to ascorbic acid supports the additive antiarrhythmic effect advocated by Hearse and Tosaki (25).

One of the widely accepted theories about IR injury is the increase in FOR and intracellular free Ca (26). Uncontrolled increase in intracellular Ca levels causes ischemic contracture and structural changes. With the application of hypocalcemic reperfusion, and the addition of Ca channel blockers to the cardioplegia solution and the IV, intracellular Ca increase was prevented (27). Mg is a physiological Ca antagonist and reduces myocardial damage during IR by blocking the FOR products generated by reperfusion (28). In a study, Mg infused intraoperatively from the aortic root showed positive effects on ischemia, IR damage, and arrhythmia during cardiac surgery (29). Prophylactic Mg has been reported to reduce postoperative arrhythmia in patients under CPB (30). If arrhythmia occurs despite Mg, it appears that the rate of recovery of these arrhythmias is then higher with other antiarrhythmic drugs (31).

During and after CPB, it has been shown that Mg levels decrease postoperatively in up to 70% of the patients when it is not replaced, and then gradually increase until the 4th postoperative day (32). The mechanism of the relationship between cellular Mg and serum Mg has not been fully determined. However, it has been demonstrated that measuring intracellular Mg concentration by radiographic microanalysis shows a Mg deficit in cardiac patients (33). Although the intracellular Mg level was not examined as a criterion of our study, we believe that these results are reliable as we have monitored the ionized fraction, which is physiologically

the most important part. Studies have claimed that the perioperative Mg level can be reliably assessed by monitoring the ionized fraction in the serum in patients undergoing cardiac surgery (34).

FOR, which occur during myocardial IR are very reactive and although they have a lifespan that is measured in microseconds, their presence can be demonstrated in tissue using spin resonance spectroscopy (35). Oxidation of polyunsaturated fatty acids with FOR in biological systems is called lipid peroxidation, and the presence of FOR reaction in studies has been proven by the demonstration of lipid peroxidation markers (36). The most frequent method used for the determination of lipid peroxidation is the measurement of the MDA level. In our study, MDA levels obtained before and after the administration of protamine increased in all three groups compared to the preoperative MDA level, but it was found that this increase was less in Groups C and CM. MDA 2 and MDA 3 value were found to be statistically significantly lower in Group C and Group CM than in Group K. Although the increase in MDA was less in group CM compared to Group C, there was no statistically significant difference between them ($p>0.05$). These results show us that high dose ascorbic acid and an ascorbic acid–magnesium combination protects the myocardium against FOR.

Many studies have shown an increase in cardiac enzyme levels after CPB (37). In studies where antioxidant agents and Mg were used to prevent myocardial IR damage, cardiac enzyme levels were measured to show myocardial damage and conflicting results were obtained (38). Although there are studies showing that high dose ascorbic acid and Mg reduce CK-MB release from the myocardium, the clinical significance of these results could not be determined (39). In our study, CK-MB and LDH levels obtained at the second hour postoperatively showed a statistically significant increase in all three groups compared to the preoperative values ($P<0.001$), but there was no additional finding suggesting myocardial damage during this period. There was no significant change in mean arterial pressure. Although not statistically significant, postoperative enzyme levels were lower in the CM group than in the other two groups. Therefore, we believe that CK-MB and LDH levels are not fully specific for myocardial damage, and that the value of cardiac enzymes has not been fully investigated in similar studies.

It has been argued that FOR occurs during myocardial IR at the same time as cellular Ca loading occurs, and endogenous defense mechanisms are insufficient. In our study, this opinion was supported by the increase in the level of MDA in Group K, which is a product of lipid peroxidation known to occur in the presence of FOR. When ascorbic acid and Mg were used to prevent the damage caused by FOR, it was shown that lipid peroxidation and arrhythmias requiring intervention were prevented. However, there was no statistically significant difference between the groups in terms of cardiac enzyme levels and hemodynamic measurements. This result is parallel to the findings in the study by Demirağ et al. (40), where diltiazem was added to the ascorbic acid. Despite this result, we believe that advanced myocardial protection methods are required in high-risk patients with preoperative ventricular dysfunction, and the protective effect of Mg and high dose ascorbic acid will be reflected in clinical findings in patients with high risk. To reach a definitive conclusion on this subject, we believe that it is necessary to conduct studies involving a greater sample size and higher risk patients.

Limitation of the Study

The first limitation of this study is that it was conducted in a single center. The second limitation of this study is that the amount of intracellular magnesium could not be shown. The third limitation is that most patients were in the low to intermediate risk group according to the NYHA.

CONCLUSION

In conclusion, the combined use of high-dose ascorbic acid and Mg in CABG operations of low to medium risk patients, did not have a greater impact in preventing myocardial IR damage during CPB in terms of cardiac enzyme levels and hemodynamic measurements than cold blood cardioplegia. However, prevention of lipid peroxidation and arrhythmias that require intervention suggests that Mg and high-dose ascorbic acid may be beneficial in a high-risk patient group.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Scientific Researches Ethics Committee of Osmangazi University Faculty of Medicine (Date: 30.06.2009, Decision No: 60).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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