

Magnesium decreases cardiac injury in patients undergoing coronary artery bypass surgery

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Background: The calcium-channel blocking effect of magnesium might have protective effects in patients undergoing cardiopulmonary bypass surgery. We assessed the effects of magnesium on hearts undergoing coronary artery bypass surgery with intermittent warm blood hyperkalemic cardioplegia in the antegrade fashion.

Patients and Methods: Twenty patients undergoing coronary bypass surgery were randomly divided into two groups, a control group who received intermittent antegrade warm blood hyperkalemic cardioplegia for myocardial protection, and a study group who received the same solution with the addition of magnesium to the cardioplegia. Extracellular substrates (creatinine phosphokinase, creatinine phosphokinase-MB group, lactate dehydrogenase, c-reactive protein, and cardiac troponin I) were measured preoperatively and postoperatively.

Results: There were significant differences in the post-operative concentrations of creatinine phosphokinase, creatinine phosphokinase-MB group, c-reactive protein, and lactate dehydrogenase after cardiopulmonary bypass ($P<0.001$) in the study group compared with the control subjects. Cardiac troponin I levels were also significantly lower in the study group after cardiopulmonary bypass ($P<0.005$).

Conclusions: Our study indicates that if magnesium is added to intermittent antegrade warm blood hyperkalemic cardioplegia, blood levels of many markers of cardiac myocardial injury after cardiopulmonary bypass are lowered. This finding may have implications for myocardial protection.

Key words: Magnesium, reperfusion, cardiopulmonary bypass, cardioplegia

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Magnesium as a physiological calcium blocker modulates calcium transport across the sarcoplasmic reticulum.²²⁻²⁴ Because calcium overload leads to reperfusion injury^{4,10,15-20} the channel blocking quality of magnesium might have protective effects in patients undergoing cardiopulmonary bypass.²⁵ The intravenous administration of magnesium incites an increase in extracellular magnesium and this may lead to a reduction in post-perfusion injury. The reduction in post-perfusion injury might be provoked through the following mechanisms: reduction of calcium overload in myocardial mitochondria (calcium hypothesis),¹⁷ conservation of intracellular ATP as magnesium-ATP^{26,27} antioxidant effect of magnesium, which is separate from its calcium antagonism effects, improved coronary blood flow by way of coronary vasodilatation, reduction of arrhythmias,^{6,7,8,28} increase in biogenic contraction,¹⁹ or reduction of catecholamine secretion to the myocardium,^{29,30} We measured the effect of addition of magnesium to the cardioplegia in patients undergoing coronary artery bypass surgery in a

randomized, controlled study.

Patients and Methods

The study was conducted at Çankaya Hospital, Ankara, Turkey, during the months of January and February 2000. We randomly divided 20 patients undergoing coronary artery bypass surgery into two groups consisting of 10 patients each. The study group was given a standard dose of 1.5 g of magnesium sulphate (Haver Laboratory, BIOSEL, Istanbul, Turkey 15%, 10 ml) preoperatively. A second dose of 1.5 g magnesium sulphate was given in the first cardioplegia. To all patients we gave a third dose of 1.5 g of magnesium sulphate in the second cardioplegia 20 minutes after the first cardioplegia. We gave a fourth dose of 1.5 g intravenous magnesium sulphate 8 hours after the end of the operation to the study group. Because all of our patients were adults, we gave them the same standard dose of cardioplegia. The control group consisted of ten patients. We also used intermittent warm blood hyperkalemic cardioplegia in the antegrade fashion in the control subjects. Magnesium

Table 1. Pre- and post-operative values for biochemical parameters in the study (n=10) and control groups (n=10).

	Study Group (n=10)		Control Group (n=10)	
	Pre-op	Post-op	Pre-op	Post-op
CK (U/L)	69.04 ± 7.05	944.44 ± 75.47*	65.77 ± 3.64	1190.66 ± 163.35*
CK-MB (U/L)	9.95 ± 2.94	21.42 ± 2.05*	8.86 ± 2.11	29.69 ± 4.67*
LDH (U/L)	369.12 ± 55.06	840.60 ± 113.99*	332.46 ± 55.51	1077.36 ± 143.21*
CRP (mg/dL)	0.42 ± 0.14	7.78 ± 1.16*	0.52 ± 0.18	11.07 ± 2.16*
cTnI (µg/L)	0.98 ± 0.36	7.00 ± 1.16*	0.96 ± 0.27	8.52 ± 0.93*

*P<0.001 for comparison of study vs. control group post-op values for CK, CK-MB, LDH, CRP; P<0.005 for comparison of study vs. control group post-op values for cTnI.

Table 2. Cardiopulmonary bypass and cross-clamp times (mean±SD) in the study (n=10) and control groups (n=10).

	Cardiopulmonary bypass times	Cross-clamp times
Control group	69.60 ± 31.8	40.20 ± 23.9
Study group	68.5 ± 29.7	41.3 ± 22.8

was not added to the cardioplegia in the control group.

Informed consent was provided by all twenty patients before taking blood levels of creatinine phosphokinase (CK), creatinine phosphokinase MB group (CK-MB), lactate dehydrogenase (LDH), c-reactive protein (CRP), and cardiac troponin I (cTnI). LDH, CK, and CK-MB serum levels were taken one hour before the operation and at 24 hours postoperatively. CTnI and CRP serum levels were taken 1 hour before the operation and at 12 hours postoperatively. The patients in the two groups were selected from patients whose ejection fractions were above 50%. The patients in the two groups were similar in age and sex. Blood samples for LDH, CK, CK-MB, and CRP were taken into normal tubes. Blood samples were analyzed with the Vitros DT Chemistry System (South Korea). Blood samples for cTnI were analyzed with the Abbott AXSYM System (Abbott, USA).

Anesthesia was given in the standard fashion for cardiopulmonary bypass patients. In all patients, we used membrane oxygenators (Dideco Inc., Mirandola, Italy), arterial filters, pump sets and auxiliaries (Bıçakçılar, Istanbul, Turkey) and non-pulsatile roller pumps. Balanced electrolyte solutions were used as primary solution. All patients were given 3 mg/kg heparin before cardiopulmonary bypass. During cardiopulmonary bypass, activated clotting time (ACT) was kept above 400 seconds. In all patients, we used warm blood antegrade hyperkalemic cardioplegia and 30-32 C (systemic internal and topical hypothermia (ice slush)). A standard midline sternotomy, and aortic and atrial cannulation were performed. Heparin was neutralized

by protamine hydrochloride after completion of cardiopulmonary bypass. Patients who had to be defibrillated electrically were not included in the study. Patients whose hearts began to beat spontaneously after the cross-clamp had been removed were included in the study.

Results were expressed as mean ± standard error of the mean. The statistical significance of the results were analyzed using the parameters in the two groups and *P* values <0.05 were accepted as meaningful. The statistical analyses were made using Mann-Whitney U-Wilcoxon Rank Sum *W* test, the most suitable test for the analyses of small sample-sized studies dealing with variables that have wide range.

Results

The pre- and post-operative blood values for the biochemical parameters are shown in Table 1. Differences in the post-operative values between the study and control groups were statistically significant. Average cardiopulmonary bypass and cross-clamp times are shown in Table 2.

Discussion

Since Hearse's early publications, we know that there is massive production of oxygen free radicals (OFR), especially during reperfusion of the myocardium.^{31,32} In prolonged ischaemia, protective mechanisms of the heart against OFR are reduced. Many antioxidants like ascorbic acids and alpha-tocopherol are reduced.^{33,34} Mitochondrial superoxide dismutase and glutathione peroxidase are increased.^{33,34} OFR production that surpasses antioxidant mechanisms' capacity causes myocardial injury. Its clinical manifestations are displayed by an increase in CK, CK-MB, LDH, CRP and cTnI levels.^{14,21} Injury occurs during the time when oxygen is replaced to the myocardium. Because of this, it is called reperfusion injury.

According to many studies, magnesium acts as a cytoprotective agent in myocardial ischaemia and reperfusion. A number of mechanisms have been proposed as regards the cytoprotective actions of magnesium: 1)

inhibition of calcium influx and reduction of cytoplasmic and mitochondrial calcium overload (the so called calcium hypothesis);^{9,17,18} 2) decreasing release of catecholamine;^{29,30} 3) magnesium's anti-inflammatory effects⁹ with a decrease of leukocyte migration to the infarct area and stimulating glutathione synthesis;³⁵ 4) the vasodilator effect of magnesium that increases collateral circulation, which may assist in decrease of OFR production (coronary microvascular protection causing an amelioration in intrinsic myogenic contraction).^{19,35,36}

Many studies indicate that cTnI is a cardioselective marker.^{39,40} The decrease in cTnI postoperatively in our study group showed that preoperative magnesium addition into the warm antegrade hyperkalemic cardioplegia protected the myocardium in patients undergoing coronary artery bypass surgery. However, our study has limitations. We

used biochemical parameters in comparing the two groups because PET scans, which would have allowed for a more comprehensive assessment, would be expensive and time consuming. Also, the number of patients in the study and the control groups were small. This limits the scope of the study in making categorical comments. In our results, the cTnI levels between the two groups were statistically significant. We believe that this was because none of our patients had myocardial infarction during or after the operation.

In the present study, we found that magnesium addition to warm antegrade hyperkalemic cardioplegia caused a decrease in the markers of cardiac myocardial injury (CK, CK-MB, LDH, CRP, cTnI) in the study group patients. This shows that magnesium can be used in cardioplegic solutions.^{3,5,11-13,21,37,38} to attenuate myocardial injury in patients undergoing cardiopulmonary bypass.

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