Effect of Intra-Operative Magnesium Supplementation in Plasma Antioxidant Levels Trace Elements and Electrolyte Balance in Serum of Coronary Artery Bypass Graft Patients

Kurian GA, Paddikkala J

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Effect of Intra-Operative Magnesium Supplementation on Plasma Antioxidant Levels, Trace Elements and Electrolyte Balance in Serum of Coronary Artery Bypass Graft Patients

G. A. Kurian¹, J. Paddikkala²

Objective: Calcium overload and oxidative stress have been identified as pathogenic factors in myocardial ischaemic reperfusion. Experimental studies have demonstrated that intravenous magnesium (Mg) can protect the ischaemic myocardium. It has a free radical scavenging effect and can act as a calcium channel blocker. Although the role of copper, iron, and other metal elements in ischaemic heart injury has been well established, clinical studies are very limited. The link between these serum metal element concentrations and oxidative stress is unclear in humans although, in experimental animal studies, severe Mg deficiency has been shown to lead to increased oxidative stress.

Methods: Ninety-two South Indian patients with acute myocardial ischaemia undergoing CABG were randomized to a study and a control group. Magnesium was administered (2 g/kg body weight) to the study group. Control patients received the same protocol without magnesium. Serum levels of copper, zinc, iron, ceruloplasmin, sodium and potassium were measured in addition to the plasma levels of antioxidant enzyme activities and cardiac marker enzymes such as troponin I, CPK MB, and LDH. Results: There was no mortality in the study group. Serum metal elements like iron and zinc were observed to be higher in concentration at the ischaemic stage while during reperfusion higher concentrations of copper, iron, and zinc were observed in both the study and the control groups. Plasma TBARS concentration in magnesium-treated and -untreated patients increased progressively during surgery and peaked during revascularization. However, plasma antioxidant enzyme activities were found to be decreased at the ischaemic stage in both groups. Cardiac marker enzymes also elevated during revascularization, however, the extent of increase (p < 0.05) was higher in the control group.

Conclusions: Our study suggests that the use of magnesium for protection of the acutely ischaemic myocardium appears to be a safe technique. Magnesium supplementation stabilizes the plasma membrane and is thereby able to withstand the oxidative stress mediated by ischaemic reperfusion.

Key words: myocardial ischaemia reperfusion, magnesium, copper, zinc, iron, CABG

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From the ¹MMM Academy of Medical Sciences, Institute of Cardiovascular Diseases, Madras Medical Mission; ²Department of Biotechnology, Amrita Cancer Research Center, Amalangan, India

Correspondence to: Gino A Kurian, M.Phil, PhD, School of Chemical and Biotechnology, SASTRA Deemed University, Thirumalaisamudram, Thanjavur, Tamil Nadu, India; e-mail: ginokurian@hotmail.com

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undergoing cardiac surgical procedures, both during surgery and in the immediate post-operative period. The aim of this prospective study, therefore, was to assess the independent effect of myocardial revascularization techniques on peri-operative levels of electrolytes and trace element concentrations of iron, copper, and zinc in South Indian patients who were either treated or not with magnesium during revascularization procedure.

Patients and Methods

Patient Population

We studied patients undergoing their CABG operation in which full revascularization was expected. Ethical approval was provided by the ethical committee of the Institute of Cardiovascular Diseases, Madras Medical Mission. Written consent was obtained from each patient.

92 South Indian patients (72 male, 20 female, mean age 62.6 ± 11.2 years) were included in this study. Patiens were randomly assigned to a magnesium treatment group and a control group. Fifty-two patients (42 male, 10 female) received magnesium (2 g/kg body weight). Forty patients (30 male, 10 female) did not receive magnesium. Patients taking antioxidants such as captropil and allopurinol were excluded from the study. Patients who received blood transfusion or blood products during surgery were also excluded since the antioxidant properties of such products are not as yet established. None of the patients were taking vitamins or dietary supplements with established antioxidant properties before the study. None of the controls had a history of cerebrovascular disease.

Anesthesia

On the day of surgery, the patient was premedicated with morphine (0.2 mg/kg) and promethazine (0.5 mg/kg) i.m. about 30–45 minutes prior to induction of anesthesia. Anesthesia was induced with thiopentone (5 mg/kg) and morphine (0.2 mg/kg) and promethazine (0.5 mg/kg) i.m. on the day of surgery. The initial post-operative serum magnesium level incidences of myocardial infarction or acute renal failure occurred. The initial post-operative serum magnesium level was provided by the ethical committee of the Institute of Cardiovascular Diseases, Madras Medical Mission. Written consent was obtained from each patient.

Surgical Technique

Standard cardiopulmonary bypass technique with normothermia (> 32 °C) was employed throughout the study. The extracorporeal circuit was primed with Ringer’s lactate solution 1.5 liter and mannitol 100 ml. Perfusion pressure was maintained at 50–70 mmHg during bypass. Cardiopulmonary bypass operation was instituted using ascending aortic cannulation and two-stage venous cannulation in the right atrium. The extracorporeal circuit consisted of a membrane oxygenator and a roller pump primed with crystalloid solution. Cardioplegia was given retrogradely except for the first two-thirds of crystalloid cold cardioplegia, which were given anterogradely. All distal and proximal anastomoses were completed before removal of the aortic cross clamp. At the end of CABG, heparin was neutralized by protamine chloride until the activated clotting time was less than 180 seconds. In the CABG group, hematocrit was kept at more than 20% during CPB.

Sampling and Analysis

Paired coronary sinus and arterial blood samples were taken at the following time points: (1) just before induction of anesthesia (group 1); (2) 10 minutes after aortic cross clamp on (group 2); (3) 30 minutes after aortic cross clamp (group 3); (4) 10 minutes after aortic cross clamp off (group 4); (5) during re-warming (group 5). Groups 2 and 3 referred the ischaemic state of the heart while group 4 referred the ischaemic reperfusion (revascularization) state.

Biochemical Parameters

Serum Zn²⁺, Cu²⁺, Ca²⁺, and Mg²⁺ were determined by Atomic absorption spectrophotometry (model A A-630-02; Shimadzu, Kyoto) using an acetylene flame and hollow cathode lamps. Sera were diluted 10 times with distilled water. Analysis wavelengths were 213.9, 324.7, 422.7, and 285.2 nm, respectively. Serum Na⁺ and K⁺ were determined after a 1:200 dilution of the sample using flame photometer. The activities of plasma antioxidants like catalase [13], GPx [14], ceruloplasmin [15], and SOD [16] were measured. Plasma TBARS level was estimated by the method of Yagi [17]. Serum concentration of troponin I was measured by commercially available enzyme immunoassays developed by Larue [18] (ERIA Diagnostics Pasteur). Lactate dehydrogenase activity and CPK MB mass concentration were analyzed by Sigma diagnostic kits.

Statistics

Data are presented as mean ± standard deviation. Data analyses were performed using SPSS software version 12.0. Comparisons within groups were made using repeated measures with one-way ANOVA. Comparisons between groups (pre-operative and surgical data) were carried out using the chi-square test. Continuous, normally distributed data were analyzed by t-test (single comparisons). Continuous non-normal data were analyzed with the Mann Whitney U test.

Results

Clinical and surgical data are described in Table 1. In the study groups, no hospital mortality, neurological accidents, incidences of myocardial infarction or acute renal failure occurred. The initial post-operative serum magnesium level was provided by the ethical committee of the Institute of Cardiovascular Diseases, Madras Medical Mission. Written consent was obtained from each patient.
was higher in patients receiving magnesium (Tab. 1). In patients who did not receive intra-operative magnesium, the incidence of post-operative hypomagnesaemia (< 1.8 mEq/l) was 35 % compared with 9 % in patients who received intra-operative magnesium.

Table 2 shows the levels of copper, iron, zinc, sodium, potassium, and calcium in the serum during CABG. During the ischaemic stage of surgery, copper and iron concentrations in the serum increased progressively whereas the zinc level in the serum was observed to be decreased. However, in the early revascularization period, the concentrations of copper, iron, and zinc in the serum were elevated and they were observed to be decreased in the late revascularization stage. Serum levels of most of these ions showed a similar pattern of change in the samples obtained from both patients who received magnesium and did not receive magnesium. However, a significant difference in the level of zinc was observed in the patient samples compared to the control group.

The levels of lipid peroxidation and plasma antioxidant activities are shown in Table 3. Plasma TBARS concentration in the patient samples compared to the control group. A significant difference in the activities of catalase and super-oxide dismutase was observed between the control and drug-treated groups. The levels of plasma ceruloplasmin were decreased in both groups during the ischaemic stage and were observed to be significantly increased during the revascularization period.

Blood gas analysis results (Tab. 4) show no significant change in their levels during surgery except for the partial pressure of oxygen, the latter showing a decreased concentration in the late phase of revascularization.

Cardiac marker proteins such as troponin I, LDH, and CKMMB showed a significant increase (Tab. 5) in their levels in serum during reperfusion of the ischaemic myocardium. However, the extent of increase was less pronounced in magnesium-treated CABG patients.

**Table 2.** Concentrations of copper, zinc, iron, sodium, potassium, and calcium in serum samples of CABG patients who received magnesium and who did not receive magnesium

**Table 3.** Comparison of measured plasma anti-oxidants in total bypass patients who received magnesium and who did not receive magnesium
Blood gas analysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Magnesium</th>
<th>No magnesium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial pressure of oxygen (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Just before induction of anesthesia</td>
<td>261.92 ± 7.10a</td>
<td>261.92 ± 7.10b</td>
</tr>
<tr>
<td>10 min after aortic cross clamp on</td>
<td>287.53 ± 60.13a</td>
<td>286.53 ± 60.12a</td>
</tr>
<tr>
<td>30 min after aortic cross clamp on</td>
<td>260.04 ± 57.84a</td>
<td>261.04 ± 57.81a</td>
</tr>
<tr>
<td>10 min after aortic cross clamp off</td>
<td>221.79 ± 58.33a</td>
<td>222.69 ± 57.33a</td>
</tr>
<tr>
<td>During re-warming</td>
<td>256.65 ± 76.98a</td>
<td>259.55 ± 74.98a</td>
</tr>
<tr>
<td>Partial pressure of carbon dioxide (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Just before induction of anesthesia</td>
<td>38.61 ± 7.40a</td>
<td>38.60 ± 7.24a</td>
</tr>
<tr>
<td>10 min after aortic cross clamp on</td>
<td>38.07 ± 5.80a</td>
<td>38.44 ± 5.41a</td>
</tr>
<tr>
<td>30 min after aortic cross clamp on</td>
<td>36.68 ± 4.10a</td>
<td>36.11 ± 4.12a</td>
</tr>
<tr>
<td>30 min after aortic cross clamp off</td>
<td>38.77 ± 4.40a</td>
<td>39.72 ± 4.49a</td>
</tr>
<tr>
<td>During re-warming</td>
<td>38.83 ± 7.40a</td>
<td>38.31 ± 7.40a</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
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<tr>
<td>Just before induction of anesthesia</td>
<td>7.42 ± 0.06a</td>
<td>7.42 ± 0.06a</td>
</tr>
<tr>
<td>10 min after aortic cross clamp on</td>
<td>7.41 ± 0.06a</td>
<td>7.41 ± 0.05a</td>
</tr>
<tr>
<td>30 min after aortic cross clamp on</td>
<td>7.41 ± 0.05a</td>
<td>7.41 ± 0.05a</td>
</tr>
<tr>
<td>10 min after aortic cross clamp off</td>
<td>7.40 ± 0.05a</td>
<td>7.41 ± 0.04a</td>
</tr>
<tr>
<td>During re-warming</td>
<td>7.39 ± 0.04a</td>
<td>7.39 ± 0.04a</td>
</tr>
<tr>
<td>Chloride (mEq/l)</td>
<td></td>
<td></td>
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<tr>
<td>Just before induction of anesthesia</td>
<td>106.67 ± 3.81a</td>
<td>105.67 ± 3.71a</td>
</tr>
<tr>
<td>10 min after aortic cross clamp on</td>
<td>108.41 ± 2.78a</td>
<td>109.41 ± 2.79a</td>
</tr>
<tr>
<td>30 min after aortic cross clamp on</td>
<td>108.88 ± 3.10a</td>
<td>108.68 ± 3.33a</td>
</tr>
<tr>
<td>10 min after aortic cross clamp off</td>
<td>108.69 ± 3.44a</td>
<td>107.49 ± 3.11a</td>
</tr>
<tr>
<td>During re-warming</td>
<td>107.07 ± 3.12a</td>
<td>106.17 ± 3.22a</td>
</tr>
<tr>
<td>Bicarbonate (mEq/l)</td>
<td></td>
<td></td>
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<tr>
<td>Just before induction of anesthesia</td>
<td>24.93 ± 1.48a</td>
<td>24.91 ± 1.58a</td>
</tr>
<tr>
<td>10 min after aortic cross clamp on</td>
<td>27.12 ± 2.03a</td>
<td>27.33 ± 2.13a</td>
</tr>
<tr>
<td>30 min after aortic cross clamp on</td>
<td>24.24 ± 2.33a</td>
<td>24.54 ± 2.36a</td>
</tr>
<tr>
<td>10 min after aortic cross clamp off</td>
<td>23.91 ± 2.46a</td>
<td>23.87 ± 2.44a</td>
</tr>
<tr>
<td>During re-warming</td>
<td>24.31 ± 2.58a</td>
<td>24.34 ± 2.51a</td>
</tr>
</tbody>
</table>

Values not sharing a common superscript (a, b) differ significantly according to the Duncan’s multiple range test at p < 0.05 when compared between the groups.

Discussion

In the present study, we observed increased lipid peroxidation products (TBARS) and decline in the plasma antioxidant status of CABG patients who received and did not receive magnesium. But the extent of decline was more pronounced in the samples from patients who did not receive magnesium. Osaka et al [19] have reported an increase in malondialdehyde (MDA) levels and decrease in the activities of enzymatic antioxidants in patients undergoing heart surgery involving cardiopulmonary bypasses. The higher production of reactive oxygen species is responsible for the elevated lipid peroxidation in reperfusion of ischaemic myocardium [20].

Reactive oxygen species play a crucial role in the pathogenesis of tissue damage in many pathological conditions via peroxidation of membrane phospholipids. Lipid peroxides generated at the site of tissue injury during revascularization in CABG could be transferred through circulation to other organs and tissues and provoke damage by propagating lipid peroxidation.

Antioxidants have been reported to protect cells against ischaemic reperfusion injury [21] by scavenging lipid peroxides that are generated at the site of reperfusion injury. The antioxidant capacity of the cell is determined mainly by the activities of antioxidative enzymes [22] like GPx, SOD, and catalase. Early studies reported changes in GPx [23], SOD, and catalase [24] in CABG patients.

SOD is a strong first line of defense against super-oxide radicals and its increased levels are more significant in the CABG group as has been explained by the fact that contact of blood with polymers of the CPB circuit releases cytokines and activates neutrophils [25] whereas the latter can produce super-oxide radicals. Thus, the improved activity of SOD in magnesium-treated patients (Tab. 3) augmented the assumption of the cardioprotective nature of magnesium on CABG patients.

Trace elements are known to play a key role in myocardial metabolism. Serum levels of trace elements like copper and zinc were observed in our study to be decreased within 30 minutes of myocardial ischaemia (Tab. 2). This might have resulted in the depletion of essential enzymes, which protect cell membranes from damage by free radicals. Trace elements, including selenium, zinc, and copper, may be protective against cardiovascular disease [26]. This may be due to the activation of antioxidant enzymes like glutathione peroxidase (GPx) and super-oxide dismutase (SOD) by selenium, zinc, and copper, respectively [26]. Even though the serum metal ion status was increased during ischaemic reperfusion (Tab. 2), a decrease was observed in the activity of antioxidant status. This indicates an irreversible damage to the enzyme [27] which is one of the characteristic features of ischaemic reperfusion injury.

The copper redox states (cupric/cuprous, Cu²⁺/Cu⁺) can function in much the same way as iron in catalyzing the Haber-Weiss reaction [28]. Thus, intracellular levels of free heavy metals (particularly copper and iron) in our present study were critical in defining the extent of hydroxyl radical production from super-oxide and hydrogen peroxide. Transition metal-binding proteins (feritin, transferrin, lactoferrin, and ceruloplasmin) act as a crucial component of the antioxidant defense system by sequestering iron and copper so that they are not available to drive the formation of the hydroxyl radical [29]. The main copper-binding protein,
ceruloplasmin, might also function as an antioxidant enzyme that can catalyze the oxidation of divalent iron [30]. Thus, the increased activity of ceruloplasmin in the late phase of revascularization in the present study suggests the protective role of magnesium supplementation.

Our findings clearly demonstrate that patients undergoing cardiac surgical procedures with extracorporeal circulation are at high risk for electrolyte depletion. Low levels of magnesium and, to a lesser degree, calcium and potassium were observed both in the controls and drug-treated patients. Nadler et al [31] reported that decreased magnesium can lead to significant renal losses of potassium. Low levels of magnesium cause not only cardiac arrhythmias but also hypertension and vasoconstriction, including constriction of coronary arteries [32]. Magnesium appears to act as a physiological calcium channel-blocking agent [31]. Moreover, the susceptibility of blood vessels (including coronary arteries and presumably the mammary arteries, which are frequently used in bypass surgery) to vasoconstrictive agents is increased by hypomagnesaemia [33]. Another potentially important mechanism is the possible role played by magnesium as a free radical scavenger in the prevention of reperfusion injury [34], which may play a key role in the development of post-operative complications. Furthermore, a number of in vitro and animal studies have shown that magnesium can prevent intracellular sodium overload and excess mitochondrial calcium uptake during ischemic injury. These two developments are key elements in the progression of ischemic injury to cell death, and both are directly linked to the extent of ischemia [35]. In addition, magnesium may be linked to prevention of neurological injury after ischemia or trauma [36]. Coronary bypass surgery has been associated with transient or even permanent neuropsychological deficits in up to 30% of patients undergoing cardiac surgical procedures [37], these injuries may be due to small thrombotic emboli occurring during surgery. Prevention of hypomagnesaemia may help to mitigate these neurological injuries. The effects of magnesium depletion can be greatly enhanced in the presence of other electrolyte disorders, especially hypokalaemia. Conversely, the effects of hypokalaemia may become manifest or be enhanced in the presence of hypomagnesaemia [31]. As is the case for hypomagnesaemia, hypokalaemia can induce cardiac arrhythmias (especially in patients with ischaemic heart disease and left ventricular hypertrophy).

In conclusion, the results of the present study demonstrate that during CABG, there is a significant change in serum metal ion concentration which can directly activate or inactivate antioxidant enzymes and thereby regulate the oxidative stress experienced during CABG. However, magnesium supplementation before aortic cross clamp can stabilize the plasma membrane of the myocardium and thereby mediate the protective effect.

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