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

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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 copper 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 oxidative stress mediated by ischaemic reperfusion. J Clin Basic Cardiol 2007; 10 (online): 11–5.

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

The interruption of blood supply to a tissue (ischaemia) followed by the re-establishment of oxygenation and nutrition (reperfusion) causes extensive damage to cardiac tissue like serious arrhythmias, myocvascular damage, new necrosis, mechanical stunning, and low cardiac output (CO) syndrome [1]. In clinical situations of angina, coronary vasospasm, and balloon angioplasty, ischaemic reperfusion is also encountered, however, it is not associated with contaminant myocyte cell death [2]. Various studies reported greater cardio-myocyte damage when increasing duration and severity of ischaemia, however, can develop, with a predisposition to a spectrum of reperfusion-associated pathologies [3]. Myocardial damage induced by ischaemia reperfusion is due, at least in part, to the generation of reactive oxygen species (ROS) [4] and calcium overload [5]. Often, the myocardium is equipped with an efficient antioxidant defense system to counteract the insult of ROS. The most important antioxidant systems are the superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) systems. Albumin, ceruloplasmin, ferritin, and hemoglobin, which are found in extracellular space, have antioxidant properties as well. Glutathione peroxidase has selenium [6] and the Cu/Zn superoxide dismutase system has copper and zinc in their respective structures, which diminish the harmful effects of free oxygen radicals. Moreover, different reports also suggest a positive correlation of trace element levels and the effects of antioxidant systems [7].

Trace elements like iron, copper, and zinc are abundant components of many proteins and often participate in the catalytic function of enzyme. Leakage of these metals from their stores often leads to deleterious reactions that cause tissue damage due to free radical attack. The relatively low reactive species mediated by redox-active metal ions often leads to tissue injury following ischaemia and reperfusion [8]. Recent reports on cardioprotection mediated by iron chelation therapy and metallaiontin emphasize the significant role of trace elements in tissue injury during ischaemic reperfusion. Moreover, the clinical trial report on element concentration in the heart tissue of patients with coronary artery disease [9] and coronary artery bypass graft [10] focuses on the need to reduce the increased levels of trace elements. On the contrary, increased levels of elements such as iron can catalyze the formation of reactive oxygen species through the Fenton and Haber reactions [11].

A number of clinical and in vitro studies have provided strong evidence that depletion of electrolytes such as magnesium, phosphate, and calcium can adversely affect outcome, especially in patients with cardiovascular disease. It is well known that hypokalaemia and hypomagnesaemia can induce cardiac arrhythmias, neuromuscular irritability, hypertension, and vasoconstriction (including constriction of coronary arteries) as well as metabolic effects, including decreased insulin sensitivity, all of which are extremely undesirable, especially in patients who have undergone cardiac surgery. Reports suggest that patients undergoing cardiac surgery with extracorporeal circulation are at high risk for electrolyte depletion [12]. The probable mechanism is a combination of increased urinary excretion and intracellular shift induced by a combination of extracorporeal circulation and decreased body temperature during surgery (hyperthermia-induced diuresis). Thus, as prophylactic supplementation of potassium, magnesium should be seriously considered in all patients.
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. Patients 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 captopril 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 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 succuronium was used to accomplish endotracheal intubation about 30–45 minutes prior to induction of anesthesia. Morphine (0.05 mg/kg) was given before incision and 0.15 mg/kg was added to the pump prime.

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 on (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 spectrophotometer (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 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 magnesium-treated and -untreated patients increased progressively during surgery and peaked during the revascularization period. However, the decline in TBARS late during revascularization was rapid in magnesium-treated patients as compared to the control group. Plasma antioxidant activities tend to decline in their activities as the ischaemic time increases in both magnesium-receiving and -free patients (Tab. 3). The highest activity of plasma catalase was observed in group 2, whereas the highest GPx activity was measured in group 1. 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 periods.

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 CKMB 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.
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 (ferritin, 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 mammmary 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 ischemia injury to cell death, and both are directly linked to the extent of ischemic injury [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 ischemic 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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