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Magnesium-flush Infusion into the Aortic Root Just Before Reperfusion Reduces the Requirement for Internal Defibrillation and Early Post-perfusion Arrhythmias

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Pre- and post-operative administration of magnesium has beneficial effects on post-operative ischaemia and reperfusion arrhythmias, but few studies have examined whether intra-operatively administered magnesium can prevent the effects of intra-operative arrhythmias. The aim of this randomized, double-blind study was to compare the effects of intra-operative magnesium or placebo on intra-operative arrhythmias in patients undergoing coronary bypass grafting. Patients received a flush infusion of magnesium or placebo into the aortic root before cross-clamp removal. The results showed that rate of spontaneous resumption of a cardiac rhythm was significantly higher, and number of shocks for defibrillation, energy requirement for defibrillation and rate of intra-operative ventricular tachyarrhythmias were significantly lower in the magnesium group, compared with the placebo group. The differences in need for temporary pacing, and in serum magnesium levels, were not significant. Intra-operative administration of magnesium has beneficial effects on the outcome of surgery. Larger, multicentre clinical investigations should now be undertaken.

KEY WORDS: Coronary artery bypass grafting; Cardiopulmonary bypass; Arrhythmias; Magnesium

Introduction

The most common complications of cardiopulmonary bypass (CPB) surgery are ischaemic reperfusion injury[1] and reperfusion-induced arrhythmias.[2] Ventricular and atrial arrhythmias have been recognized as common post-operative complications since the advent of coronary bypass grafting (CABG). Such complications include ventricular tachyarrhythmias, ventricular bradyarrhythmias, atrial fibrillation, atrial flutter and paroxysmal atrial tachycardia.[3]

Magnesium is often administered after surgery as prophylaxis or treatment for cardiac arrhythmias. Many reports show the beneficial effects of pre- and post-operatively administered magnesium for patients undergoing CABG,[4,5] and administration of magnesium in the cardioplegic solution

before CPB can decrease the incidence of post-operative arrhythmias.[6] Magnesium administered post-operatively by infusion also significantly reduced the incidence of atrial fibrillation in patients undergoing CABG.[7 – 10]

Potassium crystalloid cardioplegic solutions elevate intracellular calcium levels. Potassium cardioplegic infusion is, in part, associated with opening of adenosine triphosphate-activated potassium channels (K^+ATP channels) and calcium accumulation in coronary vascular smooth muscle.[11,12] Magnesium blocks the L-type calcium channels, reduces calcium loading and energy demands, and preserves myocardial metabolites.

Hypomagnesaemia increases the rate of ventricular and atrial arrhythmias and prolongs mechanical ventilatory support.[13,14] Intravenous administration of magnesium is thought to be beneficial because it decreases the incidence of ventricular arrhythmias and improves cardiac function in patients after CABG.[15] Magnesium administration also reduces the incidence of heart failure and mortality in patients after acute myocardial infarction (MI).[16]

Addition of magnesium to intermittent warm blood cardioplegia resulted in a lower incidence of intra- and post-operative arrhythmias in patients undergoing urgent CABG for unstable angina.[6] Optimum method, dose and timing of magnesium prophylaxis has not been clearly determined, however. These findings led us to hypothesize that flush administration of magnesium into the aortic root before cross-clamp removal may preserve myocardial metabolites and reduce intra-operative arrhythmias after ischaemic reperfusion.

This prospective, randomized, double-blind clinical study was designed to evaluate the effects of intra-operative flush administered magnesium on intra-operative reperfusion-induced arrhythmias, early post-operative outcomes, and serum magnesium levels in patients undergoing CABG.

Patients and methods

Patients recruited to the study were functional class III or IV, according to the New York Heart Association (NYHA) guidelines, and were undergoing an aortic coronary bypass operation because of coronary artery disease. The hospital ethics committee approved the study, and all patients gave informed consent. Patients were randomly divided into two groups: magnesium and placebo. The patients' clinical characteristics are shown in Table 1.

Exclusion criteria were: additional valvular heart disease; renal and hepatic dysfunction; repeat operation; patients in NYHA classes I or II; uncontrollable diabetes mellitus; and pre-operative hypomagnesaemia (< 1.5 mg/dl), hypocalcaemia (< 8.5 mg/dl) or hypokalaemia (< 3.5 mEq/l).

ANAESTHESIA AND OPERATIVE TECHNIQUES

All operations were performed under fentanyl anaesthesia (1.5 mg/h fentanyl by infusion and 1% inhaled isoflurane) and neuromuscular blockade was achieved using 0.15 mg/kg pancuronium bromide. Intravenous heparin (300 IU/kg) was administered immediately before cannulation for CPB and additional doses were given to maintain an activated clotting time of 480 s or faster. Cannulation of the aorta and insertion of a single two-stage cannula into the right atrium was used to initiate CPB. Non-pulsatile flow rates of 2.4 l/min per m^2 and moderate hypothermia (28 – 32 °C) were used. Cold crystalloid cardioplegia containing 16 mmol magnesium (+4 °C; Plegisol®, Abbott Laboratories, Abbott Park, IL, USA) was used for myocardial protection. Magnesium (10 ml

TABLE 1:
Clinical characteristics of the magnesium and control study groups

Characteristic	Magnesium group (n = 50[a])	Placebo group (n = 50[a])
Age (years)	64 ± 2.7	61 ± 3.2
Women/men	7/43	6/44
Body mass index	25.8 ± 2.7	26.1 ± 3.2
Bivascular disease	5	7
Trivascular disease	45	43
Number of grafts per patient	2.8 ± 0.9	2 9 ± 0.6
Mean ejection fraction	0.4 ± 1.9	0.4 ± 1.7
Poor ejection fraction (< 35%)	10	12
Unstable angina	3	4
Peri-operative myocardial infarction	0	0
Previous myocardial infarction	18	14
New York Heart Association Class		
III	37	35
IV	13	15
Euro-score	0.7 ± 1.3	0.8 ± 1.6
Diabetes	12	14
Chronic obstructive pulmonary disease	15	13
Serum magnesium levels before surgery (mg/dl)	2.3 ± 0.2	2.1 ± 0.3

[a]There were no statistically significant differences in the clinical characteristics between the two groups.

of 1.5 nmol/ml magnesium sulphate), or placebo (10 ml saline solution), was infused into the aortic root over a 30-s period, after distal anastomosis completion, and 5 min before cross-clamp removal. The membrane oxygenator and standard synthetic circuits were used for CPB.

Revascularization was achieved by grafting the internal mammary artery and saphenous veins. Distal anastomosis was completed under cross-clamping and cardiac stand still. All proximal anastomoses were performed using a partial side clamping of the aorta during CPB.

POST-OPERATIVE MANAGEMENT AND DATA COLLECTION

Post-operative ventilation was achieved with 60% oxygen by volume-controlled ventilation and a tidal volume of 10 ml/kg with 5 cm H_2O positive end expiratory pressure, in the intensive care unit (ICU). Extubation criteria were: haemodynamic stability; no excessive bleeding (< 70 ml/h); normothermia; and consciousness.

Haemodynamic measurements were made by standard radial, central venous catheterization. Serial plasma magnesium concentrations were recorded before surgery

and at 6 h and 24 h after the operation. Post-CPB inotropic agents, peri-operative MI, intra-aortic balloon pump usage and the need for temporary pacing were recorded. Operative mortality was defined as any death that occurred within 30 days of the operation. Ventilatory failure was defined as requiring mechanical ventilation for more than 48 h. Post-operative blood loss was measured as total volume retrieved through the chest drain, starting immediately after closure of the chest in the operating theatre.

The following were recorded to evaluate the effects of intra-operatively administered magnesium versus placebo: spontaneous resumption of cardiac rhythm or spontaneous defibrillation; number of shocks for defibrillation; energy required for defibrillation; ventricular tachyarrhythmias; and temporary pacing required for bradyarrhythmias after completion of CPB.

Heart rate and rhythm were continuously monitored and displayed (Artema®, Diascope Traveller, Albertslund, Denmark) during surgery and the first 24 h after surgery. Twelve-lead electrocardiograph recordings were performed before surgery, 1 h after surgery, and daily thereafter during the early post-operative days.

STATISTICAL ANALYSIS

Data were expressed as mean ± SD. Categorical variables were analysed using either the χ^2 test or Fisher's exact test. Continuous variables were compared using the unpaired Student's *t*-test. *P*-values < 0.05 were considered significant.

Results

A total of 100 patients were enrolled in the study, with 50 randomized to each group. The clinical characteristics of the two groups were similar (see Table 1), and there was no difference in mean age, body mass index, poor ventricular ejection fraction and previous occurrence of MI or MI after surgery.

Measures of effectiveness are shown in Table 2. Comparison of the findings between the two groups showed that the rate of spontaneous resumption of cardiac rhythm or spontaneous defibrillation was higher in the magnesium group than the control group ($P < 0.05$). The number of shocks for defibrillation, energy required for defibrillation and post-CPB ventricular tachyarrhythmias were lower in the magnesium-treatment group than in the control group ($P < 0.05$). No significant difference was found between the two groups for temporary pacing requirement, total blood loss, re-operation for bleeding, intubation time, length of ICU stay and length of hospital stay. At the time of cross-clamp removal, mean oesophageal probe temperature was 35 ± 0.2 °C in the magnesium group and 35 ± 0.6 °C in the control group.

In the control group, one patient died because of low cardiac output syndrome and multiorgan failure.

Serum levels of magnesium were in normal range (1.5 – 2.6 mg/dl) in all patients before the operation. The mean magnesium levels measured in the ICU are given in Table 2. According to these measurements, administration of 1.5 mmol magnesium before cross-clamp removal did not affect post-operative plasma magnesium levels as compared with the control group.

Discussion

Post-perfusion arrhythmias are the most common complications of CPB in patients undergoing CABG.[2] They increase morbidity because of post-operative haemodynamic instability, ventricular dysrhythmias and iatrogenic complications associated with treatment. Magnesium, like several other

TABLE 2:
Intra- and post-operative data for the magnesium and control groups showing the effectiveness of the treatment

Variable	Magnesium group (n = 50)	Control group (n = 50)	P-value
Spontaneous resumption of a cardiac rhythm	42 (84%)	14 (28%)	< 0.05
Number of shocks for defibrillation per patient	0.32 ± 0.6	1.4 ± 0.8	< 0.05
Mean energy required for defibrillation (J)	2.6 ± 0.7	17.4 ± 2.5	< 0.05
Post-cardiopulmonary bypass ventricular tachyarrhythmias	1 (2%)	14 (28%)	< 0.05
Post-cardiopulmonary bypass atrial fibrillation	2 (4%)	3 (6%)	NS
Post-cardiopulmonary bypass temporary pacing	0	1 (2%)	NS
Post-cardiopulmonary bypass inotropic usage	29 (58%)	32 (64%)	NS
Intra-aortic balloon pump support	3 (6%)	4 (8%)	NS
Cross-clamp time (min)	40 ± 1.6	44.4 ± 1.1	NS
Post-cardiopulmonary bypass myocardial infarction	0	0	NS
Total blood loss (mean) (ml)	850 ± 530	926 ± 480	NS
Re-operation for bleeding	0	1 (2%)	NS
Intubation time (h)	9.9 ± 4.4	10.8 ± 2.3	NS
Intensive care unit stay (days)	1.3 ± 0.7	1.4 ± 0.6	NS
Hospital stay (days)	7.9 ± 2.6	8.0 ± 3.2	NS
Serum magnesium levels after operation (mg/dl)	2.4 ± 0.4	1.9 ± 0.7	NS
Serum magnesium levels 24 h after operation (mg/dl)	2.5 ± 0.3	2.0 ± 0.6	NS

Data are presented as number of observations with percentages in parentheses, or as mean ± SD.
NS, not significant.

pharmacological agents such as amiodarone and sotalol, has been administered after surgery for prophylaxis and treatment of cardiac arrhythmias.[9] Administration of magnesium was shown to be beneficial in both animal and human models of ischaemic-reperfusion injury.[17,18] The effect that magnesium in chrystalloid cardioplegic solutions has on post-operative arrhythmias has predominantly been studied experimentally and clinically in ischaemic-reperfused hearts.[13,19,20]

Hypomagnesaemia is common after cardiac surgery, with an incidence of 70% after CPB.[20] Togashi *et al.*[21] showed that magnesium was transferred from the intra- to the extracelluar compartment during and after CPB. Hypomagnesaemia impairs release of nitric oxide from the coronary endothelium,[22] whereas magnesium administration transiently increases release of nitric oxide.[23] Changes in magnesium levels have profound effects on cellular metabolism and bioenergetics: metabolic pathways, mitochondrial ion transports, calcium channel activities in the cell membrane and reactions requiring adenosine triphosphate are all modified by changes in magnesium concentration.[24] It has also been demonstrated that serum magnesium concentration does not correlate with myocardial magnesium, and myocardial magnesium concentration was found to be lower in patients with post-operative arrhythmia than in those without.[25]

The pathogenesis and underlying mechanism of post-operative arrhythmias is not completely understood, and our limited knowledge has precluded development of specific therapies to prevent their occurrence. A variety of strategies have been proposed for pharmacological[26] and non-pharmacological therapies.[27] There are two goals of pharmacological therapy: control of the heart rate; and conversion to a sinus rhythm.

The mechanism by which magnesium reduces myocardial irritability and tachyarrhythmias is unknown. The cardioprotective effects of magnesium during ischaemia-reperfusion injury are mainly thought to arise from blocking of L-type calcium channels. This limits the influx of intracellular calcium that occurs during hyperkalaemic arrest and subsequent reperfusion.[28] Intracellular calcium accumulation in coronary smooth muscle cells is associated with derangements in coronary vasomotor tone and contractility after ischaemic cardioplegic infusion. Caputo *et al.*[3] demonstrated that supplementation of blood cardioplegia with magnesium prevented the metabolic derangements after ischaemia and reduced the reperfusion injury seen in the hearts of patients undergoing CABG. The best method of administration of magnesium has not previously been determined, however, and the dose and timing of magnesium prophylaxis require clarification.

One clinical trial suggested that magnesium supplementation of intermittent cold blood cardioplegia reduced the incidence of ventricular tachyarrhythmias but not the incidence of post-operative atrial fibrillation.[29] Yeatman *et al.*[5] reported that when magnesium was added to warm blood cardioplegia during the ischaemic period of CPB, there was a lower incidence of intra-operative and post-operative arrhythmias in patients undergoing urgent CABG for unstable angina. In contrast, Hecker *et al.*[30] reported that infusion of 0.25 – 0.375 mEq/kg magnesium before CPB did not affect spontaneous resumption of a cardiac rhythm. Caspi *et al.*,[15] however, showed that peri-operative administration of magnesium contributed to better myocardial recovery, and fewer post-operative ventricular tachyarrhythmias. These conflicting findings may be explained by differences in: the dose of magnesium; pre-operative serum magnesium levels; the methods used; and the timing of magnesium administration.

The effects of magnesium in cardioplegic solutions have been extensively studied, but few have examined the effects of direct flush infusion of magnesium during the reperfusion period. The findings of previous investigations led us to hypothesize that direct flush infusion

of magnesium just before the reperfusion period may be beneficial for early post-perfusion arrhythmias during CPB surgery.

We have shown that intra-operative direct flush infusion of magnesium into the aortic root, just before reperfusion, reduced the need for internal defibrillation, the number of shocks for defibrillation, energy required for defibrillation, and ventricular tachy-arrhythmias. This dosage of magnesium did not significantly change the serum magnesium levels during the early post-operative period. Patients are likely to benefit from further doses of magnesium, administered later, and we believe that larger serial studies are needed to investigate this.

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