Magnesium in cardioplegia: Is it necessary?

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Objective: To study the effectiveness of magnesium in cardioplegic solution in preventing postoperative arrhythmias and perioperative ischemia.

Design: Randomized, control study.

Setting: The cardiovascular surgery division of a major referral centre for the maritime provinces of Canada.

Patients: Fifty patients scheduled to undergo coronary artery bypass who had a normal ejection fraction, normal preoperative serum magnesium level and no history of atrial or ventricular arrhythmia were randomized into two groups of 25 patients. One group received magnesium sulfate (15 mmol/L) in the cardioplegic solution (group 1), the other (control) group did not receive magnesium sulfate in the cardioplegic solution (group 2).

Intervention: Coronary artery bypass grafting during which myocardial protection was provided by intermittent cold blood cardioplegia.

Outcome Measures: Postoperative serum magnesium levels, cardiac-related death, infarction and arrhythmias.

Results: All group 2 patients had a lower postoperative serum magnesium level than group 1 patients. There were no cardiac-related deaths in either group. More group 2 patients had ischemic electrocardiographic changes than group 1 patients ($p < 0.03$). Non-Q-wave myocardial infarction occurred in two patients (one in each group). Eight patients in group 2 had atrial fibrillation compared with five patients in group 1. Ventricular ectopia occurred significantly ($p < 0.01$) more frequently in group 2 than in group 1.

Conclusion: The addition of magnesium to the cardioplegic solution is beneficial in reducing the incidence of perioperative ischemia and ventricular arrhythmia in patients who undergo coronary bypass grafting.

Objectif : Étudier l'efficacité du magnésium en solution cardioplégique pour prévenir les arythmies postopératoires et l'ischémie periopératoire.

Conception : Étude cas-témoin randomisée.

Contexte : La division de chirurgie cardiovasculaire d'un important centre de consultation des provinces maritimes du Canada.

Patients : Cinquante patients qui devaient subir un pontage aortocoronarien, qui avaient une fraction d'éjection normale, un taux de magnésium sérique préopératoire normal et qui n'avaient aucun antécédent d'arythmie auriculaire ou ventriculaire ont été répartis au hasard en deux groupes de 25 patients. Ceux du premier groupe ont reçu du sulfate de magnésium (15 mmol/L) dans la solution cardioplégique (groupe 1), et ceux de l'autre groupe (témoin) n'ont pas reçu de sulfate de magnésium dans la solution cardioplégique (groupe 2).

Intervention : Pontage aortocoronarien au cours duquel le myocarde a été protégé par une cardioplégie froide intermittente.

Mesures des résultats : Taux de magnésium sérique postopératoires, décès liés à des problèmes cardiaques, infarctus et arythmies.

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RÉSULTATS : Tous les patients du groupe 2 présentaient un taux de magnésium sérique postopératoire plus faible que ceux du groupe 1. Il n'y a eu aucun décès lié à des problèmes cardiaques dans les deux groupes. Les patients du groupe 2 qui ont subi des changements électrocardiographiques ischémiques ont été plus nombreux que ceux du groupe 1 ($p < 0,03$). Deux patients (un de chaque groupe) ont subi un infarctus du myocarde non à onde-Q. Huit patients du groupe 2 ont été victimes de fibrillation auriculaire comparativement à cinq patients du groupe 1. L'ectopie ventriculaire a été beaucoup ($p < 0,01$) plus fréquente chez les sujets du groupe 2 que chez ceux du groupe 1.

CONCLUSION : L'ajout de magnésium à la solution cardioplégique aide à réduire l'incidence d'ischémie periopératoire et d'arythmie ventriculaire chez les patients qui subissent un pontage aortocoronarien.

Magnesium, a natural antagonist, has an important role in protecting the myocardium against the damaging effects of intracellular accumulation of calcium.[1–4] After potassium, magnesium is the most abundant intracellular cation. It is a cofactor in over 300 enzyme reactions involving energy metabolism and protein and nucleic acid synthesis. Parenterally administered magnesium sulfate has been used for several decades to treat supraventricular arrhythmias, digitalis-induced arrhythmias, paroxysmal ventricular tachycardia and *torsade de pointes*.[5] Recent studies showed that magnesium given intravenously during acute myocardial infarction may reduce the early death rate. The mechanism of action is still unclear but may be related to a direct cardioprotective effect. Magnesium can also improve myocardial performance after cardioplegic arrest.[1,4,6] In spite of these theoretic advantages, there is no unanimous agreement over the clinical advantages. To clarify this aspect, we evaluated the clinical benefits of adding magnesium to the cardioplegic solution used in coronary artery bypass grafting.

METHOD

The study population comprised patients referred for elective coronary artery bypass grafting who had an ejection fraction greater than 50%, a normal preoperative serum magnesium level (range from 0.69 to 0.90 mmol/L) and no electrocardiographic evidence of atrial or ventricular arrhythmia or ischemia while at rest. In this study, ventricular arrhythmia was defined as 10 or more successive ventricular beats. There were 50 patients. By a randomized, control method the patients were divided into two groups of 25 patients each. Group 1 patients were to receive a cardioplegic solution containing 13 to 15 mmol/L of magnesium sulfate. Group 2 patients, the control group, were to receive the cardioplegic solution without magnesium sulfate. The groups were well matched for age, sex, ejection fraction and number of arteries to be bypassed (Table I).

At operation, the systemic core temperature was maintained between 30° and 32 °C, and myocardial protection was provided with cold blood (10° to 14 °C) cardioplegia, delivered every 10 to 15 minutes. The cardioplegic solution consisted of one part crystalloid to four parts blood. Cardiac arrest was induced with high potassium perfusate (18 to 20 mmol/L) and maintained with low potassium perfusate (8 to 10 mmol/L). Concentrations of all other elements in the solution were the same for both perfusates (bicarbonate 32 to 36 mmol/L, calcium 0.5 to 0.7 mmol/L, sodium 125 to 130 mmol/L as a delivered concentration, pH 7.5 to 7.6).

Postoperatively the serum magnesium level was measured when the patient was arrived in the ICU and again after 24 hours. Ventricular and atrial arrhythmias in the first 24 hours postoperatively were recorded. With continuous monitoring, standard 12-lead electrocardiograms were obtained within 1 hour of operation, after

Table I

Characteristics of the 25 Group 1 Patients, Who Received Magnesium in the Cardioplegic Solution, Compared With Those of the 25 Group 2 (Control Group) Patients, Who Did Not Receive Magnesium in the Cardioplegic Solution

Variable	Group 1	Group 2
Mean (and SD) age, yr	67.2 (8.3)	64.9 (6.7)
Sex, M/F	16/9	17/8
Mean (and SD) ejection fraction, %	67.3 (15.2)	64.5 (13.4)
Mean (and SD) clamp time, min	50.2 (4.6)	49.5 (3.5)
Patients with previous myocardial infarction, no. (%)	20 (80)	18 (72)
Mean (and SD) vessels bypassed, no.	3.5 (0.26)	3.1 (0.7)
Mean (and SD) pump time, min	75.8 (1.9)	71.2 (1.5)
Patients taking calcium blockers, no. (%)	22 (88)	21 (84)
Patients taking beta blockers, no. (%)	19 (76)	17 (68)

8 hours and after 24 hours and additionally if ischemic changes or arrhythmias were noted at any time. The occurrence of myocardial ischemia and infarction was monitored intraoperatively and for the first 24 hours postoperatively. Ischemic electrocardiographic changes, including T-wave inversion, depressed ST segment and persistent or reversible bundle branch block (right or left of any degree) were used as measures of ischemic episodes.

Myocardial infarction was diagnosed on the basis of electrocardiographic changes and elevation of the MB fraction of creatine kinase isoenzyme more than 50 U/L or more than 4% of the total creatine kinase value. In patients who suffered myocardial infarction, the postoperative ejection fraction was reassessed by echocardiography and by isotope scanning wall-motion studies.

The findings, up to 24 hours postoperatively, were reported as means (and standard deviations). The mean value of the difference was analysed by the paired *t*-test and the χ^2 test. A probability value of less than 0.05 was considered significant.

Results

There was no cardiac-related death in either group for the duration of the study.

Group 1 patients had a significantly ($p < 0.001$) higher mean serum magnesium level postoperatively than group 2 patients (1.02 [0.41] in group 1 and 0.78 [0.12] in group 2 [normal range from 0.69 to 0.90 mmol/L]).

There was one non-Q-wave myocardial infarction in each group. There were significant ($p < 0.03$) global electrocardiographic changes in group 2 (Table II). They included T-wave inversion, depressed ST segment and new bundle branch block (right or left of any degree) appearing after the termination of cardiopulmonary bypass and persisting 8 hours or longer postoperatively.

Ventricular arrhythmia, including ventricular ectopia and ventricular tachycardia, occurred more frequently and significantly ($p < 0.01$) in group 2 (Table III). The ventricular ectopias that were considered significant and were recorded were those that were multifocal or unifocal in type, occurring at a rate of more than three a minute (this small number was used to increase the sensitivity of the comparison).

Although atrial fibrillation was observed more often in group 2 (eight patients) than group 1 (five patients), the difference was not significant.

Discussion

The exact role of magnesium as a cardioprotective agent is not clear. However, it is recognized increasingly as a beneficial cation in myocardial metabolism. Horner,[6] in a meta-analysis, showed that a 24-hour intravenous infusion of magnesium sulfate was clearly beneficial in the treatment of acute myocardial infarction. Reynolds and colleagues[1] showed that rat hearts preserved by a hyperkalemic cardioplegic solution containing magnesium had higher creatine phosphate concentrations and better diastolic and systolic ventricular recovery. Brown and associates[2] found that increasing the magnesium concentration in a crystalloid cardioplegic solution from 0 to 15 mmol/L resulted in significantly improved ventricular performance and preservation of adenosine triphosphate concentrations after normothermic and hypothermic ischemic arrest.

Magnesium and calcium ions are extremely important in myocardial metabolism because they are the most abundant intracellular cations, excluding potassium, and are critical to almost all intracellular reactions. Calcium ion is the main regulatory factor of the myocardial contraction apparatus, and magnesium is a cofactor of the magnesium-dependent ATPase system, which provides energy for myocardial contraction and allows the sodium-potassium membrane pumps to maintain intracellular homeostasis.[2,7] During cardiac surgery, hyperkalemia induces calcium ion entry into

Table II

Comparison of Postoperative Electrocardiographic Changes

Electrocardiographic change	Group 1, no. of patients	Group 2, no. of patients
T-wave inversion	5	13
ST-segment depression	3	10
Bundle branch block	7	14

Table III

Comparison of Postoperative Arrhythmias

Type of arrhythmia	Group 1, no. of patients	Group 2, no. of patients
Atrial fibrillation	5	8
Ventricular ectopia	9	17
Ventricular tachycardia	2	6

cells, which results in increased myocardial tension with a subsequent decrease in ATP. For this reason, adding magnesium to cardioplegic solution can antagonize the effect of calcium and prevent the loss of ATP due to contraction.[8–10] Brooks and Fry[8] studied the changes in the serum magnesium concentration during the first 24 hours after cardiac surgery. They found that ionized magnesium is significantly reduced. This reduction is not related to either the total plasma magnesium or the ionized calcium levels. Lower ionized magnesium could be an important causative factor in cardiac arrhythmia.

Other authors[5,11,12] who evaluated the effect of magnesium on cardiac arrhythmias found that magnesium administration prolongs conduction through the sinoatrial and atrioventricular nodal tissues, with no significant effect on atrial or ventricular refractory periods. This points out the possible advantage of magnesium in controlling the ventricular rate in atrial arrhythmia.

These studies and the results of our study support proposition of a beneficial cardioprotective effect of magnesium and that homeostasis of this forgotten ion is essential to ensure proper cardiac function.

Because this study was designed to test the intraoperative protective effect of magnesium, the serum magnesium level was measured immediately after operation, to reflect the relationship between the serum level and cardiac performance, and 24 hours later, to compare the decline in the magnesium level in both groups. From our findings there is a significantly higher serum magnesium level in group 1 than in group 2, and statistically this was an independent variable that could be responsible for the reduced incidence of ischemic changes and ventricular arrhythmia in group 1. The decline in the serum magnesium levels was comparable in both groups.

Our study supports other reports that recommend adding magnesium to the cardioplegic solution to reduce the incidence of perioperative ischemia and ventricular arrhythmia. Further studies are needed to specify the exact mechanism of action of magnesium and its role in atrial arrhythmia.

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