Does post-cardiac surgery magnesium supplementation improve outcome?

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Abstract. Hypomagnesemia has been linked with increased morbidity and mortality in critically ill patients. Since the condition is common after cardiopulmonary bypass surgery, the objective of this study was to determine whether magnesium supplementation in the immediate postoperative period may improve outcomes of patients undergoing cardiac surgery with cardiopulmonary bypass. This prospective, randomized, double-blind, placebo-controlled study was conducted in a third-level, cardiac surgery intensive care unit (ICU) at a university hospital. Two hundred and sixteen patients undergoing elective cardiac surgery with cardiopulmonary bypass were randomized to receive either an intravenous bolus of 1.5 g of magnesium sulphate followed by an infusion of 12 g of the same salt in 24 h (105 patients), or placebo (111 patients) administered according to the same schedule as the treatment group. No significant differences were found either in the primary end point (hours of intubation) or in the secondary end points (length of inotropic support, new atrial fibrillation, ventricular tachycardia or ventricular fibrillation, length of intensive care unit stay, or ICU or hospital mortality). Hypomagnesemia was present in 12% of patients on admission to the intensive care unit. The magnesium group had a greater need for pacemaker stimulation. In conclusion, under the conditions of the present study, magnesium supplementation after cardiac surgery with cardiopulmonary bypass does not favourably affect clinical outcomes.

Key words: cardiopulmonary bypass, magnesium, postoperative care, intubation time, arrhythmia, outcomes

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Magnesium (Mg) is the fourth most common mineral in the human organism and second among intracellular cations. It has calcium antagonist effects, is involved in the regulation of various ion channels and phosphorylation reactions, and serves as a cofactor in many enzymatic systems. Its plasma concentrations are not exactly indicative of the Mg pool in the organism and less than 1% of the total body Mg is represented by the plasma/serum levels, but it is the only widely clinically available Mg concentration determination; also the myocardial tissue levels may not correlate with the blood levels [1, 2].

In the intensive care unit (ICU) setting, hypomagnesemia has been linked with longer mechanical ventilatory suport [3, 4], more rhythm disorders, and a higher death rate [5, 6].

Mg treatment in the acute phase of myocardial infarction appeared favorable in the LIMIT-2 trial [7, 8] but the ISIS-4 trial, conducted the following year with a substantially larger sample, did not find improved clinical outcome in the group treated with Mg [9]. In the MAGIC-trial, administration of Mg to high-risk patients with acute myocardial infarction had no effect on mortality, nor did it improve clinical outcome [10].

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There is a high rate of hypomagnesemia after cardiac surgery [2, 3, 11-14], and low serum Mg levels correlates with major adverse cardiac events [15].

Mg treatment has been associated with a decrease in ventricular dysrhythmias [4]. With regard to atrial fibrillation, several studies have been conducted using Mg as a prophylactic agent following coronary artery bypass surgery. However, the results are inconsistent: some authors report that levels are maintained or suggest a small benefit [16-18], but others report a reduction in the incidence of atrial fibrillation [19-22]. The studies measured serum Mg levels, all agreeing that normomagnesaemia affords protection from arrhythmias [23].

Overall meta-analyses have shown that Mg reduces the risk of atrial fibrillation after cardiac surgery, but the trials included were heterogeneous in terms of study design [24-28]. Two of these meta-analyses [24, 26] reported no effect of Mg supplementation on hospital length of stay or on mortality.

The European Association for Cardiothoracic Surgery recommend prophylactic administration of Mg for prevention of postoperative atrial fibrillation in their guidelines [29]. However, a recent study of 927 non-emergency cardiac surgery patients concludes that the addition of prophylactic Mg to oral β-blocker did not reduce the incidence of atrial fibrillation [30]. We must also take into account that practices involving the perioperative use of Mg in adult cardiac surgery vary widely [31].

The aim of the present study was to determine whether the prophylactic administration of Mg in the immediate postoperative period of cardiac surgery may improve outcome for these patients.

Methods and materials

The prospective, randomized, double-blind, placebo-controlled study was carried out in a third level, 900-bed university hospital (Hospital Universitari de Bellvitge, Barcelona, Spain).

Before the start of the study, approval was obtained from the Ethics Committee of our hospital. Patients provided written, informed consent to participate in the study.

The study was designed and conducted entirely by the study team without industry support.

Subject population

Adult patients selected for elective cardiopulmonary bypass were included. The following exclusion criteria were applied:

1/ previous treatment with any type of Mg-containing supplementation (the week before the intervention),

2/ systolic blood pressure <100 mmHg when admitted to the ICU and not corrected in 1 h,

3/ last creatinine serum concentration prior to the intervention > 300 μmol/L,

4/ advanced atrioventricular block when admitted to the ICU,

5/ emergency cardiac surgery,

6/ off- pump cardiac surgery.

The patients were followed until hospital discharge or until death.

Anaesthetic management

The anaesthesia protocol comprised fentanyl and midazolam for induction, rocuronium or cisatracurium for myorelaxation, and midazolam, propofol or remifentanyl for anaesthesia maintenance. Inhaled anaesthesia was not used. Patients were extubated in the ICU according to standard criteria.

Surgical and cardiopulmonary bypass management

All operations followed the same protocol as regards surgical procedure, sternotomy and cardiopulmonary bypass. Myocardial protection consisted of intermittent anterograde and/or retrograde administration of cold blood cardioplegia (Abboplegisol® composition: calcium chloride 17.6 mg in 100 mL, magnesium chloride 325.3 mg in 100 mL, potassium chloride 119.3 mg in 100 mL, sodium chloride 643 mg in 100 mL) mixed with blood at a ratio of 1:4.

Study design

Two hundred and sixteen patients were enrolled in the study.

Randomization schedules were prepared by the Pharmacy department of our hospital. Patients were randomized into three blocks, depending on the type of surgery performed: coronary bypass,

valvular interventions, or other (including both coronary and valvular interventions).

Patients were allocated to two groups. On arrival in the ICU immediately after surgery, the Mg group (n = 105) received an intravenous bolus of 1.5 g of $MgSO_4$(Laboratories Lavoisier, Paris, France) over 5 min, followed by a continuous intravenous infusion of 12 g of Mg SO_4 over 24 h. On arrival in the ICU, the placebo group (n = 111) received a bolus of normal saline (0.9% NaCl), followed by a continuous intravenous infusion of normal saline over 24 h. Identical-appearing solutions were prepared by the Pharmacy staff, who were the only members of the study team who had access to the coded treatment assignments. The administration of infusions was blinded. The doses of Mg were based on the LIMIT-2 and ISIS-4 trials [7-9], the studies with the largest samples of patients with heart illness. In those trials, the doses were well-tolerated.

Serum Mg concentrations were determined on ICU admission and 6, 24 and 48 h later. Mg concentrations were determined in an automatic analyzer Modular System (Roche Diagnostics/Hitachi) by molecular absorption spectrometry with analyses at 505 and 600 nm at 37°C. We used the MG reagent (ref 1551353, Roche Diagnostics, Mannheim, Germany) and the calibrator c.f.a.s. (ref 759350, Roche Diagnostics, Mannheim, Germany). All analytical series were validated using control quality material Unassayed Chemistry 1 and 2 (ref 731 and 732, Bio-Rad Laboratories, Irvine, CA, USA), participating in the program of external quality evaluation Unit Unassayed Chemistry Control (Bio-Rad Laboratories). The measurement procedure has an interseries imprecision below 3% and its range measurement is between 0.03 and 2.0 mmol/L. The reference range of Mg concentrations in the healthy population is between 0.65 and 1.05 mmol/L.

All patients underwent continuous, bedside, ECG monitoring with automated, alarmed, arrhythmia detection and recall (Philips, modular monitoring system Agilent V24C, Andover, USA) during their stay in ICU. Twelve-lead ECG recordings were performed before surgery, at ICU admission, and daily until discharge. Each episode of arrhythmia was printed out and interpreted by an intensive care physician. Indications for pacemaker stimulation were: advanced atrioventricular blockade, bradycardia or heart rate <70 bpm symptomatic, as it is in patients who require a higher heart rate to maintain adequate cardiac output in immediate postoperative cardiac surgery. Hemodynamic variables, including arterial blood pressure, heart rate, left atrial pressure, and central venous pressure, were monitored continuously, and hourly urinary output was recorded.

The primary endpoint was intubation time;the secondary endpoints included: length of inotropic support, new atrial fibrillation, ventricular arrhythmias, or bradycardia or atrioventricular block needing the use of pacemaker, length of ICU stay, and ICU and hospital mortality.

Outcome measures

In all patients we followed the principles of "fast-track recovery", and the primary outcome was mean time to extubation (in hours) [32, 33]. Since the first description of the fast-track approach however, both the age and the incidence of comorbidities of patients undergoing cardiac revascularization with cardiopulmonary bypass have increased, as some patients undergo surgery without cardiopulmonary bypass and, above all, because a high percentage are revascularized by means of angioplasty [34]. This means that this procedure cannot be applied as often as in the past.

The secondary endpoints were the need for inotropic support, length of inotropic support in hours, according to the standard methodology [35], the appearance of new atrial fibrillation, ventricular tachycardia (sustained or paroxysmal) or ventricular fibrillation, bradycardia or atrioventricular blockade requiring the use of a pacemaker (in this respect we consider all the patients with at least one episode of the arrhythmias mentioned above or one episode of pacemaker activity), lenght of ICU stay, and ICU and hospital mortality.

We also determined the creatinine peak, delta serum creatinine (the difference between preoperative creatinine and the peak value), the appearance of renal insufficiency (increase of 50 μmol/L compared with preoperative creatinine), perioperative myocardial infarction (defined as new pathological Q waves in two or more contiguous ECG leads), troponin I peak and the oxygenation index (PaO_2/FiO_2 ratio) evolution over time.

Statistical analysis

Values of variables with repeated measures were compared using an analysis of variance for repeated measures. The Bonferroni *post hoc* test was used to find differences in the comparison between groups. Continuous variables were analyzed by means of Student's t test and categorical variables with the chi-square test. Data are expressed as % or mean ± SD. Statistical significance was set at $p < 0.05$. Analyses were carried out with SPSS 14.0 for Windows (SPSS, Inc., Chicago, IL, USA).

The size of the sample was adjusted to the study by England *et al.* [4]. In that study, in a sample of 100 patients undergoing cardiac surgery with cardiopulmonary bypass, the longer time to extubation in the placebo group compared with the Mg group produced a p value of 0.11. Applying contingency tables, we observed that if the same tendency was maintained, in a comparison between two groups of 61 patients, the p value would be <0.05.

Results

Table 1 describes the baseline and surgical characteristics of the sample. There were no statistically significant differences between the two groups, with the exception of the Parsonnet [36] and APACHE II [37] scores.

Serum Mg concentrations were significantly higher in the Mg group, especially at 6 and 24 h ($p<0.001$) (*figure 1*).

Twenty-six (12%) of the 216 patients had hypomagnesemia (<0.65 mmol/L) on ICU admission. There was a significant difference in the number of patients with hypomagnesemia in the two groups (19 in the placebo group and 7 in the Mg group, $p = 0.012$).

There were no statistically significant differences between the two groups with regard to the primary outcome (hours of intubation) or the secondary outcomes. Nor were there differences in the need for vasoactive support, or in the hours with vasoactive support, ICU stay, or mortality.

Table 1. Patients' baseline and surgical characteristics.

	Placebo group (n = 111)	**Magnesium group (n = 105)**	**p Value**
Age	62.7 ± 11.3	65.3 ± 9.3	NS
Sex (women/men) (n)	(34/77) 30.6/69.4%	(43/62) 41/59%	NS
BMI (kg/m$^{2)}$	27.9 ± 4.3	27.5 ± 4.2	NS
Smoking (n)	(56) 50.5%	(51) 48.6%	NS
Hypertension (n)	(64) 57.7%	(64) 61%	NS
Hyperlipidemia (n)	(56) 50.5%	(55) 52.4%	NS
Diabetes insulin (n)	(10) 9%	(8) 7.6%	NS
Diabetes non-insulin (n)	(22) 19.8%	(24) 22.9%	NS
Diuretic use (n)	(43) 38.7%	(52) 49.5%	NS
Beta-blocker use (n)	(58) 52.3%	(45) 42.9%	NS
Parsonnet score	8.8 ± 5.4	10.5 ± 6.3	<0.05
APACHE II score	10.6 ± 3.8	11.6 ± 3.4	<0.05
EF preop (%)	62.6 ± 11.9	60.5 ± 14.0	NS
Creat preop (μmol/L)	87.0 ± 21.5	93.4 ± 30.2	NS
Procedure			NS
Valve replacement (n)	(48) 43.25%	(47) 44.7%	NS
CABG (n)	(48) 43.25%	(45) 42.9%	NS
Both and others (n)	(15) 13.5%	(13) 12.4%	NS
Bypass time (min)	103.6 ± 34.3	111.6 ± 34.7	NS
Aortic cross-clamp (min)	67.5 ± 24.5	70.1 ± 26.5	NS

BMI = body mass index; diabetes insulin = diabetes needing insulin; EF preop = preoperative ejection fraction; creat preop = preoperative creatinine; CABG = coronary artery bypass graft.

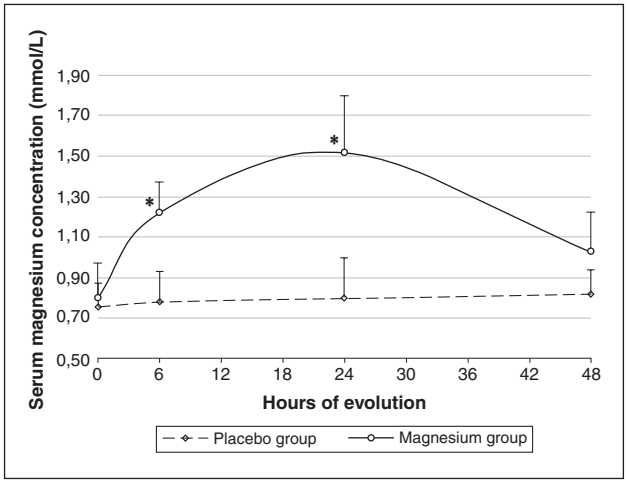

Figure 1. Serum magnesium concentration (mean values ± SE).
(* statistically significant differences between both groups, $p<0.001$).

There was one death in the ICU, due to a perioperative myocardial infarction in a patient in the Mg group. The other variables, such as perioperative myocardial infarction, troponin I peak and evolution of oxygenation index over time were similar in the two groups. The Mg group presented a higher incidence of acute renal failure (5.7% versus 2.7%), higher delta creatinine and higher creatinine peak, although the difference was statistically significant only in the last of these variables.

The incidence of new atrial fibrillation was higher in the placebo group (21.6%) than in the Mg group (15.2%), although the difference was not statistically significant. No patients had ventricular fibrillation and only two patients in each group presented ventricular tachycardia; only one cardioversion was required, and this was in the placebo group. Bradycardia (heart rate <60 per min) was present in 6.7% of the patients in the Mg group compared with 3.6% in the placebo group, and only one patient in Mg group presented advanced atrioventricular blockade; the differences were not statistically significant. The need for pacemaker stimulation was significantly higher in the Mg group ($p = 0.016$) (*table 2*).

Patients who developed new atrial fibrillation had lower serum Mg concentrations, although the differences were not statistically significant.

There was no significant difference between the placebo group and the Mg group with respect to the incidence of arrhythmias in any of the surgery groups (valve replacement, CABG and both or others).

No additional laboratory data were entered in the database except hemoglobin, haematocrit and lactate, and these did not present significant differences between placebo and Mg groups.

No adverse effects of Mg infusion were detected in any of the patients receiving the treatment.

Discussion

In this study, we found no significant differences either in the primary endpoint, the intubation time, or in the values and evolution of the oxygenation index. These findings differ from the suggestions of the England *et al.* study [4], which found non-statistically significant trends in the Mg group towards a shorter period of intubation and a lower incidence of respiratory failure; however, our study has more statistical power. Given the fact that there is no improvement in the oxygenation index, and since other studies did not find increased respiratory strength with Mg [38], the lack of modification in the intubation time seems reasonable.

With the exception of the Parsonnet and APACHE II scores, which are clinically irrelevant, the Mg and control groups did not differ significantly in terms of baseline characteristics (*table 1*).

Table 2. Postoperative data.

	Placebo group (n = 111)	Magnesium group (n = 105)	p Value
Hours intubated	13.7 ± 23.8	11.9 ± 7.5	NS
Inotropes or vasopressors (n)	(58) 52.3%	(61) 58%	NS
Hours	37.4 ± 37.8	40.8 ± 41.9	NS
PMI (n)	(12) 10.8%	(7) 6.7%	NS
Troponin I peak (μg/L)	14.0 ± 27.6	19.1 ± 102.7	NS
Acute renal failure (n)	(3) 2.7%	(6) 5.7%	NS
Delta creatinine	7.13 ± 25.67	13.59 ± 41.4	NS
Creatinine peak (μmol/L)	94.1 ± 31.1	107.1 ± 53.1	<0.05
PaO_2/FiO_2 0 h	326.4 ± 93.5	326.8 ± 90.6	NS
PaO_2/FiO_2 24 h	326.5 ± 56.4	322.0 ± 73.2	NS
PaO_2/FiO_2 48 h	318.2 ± 8.3	308.6 ± 61.3	NS
Hypomagnesemia 0 h (n)	(19) 17,1%	(7) 6,7%	<0.05
New atrial fibrillation (n)	(24) 21,6%	(16) 15,2%	NS
Hours ICU stay	78.8 ± 69.0	69.0 ± 39.9	NS
ICU mortality (n)	0	1	NS
Hospital mortality (n)	1	2	NS

PMI = perioperative myocardial infarction; PaO_2/FiO_2 = oxygenation index

The evolution of the Mg serum concentration (*figure 1*), highlights the efficacy of the Mg doses administered in increasing the availability of this cation.

The lack of differences between the two groups in terms of the percentages of patients with vasoactive support requirement and the hours of vasoactive support suggests that the possible slight increases in the cardiac index induced by Mg [4] have no substantial clinical repercussions. The similar values in the two groups for the troponin I peak and the perioperative myocardial infarction support this notion (*table 2*). We did not find outcome variables suggesting changes in myocardial contractility. As we do not have standardized measures of LVEF after the operation in all patients, we can not shed any new light in this field.

The finding that Mg has no effect on atrial fibrillation or on dangerous ventricular arrhythmias contrasts, to some extent, with previous studies [4, 20-22] carried out with other protocols, in particular including Mg administration in the operating room [11, 39, 40]. However, it is in agreement with other studies that found no improvement [16-18, 30]. In an important meta-analysis [24], Shiga *et al.* stressed the significant heterogeneity between trials with regard to supraventricular and ventricular arrhythmias, which limits the impact of their conclusions. Our study had a larger sample size than all the studies in Shiga's meta-analysis of administering Mg after surgery. Furthermore, it may be the case that studies presenting negative Mg results with regard to arrhythmias are not published, which would introduce a bias; in fact, this eventuality is suggested by the marked asymmetry of the funnel plot in the Shiga meta-analysis. The low rate of sustained ventricular arrhythmias after cardiac surgery, ranging from 0.4% to 1.4% [41], may also make any possible changes difficult to detect.

Most of the studies to prevent atrial arrhythmias in postoperative cardiac surgery patients are performed in patients undergoing CABG. There are very few studies specifically addressed towards the ability of Mg to prevent atrial arrhythmias after valvular heart surgery. Our study provides results for treatment with Mg in this type of heart surgery. The cause of atrial arrhythmias after cardiac surgery is most likely multifactorial, and some of the factors that can influence are: cardiopulmonary bypass and aortic cross-clamp, myocardial ischemia and reperfusion, local inflammatory reaction, excessive catecholamine. . ., all common in CABG and valve replacement. In any case, in our study there was no significant difference between the placebo

group and the Mg group with respect to the incidence of arrhythmias in any of the surgery groups.

Probably a 24-h Holter monitoring could have some potential advantages for detecting cardiac arrhythmias, but the system employed -Agilent, Philips- maintains all the ECG register in the memory and an automated alarm system; all records throughout the study period were reviewed.

The significant increase in the need for pacemaker stimulation in the Mg group is very probably related to the cation's calcium antagonist effects [1] and the high serum Mg concentrations reached. This does not have negative repercussions in these patients – all of whom are connected to the pacemaker – but it may be dangerous in other patients.

Our study showed a slight increase in the creatinine peak in the Mg group. This has not been previously reported, but it does not seem to be clinically relevant.

The absence of any repercussion of Mg administration on ICU and hospital mortality or on length of stay has been reported elsewhere [24, 26]. Nevertheless, as mortality rates after cardiac surgery are very low, we cannot exclude possible differences.

In our study, 12% of patients had hypomagnesemia immediately after cardiac surgery, a finding similar to other studies [3, 4, 22, 39]. Previous research has shown a strong relationship between lower postoperative plasma Mg levels and the development of new postoperative atrial fibrillation [21, 39, 42-44]. The slight increase in atrial fibrillation in the placebo group in our study, although not statistically significant, is perhaps attributable to the fact that this group had more patients with hypomagnesemia on ICU admission.

The immediate infusion of Mg or placebo at ICU admission in the present study, just at the end of surgery, made it unlikely that the lack of Mg effects was caused by a relatively late start of Mg supplementation.

Limitations of this study: 1/ The small size of the sample with hypomagnesemia limited the possibility of drawing conclusions regarding this subgroup. 2/ The fact that serum Mg concentration does not reflect the intracellular concentration of Mg. 3/ Only 43% of the study population were patients undergoing isolated CABG, probably the group that can expect greater benefits from Mg. 4/ Perhaps a more specific arrhythmia detector, such as a Holter, would have highlighted additional changes. 5/ We did not enter all concomitant medications received by the two groups of patients into the database: this could have potentially impacted the outcomes. 6/ The lack of standardized measurement of LVEF after cardiac surgery.

In conclusion, Mg supplementation after cardiac surgery involving cardiopulmonary bypass, under the conditions of the present study, does not favorably affect clinical outcomes.

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Disclosure

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