Prophylactic Intravenous Magnesium Sulphate in Addition to Oral β-Blockade Does Not Prevent Atrial Arrhythmias After Coronary Artery or Valvular Heart Surgery

A Randomized, Controlled Trial

Richard C. Cook, MD, MSc; Karin H. Humphries, DSc; Kenneth Gin, MD; Michael T. Janusz, MD; Richard S. Slavik, PharmD; Victoria Bernstein, MD; Mats Tholin, MD; May K. Lee, MSc

Background—Atrial arrhythmias (AA) are an important cause of morbidity after cardiac surgery. Efforts at prevention of postoperative AA have been suboptimal. Perioperative beta-blocker administration is the standard of care at many centers. Although prophylactic administration of magnesium sulfate (MgSO₄) has been recommended, review of all previously published trials of MgSO₄ reveals conflicting results. This study was designed to address methodological shortcomings from previous studies and is the largest randomized, placebo-controlled trial of intravenous (IV) MgSO₄ for the prevention of AA after coronary artery bypass grafting or cardiac valvular surgery.

Methods and Results—A total of 927 nonemergent cardiac surgery patients were stratified into 2 groups: isolated coronary artery bypass grafting (n=694), or valve surgery with or without coronary artery bypass grafting (n=233), and randomized to receive either 5g IV MgSO₄ or placebo on removal of the cross-clamp, followed by daily 4-hour infusions, from postoperative day 1 until postoperative day 4. All patients were treated according to an established oral β-blocker protocol. Postoperative serum Mg levels were checked and standard of care was to administer IV MgSO₄ for low serum levels. The primary end point was AA lasting ≥30 minutes or requiring treatment for hemodynamic compromise. There were no differences in the incidence of AA between patients who received IV MgSO₄ or placebo (26.4% versus 24.3%, respectively). The results were similar when broken down according to stratified groups.

Conclusions—In patients treated with a protocol for postoperative oral β-blocker after nonemergent cardiac surgery, the addition of prophylactic IV MgSO₄ did not reduce the incidence of AA. (Circulation. 2009;120[suppl 1]:S163–S169.)

Key Words: atrial fibrillation • coronary artery bypass surgery • magnesium • prevention • tachyarrhythmias

Atrial arrhythmias (AA) continue to affect up to 50% of patients after cardiac surgery, with patients undergoing valvular surgery experiencing a higher rate of AA than those undergoing isolated coronary artery bypass grafting (CABG). Numerous studies have demonstrated that postoperative atrial fibrillation (AF) is associated with prolonged length of hospital stay, greater risk of major morbidity, and increased overall costs. More importantly, recent studies have found up to a 2.3-fold increased risk of stroke in patients with postoperative AF. In terms of the effect of postoperative AF on survival, Villareal et al recently published results of the long-term follow-up of patients with postoperative AF (mean 4 years). Actuarial survival at 4 years in the postoperative AF group was 74% versus 87% in non-AF CABG patients (P<0.001).

In the adjusted analysis, the OR for mortality was 1.5 (95% CI, 1.26–1.77) for postoperative AF compared to the non-AF population. Because of the potentially increased risk of death and stroke, and because patients with recurrent or persistent AA require additional medications, including systemic anticoagulation, physicians and surgeons have been actively searching for effective strategies to reduce the incidence of postoperative AA.

Of the many different strategies studied to date, β-blockade has the most robust evidence to support its use for the prevention of postoperative AF. Multiple studies and a meta-analyses of 27 randomized, controlled trials have demonstrated that β-blocker therapy reduces the risk of AF.
by up to 61% compared to placebo. As a result, routine administration of β-blockade after CABG has become the standard of care at many institutions, including ours. Unfortunately, β-blockade alone is still associated with a 20% to 30% incidence of postoperative atrial arrhythmias²⁴; therefore, further improvements are needed.

Although magnesium sulfate (MgSO₄) is now thought to be useful for the treatment of AF,⁸,⁹ its role in preventing postoperative AF is more controversial. MgSO₄ is attractive because of its low cost, ease of administration by peripheral intravenous (IV) device, and its excellent safety profile when administered slowly.¹⁰⁻¹⁹ It is also attractive from a theoretical standpoint, because serum Mg levels have been shown to decline after cardiopulmonary bypass and do not recover to preoperative levels until 3 to 5 days after surgery, which coincides with the period during which most cases of AF develop.¹¹

Many small, randomized trials of MgSO₄ for prevention of AF have been published, and a recent meta-analysis concluded that MgSO₄ is an effective prophylactic agent for prevention of postoperative AF,²⁰ with the European Association for Cardiothoracic Surgery recommending prophylactic administration of IV MgSO₄ for prevention of postoperative AF in their recently published guidelines.²¹ Regardless, we believe that there is still clinical equipoise regarding its routine use because the evidence comes from multiple small, underpowered trials, with conflicting results, probably because of differences in study design.²² Furthermore, there have been no studies that have specifically addressed the ability of MgSO₄ to prevent AA after valvular heart surgery.

Against this background, we thought that there was a need to undertake a large, adequately powered, clinical trial of a large dose of IV MgSO₄, using a conservative definition of AA, in a setting of routine administration of β-blockade to assess the ability of IV MgSO₄ to reduce AA after cardiac surgery in the current era.

Materials and Methods

This was a prospective, double-blind, randomized trial of IV MgSO₄ versus IV saline in patients undergoing nonemergent first-time cardiac surgery at 2 institutions (Vancouver General Hospital and St. Paul’s Hospital) in Vancouver, British Columbia, Canada. Patients were enrolled from April 7, 2003 to October 12, 2007. In addition, all patients were treated with oral β-blockade (atenolol), according to a standardized protocol (Appendix A). The primary outcome was the incidence of postoperative AA, defined as AA lasting ≥30 minutes, or causing hemodynamic compromise requiring immediate intervention. Secondary outcomes included the following: incidence of new major neurological event (transient ischemic attack or cerebrovascular accident), perioperative mortality, and hospital length of stay. The study was approved by the University of British Columbia ethics committee on human research, as well as the ethics committees of Vancouver General Hospital and St. Paul’s Hospital. A data and safety monitoring board was assembled and reviewed the results on a regular basis. A single interim analysis at the midpoint of study recruitment (n=625), using the Haybittle-Peto stopping rule (P<0.001), was planned. The results are reported according to the Consolidated Standards of Reporting Trials checklist.¹²² The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Exclusion Criteria

Exclusion criteria included the following: emergent surgery (within 12 hours); procedures involving major aortic repair; permanent, persistent, or paroxysmal AF or flutter, or paroxysmal supraventricular tachycardia on current treatment with an antiarrhythmic; permanent atrial pacemaker; second-degree or third-degree A-V (aventricular) block; serum creatinine >200 μmol/L or oliguric and anuric renal failure, including all dialysis-dependent patients; subjects scheduled for off-pump surgery; subjects intolerant of β-blockers; and subjects with reactive airways disease requiring regular β-adrenergic agents such as salbutamol.

Protocol

Eligible patients were stratified at 2 participating hospitals (Vancouver General Hospital and St. Paul’s Hospital) to 1 of 2 groups: patients undergoing isolated CABG (CABG group), and patients undergoing valve surgery, with or without CABG (valve with or without CABG group). A programmer at the Canadian HIV Trials Network at St. Paul’s Hospital prepared randomization lists blocked by study site and stratum using permuted blocks of 4. The lists were inputted into a randomization computer. When a site coordinator identified an eligible, consenting patient, the site’s pharmacist was contacted to request randomization. Using their individual authorization code, each site’s pharmacist called the computer and keyed in the appropriate answers about patient eligibility and consent, after which time the computer issued a study identification number and treatment allocation. The respective pharmacy departments prepared the appropriate blinded IV solutions for the patients. The central computer also stored the proceedings of the randomization transaction, including information about the time of randomization, date of birth of the patient, and initials of the caller. Patients, surgeons, and the members of the events committee, who assessed the ECG recordings for evidence of AA, were all blinded to the treatment group.

After receiving informed consent, subjects were randomized before surgery (1:1) to receive 5 g IV MgSO₄ (MgSO₄ group) or IV saline (control group) bolus by the anesthesiologist on removal of the aortic cross-clamp. On postoperative days 1 through 4, subjects received either IV MgSO₄ (5 g in 250 mL normal saline) or IV placebo (250 mL normal saline) infusion over 4 hours daily. Patients stopped receiving the protocol drug if the primary end point occurred. Treatment of AA was according to the discretion of the treating physician.

Anesthetic Technique

The anesthetic technique at both hospitals was standardized to fast-track anesthesia. This included anesthetic induction with fentanyl 10 to 15 μg/kg or sufentanil 1 to 1.5 μg/kg, and midazolam 0.15 to 0.35 μg/kg, with sodium thiopental 1 to 2.5 mg/kg to loss of consciousness. Anesthesia was maintained with isoflurane 0.5% to 2% end-tidal in air/oxygen. After removal of the aortic cross-clamp, propofol 25 to 50 μg/kg per minute IV was initiated for up to 4 to 6 hours postoperatively until criteria for discontinuation from mechanical ventilation and early extubation were met.

Operative Technique

All operations were performed through a standard median sternotomy. Only those patients expected to have surgery with cardiopulmonary bypass were enrolled in this study. All operations were performed on arrested hearts using either warm or cold blood cardioplegia (in a ratio of 4:1 to 6:1 blood:crystalloid) run intermittently in an antegrade or retrograde fashion. Thirty-two mEq of Mg (4 g MgSO₄) was added to each liter of cardioplegia crystalloid solution because this was the standard of care at both institutions. Arterial cannulation was via the ascending aorta, with single venous cannulation via the right atrium, or bicaudal cannulation in the case of mitral valve surgery. All patients had temporary ventricular pacing wires placed at the end of surgery. The placement of temporary atrial pacing wires was at the discretion of the operating surgeon.
Postoperative Monitoring
All patients were monitored with continuous portable ECG monitoring (telemetry) for the first 5 postoperative days. Serum Mg levels were routinely checked in the cardiac surgical intensive care unit (CSICU) on arrival in the CSICU. The standard of care was to administer 2 g IV MgSO₄ for serum levels $\leq 1.2$ mmol/L or 5 g IV MgSO₄ for serum levels $\leq 0.8$ mmol/L.

Statistical Analysis
Descriptive summaries are presented as counts and proportions for categorical variables, and medians (first and third quartiles) for continuous variables. For the primary end point (AA) and the secondary end point (AA/death), the difference in the proportions between the treated and control arm were tested using the $\chi^2$ test. The primary analysis was an intention-to-treat analysis and all patients randomized were included. The per-protocol analysis was performed as a censored analysis (including patients until the study medication was stopped because of a medical reason, early discharge, death, or AA starting). Patients were excluded from the per-protocol analysis if the CABG procedure was changed to an off-pump procedure, the preoperative creatinine exceeded 200 $\mu$mol/L, the patient underwent concomitant major aortic surgery, or the bolus or IV infusions were not administered as specified. For the per-protocol analysis, the estimated probability and 95% confidence limits of developing AA by 4 days postoperatively is based on the Kaplan-Meier method, and the comparison between groups is tested using the log-rank test.

For the comparison of operative details, postoperative medication use, length of stay, and postoperative serum Mg levels, the 2 arms of the study were compared using the $\chi^2$ test for categorical variables. The nonparametric Kruskal-Wallis test was used for continuous variables.

Multiple logistic regression was used to adjust for concomitant variables in post hoc analysis to report the OR and associated 95% confidence limits.

All statistical analyses were performed as 2-sided tests with a significance level of 0.05 using the statistical analysis software SAS (version 9; SAS Institute, Inc, Cary, NC).

Determination of Sample Size
For our sample size calculations, we assumed the proportion of placebo patients developing postoperative AF after isolated CABG would be 30%. The proportion in the valve with or without CABG was assumed to be 40%. These figures were chosen after reviewing British Columbia Cardiac Registry data over the time period April 1994 to March 1999, during which time the average incidence of AA after isolated CABG was determined to be 37%, and the average incidence of AA in the valve with or without CABG group was 48%. These rates were felt to be high because the timeframe predates the routine use of $\beta$-blockade in these patients. The sample size for the study was based on a test of proportions using the arcsin transformation.

For the difference between treatments to be clinically credible, we felt it would be necessary to show an absolute difference close to 10%. The sample size calculation was based on a 2-tailed $\alpha$ of 0.05, power of 0.80, and a relative risk reduction of 30%. Sample sizes were adjusted by 2% to allow for loss to follow-up. Whereas the study was powered at 80% for each of the strata, the power for the overall assessment (CABG and valve with or without CABG groups combined) was 97.8%. This is based on 621 per group and expected proportions of 0.34 versus 0.24 in the placebo and treatment arms, respectively.

Results
The flowchart detailing screening, recruitment, and analysis of patients is provided in Figure 1. The patient characteristics and intraoperative times are summarized in Table 1. There were no differences between patients receiving MgSO₄ and...
those receiving placebo for any of these factors. The preoperative medications, serum Mg levels, incidence of open-label MgSO\textsubscript{4} use, and rate of postoperative \beta-blocker use are summarized in Table 2. Of note, 77\% of the patients were using an oral \beta-blocker preoperatively, with 69\% of the patients in both groups using a statin as well. The rates of preoperative \beta-blockade and statin use were higher in the CABG group of patients. Also, it is notable that the median serum Mg levels for both groups were on the low end of normal preoperatively (normal range 0.7–1.1 mmol/L), although not all patients had serum Mg levels available before surgery.

On an intention-to-treat basis, there was no difference for the primary end point (AA lasting at least 30 minutes, or causing hemodynamic compromise requiring immediate treatment) between the MgSO\textsubscript{4} (26.4\%) and control (24.3\%) groups overall, or by type of surgery, as shown in Figure 2. Because of the small number of events for the secondary outcomes, the results for both strata were pooled to compare between the MgSO\textsubscript{4} and control patients. There were no differences observed between groups for any of the secondary outcomes (Figure 3); however, the study was not powered to detect differences in these outcomes. With respect to median length of stay, there were also no differences between MgSO\textsubscript{4} (median, 6 days; quartile 1, 5 days; quartile 3, 8 days) and control (median, 6 days, quartile 1, 5 days; quartile 3, 7 days; \(P=0.46\)).

There were a total of 250 patients (27.0\%) who did not receive all of the doses of the study medication according to Table 1.
Consequently, significantly more patients in the control group received open-label MgSO₄ in the CSICU than the MgSO₄ group (Table 2). As well, rate of postoperative β-blocker use differed significantly between the MgSO₄ and control groups (Table 2). A second post hoc analysis was therefore performed to adjust for the use of open-label MgSO₄, and postoperative β-blocker use in a multiple logistic regression model to test for a difference between treatment groups for the primary outcome of AA developing within 4 days of surgery. All patients were included in the logistic model except for 4 cases because of missing data. After adjusting for open-label MgSO₄ and postoperative β-blocker use, there was still no significant difference between groups for the risk of postoperative AA (OR, 0.98; 95% confidence limits: 0.71, 1.35; P=0.88).

**Discussion**

The key finding of this study was that IV MgSO₄, in addition to routine β-blockade with oral atenolol, did not reduce the incidence of AA after nonemergent cardiac surgery. This result was contrary to the findings of a recent meta-analysis, which concluded that administration of supplemental Mg was associated with an 18% incidence of postoperative AA, compared to 28% in the control group.²⁰ Our study was powered to detect a 30% relative decrease in incidence of AA, from a predicted absolute incidence of 30%. However, there was essentially no difference in the rate of AA between the treatment arms and the control arms, with a very slight and nonsignificantly higher incidence of AA in the patients treated with MgSO₄. This result was stable even after controlling for protocol violations and the use of open-label MgSO₄.

Although the meta analysis by Miller et al²⁰ concluded that prophylactic administration of Mg is effective for prevention of AF after CABG, only 5 of the 20 studies included in the analysis were clearly in favor of Mg administration,¹²,¹⁴,¹⁶,²³ with 7 studies showing no reduction in AF with Mg prophylaxis.¹⁰,¹³,¹⁵,¹⁷,²⁴–²⁶ In addition, newer randomized studies published since 2002 have had conflicting outcomes (some positive,²⁷,²⁸ and others negative,²⁹,³⁰). There are 4 potential reasons for these differing outcomes, including: (1) the potential for β error secondary to small sample sizes; (2) differing definitions of atrial fibrillation; (3) differing doses of MgSO₄ administered; and (4) differing use of concomitant β-blockade. Our trial attempted to address these issues and therefore differed from most of the earlier studies of prophylactic Mg administration in several important ways.

First, our trial is the largest of its kind, with more than twice as many patients in each arm as the next nearest study, which had 200 patients in each arm.¹⁸ Most of the other trials had 50 to 60 patients in each arm, with 1 having as few as 9 patients in 1 arm.²⁰

Second, compared to other randomized trials, we had a relatively strict and conservative definition of AA (lasting ≥30 minutes on telemetry or associated with hemodynamic compromise requiring immediate therapy). Other randomized studies have had varying definitions of AA, ranging from any episode of AF lasting ≥30 seconds to any episodes of AF requiring treatment because of symptoms or hemodynamic

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**Figure 2.** Percentage of the MgSO₄ and control patients with a documented episode of atrial arrhythmia within 4 days after surgery, by surgery type and overall.

**Figure 3.** Percentage of MgSO₄ and control patients experiencing a prespecified secondary end point. AA/death indicates atrial arrhythmia or death within 4 days after surgery; CVA/TIA, in-hospital cerebrovascular accident or transient ischemic attack; death, in-hospital death.
Although there may have been a number of patients in our study who had shorter episodes of AA that were not deemed to be important according to our definition, we deliberately chose a definition of AA that we thought would be clinically important.

Third, the amount of Mg administered in our study was larger than most other studies (25 g MgSO₄ or 100 mmol Mg total) and occurred over a longer period of time (4 days postoperatively) than most of those same studies. This was performed to maximize the possible effect of supplemental Mg and to prevent a falsely negative outcome attributable to underdosing of Mg. Despite aggressive dosing, there were no adverse events that could be attributed directly to MgSO₄. Hypotension was the only event that may have been attributable to MgSO₄, but it occurred in 11.2% and 11.0% of the MgSO₄ and control patients, respectively (P=0.90).

Fourth, and perhaps most importantly, not all previous studies have used, or controlled for, concomitant β-blockade. This may have been reasonable in older studies before the evidence for the importance of β-blockade in the prevention of AA had accumulated; however, we felt we could not ignore the effect of β-blockade in the current era.

Finally, this is the first study to our knowledge to evaluate patients undergoing valvular heart surgery separately from those undergoing isolated CABG.

The data and safety monitoring board was allowed to review the data once, as set out in the study protocol, at the midway point of patient enrolment. At that time, they determined that there was no difference in the incidence of AA between the 2 treatment regimens and modeling confirmed this finding would not be altered even if the study continued to full enrollment. The data and safety monitoring board therefore recommended that the study be stopped. However, the investigators requested that the study be continued until enough patients had been enrolled into the CABG arm of the study to be certain that the negative result would not be ascribed to a β-type error.

**Limitations**

Unfortunately, several patients did not receive all of the doses of MgSO₄ according to the protocol. Therefore, in addition to the intention-to-treat analysis, a second analysis was performed, in which only patients who were treated according to the protocol were included. This analysis yielded the same results; therefore, we are confident that the findings of our study are robust.

Another potential confounding factor was the use of open-label Mg, both in the cardioplegia and in the CSICU. In the case of cardioplegia, the addition of Mg is the standard of care at our institution, and several of the participating surgeons did not feel comfortable removing it. Although this may have been a confounding factor, given the results of a recently published study, it found that patients receiving Mg in their cardioplegia, the effect of our study would have been consistent in all patients irrespective of randomization. The decision was made to allow for open-label Mg in the CSICU because serum Mg levels are routinely checked in the CSICU, and many staff members were uncomfortable with leaving patients with untreated hypomagnesemia. However, adjustment for open-label use did not alter the relationship between treatment and the development of AA.

**Conclusions**

This prospective randomized trial of MgSO₄ for the prevention of postoperative atrial arrhythmias after nonemergent CABG or valvular heart surgery showed no difference in the rate of clinically important atrial arrhythmias between patients receiving a large dose of IV MgSO₄ or placebo over a 4-day postoperative period. This study differs from most previously published studies in that both MgSO₄ and control patients were treated according to a standardized oral β-blocker protocol, in keeping with current recommendations for prophylaxis of postoperative atrial arrhythmias. Both intention-to-treat and per-protocol analyses yielded the same results. Therefore, we believe that this trial offers the most definitive evidence against the prophylactic administration of IV MgSO₄ for prevention of atrial arrhythmias after nonemergent CABG or valvular cardiac surgery when oral β-blockers are routinely administered.

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**Disclosures**

None.

**Appendix A: Protocol for β-Blocker Administration**

Start Atenolol 12.5 mg PO/NG on Post-op Day 0, and then Q AM thereafter titrated as below.

- Titrate atenolol therapy by doubling the atenolol dose daily until target heart rate of 60–70 beats per minute (bpm) is achieved, or maximum daily dosage of 200 mg/day.
- Physician to assess patient and write daily atenolol order until target HR achieved.
- Withhold atenolol and notify physician if patient is receiving inotropes or vasopressors, HR <50 bpm, SBP <90 mm Hg, PR interval >280 msec, or if the patient is being paced.

If the patient has been on inotropes or vasopressors, start atenolol on the day they are discontinued.

**References**


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