Published in final edited form as:

Anesth Analg. 2015 October ; 121(4): 861–867. doi:10.1213/ANE.0000000000000873.

Intraoperative Magnesium Administration Does Not Reduce Postoperative Atrial Fibrillation After Cardiac Surgery

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The authors declare no conflicts of interest.

Reprints will not be available from the authors.

DISCLOSURES:

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Abstract

Background—Hypomagnesemia has been associated with an increased risk of postoperative atrial fibrillation (POAF). While earlier studies have suggested a beneficial effect of magnesium (Mg) therapy, almost all of these are limited by small sample size and relatively low Mg dose. We hypothesized that high-dose Mg decreases the occurrence of new-onset POAF, and we tested this hypothesis using data from a prospective trial assessing the effect of Mg on cognitive outcomes in cardiac surgical patients.

Methods—A total of 389 patients undergoing cardiac surgery were enrolled in this double-blind, placebo-controlled trial. Subjects were randomized to receive Mg as a 50 mg/kg bolus immediately after induction of anesthesia followed by another 50 mg/kg as an infusion given over 3 h (total dose 100 mg/kg) or placebo. The effect of Mg therapy on POAF was tested with logistic regression, adjusting for the risk of AF using the Risk Index for Atrial Fibrillation after Cardiac Surgery.

Results—Among the 363 patients analyzed, after excluding patients with chronic or acute preoperative AF (Placebo: n=177, Mg: n=186), the incidence of new-onset POAF was 42.5% (95% CI: 35 – 50%) in the Mg group compared to 37.9% (95% CI: 31 – 45%) in the placebo group (p=0.40). The 95% confidence interval for this absolute risk difference of 4.6% is –5.5% to 14.7%. The time to onset of POAF was also identical between the groups, and no significant effect of Mg was found in logistic regression analysis adjusting for AF risk (odds ratio 1.09 with 95% CI 0.69 – 1.72, p=0.73).

Conclusions—High-dose intraoperative Mg therapy did not decrease the incidence of new-onset POAF after cardiac surgery.

Introduction

New-onset postoperative atrial fibrillation (POAF) is a common complication of cardiac surgery. The incidence ranges between 27–63%, with the highest risk seen in combined coronary artery bypass graft (CABG) and valve surgery.^{1–3} POAF has a peak incidence on postoperative day 2⁴ and is associated with several adverse outcomes, including increased cardiovascular, renal, and cerebral complications; increased cost of care and resource utilization; and decreased long-term survival.^{1,5–8}

Hypomagnesemia has been associated with an increased risk of AF, both after cardiac surgery^{9,10} and in ambulatory settings.^{11,12} Hypomagnesemia is believed to promote AF through a variety of mechanisms, including effects on atrioventricular conduction, action potential duration, and the atrial effective refractory period.¹³ Specifically, in isolated rabbit hearts, magnesium (Mg) produces a significant and consistent prolongation of the atrial effective refractory period,¹³ thereby reducing myocardial excitability. Furthermore, Mg decreases the rate of diastolic depolarization of sinoatrial pacemaker cells.¹⁴ The interaction between surgical stress-induced sympathetic hyperactivity and Mg also appears to be important. The high concentration of norepinephrine released perioperatively promotes the efflux of Mg from cells,¹⁵ altering cardiomyocyte excitability and automaticity. Thus, the administration of Mg may attenuate sympathoadrenal-mediated arrhythmias.^{16,17}

While several trials and meta-analyses have suggested a beneficial effect of Mg administration in preventing POAF,^{18–21} many of these studies were limited by small sample size, relatively low Mg dosage, and an inability to account for concomitant medications known to influence POAF. We hypothesized that high-dose Mg decreases the occurrence of new-onset POAF, and we tested this hypothesis using data from a prospective trial assessing the effect of Mg on cognitive outcomes in patients undergoing cardiac surgery.

Methods

Study Design

This study is a secondary analysis of a prospective, double-blind, randomized trial of IV Mg versus saline that was designed to evaluate neurocognitive outcomes, as previously published.²² The primary outcome for the current analyses was the incidence of new-onset POAF of any duration. Data relevant to this outcome were prospectively collected during the original clinical trial.

With approval from the Duke University Health System Institutional Review Board and written informed consent, 389 patients scheduled to undergo CABG, valve, or CABG plus valve surgery with cardiopulmonary bypass (CPB) were enrolled in this prospective, randomized, double-blind, placebo-controlled clinical trial. Exclusion criteria included planned circulatory arrest, history of symptomatic cerebrovascular disease (e.g., stroke with residual deficit), psychiatric illness (e.g., any clinical diagnosis requiring therapy), renal failure (defined as serum creatinine >2 mg/dL), hepatic insufficiency (defined as aspartate aminotransferase and/or alanine aminotransferase >1.5x the upper limit of normal), higher

alcohol consumption (defined as >2 drinks/day), inability to read, less than a seventh-grade education, or score of <24 on baseline Mini Mental State examination. Enrolled subjects were randomized to receive either Mg, as a 50 mg/kg bolus over 20 min after the induction of anesthesia followed by another 50 mg/kg infused over 3 h (for a total dose of 100 mg/kg), or placebo (normal saline administered as a bolus and identical volume and duration infusion to the Mg group to preserve blinding). A group assignment schedule was prepared using a randomization function in SASTM (Statistical Analysis System; SAS Institute Inc., Cary, NC, USA) and stored in consecutively numbered sealed envelopes until allocation. Randomization occurred prior to surgery after confirming the procedure type and planned use of CPB.

The patient's ECG was continuously monitored after surgery with telemetry monitoring until hospital discharge. POAF was diagnosed by telemetry or 12-lead ECG and was defined as a supraventricular tachycardia with the absence of distinct p-waves and irregular R-R intervals.²³ POAF was considered new-onset if it occurred postoperatively at any time prior to hospital discharge.

Patient Management

Anesthesia was induced with midazolam and fentanyl and maintained with isoflurane. All patients underwent nonpulsatile, hypothermic (30–32°C) CPB with a membrane oxygenator and arterial line filter via a pump primed with crystalloid. Serial hematocrit levels were maintained at 0.21. Patients were heparinized (300–400 U/kg) to a target activated coagulation time of >480 s prior to the initiation of CPB. Pump flow rates of 2–2.4 L•min⁻¹•m² were maintained throughout CPB to maintain a mean arterial pressure of 50–80 mmHg. Arterial blood gases were measured every 15–30 min to maintain PaCO₂ at 35–40 mmHg unadjusted for temperature (α -stat) and PaO₂ at 150–250 mmHg.

Preoperative and daily postoperative medication therapy was also recorded. The standard of care postoperatively was to administer 4 g of MgSO₄ IV for serum levels 1.8 mg/dl or 2g of MgSO₄ for serum levels 1.8 – 2.0 mg/dl.

Laboratory Assessments

In the first 121 patients, blood was sampled at baseline, on admission to the intensive care unit, and at 24 h and 48 h after the initial bolus for the measurement of serum Mg levels. Subsequently, to enhance patient safety, an additional blood sample was obtained immediately after the Mg bolus dose.

Statistical Analysis

Categorical and continuous demographic data were compared between the groups with χ^2 test, Wilcoxon rank-sum, or *t* test, as appropriate. The primary analyses were conducted according to the intention-to-treat principle. Descriptive summaries are presented as counts and proportions for categorical variables and mean $\pm$ standard deviation for continuous variables. For the primary endpoint of the incidence of POAF, the effect of magnesium administration was evaluated using the χ^2 test. A logistic regression model was pre-specified to test the effect of magnesium treatment and to account for the risk of developing AF using

the Risk Index for Atrial Fibrillation after Cardiac Surgery score, as previously described,¹ and subsequently modified to include preoperative statin use (Table 1). Briefly, from a derivation cohort of 3093 patients, associations between predictor variables and postoperative atrial fibrillation were identified to develop a risk model, which was subsequently assessed in a validation cohort of 1564 patients. Risk factors associated with atrial fibrillation were advanced age, history of atrial fibrillation, valve surgery and postoperative withdrawal of a beta-blocker or an angiotensin-converting enzyme inhibitor. Conversely, reduced risk was associated with postoperative administration of beta-blockers, ACE inhibitors, statins, potassium supplementation and nonsteroidal anti-inflammatory drugs. To develop relative weights for the predictors in the Multicenter Study of Perioperative Ischemia risk index, the parameter estimates of the final logistic model were multiplied by 10 and rounded to the nearest integer. The relative weight was then assigned to each binary predictor as well as to each age category (10-year increments). The risk score for each patient was calculated by summing the relative weights across the predictors present for a particular patient. The low risk group contained scores below 14 (25th percentile); the medium risk group contained scores between 14 and 31 (25th to 75th percentile); and the high risk group contained scores higher than 31 (75th percentile).

The linear regression model used to evaluate the primary endpoint included an interaction test and a quadratic test of the assumption of linearity between the AF risk index and the logit linearity of AF risk; linearity was also verified by inspection of AF proportions in deciles of risk. Model fit was assessed with the Hosmer-Lemeshow test. All analyses were performed with SASTM version 9.3 (SAS Institute Inc., Cary, NC, USA); $p < 0.05$ was considered significant.

In the parent trial, we expected that the incidence of cognitive deficits in patients undergoing cardiac surgery would be $\approx 40\%$. We hypothesized that magnesium treatment would decrease this incidence to 25%, and a sample size of 170 per group would yield power of 80% at a significance level of 0.05 to detect this difference. To allow for a 15% loss to follow-up, we intended to recruit a total of 400 patients. Since the sample size was determined by the parent trial, additional power analyses related to new-onset POAF were not conducted.

Results

A CONSORT diagram detailing the screening, recruitment, and analysis of patients is presented in Figure 1. Prior to the analysis, 14 patients who received placebo and 11 patients who received Mg were excluded because of documented preoperative cardiac rhythm other than normal sinus rhythm (i.e., both acute AF and chronic persistent AF), leaving 177 patients in the placebo group and 186 patients in the Mg group for final analysis. Patient characteristics and pertinent intraoperative details are summarized in Table 2. As expected from randomization, there were no statistically significant differences between the Mg and placebo groups with respect to demographic characteristics, although there was a trend towards more females in the placebo group. Preoperative Mg levels were not different between the two groups. After the bolus dosing, serum Mg levels were significantly higher in the Mg treatment group at all time-points (Figure 2).

There was no difference in the proportion of patients with new-onset POAF between the Mg group (42.5%, 95% confidence interval [CI], 35 – 50%) and the placebo group (37.9%, 95% CI, 31 – 45%; $p=0.40$). In a secondary “as-treated” analysis, 5 placebo patients were reassigned to the Mg group, but once again there was no difference in the incidence of POAF (Mg 41.4%, 95% CI, 34–48% vs. Placebo, 39.0%, 95% CI, 32–46%; $p=0.64$). Of these 5 placebo patients reassigned to the Mg group for the “as-treated” analysis, 1 had been incorrectly randomized and the other 4 had received magnesium (2 g) intraoperatively for the management of ventricular arrhythmias. The proportion of patients receiving other medications known to have an association with AF (either with AF risk or those medications used as treatment for AF) preoperatively and postoperatively, but prior to the onset of AF, was not different between patients receiving Mg compared to placebo (Table 3). Finally, there was no difference between treatment groups with regard to duration of POAF (Mg: 2 [1–4] days vs. Placebo: 2 [1–4] days; $p=0.91$), time to onset of POAF (Mg: 2 [2–3] days vs. Placebo: 2 [1–3] days; $p=0.71$), recurrence of atrial fibrillation (mg: 44.3% vs. Placebo: 40.3%; $p=0.63$) or in the rate of atrial fibrillation at discharge (Mg: 7.2% vs. Placebo: 10.7%; $p=0.54$).

The AF risk index score, reported as (median, mean $\pm$ SD), was similar between the treatment groups (Mg: 14, 16.5 $\pm$ 11 vs. Placebo: 13, 14.8 $\pm$ 11; $p=0.142$). As expected, the AF risk index score was different between patients who did (20, 21 $\pm$ 13) and those who did not (12, 12.0 $\pm$ 9) develop postoperative AF ($p<0.0001$). The interaction between treatment groups and risk level for AF was also not significant (Low Risk – Mg: 30.7% vs. Placebo: 23.0%, $p=0.23$; Medium Risk – Mg: 46.2% vs. Placebo: 51.6%, $p=0.52$; High Risk – Mg 80.0% vs. Placebo 84.6%, $p=0.40$). Finally, no significant effect of Mg on POAF was found in logistic regression analysis adjusting for the AF risk score (Mg treatment odds ratio 1.09 with 95% CI 0.69 – 1.72, $p=0.73$, area under the ROC curve, 0.72). The Hosmer-Lemeshow test for goodness of fit was non-significant for lack of fit ($p=0.51$).

Discussion

In this prospective, randomized, double-blinded, placebo-controlled study of the administration of IV Mg versus saline during adult cardiac surgery with CPB, we found that systemic, high-dose intraoperative Mg therapy did not reduce the incidence of new-onset POAF.

Mg has several antiarrhythmic properties that make it a good pharmacologic candidate for the prevention and treatment of arrhythmias.^{24,25} Consistent with these electrophysiologic actions, Mg administration has been shown in several clinical studies to significantly improve the rate of chemical^{26–28} and electrical cardioversion²⁹ of atrial arrhythmias. Investigations of Mg prophylaxis for the prevention of POAF in the context of cardiac surgery appeared to confirm these beneficial results.^{18–21} However, several of these studies were limited by small sample size, improper blinding, and the use of a lower dose of Mg than in the current study. In fact, by combining studies on Mg prophylaxis in CABG surgery that were properly blinded and with sufficient patient sample sizes, Hazelrigg et al.³⁴ failed to find an overall reduction in postoperative atrial or ventricular arrhythmias. Cook et al.³⁵ were also unable to demonstrate a difference in the rate of clinically important atrial

arrhythmia in patients receiving Mg versus placebo in addition to routine beta-blockade. Most of these studies, however, had not adequately adjusted for the confounding effects of beta-blockers, ACE inhibitors, statins, potassium, and non-steroidal anti-inflammatory drugs. In our randomized, placebo controlled, double-blind study, despite adjusting for all relevant medications given prior to the onset of POAF, we also could not find a benefit for intraoperative Mg administration in preventing POAF after cardiac surgery.

Hypomagnesemia is common after cardiac surgery, and it is standard practice to correct the deficit with IV Mg. However, serum ionized Mg levels do not necessarily reflect intracellular levels, and the equilibration between tissue compartments and intracellular concentrations is often a slow process.²⁴ Thus, serum Mg is a poor marker of intracellular magnesium homeostasis, and its administration has unproven effects on tissue and intracellular levels of Mg.³⁰ Moreover, although patients with arrhythmias have been shown to have a relative deficiency in intracellular Mg,^{24,27} the dose and duration of treatment required to adequately restore intracellular Mg concentrations is not known. Importantly, the timing of prophylactic Mg therapy has been variable among studies and may represent a critical factor in the success or failure of this intervention. A previous meta-analysis indicated that lower doses of Mg (defined as mean cumulative dose of 8.2 g) are more effective than moderate-to-higher doses (mean cumulative dose of 15 g) in reducing postoperative AF.³² In our study, we administered a combination of a bolus dose plus infusion to achieve a total cumulative Mg dose of 100 mg/kg (mean dose of 8.4 g). This dosing produced statistically significantly higher serum Mg concentrations at all measured time points when compared to patients who received placebo. The immediate and postoperative serum levels achieved in our study were similar to those achieved by Cook et al.³⁵ Although statistically higher than placebo, the difference in the mean serum concentration of Mg between our treatment and placebo groups fell to a mean of 0.27 mg/dL by 24 h [Mg, 2.31 ± 0.38 mg/dL vs. Placebo, 2.04 ± 0.33 mg/dL] and 0.15 mg/dL by 48 h [Mg, 2.25 ± 0.30 mg/dL vs. Placebo, 2.10 ± 0.25 mg/dL] differences that are not likely to be clinically significant. In fact, with the peak incidence of POAF occurring around day 2, the minimal elevation in serum Mg in the treatment group at 48 h may partially explain the lack of benefit in preventing POAF. However, Cook et al.³⁵ extended their treatment to postoperative day 4 and were still unable to reduce the incidence of POAF.

Sympathetic activation is postulated to be a mechanism underlying POAF.³³ It has been hypothesized that Mg exerts a prophylactic effect by inhibiting adrenergic-mediated automaticity. However, there is a discrepancy in the time course of sympathetic activation and POAF, with the peak of sympathetic activation occurring around 24 h postoperatively whereas the peak in the onset of POAF occurs between 2 and 4 d postoperatively.³⁴ The inflammatory response induced by cardiac surgery, however, has a time course that more closely mirrors that of POAF.^{35,36} The apparent efficacy of specific anti-inflammatory drugs, particularly statins and colchicine,^{37,38} in reducing the incidence of POAF, combined with the failure of Mg and other modulators of sympathetic hyperactivity to fully prevent POAF³⁹ suggest that the pursuit of inflammatory mechanisms of POAF may be more fruitful.

The primary limitation of this study is that it is a secondary analysis of a prospective trial designed to evaluate neurocognitive outcomes in the setting of intraoperative high-dose Mg administration. As such, the administration of postoperative medications that are potentially relevant to POAF was not standardized, although we did not see a difference between groups in the preoperative or postoperative administration of relevant medication. Furthermore, we recorded all medications administered prior to the onset of POAF, and thus, unlike prior studies, we are able to more accurately account for the temporal relationships between all (i.e., not just beta-blockers) medication therapy and POAF. A second limitation is that our intervention was limited to the intraoperative period. It is possible that high-dose Mg therapy extended into the postoperative period could alter the occurrence of POAF. However, a standardized postoperative magnesium treatment protocol was used, and we note that the Mg levels were statistically higher in the treatment group. Finally, our definition of new-onset POAF included POAF of any duration and may have been too liberal. We therefore repeated the analysis in the cohort of patients (n=340) who received treatment for POAF (i.e. “significant” AF). In this subgroup, once again, the incidence of POAF did not differ between the treatment groups (Mg: 21% vs Placebo: 15%, adjusted p=0.33).

Although many pharmacological approaches to preventing atrial fibrillation after cardiac surgery have been investigated,^{40,41} the studies evaluating Mg have yielded mixed results. We found that, despite significantly higher Mg levels in the intraoperative and immediate postoperative period, high-dose intraoperative Mg therapy did not decrease the incidence of new-onset POAF. Considering the high incidence of AF after cardiac surgery and its potential for significant short- and long-term morbidity, especially embolic stroke, further investigation into preventative strategies is warranted. Given the presumptive multifactorial etiology of POAF, its effective prevention will likely require a multimodal pharmacologic approach.

Acknowledgments

Funding: This work was supported in part by grants HL069081 (Dr. Newman), HL096978, HL108280, and HL109971 (Dr. Mathew) and grant M01-RR-30 from the National Institutes of Health, Washington, DC, and by the Division of Cardiothoracic Anesthesiology and Critical Care Medicine, Department of Anesthesiology, Duke University Medical Center, Durham, NC.

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Figure 1.
CONSORT diagram showing the flow of study participants.

Figure 2. Serum concentration of magnesium at the five measurement time-points. Data are mean $\pm$ SD. *P<0.001.

Table 1**Modified Risk Index for Atrial Fibrillation after Cardiac Surgery**

Predictor	Incidence of Postoperative AF No./Total (%)	Risk Score	OR (95% CI)	P Value
Age, y				
< 30	0	0	1.74 (1.58 – 1.92)	<0.001
30–39	2/36 (5.6)	6		
40–49	19/229 (8.3)	12		
50–59	160/795 (20.1)	18		
60–69	378/1145 (33.0)	24		
70–79	377/817 (46.1)	30		
80	40/68 (58.8)	36		
Medical history				
Atrial fibrillation	142/268 (53.0)	7	2.04 (1.52 – 2.75)	<0.001
Chronic obstructive pulmonary disease	137/320 (42.8)	4	1.42 (1.09 – 1.86)	0.010
Concurrent valve surgery	154/286 (53.9)	5	1.67 (1.25 – 2.23)	<0.001
Withdrawal of treatment				
Beta-blockers	396/784 (50.5)	7	1.95 (1.55 – 2.46)	<0.001
ACE-I	320/692 (46.2)	5	1.65 (1.34 – 2.02)	<0.001
Preoperative and postoperative treatment				
Beta-blockers	228/1289 (17.7)	–7	0.50 (0.39 – 0.62)	<0.001
ACE-I	126/626 (20.1)	–5	0.61 (0.48 – 0.78)	<0.001
Statins	128/665 (19.3)	–5	0.58 (0.46 – 0.74)	<0.001
Postoperative Beta-blockers	51/228 (17.7)	–11	0.32 (0.22 – 0.46)	<0.001
Other treatment				
Potassium supplementation	774/2688 (28.8)	–5	0.62 (0.49 – 0.79)	<0.001
NSAIDs	173/934 (18.5)	–7	0.50 (0.41 – 0.62)	<0.001

OR, odds ratio; ACE-I, angiotensin-converting enzyme inhibitor; NSAID, nonsteroidal anti-inflammatory drug.

Table 2

Characteristics of the subjects allocated to treatment with magnesium versus placebo.

Variable	Magnesium (n = 186)	Placebo (n = 177)	P Value
Age (SD), y	68.2 (8.3)	67.8 (7.9)	0.68
Sex, % female	26.3	35.6	0.06
Race, % white	81.2	75.1	0.16
Weight (SD), kg	83.6 (14.5)	81.2 (15)	0.12
History of hypertension, %	80.7	80.1	0.90
Diabetes mellitus, %	36.8	34.7	0.68
Previous MI, %	32.2	31.6	0.89
Ejection fraction (SD)	52.4 (11.8)	52.9 (12.8)	0.46
Magnesium level at baseline (SD)	1.92 (0.24)	1.89 (0.27)	0.16
Surgical procedure, %			0.94
CABG	80.7	79.7	
CABG+valve	14.5	14.7	
Valve	4.8	5.7	
Redo surgery, %	0.5	0.0	0.99
Number of grafts	3.2 (1.2)	3.1 (1.3)	0.56
Cross-clamp time (SD), min	82.8 (33.5)	81.2 (33.9)	0.45
CPB time (SD), min	134.8 (49.4)	132.8 (52.7)	0.46

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass

Table 3

Perioperative Medication Administration

Variable	Magnesium (n = 186)	Placebo (n = 177)	P value
Medications given <u>before</u> AF onset			
Beta-blocker preop but not postop, %	16.1	10.7	0.13
Beta-blocker preop and postop, %	51.1	50.9	0.97
Beta-blocker postop only, %	22.6	26.6	0.38
ACE-I preop but not postop, %	43.6	35.0	0.10
ACE-I preop and postop, %	12.4	18.1	0.13
Statin preop and postop, %	38.7	37.3	0.78
Potassium postop, %	81.2	83.6	0.54
NSAID or COX-2 inhibitor postop, %	19.4	17.0	0.55

All results were analyzed with the chi-square test. AF, atrial fibrillation; ACE-I, angiotensin-converting enzyme inhibitor; NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase.