SPECIAL ARTICLE

Magnesium Prophylaxis for Arrhythmias after Cardiac Surgery: A Meta-analysis of Randomized Controlled Trials

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BACKGROUND: Magnesium supplementation may reduce the incidence of arrhythmias, which often occur after cardiac surgery; however, recent findings of the effectiveness of magnesium prophylaxis have yielded discrepant results.

METHODS: We searched electronic databases for randomized controlled trials of magnesium for the prevention of arrhythmias after cardiac surgery. The primary outcomes comprised the incidence of supraventricular and ventricular arrhythmias, and the secondary outcomes comprised serum magnesium concentration, length of hospital stay, myocardial infarction, and mortality. Effect sizes were estimated using a random-effects model.

RESULTS: Seventeen trials (n = 2069 patients) met the inclusion criteria. Pooled serum magnesium concentration at 24 hours after surgery in the treatment group was significantly higher than that in the control group (weighted mean difference = 0.45 mmol/L [1.1 mg/dL]; 95% confidence interval [CI]: 0.30 to 0.59 mmol/L [0.7 to 1.4 mg/dL]; $P < 0.001$). Magnesium supplementation reduced the risk of supraventricular arrhythmias (relative risk [RR] = 0.77; 95% CI: 0.63 to 0.93; $P = 0.002$) and ventricular arrhythmias (RR = 0.52; 95% CI: 0.31 to 0.87; $P < 0.0001$), but had no effect on the length of hospital stay (weighted mean difference = −0.28 days; 95% CI: −0.70 to 1.27 days; $P = 0.48$), the incidence of perioperative myocardial infarction (RR = 1.03; 95% CI: 0.52 to 2.05; $P = 0.99$), or mortality (RR = 0.97; 95% CI: 0.43 to 2.20; $P = 0.94$).

CONCLUSION: Administration of prophylactic magnesium reduced the risk of supraventricular arrhythmias after cardiac surgery by 23% (atrial fibrillation by 29%) and of ventricular arrhythmias by 48%. Supplementation had no notable benefit with respect to length of hospitalization, incidence of myocardial infarction, or mortality. **Am J Med. 2004;117:325–333.**

Arrhythmias, which may be multifocal, occur frequently after cardiac surgery. Atrial arrhythmias develop in 11% to 40% of patients after coronary artery bypass grafting and in more than 50% of patients after valvular surgery (1), and can prolong hospital stay by 3 to 5 days (2,3), with substantial cost implications (3). Further, they are a major cause of morbidity during the postoperative period. Thromboembolism caused by atrial tachyarrhythmias, particularly atrial fibrillation, can have neurologic consequences. The risk of stroke during the postoperative period in patients who develop atrial fibrillation is twice that of those without atrial fibrillation (1,2). In contrast, fatal ventricular arrhythmias are rare (incidence of 0.41% to 1.4%) after cardiac surgery (4), but patients with sustained ventricular arrhythmia after surgery have a poor prognosis, with a reported in-hospital mortality rate of up to 50% (4). Postoperative atrial fibrillation also increases the risk of postoperative ventricular arrhythmia or fibrillation by twofold (2).

Recent reviews have cited beta-blockers (5), class III antiarrhythmic agents (5), and calcium antagonists (6) as effective pharmacologic interventions for the prevention of atrial fibrillation or supraventricular arrhythmias. Digitalis has not been recommended despite favorable results shown in individual studies (7). Magnesium supplementation is a promising option for reducing the risk of supraventricular arrhythmias, including atrial fibrillation. Hypomagnesemia is common following cardiac surgery because the initiation of extracorporeal circulation during surgery may dilute the circulating blood volume, and because the use of diuretics during and after surgery may promote urinary excretion of magnesium (8). Magnesium supplementation may suppress arrhythmias by multiple mechanisms, including the alteration of atrioventricular conduction, modulation of calcium influx through L-type calcium channels, or protection from reperfusion injury (9–11). However, these mechanisms are not fully understood. Recent studies of the use of pro-

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Manuscript submitted September 29, 2003, and accepted in revised form March 4, 2004.

phylactic magnesium for preventing arrhythmias have yielded conflicting results (12–14), probably due to inadequate statistical power, and thus questions remain with regard to patient morbidity and mortality.

METHODS

Literature Search

We searched the literature for all reports of randomized controlled trials that tested the effects of prophylactic magnesium, compared with that of treatments without magnesium, on the development of arrhythmias after cardiac surgery. Trials were identified from MEDLINE (1966 through June 2003), EMBASE (1980 through June 2003), and the Cochrane Central Register of Controlled Trials (Issue 3, 2003). No language restrictions were applied. The initial search terms were *magnesium*, *arrhythmia*, *dysrhythmia*, and *cardiac surgery*, filtered by *randomized controlled study*. A manual search of references from reports and reviews was also performed.

Selection Criteria and Quality Assessment

Our inclusion criteria were as follows: prospective, randomized, single- or double-blind design; use of magnesium alone as treatment; inclusion of a control group (placebo or routine care); sufficient data to calculate dichotomous outcome; magnesium administration via any possible route (intravenous, central, or intracoronary); and use of a single, fixed dose of magnesium.

Assessment of the methodological quality of the included studies was carried out by two independent investigators (TS and ZW). Disagreements were resolved by consensus. Each study was assessed using the 5-point scale introduced by Jadad et al (15), which examines randomization, double-blinding, withdrawals, and dropouts. Briefly, if the study was described as randomized, 1 point was assigned. If the randomization process was appropriate, an additional point was assigned. If the randomization was inappropriate (e.g., allocation by date of birth), the original point was lost. One point was assigned if a study was described as blinded. If the blinding method was appropriate, an additional point was assigned. Finally, 1 point was assigned if a study described the number of, and reasons for, withdrawals and dropouts. The maximum possible score was 5.

Data Extraction and Outcome Measures

We extracted information on patient characteristics, surgery, dose, route of magnesium administration, incidence of supraventricular arrhythmias (including atrial fibrillation) and ventricular arrhythmias, adverse effects, length of hospital stay, mortality, and incidence of myocardial infarction. Data were extracted by two independent investigators (TS and ZW). Disagreements or uncertainties were resolved by consensus. When results were not presented in the original paper in a dichotomous form, attempts were made to obtain additional data from the authors. Where these data were not available, the trials were excluded from the meta-analysis.

Primary outcomes of the studies included the incidence of atrial fibrillation, supraventricular arrhythmia, or ventricular arrhythmia. We defined supraventricular arrhythmia as atrial fibrillation, atrial flutter, atrial tachycardia, or supraventricular tachycardia. Ventricular arrhythmia was defined as ventricular tachycardia (sustained or paroxysmal) or ventricular fibrillation. Atrial and ventricular extrasystole, bigeminy, and couplets were excluded from our definition because they were considered lower degrees of arrhythmia and thus clinically irrelevant. The observation period for supraventricular or ventricular arrhythmia started from the declamping of the aorta to the end of the follow-up period as indicated in each study.

Secondary outcomes included serum magnesium concentration on postoperative day 1 in each group, length of hospital stay, incidence of myocardial infarction, and mortality. We extracted the data for serum magnesium concentration and length of hospital stay if they were reported as means $\pm$ SD or SEM.

Statistical Analysis

Treatment effects for dichotomous and continuous outcomes were expressed as relative risks or weighted mean differences. These effect sizes were estimated using a random-effects model (16). When there were no outcomes in one or both groups, 0.5 was added to each cell of the respective contingency table. Homogeneity of effect size across trials was tested using the Cochran Q test. Sensitivity analyses were performed to identify sources of heterogeneity when significant; this was based on methodological quality according to the Jadad score.

To assess the potential for publication bias, a funnel plot was constructed in which the log of relative risks was plotted against associated SEs (17). In addition, a rank correlation of the association between standardized log relative risks and associated SEs was performed with the Kendall correlation coefficient. The correlation between sample size and relative risk would be high if small studies with null results were less likely to be published (17). A significant correlation between sample size and relative risk would not exist in the absence of publication bias. Statistical significance for treatment effects was defined by $P < 0.05$, heterogeneity was defined by $P < 0.1$, and publication bias was defined by $P < 0.1$. Analyses were performed using Number Cruncher Statistical System 2004 (NCSS Statistical System, Kaysville, Utah).

RESULTS

Of the 28 trials identified, 11 failed to meet our inclusion criteria and were excluded. Three had no control group

(18–20), four had no randomized design or the randomization process was unclear (21–24), one had insufficient data (no dichotomous outcome) (25), one did not use magnesium as prophylaxis (26), one did not report details on supraventricular or ventricular arrhythmias (27), and one had nonspecific data for which we attempted to contact the authors but received no response (28). Thus, 17 randomized controlled trials were included in our analysis (Table). The median Jadad score was 4 (range, 1 to 5).

Effect of Magnesium on Arrhythmias

The mean (± SD or SEM) serum magnesium concentrations at 24 hours after surgery were given for 11 trials (12,13,29–36,41). Pooled serum magnesium concentrations at 24 hours after surgery in the treatment group were significantly higher than that in the control group (weighted mean difference = 0.45 mmol/L [1.1 mg/dL]; 95% confidence interval [CI]: 0.30 to 0.59 [0.7 to 1.4 mg/dL]; $P < 0.001$; P for heterogeneity < 0.001).

Sixteen trials (n = 2029 patients) evaluated the use of magnesium for the prevention of supraventricular arrhythmias (Figure 1). Supraventricular arrhythmias occurred in 234 of 1014 patients in the magnesium group compared with 312 of 1015 patients in the control group (relative risk [RR] = 0.77; 95% CI: 0.63 to 0.93; $P = 0.002$), with significant heterogeneity among trials ($P = 0.08$).

Ten trials evaluated the use of magnesium for the prevention of ventricular arrhythmias, yielding a total of 1195 patients (Figure 2). Ventricular arrhythmias occurred in 36 of 596 patients in the magnesium group compared with 79 of 599 patients in the control group (RR = 0.52; 95% CI: 0.31 to 0.87; $P < 0.0001$; P for heterogeneity = 0.08).

In the sensitivity analysis involving atrial arrhythmia (Figure 3), atrial fibrillation occurred in 161 of 826 patients in the magnesium group compared with 227 of 823 patients in the control group (RR = 0.71; 95% CI: 0.55 to 0.93; $P = 0.003$). Heterogeneity did not improve among studies ($P = 0.04$).

Treatment effects did not appear to be affected by the quality of the trials. Sensitivity analysis showed that for 12 trials that were considered to be of high quality (Jadad score ≥3), the relative risk for supraventricular arrhythmias was 0.75 (95% CI: 0.61 to 0.93; $P = 0.002$; P for heterogeneity = 0.07); and for 7 trials, the relative risk for ventricular arrhythmias was 0.46 (95% CI: 0.23 to 0.90; $P = 0.001$; P for heterogeneity = 0.05).

Outcome and Adverse Effects

Seven trials (n = 1227) reported the length of hospital stay (12,14,30,34,39–41). The weighted mean difference in length of hospital stay between the magnesium and control groups was 0.28 days (95% CI: −0.70 to 1.27 days; $P = 0.48$), with significant heterogeneity among trials ($P < 0.0001$). Nine trials (n = 1191) reported the incidence of myocardial infarction (13,29–31,33,36,39,40,41). Myocardial infarction occurred in 12 of 601 patients in the magnesium group and in 11 of 590 patients in the control group. Magnesium showed no significant benefits in preventing myocardial infarction (RR = 1.03; 95% CI: 0.52 to 2.05; $P = 0.99$), with homogeneity among trials ($P = 1.00$). Twelve trials reported mortality, yielding a total of 1588 patients (12,13,29–31,33,34,36,38–41). Mortality occurred in 7 of 794 patients in the magnesium group and in 8 of 794 patients in the control group. Magnesium had no effect on mortality (RR = 0.97; 95% CI: 0.43 to 2.20; $P = 0.94$), with no homogeneity among trials ($P = 0.98$).

Five trials comprising 648 patients (27% of the patients in the meta-analysis) studied the prevalence of side effects (12,14,34,35,38). No severe bradycardia or hypotension was reported. Only one trial (38) reported cardiac arrest in the magnesium group, but it is uncertain whether magnesium was responsible for that event.

Publication Bias

There was marked asymmetry of the funnel plot, confirmed by a significant Kendall correlation coefficient of −0.47 for supraventricular arrhythmias ($P = 0.01$), suggesting the presence of publication bias. No evidence of publication bias was found in the analysis of ventricular arrhythmias (Kendall correlation coefficient: −0.38, $P = 0.14$).

DISCUSSION

The incidence of supraventricular arrhythmias following coronary artery bypass is 11% to 40% (1), and the incidence is higher in patients who have valvular surgery alone or combined with coronary artery bypass (1,4). Atrial fibrillation is the most common arrhythmia, with a prevalence of 17% to 33% in patients undergoing coronary artery bypass surgery (43). In our analysis, most patients underwent elective coronary artery bypass grafting alone. The incidence of supraventricular arrhythmias was 31% and the incidence of atrial fibrillation in the control group was 27%, which corresponds well with the general prevalence. Therefore, the external validity of the results appears to be confirmed. We also believe that the internal validity of the results is confirmed because our meta-analysis focused only on randomized controlled trials, and quality assessment of included trials was performed according to the recommendation of Jadad et al (15).

A large-scale meta-analysis has shown that a variety of β-adrenergic antagonists reduce the risk of atrial fibrillation by about 60% (5). In our analysis, magnesium reduced the risk of atrial fibrillation by 29%. The number of patients needed to be treated to prevent atrial fibrillation by prophylactic magnesium would be higher, and thus its

Table. Summary of Randomized Placebo-Controlled Trials Meeting the Inclusion Criteria

First Author (Reference)	Jadad Score	Type of Surgery	Participants				Magnesium Supplementation (Route)	Regimen of Magnesium Administration*	Follow-up (days)
			Magnesium Group		Placebo Group				
			Mean Age (years)	Number (M/F)	Mean Age (years)	Number (M/F)			
Fanning (29)	4	Coronary artery bypass with cardiopulmonary bypass	59	49 (35/14)	62	50 (39/11)	Magnesium sulfate (IV)	22.3 mmol over the first 4 postoperative days	4
England (30)	5	Coronary artery bypass, valve replacement, or both combined	60.3	50 (29/21)	62.2	50 (34/16)	Magnesium chloride (IV)	2 g after the termination of cardiopulmonary bypass	1
Colquhoun (31)	4	Coronary artery bypass with cardiopulmonary bypass	57.1	66 (55/11)	58.7	64 (51/13)	Magnesium chloride (IV)	50 mmol during the first 48 h after surgery	1
Parikka (32)	2	Coronary artery bypass with cardiopulmonary bypass	57	69	54	71	Magnesium sulfate (IV)	40 mmol during the first 24 h and 30 mmol during the next 24 h	4
Caspi (33)	4	Coronary artery bypass with cardiopulmonary bypass	60	50 (34/16)	62	48 (38/10)	Magnesium sulfate (IV)	16 mmol continuously from the anesthetic induction to aortic cross-clamping, and 32 mmol until 24 h later	3
Karmy-Jones (34)	3	Coronary artery bypass, valve replacement, or both combined	64.5	46 (28/18)	60.2	54 (38/16)	Magnesium sulfate (IV)	Six doses (9.6 mmol) in the first 24 h after surgery	1
Nurozler (35)	2	Coronary artery bypass with cardiopulmonary bypass	56.3	25 (23/2)	53.6	25 (23/2)	Magnesium sulfate (cardioplegia and IV)	16 mmol/L in cardioplegia, 50 mmol on the first operative day and 12.5 mmol per day from second to fifth days	5
Shakerinia (36)	1	Coronary artery bypass with cardiopulmonary bypass	67.2	25 (16/9)	64.9	25 (17/8)	Magnesium sulfate (cardioplegia)	13 to 15 mmol/L of cardioplegic solution	1
Jensen (37)	4	Coronary artery bypass with cardiopulmonary bypass	61	29	61	28	Magnesium sulfate (IV)	110 mmol after operation until the next 3 days	3
Treggiari-Venzi (38)	5	Coronary artery bypass with cardiopulmonary bypass	65	47 (42/5)	65	51 (43/8)	Magnesium sulfate (IV)	Immediately after surgery, 72-h infusion (16 mmol/24 h)	3

Table. Continued

First Author (Reference)	Jadad Score	Type of Surgery	Participants				Magnesium Supplementation (Route)	Regimen of Magnesium Administration*	Follow-up (days)
			Magnesium Group		Placebo Group				
			Mean Age (years)	Number (M/F)	Mean Age (years)	Number (M/F)			
Bert (39)	4	Coronary artery bypass with normothermic cardiopulmonary bypass	62.7	63 (56/7)	63.6	60 (50/10)	Magnesium sulfate (IV)	48 mmol from termination of cardiopulmonary bypass to the first 4 postoperative days	4
Toraman (14)	4	Coronary artery bypass with moderate hypothermic cardiopulmonary bypass	62	100 (78/22)	61.4	100 (83/17)	Magnesium sulfate (IV)	6 mmol on the day before surgery, and once daily for 4 days after surgery	5
Fortani (40)	3	Coronary artery bypass with cardiopulmonary bypass	64	54 (46/8)	64	50 (44/6)	Magnesium sulfate (IV)	6 mmol/d for 5 days starting just before cardiopulmonary bypass	30
Wilkes (13)	5	Coronary artery bypass with cardiopulmonary bypass	63.2	43 (32/11)	61.1	42 (33/9)	Magnesium sulfate (IV)	13.4 mmol (mean) for 1 day	3
Yeatman (41)	3	Coronary artery bypass with cardiopulmonary bypass	62.9	200 (157/43)	63.8	200 (166/34)	Magnesium sulfate (cardioplegia)	5 mmol in cardioplegic solution	3
Jian (42)	2	Repair of ventricular septal defect	4.6	20	5.1	20	Magnesium sulfate (cardiopulmonary bypass prime solution)	0.25 mmol/kg at initiation of cardiopulmonary bypass	1
Kaplan (12)	2	Coronary artery bypass with cardiopulmonary bypass (100 [50/50]) and without cardiopulmonary bypass (100 [50/50])	57.6	100 (76/24)	59.9	100 (74/26)	Magnesium sulfate (IV)	12.2 mmol preoperatively, perioperatively, and on postoperative days 0, 1, 2, and 3	2

* To convert units of g and mEq to mmol, the following conversions were used; 1 g = 8 mEq = 4 mmol for $MgSO_4$, and 12.15 mg = 1 mEq = 0.5 mmol for Mg^{2+}.
F = female; IV = intravenous; M = male.

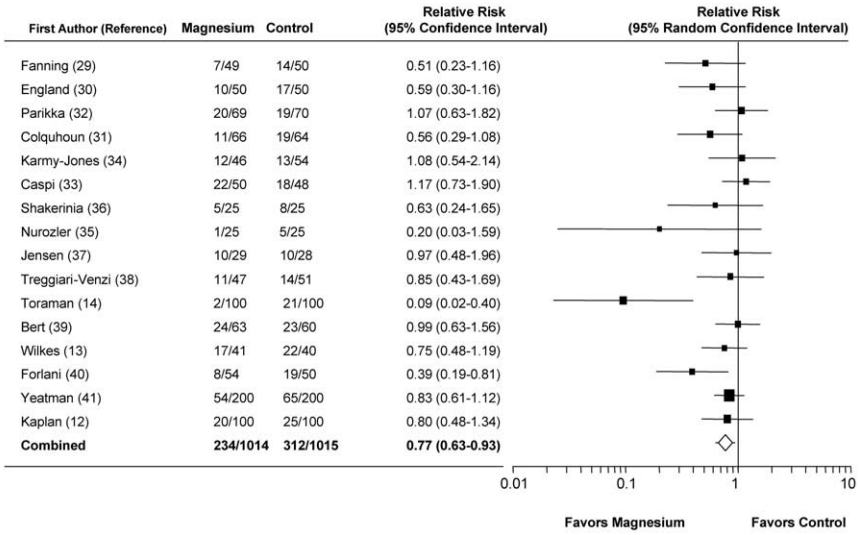

Figure 1. Forest plots for the effects of perioperative magnesium administration on the relative risk of supraventricular arrhythmias. Diamonds indicate pooled relative risks; horizontal lines denote 95% confidence intervals; squares represent point estimates. The size of the square is proportional to the sample size.

antiarrhythmic properties would be less powerful than those of beta-blockers. However, in view of the number needed to harm, possible side effects of magnesium or beta-blockers, such as hypotension or bradycardia, were rare in our analysis. Magnesium is associated with minimum side effects as long as the serum concentration is maintained at an optimal level. Comparisons with meta-analyses of amiodarone or sotalol suggest that the number needed to treat would again be higher with magnesium (4,7), suggesting that the antiarrhythmic effects of magnesium would be less powerful than those of amiodarone or sotalol. Although these meta-analyses did not assess adverse effects, and the number needed to harm for these two agents are not known (4,7), the potential for serious adverse effects, particularly proarrhythmic effects of class III antiarrhythmic agents, should be considered (44). Prophylactic magnesium may be a safe and moderately effective option in the prevention of supraventricular arrhythmias.

Magnesium is an established treatment for polymorphic ventricular arrhythmia, torsade de pointes, and digitalis-induced tachyarrhythmias (9,45), yet the extent of

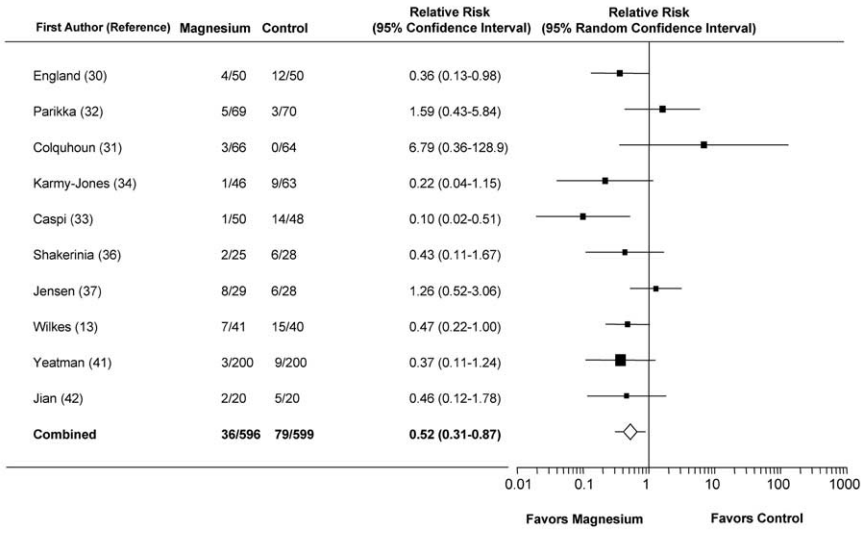

Figure 2. Forest plots for the effects of perioperative magnesium administration on the relative risk of ventricular arrhythmias. Diamonds indicate pooled relative risks; horizontal lines denote 95% confidence intervals; squares represent point estimates. The size of the square is proportional to the sample size.

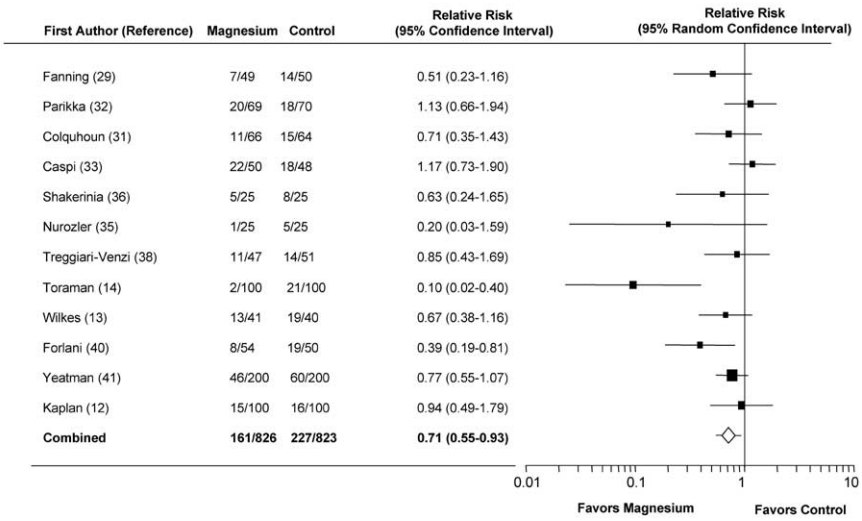

Figure 3. Forest plots for the effects of perioperative magnesium administration on the relative risk of atrial fibrillation. Diamonds indicate pooled relative risks; horizontal lines denote 95% confidence intervals; squares represent point estimates. The size of the square is proportional to the sample size.

its prophylactic effects on the development of ventricular arrhythmias has remained inconclusive. Our analysis showed that magnesium prophylaxis is effective against clinically relevant ventricular tachycardia and ventricular fibrillation during the perioperative period. It reduced the risk of ventricular arrhythmias by 48% with a number needed to treat of 8, indicating that if 100 patients undergoing cardiac surgery were to receive an adequate prophylactic dose of magnesium, 13 would not develop ventricular arrhythmias. These 13 patients would develop ventricular arrhythmias had they received placebo.

Our definition of ventricular arrhythmias included paroxysmal and sustained ventricular tachycardia and ventricular fibrillation. The rate of sustained ventricular tachycardia or fibrillation after cardiac surgery is much lower than that of paroxysmal ventricular tachycardia (4). Nevertheless, once ventricular tachycardia or fibrillation occurs, half of patients will have a recurrent event and a poor cardiac outcome (4). Thus, prophylactic treatment is crucial.

Aranki et al (3) demonstrated that atrial fibrillation is a major predictor of longer hospitalization. Despite a decreased incidence of atrial fibrillation in our magnesium group, magnesium supplementation did not shorten the hospital stay, a null effect that was not anticipated. Further, a relatively small number of samples (seven trials) with considerable heterogeneity failed to determine whether magnesium shortens the length of hospitalization. Prophylaxis also had no significant benefit in reducing the likelihood of myocardial infarction or mortality. A recent large randomized controlled trial showed that magnesium had no effect on 30-day mortality in high-risk patients with acute myocardial infarction (46). However, patients in our study underwent surgery whereas those in that study did not. Our impression is that outcome after cardiac surgery may depend on the surgery itself, rather than on adjunct therapies such as magnesium supplementation. Moreover, the rate of myocardial infarction or mortality was so low (0% to 4%) in the control group in our meta-analysis that statistical power might have been inadequate. A large randomized trial is needed to examine the effects of magnesium on secondary outcomes after cardiac operations.

Our meta-analysis has several limitations. Homogeneity among trials was rejected in terms of primary outcomes and several secondary outcomes. We should explore the sources of heterogeneity even though it was not highly significant ($P = 0.08$). Language restrictions, which are considered to cause "language bias," were eliminated prior to our analysis, although only English-language publications were identified consistently. A subgroup analysis focusing on the incidence of atrial fibrillation and sensitivity analysis did not resolve the heterogeneity, perhaps because of the publication bias identified in our analysis or the diversity of the dose regimen and subsequent effects. Examination of the dose-response effect of magnesium on the prevention of arrhythmias may be necessary. The trials included were published from the early 1990s to 2003, when rapid advances occurred in the field of cardiac surgery. Therefore, there may be differences in surgical technique, method of cardioprotection, temperature of extracorporeal circulation, postoperative care, and other perioperative details. These potential sources of heterogeneity may limit definitive conclusions.

In conclusion, our meta-analysis suggests that prophylactic magnesium reduces the risk of supraventricular arrhythmias after cardiac surgery by 23% (atrial fibrillation by 29%)

and of ventricular arrhythmias by 48%, but has no effects on the length of hospital stay, perioperative myocardial infarction, or mortality. However, the homogeneity among trials may limit the formulation of definitive conclusions.

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