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Role of Prophylactic Magnesium Supplementation in Prevention of Postoperative Atrial Fibrillation in Patients Undergoing Coronary Artery Bypass Grafting: a Systematic Review and Meta-Analysis of 20 Randomized Controlled Trials.

Rahul Chaudhary[1], Jalaj Garg[2], Mohit Turagam[3], Rohit Chaudhary[4] , Rahul Gupta[5], Talha Nazir[6], Babak Bozorgnia [6], Dhanunjaya Lakkireddy[7]

[1]*Department of Medicine, Mayo Clinic, Rochester, MN.*
[2]*Division of `Cardiology, Cardiac Arrhythmia Service, Medical College of Wisconsin Milwaukee, WI .*
[3]*Helmsley Electrophysiology Center, Icahn School of Medicine at Mount Sinai Hospital, New York, NY .*
[4]*Peter Lee Associates, Sydney, Australia .*
[5]*Department of Medicine, Westchester Medical Center, New York Medical College, Valhalla, NY .*
[6]*Division of Cardiology, Lehigh Valley Health Network, Allentown, PA .*
[7]*Kansas City Heart Rhythm Institute and Research Foundation, Kansas City, Kansas .*

Abstract

Background : Several randomized trials have evaluated the efficacy of prophylactic magnesium (Mg) supplementation in prevention of post-operative atrial fibrillation (POAF) in patients undergoing cardiac artery bypass grafting (CABG). We aimed to determine the role of prophylactic Mg in 3 different settings (intraoperative, postoperative, intraoperative plus postoperative) in prevention of POAF.

Methods: A systemic literature search was performed (until January 19, 2019) using PubMed, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials to identify trials evaluating Mg supplementation post CABG. Primary outcome of our study was reduction in POAF post CABG.

Results: We included a total of 2,430 participants (1,196 in the Mg group and 1,234 in the placebo group) enrolled in 20 randomized controlled trials. Pooled analysis demonstrated no reduction in POAF between the two groups (RR 0.90; 95% CI, 0.79-1.03; p=0.13; I^2=42.9%). In subgroup analysis, significant reduction in POAF was observed with postoperative Mg supplementation (RR 0.76; 95% CI, 0.58-0.99; p=0.04; I^2=17.6%) but not with intraoperative or intraoperative plus postoperative Mg supplementation (RR 0.77; 95% CI, 0.49-1.22; p = 0.27; I^2=49% and RR 0.92; 95% CI, 0.68-1.24; p = 0.58; I^2=51.8%, respectively).

Conclusions: Magnesium supplementation, especially in the postoperative period, is an effective strategy in reducing POAF following CABG.

Introduction

Coronary artery bypass grafting (CABG) is the mainstay for the treatment of coronary artery disease in select patient population unless contraindicated [1]. During the cardiopulmonary bypass (CBP), cardioplegic perfusion is intermittently discontinued (15 minutes to up to 30 minutes, depending upon institutional practice) for distal anastomoses construction during which the myocardium is predisposed to ischemic injury [2-5], thereby resulting in ischemic-reperfusion injury [6] and/or reperfusion-induced atrial/ventricular arrhythmias [7,8]. New onset atrial fibrillation is the most common arrhythmia observed postoperatively with incidence ranging from 25% to 40%; typically peaking on post-operative day 2 [9-12]. Development of post-operative atrial fibrillation (POAF) also increases the risk of heart failure, stroke and deterioration in patient's hemodynamic status resulting in increased in-hospital mortality [13,14].

Multiple randomized clinical trials have evaluated the role of prophylactic magnesium (Mg) supplementation for prevention of POAF, with conflicting results [15-34]. With increasing evidence (and addition of new trials) we aimed to assess the role of prophylactic Mg supplementation in reduction of POAF. In addition, we also evaluated the role of prophylactic Mg in three different settings (intraoperative, postoperative, or in combination) in prevention of POAF..

Key Words

Magnesium, Atrial Fibrillation, Coronary artery bypass grafting, CABG.

Corresponding Author
Jalaj Garg, MD FACC FESC Division of Cardiology, Cardiac Arrhythmia Service Medical College of Wisconsin 10000 Innovation Drive Milwaukee, WI 53226

Methods

Search Strategy and Study Selection

We searched PubMed, The Cochrane Library, EMBASE, EBSCO, Web of Science and CINAHL databases from inception through January 19, 2019 to identify trials evaluating Mg supplementation in patients undergoing CABG surgery using the key words: magnesium, coronary artery bypass grafting, CABG and atrial fibrillation. The eligibility criteria for our systematic review and meta-analysis included: (1) randomized controlled study design; (2) human subjects undergoing CABG surgery only; (3) received Mg supplementation intraoperatively, postoperatively or in combination; (4) reported periprocedural incidence of atrial fibrillation; and (5) literature published in English. All studies without a comparator arm, undergoing concomitant valve repair, studies that did not report clinical outcomes, off-pump CABG surgery and observational studies/case reports were excluded from the analysis [Figure 1]. We used the longest available follow-up data from the individual studies for our analysis.

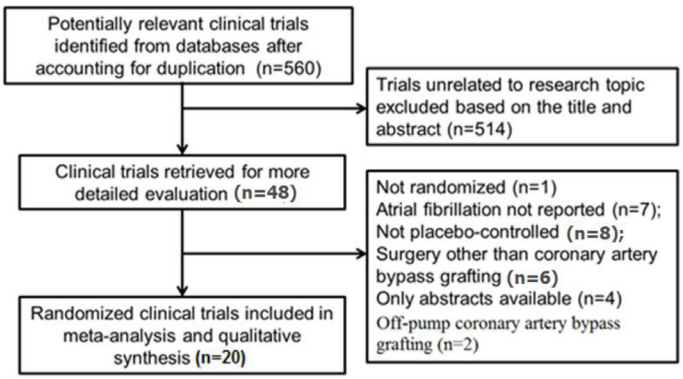


Figure 1: Process of study selection (PRISMA statement)

Data extraction and Quality appraisal

Clinical, interventional, and outcome data were extracted from individual studies by 2 independent abstractors (RC and JG) and entered into a data extraction form. This included information about study design, patient characteristics (age, gender, Mg supplementation, POAF, length of stay, aortic cross clamp time and follow up period). Jadad score was independently calculated by 2 investigators (RC and JG) [Table 1] [34]. Any disparities between the two investigators were discussed with a third investigator (MT) until consensus was reached. Final results were reviewed by senior investigators.

Outcome Variables

The primary outcome of our study was reduction in POAF burden. In order to assess possible differences in the timing of Mg administration, we further divided trials into three subdivisions (secondary outcomes): intraoperative, postoperative and a combination of intra-and postoperative Mg administration.

Statistical analysis

We conducted a meta-analysis of summary statistics from the individual trials because detailed, patient-level data were not available for all trials. Summary estimates and 95% confidence intervals (CI) were reported for continuous variables as difference in means. Mantel-Haenszel risk ratio (RR) fixed effects model was used to summarize data across treatment arms. We evaluated heterogeneity of effects using the Higgins I-squared (I^2) statistic [36]. In cases with heterogeneity (defined as I^2 >25%), random effects models of DerSimonian and Laird [37] were used. Publication bias was estimated visually by funnel plots [38,39]. If any bias was observed, further bias quantification was measured using the Begg-Mazumdar test [40], and Egger test [38]. All analyses were conducted using Comprehensive Meta-Analysis 2.0 software (Biostat, Inc., Englewood, NJ).

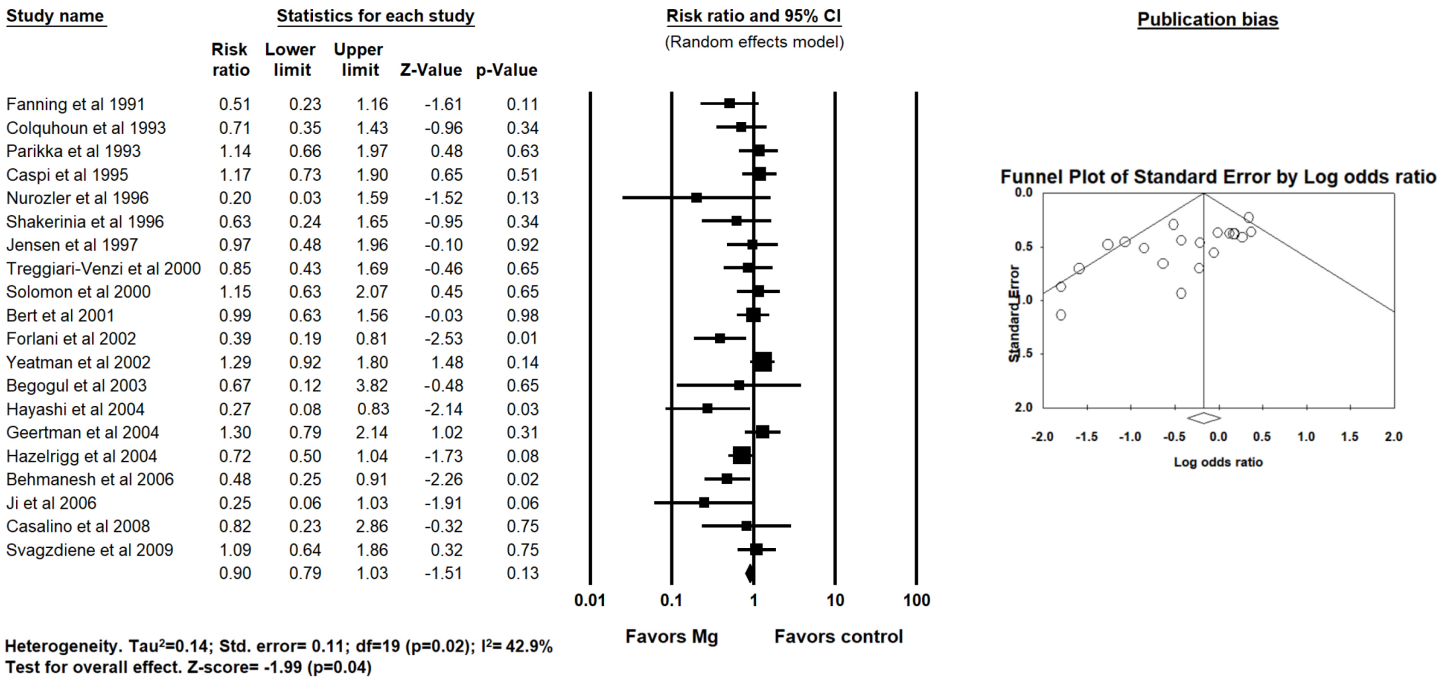


Figure 2: Forest plot demonstrating the effects of magnesium supplementation compared to placebo on post operative atrial fibrillation after CABG surgery (random effects model)

Table 1: Characteristics of participating studies (data presented as control group/study group)

Study name	No. of patients	Mean age (years)	Men (%)	Mean LVEF (%)	Previous MI (%)	Blinding	Infusion	Total amount (mmol)	Duration of aortic clamping (mean)	POAF (n)	Follow-up duration (hrs)	Jadad score
Intraoperative Magnesium supplementation												
Shakerinia et al 1996	25/25	65/67	68/64	65/67	72/80	NS	MgSO4	NA	NA	8/5	24	1
Yeatman et al 2002	200/200	63/64	78/83	NA	NA	DB	MgSO4	20	47/49	45/58	NA	3
Begogul et al 2003	50/50	61/64	88/86	40/40	14/18	DB	MgSO4	16	44/40	3/2	24	2
Hayashi et al 2004	35/35	NA	66/74	52/50	NA	NS	MgSO4	NA	62/47	11/3	NA	1
Ji et al 2006	20/20	56/59	60/70	47/49	12/11	NS	MgSO4	NA	59/61	8/2	NA	3
Casalino et al 2008	49/48	66/68	74/75	54/56	40/43	NS	MgSO4	32	38/37	5/4	120	2
Svagzdiene et al 2009	106/52	65/65	NA	44/46	NA	NS	MgSO4	NA	47/52	28/15	72	1
Postoperative Magnesium supplementation												
Fanning et al 1991	50/49	62/59	78/71	49/50	42/35	DB	MgSO4	84	66/66	14/7	96	4
Colquhoun et al 1993	64/66	59/57	80/83	NA	53/45	DB	MgCl	50	52/51	15/11	96	4
Parikka et al 1993	71/69	54/57	82/84	59/61	NA	NS	MgSO4	70	NA	18/20	48	2
Nurozler et al 1996	25/25	54/56	92/9%	66/67	28/32	DB	MgSO4	100	52/46	5/1	120	2
Jensen et al 1997	28/29	61/61	100/100	NA	NA	DB	MgSO4	110	NA	10/10	72	4
Treggiari-Venzi et al 2000	51/47	65/65	84/89	57/62	45/3%	DB	MgSO4	48	103/91	14/11	72	5
Behmanesh et al 2006	50/50	63/66	93/81	NA	50/36	NS	MgSO4	NA	44/44	21/10	168	3
Intra- + Postoperative magnesium supplementation												
Caspi et al 1995	48/50	62/60	83/89	49/48	NA	NS	MgSO4	48	45/50	18/22	36	4
Solomon et al 2000	82/85	61/62	73/80	54/53	NA	NS	MgSO4	150	63/60	16/19	24	4
Bert et al 2001	60/63	64/63	83/8%	49/48	NA	NS	MgSO4	49	60/55	23/24	96	4
Forlani et al 2002	50/54	64/64	88/85	55/52	66/65	NS	MgSO4	37	47/48	19/8	720	4
Geertman et al 2004	73/74	62/64	79/79	NA	NA	DB	MgSO4	50	48/50	19/25	36	4
Hazelrigg et al 2004	97/105	64/62	68/74	51/53	NA	DB	MgSO4	NA	55/61	41/32	120	4

Table 2: Baseline demographics of study population

Baseline Characteristic	Mg supplementation	Placebo	N	Studies (n)	RR or SMD (95% CI)	Heterogeneity		P for overall effect
						P value	I^2 (%)	
Age, yrs	62.3	61.6	2,008	15	0.21 (0.03 to 0.40)	0.02	75.58	<0.0001
Males, %	79.6	78.4	1,986	16	1.02 (0.98 to 1.06)	0.97	0	0.37
Hypertension, %	49.1	48.0	669	7	0.96 (0.86 to 1.09)	0.73	0	0.55
Diabetes mellitus, %	21.0	18.0	1,169	9	1.11 (0.73 to 1.67)	0.02	53.99	0.63
History of myocardial infarction, %	47.3	48.6	966	11	0.97 (0.86 to 1.10)	0.88	0	0.62
Preoperative use of beta-blockers, %	63.0	67.8	1,723	15	0.95 (0.87 to 1.03)	0.06	39.26	0.21
Need for vasopressors post-surgery, %	29.5	31.9	958	7	0.83 (0.62 to 1.12)	0.11	42.09	0.22

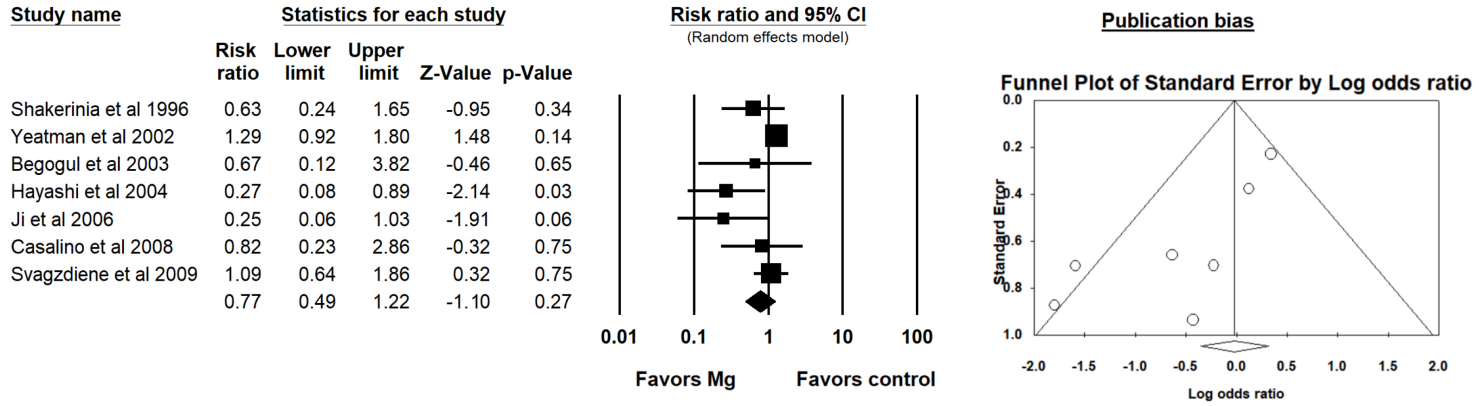
RR=Relative Risk; SMD=Standardized Mean Difference

Results

We included 20 randomized controlled trials [15-34] with a total of 2,430 patients - 1,196 patients in Mg supplementation group, while 1,234 patients in the placebo group. [Table 1] describes the baseline characteristics of included studies including patient demographics, Mg regimens, and incidence of POAF. [Table 2] describes the differences in baseline characteristics between Mg supplementation and placebo groups of included studies.

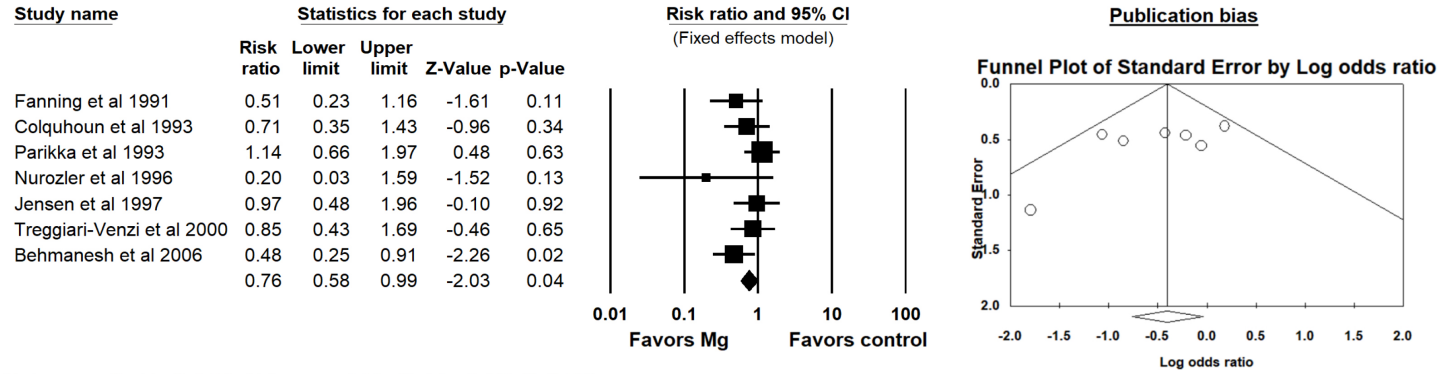
Four hundred and thirty patients received Mg intraoperatively, 335 patients received Mg postoperatively while 431 patients received Mg both intra- and post-operatively. By using random-effects model, pooled analysis for the primary outcome demonstrated no difference in POAF between the two groups (22% versus [vs.] 29% for Mg and placebo groups respectively, RR 0.90; 95% CI, 0.79-1.03; p = 0.13; I^2=42.9%) [Figure 2].

No significant difference was observed between the two groups for length of stay (6.75 days vs 6.77 days for Mg and placebo arm respectively, SMD 0; 95%CI -0.13 - 0.13, p=1.00; I^2=0%), perioperative myocardial infarction (MI) (2.7% vs. 2.2% for Mg and placebo groups respectively, RR 1.26, 95% CI, 0.67 - 2.38, p=0.47; I^2=0%), perioperative mortality (0.6% vs 0.6% for Mg and placebo groups respectively, RR 1.06, 95% CI, 0.43 - 2.62, p=0.90; I^2=0%), aortic cross-clamping time (53 minutes vs. 55 minutes for Mg and placebo groups respectively, SMD -0.12, 95% CI -0.55 - 0.32, p=0.60;I^2=95%) and duration of CPB (89 minutes vs. 88 minutes for Mg and placebo groups respectively, SMD 0.30, 95% CI -0.05 - 0.66, p=0.09; I^2=91%).



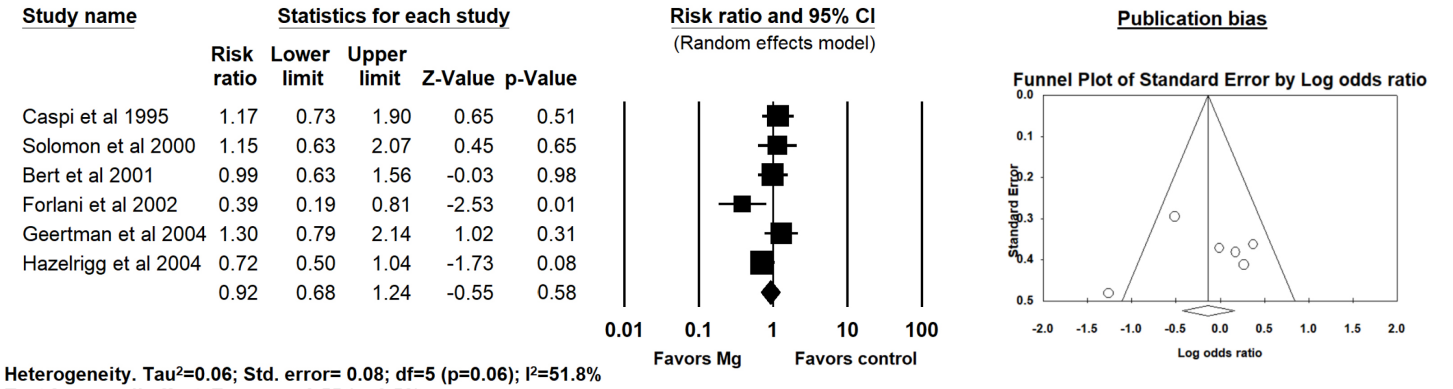
Heterogeneity. Tau²=0.15; Std. error= 0.20; df=6 (p=0.06); I²=48.9%
Test for overall effect. Z-score= -1.09 (p=0.27)

Figure 3: **Forest plot demonstrating the effects of intraoperative magnesium supplementation compared to placebo on post operative atrial fibrillation after CABG surgery (random effects model).**



Heterogeneity. Tau²=0.02; Std. error= 0.09; df=6 (p=0.29); I²=17.6%
Test for overall effect. Z-score= -2.02 (p=0.04)

Figure 4: **Forest plot demonstrating the effects of postoperative magnesium supplementation compared to placebo on post operative atrial fibrillation after CABG surgery (fixed effects model since I²<25%).**



Heterogeneity. Tau²=0.06; Std. error= 0.08; df=5 (p=0.06); I²=51.8%
Test for overall effect. Z-score= -0.55 (p=0.58)

Figure 5: **Forest plot demonstrating the effects of intraoperative+postoperative magnesium supplementation compared to placebo on post operative atrial fibrillation after CABG surgery (random effects model).**

Table 3: Summary of Egger's and Begg's test for publication bias

Outcomes	Egger's test p-value	Begg's test p-value
Overall POAF	0.002	0.008
POAF (Intraoperative Mg)	0.01	0.13
POAF (Postoperative Mg)	0.18	0.54
POAF (Intra- + Postoperative Mg)	0.84	1.00

p-value of <0.05 indicates publication bias

Intraoperative Magnesium supplementation subgroup

In 7 trials that evaluated prophylactic intraoperative Mg supplementation, 16% patients had POAF in the intraoperative Mg arm vs. 24% in the placebo arm with no reduction in POAF (RR 0.77; 95% CI: 0.49 - 1.22; p=0.27; I^2=48.9%) [Figure 3].

There were no significant differences observed between the two groups for perioperative MI (2.1% for Mg and placebo groups respectively, RR 1.00; 95% CI 0.29 - 3.40, p=1.00, I^2=0%), perioperative mortality (0.3% vs. 0.5% for Mg and placebo groups respectively, RR 1.44, 95% CI 0.23 - 9.04, p=0.70; I^2=18.16%), aortic cross-clamping time (SMD -0.10, 95% CI -1.46 - 1.28, p=0.89; I^2=98.33%) and duration of CPB (SMD 0.77, 95% CI -0.14 - 1.67, p=0.09; I^2=96.15%).

Postoperative Magnesium supplementation subgroup

Seven trials that evaluated postoperative Mg supplementation, there was a significant reduction in the incidence of POAF (20% vs 29% for Mg and placebo groups respectively, RR 0.76; 95% CI 0.58 - 0.99; p=0.04; I^2=17.6%) [Figure 4].

There were no significant differences observed between the two groups for perioperative MI (1.9% vs. 2.0% for Mg and placebo groups respectively, RR 0.98; 95% CI 0.25 - 3.77, p=0.97; I^2=0%), perioperative mortality (0.5% vs. 0.9% for Mg and placebo groups respectively, RR 0.79, 95% CI 0.17 - 3.66, p=0.77; I^2=0%), aortic cross-clamping time (SMD -0.32, 95% CI -0.74 - 0.10, p=0.14; I^2=75.28%) and duration of CPB (SMD -0.08, 95% CI -0.38 - 0.21, p=0.57; I^2=51%).

Intraoperative plus Postoperative Magnesium supplementation subgroup

In six trials evaluating a combined intra and postoperative magnesium supplementation strategy, no reduction in POAF (31% vs 34% for Mg and placebo groups respectively, RR 0.92; 95% CI 0.68 - 1.24; p=0.58; I^2=51.8%) [Figure 5], perioperative MI (RR 1.60; 95% CI 0.66 - 3.90, p=0.30; I^2=0%), perioperative death (RR 1.14; 95% CI 0.28 - 4.65, p=0.86; I^2=0%) and aortic cross-clamp time (SMD 0.03, 95% CI -0.15 - 0.22, p=0.73; I^2=40%) was observed. However, CPB time was significantly more in Mg group compared to placebo (90 minutes vs. 85 minutes, respectively, SMD 0.19, 95% CI 0.003 - 0.37, p=0.04; I^2=0%).

Publication bias and Quality appraisal

A significant publication bias was identified overall for POAF [Table 3]. Upon further stratification based on timing of Mg administration, publication bias was significant for intra-operative strategy only. No publication bias was observed for perioperative MI, mortality, aortic cross-clamping time and duration of CPB. The publication bias observed did not change even after adjustments using Duval and Tweedie's trim and fill and addition of imputed studies.

Discussion

The current meta-analysis analyzed 2,430 patients and demonstrated a significant reduction in POAF among patients undergoing on-pump CABG surgery who received prophylactic Mg supplementation in the postoperative period only. No significant differences were observed in perioperative MI, mortality, aortic cross-clamp time or duration of CPB between the two groups. To the best of our knowledge, this is the first meta-analysis demonstrating the role of prophylactic Mg supplementation (and different administration strategies) in patients undergoing on-pump CABG surgery in preventing POAF [41-46].

The precise mechanism by which prophylactic Mg supplementation reduces POAF remains unclear. Hypomagnesaemia has been shown to be proarrhythmic with studies demonstrating an increased risk of atrial and ventricular arrhythmias [47,48]. In addition, studies have shown that serum Mg levels do not correlate with myocardial tissue magnesium levels [49], with low extracellular Mg associated with abnormalities of depolarization, repolarization and automaticity [50]. Mg supplementation therefore significantly increases atrial refractoriness by prolonging the action potential duration and atrial effective refractory period [51-53]. A possible explanation to the efficacy of postoperative Mg supplementation in reducing POAF, as observed in our study, likely stems from the myocardial Mg depletion in immediate postoperative period (circulating volume dilution from extracorporeal support, use of diuretics which promotes Mg excretion and/or norepinephrine induced redistribution of Mg from intracellular to extracellular compartment). Myocardial Mg depletion would not be reflected on serum Mg levels; and therefore could be responsible for provoking atrial arrhythmias despite normal serum Mg levels. Magnesium supplementation in the postoperative period possibly offsets this process. In addition, POAF predominantly occurs between postoperative day 1 and day 4 with the peak incidence at day 2, which is often associated with hypomagnesemia. This time course also correlates with increased sympathetic activation (from surgical stress and exaggerated by ß-blockers withdrawal) and has been associated with POAF. Therefore, prophylactic Mg supplementation postoperatively may attenuate adrenergic medicated automaticity and reduce the incidence of POAF as observed in this study. Interestingly, there was no reduction in POAF in patients with intraoperative or intraoperative plus post-operative magnesium supplementation. The exact explanation remains uncertain. Theoretically, the duration of aortic cross-clamp time and CPB might be responsible for POAF reduction, nonetheless no significant differences were observed between the two groups.

Development of POAF after CABG adds a potentially preventable significant burden to healthcare and is associated with increased length of hospital stay. In a study by Aranki et al, length of stay increased from 9.3 ± 19.6 days to 15.3 ± 28.6 days (p=0.001), which was estimated to an additional charge of $10,055 for in-patient hospital charges per patient [54]. Multiple agents have been explored

to reduce the incidence of POAF after CABG including beta-blockers, anti-arrhythmic agents (sotalol and amiodarone) and Mg supplementation. Amongst these agents, Mg is the least likelihood of drug interactions and side effects, is readily available, well tolerated by patients and inexpensive [55].

Due to multiple randomized clinical trials exploring the role and utility of Mg prophylaxis, several meta-analyses have been conducted in the past. The results of our study contrasts from the previously reported meta-analyses by Gu et al and De Oliveira et al, both of which demonstrated an overall reduction in POAF with magnesium supplementation (RR=0.64; 0.50-0.83 and OR=0.69; CI 0.53-0.90, respectively) [43,44]. In a sub-analysis by De Oliveira et al comparing POAF between high-quality and low-quality studies, no reduction of POAF was found with magnesium supplementation in higher quality studies but a significant reduction was seen with low-quality studies. However, no such differences were found in our sub-analysis without any significant reduction in POAF when stratified by high or low-quality studies (data not shown).

There are several limitations in this study. First, the studies included in this study span a time of 25 years during which there has been tremendous evolution in the surgical techniques. Second, majority of trials included in our analysis did not specify concomitant use of beta-blockers, which might have overestimated the effectiveness of Mg in the postoperative sub-group. Finally, a publication bias was observed in the overall results of the study and the included trials had diverse dosing regimens, mode of supplementation and follow-up time period. However, no significant heterogeneity was observed for POAF reduction in the postoperative Mg supplementation group.

Acknowledgement

None.

Conclusions

Magnesium supplementation, especially in the postoperative period, is an effective strategy in reducing POAF following on-pump CABG surgery. Further large randomized controlled trials are needed to validate our results and whether this reduced incidence of POAF would translate into reducing length of stay and healthcare cost.

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