

Effect of prophylaxis of magnesium sulfate for reduction of postcardiac surgery arrhythmia: Randomized clinical trial

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ABSTRACT

Background: Arrhythmia is a common complication after heart surgery and is a major source of morbidity and mortality. **Aims:** This study aimed to study the effect of magnesium sulfate ($MgSO_4$) for reduction of postcardiac surgery arrhythmia. **Setting and Design:** This study is performed in the cardiac operating room and Intensive Care Unit (ICU) of Shahid Madani Hospital of Tabriz (Iran) between January 1, 2014, and September 30, 2014. This study is a double-blind, randomized controlled trial. **Materials and Methods:** In Group 1 (group magnesium [Mg]), eighty patients received 30 mg/kg $MgSO_4$ in 500 cc normal saline and in Group 2 (group control), eighty patients received 500 cc normal saline alone. **Statistical Analysis:** The occurrence of arrhythmia was compared between groups by Chi-square and Fisher's exact test. In addition, surgical time, length of ICU stay, and length of hospital stay were compared by independent *t*-test. $P < 0.05$ was considered as significant. **Results:** There was a significant difference in the incidence of arrhythmia between two groups ($P = 0.037$). The length of ICU stay was 3.4 ± 1.4 and 3.73 ± 1.77 days in group $MgSO_4$ and control group, respectively, and there was no statistically significant difference between two groups ($P = 0.2$). **Conclusion:** Mg significantly decreases the incidence of all type of postcardiac surgery arrhythmia and hospital length of stay at patients undergo cardiac surgery. We offer prophylactic administration of Mg at patients undergo cardiac surgery.

Key words: Arrhythmia; Cardiovascular research; Magnesium; Prevention; Surgery

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INTRODUCTION

Arrhythmia is a common complication after heart surgery and is a major source of morbidity and mortality.^[1] Atrial arrhythmia after cardiac surgery is a most common arrhythmia.^[2] Despite advances in surgical technique, anesthesia, and intraoperative myocardial protection, the incidence of atrial fibrillation (AF) in patients undergoing coronary artery bypass graft (CABG) has not decreased.^[3] The incidence of atrial arrhythmia after CABG, mitral valve replacement, aortic valve replacement, and heart transplantation are 31.9%, 63.6%, 48.8%, and 11.1%, respectively.^[4] These arrhythmia increase mean hospital length of stay 4.9 days.^[5] Age, male gender,

hypertension, need for an intraoperative intra-aortic balloon pump, postoperative pneumonia, ventilation for >24 h, and return to the Intensive Care Unit (ICU) are

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the independent predictor factor.^[5] AF increase the incidence of postsurgery complication such as cognitive changes, renal dysfunction, infection, congestive heart failure, myocardial infarction (MI), reintubation, stroke, and mortality.^[6-8] Several drugs such as beta-blocker, digoxin, amiodarone, sotalol, verapamil, procainamide, statins, and steroids are used to prevent postcardiac surgery atrial arrhythmia.^[9-12] However, ten percent of patients undergoing cardiac surgery will experience AF despite the use of amiodarone and other antiarrhythmic treatments.^[13]

Currently, some study verified the effect of magnesium sulfate ($MgSO_4$) for the prevention of postcardiac surgery; however, the effect of $MgSO_4$ is controversial. Shepherd *et al.* performed a systemic review to compare $MgSO_4$ and so^[14] magnesium (Mg) as a calcium antagonist, energy transfer regulator, and membrane stabilizer has several physiological and pharmacological effects.^[15] Minimal negative inotropic effect and high therapeutic window of intravenous (IV) Mg proposed as an efficient and safe agent in the treatment of AF.^[16,17] However, the therapeutic effect of Mg in the treatment of AF is controversial.^[18-21] Cook *et al.* evaluated 21 randomized controlled trial and they conclude that $MgSO_4$ does not prevent postcardiac surgery AF.^[21] Therefore, this study aimed to study the effect of $MgSO_4$ for the reduction of postcardiac surgery arrhythmia.

MATERIALS AND METHODS

Study design and setting

This study is a prospective, randomized, double-blind, placebo-controlled trial that performed in the cardiac operating room and ICU of Shahid Madani Hospital between January 1, 2014, and September 30, 2014. The Ethic Committee of Tabriz University of Medical Sciences approved the study (Approved No: 92118). Written informed consent was obtained from all patients the day before surgery. The study was registered at Iranian Register of Clinical Trials as registration no: IRCT2014010716117N1. The trial was conducted in compliance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Patients

This study was conducted on 160 consecutive adult patients that underwent elective cardiac surgery. Inclusion criteria were adult older than 18 years, normal sinus rhythm, and stable hemodynamic. Exclusion criteria were chronic AF, heart rate <50, prior

history of AF, previous history of cardiac surgery, systolic blood pressure <100 mmHg, recent MI (at previous 6 weeks), current use of antiarrhythmic medication such as amiodarone, digoxin, current use of warfarin, patients with pacemaker, atrioventricular (A-V) block, ejection fraction <30%, renal failure (creatinine >2.5 mg/dl), pregnancy, hepatic dysfunction (International Normalized Ratio >2, aminotransferases >100 IU), severe lung diseases forced expiratory volume 1 s <30% of predicted normal value (postbronchodilator) and $PaCO_2$ >7.33 kPa, hyperkalemia (K >4.8 mmol/L), and pulmonary arterial hypertension (mean pulmonary artery pressure >30 mmHg).

Preoperative and postoperative management

Before transfer to the operating room, all patients received similar premedication (1 mg oral lorazepam at night before surgery, 0.1 mg/kg intramuscular [IM] morphine sulfate IV and 0.5 mg/kg IM promethazine 1 h before surgery). Moreover, induction of anesthesia in all patients was performed with similar total intravenous anesthesia (TIVA) protocol (lidocaine 1 mg/kg, cisatracurium 0.2 mg/kg, midazolam 0.15 mg/kg, and fentanyl 5 μ g/kg). Anesthesia maintained with TIVA. All patients underwent continuous cardiac monitoring, invasive blood pressure monitoring, and central vein pressure monitoring. Weaning from mechanical ventilation and catecholamine infusion, pulmonary artery catheter removal, and tracheal extubation was done based on the standard guideline.

Intervention

Patients were divided randomly into two groups. We balanced randomization using permuted blocks of five and did not stratify for baseline characteristics. Eighty patients were given 30 mg/kg $MgSO_4$ in 500 cc of isotonic solution IV over 2 h. The other eighty patients were given 500 cc solutions IV as placebo over 2 h. Based on the previous study, dosage of 30 mg/kg was selected.^[22,23] During the infusion period, a Holter electrocardiogram recording was obtained. In addition, 12 leads electrocardiograms were recorded every 12 h.

Patients and investigator were blinded to drug. For insurance of blinding, the independent pharmacologist was not involved in the patient allocation and data gathering. The study solutions were prepared daily in identical packs of equal volume with particular code numbers. Each research package appeared the same to the naked eye.

Study end points

The primary end point of the study was considered as the prevention of AF. The occurrence of AF was recorded as treatment failure, and the study was terminated. In this situation, the treatment regime was available to the therapeutic staff and the patient was treated as appropriate. Two independent investigators detected the arrhythmia episodes. Supraventricular tachycardia was defined as an arrhythmia of more than three narrow complexes at a rate >100 b.p.m, lasting more than 30 s. AF was defined as totally irregular atrial rhythm leading to irregular ventricular rhythm,^[24] ventricular tachycardia (VT) was defined as 10 or more consecutive ventricular beat.^[25] Ventricular fibrillation (VF) was defined as spiral, turbulence, irregular, and chaotic ventricular rhythm.^[26]

Data collection

Data were collected by a researcher who was unaware of treatment groups. Demographic and baseline characteristics (age, sex, comorbidity and beta-blocker usage) of the patients were recorded. Postoperative complications and drug-related side-effects were recorded. Data obtained from the Holter ECG recording were the occurrence of AF, VF, junctional rhythm, VT, A-V block, premature VT, and premature atrial tachycardia.

Statistical analysis

Data were analyzed with SPSS 19 (IBM Corporation, USA). Continuous variables were expressed as mean (standard deviation) and categorical as frequency and percentage. The percentage of the occurrence of arrhythmia was compared between groups by Chi-square and Fisher's exact test. In addition, surgical time, length of ICU stay, and length of hospital stay were compared by independent *t*-test. $P < 0.05$ was considered as significant.

To achieve the sample size, based on the previous study, the prevalence of AF after cardiac surgery was reported about 4% and 20% in Mg-treated and placebo-treated groups.^[27] By considering the power of 90% and $\alpha = 0.05$, eighty patients were calculated to be enough in each group.

RESULTS

During January 1, 2014–September 30, 2014, after consideration of inclusion and exclusion criteria, 160 patients enrolled in this study [Figure 1]. There is no drop out objects after randomization. The participant demographic data are shown in Table 1.

There were no statistically significant differences regarding sex and age between two groups ($P = 0.476$ and $P = 0.231$, respectively). The use of cardiopulmonary bypass pump during cardiac surgery was 67.5% (56 patients) and 68.8% (57 patients) in Mg and control groups, respectively ($P = 0.223$). The mean surgical times were 5.9 (1.2) h and 5.7 (1.1) h in Mg and control groups, respectively ($P = 0.212$).

Hemodynamic values in two studied groups have no difference during the postoperative course. In addition, no difference was observed in arterial blood gas or blood concentration of potassium and ionized calcium ($P > 0.05$). In the Mg group, arrhythmia occurred in 16 of 80 patients (20%) and in the control group, arrhythmia occurred in 27 of 80 patients (33.75%). There was a significant difference in the incidence of arrhythmia between two groups ($P = 0.037$). AF was the most common arrhythmia. The onset and type of arrhythmia in both groups are shown in Table 2.

The length of ICU stay was 3.4 (1.4) and 3.73 (0.77) days in Mg and control groups, respectively ($P = 0.2$). The length of hospital stay was 6.68 (1.45) and 7.82 (2.39) days in Mg and control groups, respectively. There was a statistically significant difference between two groups ($P < 0.001$).

DISCUSSION

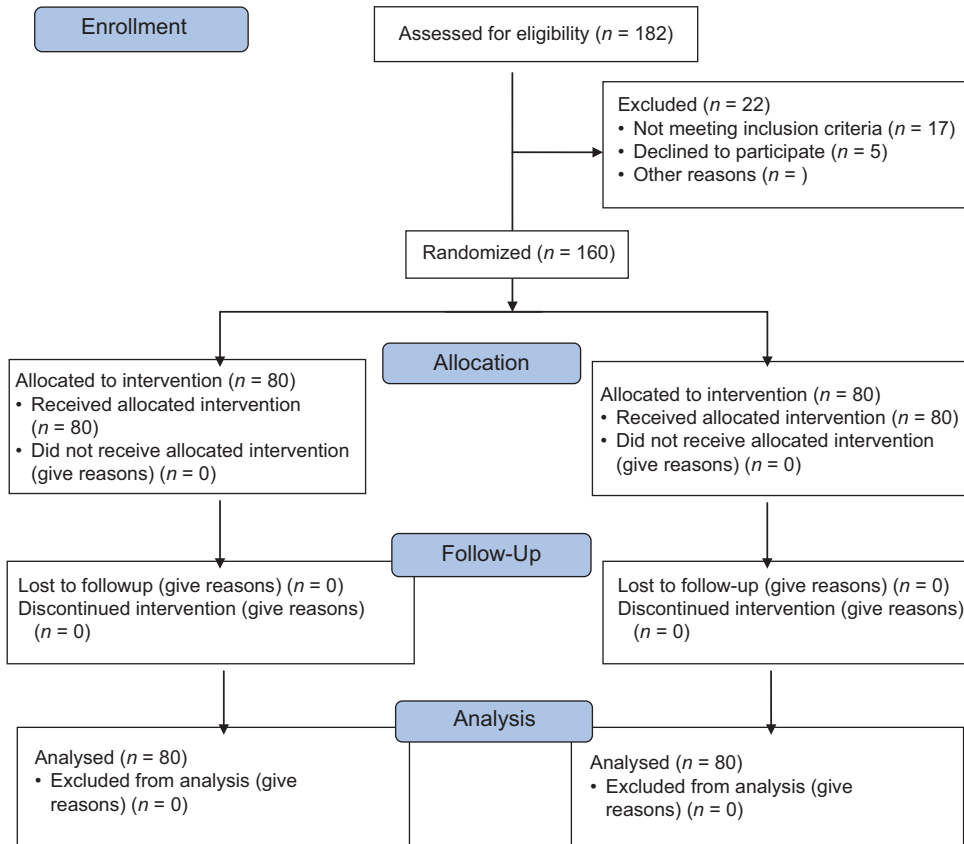
Based on this study, $MgSO_4$ significantly decreased the incidence of arrhythmia at patients who underwent elective cardiac surgery. Mg compared with placebo, decreased the incidence of arrhythmia up to 59%. Moreover, Mg significantly decreased the hospital length of stay.

Table 1: Preoperative and demographic characteristics of the patients in the study sample

Variable	Magnesium sulfate (n=80)	Placebo (n=80)	P
Sex (male/female)	61/19	56/24	0.48
Mean age (range)	59.6 (40-73)	61.7 (43-77)	0.21
Comorbidity (%)			
Total	68 (85.0)	68 (85.0)	0.99
Hypertension	20 (25.0)	19 (23.75)	0.85
Ischemic heart diseases	32 (40.0)	34 (42.5)	0.75
Diabetes mellitus	10 (12.5)	9 (11.25)	0.81
Chronic obstructive pulmonary disease	5 (6.25)	5 (6.25)	0.99
Hyperthyroidism	1 (1.25)	1 (1.25)	0.99
Beta-blocker use (%)	50 (62.5)	48 (60.0)	0.75



CONSORT 2010 Flow Diagram

**Figure 1:** The CONSORT flowchart

In a comparison of our results, Tiryakioglu *et al.* study showed the prophylactic use of $MgSO_4$ is effective at preventing arrhythmia that may occur following coronary bypass operations.^[28] In addition, Toraman *et al.* concluded that the use of Mg in the preoperative and early postoperative periods is highly effective in reducing the incidence of AF after CABG.^[29] Some meta-analysis investigated the effect of Mg about the prevention of arrhythmia after cardiac surgery. Burgess *et al.* examine 22 trials that verified the effect of Mg to prevent postoperative AF. Based on their meta-analysis, Mg prevents postoperative AF, but there was a significant heterogeneity between trials. The source of heterogeneity partly was explained by concomitant use of beta-blockers. Furthermore, the lack of data about the incidence of VF and VT was their major limitation.^[30] The result of our study is similar to this meta-analysis, but we verified the effect of Mg on all type of arrhythmias such as AF, VF, VT, premature ventricular complex, premature atrial complex, and

junctional rhythms. Based on our study, prophylactic Mg decreased all type of arrhythmias such as AF, VF, VT, and junctional rhythm. In contrary, Cook *et al.* conducted a meta-analysis to identify the effect of Mg to prevent postoperative AF. They investigated 21 trials that compared Mg with placebo. They claimed that previous studies had serious methodology problem such as lack of blinding, failure to conduct an intention-to-treat analysis, and AF as a secondary end point.^[21] They excluded those studies, and based on rest studies, they concluded that prophylactic Mg did not have a beneficial effect to prevent postoperative AF after cardiac surgery.^[21] In this study, we tried to resolve these imperfections. Our study was double-blind, randomized trial. In our study, there was not any drop out patients, and we used full analysis set.

Chronic use of beta-blocker by the patients was the major limitation of this study. About 60% and 62.5% of patients were using beta-blocker in control

Table 2: The onset and type of arrhythmia

Arrhythmias	Magnesium sulfate (n=80)	Placebo (n=80)	P
All times			
Total (%)	16 (20.0)	27 (33.75)	0.047
Arterial fibrillation	8	7	
Ventricular fibrillation	2	4	
Junctional rhythm	1	4	
Ventricular tachycardia	1	4	
A-V block	1	2	
Premature ventricular contraction	2	3	
Premature arterial contraction	1	3	
Before CPB			
Total (%)	1 (1.25)	7 (8.75)	0.027
Arterial fibrillation	0	1	
VF	0	2	
VT	1	2	
Premature ventricular contraction	0	1	
Premature arterial contraction	0	1	
During rewarming			
Total (%)	3 (3.75)	5 (6.25)	0.47
Arterial fibrillation	1	1	
VF	2	1	
Junctional rhythm	0	2	
Premature ventricular contraction	0	1	
During CPB weaning			
Total (%)	3 (3.75)	5 (6.25)	0.47
Arterial fibrillation	3	1	
VF	0	1	
VT	0	2	
Junctional rhythm	0	1	
After CPB			
Total (%)	2 (2.5)	2 (2.5)	0.99
Arterial fibrillation	1	0	
A-V block	1	2	
During ICU admission			
Total (%)	7 (8.75)	8 (10.0)	0.79
Arterial fibrillation	3	5	
VF	0	0	
Junctional rhythm	1	1	
Premature ventricular contraction	2	1	
Premature arterial contraction	1	1	

CPB: Cardiopulmonary bypass, ICU: Intensive Care Unit, VT: Ventricular tachycardia, VF: Ventricular fibrillation, A-V: Atrioventricular

and Mg groups, respectively. Failure to classify patients according to the type of cardiac surgery was the other limitation of our study. In addition, we do not monitor Mg concentration in the studied patients. It is well known that patients presenting for cardiac surgery are

frequently Mg deficient. Hence, if the serum Mg level was assessed during the study, it may conclude that the therapeutic effect of Mg administration may have been achieved by correction of preexisting hypomagnesemia.

Mg significantly decreases the incidence of all type of postcardiac surgery arrhythmia and hospital length of stay at patients undergo cardiac surgery. We offer prophylactic administration of Mg at patients undergo cardiac surgery.

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Conflicts of interest

There are no conflicts of interest.

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