Magnesium Sulfate for Prophylaxis against Postoperative Atrial Fibrillation after Isolated Cardiac Valve Replacement Surgery in Adult Patients with Rheumatic Heart Disease: A Randomized Controlled Trial

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Abstract

Objectives: To evaluate the role of prophylactic magnesium sulfate administration in preventing postoperative atrial fibrillation (POAF), attenuating the inflammatory response and promoting myocardial protection after isolated cardiac valve replacement surgery in adult patients with rheumatic heart disease.

Design: Prospective randomized, double-blind placebo-controlled trial.

Methods: Sixty-four adult patients undergoing isolated cardiac valve replacement surgery were divided into two equal groups (32 patients in each). Patients in magnesium group (group M) received 2.5 gm of magnesium sulfate (dissolved in 100 mL of isotonic saline and infused over 2 h), twelve h preoperatively, within the first hour of ICU arrival, and on the 2nd and 3rd postoperative days (group M). Patients in the control group (group C) received a placebo of isotonic saline at the same time periods.

Results: Prophylactic magnesium sulfate significantly decreased the incidence of POAF compared to the placebo group (P=0.005). White blood cell (WBC) count showed no significant difference between the two groups. C-reactive protein (CRP) level showed significant reduction during the 3rd, 4th, and 5th postoperative days in group M compared to group C (P=0.001, 0.001 & 0.012 respectively). Serum level of interleukin-6 (IL-6) showed a significant reduction on the 5th postoperative day in group M compared to group C (P=0.001). Both groups showed no significant differences in serum levels of troponin I during the study.

Conclusion: Prophylactic use of magnesium sulfate in patients with rheumatic heart disease undergoing isolated cardiac valve replacement surgery can decrease the incidence of POAF. It may play a role in attenuating the inflammatory process associated with the use of cardiopulmonary bypass (CPB).

Keywords: Magnesium sulfate; Postoperative atrial fibrillation; Cardiac valve surgery; Rheumatic heart disease

Introduction

Cardiovascular diseases represent significant health challenges worldwide. Most heart disease patients are subject to surgical intervention [1]. Despite advances in cardiac surgery, both in surgical techniques and perioperative care, patients are still at risk of postoperative complications resulting in bad prognoses and high financial burdens [2]. Among major post-cardiac surgery complications are arrhythmias especially atrial fibrillation (AF) [3]. AF is characterized by irregularly irregular rhythm with high atrial rate (350-500 beats/min) that causes loss of atrial kick and hence reduction of left ventricular filling. Consequently, stroke volume decreases leading to hemodynamic instability [4]. Conventional management of postoperative atrial fibrillation (POAF) usually focuses on atrial conduction, refractory period, and the role of the sympathetic nervous system, while novel therapies target the relationship between the occurrence of POAF and the inflammatory process, oxidative stress, and atrial remodeling [5]. Magnesium is fourth most common cation in the body and the second most abundant one inside the cells. It is an important factor in different enzymatic reactions involving nucleic acid synthesis and energy metabolism. Several studies attributed its membrane stabilizing, anti-arrhythmic and anti-inflammatory actions to its effect as a calcium antagonist [6]. During stress, magnesium appears in a relatively high amount in urine resulting in a decrease in its serum level. This depletion in the serum level of magnesium causes stress at the cell membrane level which further decreases its serum level “vicious circle” resulting in severe complications such as cardiac dysrhythmias, which appear in the form of supraventricular tachycardia, atrial fibrillation, prolonged P-R and Q-T segments, and even ventricular fibrillation [7].

The primary outcomes were to evaluate the effect of prophylactic magnesium sulfate administration on the incidence of POAF after isolated cardiac valve surgery in adult patients and to detect its anti-inflammatory and cardioprotective effects.

Patients and Methods

This prospective randomized, double-blind placebo-controlled trial was carried out from September 2017 to February 2018, after approval from the ethics committee for research of faculty of medicine, Assiut
In this study, we used a definition of POAF as any episode of AF lasting for more than five minutes with or without symptoms or any episode of AF that required intervention to maintain hemodynamic stability [8]. Any attack of POAF starting from ICU arrival and for the first five postoperative days was planned to be managed according to a preset protocol; whenever POAF episode is detected, 12-leads ECG is recorded, and arterial blood gas sample is taken for correction of any acid-base or electrolyte disturbance. If the episode of POAF is associated with hemodynamic instability, direct cardioversion is used. If the patient is hemodynamically stable, intravenous amiodarone is used (150 mg over 10 min, then 1 mg/min for 6 h, then 0.5 mg/min for 18 h) followed by oral amiodarone (400 mg twice daily for five days followed by 200 mg once daily for seven days). If sinus rhythm is not established within 24 h of medical treatment, then external electrical cardioversion is performed.

### Study measurements

Occurrence of POAF starting from ICU arrival and for the first five postoperative days; serum levels of potassium and magnesium, serum level of CRP and WBC count 12 h preoperatively (just before administration of the first dose of magnesium sulfate or placebo) as baselines, then on the 1st, 2nd, and 3rd postoperative days (two h after the end of drug infusion from an intravenous line other than the infusion line), then 24 and 48 h later (the 4th and 5th postoperative days); serum level of interleukin-6 (IL-6) post-induction, at the end of CPB, 6 h after CPB, then 24 and 120 h after induction of anesthesia; serum level of cTnI 12 and 24 h after induction of anesthesia. Duration of inotropic support was recorded with the calculation of the mean 24 h and the maximum 24 h inotropic scores. Inotropic score (IS) per hour=[(dopamine dose (µg/kg/min)+dobutamine dose (µg/kg/min) +100 X epinephrine dose (µg/kg/min]) [9]. The mean 24 h IS was obtained by averaging the hourly scores for 24 h, while the maximum 24 h IS is the highest value during the first 24 h of the study.

### Statistical analysis

Data were analyzed using SPSS (version 23). Normality of data was tested by Kolmogorov-Smirnov test. The incidence of POAF was presented as numbers and percentages and analyzed using Fisher's exact test. Other categorical data were presented as numbers and percentages and analyzed using Chi-square test. Continuous numerical variables were presented as mean ± SD and analyzed using independent samples t-test for normally distributed data, or presented as median and interquartile range and analyzed using Mann-Whitney test for non-parametric data. P-value<0.05 was considered statistically significant.

The sample size was calculated based on a previous study of patients undergoing CABG surgeries on CPB, in which the incidence of POAF was 10% in patients receiving prophylactic magnesium sulfate versus 43.8% in the control group [10]. The sample size was estimated to be 26 patients in each group, with a power of 80% and an α error of 0.05. We enrolled 32 patients in each group to compensate for dropouts.

### Results

Figure 1 shows the CONSORT flow chart of the study. The intervention was discontinued for one patient in Group M (AV block that required postoperative pacing) and two patients in group C (one with AV block that required postoperative pacing, and the other with postoperative renal impairment). So, analysis included 31 patients in
There were no significant differences between the two groups regarding age, sex, weight, body mass index (BMI), preoperative left ventricular ejection fraction (LVEF), left atrial diameter, type of surgery, duration of anesthesia, duration of CPB, cross-clamp time, the lowest hematocrit (HCT), or the lowest temperature (Table 1).

### Table 1: Patient Characteristics, Lesion Characteristics, and Operative Details.

|                     | Group M (n=31) | Group C (n=30) | P Value |
|---------------------|---------------|---------------|---------|
| Age (Years)         | 32.45 ± 9.08  | 30.27 ± 7.73  | 0.316   |
| Sex                 |               |               |         |
| Male                | 14 (45.2%)    | 17 (56.7%)    | 0.369   |
| Female              | 17 (54.8%)    | 13 (43.3%)    |         |
| Weight (Kg)         | 59.77 ± 12.83 | 65.20 ± 16.46 | 0.156   |
| Body Mass Index (Kg/m²) | 22.38 ± 4.69 | 24.07 ± 5.07  | 0.182   |
| Preoperative LVEF (%)| 63.03 ± 5.57  | 61.33 ± 5.83  | 0.249   |
| Left Atrial Diameter (Cm)| 4.77 ± 0.72 | 5.17 ± 0.96 | 0.074 |
| Type of Surgery     |               |               |         |
| Single MV Replacement | 14 (45.2%) | 16 (53.3%) | 0.794   |
| Single AV Replacement | 8 (25.8%) | 6 (20.0%) |         |
| Combined MV & AV Replacement | 9 (29.0%) | 8 (26.7%) |         |
| Duration of Anesthesia (Hours) | 6.47 ± 1.05 | 5.95 ± 1.18 | 0.075   |
| Duration of CPB (Minutes) | 120.26 ± 30.43 | 115.97 ± 33.72 | 0.604   |
| Cross Clamp Time (Minutes) | 73.97 ± 30.93 | 71.87 ± 26.92 | 0.778   |
| Lowest HCT (%)      | 23.29 ± 1.40  | 22.83 ± 1.58  | 0.235   |
| Lowest Temperature (°C) | 28.87 ± 1.20 | 28.43 ± 1.17 | 0.173   |

**Cardiac rhythm**

Regarding the cardiac rhythm after declamping, there was no significant difference between the two groups (P=0.806). In group M, we had 19 patients (61.3%) of sinus rhythm, three patients (9.7%) of AF, four patients (12.9%) of AV block, and five patients (16.1%) of ventricular tachycardia or fibrillation (VT/VF). In group C, we had 16 patients (53.3%) of sinus rhythm, four patients (13.3%) of AF, one patient (3.3%) of supraventricular tachycardia (SVT), three patients (10%) of AV block and six patients (20%) of VT/VF (Table 2).

The incidence of POAF during the first five postoperative days was significantly lower in group M compared two group C (P=0.005). Only four cases (12.9%) developed POAF in group M versus 14 cases (46.7%) in group C (Table 2). In group M, POAF cases occurred on the 2nd postoperative day (2 cases) and the 3rd postoperative day (2 cases); Patients were hemodynamically stable during the attacks, so they were managed by amiodarone therapy according to the preset protocol. In group C, POAF cases occurred on the 1st, 2nd, 3rd, and 5th postoperative days (2, 6, 4, and 2 cases respectively). Three out of the 14 cases in group C were associated with hemodynamic instability, so synchronized cardioversion was used to control the attacks, while the remaining 11 cases were hemodynamically stable and managed by amiodarone therapy. In all cases, blood samples were taken for...
correction of any electrolyte or acid-base imbalance as a part of the preset protocol.

| Rhythm Declamping     | Group M (n=31) | Group C (n=30) | P Value |
|-----------------------|----------------|----------------|---------|
| Sinus                 | 19 (61.3%)     | 16 (53.3%)     | 0.806   |
| AF                    | 3 (9.7%)       | 4 (13.3%)      |         |
| SVT                   | 0 (0%)         | 1 (3.3%)       |         |
| AVB                   | 4 (12.9%)      | 3 (10%)        |         |
| VT/VF                 | 5 (16.1%)      | 6 (20%)        |         |
| POAF (Day 1-5)        | 4 (12.9%)      | 14 (46.7%)     | 0.005*  |

Data are expressed as numbers and (percentages). M: Magnesium Sulfate, C: Control, n: number of patients, AF: Atrial Fibrillation, SVT: Supraventricular Tachycardia, AVB: Atrioventricular Block, VT: Ventricular Tachycardia, VF: Ventricular Fibrillation, POAF: Postoperative Atrial Fibrillation. P-value <0.05 is considered significant. *denotes significant difference between both groups.

### Table 2: Cardiac Rhythm.

#### Serum electrolytes

Baseline serum magnesium showed no significant difference between both groups. During the first five postoperative days, serum magnesium levels were significantly higher in group M compared to group C (Figure 2). There were no significant differences between both groups regarding the serum potassium level preoperatively or during the first five postoperative days (Table 3).

![Figure 2: Serum Magnesium with SD (mean ± SD). M: Magnesium Sulfate; C: Control. * Denotes significant difference compared to the control group.](image)

**Figure 2: Serum Magnesium with SD (mean ± SD). M: Magnesium Sulfate; C: Control. * Denotes significant difference compared to the control group.**

| Time     | Group M | Group C | P value |
|----------|---------|---------|---------|
| Baseline | 4.05 ± 0.44 | 4.21 ± 0.43 | 0.154   |
| Day 1    | 4.21 ± 0.44 | 4.30 ± 0.54 | 0.477   |
| Day 2    | 4.28 ± 0.55 | 4.31 ± 0.54 | 0.794   |
| Day 3    | 4.33 ± 0.55 | 4.23 ± 0.43 | 0.45    |
| Day 4    | 4.38 ± 0.51 | 4.40 ± 0.50 | 0.862   |
| Day 5    | 4.33 ± 0.51 | 4.47 ± 0.50 | 0.294   |

Data are expressed as mean ± SD. M: Magnesium Sulfate, C: Control, n: number of Patients. P value <0.05 is considered significant.

### Table 3: Serum potassium (mmol/L).

**WBC count**

There was no significant difference between both groups regarding the baseline WBC count. Postoperatively, the WBC count increased dramatically; however, there were no significant differences between both groups on the first five postoperative days (Table 4).

| Time     | Group M | Group C | P value |
|----------|---------|---------|---------|
| Baseline | 7.08 ± 1.37 | 7.75 ± 1.69 | 0.091   |
| Day 1    | 17.11 ± 2.85 | 17.40 ± 3.52 | 0.723   |
| Day 2    | 16.58 ± 2.57 | 17.78 ± 3.58 | 0.139   |
| Day 3    | 15.97 ± 2.59 | 17.12 ± 3.39 | 0.139   |
| Day 4    | 15.22 ± 2.63 | 16.30 ± 3.44 | 0.172   |
| Day 5    | 13.84 ± 2.95 | 14.91 ± 4.17 | 0.252   |

Data are expressed as mean ± SD. M: Magnesium Sulfate, C: Control, n: number of Patients. P value <0.05 is considered significant. * denotes significant difference between both groups.

### Table 4: White Blood Cell Count (× 10³/mm³).

**C-reactive protein**

No significant differences between the two groups regarding the serum levels of CRP during the 1st and 2nd postoperative days (P1=0.971 and P2=0.812); however, the serum levels of CRP during the 3rd, 4th and 5th postoperative days were significantly lower in group M compared to group C (P3=0.001, P4=0.001 and P5=0.012) (Figure 3).

![Figure 3: C-reactive protein (Median). M: Magnesium Sulfate; C: Control; CRP: C-Reactive Protein. * Denotes significant difference compared to the control group.](image)

**Figure 3: C-reactive protein (Median). M: Magnesium Sulfate; C: Control; CRP: C-Reactive Protein. * Denotes significant difference compared to the control group.**
Interleukin-6

There were no significant differences between the two groups regarding the serum levels of IL-6 post-induction, at the end of CPB, 6 h post-CPB or 24 h after induction of anesthesia (Table 5); however, the serum level of IL-6 was significantly lower in group M compared to group C in the 5th Postoperative day (P=0.001) (Figure 4).

Troponin I

The serum levels of cTnI showed no significant differences between the two groups when measured 12 h or 24 h after induction of anesthesia (Table 5).

Inotropic support

There were no significant differences between the two groups regarding the duration of inotropic support, the mean 24 h IS, or the maximum 24 h IS (Table 6).

Table 6: Inotropic Support.

| Duration of inotropic support (Hours) | Group M (n=31) | Group C (n=30) | P value |
|--------------------------------------|----------------|----------------|---------|
| Mean 24 h IS                          | 19 (11.0-24.0) | 21.5 (7.5-27.0) | 0.954   |
| Maximum 24 h IS                       | 5 (4.00-7.00)  | 6.5 (5.00-8.50) | 0.07    |

Data are expressed as median and (interquartile range). M: Magnesium Sulfate; C: Control; n: Number of Patients; IS: Inotropic support. P value <0.05 is considered significant.

Discussion

POAF is one of the most common complications after cardiac surgery with a range between 27% and 63%. Its risk increases in combined CABG and valve surgery. POAF gains its importance from its related adverse outcomes as stroke, congestive heart failure, and renal dysfunction which leads to prolonged hospitalization and subsequently high financial burden [11].

Over many years, magnesium was used in the management of atrial and ventricular arrhythmia [12]. Hypomagnesaemia is frequently seen after cardiac surgery, mainly during the 1st postoperative days. It may be related to the perioperative hemodilution, diuretics use, increased anabolic activity and elevation of adrenal hormones due to stress. Whatever the cause of the condition, hypomagnesemia increases the risk of post-cardiac surgery arrhythmia [13].

In this study, we evaluated the effect of prophylactic administration of magnesium sulfate on the incidence of POAF. Also, this study evaluated the anti-inflammatory and cardioprotective effects of magnesium sulfate.

Our results showed that prophylactic administration of magnesium sulfate reduced the incidence of POAF. In agreement to our finding, Nurozler et al. in a controlled double-blind trial that included patients with good left ventricular function and without preoperative arrhythmias who were undergoing CARG surgeries, reported that the use of magnesium sulfate for the first five postoperative days reduced the incidence of POAF [14].

Tiryakioğlu et al. compared the prophylactic use of magnesium sulfate versus amiodarone in patients undergoing CABG and reported that both drugs were effective to prevent postoperative arrhythmia and POAF. Also, they stated that the use of magnesium sulfate might counteract the side effects of low postoperative levels of magnesium [15]. In our study, we used a similar protocol of magnesium sulfate.
administration but with different doses and for isolated valve replacement surgeries.

Two factors may have impacts on the role of magnesium in the management of POAF: dose and time of administration. Christiansen et al. in a double-blind placebo-controlled trial found that atrioventricular node conduction was prolonged by using intravenous magnesium in a dose of 5 mmol with no further prolongation when using higher dosages. The same study also reported that lower doses of magnesium (defined as a mean cumulative dose of 8.2 gm) were more effective than moderate to high doses (mean cumulative dose of 15 gm) in reducing POAF [12].

Miller et al. in their meta-analysis and Torman et al. in their study reported that administration of magnesium in the preoperative and early postoperative periods reduced the incidence of POAF effectively in CABG surgeries [16,17].

Kiziltepe et al. in their study reported the efficacy and safety of magnesium sulfate for arrhythmias developed after open-heart surgery. Also, they reported that the antiiarrhythmic effect of magnesium sulfate might be related to its pharmacological properties and not to normalization of its serum concentration, so they recommended its use as a first line antiarrhythmic agent even without routine assessment of its serum level [18].

It is worth to mention that serum magnesium level, whether total or ionized, is not a reliable indicator of the total body stores of magnesium and that Low myocardial magnesium content may be an indicator of arrhythmia [13]. So, the value of serum magnesium remains questionable and further studies are needed to show the relevance of serum magnesium and arrhythmia.

Carrio et al. in a controlled trial, reported that magnesium supplementation did not decrease the incidence of POAF in cardiac surgery with CPB [19], but, it worth to mention that magnesium was given only in the immediate postoperative period.

Surprisingly, Lancaster et al., in a large observational study, reported that potassium and magnesium supplementations are ineffective for the prevention of POAF and that higher serum levels of potassium and magnesium were associated with increased risk of POAF after cardiac operation. Furthermore, this study suggested that the mechanism of POAF is not related to electrolyte deficit [20].

Inflammatory response syndrome (SIRS) in open cardiac surgery is mainly attributed to the use of CPB. Once initiated, inflammatory mediators including interleukins (IL-1, IL-2, IL-6, IL-8) and tumor necrosis factor (TNF) are released. These mediators can stimulate leukocyte activation, chemotaxis and leukocyte-endothelial adherence which lead to tissue damage and multiple organ dysfunctions [21].

In our study, we evaluated the effect of magnesium sulfate administration on the inflammatory response provoked by cardiac surgery by comparing the WBC count and serum levels of CRP and IL-6 between both groups. There were no significant differences between both groups regarding the WBC count during the first five postoperative days. However, the serum levels of CRP on the 3rd, 4th, and 5th postoperative days; and the serum level of IL-6 on the 5th postoperative day were significantly lower in magnesium group.

In agreement with this result, Aryana et al. reported that magnesium sulfate infusion could suppress part of the inflammatory response after CABG with CPB as demonstrated by reduced postoperative serum level of IL-6 [1].

Many studies reported that magnesium can modulate cellular events involved in inflammation through different mechanisms including inhibition of NMDA dependent cellular pathways and decrease of leukocyte migration to the infarct area. In addition, hypomagnesemia itself can activate inflammatory neurotransmitters, with an inverse relationship between serum level of magnesium and serum levels of some of the inflammatory markers such as CRP and TNF-alpha [1,22-24].

In this study, we used the serum level of cTnI, both 12 and 24 h after induction of anesthesia, to evaluate the cardioprotective effect of magnesium sulfate. Our results showed no significant differences between both groups.

Magnesium supplementation is reported to have cardioprotective effects through inhibition of calcium influx and hence reduction of cellular calcium overload and through the decrease of the release of catecholamines. As well it improves collaterals of coronary circulation by its vasodilator effect [22].

It is worth to mention that magnesium treatment in the acute phase of myocardial infarction was favorable in LIMIT-2 trial [25], but ISIS-4 trial, conducted later with a substantially larger sample, did not find an improved clinical outcome in the group treated with magnesium [26]. Also, De Oliveria et al., in a meta-analysis, reported no effect of magnesium supplementation on the incidence of postoperative myocardial infarction [27].

A limitation of this study was the inability to measure other inflammatory markers such as IL-8 and TNF due to financial obstacles.

We recommend further trials to study the correlation between the intracellular and the serum levels of magnesium and their relation to POAF after cardiac valve replacement surgery.

Conclusion

In conclusion, prophylactic use of magnesium sulfate in patients with rheumatic heart disease undergoing isolated cardiac valve replacement surgery can decrease the incidence of POAF. It may play a role in attenuating the inflammatory process associated with the use of cardiopulmonary bypass.

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