INTRA VENOUS MAGNESIUM PREVENTS ATRIAL FIBRILLATION AFTER VALVULAR HEART SURGERY

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Abstract

Introduction:

Atrial fibrillation (AF) is a common complication after cardiac surgery, its frequency ranges between 25–40% reaching upto 50% following bypass surgeries as reported in previous studies. Several reports have indicated that postoperative AF is associated with significantly increased morbidity and mortality. Our primary aim in this study was to investigate the effectiveness of prophylactic magnesium sulfate in the prophylaxis of atrial fibrillation and compare them with a control group during and following cardiac surgery.

Materials and methods:

After IREB approval,100 patients who were scheduled to undergo elective cardiac valvular surgery and had provided informed written consent were studied from January 2007 until January 2009 in cardiovascular department of Postgraduate Medical Institute Lady Reading Hospital Peshawar. Operations and management of atrial fibrillations were performed by the same surgical team. Data were statistically described in terms of the mean ± standard deviation (SD), a frequency (number of cases) or a percentage when appropriate. The chi-squared ($\chi^2$) test was performed to compare categorical data. P values of 0.05 or < 0.05 were considered statistically significant.

Results:

In the treatment group (n = 50) 64 % of the patients were women and 36% were men, the average age was 36 ± 12.9 years (range 20-60 years). The control group also consisted of 50 patients 40 men and 30 women, mean age 40 ± 11.35 years, age range 20-60 years). Data collected were the number of patients, preoperative patient characteristics, preoperative medications, surgery specifications, LOS (length of
stay) in ICU and in the hospital. LOS in ICU as well as in the ward were significantly long in our control group compare to treatment group. The rest of data were significantly not different in both of our studied groups.

Blood magnesium sulfate levels in both groups were not significantly different in Preoperative, perioperative, and postoperative patients. Frequency of AF (atrial fibrillation) in the treatment group was significantly lower (P <0.05) compare to control group. No mortality was recorded in our studied groups.

**Conclusion:**

Magnesium provides good pre, intra and postoperative control of arrhythmias without any significant adverse effects, therefore it should be encouraged in open heart surgeries.

**Keywords:**

Magnesium sulfate, Arrhythmias
Introduction:

Atrial fibrillation (AF) is a common complication after cardiac surgery, its frequency ranges between 25–40% reaching up to 50% following coronary artery bypass grafting (CABG) as reported in previous studies. Several reports have indicated that postoperative AF is associated with significantly increased morbidity and mortality, high risk of a cerebrovascular accident, longer hospital stay, higher hospital costs, compromised cardiac function, adverse effects from drugs used to prevent AF and decreased long-term survival.

Risk factors of postsurgical AF could be divided into: preoperative, intra-operative and postoperative. Preoperative factors mainly include: a. Atrial tissue damages due to age, b. Heart diseases and c. Electrolytic imbalance, obesity, male gender, may also predispose to AF. Intra-operative risk factors could be attributed to increased sympathetic activation due to stimulation of catecholamines, reflex sympathetic activation from volume loss, anemia, pain, adrenergic drug administration and extracorporeal circulation. Postoperative AF may be correlated with hemodynamic deterioration, stroke, hypomagnesemia and others as increase in postoperative P-wave dispersion and exaggerated inflammation reaction. It has been reported that postoperative atrial fibrillation can occur at any time during the entire postoperative course, but especially between the 2nd and 5th postoperative days.

As Hypomagnesemia is one of the most common cause and 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. There are many pharmacologic agents to prevent postoperative atrial fibrillation (POAF) but none of them are effective for all patients and are free of complications. Magnesium, like several other pharmacologic agents has been used in the prophylaxis of postoperative AF with varying degrees of success and seems to be with great promise to prevent POAF following cardiac surgeries. Magnesium exerts its antiarrhythmic effects in part by inhibiting L-type calcium channels which reduces sinus node rate firing, prolongs atrioventricular conductance, and increases atrioventricular node refractoriness and inward rectifier potassium channels in the cardiac action potential.

Our primary aim in this study was to investigate the effectiveness of prophylactic magnesium sulfate in the prophylaxis of atrial fibrillation and compare them with a control group during and following cardiac surgery.
Materials and methods

After IREB approval, 100 patients who were scheduled to undergo elective cardiac valvular surgery and had provided informed written consent were studied from January 2007 until January 2009 at Post graduate Medical Institute Lady Reading Hospital Peshawar. To investigate the effect of magnesium sulfate on the development of postoperative atrial fibrillation, we conducted a prospective randomized placebo-controlled trial in 100 consecutive patients who underwent elective and initial valvular operations in our center. Operations and management of atrial fibrillations were performed by the same surgical team.

Among these 50 patients were enrolled into either of two groups in a randomized study: group M (n = 50) received magnesium sulfate, while group S (n = 50) received normal saline. The sequence of administration of placebo or magnesium sulfate was randomized and the sequence of randomization was concealed using sequentially numbered envelopes provided by an independent investigator. Studies were included only if they met all of the following criteria. The primary outcome measure was the incidence of postoperative AF or atrial flutter except where total incidence of supraventricular arrhythmia was documented. Two other outcome measures, length of stay (LOS) in ICU and in ward were also analyzed.

Exclusion criteria included history of atrial fibrillation, history of paroxysmal atrial fibrillation even though the patient is in sinus rhythm just before the operation, preoperative heart rate of less than 50 beats/min, redo surgery, blood pressure of less than 100 mm Hg, history of renal failure (serum creatinine level > 2.0 mg/dL), and severe respiratory function disorder.

Patients were anesthetized with a standard technique including propofol 1–2 mg/kg, morphine 0.1 mg/kg, and pancuronium 0.1 mg/kg to facilitate tracheal intubation. Anesthesia was maintained with sevoflurane 2 % in 60 % oxygen/air mixture together with incremental boluses of pancuronium 1 mg when required. Patients were monitored by five-lead ECG, pulse oximetry, central venous line, invasive arterial blood pressure, capnography, urine output, serial blood gas analysis to monitor oxygenation, ventilation, acid–base balance, and electrolytes including potassium and magnesium. Group ‘M’ received magnesium sulfate 80 mg/kg in 100 ml 0.9 % saline in 30 min preoperatively while S group received normal saline. As the incidence of AF varies and depends on the type of surgery, surgical technique, and management,
we elected to determine its incidence in our center utilizing same resources, surgical technique, surgical team and management to exclude any confounding factors.

Group ‘M’ received a magnesium sulfate infusion at a rate of 80 mg/kg in 30 min intraoperatively. Atrial fibrillation is diagnosed on a 5-lead electrocardiogram (ECG). Atrial fibrillation was defined as an episode of atrial fibrillation or flutter lasting >30 s and by the absence of P waves, unorganized electrical activity in their place, and irregular R–R intervals due to irregular conduction of impulses to the ventricles based on the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for the management of patients with atrial fibrillation. Postoperatively first sample for arterial blood gas analysis was obtained just after arrival in the ICU to check for oxygenation, ventilation, acid–base disturbance and any electrolyte disturbance. Serial samples were then taken regularly every 4 h and as needed. Atrial fibrillation was monitored during the ICU stay through routine hemodynamic monitoring including heart rate and blood pressure as well as daily ECG. Additional ECG was done if the patient complained of palpitation or in the presence of an irregular pulse. Treatment group patients were extubated whenever they occupied the extubation criteria.

Hypokalemia and hypomagnesemia were defined as a serum potassium level below 3.5 mmol/l and a serum magnesium level below 1.3 mmol/l respectively. Potassium and magnesium supplementation was provided when hypokalemia and hypomagnesemia were diagnosed. In addition the side effects of both drugs were also assessed. After discharge from the ICU daily ECG and serial blood gas analysis was continuously monitored during the postoperative period and any electrolyte disturbance such as hypokalemia or hypomagnesemia was vigorously corrected. Onset of atrial fibrillation was considered as sufficient criteria for the initiation of treatment. Amiodarone or β-blocker was used in case of resistant arrhythmias.

**Statistical methods**

Power analysis of the occurrence of AF in the two study groups was performed as the primary outcome of this study. The chi-squared test was chosen to perform the analysis the α-error level was fixed at 0.05 or < 0.05 and the sample size was 50 participants for each group. Calculations were done using the SPSS, Power and Sample Size Calculations software package, version 17. Data were statistically described in terms of the mean ± standard deviation (SD), a frequency (number of cases) or a percentage when appropriate.
Results

In the treatment group (n = 50) 64% of the patients were women and 36% were men, the average age was 36 ± 12.9 years (range 20-60 years). The control group also consisted of 50 patients 40 men and 30 women, mean age 40 ± 11.35 years, age range 20-60 years). All patients underwent elective valve replacement surgery. They all had sinus rhythm preoperatively. Data collected were the number of patients, preoperative patient characteristics, preoperative medications, surgery specifications, LOS in ICU and in the hospital of both studied groups are summarized in Table 1.

Blood magnesium sulfate levels were measured 12 hours before the operation, 1 hour after the operation and at the first, second, and third postoperative days Normal limits of magnesium sulfate level were considered to be 1.8 to 2.5 mg/dL. Potassium replacement was done to keep potassium levels between 4.0 and 5.0 mmol/L to prevent electrolyte imbalance.

Preoperative, perioperative, and postoperative plasma magnesium sulfate levels of patients and frequency of AF in the treatment and control groups are shown in table 2. There was no difference between groups in terms of timing of extubation, only two patients in our saline group showed resistant arrhythmias, which were treated with amiodarone infusion @ 500ug/kg for two days. No mortality was recorded in our studied groups.
Discussion

The incidence of Atrial fibrillation is higher in patients who have valvular surgery alone or combined with coronary artery bypass. Although its causes are not clear, it is multifactorial advanced age and low magnesium sulfate levels are substantial risk factors. In addition to the above risk factors cardiopulmonary bypass, metabolic changes, body temperature, electrolyte imbalances, anesthetic agents, durations of cardiopulmonary bypass and aortic crossclamping, stress, age-related atrial atrophic changes and discontinuation of preoperatively used β-blockers might also contribute to the development of atrial fibrillation. Low magnesium concentrations are independent risk factors of AF after cardiovascular surgery. Magnesium sulfate reaches its minimum level at the first postoperative day. Magnesium sulfate deficiency is due to hemodilution and intraoperative and postoperative cellular depletion. Diuretic use, secondary hyperaldosteronism, high levels of epinephrine, increased anabolic activity, extreme stress caused by sympathetic activity and increased urinary loss contribute to this decrease. A low magnesium sulfate level is arrhythmogenic because a decrease in magnesium sulfate level increases the sensitivity of atrial myocardium and arrhythmias such as atrial fibrillation might develop. These findings indicate the need for magnesium sulfate supplementation after and during cardiac surgery. In atrial fibrillation with high ventricular response, cardiac output decreases and oxygen consumption of the heart increases. This situation might lead to severe hemodynamic problems, particularly in patient with left ventricular dysfunction. Several studies have been conducted using magnesium as prophylaxis agent postoperatively. Intracellular magnesium levels are significantly lower in cardiac surgery patients compared with healthy volunteers, the onset of POAF following generally occurs between 24 and 96 h postoperatively, with a peak incidence on the second postoperative day and that it is often associated with hypomagnesaemia, intravenous magnesium supplementation during this period may play a key role in the suppression of POAF. Miller and colleagues in one of their meta-analysis showed that magnesium administration significantly reduced the frequency of postoperative AF. Rasmussen and colleagues found that magnesium sulfate prophylaxis provided a decrease from 47% to 21% in all arrhythmias. Our study showed a significant difference (P = 0.05) regarding frequency of AF in both groups. Preoperative administration of magnesium was more effective in prevention of postoperative AF then intraoperative or postoperative prevention. Mortality and LOS were not affected significantly. We started magnesium preoperatively and found very good control of fibrillation in M group. One problem with the use of antiarrhythmic agents to prevent postoperative AF is that the majority of patients are exposed to drugs for
which there is no actual need. Intravenous magnesium is appealing because it is associated with minimum side effects as long as the serum concentration is maintained at an optimal level. The mechanisms by which magnesium administration reduces the incidence of postoperative AF are not entirely known, but it is believed to significantly increases atrial refractoriness. Magnesium sulfate suppresses the cardiac arrhythmia seen during acute myocardial infarction. Magnesium sulfate decreases afterload, provides coronary vasodilatation, decreases platelet aggregation and protects the cell against ischemia and reperfusion. The combination of the treatment effects of correcting magnesium depletion and of increasing atrial refractoriness caused by magnesium administration is probably responsible for the overall beneficial effect of magnesium. Maslow and colleagues reported that intraoperative administration of magnesium sulfate decreased the incidence of postoperative atrial tachyarrhythmia. However, its administration alone is not sufficient for the prophylaxis of atrial fibrillation, other causes for atrial fibrillation must be excluded and treated. Individual studies have shown that a high dose of magnesium was significantly more effective than a low dose in preventing AF. Examination of the dose-response effect of magnesium on the prevention of arrhythmias may be necessary. Abraham and associates reported that administration of a single dose of 2.4 g of magnesium sulfate during the early phase of acute myocardial infarction decreased ventricular arrhythmia incidence from 34.8% to 14.6%. Demographic bias for example in one study showed that patients in the magnesium group had a higher ratio of male gender (98% versus 86% \( P = 0.02 \)). This characteristic male gender has been consistently a risk factor for the development of POAF, most of our patients in both groups were female but there was no significant difference regarding sex in both treatment groups. Mean duration of hospitalization after atrial fibrillation extended the duration of hospitalization in two groups. LOS in ICU and in ward were significantly prolonged in control group compared to treatment group. Mehmet Kaplan et al demonstrated that atrial fibrillation is a major predictor of longer hospitalization savings. In conclusion atrial fibrillation which develops early after CABG surgery is a serious cause of morbidity and extends the duration of hospitalization. Thus prevention of atrial fibrillation would not only provide physiologic and hemodynamic benefits but will also cause cost.

We preferred the intravenous route instead of the oral route to attain a rapid and effective result. No doubt magnesium provides good pre, intra and postoperative control of arrhythmias without any significant adverse effects, therefore it should be encouraged in open heart surgeries.
REF


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30. Mehmet Kaplan, MDa, Mustafa Sinan Kut, MDb, Umit Akif Icer, MDb, Mahmut Murat Demirtas, MDb Intravenous magnesium sulfate prophylaxis for atrial fibrillation after coronary artery bypass surgery 2003 The American Association for Thoracic Surgery.

<table>
<thead>
<tr>
<th>Magnesium sulfate (n = 50)</th>
<th>Control (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
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<tr>
<td>--------------------------</td>
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<tr>
<td>Age (years)</td>
<td>36 ± 12.9</td>
<td>40 ± 11.35</td>
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<tr>
<td>Male/female</td>
<td>18/32</td>
<td>20/30</td>
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<tr>
<td>FEV1</td>
<td>83 ± 12.1</td>
<td>88 ± 9.26</td>
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<tr>
<td>ICU stay (h)</td>
<td>48 ± 4.4</td>
<td>60.8 ± 2.89</td>
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<tr>
<td>Hospital stay (days)</td>
<td>6.2 ± 1.03</td>
<td>8.1 ± 0.99</td>
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<tr>
<td>MVR/AVR/DVR</td>
<td>23/12/15</td>
<td>20/13/17</td>
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<tr>
<td>β-blockers/ Ca^{2+} chan blockers</td>
<td>28/22</td>
<td>35/15</td>
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Table No 2

<table>
<thead>
<tr>
<th></th>
<th>Magnesium sulfate (n = 50)</th>
<th>Control (n = 50)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Preoperative (Mg level)</td>
<td>1.76 ± 0.21</td>
<td>1.66 ± 0.023</td>
<td>0.464 (NS)</td>
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<tr>
<td>Perioperative, (Mg level)</td>
<td>2.50 ± 0.25</td>
<td>1.79 ± 0.10</td>
<td>0.471 (NS)</td>
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<td>First postop day(Mg level)</td>
<td>2.6 ± 0.096</td>
<td>1.80 ± 0.044</td>
<td>0.658 (NS)</td>
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<td>Second postop day (Mg level)</td>
<td>2.64± 0.24</td>
<td>1.83 ± 0.10</td>
<td>1.210(NS)</td>
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<tr>
<td>Third postop day (Mg level)</td>
<td>2.50 ± 0.26</td>
<td>2.52 ± 0.08</td>
<td>0.083 (NS)</td>
</tr>
<tr>
<td>Frequency of AF</td>
<td>10 (20 %)</td>
<td>20 (40 %)</td>
<td>0.005 (significant)</td>
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