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ORIGINAL ARTICLE

A comparative study between amiodarone and magnesium sulfate as antiarrhythmic agents for prophylaxis against atrial fibrillation following lobectomy

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Abstract

Purpose Atrial fibrillations are common after thoracic surgery. Amiodarone and magnesium sulfate have been used for the management of atrial fibrillation following cardiac and non-cardiac surgery. However, to our knowledge, comparisons of both drugs with each other and with a control group in relation to the prevention of AF following lung surgery have not been performed. Our primary aim in this study was to prospectively evaluate the prophylactic effects of magnesium sulfate and amiodarone used separately and compare them with a control group analyzed retrospectively during and following lobectomy surgeries.

Patients and methods The prophylactic value of amiodarone (group A; 219 patients) administered as an intravenous infusion (15 mg/kg for 48 h postoperatively) after a loading dose (5 mg/kg) was compared with magnesium sulfate (group M; 219 patients) administered intravenously as a loading dose (80 mg/kg magnesium sulfate over 30 min preoperatively) and then as an intravenous infusion (8 mg/kg/h for 48 h) in 438 patients undergoing lobectomy. These two groups were compared with a control group of 219 patients who were analyzed retrospectively.

Results The results showed significantly lower incidences of AF in groups A and M when compared with group C ($P < 0.05$). There was no significant difference between the amiodarone and magnesium sulfate groups. However, the incidence of postoperative AF was lower in the amiodarone group, where only 21 (10 %) patients developed AF in comparison to 27 (12.5 %) patients in the magnesium sulfate group. Group C showed a higher incidence, 44 (20.5 %) patients, when compared with both groups. In addition, there were significant differences between the three groups concerning intensive care unit (ICU) and total hospital stays ($P < 0.05$).

Conclusion Our study showed that during the intra- and postoperative periods, both amiodarone and magnesium sulfate are effective at preventing the incidence of atrial fibrillation following lung resection surgery in comparison to the control group.

Keywords Magnesium sulfate · Amiodarone · Atrial fibrillation · Lobectomy

M. A. Khalil · A. E. Al-Agaty · W. G. Ali
Department of Anesthesia, Faculty of Medicine,
Cairo University, Giza, Egypt

M. A. Khalil (✉)
Department of Anesthesia, Saad Specialist Hospital,
Prince Faisal Bin Fahad Street, Al-Khobar 30353,
Kingdom of Saudi Arabia
e-mail: mohamedkhalil404@hotmail.com

M. S. Abdel Azeem
Department of Critical Care, Faculty of Medicine,
Cairo University, Giza, Egypt

Introduction

Atrial fibrillation frequently complicates pulmonary surgery resection, with an incidence ranging from 10 to 42 % [1]. It is associated with significantly increased morbidity and mortality, high risk of a cerebrovascular accident, longer hospital stay, higher hospital costs, and decreased long-term survival [2, 3].

Many risk factors have been related to the prevalence of postoperative atrial fibrillation, including old age, prior heart disease, chronic obstructive pulmonary disease [4], previous arrhythmias, and type of surgery [2]. 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 [5].

Amiodarone and magnesium sulfate have been used to control atrial fibrillation following cardiac and non-cardiac surgery. Despite the significant incidence of AF following cardiac surgery, several reports had studied the effect of both magnesium sulfate and amiodarone on the incidence of postoperative AF [6, 7]. Furthermore, a previous study showed that prophylactic infusion of magnesium sulfate is effective at reducing the incidence of atrial tachyarrhythmias following thoracic surgery [8]. Similarly, low-dose oral amiodarone was reported to reduce the incidence of atrial fibrillation after lung resection [9].

However, to our knowledge, comparisons of both drugs with each other and with a control group in relation to the prevention of AF for lung surgeries have not been performed. Our primary aim in this study was to prospectively evaluate the prophylactic effects of magnesium sulfate and amiodarone used separately and compare them with a control group analyzed retrospectively during and following lobectomy surgery.

Materials and methods

Patient population

After IRB approval, 657 patients who were scheduled to undergo elective lung resection surgery and had provided informed written consent were studied from January 2007 until January 2009 at Cairo University Hospitals. Among these, 438 patients were enrolled into either of two groups in a prospective randomized double-blinded study: group M ($n = 219$) received magnesium sulfate, while group A ($n = 219$) received amiodarone. The other 219 patients were previous cases encountered in our department, who were studied retrospectively. The sequence of administration of amiodarone or magnesium sulfate was randomized. Randomization was performed according to a computer-generated list, and the sequence of randomization was concealed using sequentially numbered envelopes provided by an independent investigator.

Only patients in whom pulmonary resection was possible for lobectomy were included. The two main reasons for lung resection were malignancy and suppurative lung disease (lung abscess and bronchiectatic lesions). All hypertensive patients were on preoperative selective beta-blockers and/or Ca^{2+} channel blocker treatment. No patient was undergoing statin therapy. Excluded patients were those with permanent atrial fibrillation, previous lung resection, asthmatic patients, and patients with previous cardiac surgery, a history of thyroid disease, or coexisting cardiac or renal disease.

Anesthetic technique

A 16 or 14G venous cannula together with a 20G radial arterial catheter and a thoracic epidural catheter were inserted before surgery. All patients were anesthetized with a standard technique including propofol 1–2 mg/kg, fentanyl 2 µg/kg, and pancuronium 1 mg/kg to facilitate tracheal intubation. One-lung ventilation was achieved by inserting a double lumen tube, and fiber-optic bronchoscopy was used to ensure an appropriate insertion position.

Anesthesia was maintained with sevoflurane 2 % in 60 % oxygen/air mixture together with incremental boluses of pancuronium 1 mg and fentanyl 50 µg when required. Patients were monitored by five-lead ECG, pulse oximetry, invasive arterial blood pressure, capnography, urine output, serial blood gas analysis to monitor oxygenation, ventilation, acid–base balance, and electrolytes (including potassium and magnesium; deficiencies in these elements play an important role in the pathogenesis of arrhythmia). A blood sample was drawn in the setting of one-lung ventilation, and a second one was obtained at the end of surgery, just before shifting the patient to the ICU.

Before starting the operation, patients were allocated using a table of random numbers and sealed envelopes into one of two groups consisting of 219 patients each. Group A received a loading dose of 5 mg/kg amiodarone over 30 min, started at the beginning of surgery, while a maintenance dose of 15 mg/kg was infused over 48 h postoperatively. Group M received 80 mg magnesium sulfate/kg ideal weight in 100 ml dextrose 5 % water 30 min preoperatively; this dose has been shown to be effective at reducing the incidence of atrial fibrillation following coronary artery bypass grafting (CABG) [10]. To assure the blindness of the study, both drugs, amiodarone and magnesium sulfate, were infused for the same period (48 h). In addition, the investigators who were responsible for drug preparation and infusion were neither involved in nor aware of the nature of the assessment at any time during the study. As the incidence of AF varies between 10 and 42 %, and depends on the type of surgery, surgical technique, and management, we elected to determine its incidence in our center [11]. For these reasons, the two groups of patients were compared with another control group consisting of 219 patients who were previously operated upon in our center, undergoing similar lung surgery by the same surgical team, and so were studied retrospectively here.

Postoperative ICU course

Postoperatively, patients in group A received a continuous amiodarone infusion at a rate of 15 mg/kg for 48 h, while patients in group M received a magnesium sulfate infusion at a rate of 8 mg/kg/h for 48 h [10, 12]. Atrial fibrillation is diagnosed on a 12-lead electrocardiogram (ECG), an investigation performed routinely whenever an irregular heartbeat is suspected. 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 [13, 14]. Postoperative atrial fibrillation was monitored during the ICU stay through continuous ECG monitoring and after the patient had been transferred to the ward during the hospital stay; atrial fibrillation was monitored 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.

After discharge from the ICU, all patients were monitored with an alarm-triggered telemetry system and double-checked for overlooked events every morning for at least four days. In addition, a 12-lead ECG was obtained if clinical observation or telemetric monitoring detected any arrhythmia. Postoperative analgesia was maintained with patient-controlled epidural analgesia with 0.125 % bupivacaine and fentanyl 2 μg/ml according to the following regimen: 5 ml as an initial bolus dose, a continuous infusion rate of 4 ml/h, a bolus dose of 2 ml, and a 10 min lockout period. Serial blood gas analysis was continuously monitored during the postoperative period, and any electrolyte disturbance such as hypokalemia or hypomagnesemia was vigorously corrected. The 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. 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.

Power analysis

Power analysis of the occurrence of AF in the three 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, and the sample size was 219 participants for each group. Based on the recorded incidence of AF in each group (9.6 % in the amiodarone, 12.3 % in the $MgSO_4$, and 20.1 % in the control groups), the final result was that the present study has a power of 60.1 % to detect the difference between the $MgSO_4$ and control groups, 87.3 % to detect the difference between the amiodarone and control groups, and 14.7 % to detect the difference between the $MgSO_4$ and amiodarone groups. Calculations were done using the PS: Power and Sample Size Calculations software package, version 2.1.30 for MS Windows (see http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize).

Statistical methods

Data were statistically described in terms of the mean ± standard deviation (±SD), a frequency (number of cases), or a percentage when appropriate. Comparison of numerical variables between the study groups was achieved using a one-way analysis of variance (ANOVA) with post hoc multiple two-group comparisons. The chi-squared (χ^2) test was performed to compare categorical data. The exact test was used instead when the expected frequency was less than 5. *P* values of <0.05 were considered statistically significant. All statistical calculations were done using the software package SPSS (Statistical Package for the Social Science, version 15; SPSS Inc., Chicago, IL, USA) for Microsoft Windows.

Results

Demographic and preoperative data are presented in Table 1. There were no statistically significant differences among the three groups.

For the postoperative period, our study showed that the incidence of postoperative atrial fibrillation was lower in the amiodarone group (21 patients; 10 %) than in the magnesium sulfate group (27 patients; 12.5 %), but there was no statistically significant difference between the two groups. However, when compared with the control group (amiodarone vs. control and magnesium sulfate vs. control groups), there were significant changes ($P < 0.05$) (Table 2). The control group showed a higher incidence of AF (44 patients; 20.5 %).

In addition, for the 27 patients in group A, 6 of them developed a normal sinus rhythm after the start of amiodarone treatment following the failure of magnesium sulfate to restore their normal rhythm. For the 44 patients in the control group, amiodarone treatment was started in order to produce pharmacological cardioversion, but only 16 patients developed a normal sinus rhythm. It should be noted that all of the patients in the three groups who did not develop a normal rhythm and were still undergoing postoperative atrial fibrillation in spite of amiodarone treatment

Table 1 Preoperative and demographic data

	Amiodarone ($n = 219$)	Magnesium sulfate ($n = 219$)	Control ($n = 219$)	P value
Age (years)	63.4 ± 4.06	64.2 ± 3.8	63.7 ± 3.1	0.072
Male/female	152/67	154/65	149/70	0.873
Hypertension	131 (60 %)	129 (59 %)	133 (61 %)	0.927
Smoking	142 (65 %)	151 (69 %)	140 (64 %)	0.498
COPD	32	43	45	0.223
Diabetes	43	52	48	0.580
FEV1%	80.8 ± 0.51	80.9 ± 0.54	80.8 ± 0.56	0.080
Benign/malignant lesion	105/114	108/111	102/117	0.848
β-blockers (selective β-1)	111	102	118	0.309
Ca^{2+} channel blockers	59	53	62	0.611

COPD chronic obstructive pulmonary disease, *FEV1* forced expiratory volume in 1 s

Table 2 Postoperative data

	Amiodarone ($n = 219$)	Magnesium sulfate ($n = 219$)	Control ($n = 219$)	P value
Bradycardia (<60/min)	133 (61 %)	128 (58.5 %)	129 (59 %)	0.927
Hypotension (>20 % baseline)	151 (69 %)	142 (65 %)	140 (64 %)	0.498
Postoperative AF	21 (10 %)†	27 (12.5 %)‡	44 (20.5 %)*	0.005
Blood transfusion (units)	1.72 ± 0.28	1.74 ± 0.29	1.68 ± 0.27	0.075
ICU stay (h)	24.8 ± 0.86	32.5 ± 0.94	43.8 ± 1.2*	<0.001
Hospital stay (days)	4.2 ± 0.17	6.1 ± 0.19	8.3 ± 0.17*	<0.001

AF atrial fibrillation, *ICU* intensive care unit

* Significant difference between the three groups

† the amiodarone and control groups, or ‡the magnesium sulfate and control groups

were hemodynamically stable: there was no need to give any electrical cardioversion.

Concerning the ICU stay, there was a statistically significant difference between the three groups ($P < 0.05$), where patients in the amiodarone group stayed for the shortest period (24.8 ± 0.86 h) in comparison to patients in the magnesium and control groups (32.5 ± 0.94 and 43.8 ± 1.2 h, respectively) (Table 2). Also, patients in the amiodarone group had significantly different total durations of their hospital stays from the magnesium and control patients ($P < 0.05$), (4.2 ± 0.17, 6.1 ± 0.19, and 8.3 ± 0.17 days, respectively) (Table 2).

The main detected side effect of amiodarone infusion was hypotension due to its myocardial depressant and vasodilatory properties. However, this hypotension was easily managed by intravenous fluid hydration without any significant adverse clinical effects. Additionally, there was a case of bradycardia with a heart rate of less than 60/min; however, there was no significant difference between the three groups. For blood transfusion, there was no significant difference between the three groups. No mortality was recorded in our study.

Discussion

Our study showed that amiodarone and magnesium sulfate are effective at preventing the postoperative occurrence of atrial fibrillation following lung resection surgery. There was no significant difference in the prophylactic effects of both drugs. The percentage of patients in group A who developed AF was (10 %), and the equivalent percentage in group M was (12.5 %), which is significantly less than the percentage of patients in group C (20.5 %).

Many studies have shown that the prevalence of atrial fibrillation following lung resection may reach up to about 40 % [15–19]. There are certain risk factors that may increase the risk of this postoperative complication, such as elderly patients, those with a history of previous arrhythmias, and underlying heart disease [20, 21].

Many trials have shown the importance of prophylactic administration of antiarrhythmic agents in cardiothoracic surgery to reduce the incidence of intra- and postoperative atrial fibrillation, leading to a reduction in postoperative pulmonary complications, morbidity, mortality, and costs.

Ciriaco et al. [15] reported a success rate of about 90 % when using amiodarone to establish normal sinus rhythm in patients with supraventricular tachycardia. This is in agreement with our results, which showed that postoperative atrial fibrillation occurred in about 10 % of patients in the amiodarone group, and about 13 % in the magnesium group. In a study done by Van Mieghem et al. [22], it was found that amiodarone may result in the development of adult respiratory distress syndrome after pneumonectomy. However, Nikolaos and Michalis [12] demonstrated that amiodarone may be safely used as an antiarrhythmic agent in supraventricular tachyarrhythmias after lung cancer surgery. This was in agreement with our results, where no significant side effects for amiodarone were detected due to its use for only a short period.

Additionally, antiarrhythmics have been widely used in atrial fibrillation prophylaxis following coronary artery bypass operations. Forlani et al. [23] determined that there was a significant reduction in atrial fibrillation upon the administration of a combination of sotalol and magnesium. Another study done by Aerra et al. [24] also proved that a combination of sotalol and magnesium can significantly reduce the incidence of postoperative atrial fibrillation after coronary surgery.

Previous studies have shown that serum magnesium levels were low in patients who developed postoperative atrial fibrillation [25, 26]. A study done by England et al. [27] showed the importance of magnesium supplementation in reducing postoperative atrial fibrillation after cardiac surgery. However, frequent monitoring of magnesium in our patients did not show any abnormal levels during the study period.

However, one study done by Hazelrigg et al. [10] showed that prophylactic magnesium does not significantly reduce postoperative atrial fibrillation. In that study, they found that the most significant benefit of supplemental magnesium is the reduction of the incidence of atrial fibrillation during the first postoperative day. This may be related to the fact that the increase in extracellular Mg is not always associated with a similar increase in intracellular Mg immediately after systemic infusion, which is important for controlling the arrhythmia process.

Other studies have compared different doses of magnesium sulfate, placebo, amiodarone, and diltiazem following atrial fibrillation [28]. Magnesium was significantly more effective than diltiazem for restoring normal sinus rhythm within the first 15 postoperative hours. However, in a recent study done by Tiryakioglu et al. [6], it was demonstrated that the prophylactic use of either amiodarone or magnesium sulfate is effective at preventing arrhythmias following coronary artery bypass operations. They also showed that amiodarone is more effective in atrial fibrillation resistant cases treated with magnesium. In our study, we tried as much as we could to keep the patients normovolemic, using blood transfusion in cases of significant bleeding, in a trial aiming to prevent hypovolemia and anemia, as it is suggested in many studies that these two factors play an important role in the pathogenesis of postoperative atrial fibrillation [29–31].

Our study had several limitations; first, many patients were hypertensive and were on preoperative beta-blocker and/or calcium channel blocker, which could influence our results. However, a previous trial (COMPACT) investigated the impact of selective versus nonselective beta-blockers on the incidence of postoperative atrial fibrillation [14]. Further study showed that selective beta-blockers had a low impact on the incidence of AF when compared with nonselective beta-blockers [32]. In our study, all of our patients were on selective beta-blockers, which limit their effect on our results. Also, the control group patients were studied retrospectively. Therefore, it is recommended that placebo-controlled, double-blinded patients should be included in future studies. Additionally, it is recommended that older patients than those studied here should be included, as it is well known that age plays an important role in the incidence of postoperative atrial fibrillation following lung resection. Finally, it is also recommended that multicenter studies should be performed in order to get more positive data on the efficacies of both drugs, which generally require a larger number of patients.

In conclusion, our study showed that both amiodarone and magnesium sulfate are effective at preventing postoperative atrial fibrillation following lung resection in comparison to the control group.

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