Addition of dexamethasone to magnesium decreases atrial fibrillation following coronary artery bypass grafting surgery

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Objective
Atrial fibrillation (AF) is a frequent complication that occurs within the first 5 days after cardiac surgery with a reported incidence of 20–40%. It might lead to significant morbidity, such as stroke and myocardial infarction. This prospective study aims to assess the potential benefit of adding a standard dose of dexamethasone to intravenous magnesium (Mg) in the case of AF after coronary artery bypass grafting (CABG).

Patients and methods
This was a prospective, randomized, parallel group study conducted in Ain Shams University Hospital.
One hundred patients scheduled for elective primary isolated CABG were included. All patients had a preoperative sinus rhythm.
Patients in the dexamethasone plus magnesium (DMg) group (50 patients) received two doses of intravenous dexamethasone (6 mg each) along with two doses of Mg supplementation (2 g each) within the first postoperative day.
Patients in the Mg-only group (50 patients) received two doses of Mg supplementation (2 g each) at the similar time as patients in the DMg group.
Continuous ECG recording was carried out for the first 72 h for all patients. Incidence of postoperative complications caused by dexamethasone was recorded.

Measurements and main results
All patients (50 in each group) completed the study. There was no significant difference between the two study groups with regard to demographic data, preoperative comorbidities, and surgical factors. The incidence of postoperative AF was significantly lower in the DMg group ($P < 0.05$) compared with the Mg-only group. There was no significant difference between the study groups regarding duration of postoperative ICU stay and extubation time. There was no significant difference between the study groups regarding incidence of chest infection ($P = 0.7$), sternal wound infection ($P = 0.5$), and urinary tract infection ($P = 0.6$).

Conclusion
Addition of dexamethasone (12 mg) to $MgSO_4$ (2 g) seems to decrease the incidence of new-onset AF in primary isolated elective CABG surgery without an increased incidence of complications.

Keywords:
atrial fibrillation, coronary artery bypass grafting, cardiac surgery, dexamethasone, magnesium

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Introduction

New-onset postoperative atrial fibrillation (AF) is the most common postoperative complication after coronary artery bypass grafting (CABG) surgery, with a reported incidence of 20–40% [1]. It is associated with postoperative morbidities such as cerebrovascular complications and infections (e.g. septicemia, pneumonia, and mediastinitis), which are associated with prolonged hospital stay and increased costs [2,3]. Obesity, male sex, chronic obstructive pulmonary disease, advanced age, hypertension, prior history of AF, preoperative use of digoxin or milrinone, or increased incidence of electrolyte imbalance such as hypomagnesemia or hypokalemia following cardiac surgery increase the risk of developing postoperative AF [4]. Cardiac surgery with extracorporeal circulation is known to be associated with systemic inflammatory response [5], which may be in part responsible for postoperative AF. Complement and C-reactive protein complex levels and the number of white blood cell markers of inflammatory reactions are elevated in patients who develop AF [6]. Thus, corticosteroid prophylaxis in cardiac surgery has been used for about 30 years. The aim of our study was to compare the effectiveness of dexamethasone (12 mg)

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when combined with magnesium (Mg) (2 g) intravenous infusion on prophylaxis of AF following cardiac surgery.

Patients and methods

After obtaining the approval of medical ethical committee of Ain Shams University, 100 patients scheduled for primary isolated elective on-pump CABG surgery at Ain Shams University Hospital (Cairo, Egypt) were enrolled in this study. All patients were of physical status ASA II–III, with normal sinus rhythm. This prospective randomized parallel group study was conducted in 2014. Exclusion criteria included the need for emergency surgery, previous episodes of AF, history of myocardial infarction or renal failure, uncontrolled diabetes mellitus, active tuberculosis (TB), or known allergy, and contraindication to steroids. Patients taking calcium channel blockers, previous magnesium sulfate ($MgSO_4$), steroids, or inotropes were also excluded.

After obtaining written informed consent from all patients, they were randomized by means of closed envelopes into two equal groups: the Mg-only group and the dexamethasone plus magnesium (DMg) group. Patients in the Mg-only group received intravenous infusion of $MgSO_4$ (2 g) dissolved in 100 ml saline over 5 min in the postsurgical cardiac ICU for 2 days. Patients in the DMg group received intravenous dexamethasone (12 mg) in addition to the same dose of $MgSO_4$.

In the preparation room the anesthesiologist secured an 18-G cannula and administered intravenous midazolam 0.05 mg/kg and started an infusion of Ringer's acetate. Standard monitoring was initiated in the form of a five-lead ECG with ST-segment monitoring, pulse oximetry, end tidal CO_2 and invasive arterial blood pressure monitoring, and assessment of nasopharyngeal and skin temperature and urine output. Before induction of anesthesia, a baseline laboratory evaluation was carried out, including prothrombin time, hemoglobin, hematocrit, and fibrinogen level. Anesthesia was induced using thiopental (5–7 mg/kg) and fentanyl (5 mg/kg). Pancuronium (0.08 mg/kg) was used to facilitate endotracheal intubation. Patients were mechanically ventilated in volume-controlled mode to maintain the end expiratory CO_2 at 34–36 mmHg. Anesthesia was maintained with isoflurane 1.2%. Fentanyl (3–5 mg/kg) and pancuronium bromide 0.01 mg/kg were given.

Surgeries were performed on all patients by the same surgical team. Systemic heparinization was carried out before institution of cardiopulmonary bypass (CPB) using unfractionated heparin at an initial dose of 300 IU/kg. A celite activated clotting time above 400 was targeted before institution of CPB. CPB was instituted using Sarns Machine (Harrison, Michigan, USA) primed with 1500 ml of lactated Ringer's solution at a flow rate of 2.6 l/min/m^2 and a Trillium Affinity NT Oxygenator (Medtronic, Minneapolis, USA). Mild hypothermia (32°C) was maintained during CPB. Myocardial protection was achieved with cold cardioplegic solution (20°C). During CPB, homologous packed red blood cells were transfused if hemoglobin concentration was below 6 g/dl. The effect of heparin was reversed at the end of CPB with protamine 1 mg for every 100 U of heparin administered.

Following transfer to the ICU, all patients had their ECG continuously monitored for 72 h. The incidence of AF was documented. Episodes of atrial flutter and supraventricular tachycardia were not included in the study. Four hours after admission into the ICU, all patients (in both groups) received an intravenous infusion of $MgSO_4$ (2 g), dissolved in 100 ml saline, over 5 min. On the morning of day 1, patients received a second dose of intravenous infusion of $MgSO_4$ (2 g) dissolved in 100 ml saline over 5 min. Patients in the DMg group also received intravenous dexamethasone (6 mg) in addition to $MgSO_4$ following the same regimen. On the morning of day 1, all patients (in both groups) received a second dose of intravenous infusion of $MgSO_4$ (2 g), dissolved in 100 ml saline, over 5 min. Patients in the DMg group received a second dose of intravenous dexamethasone (6 mg). The following dose regimen was followed for amiodarone. Amiodarone was started at 150 mg loading dose and maintained at 60 mg/h for the first 6 h and at 30 mg/h for the remaining 72 h and continued at 200 mg/day orally for 15 days after discharge for patients who still had AF.

The primary outcome was the incidence of AF in the first 72 h following surgery. AF was defined as an episode lasting longer than 5 min irrespective of the need for active treatment. The numbers of patients who recovered spontaneously or required treatment (amiodarone+electrical cardioversion) were recorded. Secondary outcomes included extubation time, length of stay, and the incidence of steroid-related complications such as infection of sternal wound, chest infection, and urinary tract infection.

Statistical analysis

Statistical software programs Statistical Package for the Social Sciences, version 17 (SPSS Inc., Chicago, Illinois, USA), at 95% confidence interval and power of 80% with an *a* error of 5%, were used for the analysis of data. Sample size calculation was based on the protocol followed in another study by Abbaszadeh *et al.* [7].

Results of continuous measurements were presented as mean ± SD and results of categorical measurements were presented as number and percentage. A *P*-value less than 0.05 was considered to be significant.

The Student *t*-test was used to determine the significance of the study parameters between the two groups of metric parameters. The χ^2 test/Fisher's exact test was used to determine the significance of the study parameters on a categorical scale between two or more groups.

Results

All patients (50 in each group) completed the study. There was no significant difference in patients' demographic data, preoperative comorbidities, or surgical factors between the two groups (Table 1).

Four and 11 patients developed AF in the DMg and Mg groups, respectively (Table 2). Patients in the DMg group had a significantly lower incidence of AF than did patients in the Mg-only group during the first 72 h after CABG. Management of AF is detailed in Table 2. There was no significant difference between the study groups regarding duration of postoperative ICU stay and extubation time.

Regarding the incidence of chest infection, sternal wound infection, and urinary tract infection, there was no significant difference between the patients in both groups (Table 3). All studied patients were discharged from the ICU on the first postoperative day and from the hospital on the sixth or seventh postoperative day.

Table 1 Demographic data, risk factors, and surgical factors

Demographic and surgical data	Groups		*P*-value
	Group DMg	Group Mg only	
Age	64.4 ± 7.0	63.1 ± 6.9	0.362
Sex (%)			
Female	33	26	0.9013
Male	17	14	
Cross-clamp time (min)	65.0 ± 19.0	69.5 ± 23.3	0.293
Bypass time (min)	105.4 ± 35.4	110.0 ± 33.4	0.506
Number of grafts			
1	6 (12)	4 (8)	0.164
2	13 (26)	7 (14)	
3	26 (52)	27 (54)	
4	5 (10)	12 (24)	
Hypertension	33 (66)	28 (56)	0.305
Diabetes	17 (34)	22 (44)	0.305

Age, cross-clamp time and bypass time were expressed as mean ± SD; other data were expressed as [*N* [%]]; DMg, dexamethasone plus magnesium; Mg, magnesium.

Discussion

AF is the most common arrhythmia after cardiac surgery. Its incidence varies depending on the type of surgery. Postoperative AF may cause hemodynamic deterioration predisposing to stroke and increased mortality. Effective prophylaxis of postoperative AF might reduce hospitalization and overall morbidities [8].

This study was conducted to find out a better way to decrease the incidence of new-onset AF during the first 3 days after CABG. The doses of dexamethasone and Mg were based on the current literature. In this prospective randomized clinical trial, patients who received intravenous DMg had significantly less incidence of postoperative AF compared with patients who received Mg only.

Previous studies have found several confounding factors of AF after cardiac surgery [9]. Thus, we adjusted other independent factors such as age, sex, and number of grafts. Kohno *et al.* [10] compared the incidence of AF in 100 patients who received a daily infusion of 10 mmol of $MgSO_4$ for 3 days after surgery with the incidence in another 100 patients who did not receive $MgSO_4$. The incidence of postoperative AF was significantly lower in the Mg group compared with the untreated group ($P = 0.001$) [10]. Toraman *et al.* [11] performed a randomized controlled study in 200 patients by giving them 6 mmol of Mg both preoperatively and postoperatively. Only 2% of patients receiving Mg developed AF compared with 21% in the control

Table 2 Comparison of the incidence of atrial fibrillation, duration of postoperative intensive care unit, and extubation time between the study groups

Incidence of atrial fibrillations and response to treatment	Group DMg ($n = 50$) [*N* (%)]	Group Mg only ($n = 50$) [*N* (%)]	χ^2	*P*-value
Incidence of AF	4 (8.0)	11 (22.0)	3.843	0.049
Spontaneous recovery	2 (50.0)	5 (45.45)	1.382	0.239
Medical recovery	1 (25.0)	4 (36.36)	1.895	0.168
Electrical cardioversion	1 (25.0)	2 (18.9)	0.344	0.557
Duration of postoperative ICU (mean ± SD) (h)	30.0 ± 7.0	29.0 ± 5.0	0.822	0.413
Extubation time (mean ± SD) (h)	4.3 ± 1.5	4.5 ± 1.4	0.689	0.492

AF, atrial fibrillation; Mg, magnesium.

Table 3 Descriptive table showing the incidence of postoperative complications from steroids

Complications of steroids	Dexamethasone + Mg group [*N* (%)]	Mg-only group [*N* (%)]	Total [*N* (%)]	χ^2	*P*-value
Chest infection	5 (10.0)	4 (8.0)	9 (9.0)	0.122	0.727
UTI	3 (6.0)	2 (4.0)	5 (5.0)	0.211	0.646
Sternal wound infection	4 (8.0)	6 (12.0)	10 (10.0)	0.361	0.548

Mg, magnesium; UTI, urinary tract infection.

group [11]. This was different from our study, as we administered $MgSO_4$ with or without dexamethasone only postoperatively. Halonen *et al.* [12] showed that there was a significant decrease in the incidence of AF after the administration of 100 mg hydrocortisone compared with placebo. Corticosteroid treatment remained a significant independent predictor of the absence of postoperative AF.

Increased risk for complications such as wound infections and stress ulcer could be a concern with corticosteroid therapy [13]. We found that administration of dexamethasone (12 mg) was feasible and well tolerated and noted no serious complications associated with intravenous administration of corticosteroids. Prasongsukarn *et al.* [14] showed that there was significant decrease in the incidence of AF after administration of intravenous methylprednisolone (100 mg) before surgery and 4 mg of dexamethasone intravenous every 6 h for 1 day after surgery compared with placebo (P = 0.003) without development of remarkable complications.

In another study, Ho and Tan [15] showed that corticosteroid prophylaxis significantly reduced the risk of AF (P < 0.01) and length of stay in the ICU (P < 0.01) and hospital stay (P = 0.03), compared with placebo. The use of corticosteroids was not associated with an increased risk for infection (P = 0.73), but hyperglycemia requiring insulin infusion after corticosteroid prophylaxis was common (P < 0.01) [15].

A meta-analysis showed that intravenous Mg significantly reduced the incidence of postoperative AFs after CABG. This finding encourages the use of intravenous Mg to prevent postoperative AFs after CABG [16].

Van Osch *et al.* [17] showed that there was no statistically significant difference in the incidence of postoperative AFs between the dexamethasone group and the placebo group (P = 0.14).

This disagreed with our findings.

The major limitation of our study was related to the lack of blinding as it leaves the trial open to observer bias. We suggest further prospective double-blind trials on other cardiac procedures adopting the same treatment medications.

Conclusion

Addition of dexamethasone (12 mg) to $MgSO_4$ (2 g) seems to decrease the incidence of new-onset AF in primary isolated elective CABG surgery but with few potential side effects.

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Conflicts of interest

There are no conflicts of interest.

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