

Comparative Study between Pre-operative Magnesium Sulphate versus Dronedarone for Prophylaxis against Atrial Fibrillation after Coronary Artery bypass grafting (CABG)

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Abstract: Background: The incidence of postoperative atrial fibrillation (POAF) varies according to the type of surgery. POAF is the most commonly observed arrhythmia after coronary artery bypass grafting (CABG) and is associated with increased morbidity, mortality and prolonged hospitalization due to hemodynamic instability and thromboembolic complications. **Aim of the work:** to conduct a comparative study between magnesium sulphate (Mgso4) versus Dronedarone reducing incidence of atrial fibrillation after coronary artery bypass grafting. **Patients and methods:** This comparative study was performed in the cardiac operating room and ICU of Ain Shams University Hospitals. The study was performed on 60 patients who had undergone successful CABG. The local Ethics Committee approved of the study, and personal informed consent was taken. Methods of drug administrations, dosages were assessed. Also, Specific clinical interventions and follow-up was determined. The primary outcome was incidence of postoperative AF. Supraventricular arrhythmias other than AF (e.g. tachycardia's and atrial flutter) and all other nonatrial arrhythmias were excluded. **Results:** There were no statistical difference among the both groups in terms of demographic, comorbidities, clinical and laboratory parameters. Incidence of AF was more common in 2nd group (36.7%) versus (23.33%) in first group with significant statistical difference between both groups. **Conclusion:** Postoperative AF is a common complication for contemporary patients undergoing CABG. The use of Mg to prevent AF after CABG was statistically significant and appears to reduce risk of atrial fibrillation after cardiothoracic surgery and is free of significant adverse events.

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Key words: Magnesium Sulphate, Dronedarone, Prophylaxis Atrial Fibrillation, CABG

1. Introduction

Atrial fibrillation (AF) is the most common serious cardiac arrhythmia in the surgical setting. The incidence of postoperative atrial fibrillation (POAF) varies according to the type of surgery. Atrial fibrillation develops in 3% of unselected adults aged \geq 45 years undergoing noncardiac surgery, but it is much higher (30%) in thoracic surgery⁽¹⁾.

Postoperative atrial fibrillation (POAF) is the most commonly observed arrhythmia after coronary artery bypass grafting (CABG) and is associated with increased morbidity, mortality and prolonged hospitalization due to hemodynamic instability and thromboembolic complications. The exact mechanisms underlying POAF after cardiac surgery are not clearly understood. Intraoperative ischemia, electrolyte imbalance, increased postoperative sympathetic activity, and structural changes in atrial tissue caused by age, hypertension and volume overload are suggested to play a role⁽²⁾.

Particularly, magnesium seems to be with great promise to prevent POAF following CABG. A previous randomized studies of magnesium for prevention of atrial fibrillation after CABG including

eight randomized controlled trials was published in 2005. The analysis showed that intravenous magnesium is associated with a significant reduction in the incidence of atrial fibrillation after CABG⁽³⁾.

Magnesium plays an essential role in many fundamental biological processes, as it is involved in more than 300 metabolic reactions. It participates in many enzymatic reactions, binding to a substrate or directly to an enzyme, thus altering its structure. Magnesium is class V antiarrhythmic drug. Mechanisms of the antiarrhythmic function of magnesium are only partially known. As magnesium is a cofactor of the membrane Na-K pump, its deficiency can reduce the pump's activity, leading to partial depolarization and changes in the activity of many potential-dependent membrane channels⁽⁴⁾.

Dronedarone is a drug mainly indicated for cardiac arrhythmias or dysrhythmias. It was approved by the FDA on July 2, 2009. It was recommended as an alternative to amiodarone for the prophylaxis of atrial fibrillation and atrial flutter in people whose hearts have either returned to normal rhythm or who undergo drug therapy or electric shock treatment. It is a class III antiarrhythmic drug⁽⁵⁾.

Mechanism of action has been termed a “multichannel blocker” however it is unclear which channel (s) play a pivotal role in its success. Thus, dronedarone's actions at the cellular level are controversial with most studies suggesting an inhibition in multiple outward potassium currents including rapid delayed rectifier, slow delayed rectifier and ACh-activated inward rectifier (6).

The reduction in K^+ current in some studies was shown to be due to the inhibition of K-Acetyl choline channel or associated GTP-binding proteins. Reduction of K^+ current by 69% led to increased action potential duration and increased effective refractory periods, thus shown to suppress pacemaker potential of the SA node and return patients to a normal heart rhythm. It is also believed to reduce inward rapid Na current and L-type Ca channels (7).

Aim of the Work

The aim of the study is to conduct a comparative study between magnesium sulphate ($MgSO_4$) versus Dronedarone reducing incidence of atrial fibrillation after coronary artery bypass grafting.

2. Patients and Methods

This study was a comparative and metanalysis study that performed in the cardiac operating room and ICU of Ain Shams University Hospitals. The study was performed on 60 patients who had undergone successful CABG. The local Ethics Committee approved of the study, and personal informed consent was taken.

Inclusion criteria:

The study included patients of either sex, undergoing elective isolated CABG.

The study excluded patients with previous history of AF, New York Heart Association class IV congestive heart failure despite treatment, persistent hypotension (systolic blood pressure <80 mmHg), sinus bradycardia <50/min, PR interval greater than 220 milliseconds, second- or third-degree AV block, acute or chronic renal failure, serum creatinine >2.0 mg/dl, patients using intra-aortic balloon pump, implanted pacemaker, emergency surgery and patients on group I and III antiarrhythmic drugs.

3. Methods

Thirty patients were given 3 g of magnesium sulphate ($MgSO_4$) [20 ml = 24.32 mEq/L Mg^{+2}] in 100 cc of isotonic 0.9% solution intravenously for 2 hours at the following times: 12 hours prior to the operation, immediately following the operation, and on postoperative days 1, 2, and 3 (Group 1). The other group of 30 patients was given dronedarone 400 mg twice daily preoperative and postoperative on postoperative days 1, 2, and 3 (Group 2). Anti-

arrhythmia drugs used in the preoperative period were halted 24 hours before the operation.

Preoperatively:

History taking: A thorough and detailed history was taken, as regards the age, sex Clinical examination. A complete clinical general and local cardiological examination was performed.

Laboratory investigations: Complete blood count (CBC), Kidney function tests, Liver function tests, ABO Grouping, PTT and PT and viral markers.

Preoperative counseling: In the preoperative visit prior to surgery, a brief explanation of the steps of the operation, the post-operative events and the intensive care stay. The visual analogue scale for pain assessment in the post-operative period is instructed to the patients in the preoperative visit.

Preoperative preparation: All patients received their morning dose of cardiac medications before transfer to the operating theatre. Two large pored peripheral venous cannula were inserted. Sedation was optimized using 0.03-0.07 mg/Kg midazolam.

Statistical analysis was performed depending on demographic data and clinical characteristics and preoperative ABO blood grouping classification.

Intra-operative procedures:

Anesthetic technique

- The intraoperative anesthetic technique was the same for all patients and consisted of A 20 gauge non-dominant radial artery cannula was inserted using local anesthesia. Two blood samples were withdrawn from the arterial line, the 1st for preoperative baseline activated clotting time (ACT) and the 2nd for baseline arterial blood gas (ABG) analysis.

- Monitoring started using five leads ECG, then Fentanyl 5-10 μ g/Kg, and endotracheal intubation was facilitated with the use of Pancuronium 0.02 mg/Kg and a supplemented hypnotic does of propofol 0.5-1 mg/Kg.

- Additional dose of Fentanyl 100-200 μ g was given in an on need bases.

- After full muscle relaxation, the trachea was intubated orally with an appropriate sized endotracheal tube. Anesthesia in all patients was maintained with inhalational Isufloflorane 0.5-1.0 %.

Cardiopulmonary bypass (CPB)

The membrane oxygenators were used. Hematocrite was kept around 28% during CPB. Myocardial protection was carried out through antegrade blood cardioplegia. Cardioplegia infused into the ascending aorta with pressure. Induced cardiac standstill was usually achieved within one minute. Cardioplegia was given in a dose of 15-20 ml/Kg every 20-30 minutes.

II -Postoperative follow-up:

Twelve lead ECG of the patients were taken on the morning of the operation day and patients showing arrhythmia other than AF or ischemia were excluded from the study. Clinical follow-up of patients in ICU was recorded.

Statistical analysis

The collected data were statistically analyzed using SPSS software statistical computer package version 23. For qualitative data, comparison between two groups and more was done using Chi-square test (χ^2). For comparison between means of two groups, parametric analysis (t-test) and non-parametric analysis (Z-value of Mann-Whitney U-test) were used. For comparison between means of the same group before and after treatment, parametric analysis (paired t-test) and non-parametric analysis (Z-value of Wilcoxon Signed Ranks test) were used. Correlation between variables was evaluated using Pearson's correlation coefficient. Significance was adopted at

$p < 0.05$ for interpretation of results of tests of significance.

-Types of interventions:

Interventions of interest included those related to the use of Dronedarone or (MgSO₄) in AF prophylaxis post CABG versus placebo or versus each other. Methods of drug administrations, dosages and use of other antiarrhythmic drugs will be assessed. Also, Specific clinical interventions and follow-up was determined.

-Types of outcome measures:

The primary outcome was incidence of postoperative AF. Supraventricular arrhythmias other than AF (e.g. tachycardia's and atrial flutter) and all other nonatrial arrhythmias were excluded. The length of postoperative stay and the total length of hospital stay were additional outcomes.

3. Results

Table (1): General characteristics of the study patients

Parameters	MgSO ₄	Dronedarone	P-value
	n=30	n=30	
Age	54.87±7.02	53.02±7.47	0.12
Gender (male)	21(70%)	22(73.3%)	0.45
BMI	24.65±1.93	23.79±2.12	0.10

Table (2): Risk factors of the study patients

Parameters	MgSO ₄	Dronedarone	P-value
	n=30	n=30	
Dyslipidemia	12(40%)	14(46.7%)	0.28
DM	19(63.3%)	18(60%)	0.69
Hypertension	20(66.7%)	18(60%)	0.12

Table (3): Comorbidities of the study patients

Parameters	MgSO ₄	Dronedarone	P-value
	n=30	n=30	
Past history of CAD	8(26.7%)	9(30%)	0.54
Peripheral vascular disease	2(6.7%)	3(10%)	0.31
COPD	3(10%)	4(13.3%)	0.40
History of renal impairment	5(16.7%)	4(13.3%)	0.71

Table (4): Cardiac function of the study patients

Parameters	MgSO ₄	Dronedarone	P-value
	n=30	n=30	
SBP (mmHg)	136.54±16.63	128.39±16.95	0.23
DBP (mmHg)	70.28±9.27	73.12±8.96	0.55
EF %	51.41±8.32	52.21±7.07	0.54

Table (1) shows that 60 patients were included in this study; the mean of their ages was 54.87 ± 7.02

years in Mgso₄ group and 53.02 ± 7.47 in dronedarone group. 21 patients (70%) were males in

Mgso4 group and 22 patients (73.3%) were males in dronedarone group.

Table (2) shows the most frequent risk factor was hypertension (66.7%) in Mgso4 group and (60%) in dronedarone group followed by diabetes (63.3%) in Mgso4 group and (60%) in dronedarone group beside other risk factors as dyslipidemia.

In table (3): Comorbidities in the studied patients were mostly past history of CAD 26.7% in Mgso4 group and 30% in dronedarone group, COPD or chest diseases 10% in Mgso4 group and 13.3% in dronedarone group, previous vascular disease 6.7% in Mgso4 group and 10% in dronedarone group. The least comorbidity was history of renal impairment 16.7% in Mgso4 group and 13.3% in dronedarone group.

Table (4) shows cardiac functions mean values of systolic blood pressure (mmHg) 136.54 ± 16.63 in Mgso4 group and 128.39 ± 16.95 in dronedarone group, diastolic blood pressure 70.28 ± 9.27 in Mgso4 group and 73.12 ± 8.96 in dronedarone group, ejection fraction (%) 51.41 ± 8.32 in Mgso4 group and 52.21 ± 7.07 in dronedarone group.

Table (5) shows laboratory mean values of renal functions Urea (mg/dl) 40.75 ± 3.17 in Mgso4 group and 45.14 ± 17.35 in dronedarone group, Creatinine (mg/dl) 1.17 ± 0.36 in Mgso4 group and 0.95 ± 0.41 in dronedarone group, Albumin (g/dl) 3.97 ± 0.39 in Mgso4 group and 4.11 ± 0.55 in dronedarone group, Hemoglobin (g/dl) 10.72 ± 1.29 in Mgso4 group and 11.16 ± 1.60 in dronedarone group.

Table (6) shows mean values of operative and postoperative parameters, cardiopulmonary bypass time > 60 minute 50% in Mgso4 group and 43.33% in dronedarone group, aortic-cross clamp time (min) 80.26 ± 9.11 in Mgso4 group and 78.93 ± 13.41 in dronedarone group, inotrope support 23.3 % in Mgso4 group and 30% in dronedarone group, mean number of grafts 3.2 ± 1.1 in Mgso4 and 3.0 ± 1.2 in dronedarone group, incidence of atrial fibrillation 23.33 % in Mgso4 group and 36.7 % in dronedarone group, length of stay in ICU (hours) 58.2 ± 18.34 in Mgso4 group and 61.86 ± 11.60 in dronedarone group.

Table (5): Laboratory mean values of study patients

Parameters	MgSO4	Dronedarone	P-value
	n=30	n=30	
Urea (mg/dL)	40.75±3.17	45.14±17.53	0.29
Creat (mg/dL)	1.17±0.36	0.95 ±0.41	0.06
Albumin (g/Dl)	3.97±0.39	4.11±0.55	0.28
HB (g/dl)	10.72±1.29	11.16±1.60	0.21

Table (6): Operative and postoperative parameters

Parameters	MgSO4	Dronedarone	P-value
	n=30	n=30	
CPB time >60Min.	15(50%)	13(43.33%)	0.081
Aortic-cross clamp time, min	80.26±9.11	78.93±13.41	0.39
Inotrope support	7(23.3%)	9(30%)	0.12
Mean number of grafts	3.2± 1.1	3.0 ± 1.2	0.35
Incidence of AF	7(23.33%)	11(36.7%)	0.021*
length of stay in ICU (hours)	58.2±18.34	61.86±11.60	0.15

CPB: Cardiopulmonary bypass

4. Discussion

AF is the most common arrhythmia that occurs after cardiac surgery (8). AF is an undesired but frequent complication of CABG observed in 10–40% of cases. It prolongs a patient's stay in the intensive care unit or hospital, and it disturbs a patient's comfort. In addition, AF postpones full recovery after CABG. POAF normally occurs between days 2 and 4 after surgery, with the maximum incidence seen on postoperative day 2, with 80% and 94% of patients suffering POAF having it by day 4 and by the end of

day 6, respectively. It was estimated that POAF lengthened hospital stay by 4.9 days (9).

Because AF is one of the most commonly encountered complications after cardiac surgery, extensive efforts have been made to identify an effective method of preventing AF. Numerous pharmacologic agents have been used, with varying degrees of success. Of these, B-blockers, amiodarone, sotalol, and IV MgSO4 have been identified as being the most with amiodarone and sotalol being the most poorly tolerated (10).

Combined coronary artery bypass surgery (CABG) and valvular surgery have the highest risk of POAF (60–80%). Differences in incidence rates are likely related to patient populations, pre-existing comorbidities, and distinct surgical stressors and insults on the myocardium. Furthermore, diverse methods of detection, surveillance, and study methodologies also contribute to the reported variability. POAF typically occurs on postoperative day 2, with 70% of cases occurring within the first four postoperative days⁽¹¹⁾.

While POAF is typically self-limited with an average duration of 11–12 h and 80% of cases self-resolving to normal sinus rhythm within 24 h after initial onset⁽¹²⁾, a substantial proportion of patients will experience a second episode. If a recurrence occurs, the majority will occur within 2 days of the first episode. Clinical manifestations of POAF do not appear to differ from the signs and symptoms of AF in the non-cardiac or non-operative setting. Hemodynamic instability, reduced cardiac output, and hypotension are all signs indicative of POAF after cardiac surgery. However, the diagnosis is made relatively quickly because cardiac surgical patients receive telemetry surveillance or serial electrocardiograms in the immediate postoperative period⁽¹³⁾.

In this study, sixty patients were included in this study; they were divided into two groups. First group were patients who received MgSO₄ sulphate perioperative and second group were patients who received Dronedarone. There were no statistical difference among the both groups in terms of demographic, comorbidities, clinical and laboratory parameters. We found that the incidence of AF was more common in 2nd group (36.7%) versus (23.33%) in first group with significant statistical difference between both groups ($p=0.021$). Based on this study, MgSO₄ significantly decreased the incidence of arrhythmia at patients who underwent elective CABG surgery. In agreement with **Tiryakioglu et al**⁽¹⁴⁾ that showed the prophylactic use of MgSO₄ is effective at preventing arrhythmia that may occur following coronary bypass operations. In addition, **Toraman et al**⁽¹⁵⁾ that concluded that the and early postoperative periods is highly effective in reducing the incidence of AF after CABG.

Despite advances in surgical techniques, postoperative new-onset AF remains a common arrhythmia after CABG, possibly because of the increasing age and illness of patients undergoing CABG and advances in continuous monitoring technology. Various preoperative and postoperative factors, including advanced age, hypertension, discontinuation of β -blockers, bleeding, and right coronary artery stenosis, have all been suspected to

increase the incidence of postoperative AF. Strategies for the prevention of postoperative AF have focused mainly on antiarrhythmic medication such as digitalis, β -blockers, calcium channel blockers, and amiodarone⁽¹⁶⁾.

According to the Framingham study, the overall average incidence of AF in all populations is 1.7%; it is age dependent and attains a level of 2–4% among those older than 70 years of age⁽¹⁷⁾. The incidence of AF in those with ischemic heart disease may reach 4.8% in women and 6.2% in men depending on the severity of the disease.

Other possible risk factors, such as age, hypertension, male sex, bleeding, and grafting of the right coronary artery were not found to be risk factors for postoperative AF on univariate analysis⁽¹⁶⁾.

Parenteral magnesium was reported to be superior to amiodarone in studies of acute atrial tachyarrhythmia. Davey et al.⁽¹⁸⁾ have shown that magnesium sulphate slows the heart rate and prevents supraventricular arrhythmia. They also found that AF frequently returns to normal sinus rhythm in patients treated with magnesium sulphate. Lastly, they reported that magnesium-related hypotension and bradycardia are potential risk factors for AF.

Our study differ in sample size, 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 and Mg groups, respectively. 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. However, the sufficiency and reliability of amiodarone in preventing arrhythmia is controversial. Oral amiodarone is known to be insufficient for preventing postoperative arrhythmia, but sometimes the preoperative loading dose can prove sufficient. Amiodarone given during the preoperative period has been reported to react with anesthetic agents and cause pulmonary dysfunction, hypotension, hepatic dysfunction, and low heart flow⁽¹⁹⁾.

Mg has several antiarrhythmic properties that make it a good pharmacologic candidate for the prevention and treatment of arrhythmias⁽²⁰⁾. Consistent with these electrophysiological actions, Mg administration has been shown in several clinical studies to significantly improve the rate of chemical and electrical cardioversion⁽²¹⁾ of atrial arrhythmias. Investigations of Mg prophylaxis for the prevention of POAF in the context of cardiac surgery appeared to confirm these beneficial results⁽²²⁾.

Dronedarone is a benzofuran derivative, related to amiodarone, whose toxic effects involving thyroid and pulmonary fibrosis are absent in this new anti-arrhythmic drug because of removal of the iodine moieties⁽²³⁾.

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Dronedarone is less effective for the prevention of recurrent AF compared with amiodarone. In trials to date, Dronedarone has not shown evidence of proarrhythmia (tachyarrhythmia or bradyarrhythmia), torsades de pointes, or amiodarone-like organ toxicity affecting the thyroid or the lungs. Magnesium sulphate work safely and sufficiently rapidly in POAF prevention. On the other hand, dronedarone is associated with fewer adverse events requiring discontinuation of treatment.

We did not observe any side effects in the dronedarone group in the present study. According to our observations, both drugs are safe. Magnesium is a cation that functions by lengthening the refractory period at the atrioventricular node. Thus, magnesium likely has an important role in preventing and treating atrial fibrillation, especially considering that serum magnesium levels below 0.8 mmol/L trigger atrial fibrillation. Thus, dose loading with magnesium can prevent the arrhythmia caused by the postoperative decrease in this caution. In our study we observed that the serum magnesium levels were low in the postoperative period, although never below 0.8 mmol/L⁽¹⁵⁾.

Conclusion

Postoperative AF is a common complication for contemporary patients undergoing CABG. The use of Mg to prevent AF after CABG was statistically significant and appears to reduce risk of atrial fibrillation after cardiothoracic surgery and is free of significant adverse events. Also, the low cost and minimal risk of magnesium therapy suggest the need for magnesium administration to patients after cardiothoracic surgery.

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