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Original Research Article

A study of the effects of intravenous magnesium sulphate on post-operative atrial fibrillation in patients undergoing off pump coronary artery bypass grafting (CABG)

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ABSTRACT

Background & Aims: Atrial fibrillation (AF) occurs in almost 30% of patients undergoing coronary artery bypass grafting (CABG). Around 80% of these patients have decreased levels of total and ionized serum magnesium postoperatively. The association between magnesium deficiency and post CABG AF is still undetermined. Therefore, a large variety of prophylactic strategies have been assessed including perioperative magnesium administration. However, the efficacy is still questionable.
The aim of this study was to find out any correlation of serum magnesium levels with the incidence of post-operative atrial fibrillation in patients undergoing off pump CABG and whether magnesium supplementation modifies the incidence.
Materials and Methods: One hundred fifty patients undergoing CABG were selected and divided into treatment and control groups. Perioperative serum magnesium assays were done, and patients were monitored in the postoperative period for occurrence of Atrial Fibrillation.
Results: The risk of post CABG atrial fibrillation was more among females, obese patients, patients with EF < 50% and RWMA. Post-operative AF occurred in 5 patients in the treatment group (n = 75) and 11 patients in the control group (n = 75).
Conclusion: The proportion of patients with post-operative atrial fibrillation among cases (6.7%) was lower than that of controls (14.7%) which may indicate an important role of magnesium in prevention of AF following cardiac surgeries. The results however didn't reach a statistical significance which could be due to sample size, the duration and design of the study and the period of post-operative AF monitoring.

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1. Introduction

Atrial Fibrillation (AF) is the most common arrhythmia occurring in nearly 30% of patients undergoing coronary artery bypass grafting (CABG). It's onset is usually between 24 to 96 hours postoperatively, with a peak incidence between second and third postoperative days. It potentially leads to prolonged hospitalization and significant morbidity, particularly hemodynamic deterioration and thromboembolism. The aetiology of AF after CABG is unclear and is most likely multifactorial. Almost 80% of patients undergoing CABG have decreased levels of total and ionized serum magnesium postoperatively.[1,2] This reduction is due to several determinants mainly haemodilution, elevated catecholamine levels, and increased urinary loss.[3] The association between magnesium

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deficiency and post CABG AF is still unknown. However, most proposed theory explained the importance of magnesium in stabilizing the cellular transmembrane potential, suppressing excessive intracellular calcium influx and energy requirements, preserving myocardial metabolites and reducing the severity of reperfusion injuries.[4,5] Consequently, perioperative magnesium administration has been suggested to play a role in the prophylaxis of AF after CABG.

2. Aims and Objectives

The aim of this study was to find out any correlation of serum magnesium levels with the incidence of post-operative atrial fibrillation in patients undergoing off pump CABG.

3. Materials and Methods

Sample size was limited to 150 patients (75 patients in each group). As per the study by Miller et al.[6] the incidence of post-operative AF following magnesium administration was reduced from 25% in the control group to 8% in the treatment group. This calculator used the following formula for calculation of the sample size n:

n = (Zα/2+Zβ) 2 * (p1(1-p1) + p2(1-p2)) / (p1-p2) 2,

[Zα/2 is the critical value of the normal distribution at α/2 (e.g., for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Zβ is the critical value of the normal distribution at β (e.g., for a power of 80%, β is 0.2 and the critical value is 0.84) and p1 and p2 are the expected sample proportions of the two groups. Here p1=25% and p2= 8%.]. Hence, there was a need of 75 study subjects per group with 82% power at 95% confidence level. The number of patients in each group will be in the ratio of 1:1 and the required sample size was 150. The study was conducted over a period of one year from January 2016 to December 2016. Patients undergoing elective off-pump CABG done by a single surgeon were included in our study. Patients excluded from our study were patients with pre-existing AF or SVT, permanent pacemaker, valvular heart disease, post operative acute myocardial infarction, renal failure, hypokalaemia, posted for emergency or re-do surgery, requiring LV Assist Devices (LVAD) and those receiving oral or injectable magnesium.

After obtaining necessary institutional ethical clearance and informed consent, patients were allocated into two groups either to receive magnesium or placebo. The patients in the treatment group (n = 75) received 40 mg/kg of Magnesium Sulphate (50% w/v) in 100 ml of 0.9% saline solution intravenously over 15 to 20 minutes as follows:

1. During induction,
2. 1st post-operative day (POD at 8am
3. 2nd POD at 8am

The patients in the control group (n = 75) received 100 ml of 0.9% saline solution as per the above schedule.

Serum Magnesium assays were done as follows:

1. Preoperative Serum Magnesium
2. 1^{st} POD Serum Magnesium at 10 am
3. 2^{nd} POD Serum Magnesium at 10 am

Patients were monitored in the postoperative period for occurrence of Atrial Fibrillation on the 1st & 2nd postoperative days using continuous alarm-triggered ECG Monitoring. Statistical Analysis was performed with help of Epi Info™ 3.5.3. χ 2 test was used to demonstrate the association between different variables. Corrected $\chi 2$ test was applied in case of any one of cell frequency is found to be less than 5 in the bivariate frequency distribution. Test of proportion (Z-test) was used to test the significant difference between two proportions and t-test to describe the significant difference between means. Odds Ratio (OR) with 95% confidence interval (CI) was calculated to detect the risk factors. $p \leq 0.05$ was taken to be statistically significant and confidence intervals was set at 95%.

4. Results

In our observation the mean age (mean ± SD) of the cases was 61.28 ± 7.77 years with range 42 – 79 years and the median age was 61 years. The mean age (mean ± SD) of the controls was 60.00 ± 8.74 years with range 37 – 77 years and the median age was 61 years. Corrected Chi-square test revealed that there was no important association between age and two groups (p = 0.13). t-test showed that there was no significant difference in mean age of the patients of the two groups (t148 = 0.94; p = 0.34). No obvious association between gender and two groups of patients were demonstrated in corrected chi-square test (p = 0.59). The mean BMI (mean ± SD) of the cases was 25.30 ± 2.96 kg/m^2 with range 17.30 – 34.33 kg/m^2 and the median was 25.39 kg/m^2. The mean BMI (mean ± SD) of the controls was 24.62 ± 2.75 kg/m^2 with range 16.70 – 30.08 kg/m^2 and the median BMI was 25.15 kg/m^2. Corrected Chi-square test showed that there was no significant correlation between BMI and two groups (p = 0.57). t-test revealed that there was no significant difference in mean BMI of the patients of the two groups (t148=1.45; p = 0.14). Thus, the patients of the two groups were matched for their age, gender and BMI. The mean left ventricular ejection fraction (mean ± SD) of the cases was 50.37 ± 8.93% with range 30 – 65% and the median was 48%. The mean left ventricular ejection fraction (mean ± SD) of the controls was 49.56 ± 9.30% with range 25 – 63% and the median was 48%. t-test showed that there was no striking difference in mean ejection fraction of the patients of the two groups (t_{148} = 0.54; p = 0.59). There was no significant association between RWMA (Regional Wall Motion Abnormality) and the two groups (p = 0.86) as demonstrated by corrected chi-square

test. Hence, the proportion of patients with RWMA was more or less equally distributed in both the groups. There was no significant difference in mean pre-operative level of magnesium among the patients of the two groups (p = 0.13). Mean level of magnesium of the cases on post-operative day 1 and day 2 were notably higher than that of controls (p < 0.0001) Table 1. Chi-square test showed that there was important association between level of magnesium on post-operative day 1 and two groups of patients (p = 0.016) Table 2. The risk of the hypomagnesaemia on postoperative day 1 was 8.83 times more among the controls as compared to the cases and the risk was significant [OR-8.83(1.07, 72.51); p = 0.016]. There was notable association between level of magnesium on post-operative day 2 and two groups of patients (p = 0.0002) Table 3. The risk of hypomagnesaemia on postoperative day 2 was 5.41 times more among the controls as compared to the cases and the risk was remarkable [OR-5.41(2.06, 14.20);p = 0.0002]. Post-operative AF occurred in 5 patients in the treatment group (n = 75) and 11 patients in the control group (n = 75). The proportion of patients with post-operative atrial fibrillation among cases (6.7%) was lower than that of controls (14.7%) but it was not significant (Z =1.83; p = 0.067) Table 4. Corrected Chi-square test showed that there was no significant association between day of occurrence of post-operative atrial fibrillation and two groups of patients (p = 0.30) Figure 1. There was no considerable association between occurrence of post-operative atrial fibrillation and age groups of the patients (p = 0.61). The risk of post-operative atrial fibrillation was 2.14 times more among females as compared to males [OR-2.14(0.54, 8.53); p = 0.26] which was not significant. The risk of post-operative atrial fibrillation was 2.58 times more among the patients with obesity as compared to the patients without obesity [OR-2.58(0.79, 8.41); p = 0.11] but the risk was not notable. Our study population elicited pronounced risk of post-operative atrial fibrillation among the patients with EF% <50 as compared to the patients with EF% ≥ 50 [OR-3.09(1.01, 10.07); p = 0.04] Table 5. There was a major risk of post-operative atrial fibrillation among the patients with RWMA which was 3.73 times more as compared to the patients without RWMA [OR-3.73(1.02, 13.69); p = 0.03] Table 6.

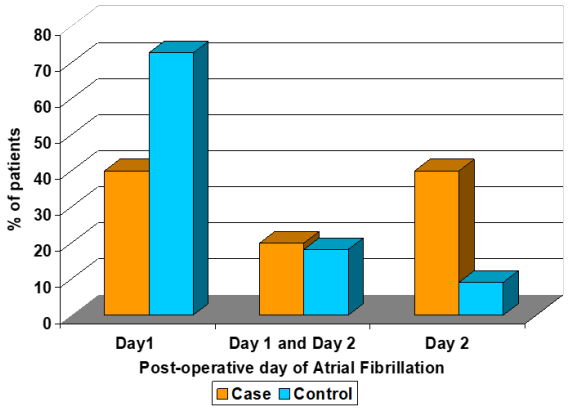

Fig. 1: X^2 = 2.34; p = 0.30; NS—Not Significant

5. Discussion

The incidence of atrial fibrillation after CABG is 10% to 40%. It's aetiology is multifactorial with advanced age and low levels of magnesium being considered as the major determinant factor. Atrial fibrillation with high ventricular rate causes reduction in cardiac output and increased myocardial oxygen consumption leading to severe hemodynamic problems specially in patients with left ventricular dysfunction. In addition to cardiopulmonary bypass, metabolic changes, body temperature, composition and pattern of administration of cardioplegia, insufficient right atrial protection with cardioplegia during aortic cross clamping, electrolyte imbalances, anaesthetic agents, duration of cardiopulmonary bypass and aortic cross clamping, suture technique for atrial cannulation, stress, atrial enlargement, atrial infarction, local surgical trauma, local pericardial inflammation, pericardial dissection, age-related atrial atrophic changes, and discontinuation of preoperatively used β-blockers might also contribute to the occurrence of post CABG AF. Therefore, a large variety of prophylactic strategies have been assessed including perioperative magnesium administration. However, the efficacy is still questionable.

In our observation, there was no noticeable difference in mean pre-operative level of magnesium among the patients of the two groups. Mean level of magnesium of the cases on post-operative day 1 and day 2 were significantly higher than that of controls. The risk of hypomagnesaemia on postoperative day 1 (8.83 times) and postoperative day 2 (5.41 times) was more among the controls as compared to the cases. The risk of post CABG atrial fibrillation was predominant among females, obese patients, patients with EF < 50% and in patients with RWMA. The proportion of patients with post-operative atrial fibrillation among cases (6.7%) was lower than that of controls (14.7%).

Magnesium exhibits 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. The efficacy of magnesium administration in the occurrence of atrial fibrillation after CABG remains debatable. Optimal dose and timing of the administration also need further explanation. The purpose of our observation was to assess the effect of 3-day administration of magnesium on postoperative atrial fibrillation and to find the determinants that can influence the efficacy of this treatment. Numerous

Table 1: Comparison of levels of serum magnesium on different days in the cases and controls

Descriptive Statistics	Cases (n=75)	Controls (n=75)	t-value (t148)	p-value
Pre-operative level of serum magnesium				
Mean ± S.D	2.02 ± 0.22	1.95 ± 0.34		
Median	2.0	2.0	1.49	0.13
Range	1.50 – 2.60	0.60 – 2.80		
Post-operative level of serum magnesium on Day 1				
Mean ± S.D	2.16 ± 0.27	1.78 ± 0.30		
Median	2.1	1.80	8.15	<0.0001*
Range	1.50 – 3.00	1.10 – 2.70		
Post-operative level of serum magnesium on Day 2				
Mean ± S.D	2.31 ± 0.34	2.02 ± 0.31		
Median	2.3	2.0	5.45	<0.0001*
Range	1.70 – 3.30	1.30 – 3.10		

Table 2: Level of magnesium on post-operative day 1 in the two groups of patients

Level of magnesium on post-operative Day 1	Case (n=75)	Control (n=75)	Total
Below normal	67	74	141
Row %	47.5	52.5	100.0
Col %	89.3	98.7	94.0
Normal	8	1	9
Row %	88.9	11.1	100.0
Col %	10.7	1.3	6.0
Total	75	75	150
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

X^2 = 5.79; p = 0.016; S—Significant

Table 3: Level of magnesium on post-operative day 2 in the two groups of patients

Level on magnesium of post-operative Day 2	Case (n=75)	Control (n=75)	Total
Below normal	51	69	120
Row %	42.5	57.5	100.0
Col %	68.0	92.0	80.0
Normal	24	6	30
Row %	80.0	20.0	100.0
Col %	32.0	8.0	20.0
Total	75	75	150
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

X^2 = 13.50; p = 0.0002; S—Significant

Table 4: Distribution of post-operative atrial fibrillation in the two groups of patients

Post-operative Atrial Fibrillation	Case (n=75)	Control (n=75)	Total
Yes	5	11	16
Row %	31.3	68.8	100.0
Col %	6.7	14.7	10.7
No	70	64	134
Row %	52.2	47.8	100.0
Col %	93.3	85.3	89.3
Total	75	75	150
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

X^2 = 2.51; p = 0.11; NS- Not Significant

Table 5: Post-operative atrial fibrillation and ef% of the patients

EF%	Post-operative Atrial Fibrillation		Total
	Yes	No	
<50	12	66	78
Row %	15.4	84.6	100.0
Col %	75.0	49.3	52.0
≥50	4	68	72
Row %	5.6	94.4	100.0
Col %	25.0	50.7	48.0
Total	16	134	150
Row %	10.7	89.3	100.0
Col %	100.0	100.0	100.0

X^2 = 3.80; p = 0.04; S—Significant

Table 6: Distribution of RWMA and two groups of the patients

RWMA	Case (n=75)	Control (n=75)	Total
Present	42	43	85
Row %	49.4	50.6	100.0
Col %	56.0	57.3	56.7
Absent	33	32	65
Row %	50.8	49.2	100.0
Col %	44.0	42.7	43.3
Total	75	75	150
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean ± S.D	25.30 ± 2.96	24.17 ± 2.77	
Median	25.39	23.80	
Range	17.30 – 34.33	16.70 – 30.08	

X^2 = 0.02; p = 0.86;NS—Not Significant

studies published previously shows variation in the dosing and timing of magnesium administration. This variation probably accounts for the inconsistency in the reported outcomes of the magnesium trials. The study by Fanning et al[7] administered 96 meq of Mg^{2+} over first 24 hrs and an additional 72 meq of Mg^{2+} up to 96 hrs postoperatively in 99 patients undergoing CABG but could not demonstrate any significant reduction in the incidence of postoperative atrial fibrillation in the study group as compared to the control group although, there was a significant decrease in the number of episodes of atrial fibrillation in the study group. On the contrary, a similar concurrent study by Parikka et al.[8] supplementing 70 mmol of Mg^{2+} to 140 patients undergoing CABG failed to demonstrate any beneficial effects of magnesium. However, Karmy Jones et al.[9] supplemented 2.4 g of magnesium sulphate administration every 4 hours for a total dose of 14.4 g in the first 24 hours which resulted in a significant reduction in the incidence and severity of VTs. Maslow et al.[10] demonstrated the beneficial role of intraoperative magnesium supplementation on postoperative atrial tachyarrhythmias (POAT) in patients undergoing off pump coronary artery bypass grafting (OPCABG). The author used a single dose of intravenous magnesium before manipulation of the coronary arteries. In another similar study, Kaplan and associates[11] administered 3g of magnesium sulphate in 100 mL of saline solution over 2 hours (50 mL/h) preoperatively, intraoperatively, and postoperatively at days 0, 1, 2, and 3. No obvious difference was found between the 2 groups (P > 0 .05). However, a meta-analysis by Shiga and associates[12] on the effectiveness of magnesium sulphate prophylaxis for arrhythmias after CABG demonstrated that administration of prophylactic magnesium reduced the risk of supraventricular arrhythmias after cardiac surgery by 23% and of atrial fibrillation by 29%. A meta-analysis in 2012 by Gu et al.[13] showed that intravenous magnesium significantly reduced the incidence of POAF by 36%. On the contrary, the meta-analysis[14] mentioned that Mg^{2+} supplementation does not prevent postoperative AF after cardiac surgery. It contradicts the European Association of Cardio-Thoracic Surgery guidelines,[15] which gives a grade A recommendation to the use of prophylactic Mg^{2+} in addition to other strategies, and the Canadian Cardiovascular Society guidelines,[16] which recommended prophylactic intravenous Mg^{2+} for patients who have a contraindication to β-blockers and amiodarone to minimize the incidence of AF for patients undergoing cardiac surgery. In another prospective, randomized, double‑ blind study by Naghipour et al.[17] one group

received 30 mg/kg MgSO4 in 500 cc of normal saline i.v over 2 hrs and rest of the patients were given 500 cc normal saline i.v as placebo over 2 hrs. There was a significant difference in the incidence of arrhythmia between two groups (P = 0.037). Mg^{2+} compared with placebo, decreased the incidence of arrhythmia up to 59%.

Another reason for the discrepancy in results may ascribe to the daily dose of magnesium. Normal or high concentrations of serum magnesium can coexist with suboptimal magnesium supply and correcting only the values of serum magnesium may not eliminate the clinical consequences of magnesium abnormality in the tissue. Low level of myocardial magnesium is considered to cause postoperative arrhythmias. However, controversies persist concerning the efficacy of prophylactic magnesium infusion and the current studies demonstrate only conflicting statements regarding the cellular regulation of exogenous magnesium. Whether serum magnesium concentrations represent the true state of magnesium metabolism remains questionable, and because of these uncertainties, the clinical relevancy of serum magnesium monitoring with AF treatment requires further investigation. The discordant results of the magnesium studies reported in the literature may also be attributed to the period of AF monitoring.

6. Conclusion

The role of magnesium in preventing post CABG AF seems debatable. The results of our study demonstrated a possible advantage of magnesium supplementation in prevention of AF following CABG. The results however didn't reach a statistical significance which could be due to smaller sample size, the duration and design of the study and the period of post-operative AF monitoring.

7. Source of Funding

None.

8. Conflict of Interest

None.

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