Original Research Article

Role of serum magnesium levels in cardiac arrhythmias

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Received: 27-05-2021 / Revised: 12-07-2021 / Accepted: 20-08-2021

Abstract

Background: Magnesium deficiency leads to enhanced vascular endothelial injury and promotes platelet-dependent thrombosis.It has possible involvement in stent thrombosis. Theoretically serum Mg levels have been shown to decline after cardiopulmonary bypass and do not recover to preoperative levels until 3 to 5 days after surgery, which coincides with the period during which most cases of AF develop. In this context, this prospective study was conducted with aims and objectives to review and evaluate the role of serum magnesium levels in cardiac arrhythmias and whether to include serum magnesium level monitoring as routine investigation. **Methods:** A Prospective study done at Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bangalore, from January 2016 to December 2017. Hundred patients with normal sinus rhythm who had undergone treatment, in preoperative, intraoperative and postoperative period, undergoing procedures in cath lab; who had arrhythmias, during the course of treatment were included in the study .they were monitored with Standard ECG, Arterial blood pressure and hemodynamic parameters .Venous blood sample was drawn and sent to Lab and serum magnesium level was measured and subjected to statistical analysis. Data variables comparison was done by ANNOVA test and their relationship was evaluated using correlation tests. **Results:** Majority of the patients were males and 52% patients were above 61 year age. Among the study patients 66% had Coronary Atherosclerotic Diseases. and 44% patients had other cardiac diseases like valvular heart diseases, Atrial Septal Defect and Ventricular Septal Defects.significant number (79%) of patients had arrhythmias during Post operative period, compared to Pre and Intra operative period with 12% and 6% respectively. 61% of the patients had Atrial Fibrillation and 38% had ventricular fibrillation during post operative period. Significant number of patients (58%) had low serum Magnesium levels during arrhythmia with P value of <0.05. 65% of post operative cardiac patients had significantly low serum Magnesium levels with P value of <0.05 .66% of patients with AF had significantly low magnesium value ($p<0.05$). In this study group post operative patients who had low serum magnesium level had significantly more incidences of arrhythmias with mean level of serum Magnesium <1.8 mg/dl. patients with low serum Magnesium levels had significantly higher incidence of Atrial Fibrillation. **Conclusions:**In light of its simplicity, cost-effectiveness and safety, monitoring the serum magnesium level is another first-line option for management of patients with arrhythmias in the intraoperative, perioperative, postoperative setup in hospitalized cardiac patients.

Keywords: Magnesium deficiency, Arrythmia, Atrial Fibrillation[AF],Ventricular Fibrillation[VF],Supraventricular Tachycardia[SVT], Magnesium sulphate, Cardiac surgery,Cardiac Cath lab procedures,Post operative period.

Introduction

The important human element magnesium (Mg) is an activator of more than 300 enzymes. Thus, Mg plays an important role in numerous diverse diseases including cardiovascular disorders .Several studies have indicated the relationship between Mg and the prognosis of coronary artery disease (CAD). Data from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHANES) showed that serum Mg level was inversely associated with cardiovascular related deaths and hospitalizations. In a northern German population-based sample, a low serum Mg level was a significant independent predictor of all-cause and cardiovascular mortality after adjustment for cardiovascular risk factors including diabetes and hypertension[1, 2].

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However, the relationship between serum Mg level and the prognosis with DES implantation is not clearly understood. Hypomagnesemia was found associated with poor glycemic control and various long-term complications of diabetes mellitus.**:**Magnesium deficiency leads to enhanced vascular endothelial injury and promotes platelet-dependent thrombosis, also has possible involvement in stent thrombosis . Although magnesium sulfate (MgSO4) is now thought to be useful for the treatment of Atrial fibrillation(AF),its role in preventing postoperative AF is more controversial. Magnesium Sulphate (MgSO4) is attractive because of its low cost, ease of administration by peripheral intravenous line, and its excellent safety profile when administered slowly. Theoretically serum Mg levels have been shown to decline after cardiopulmonary bypass and do not recover to preoperative levels until 3 to 5 days after surgery, which coincides with the period during which most cases of AF develop, which coincides with the period during which most cases of AF develop [1,2].Magnesium is of great importance in cardiac arrhythmias. It increases the ventricular threshold for fibrillation. Sinus node refractoriness and conduction in the AV node are both prolonged. Main indications for intravenous application of magnesium are Torsade de pointes tachycardias, digitalis toxicity

induced tachyarrhythmias and multifocal atrial tachycardias. Additionally, patients with ventricular arrhythmias due to overdoses of neuroleptics or tricyclic antidepressants may profit from i.v. magnesium. Monomorphic ventricular tachycardias and ventricular arrhythmias refractory to class III antiarrhythmics have been shown to respond to i.v. magnesium. Recent publications have documented that perioperative use of magnesium can reduce the incidence of arrhythmic events on the atrial and ventricular level. Oral magnesium has been used for many years in patients with symptomatic extrasystoles. Studies show that the incidence of extrasystoles as well as patients' symptoms are reduced during oral magnesium therapy [3]

Clinical electrophysiological effects of magnesium (Mg2+) are known for more than 60 years. Mg2+ is a cation to be found ubiquitously in the human body and is involved in more than 300 different enzymatic reactions. However, so far this ion has not been established as a standard therapeutic tool for the treatment of supraventricular tachyarrhythmia. This may be explained by the inconsistent efficacy of Mg2+, partly in relationship to a given plasma Mg(2+)-concentration, partly caused by the uncertainty regarding the dosage and injection rate or the unawareness of the clinical effects of the cation. Mg2+ influences myocardial metabolism by its effects on contractility and electrical activity. Both effects are closely linked. About 12% of cardiac Mg2+ is found in the mitochondria and 2 to 3% in the myofibrils. A large portion is incorporated in adenosin mono-, di- and triphosphate. Mg2+ affects intracellular calcium by inhibiting the influx of calcium into the myocyte through sarcolemmal channels, by modulation of cyclic AMP and by competing with calcium for binding to a single high affinity site on actin. Mg2+ has been linked to a naturally occurring calcium channel blocker[2].

Furthermore Mg2+ blocks the outward current through some potassium channels resulting in an inward rectification of these channels. This suggests that internal magnesium functions as a potassium channel-blocking agent[4]. Early afterdepolarizations are oscillations in the membrane potential and lead to triggered activity and therefore are the electrophysiological substrate of "torsade de pointes" type of ventricular flutter. Mg2+ is able to inhibit both early afterdepolarizations and tachyarrhythmias[5]. Additionally Mg2+ interferes with the sodium-potassium-ATPase system by stabilizing the transmembrane gradient of both cations. Mg2+ deficiency alters this balance and leads to increased neuromuscular excitability. Digitalis is able to block the sodium-potassium-ATPase system, which can be cancelled by Mg2+ [6]. Thus the first clinical reports of the therapeutic use of Mg2+ refer to digitalis-induced atrial arrhythmia and ventricular ectopy which could be converted to sinus-rhythm or suppressed by the intravenous application of Mg2+ in 1935. Some years later, the first successful termination of paroxysmal supraventricular and ventricular tachycardia following application of 1.5 to 3 g of Mg2+ was published. But only in the late eighties, systematic studies of the electrophysiological effects of Mg2+ were performed and clinical use was first tested in random fashion in the nineties. Summarizing studies in older patients with different heart diseases and young healthy volunteers the most pronounced and clinically important effect seems to be related to the modulation of the AV node function. The prolongation of the PR interval by 7 to 12% without changing significantly heart rate, QRS duration and QT duration, can be considered a consistent and reproducible effect of Mg2+[7].In electrophysiological studies a prolongation of the AH interval by 8 to 18%, of the Wenckebach cycle length by up to 20% and of the refractory period of the AV node by 6 to 20% is usually observed, but no change of the retrograde conduction, or the HV interval can be found [2].Furthermore sinus node recovery time increases by 10% and sinuatrial conduction time by up to 25%. There is no significant effect on intraventricular conduction and atrial and ventricular refractory period.Additionally no significant effect on the anterograde and retrograde refractory period of accessory pathways could be measured; however in some cases (up to 40%) an anterograde block in the accessory pathway may be observed after intravenous Mg(2+)-injection[8]. For the treatment of paroxysmal atrioventricular tachycardia like AV-nodal reentrant tachycardia or orthodromic atrioventricular reentrant tachycardia in WPW syndrome, Mg2+ has been applied in a limited number of recent prospective but uncontrolled studies[9].In this context, this prospective study was conducted with aims and objectives to review and evaluate the role of serum magnesium levels in cardiac arrhythmias and to include serum magnesium level monitoring as routine investigation.

Materials and Methods

Candidates for CABG, Valvular heart seargeries (Aortic, Mitral Valve) Atrial septal defects, Ventricular septal defect, Cath lab procedures like CAG and PTCA etc. who had undergone treatment at Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bangalore, during the period from January 2016 to December 2017. Patients with prior normal sinus rhythms were included in the study with 100 patients (55 males, 45 females). Exclusion criteria consisted of:- Presence of any kind of arrhythmias, patients on anti-arrhythmic medications, past surgical history of CABG (redo), valve surgeries and renal failure, patients with pace makers, internal cardiac defibrillators and pregnant patients and patient refusal for study.

As per the inclusion and exclusion criteria mentioned above, patients were monitored with ECG and Hemodynamic monitoring as a part of routine treatment protocol. Out of those patients, who developed arrhythmia, at the time of arrhythmia, venous blood sample was drawn and sent to the biochemistry laboratory and serum magnesium level was measured by ENDPOINT CALORIMETRIC METHOD with XYLIDYL BLUE TEST. Like these 100 patient who had developed any type of arrhythmias appeared on the monitor was identified and rechecked, then confirmed by 12 lead ECG, their venous blood samples were drawn at the time of arrhythmia and sent to the laboratory and serum magnesium level were analyzed. Out of those 100 patients, 58 patients has low serum magnesium level (<1.8mg/dL) which is statistically significant with P<0.05.

Data variables comparison was done by ANNOVA test and their relationship was evaluated using correlation tests. The P-values <0.05 was considered significant for all tests.

Results

In this study, the following were the results noted

Table 1: Distribution of Patients by gender and age

Gender	Number	Percentage
Female	45	45%
Male	55	55%
Total	100	100%
Age Group	**Number**	**Percentage**
< 40 years	20	20%
41-60	28	28%
>61 years	52	52%
Total	100	100%

Majority of the patients were males and 52% of our study patients were above 61 year age.(Table 1)

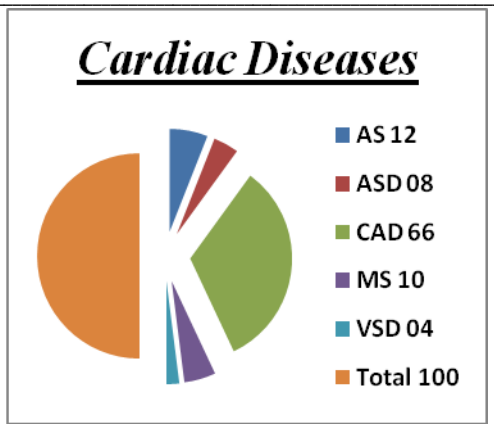

Fig 1:Cardiac disease

Among the study patients 66% had Coronary Atherosclerotic Disease compared to other cardiac diseases like valvular (Aortic stenosis and Mitral stenosis) and Atrial Septal Defect and Ventricular Septal Defects.(Figure 1)

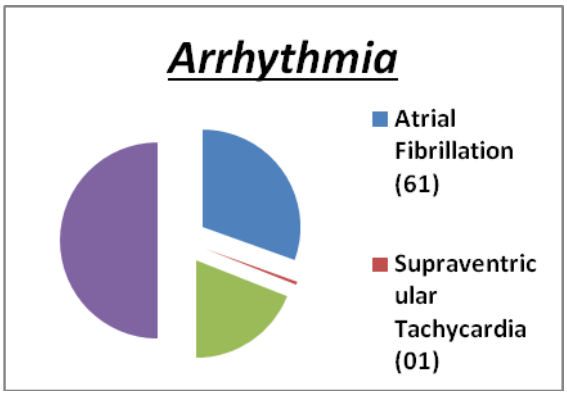

Fig 2: Type of Arrhythmia found in sampled patient

61% of the patient had Atrial Fibrillation and 38% had ventricular fibrillation during post operative period (Figure 2)

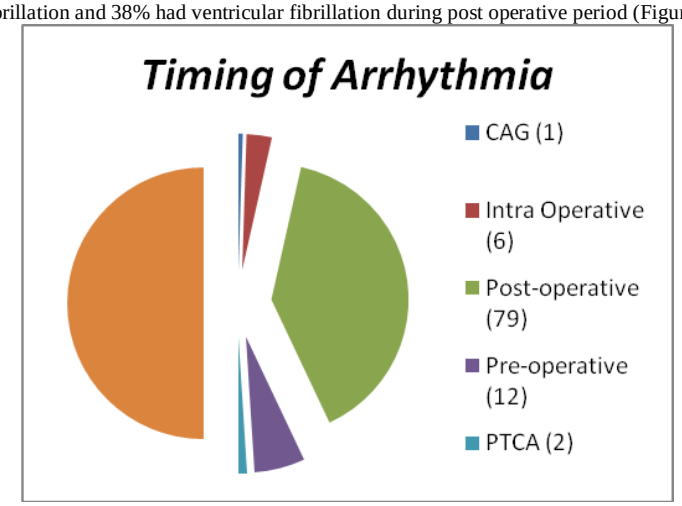

Fig 3: Timing of Arrhythmia in the sampled patient

Majority (79%) of patients had arrhythmias during Post operative period, compared to Pre and Intra operative arrhythmias with 12% and 6% respectively (Figure 3)

Table 2: Patient by level of Magnesium

Serum Magnesium level	Number of patients	Percentage
<1.8 mg/dL	58	58%
>1.8 mg/dL	42	42%
Total	100	100%

Significant number of patients (58%) had low serum Magnesium levels during arrhythmia with P value of <0.05 (Table 2)

Table 3: Association of Serum Magnesium level and timing of Arrhythmia

Serum magnesium Level	Timing of Arrhythmia					Total
	CAD	Intra Operative	Post- Operative	Pre-Operative	PTCA	
Sr Mg <1.8mg/dL	0	1(17%)	52 (65%)	3(25%)	2	58
Sr Mg >1.81mg/dL	1	5(83%)	27(35%)	9(75%)	0	42
Total	1	6	79	12	2	100

P value <0.05

65% of post operative cardiac patients had significantly low serum Magnesium levels withP value of <0.05 compared normal magnesium levels in similar diseases .(Table 3)

Table 4: Association of Serum Magnesium with the type of Arrhythmia

Serum magnesium	Type of Arrhythmia			Total
	Atrial Fibrillation	Supraventricular Tachycardia	Ventricular Fibrillation	
Sr Mg <1.8	40 (66%)	1	17(45%)	58
Sr Mg >1.81	21 (34%)	0	21(55%)	42
Total	61	1	38	100

66% of patients with AF had significantly low magnesium value (p<0.05) (Table 4)

Table 5: Mean Value of Magnesium and association to time of Arrhythmia (ANOVA)

Timing of Arrhythmia	Mean level of Magnesium	Number of patients
Intra operative	2.21	6
Post-Operative	1.8	79
Pre-Operative	1.9	12
PTCA	1.4	2
Total	1.84	100

In this study group post operative patients found to have low serum magnesium level had significantly more incidences of arrhythmias with mean level of serum Magnesium <1.8 mg/dl with p value <0.05. (Table 5)

Table 6: Mean value of Magnesium and association with type of arrhythmia (ANNOVA)

Timing of Arrhythmia	Mean level of Magnesium	Number of patients
Atrial Fibrillation	1.76	61
Supraventricular Tachycardia	1.6	1
Ventricular Fibrillation	1.9	38
Total	1.84	100

Patients with low serum Magnesium levels had significantly higher incidence of Atrial Fibrillation. (Table 6)

Discussion

This study examined the predictive value of serum magnesium levels on the incidence of arrhythmias during its occurrence.Serum magnesium level of less than 1.8 mg/dL was associated with a increased risk of arrhythmias. Although the presence of an association between a low magnesium level and adverse events is not surprising, the strength of the association is unexpected. we compared low magnesium levels with normal magnesium levels in a dichotomous fashion. Unfortunately, serum magnesium levels do not provide adequate data about total body magnesium levels[10]. Several investigators have reported a high incidence of systemic Mg deficiency in patients with diabetes mellitus. Therefore the relationship between Mg deficiency and diabetes mellitus should be investigated in large populations in future studies. It has been suggested that Mg deficiency is associated with tachyarrhythmias, especially as a complication of arrhythmias in acute myocardial infarction[13]. Mg infusion has been used clinically for treating patients with ventricular arrhythmia [14].The most prominent difference between the present study is 61 percent post operative AF and In various studies, the rate of AF has been reported to be from 16 to 42% [4, 6,7,8,11]. all cases of AF have been considered, in the present study, were included. Vester EG et al. reported an AF rate of 7% and AF episodes rate of 24%[12].Many studies have reported AF as a part of supraventricular dysrhythmias and did not report it separately. In our study of patients with AF, the exclusion of patients with combined valvular and coronary surgery, with renal failure, and patients with previous history of CABG, could decrease the overall number of patients with AF. The use of prophylactic methods (ß-blockers), improvement of surgical techniques (by time), routine use of myocardial protection methods (e.g. using warm colloid cardioplegic solutions), using antegrade/retrograde methods for myocardial circulation, using various filters and medications reducing body reaction to CPB,Increasing the speed of surgeries and decreasing duration of CPB and cross-clamping, could also be effective in lowering rates of AFThis study shows that there is a relationship between Mg serum levels and postoperative arrhythmias and monitoring serum magnesium level is must before the administration of supplemental doses of Mg sulfate seems to play a protective role against occurrence of arrhythmias by maintaining Mg serum levels within normal limits and preventing hypermagnesemia. These administered amounts, however, may cause complications due to the rise in Mg serum levels. It appears that the administration of supplemental Mg sulfate does not keep Mg serum in high levels for long time and thus does not prevent AF or other post CABG surgical arrhythmias. Based on these results, it is a must to monitor serum magnesium levels as routine investigation protocol to rule out hypomagnesemia and prophylactically prevent cardiac arrhythmias which could occur due to low magnesium levels and can have better patient treatment outcomes and low hospital stay and economic benefit to the patients. Further studies are needed to define more efficient diagnostic protocols to measure total body magnesium levels both ionic and non ionic forms and intra erythrocytic levels and the pathophysiology of postoperative dysrythmias, and rule out all other causes of arrhythmias including hypo magnesemia particularly AF, is to be elucidated.

Conclusions

This study proves the pro-arrhythmic effects of deficient serum magnesium, and the antiarrhythmic effects of normal serum magnesium. The proarrhythmic effects are markedly seen most in postoperative patients than the pre operative and intra operative magnesium deficient patients.

Serum magnesium should be monitored and given equal or more importance as other electrolytes in the above scenario and should not be ignored.The present study should not be considered an argument

for implicating magnesium deficiency with tachyarrhythmias. However,in light of its simplicity, cost-effectiveness and safety, monitoring the serum magnesium level is another first-line option for management of patients with arrhythmias in the intraoperative, perioperative, postoperative setup.Other factors for arrhythmias like hypokalemia hyperkalemia, hypercarbia, hypothermia, hypovoleumia, hypoglycemia and toxins, cardiac tamponade, tension pneumothorax, trauma also to be ruled out and prompt treatment to be given, along with monitoring serum magnesium level to rule out hypomagnesimia and to treat it along with the factors mentioned above for better patient safety and treatment outcome.

List of abbreviations used

ASD – Atrial Septal Defect
AF – Atrial Fibrilation
AS – Aortic stenosis
CABG – Coronary Artery Bypass Graft
CAD – Coronary Atherosclerotic Disease
CAG – Coronary Angiogram
DES – Drug Eluting Stent
EF – Ejection Fraction
PTCA – Percutaneous Transluminal Coronar
MS – Mitral Stenosis
VSD – Ventricular Septal Defect
y Angioplasty

Reference

1. Sasaki S, Oshima T, Teragawa H, Matsuura H, Kajiyama G, Kambe M.Rinsho Byori. Magnesium status in patients with cardiovascular disease.1999 May;47(5):396-401. Review.
2. Haigney MC, Berger R, Schulman S, Gerstenblith G, Tunin C, Silver B, Silverman HS, Tomaselli G, Calkins H.J Cardiovasc Electrophysiol.Tissue magnesium levels and the arrhythmic substrate in humans. 1997 Sep;8(9):980-6.
3. Stuhlinger H G,Kiss K,Smetana R.Significance of magnesium in cardiac arrhythmias.Wien Med Wochenschr. 2000; 150(15-16):330-4.
4. Maciejewsk, Górecki A, Łukaszewicz R, Ceremuzyński L.Acute coronary syndrome: potassium, magnesium and cardiac arrhythmia. Kardiol Pol. 2003 ;59(11):402-7
5. Keren A, Tzivoni D.Torsades de Pointes : Prevention and Therapy.Cardiovasc Drugs Ther. 1991;5(2):509-13.
6. Ceremuzyński L, Makowska Hypomagnesemia in heart failure with ventricular arrhythmias. Beneficial effects of magnesium supplementation. E.J Intern Med. 2000 ;247(1):78-8.
7. Parikka H, Toivonen L, Naukkarinen V, Tierala I, Pohjola-Sintonen S, Heikkilä J, Nieminen MS.Decreases by magnesium of QT dispersion and ventricular arrhythmias in patients with acute myocardial infarction.Eur Heart J. 1999 ;20(2):111-20.
8. Cook , Humphries KH, Gin K, Janusz MT, Slavik RS, Bernstein V, Tholin M, Lee MK.Prophylactic intravenous magnesium sulphate in addition to oral beta blockade does not prevent atrial arrhythmias after coronary artery or valvular heart surgery:a randomized controlled trial. Circulation. 2009;120(11 Suppl):S 163-9.
9. Vester E G. Clinico-electrophysiologic effects of magnesium, especially in supraventricular tachycardia.1997;22 Suppl 1:40-50
10. Stuhlinger H G,Kiss K,Smetana R.Significance of magnesium in cardiac arrhythmias.Wien Med Wochenschr. 2000; 150(15-16): 330-4.
11. Tsuji A, Araki K, Maeyama K, Hashimoto K.Effectiveness of oral magnesium in a patient with ventricular tachycardia due to hypomagnesemia. J Cardiovasc Pharmacol Ther. 2005 ;10(3): 205 -8.
12. Vester E G. Clinico-electrophysiologic effects of magnesium, especially in supraventricular tachycardia.1997;22 Suppl 1:40-50.
13. Richard C. Cook, Karin H. Humphries, Prophylactic Intravenous Magnesium Sulphate in Addition to Oral -Blockade Does Not Prevent Atrial Arrhythmias After Coronary Artery or Valvular Heart Surgery A Randomized, Controlled Trial, Circulation, 2009;S 163-S 169.
14. Toshiya Shiga, Zen'ichiro Wajima, Magnesium Prophylaxis for Arrhythmias after Cardiac Surgery: A Meta-analysis of Randomized Controlled Trials, September 1, 2004, The american journal of medicine,2004,117,325-333

Conflict of Interest: Nil
Source of support:Nil