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Adesh University Journal of Medical Sciences & Research

Article in Press

Original Article

Correlation of magnesium and calcium in the management of cardiac arrhythmia: Perspectives for better outcome

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Received: 06 May 2021
Accepted: 19 August 2021
EPub Ahead of Print: 27 Sep 2021
Published:

DOI
10.25259/AUJMSR_19_2021

Quick Response Code:

ABSTRACT

Objectives: To find correlation between serum Mg, serum Ca, and cardiac arrhythmia.

Materials and Methods: The present case–control analytical study includes records of 100 participants; 50 patients (both male and female average age: 47 ± 12 years, mean ± SD) admitted during the period of March 2019–March 2020 into the Coronary Care Unit of LG Hospital, AMCMET Medical College who were clinically diagnosed as arrhythmia and 50 subjects for control group from OPD patients coming to the same institution for health check-up. Mg was estimated with xylitol blue colorimetric end-point method and Ca was estimated by NM-BAPTA Method by Roche Cobas c311 instrument.

Results: In 50 cases, mean Mg value was 1.454 mg/dl and SD 0.2566 while in control group, mean value was 2.2 mg/dl and SD is 0.3110 with 95% confidence interval of 1.381–1.527 and 2.199–2.375 for cases and controls group, respectively, which was statistically significant ($p < 0.0001$). In 50 cases, mean Ca value was 8.6426 mg/dl and SD 1.3 mg/dl while in control group, mean value was 9.5 mg/dl and SD 0.47 with 95% confidence interval of 8.268–9.018 and 9.377–9.643 for cases and controls, respectively, which was statistically significant ($p < 0.0028$) and shows correlation between serum Ca and serum Mg which are low in cardiac arrhythmias. Receiver operating characteristic analysis of Ca: Mg (3.36) ratio showed optimum cutoff in diagnosis of cardiac arrhythmia.

Conclusion: We concluded that serum Mg and Ca along with Ca/Mg ratio should be considered as an important parameter for investigation of cardiac disorders, especially for patients of cardiac arrhythmia.

Keywords: Calcium, Cardiac arrhythmia, Magnesium

INTRODUCTION

Magnesium (Mg) is the second most abundant intracellular cation among all of cations inside the cell. It is involved in more than 300 chemical reactions of enzymes in the body. Mg is an important component of bones along with calcium (Ca). Mg is also one of the essential elements because of its action as anti-platelet, anti-vasospastic, β-adrenoreceptor blocking action, anti-arrhythmic, and other cardioprotective effects, supporting the rationale for its use in acute myocardial infarction.[1] Normal value of Mg is 1.6–2.6 mg/dl in adults. Out of total body Mg, majority is complexed in bone along with Ca, 1% is in the serum, and 31% is diluted in the cytoplasm or attached to ATP or enzymes.[2]

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Serum Mg values below the threshold of 1.6 mg/dl are defined as hypomagnesemia. However, the majority of patients with decreased total Mg have low serum Mg as well as low intracellular Mg concentration. Moreover, changes in Mg levels also affect serum Ca level. Extracellular Mg reduces ion movement rate through L-type Ca channel. Hence, Mg is physiological Ca antagonist. Hence, in the conclusion, mechanism of the action of Mg is similar to the Ca channel blockers.[3]

Hypomagnesemia has been associated with hypocalcemia. However, decreased body Mg can cause a depletion in PTH levels, raise in tissue resistance to PTH, and reduce active Vitamin D concentration[4] and ultimately lead to decreased serum Ca.

Hypomagnesemia is observed in many patients of arrhythmias. Cardiac arrhythmia occurs due to abnormal change in rate or rhythm of SA node and conducting system in heart. Cardiac arrhythmias can be bradycardia (heart blocks) or tachycardia (flutter or fibrillation). Mg helps in normal functioning of ion channels in heart. Mg acts as cofactor for many ATP-dependent enzymes like sodium-potassium ATPase deficiency of Mg reduces the activity of sodium potassium pump leading to partial depolarization of ion channels. Reduced amount of Mg leads to disturbance in resting membrane potential of cardiac muscles resulting in cardiac arrhythmias.[5]

Mg is an easily available biomarker for assessment in cardiac arrhythmia in clinical setting for better management in ICCU. Parenteral administration of Mg leads to sinus bradycardia, increases propagation time through atrioventricular node, and increases refractory period. Although with recent knowledge, it is difficult to anticipate exact effect of hypomagnesemia and its supplementation on cardiac electrophysiology.

Mg has cardioprotective properties, but proof of its role as a prognostic factor in the patient with arrhythmia is scarce. Study by Abraham *et al*., Rashmushan[6] has one of the studies, the study has shown that administration of Mg in patients of AMI was associated with less arrhythmia in cardiac patients. In the view of increased prevalence of decreased Mg in ICCU patients, it is advisable to measure Mg level routinely.[7,8]

Intravenous infusion of Mg sulfate has been beneficial in controlling arrhythmia and also has neuroprotective effect in decreasing severity in ICU patients.[9-12]

The main aim of our study was to find correlation between serum Mg, serum Ca, and cardiac arrhythmia.

MATERIALS AND METHODS

Our study was case–control analytical study

Study population: In the present study, record of total 100 participants; 50 patients who satisfied inclusion, exclusion criteria for cases (both male and female average age: 47 ± 12 years, mean ± SD), and who were admitted during the period of March 2019–March 2020 into the Coronary Care Unit of LG Hospital, AMCMET Medical College who were clinically diagnosed as arrhythmia and 50 subjects for control group from OPD patients coming to the same institution for health check-up was recorded.

Inclusion criteria (cases)

The following patients were included in the study:
1) Patient with atrial and ventricular arrhythmia
2) Chronic parenteral therapy

Inclusion criteria (controls)

Age- and gender-matched healthy subjects coming for health checkup were included in the study.

Exclusion criteria (cases and controls)

The following participants were excluded from the study:
1) Previous H/O of angina
2) Diabetes mellitus
3) Hypertension
4) Cardiomyopathy
5) Patient on pacemaker
6) Drugs affecting Mg level such as beta-blocker, diuretic, and bedaquiline.
7) Pregnant women.

Specimen preparation

Serum was collected in plain Vacutainer for the estimation of serum Mg and serum Ca. After collection, sample allowed to clot for 20 min and then centrifuged for proper separation of serum.

Mg was estimated with xylitol blue colorimetric end-point method by Roche Cobas c 311. The method is based on the reaction of Mg with xylidyl blue in alkaline solution containing ethylene glycol tetraacetic acid, to mask the Ca in the sample. In alkaline solution, Mg forms a purple complex with xylidyl blue, diazonium salt. The Mg concentration is measured photometrically through the decrease in the xylidyl blue absorbance.

Ca was estimated by 5-nitro-5'-methyl-BAPTA (NM-BAPTA) method. In this method, Ca ions react with NM-BAPTA under alkaline conditions to form a complex. This complex reacts in the second step with EDTA. The change in absorbance is directly proportional to the Ca concentration and is measured photometrically by Roche Cobas c 311.

Statistical analysis

Data were analyzed using GraphPad.

RESULTS

Sample size was 100 subjects, out of which 50 were patients of arrhythmia and 50 were control group. Table 1 shows mean and SD of serum Mg and serum Ca in cardiac arrhythmic cases and controls.

In 50 cases, mean Mg value was 1.454 Mg/dl and SD 0.2566 while in control group, mean value was 2.2 mg/dl and SD was 0.3110 with 95% confidence interval of 1.381–1.527 and 2.199–2.375 for cases and controls group, respectively.

In 50 cases, mean Ca value was 8.6426 Mg/dl and SD 1.3 Mg/dl while in control group, mean value was 9.5 mg/dl and SD 0.47 with confidence interval of 8.268–9.018 and 9.377–9.643 for cases and controls, respectively.

Mann–Whitney U-test was used for finding association between Ca and Mg values.

As compared to the control healthy group, the cardiac arrhythmia patients were found to have significantly decreased level of serum Mg and Ca, with $p < 0.0001$ and < 0.0028, respectively. Furthermore, there was a weak positive correlation of 0.18 which shows that both the values of Ca and Mg move in the same direction [Table 1].

Table 2 and Figure 1 shows area under the curve with sensitivity and specificity of Ca/Mg ratio. Area under curve (AUC) of 0.893 means that the chance that the readings will correctly distinguish a healthy normal person from an ill (cardiac arrhythmia) person is 89%.

The receiver operating characteristic curve of Ca/Mg showed an optimum cutoff at 3.36 with 96% sensitivity and 80% specificity, with significant area under the curve (AUC=0.893).

DISCUSSION

Cardiac arrhythmia is a group of cardiac disease for major cause of sudden death, so efforts have been made to identify risk factors. Mg deficiency is one of the major risks for etiology for cardiac arrhythmia.

In the present study Table 1 shows 50 cases mean Mg value is 1.454 mg/dl and SD 0.2566 while in control group, mean value is 2.2 mg/dl and SD is 0.3110 with 95% confidence interval of 1.381–1.527 and 2.199–2.375 for cases and controls group, respectively ($P < 0.0001$), which is statistically significant, also similar to the previous studies which have reported an association between decrease serum Mg and atrial fibrillation (AF) risk in the context of cardiac surgery.[13]

Serum Mg concentration is not a reflection of Mg storage of the body, however, serum Mg correlates well with intracellular Mg levels.[14] Decrease Mg led to pathogenesis of arrhythmia in experimental studies.[15] It was observed in rodents, the Mg deficiency augments the pro-arrhythmic effect of hypokalemia[16] and increase Mg reduces the development of ventricular reperfusion arrhythmias.[17] In humans, hypomagnesemia is associated with the development of AF after coronary artery bypass surgery.[13] Some studies suggest that Mg supplementation decreases the incidence of post-operative AF.[18-24] It is not known whether hypomagnesemia is associated with the development of AF in ambulatory individuals, particularly those without existing cardiovascular disease. Such correlations could have public health impact because low Mg value is very common and easily correctable.

However, Mg has several effects one of the most in cardiac conduction system. It is an important cofactor for Na-K ATP pump, which regulates the movement of sodium and potassium across the cell membrane.[25] Mg supplements increase atrioventricular node conduction time,[26] whereas decrease serum Mg concentration increases sinus node automaticity.[27] Many studies have shown that intravenous Mg infusion can manage rate control in AF and involve in maintenance of sinus rhythm.[28] However, hypomagnesemia leads to increase the dose of digoxin required for rate control[29] and reduce the threshold for digoxin-related arrhythmias.[30] In small metabolic unit studies, decrease dietary intake of Mg to less than one-half of the recommended daily allowance increased supraventricular ectopy[31] and risk of AF.[32] Another recent study shows an inverse relation between Mg status and sudden cardiac death, potentially giving further support to the link between hypomagnesemia and cardiac arrhythmias.[33] Horner's study revealed that infusion of Mg in acute myocardial infarction was associated with 49% reduction in ventricular arrhythmias and 54% reduction in supraventricular tachycardia.[34] Neuromuscular hyperexcitability associated with tetany and convulsion. Hypomagnesemia led to hypocalcemia due to end-organ resistant action of PTH which led to decrease serum Ca. Cardiac arrhythmia has been associated with Mg deficiency and partly caused by hypokalemia and intracellular potassium depletion due to alteration of Na/K ATPase in Mg deficiency.[35] In 50 cases,

Table 1: Mean and S.D of serum Mg and serum Ca in cardiac arrhythmic cases and controls.

Parameter	Case (mean)	Case (SD)	Control (mean)	Control (SD)	*P* value	r value
Serum Mg	1.454	0.2566	2.2	0.3110	<0.0001	0.18
Serum Ca	8.6426	1.3	9.5	0.47	,< 0.0028	

Mg: Magnesium, Ca: Calcium

Table 2: Area under the curve.

Test result variable(s): Ca/Mg ratio				
Area	Std. error	Asymptotic sig.[b]	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.890	0.038	0.000	0.815	0.965

The test result variable(s): Ca/Mg ratio has at least one tie between the positive actual state group and the negative actual state group. [a]Under the non-parametric assumption, [b]null hypothesis: True area=0.5.
Mg: Magnesium, Ca: Calcium

Parameters	Optimum cut-off	Sensitivity	Specificity	AUC
Ca/Mg ratio	3.36	96%	80%	0.893

Mg: Magnesium, Ca: Calcium, AUC: Area under curve

Table 3: Correlation of Ca:Mg ratio.

Parameters	Control (*n*=50)	Cardiac arrhythmia (*n*=50)	*P* value
Ca/Mg ratio	4.232+0.614	6.152+1.461	<0.0001

Above data represent Ca:Mg ratio in case and control highly significant with *P*<0.0001, which shows ratio is higher in arrhythmia than normal control group. Ca: Calcium, Mg: Magnesium

mean Ca value is 8.6426 Mg/dl and SD 1.3 Mg/dl while in control group, mean value is 9.5 Mg/dl and SD 0.47 with confidence interval of 8.268–9.018 and 9.377–9.643 for cases and controls, respectively ($P < 0.0028$), which is statistically significant. Hence, there is correlation between low serum Mg, serum Ca, and arrhythmias. Ca: Mg ratio is higher in arrhythmia than normal persons.

Low Ca may lead to arrhythmias by impairing both depolarization and repolarization of cardiac myocytes. Physiologically, Ca blocks sodium channels and prevents depolarization. Hence, decrease in Ca allows increase in sodium passage and lowers the depolarization threshold, causing greater myocardial irritability.[36] The pathogenesis through which low serum Ca levels may lead to sudden cardiac death is not understood properly. Patients with sudden cardiac arrest had a more prolonged QT interval, indicating toward an arrhythmic phenomenon as a potential cause. Decrease in Ca, Mg, and potassium is all known to be correlated with prolonged QT intervals, which have been shown to be an independent risk of sudden cardiac death in the general population.[37]

Cal/Mg ratio as shown in Table 2 and Figure 1 is also significant at 3.36 cutoff with 95% sensitivity and 80% specificity. Table 3 shows correlation of Ca:Mg ratio statistically significant having *P* value < 0.0001

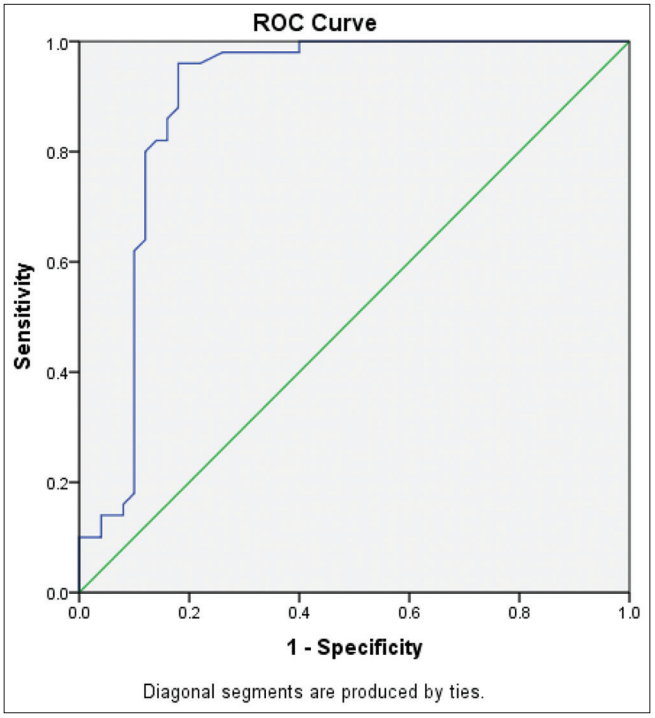

Figure 1: Receiver operating characteristic curve is between Ca/Mg ratio of cases and controls.

CONCLUSION

Mg and Ca along with Ca/Mg ratio should be consider as an important parameter for investigation of cardiac disorder, especially for the cardiac arrhythmia along with other laboratory tests such as Na^+, k^+, and Cl^-. It could be time saving, cost effective, and easy for differential diagnosis and better outcome with available Mg supplements in cardiac arrhythmias. Still further studies are needed to study the correlation of various cations and Mg deficiency leads to other cardiac complication such as arrhythmias, myocardial infarction, and other cardiovascular complication.

Acknowledgment

Special support from the medicine department for confirmed clinical diagnoses with other clinical details of these patients on laboratory evaluation forms.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Patel UH, Jagrit NN, Madole MB, Panchal SS. Correlation of magnesium and calcium in the management of cardiac arrhythmia: Perspectives for better outcome. Adesh Univ J Med Sci Res, doi: 10.25259/AUJMSR_19_2021