Original Research Article

Serum magnesium levels and mean platelet volume (MPV) as biomarkers in acute myocardial infarction

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Abstract

Background: Myocardial infarction which is an outcome measure in clinical trials, observational studies and quality assurance program have several conventional risk factors which include older age, hypertension, diabetes, decreased physical activity, alcohol intake, smoking, abdominal obesity, high-risk diet, psychological stress. Hypomagnesemia and means platelet volume is now recognized as a significant risk factor for atherogenesis, and thus for hypertension, ischemic heart disease, cardiac arrhythmias, coronary vasospasm, sudden cardiac death, cerebrovascular accident, and myocardial infarction.

The aim of the study: To determining the relationship between serum Magnesium levels on platelet reactivity in Acute Myocardial infarction. Therefore in this study, we attempted to find the impact of serum Magnesium level on the Mean Platelet Volume and the use of these parameters as novel biomarkers to predict AMI.

Materials and methods: A case-control study was carried out in the Department of Cardiology, Govt. Royapettah Hospital/ Kilpauk Medical College. Totally 88 Acute Myocardial Infarction patients (for the estimated prevalence of 30.36% in urban Indian population) admitted in the Intensive Coronary Care Unit between July to October 2015 and 88 age and sex-matched apparently normal individuals were included. Fasting venous peripheral blood samples were drawn within 48 hours of admission. Blood samples were taken into standardized trisodium citrate tubes (stored at room

temperature) and a sterile vacutainer which was serum separated, aliquoted into 2 Eppendorf's and stored at minus 20 º C until further analysis.

Results: Both the Systolic and Diastolic Blood pressure was significantly elevated in the cases (p= 0.000) which was statistically significant. The Fasting Blood Glucose levels were raised in AMI patients (p=0.001) although only 38.6% were known Diabetics. Urea levels were increased in cases (p=0.007) which was significant. The serum magnesium values were significantly lower in AMI patients in comparison to the normal individuals (p= 0.000) and the Mean Platelet Volume was significantly elevated in the cases than the control (p=0.004).

Conclusion: Our study demonstrated that Magnesium levels were reduced in AMI patients and that Mean platelet Volume was elevated in AMI patients however a cause-effect relationship between the two parameters was not established. However, we propose that MPV and Magnesium may be useful biomarkers in identifying patients with increased risk for AMI. Further, a cohort study design including all the confounding variables can better address their relationship and role as adjuvant biomarkers in the diagnosis of AMI.

Key words

Serum Magnesium, Mean Platelet Volume, Acute Myocardial Infarction, Renal Profile.

Introduction

Coronary Heart Disease leads to more death and disability in low- and middle-income countries [1]. In contrast to the developed world there is a relatively early age of CVD deaths in the developing countries [2]. India has the highest burden of the acute coronary syndrome in the world with 31.7% deaths due to Myocardial infarction (MI), which is the most common contributor of morbidity and mortality worldwide [3]. Thus MI poses a great economic strain on our country. Myocardial infarction which is an outcome measure in clinical trials, observational studies, and quality assurance program has several conventional risk factors which include older age, hypertension, diabetes, decreased physical activity, alcohol intake, smoking, abdominal obesity, high-risk diet, psychological stress [4, 5]. Hypomagnesemia is now recognized as a significant risk factor for atherogenesis, and thus for hypertension, ischemic heart disease, cardiac arrhythmias, coronary vasospasm, sudden cardiac death, cerebrovascular accident, and myocardial infarction [6]. Magnesium is the second most common intracellular cation that has a dynamic role in the maintenance of myocardial metabolism, electrophysiology, ion gradient across membranes, anti-inflammatory, antioxidant activity and thus plays an important role in reducing myocardial damage, reperfusion injury and associated complications in myocardial infarction patients. Magnesium may be a promising agent for the protection of ischemic myocardium and modulation of reperfusion injury [7, 8]. During AMI the serum Magnesium concentration decreases significantly. It is found that Hypomagnesaemia in AMI patients' augments catecholamine-induced myocardial necrosis [9], elevates circulating levels of inflammatory cytokines, leading to multifocal necrosis resulting in larger infarct size at the time of coronary occlusion [10]. The stress of AMI can intensify the patient's magnesium requirement because of myocardial and urinary losses of magnesium [11]. Thus hypomagnesemia is both a cause and consequence of Acute Myocardial Infarction. In addition to the above-mentioned mechanisms, Magnesium can play a critical role in the pathogenesis of myocardial infarction and reperfusion injury indirectly by its influence in regulating platelet activity. Magnesium maintains platelet volume by maintaining the activity of ATPase pumps across the membrane. It has been shown that magnesium deficiency increases circulating levels of IL-6 resulting in thrombocytosis and production of larger platelets

[12]. Larger platelets are more reactive, produce more prothrombotic factors and show greater aggregation [13]. Since Mean platelet volume (MPV) provides the accurate measure of platelet size, it is a potential marker of platelet reactivity [14]. MPV is found to be an independent risk factor for MI in Coronary Artery disease patients and for death and recurrent vascular events after MI. An elevated mean platelet volume (MPV) has been associated with a poor outcome among survivors of myocardial infarction [15].

Materials and methods

A case-control study was carried out in the Department of Cardiology, Govt. Royapettah Hospital/ Kilpauk Medical College. Totally 88 Acute Myocardial Infarction patients (for the estimated prevalence of 30.36% in urban Indian population) admitted in the Intensive Coronary Care Unit between July to October 2015 and 88 age and sex-matched apparently normal individuals were included. Fasting venous peripheral blood samples were drawn within 48 hours of admission. AMI is defined as; the rise of cardiac bio-marker (cardiac troponin cTn) with symptoms of ischemia or new significant ST-segment –T wave (ST-T) changes or echocardiographic evidence of loss of viable myocardium or Regional Wall Motion Abnormality. Both ST-segment Elevated MI (STEMI) and Non-ST-segment Elevated MI (NSTEMI) patients were included. Patients with renal disease or under diuretic treatment and Magnesium supplementation were excluded as this was likely to alter the measured parameters. This study conforms to widely accepted ethical principles guiding human research and permission for the study was obtained from the institutional ethical committee. Patient information sheet in regional language was given and informed consent was obtained from all participants.

Laboratory methods

Fasting venous peripheral blood samples were drawn within 48 hours of admission. Blood samples were taken into standardized trisodium citrate tubes (stored at room temperature) and a sterile vacutainer which was serum separated, aliquoted into 2 Eppendorf's and stored at minus 20 ºC until further analysis. One aliquot was utilized for routine investigations:

1) Fasting Blood Sugar estimated by glucose oxidase (GOD)/ peroxidase (POD) method.
2) Urea estimated using UV-GLDH method.
3) Creatinine measured using Modified Jaffe's Reaction.

The second aliquot was used for Serum Magnesium estimation based on Calmagite-EGTA method (Colorimetric- End Point Assay). All the biochemical analysis was done using MERCK semi-automated clinical chemical analyzer.

Trisodium citrated tubes were used opposed to the standardized EDTA tubes as MPV changes are less with acid citrate and had better accuracy and reproducibility than EDTA [16]. Mean Platelet Volume was estimated within 30 minutes of sample collection using Automated Hematology Analyzer, SYSMEX XE-2100 based on Impedance Automated Pulse Analyzer method.

Statistical analysis

Data was analyzed using SPSS 17 (SPSS Inc., Chicago, Illinois, USA) software for Windows. Continuous variables were expressed as mean ± SD, whereas categorical variables are presented as absolute values and percentages. To compare continuous variables, we used Student's t-test or the Mann–Whitney U test, where appropriate. Categorical variables were compared via the chi-square test. Logistic regression analysis was performed to determine if an independent relationship exists between MPV and Magnesium. The cut-off values of Magnesium and MPV predicting AMI were obtained from Receiver Operating Curve analysis. For all tests, a p-value less than 0.05 was considered to be statistically significant. The odds ratio was calculated using MedCalc statistical software for biomedical research version 18.11 (Belgium, Frank Schoonjans).

Results

Our study comprised of 88 Acute Myocardial Infarction patients (78 males, 10 females), with a mean age of 52 ±12 (range 22 to 86 years). Majority of the AMI patients, 95.5% of them were diagnosed with ST-segment Elevated MI. There was no statistically significant difference between the age, sex and coronary risk factors such as active smokers, known hypertensives and known diabetic subjects as p>0.05 given in both the Systolic and Diastolic Blood pressure was significantly elevated in the cases (p= 0.000) which was statistically significant. The Fasting Blood Glucose levels were raised in AMI patients (p=0.001) although only 38.6% were known Diabetics. Urea levels were increased in cases (p=0.007) which is significant. The serum magnesium values were significantly lower in AMI patients in comparison to the normal individuals (p= 0.000) and the Mean Platelet Volume was significantly elevated in the cases than the control (p=0.004). There was no significant correlation between the serum Magnesium levels and the Mean Platelet Volume in both the AMI group (p= 0.2950) and the control group (p=0.5653). However, the regression model summary in AMI patients showed a negative small correlation (r2 = 0.019) very low-value low relationship with MPV and magnesium (**Table – 1**).

Table – 1: Results of the parameters measured in the study population.

	AMI patients	**Controls**	**p-Value**
Male gender, %	88.6	88.6	0.598
Age, years	52.2 ±12.1	51.9 ±12.2	0.598
SBP, mmHg	128.6±14.6	119.5±4.7	**0.000**
DBP, mmHg	87± 12.1	78.8±3.5	**0.000**
Smokers,%	50	3.4	0.364
FBS, mg/dl	125.2 ±77.1	89.3 ±51.3	**0.001**
Urea, mg/dl	21.8 ±10.8	18± 7.4	**0.007**
Creatinine, mg/dl	0.93± 0.3	1.4± 2.8	0.145
Serum Magnesium, mg/dl	1.48±0.41	2.42±0.75	**0.000**
MPV	9.34±0.77	9.01±0.68	**0.004**
Acute Myocardial Infarction patients			
STEMI %	95.5	STEMI %	95.5
Known Hypertensives,%	18.2%	Known Hypertensives,%	18.2%
Known Diabetics,%	38.6	Known Diabetics,%	38.6
Previous h/o Ischemic Heart Disease,%	12.5	Previous h/o Ischemic Heart Disease,%	12.5

Abbreviations: AMI= Acute Myocardial Infarction; DBP= Diastolic Blood Pressure; FBS= Fasting Blood Sugar; MPV= Mean Platelet Volume; SBP= Systolic Blood Pressure; STEMI= ST-segment Elevated Myocardial Infarction.

The criterion used to categorize individuals in the study population as Hypomagnesemia was serum Magnesium levels < 1.6 mg/ dl (devised from a previous study establishing a reference range for Magnesium in Indian population). The odds ratio for Hypomagnesemia in the study population obtained was 11.64 (95% Confidence interval; p<0.0001) which was statistically significant. The odds ratio for obtained having larger and reactive platelets were 1.44 times higher which was not statistically significant (95% Confidence interval; p=0.2604). The Receiver Operating Curve analysis for Magnesium (**Figure - 1**) provided criteria of serum Magnesium level ≤ 2.1 mg/dl for prediction of Acute Myocardial Infarction which is statistically significant (p<0.0001).

The cut-off value obtained for Mean Platelet Volume (**Figure - 2**) was MPV≥ 9.9fl which is significant (p=0.0507). The best cut-off values for predicting Acute Myocardial Infarction

obtained using Receiver Operating Curve analysis were (sensitivity 18.2%; specificity 100%) and Magnesium (sensitivity 95.5 %; specificity 63.6%).

Figure – 1: ROC curve for prediction AMI using magnesium.

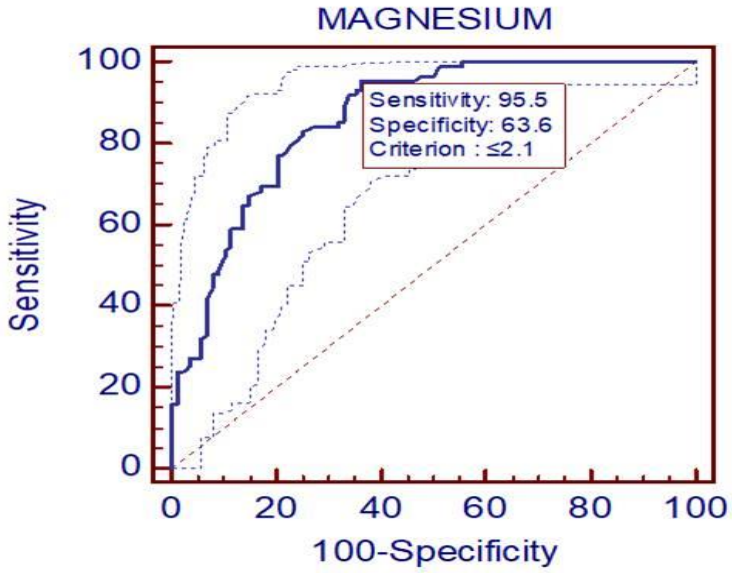
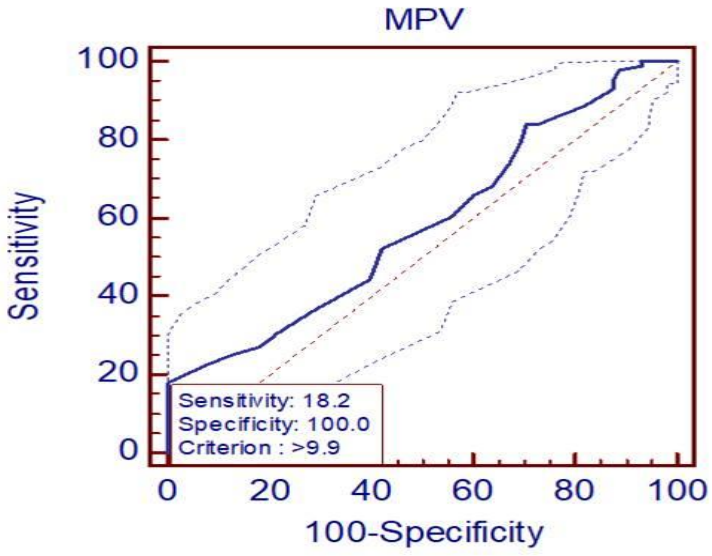


Figure – 2: ROC curve for prediction of AMI using mean platelet volume (MPV).



Discussion

Eighty-eight patients admitted to the Kilpauk Medical College ICCU diagnosed with Acute Myocardial Infarction were compared to 88 normotensive, normoglycemic individuals with no previous history suggestive of myocardial ischemia. The majority of the AMI patients were males 88.6% (78 male, 10 female) in accordance to the fact that men are more prone for CAD than women, probably due to the protective effect of estrogen [16]. The mean age of acute myocardial infarction in patients was 52 ± 12 years similar to the mean age of AMI obtained from several studies in the Indian population (53 years). Of this, 22.7% were less than 40 years of age thus in line with the rising trend of premature coronary

events in our population [17]. With respect to the coronary risk factors, 50% of the AMI patients were active smokers but the difference was not statistically significant. Smoking has been associated with twofold risk for fatal MI in India [18]. Hypertension is an established risk factor for MI, 18.2% of the AMI patients were known hypertensives and both the Systolic and Diastolic Blood Pressure was raised in the MI patients in comparison to control population. The increase in Blood pressure may be attributed to the response to stress by the physiologic mechanisms [19]. Only 38.6% of the patients have known the case of Diabetes Mellitus however the Fasting Blood Glucose levels were elevated significantly in the cases. Studies have shown that Blood glucose was found to be elevated in the immediate period following an AMI irrespective of the Diabetic status of the patient as a response to acute stress [20]. The concentration of Urea is significantly elevated in AMI patients. A similar result has been observed in a study which indicated that a rise in plasma urea level was common if not universal after myocardial infarction and is caused by either a fall in the glomerular filtration rate or an increased urea production rather than a mixture of the two [21]. The study between the serum Magnesium levels and Myocardial Infarction done by Guipeng AN, et al. [22] showed a significant decrease ($p<0.01$) of magnesium in MI similar to this study the serum Magnesium levels were found to be significantly decreased ($p=.000$) in cases when compared to that of the control group. This shows the association of hypomagnesemia with acute myocardial in our study, which validates the observed results. Hypomagnesemia is associated with the initiation and propagation of free radical myocardial tissue damage through oxidation of myoglobin, which is essential for intracellular transport and storage of oxygen [23]. In our study, we found that AMI patients had 11.6 times increased the risk of Hypomagnesemia. Various studies which observed the effects of oral Magnesium supplementation have shown that it improved the lipid profile, improvement in brachial artery endothelial function and exercise tolerance in CAD patients [24, 25]. These findings suggest that serum Magnesium levels should be measured in patients with Acute Myocardial infarction and those with an increased risk of MI and supplemented when found to be deficient.In an attempt to use Magnesium as a marker for prediction of MI we obtained a cut-off value of serum Magnesium $\leq$ 2.1 mg/dl which to our knowledge was not attempted in previous studies. The Mean Platelet Volume is significantly increased ($p=0.002$) in AMI patients when compared with the control group. This finding was in accordance with several studies that demonstrated patients with AMI had higher Mean Platelet Volume ($p < 0.05$). Evidence from the Diet and Reinfarction Trial (DART) shows those with an elevated MPV had a significantly higher risk of death than those with a normal MPV. The increase of mean platelet volume is an independent predictor for recurrent myocardial infarction and death in the late phase [26]. Thus, larger platelets play a specific role in coronary thrombosis and MI. Since MPV is readily available with routine hematological analysis and patients with raised an MPV can be easily identified. George Endler et al found that patients with preexisting coronary artery disease and an increased MPV ($\geq$11.6 fL) are at higher risk of myocardial infarction [27]. In one study an MPV of $\geq$11.1 fL was the best cut-off value in predicting Troponin positive Acute Coronary Syndrome with a sensitivity of 84% and a specificity of 65% ($P=0.000$) [28]. In our study, an MPV$\geq$9.9Fl was the best cut-off value in predicting Acute Myocardial Infarction. As suggested by Agrawal BK et al. MPV can be used as an adjuvant in the diagnosis of AMI as other cardiac biomarkers are time-dependent and within the normal limit at the first three hours after the initiation of AMI [29]. However, a small negative very low-value relationship was found between Magnesium and MPV in AMI patients. A larger study population might provide a better insight into this cause-effect association between the Mg and MPV. Ryzen E, et al. suggested that serum Magnesium levels, like Potassium, often remains normal despite the depletion of total body magnesium [30].

Conclusion

Serum Magnesium and Mean Platelet Volume are common laboratory tests that are often neglected and underutilized parameters. Our study demonstrated that Magnesium levels were reduced in AMI patients and that Mean platelet Volume was elevated in AMI patients however a cause-effect relationship between the two parameters was not established. However, we propose that MPV and Magnesium may be useful biomarkers in identifying patients with increased risk for AMI. Further, a cohort study design including all the confounding variables can better address their relationship and role as adjuvant biomarkers in the diagnosis of AMI.

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