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Impact of Serum Uric Acid Levels on Cardiovascular Outcomes in The Myocardial Infarction

KEYWORDS: Uric acid, cardiac failure, killips class

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ABSTRACT *BACKGROUND: Most sudden deaths in acute myocardial infarction occur within one hour due to ventricular fibrillation and also due to left ventricular failure when there is an extensive injury1.Rest of the deaths following myocardial infarction happen within first one week and death cannot be predicted and occurs suddenly. Hence many trials have been conducted to identify markers that would be helpful to predict the risk of such adverse cardiac events.*

AIM: The aim of this study is ascertain uric acid as a predictor for mortality and morbidity and risk of developing adverse cardiac events like sudden cardiac death and congestive heart failure following acute myocardial infarction.

OBJECTIVE: 1.To validate the prognostic significance between quantitative serum uric acid level on admission and high Killip's class status in acute myocardial infarction.

2. Quantification of incidence of cardiac failure and mortality in relation to serum uric acid levels

STUDY DESIGN: prospective observational study

MATERIAL AND METHODS: This study included 100 patients of acute myocardial infarction of which patient who had a normal uric acid level were taken as a control group and the rest who had elevated uric acid level were taken up as a study group.

Statistical methods: Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. P-value< 0.05 is considered as significant.

RESULTS: The mean serum uric acid in males was 6.23 mg/dl and in females was 5.98 mg/dl. In study group 40% are in Killip I&II and 60% in Killip class III&IV in comparison to control group 75% are in Killip I&II and 25% in Killip class III&IV.

Incidence of heart failure in total population was 41% in which males were 80%, females were 20 %. In study group 64% developed heart failure in comparison to 73% in control group.

Incidence of mortality in patients with study group was 26% and in patients with control group was 6 %.

CONCLUSION: Elevated Uric Acid (UA) levels is a good marker of oxidative stress and useful to assess the prognostic events in acute myocardial infarction.

INTRODUCTION:

Acute Myocardial Infarction (AMI) is the leading cause of mortality in both developed and developing countries[2,3] as they are emerging out in epidemic proportions throughout the world. Factors contributing to death following acute myocardial infarction are many.

These factors relate mainly to electrical disturbances in the form of arrhythmia[4,5] and mechanical disturbances in the form of pump failure .[6,7]

Hence many trials have been conducted to find identify markers that would be helpful to predict the risk of such adverse cardiac events.

Previous studies[8,9,10,11] have established that Serum Uric Acid (SUA) levels reflect circulating xanthine oxidase activity and oxidative stress[12] production following acute myocardial infarction.

Free radicals produced in large amounts during myocardial ischemia and reperfusion, take part in the degradation of cellular and sub cellular membrane structures. The source of oxygen radicals in ischemic myocardium are neutrophils recruited into the necrotic region as well as metabolic transformation of Hypoxanthine and Xanthine to Uric acid[13].

The increased plasma uric acid concentration observed in patients with ischemic heart disease could arise from up-regulated vascular adenosine synthesis associated with ischemia in cardiac tissue and the subsequent degradation of adenosine to uric acid by endothelium. This uric acid undergoes rapid efflux to the vascular lumen due to low intra cellular pH and negative membrane potential. Xanthine oxidase activity, uric acid synthesis are increased in vivo under ischemic conditions, therefore elevated serum uric acid may act as a marker of underlying tissue ischemia.

Thus it is evident that elevated Uric Acid (UA) levels is a good marker of oxidative stress and useful to assess the prognostic events in acute myocardial infarction.

STUDY DESIGN AND METHODS: prospective observational study

STUDY POPULATION:

This study was conducted in the Department of Medicine

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and Department of Cardiology, MAHATMA GANDHI MEMORIAL HOSPITAL/KAKATIYA MEDICAL COLLEGE, WARANGAL during the period of February 2014 to August 2015. Total number of patients included in this study were 100.

INCLUSION CRITERIA:
Patients with a diagnosis of acute ST Elevation Myocardial Infarction were entered into the study. A definite diagnosis of acute ST Elevation Myocardial Infarction was made if the patients satisfied the following criteria:

1. A history of typical retrosternal compressive chest pain lasting for more than 30 minutes, not relieved by rest or nitrates.
2. Typical ECG changes of acute ST Elevation Myocardial Infarction.

EXCLUSION CRITERIA: 1. Patients with elevated renal parameters and on diuretic & aspirin therapy.
2. Patients with Gout, diabetes mellitus, chronic alcoholism, history of Ischemic Heart Disease.

Above patients were excluded because the coexisting disease or drug therapy might itself produce a high uric acid level.

Very late presentations of patients more than 72 hours also excluded since uric acid level tends to fall subsequently (Journal of the Indian Medical Association 1977 Sep1).

History, physical examination, routine laboratory investigations were performed in all subjects. Patients are categorized based on Killip's classification at admission and heart failure was diagnosed on Framingham criteria and further classified on 2D echo cardiogram (left ventricular ejection fraction (LVEF)) into heart failure with EF>50%and <50%.

Qualifying patients received thrombolytic therapy with 1.5 million units of streptokinase followed by heparin for 5 – 7 days.

Assessment of left ventricular ejection fraction by echocardiography was performed either on day 4 or 5 of hospitalization in most patients or earlier if clinically indicated.

FOLLOW UP:
All the patients were followed up for a period of 7days. During follow up any changes in Killip's classification, features of cardiac failure and any mortality were noted in both group of patients. Routine daily physical examination was done. ECG's were taken daily and additional investigations carried out if necessary. Patients were discharged at 8th day if they were stable, otherwise their hospital stay was prolonged.

Framingham criteria for heart failure like JVP elevation, basal rales, acute pulmonary edema, S3 gallop, tachycardia (>100/min), lower extremity edema were used in this study for making a diagnosis of CCF.

URIC ACID ESTIMATION:[14,15,16]
Immediately after admission, blood sample of 3cc was drawn by veni puncture and transferred to dry plain bottle and taken to biochemistry laboratory.

The method used for analysis is enzymatic method (Uricase method) by using auto analyzer. In our laboratory, values taken as normal range 3.4-7.0 for males and 2.4- 6.0 mg/dl for females.

RESULTS:-
HYPERURICEMIA & POPULATION WITH NORMOURICEMIA:
Out of 100 patients studied, 53 patients had normal uric acid level and they were taken up as control group. Of which 43 (81%) were males and 10 (19%) were females. The remaining 47 patients had elevated serum uric acid level and they were taken up as study group of which 34(72.3%) were males and 13 (27.7%) were females. Both were compared with various out comes.

In this study, the mean serum uric acid levels in males & females were 6.25 mg/dl & 5.98 mg/dl respectively. The mean serum uric acid levels in study group and control were 7.48 mg/dl & 4.94 mg/dl respectively.

CLINICAL STATUS- KILLIP CLASS & SERUM URIC ACID:
In this study, 23, 36, 18, 23 patients presented with Killip class I, II ,III, IV respectively. Killip class III & IV were taken as high risk category in this study and evaluated whether high uric acid concentration after myocardial infarction correlated with this high risk Killip class.

When clinical status of patients based on killip class I to IV and uric acid were analyzed, the following observations were made. In the patients with normal serum uric acid level, 75 % belonged to I & II Killip class and only 25% belonged to Killip class III & IV whereas in patients with hyperuricemia 40 % belonged to Killip class I & II and 60% belonged to Killip class III &IV.(diagram 1)

The results of this study showed significant association between high serum uric acid levels and higher Killip class (III &IV) of heart failure ($p < 0.05$).Hence uric acid can also be used as a predictor of prognosis.

HEART FAILURE:
It was observed that 41 out of 100 patients in this study had heart failure in the post Myocardial Infarction period. So the incidence of heart failure was 41 %. Of which 28(68.2%) were males, 13(31.8%) were females and among 41 heart failure patients, 30 patients had high uric acid level and 11 patients had normal uric acid level.

It was also found that 30 out of 47 patients in study group had heart failure amounting to an incidence of 64 % heart failure While only 11 out of 53 patients in control group had heart failure amounting only 21% of patients with normal uric acid level had heart failure. The above figures suggest that the occurrence of heart failure is high in patients with high uric acid level.

It shows there was significant association between raised seum uric acid levels and incidence of heart failure in patients with AMI ($p < 0.05$).

ECHOCARDIOGRAM:
In high uric acid population, 17 (36%) patients had LVEF <50% and 30 (64%) patients had LVEF >50% whereas in normal uric acid level population,8 (15%)patients had LVEF <50% and 45(85%) patients had LVEF >50%.Among 17 hyperuricemic patients, 16(85%) are males and 9(53%) are females. Patients who had elevated serum uric acid level, in heartfailure patients with EF<50% hyperuricemia is significantly associated with LVEF <50% ($p < 0.05$) significant correlation with uric acid levels

ARRHYTHMIA:
It was observed that 7 out of 100 patients developed ar-

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rhythmias in this study. So the incidence of arrhythmias was 7% of which86% were (6) males, 14% was (1)female. 3 patients had ventricular tachycardia and 4 patients had supra ventricular tachycardia among 7 arrhythmias, So patients who had high uric acid level(5) and normal uric acid level (2)contributed to 71% and 29% respectively to arrhythmias .

It was also found that 5 patients out of 47 patients with high uric acid level had arrhythmias amounting to an incidence of 11% arrhythmias in study group. While only 2 out of 53 patients with normal uric acid level had 4 % arrhythmias only(p is 0.17939).

The above findings suggest that the occurrence of arrhythmias is also high in patients with high uric acid level. But hyperuricemia was not significantly associated with development of arrhythmias in this study (p is 0.17939(NS).

The above studies & present study tells there is a high incidence of arrhythmias when there is an elevated serum uric acid level and it is hypothetical an increased uric acid level may be arrhythmogenic. Further studies are needed to conclude it.

MORTALITY:

To find out the prognostic significance of elevated uric acid level following acute myocardial infarction, mortality rate in patients with normal and high uric acid level were separately calculated. 15 out of 100 patients died due to their cardiac ailments in this study. This amounts to mortality rate of 15% of which 14 (93%) were males, 1 (7%) was female.

It was observed that among 15 deaths, 12 deaths were contributed by patients with high uric acid levels and 3 deaths by those who had normal uric acid levels. Thus 80% of deaths occurred in those who had a highuric acid level and only 20% in those who had a normal uric acid level. It was also found that 12 out of 47 patients with high uric acid level died. This implies a mortality rate of 26% in patients study group in comparision to a mortality rate of 6 % in control group following myocardial infarction (p <0.05)

This striking difference in the mortality figures for both group of patients implies uric acid level can be used as a predictor of mortality following myocardial infarction. The association between hyperuricemia and mortality was found to significant (p <0.05). (diagram 2)This study revealed that patients who developed short term adverse events like mortality following myocardial infarction had high uric acid concentrations.

Present study also parallels with previous authors and uric acid can be used as a good predictor of mortality.

CONCLUSION:

1. There is a significant association between elevated SUA and cardiac failure which has objective correlation with echo cardio graphic evaluation of LV dysfunction.
2. Patients with high SUA level belonged to higher Killip class (III & IV).
3. Elevated serum uric acid level may be arrhythmogenic and has correlated with short term mortality in acute myocardial infarction.
4. Measuring serum uric acid level is one of the predict able prognostic indicator in acute myocardial infarction as serum uric acid is an economical bio marker that is readily, quickly and reliably obtainable and thus along with Killip's classification should be incorporated for risk stratification in patients with AMI.

LIMITATIONS OF STUDY

We believed that a greater cohort would be desirable to improve the power of the study.

We also relied on clinical data to rule out infection and other inflammatory diseases before sampling, but we cannot exclude that some patients had unrecognized conditions responsible for the elevated serum uric acid levels observed.

We supposed to mean that these limitations might not have a significant influence on study data interpretation.

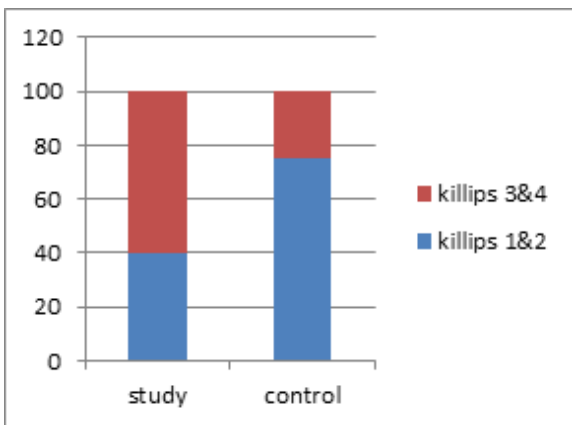

Diagram 1 shows the KILLIPS classification in study and control groups.

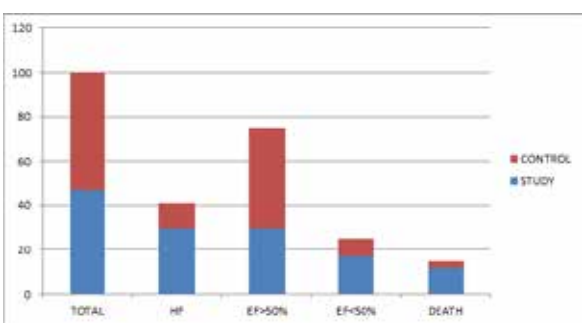

Diagram 2 shows the various cardiac outcomes in study and control groups.(P<0.05 in case of heart failure and mortality and ejection fraction)

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