Original Research Paper

Volume-8 | Issue-8 | August-2018 | PRINT ISSN No 2249-555X

General Medicine

ASSESMENT OF PREGNANCY ASSOCIATED PLASMA PROTEIN – A (PAPP- A) AS A PREDICTOR OF ACUTE CORONORY SYNDROME IN PATIENTS PRESENTING WITH CHEST PAIN

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ABSTRACT Acute coronary syndromes (ACS) are a major cause of morbidity and mortality in the world today. Early diagnosis limits myocardial damage in ACS patients. Presently, we use cardiac troponins I and T which are sensitive and specific biomarkers for diagnosing ACS, but they are released in circulation only after tissue damage. There is a need of new biomarkers that would appear in the circulation before significant myocardial necrosis develops. Lately pregnancy associated plasma protein- A (PAPP- A) has emerged as an interesting bio marker in this context. The present study is undertaken in patients admitted to the emergency department with chest pain and finally diagnosed as ACS at Osmania Govt. hospital. In this study, total 88 subjects were included, out of them 50 were patients of acute coronary syndrome and 38 were healthy controls. The mean PAPP-A levels were estimated in both ACS patients and healthy controls. Mean PAPP-A levels were significantly elevated 0.673+ 1.2 in ACS patients compared to 0.1025+ 0.38 in healthy control ($P < 0.001$). The mean Troponin-I levels were estimated in both ACS patients and healthy controls 17.61+ 19 in ACS patients and 0.702+ 0.8 in healthy controls, $P < 0.001$

KEYWORDS : Acute Coronary Syndrome, Cardiac Troponins, Pregnancy Associated Plasma Protein A (PAPP-A).

INTRODUCTION:

Acute coronary syndromes (ACS) are a major cause of morbidity and mortality in the world today. Early diagnosis can limit myocardial damage in ACS patients. Circulating markers of myocardial necrosis, most commonly cardiac troponins I and T due to their superior sensitivity and tissue – specificity, are widely used in the diagnosis of ACS patients along with the electrocardiogram[1].

The limitation of cardiac troponins has been that as markers of myocardial necrosis they are, released into the circulation only after damage of the heart muscle tissue. Moreover, with the methods previously available, it took several hours after the onset of symptoms for the elevations to become detectable[2].

However, the tests for cardiac troponins have lately evolved significantly and become more and more sensitive. This has enabled the detection of even lower elevations earlier in the course of ACS[3,4,5].

In recent years a major objective in cardiovascular disease research has been to find new biomarkers that would appear in the circulation before significant myocardial necrosis develops. Such markers are anticipated to enable earlier diagnosis of the patients arriving at the emergency unit with symptoms of ACS such as chest discomfort and shortness of breath. Numerous candidate molecules have appeared which are linked to the various pathological processes leading to or associated with ACS. Lately, pregnancy associated plasma protein A (PAPP A) has emerged as an interesting candidate marker in this context.

Elevated PAPP A can be used to diagnose onset of ACS even before infarction has set in[6]. In general, the concentration of PAPP –A is found to be very low in adult males and non-pregnant women[7]. In addition to the association of elevated PAPP-A levels with atherosclerotic vascular disease,[8] recently PAPP –A was found to be a useful biomarker for cardiovascular dysfunction[9] .The present study was undertaken to evaluate if PAPP – A is an early diagnostic marker for acute coronary syndrome in patients presenting with chest pain.

AIMS AND OBJECTIVES OF THE STUDY

1. Study of the PAPP- A in patients admitted to the emergency department with chest pain and finally diagnosed as ACS.
2. Correlation of PAPP-A levels in sub-types of ACS.
3. Comparison of PAPP A and troponin I in subtypes of ACS.

MATERIALS AND METHODS

The case control study was conducted in the Department of general medicine, Department of biochemistry, Department of cardiology Osmania General Hospital, Hyderabad.

The study sample consisted of 88 subjects divided into two groups: Group 1 of 50 patients diagnosed of acute coronary syndrome (Mean age 55 ± 20 years) and Group 2 of 38 controls(Mean age 50 ± 20 years). Informed oral consent was taken from all individuals who took part in the study. EXCLUSION CRITERIA considered during the selection of study population were Liver or kidney disorder, Cerebro vascular accident, Malignancy, Pregnancy.

Specimen collection:

5 ml Venous blood was drawn from all groups within 6 hours of presentation to emergency department, in red capped tubes. Blood was allowed to clot and serum separated thereafter. Hemolysed and lipemic samples were not accepted.

Serum was stored in aliquots at -20º c for estimation of PAPP A and Troponin I.

Statistical Analysis

Statistical analysis was performed using Graph pad prism software version 6. Data are expressed as mean ± standard deviation of various parameters in different groups. P value and unpaired t test was used to assess the significance. $p < 0.05$ was considered to be statistically significant.

OBSERVATIONS & RESULTS

A total of 88 subjects included in the study. Among them 50 patients were diagnosed as coronary artery disease based on ECG, Cardiac biomarkers (PAPP-A and Torponin – T) and 2D Echocardiography.

Among 50 members of ACS patients, were diagnosed as ST Segment elevation myocardial infarction (STEMI)[10], 15 were diagnosed NON ST Segment elevation myocardial infarction (NSTEMI)[10] and 15 were diagnosed as unstable angina(UA)[10].

38 were age and sex matched healthy controls.
The following parameters are analysed

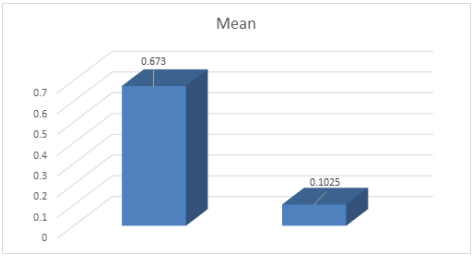
Serum PAPP – A
Serum Troponin – I
Mean serum levels of PAPP-A and Troponin –I were analysed separately in the two groups.

The results obtained for PAPP-A were as follows:

PAPP –A in Controls and ACS patients

The levels of PAPP-A in ACS patients is 0.673 ± 1.221 where as the levels of PAPP-A in normal healthy controls is 0.102 ± 0.38.

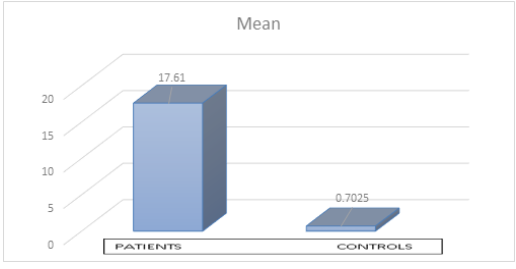
PAPP –A in Controls and ACS patients



Troponin – I in Controls & ACS Patients

The analysis of Troponin – I showed the following results
Mean serum value of Troponin I in ACS patients is 17.61 + 19.44. Whereas Troponin – I in normal healthy controls is 0.702 + 0.84 .

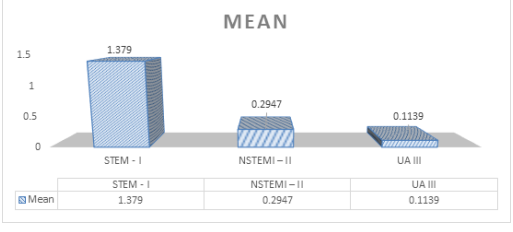
Troponin – I in Controls & ACS Patients



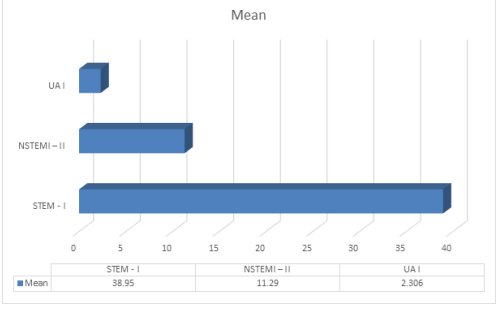
Mean Serum levels of PAPP – A in subtypes of ACS

Levels of PAPP – A and Troponin – I in sub types of ACS were analysed separately in 50 ACS patients.

Mean Serum levels of PAPP – A in subtypes of ACS



Mean serum levels of Troponin – I in each subtypes of ACS
Diagram of mean of troponin I in subtypes of ACS.



DISCUSSIONS

In the present study 50 patients of acute coronary syndrome were studied. As hypertension, diabetes, dyslipidemia, smoking and alcoholism are risk factors for acute coronary syndrome, history regarding this is considered and as incidence of ACS differ according to age and sex, age and sex were also included.

As per the study, among 50 patients, 20 were STEMI patients. In these patients, STEMI is more common in men and women. 17 were men and 3 were women. Mean age group was 50 + 20. Smoking history is present in 15 patients out of 20 and history of alcoholism is present in 18.History of hypertension is present in 20 patients, diabetes in 17 patients and dyslipidemia in 20 patients. This is in consistent with various studies showing the association of major cardio vascular risk factors with the development of ACS. Smoking, hypertension, dyslipidemia, and diabetes are demonstrated to be risk factors especially in younger individuals. A half of ACS population in the < 45 years age subgroup possessed all four ACS risk factors in one study. These results call for attention and implementation of prevention programmes11.In this study, 15 members with diagnosed as NSTEMI. Mean age group is 40 + 15 more common in men than in women history of smoking is present 10 members and history of alcoholism is present 9 members out of 15 patients. hypertension in 15 patients and diabetes in 13 patients. dyslipidemia is present in all patients. Another 15 members were diagnosed as unstable angina based on their typical presentation and ECG and Echo changes. Mean age group among these patients is 45+ 15. More common in men than in women history of smoking is present in 12 members and history of alcoholism is present in 5 members out of 15 patients. Hypertension in 12 patients and diabetes in 10 patients. Dyslipidemia is present in all the patients.

PAPP – A in Acute Coronary Syndrome

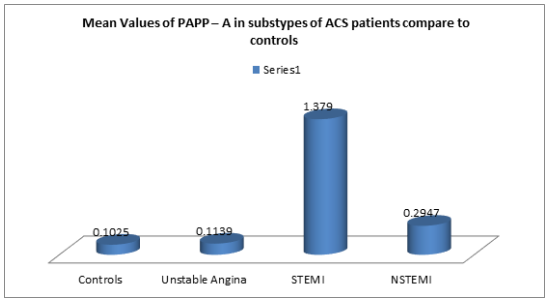
In the present study, mean serum PAPP - A levels are 0.673 + 1.221 in ACS patients where as a PAPP – A level are 0.102 + 0.38 in normal subjects.

This is in consistent with various previous studies, suggesting the elevation of PAPP – A in acute coronary syndromes.

Headchen and colleagues (2005) studied a heterogenous population of individuals who had arrived at the emergency room with chest pain. PAPP – A concentration were significant higher in those patients who were later diagnosed with ACS. During the index hospitalization than in those who were diagnosed with stable angina (or) who did not have coronary heart disease[12].

Similarly in a study by Elesber and colleagues (2007) the admission serum sample PAPP-A concentrations were higher in those intermediate to high risk chest pain patients who were subsequently diagnosed with ACS than in those patients who were diagnosed with non cardiac chest pain[13].

In this study the mean serum levels of PAPP- A in UA, NSTEMI and STEMI are 0.113 + 0.3006, 0.294 + 0.393, 1.379 + 1.66 respectively, among 50 patients of acute coronary syndrome, suggesting that PAPP – A levels are more in STEMI and NSTEMI than in unstable angina compared to that of normal controls. PAPP – A level are significantly higher in blood samples from patients diagnosed with MI or UA than in samples from normal coronary arteries.



This is in comparison with previous studies, Rossen and Colleagues (2007) suggesting that circulating PAPP-A levels were lower in NSTEMI patients than in STEMI patients and yet lower levels are seen in healthy controls[14]. Miedema and colleagues reported on higher circulating PAPP-A levels in ACS patients than in patients with stable angina or in asymptomatic CAD patients[15]. Lin and colleagues noticed higher serum PAPP-A in STEMI and UA patients than instable angina patients and controls16. Schools and colleagues studied high PAPP – A (2009) studied high PAPP – A levels in STEMI patients compared to high risk. NSTE ACS patients or low risk NSTE – ACS patients with even lower level[17].

Mc Cam and colleagues found higher PAPP- A levels in the admission samples of those patients with acute ischemic type chest pain who were later diagnosed with MI than in those without MI diagnosis[18].

In the present study, mean serum Troponin-I levels are 17.61+ 19.49 in ACS patients whereas Troponin-I levels are 0.7025+ 0.8 in normal subjects.

In this study, the mean serum levels of Troponin-I in UA, NSTEMI and STEMi are 2.306 + 1.83, 11.29 + 7.84, 38.95+ 16.86 respectively. Among 50 patients of acute coronary syndrome, suggesting that Troponin levels are more in STEMI, NSTEMI, UA patients compared to normal controls. Troponin-I levels are significantly higher in blood samples from patients diagnosed with MI.

P value calculated by unpaired t test for PAPP – A is 0.0082. As it is < 0.05 it is considered significant. P value for Troponin – I is < 0.001. As it is ($P < 0.05$), it is considered significant. This study showed significant elevation of PAPP – A in ACS patients like that of Troponin I. So, PAPP –A is considered as a cardiac biomarker along with troponin I in patients with ACS.

Laterza et al concluded PAPP- A to be a modest predictor of adverse cardiac events at 30 days19.Huschen et al in a sanitary study should PAPP – A was a powerful predictor both in patients with low and high troponin levels[20].

These studies are consistent with the present study showing an elevation of PAPP-A in acute coronary syndrome patients.

CONCLUSIONS

1. PAPP–A might be useful as an indicator for early diagnosis of ACS, consequently, be an important clinical aid in reducing the incidence of ACS, disability and mortality associated with this condition.
2. The estimation of PAPP–A along with regular markers of myocardial necrosis in patients suspected of ACS might prove to be an important tool for diagnosis of ACS.
3. Elevation of PAPP–A levels in cases of UA, when myocardial necrosis markers are within the normal range and ECG changes are inconclusive, highlights the utility of PAPP – A in early diagnosis of ACS.

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