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ISCHEMIA MODIFIED ALBUMIN(IMA)-A SENSITIVE MARKER IN THE EARLY DIAGNOSIS OF ACUTE CORONARY SYNDROM(ACS)?

General Medicine

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ABSTRACT

Background: Diagnosing a case of Acute Coronary Syndrome in the emergency department is quite challenging. Early diagnosis and treatment helps in reducing mortality.

Materials and methods: A total number of 120 patients were included who came to the emergency department with symptoms suggestive of ACS. IMA was done along with the routine work up and compared with the routine cardiac markers.

Results : Mean IMA value was 88.83 + 7.575u/ml in UA group, 87.32 + 9.250u/ml in MI group and 55.96 + 25.332u/ml in NICP group which showed a sensitivity of 92% and specificity of 87% compared to CKMB which was 68% sensitive and 70% specific. The positive predictive value of the test was 88% and negative predictive value was 94%. In 14 patients an early diagnosis could be made when compared with Trop-I.

Conclusion: IMA is a very potent marker for the early diagnosis of ACS thus reducing in hospital mortality rates due to delayed diagnosis.

KEYWORDS

Ischemia Modified Albumin, Acute Coronary Syndrome, Albumin Cobalt Binding Test

INTRODUCTION

Ischemia occurs when there is a supply demand mismatch in cardiac blood flow. If the ischemia is reversible, no myocardial damage occurs. If the ischemia is prolonged there will be cellular necrosis and myocardial infarction. The interventional challenge for medicine is to be able to identify acutely impaired myocardial perfusion before necrosis has occurred.

Patients with acute chest pain suggestive of Acute coronary syndrome (ACS) can have a heterogeneous array of conditions, including non-ischemic chest pain (NICP), transient myocardial ischemia, Unstable Angina (UA), ST segment elevation myocardial infarction (STEMI), and non-ST segment elevation infarction (NSTEMI).

The triage and treatment of patients who present to emergency departments (EDs) with symptoms potentially indicative of acute cardiac ischemia remain problematic and continue to challenge clinicians. More than 6 million patients present annually to United States EDs with suspected acute coronary syndromes (ACS) of whom only 17% are finally diagnosed with coronary disease. In India also this number is growing. Patients are hospitalized or held for observation and although ACS is often ruled out, this imposes a substantial financial burden and inconvenience to the patient and medical system.[1,2,3]

The patients presenting to the ER can present with a variety of symptoms ranging from vague epigastric discomfort to severe chest pain. Reaching to the correct diagnosis at the earliest is mandatory as delayed or mis-diagnosis can lead to increased mortality rates. Ischemia-modified albumin (IMA), a Food and Drug Administration-approved serum biomarker of cardiac ischemia and a risk stratification tool for suspected acute coronary syndrome, is produced during an ischemic condition or attack and is present in the blood in early and easily detectable levels.[4,5] The increase in markers that predict myocyte necrosis during or after CABG surgery usually parallels with a poor prognosis of the patient. IMA is a marker formed after damage in the N terminal region of the albumin in ischemic conditions. Endothelial or extracellular hypoxia, acidosis, and free oxygen radicals have been shown to cause IMA increase.[6]

AIMS & OBJECTIVES

To establish the significance of IMA in differentiating ACS from non-ischemic chest pain by correlating with other cardiac biomarkers-cardiac Troponin I & CKMB.

MATERIALS AND METHODS

This study was performed at AJ Institute of Medical Sciences, Mangalore and was approved by the ethics committee.120 subjects, both males and females within the age group 25-80years were recruited who had presented in the ER with symptoms suggestive of myocardial ischemia within 6 hours of onset. CKMB and cardiac troponin I (at 0 & 6hours) were estimated along with ECG analysis.

INCLUSION CRITERIA:-

Patients presenting in the ER with the following symptoms:

- Chest pain
- Heaviness
- Breathlessness
- Left arm pain
- Syncope
- Palpitations
- Jaw pain
- Epigastric pain
- Hyper/hypotension

EXCLUSION CRITERIA:-

Since normal albumin levels are necessary for the estimation of IMA,patients with renal diseases,cirrhosis,serum albumin less than 2g/dl were excluded.

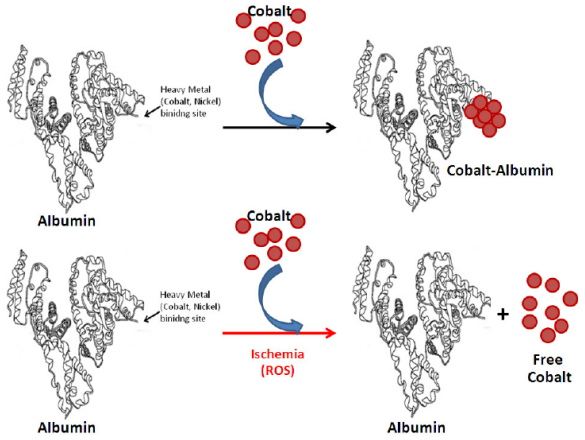
History of infections,gastrointestinal diseases,stroke,muscle injury were excluded as IMA is elevated in these conditions too.

METHODS

Between May 2014 and July 2015,120 patients who presented with symptoms suggestive of ACS were recruited. Demographics and clinical information were recorded for each patient. On admission, history and examination done, appropriate investigations including CKMB, Troponin-I were done along with routine 12-lead ECG and echocardiography.

ALBUMIN COBALT BINDING TEST (ACB Test) :

IMA was measured by the albumin cobalt binding test (ACB Test) on the Roche Cobas MIRA PLUS instrument. The mechanism whereby IMA represents a marker of ischemia is based upon the fact that human serum albumin (HSA) has the ability to bind certain transition metal ions, particularly cobalt and copper, at the N-terminus. Bar-Or has previously reported that exposure of albumin to ischaemic tissue changes the structure of HSA N-terminus such that it can no longer bind cobalt.[7,8]



PRINCIPLE OF ALBUMIN COBALT BINDING (ACB) ASSAY[9]

In physiological conditions, albumin capable of binding with metal ions such as cobalt, copper, and nickel, at amino terminal end of the protein. During ischemia, N-terminal portion of albumin, especially at aspartate-alanine-histidine-lysine sequences, is modified and result in the reduction in albumin-metal ions binding ability.

The Normal Value of IMA: The suggested normal value of IMA by using ACB test is < 85 U/mL. Any result greater than that value is claimed as myocardial ischemia.[10,11]

We pooled the blood samples and did the ACB test concurrently. All the 120 samples were collected in serum separated tubes. -20° C was the freezing point set to store the collected sample. All samples were kept for freezing within two hours of collection. 95 [micro]l of a patient sample and 5 [micro]l of cobalt chloride (CoII), are incubated for five minutes. To this incubated mixture, 25 [micro]l of dithiothreitol (DTT) was added. DTT forms a coloured complex with Co(II) that is not bound at the N-terminus of albumin, and this complex is measured spectrophotometrically at 500 nm. Duplicate IMA values were obtained with the mean recorded as the result of the assay. The frozen samples were gyred after warming. It showed no significant difference in assay results from the fresh specimens.

ECG CLASSIFICATION:-

Positive ECGs were those with ST segment depression or elevation ≥ 0.1 mV, or T wave inversion ≥ 0.2 mV (in ≥ two contiguous leads). ECGs showing no ST segment shifts or T wave changes (apart from lead III or V1) were considered negative. Equivocal or uninterpretable ECGs (that is, left bundle branch block, paced rhythm, extensive pathological Q waves, and/or persistent ST segment elevation after previous AMI) were considered to be negative in this study.

CREATININE KINASE-MB:-

Blood was collected at the time of admission and >25U/l was considered to be significant.

CARDIAC TROPONIN I:-

Cardiac troponin I was measured at admission and after 6 hours by rapid chromatographic immunoassay.

STATISTICAL ANALYSIS: - Subject characteristics were reported as descriptive statistics, with means, medians, SDs, and ranges. Characteristics incorporated in multivariable analyses included age, sex, diabetes, hypertension, smoking, time to hospitalization. Categorical variables will be analyzed with "Fischer's exact test". 2 by 2 tables will be used to assess the diagnostic value of IMA as positive and negative predictive values, sensitivity and specificity will be calculated with 95% confidence interval.

RESULTS:

ESC/ACC criteria was adhered to for the reporting of the results of the study. Of the enrolled 120 subjects, ACS was diagnosed in 102 patients and NICP in 36 patients. Out of 102 ACS patients, 30 had STEMI, 14 had NSTEMI and 40 had UA.

The table below represents patient characteristics in each group.

Clinical Parameter	NICP (n=36)	UA (n=40)	MI (n=44)
DM	17	24	19
HTN	17	16	17
Smoking	16	11	20
Mortality	0	4	8

Comparing IMA values in all 3 groups:

Clinical parameter	NICP(n=36)	UA(n=40)	MI(n=44)	P value
IMA (mean value)	55.96 ± 25.332	88.83 ± 7.575	87.32 ± 9.250	NICP vs.UA, P=0.0001 NICP vsMI, P.=0.001 UA vs. MI,P=1.00
Elevated IMA	5	36	38	

IMA value was elevated in 5 of 36 patients in NICP group whereas it was elevated in 36 of 40 patients in UA group and 38 of 44 patients in MI group.

Comparing IMA,CKMB,TROP-I in all the 3 groups:

Biochemical parameters	NICP (n=36)	UA (n=40)	MI (n=44)
Elevated IMA	5	36	38
CKMB	0	0	40
Positive Troponin-I at admission	0	0	24
Positive Troponin-I after 6 hours	0	30	44

CKMB was elevated in all 40 patients. Comparing IMA with Trop-I showed that IMA was elevated in 38 of 44 patients at admission whereas Trop-I was positive in only 24 of the 44 patients. So in 14 patients an early diagnosis could be made when compared with Trop-I.

IMA vs CK-MB

Efficiency of Serum IMA and CK-MB levels as marker of Cardiac Ischemia

	Serum IMA	Serum CKMB
Sensitivity	92%	68%
Specificity	87%	70%
Positive predictive value	88%	59.2%
Negative predictive value	94%	72.2%
Odds ratio	45.88 (14.491-145.261)	4.709 (1.830-12.065)

This showed a sensitivity of 92% and specificity of 87%. The positive predictive value of the test was 88% and negative predictive value was 94%.

DISCUSSION :

Cardiac markers play a vital role in the diagnosis and risk stratification of patients with chest pain and suspected acute coronary syndrome (ACS). The cardiac markers used commonly nowadays are creatinine kinase-MB, cardiac troponins(cTropT,cTropI), myoglobin. These cardiac markers are released only after myocardial necrosis sets in. This is where the role of IMA comes in where the release of the same occurs before necrosis happens. IMA starts increasing within 6 to 10 minutes of ischemia, reaches peak by 4 hrs and returns to baseline after 6-12 hrs in transient ischemic conditions, like after Percutaneous transluminal angioplasty.[12] Whereas the N-Terminal oxidative damage to albumin is cumulative and the repair is slow in cardiac ischemia, and the level also will not raise after 6 hours.

In our study, IMA testing in 120 patients with chest pain established the significance of early diagnosis of myocardial infarction before myocardial necrosis happened .Comparing CK-MB and TropI with IMA, 92% sensitivity and 87% specificity proves the role of IMA, a sensitive marker,in the early diagnosis of ACS. It helped us to differentiate ACS from NICP thus, providing necessary treatment without delay. Significant p values proved that IMA aids in differentiating NICP from UA and NICP from MI.But it did not help us to differentiate UA from MI. A study conducted in India by Chawla et al[13] found that IMA demonstrated good discrimination between the ischemic and the nonischemic patients with an Odds Ratio of 16.9 (6.29 - 46.87) than CKMB which showed an Odds Ratio of 2.07 (1.18 -

6.08). Sensitivity and specificity of IMA for the detection of ACS was 78.0% and 82.7% compared to 58.0% and 60.0%, respectively for the CK-MB assay.

Results in the study of Quiles et al[14] confirmed that IMA is an early marker of ischemia in the setting of PCI. Thirty-four patients who underwent elective single-vessel PCI for the management of stable angina pectoris were studied. Serum albumin measurements were within the reference intervals in all patients. Blood samples were drawn from a femoral artery sheath 10 min before PCI and within 5 min after the last balloon inflation. IMA concentrations in all patients increased significantly after PCI from baseline to post-PCI (59.9 to 80.9 kilounits/L; *P* _0.0001). IMA was higher in patients with more balloon inflations, higher pressure inflations, and longer inflation duration. However, because there was some scatter in the correlations, factors such as the severity and extent of the lesion and the presence or absence of collateral blood supply may also play a role in IMA concentrations. In the study by Bhagavan et al[15]. ACB assay results (using an assay independent of the Ischemia Technology IMA test) were correlated with final discharge diagnoses in 75 ED patients with myocardial ischemia and 92 nonischemic patients. The diagnosis of myocardial ischemia, with or without MI, was based on clinical signs and symptoms, imaging, ECG, and serum cardiac biochemical markers such as CK-MB and cTnI. The sensitivity and specificity for myocardial ischemia were 88% and 94%, respectively, and the positive and negative predictive values were 92% and 91%. The ACB test, however, was a poor discriminator between ischemic patients with and without MI. This compared well with our study.

Limitations are many. IMA increases in all ischemic conditions like renal diseases, liver diseases, cerebrovascular accident, neoplasms, radiofrequency catheter ablation, cardioversion, thromboembolic conditions, diabetes due to oxidative stress. Also, a serial assay of IMA was not done. So, IMA kinetics was not fully understood.

CONCLUSION

We were able to conclude that IMA is a sensitive marker in the early diagnosis of acute coronary syndrome. It helped us to differentiate ACS from NICP and to provide treatment at the early phase before necrosis has happened.

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