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Efficacy of Ischemia Modified Albumin in early diagnosis of Acute Coronary Syndrome at a Rural Teaching Hospital.

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Abstract

Context and Aim: Acute Coronary Syndrome (ACS) are a set of disorders occurring due to decrease blood perfusion of myocardial tissue resulting in myocardial ischemia. Ischemia results in the modification of albumin at its N-terminus region referred to as Ischemia Modified Albumin (IMA) The present study was undertaken to determine the clinical utility of IMA in the diagnosis of ACS in a rural teaching hospital.

Settings and Design: A cross-sectional study was done at a rural tertiary care teaching hospital.

Materials and methods: Thirty clinically diagnosed patients suffering from ACS and thirty age and sex-matched healthy persons were taken as controls. The serum sample was tested for CK-MB, cTnI, and IMA. IMA levels were estimated by Albumin Cobalt Binding assay. Statistical analysis was done using the student 't-test and Receiver Operating Curve (ROC) was prepared to determine performance characteristics and optimal cut-off of the IMA assay.

Results and Observation: The ACS patient had a significantly higher IMA value of 0.65±0.23 compared to 0.41±0.11 in controls ($p<0.0001$). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IMA were 80%, 76.67%, 77.42%, and 79.31% respectively for the diagnosis of ACS based on a cutoff value of 0.4775 ABSU. 80% of ACS patients had an IMA value greater than the cut-off value compared to 63.33% having CK-MB value >25U/L and 53.33% having positive troponin test.

Conclusion: IMA test showed high sensitivity, specificity, PPV, and NPV and hence may be a useful marker in early diagnosis of ACS.

Key messages: IMA testing can bring a new dimension for care and management of patients presented with the acute coronary syndrome.

Keywords: Acute coronary syndrome, Ischemia modified albumin, Myocardial ischemia, Troponin –

Introduction

Myocardial ischemia, resulting from lack of adequate blood perfusion to myocytes, is underlying mechanism of Acute Coronary Syndrome (ACS) and if prolonged, leads to inadequate oxygen and nutrients supply demand mismatch, resulting in irreversible myocardial necrosis myocyte death, a condition called as myocardial infarction (MI). [1-3]

ACS is associated with high rates of mortality, as about 17 million deaths occur worldwide due to cardiovascular diseases. In India alone the deaths have risen from 1.17million in 1990 to 1.5million in 2000 and 2.03million in 2010 and still the graph is rising. [1,4]

Diagnosis of ACS is based, firstly on clinical presentation, which may be varied and not specific with many atypical presentations. [1,2,4,5] Secondly, ECG (electro cardio graphy) changes, which may be simple, fast and reliable method of early diagnosis of ACS, but half of patients with ACS have no significant ECG changes at time of presentation to emergency department (ED) and hence misdiagnosed.

Further, ECG changes is sensitive to diagnose only 50% of cases having regional wall motion abnormality or myocardial perfusion defects and moreover changes may occur due to confounding factors such as early repolarization, left ventricular hypertrophy and left bundle branch block. Echocardiography is limited by non-ischemic etiologies responsible for wall motion defects.[3]

Lastly, biochemical markers, such as creatine kinase-MB (CK-MB), cardiac troponins(T&I), lactate dehydrogenase (LDH)etc., are analyzed and though these conventional markers are highly sensitive and specific but are raised only after 3-6 hours of onset of myocardial injury until which irreversible myocardial damage has already set in. [1,3,5] Since these markers require cell necrosis to occur, they are absent during early reversible period of ACS such as unstable angina (UA).[5]

It is important to identify myo car dial ischemia before irreversible necrosis develops and hence there is a need for newer biochemical markers which detects early reversible myocardial ischemia. [6,7]

Thus, an increasing attention is paid for a sensitive biochemical marker which can detect myocardial ischemia early even in absence of myocardial necrosis and may be helpful in categorizing patients as low risk group (risk stratification) and thus reducing the cost of unnecessary admissions.

Ischemia modified albumin (IMA) is a type of biological marker in early diagnosis of presence of ACS in patients presented to ED with a cardiac type of chest pain.IMA, a type of human serum albumin is modified at its N-terminal region constituting amino acid sequence N-asp-ala-his-lys, by myocardial ischemic attack. [1-8]

Albumin cobalt binding assay (ACB) is a quantifiable test for biochemical diagnostic evaluation of human serum albumin to detect presence of IMA in patient's plasma by measuring albumin binding ability to bind transitional metal ions especially cobalt. The test was first developed by Bar-Or D et al,and is based on observation that the affinity of the N terminus of albumin for cobalt ion is reduced in patients with myocardial ischemia.[6]

A large number of studies have demonstrated the usefulness of IMA testing in diagnosis of ACS as an early marker before the rise of conventional markers such as CK-MB and troponins.[1,3,4,8]However, a study of large cohort of patients with ACS demonstrated a poor sensitivity and negative predictive value for diagnosing non ST elevation ACS.[9] Moreover, false positive results may occur due to infections, end stage renal diseases, liver cirrhosis, active cancer, increased serum fatty acid (FA) level etc., which also binds to cobalt binding site resulting in high IMA in patients without myocardial ischemia.[10,11]

A recent meta-analysis also reported a poor specificity and insufficiently high sensitivity of serum IMA, limiting its use for the diagnosis of ACS.[12] Inspite of this limitation, IMA levels may be used as a rule out test,[11] especially in rural population where the afford ability for an array of diagnostic test is not feasible.

Hence the present study is undertaken to measure IMA in patients admitted to ED with chest pain in a rural teaching hospital where the affordability of patients to undergo an array of test for diagnosis of ACS may not be economical.

Material and Methods

Study Design

A prospective cross-sectional study was done.

Setting

The study was conducted at rural tertiary care teaching hospital

Ethical clearance

Ethical clearance was obtained from institutional ethical committee.

Study Population and Sample size

Patients above 18 years of age presenting with acute chest pain or manifestations suspicious of ACS in ED and admitted to intensive cardiac care unit (ICCU) were enrolled for the study. Of these 30 cases who were clinically diagnosed as suffering from ACS were considered for the study.

30 age and sex matched healthy persons were taken as controls. Patients suffering renal diseases, liver cirrhosis, stroke, skeletal muscle injury, malignancy, trauma, patients with non-ischemic chest pain and patients' serum albumin less than 2 gm/dl were excluded from the study.

Demographic data of patients, ECG findings, echocardiography findings and clinical diagnosis of these patients were obtained from patient's records.

After obtaining informed consent, 5ml of blood sample was drawn under aseptic precautions from the patients and collected in two test tubes The serum from first test tube was tested for routine blood investigations, serum CK-MB and Cardiac troponin I (cTn-I). CK-MB was analyzed by immune-inhibition method where CK-MB activity is measured in the presence of antibody to CK-M monomer. The test was carried using standard kits from Erba diagnostics on Erba chem 5 plus semi auto analyzer. cTn-I was qualitatively analyzed using a rapid chromatographic immunoassay.

The serum from second test tube was separated & aliquoted and stored at – 20^0C until measurement for IMA. At the time of analysis frozen samples were thawed and gently vortexed.

Ischemia Modified Albumin

Ischemia modified albumin was measured by albumin cobalt binding (ACB) assay, a colorimetric method described by Bar-Or D et al. [6] This assay is based on the observation that, myocardial ischemia causes changes in the serum albumin that is demonstrated by

reduced exogenous cobalt ions binding at its N-terminal end.

The concentration of IMA is determined by addition of known amount of cobalt to serum specimen and measurement of unbound cobalt which binds with dithiothreitol forming a dark brown colour. An inverse relationship exists between the level of albumin bound cobalt and the intensity of colour formation, measured at 470nm.To 200 µl of patient serum, 50 µl $CoCl_3$was added followed by vigorous mixing and incubation for 10 minutes at room temperature.

Then 50 µl of DTT was added, mixed and kept for 2 minutes incubation. Finally, 1 ml of normal saline was added to stop the reaction. The absorbance of assay mixture was read at 470 nm using Spectrophotometer (Shimadzu UV visible Spectrophotometer 1601). The blank was similarly prepared with the exclusion of DTT. The result was expressed as Absorbance units (ABSU)

The results were presented as mean ±standard deviation for continuous variables. Statistical analysis was done using student's' test for continuous variables and chi square test was done for categorical variable.

A p value <0.05 was considered as statistically significant. Receiver Operating Curve (ROC) was prepared to determine the diagnostic value of IMA levels using GraphPad Prism 7.03 and sensitivity, specificity, positive predictive value and negative predictive value for ACS was calculated.

Results

A total 60 of subjects, 30 as cases of ACS and 30 age and sex matched healthy subjects were enrolled and analyzed for the study parameters. Table 1 shows the demographic details and biochemical data of the study population. The ACS patients had statistically significant higher blood glucose values.

Table 1: Demographic and biochemical data of the study population

	Control	**Acute Coronary Syndrome Patients**	P value
Age	54.97±15	58.63±11.51	0.293
Male	18 (60%)	20 (66.66%)	0.592
Female	12 (40%)	10(33.33%)	
Glucose	107.8±40.25	167.8±104.43	0.004*
Urea	22.60±6.61	25.14±9.65	0.233
Creatinine	0.93±0.23	1.01±0.2	0.156

*- P<0.05, statistically significant

Among the ACS patients 53.33% were known diabetic and 56.66% of them were known hypertensive as shown in Table 2. The mean CK-MB values in ACS patients were 42.86±29.31 and 16 ACS patients had troponin positive test (Table 2).

Table 2: Clinical and Cardiac Profile characteristics in Acute Coronary Syndrome patients

Characteristics	Frequency (%)
Diabetes Mellitus	16 (53.33)
Hypertension	17 (56.66)
Troponin (Number of positivecases)	16 (53.33)
	Mean ± SD
CK-MB (U/L)	42.86±29.31

SD – Standard Deviation

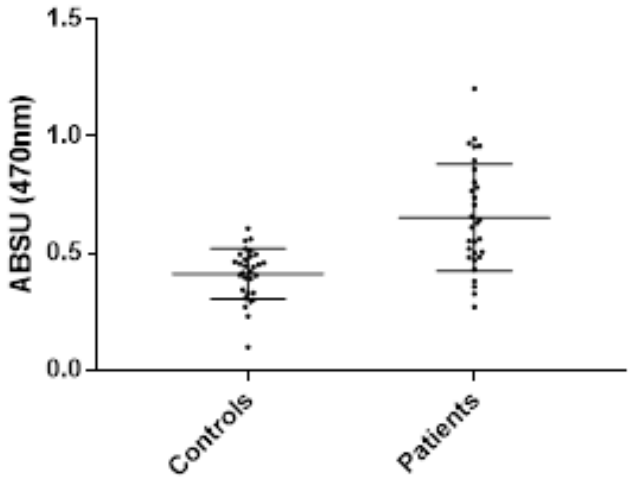
Table 3 compares the IMA values between the cases and controls which is significantly higher in ACS cases with P value of <0.0001.

Table 3: Ischemia Modified Albumin in cases and controls

	Controls	Acute Coronary Syndrome Patients
Mean IMA (ABSU)	0.41	0.65
SD	0.11	0.23
P value	<0.0001	

IMA- Ischemia Modified Albumin, ABSU- Absorbance units, SD – Standard Deviation

Figure 1: Distribution of Albumin Cobalt binding test results for controls and ACS patients

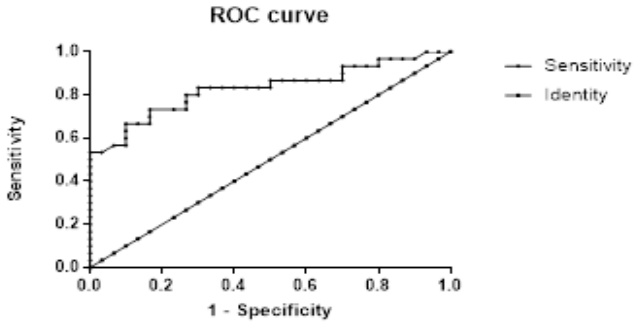


ABSU- Absorbance units

Figure 1 shows a scatter plot of distribution of ACB test results in both controls and ACS patients. Based on ABSU data,ROC curve was prepared to determine performance characteristics and optimal cut off of IMA assay. The area under curve (AUC) was found to be 0.8289 (95% CI, 0.7215 to 0.9363) ($p<0.0001$) (figure 2).

Based on the ROC curve analysis, the cut of point of IMA was 0.4775 to diagnose ACS which is close to 0.5 ABSU reported earlier.[2] Based on this cutoff, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of IMA in diagnosis the of ACS is 80%, 76.67%, 77.42% and 79.31% as shown in table 4.

Figure 2: Receiver Operative Curve for ACS patients in IMA values



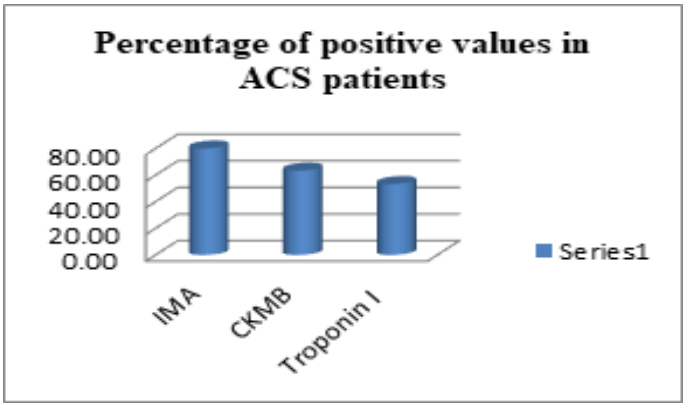
ROC: Receiver Operating Curve

Table 4: Diagnostic efficiency of IMA in diagnosis of ACS (cut of value- 0.4775)

Parameter	Value (%)	95% Confidence Interval
Sensitivity	80	61.43% - 92.29%
Specificity	76.67	57.72 – 90.07%
Positive Predictive Value	77.42	63.63 - 87.05%
Negative Predictive Value	79.31	64.60 - 88.96%

Twenty-four (80%) of ACS patients had IMA value of ≥ 0.4775 Absorbance units (ABSU) in comparison to nineteen patients (63.33%) having CKMB > 25U/L and sixteen patients (53.33%) having positive troponin test (Figure 3)

Figure 3: Bar diagram showing Percentage of positive cardiac markers in ACS patients



IMA: Ischemia Modified Albumin, CK-MB: Creatine kinase MB

Discussion

The present study was undertaken to estimate the serum IMA and evaluate its diagnostic performance in ACS patients. In the present study, the mean IMA ABSU was statistically significantly higher in ACS patients compared to healthy controls($p<0.0001$).

In a similar study by Chawla R et al, IMA levels in ACS cases compared to healthy controls showed significantly higher values.[5] Similarly many studies have reported elevated IMA levels in ACS patients compared to either healthy controls or patients with non-cardiac chest pain. [1,4,8,13]

A study by Ertekin B et al compared the IMA levels between normal healthy controls and ischemic patients comprising of ACS and acute ischemic stroke (AIS) and reported elevated levels in ischemic patients but no significant difference was found in patients between ACS and AIS cases. They also reported high sensitivity, specificity, PPV, NPV and concluded that IMA could be a useful diagnostic marker in ACS and AIS patients.[14]

Bhagvan N V et al reported high ABSU units in patients with myocardial ischemia compared to non-myocardial ischemia patients with high sensitivity, specificity and concluded that ACB test may serve as a useful diagnostic tool in ED for the assessment of myocar dial ischemia but is a poor discriminator between ischemic individual with and without MI. [2]

IMA levels are increased in all patients of myocardial ischemia whether it is reversible ischemia or irreversible necrosis. It does not differentiate ACS patients with ST segment elevation from patients with NSTEMI and UA. [1,15] But a study from Chennai reported a significant difference in IMA levels between controls, non-cardiacchest pain patients, UA, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI)patients. The authors also reported assessment of IMA to be superior to cTnI and CK-MB in early diagnosis of ACS.[8] In the present study 80% of patient had IMA levels greater than the cut off value compared to 63.33% and 53.33% of patients having elevated levels of CK-MB and cTnI levels.

In the present study the sensitivity, specificity, PPV and NPV was 80%, 76.67%, 77.42% and 79.31% respectively. This is similar to the diagnostic efficiency reported by Chawla R et al who found a lower diagnostic efficacy of CK-MB compared to IMA. The authors concluded that IMA can serve to be better detector of myocardial ischemia than CK-MB.[5] Other studies have demonstrated higher sensitivity and specificity of IMA,[2]and especiallywhencompared to sensitivity and specificity of cTnI in diagnosing ACS patients.[4]

Another study with large sample size showed a high NPV and sensitivity which will help the clinician to more safely and cost effectively identify low risk patients.[16] A study by MK Sinha et al, showed the sensitivity to diagnose acute ischemic chest pain especially unstable chest pain was highest with IMA with greater PPV compared to ECG and cTnI even though the specificity was lower compared to these two markers.[3]

However, some studies have reported no advantage of IMA in evaluation of ACS patients. Charpentier S etal, studied clinical utility of IMA and heart fatty acid binding protein (h-FABP) in a large cohort of patients with non-ST elevation MI, and reported IMA as a poor predictor of ACS.[9] But the patients in this study were enrolled upto12 hours of last episode of chest pain and probably the levels of IMA has decreased by the time patients are admitted.

Many other studies have also questioned the diagnostic accuracy of IMA in patients with chest pain. ACB assay has also been found to be increased in patients exposed to trauma and the probable cause for this is hypoalbuminemia, which lowers cobalt uptake by albumin.[17]A multicentric study by Keating L et al reported a low specificity of IMA with a large number of false positives and concluded that it is ineffective tool in risk stratification of patients with chest pain, but the study could not rule out the possibility of reversible cardiac ischemia in which IMA may be raised compared to reference standard cTnI.[18]In contrast, another study by Shu-Ming Pan et al showed a high specificity for prediction of discharge diagnosis of ACS, but in this study the IMA was measured with a modified test with ultra-filtration technique to remove the interference from proteins.[19]

The advantage of this test is, it is elevated very early before necrosis sets in. It has a synergistic role in early diagnosis of ACS in combination with other markers as shown in many studies. [3,4,19,20] Nevertheless IMA may be a poor discriminator of reversible myocardial ischemia from irreversible myocardial necrosis as in MI patients.[2] IMA alone may not fulfill the criteria of ideal diagnostic marker but when used in conjunction with other biomarkers, may reduce inappropriate hospital admission or mistakenly discharged patient with MI.

The limitations of present study is low sample size, we have not analyzed the IMA levels in different categories of ACS (because of lower sample size and majority of ACS patients being diagnosed as STEMI), and there is no serial testing of these biomarkers.

Conclusion

Based on the present study demonstrating IMA test having high sensitivity, specificity, PPV and NPV and greater number of ACS patients showing elevated IMA levels compared to CKMB and troponin I, it can be concluded the IMA can be a useful biomarker for early diagnosis of ACS.

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