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ISCHEMIA MODIFIED ALBUMIN AN EARLY SERUM BIOMARKER IN DIAGNOSING ACUTE CORONARY SYNDROME

Cardiology

M. Ashok Assistant Professor, Department Of Cardiology, K.A.P. Viswanatham Government Medical College, Tiruchirapalli

R. Freethi* Assistant Professor, Department Of Biochemistry, Government Medical College, Pudukottai *Corresponding Author

K. Vanitha Assistant Professor, Department Of Biochemistry, K.A.P. Viswanatham Government Medical College, Tiruchirapalli

S. Syed ali fatima Assistant Professor, Department Of Biochemistry, K.A.P. Viswanatham Government Medical College, Tiruchirapalli

ABSTRACT

BACKGROUND: Acute coronary syndrome comprises of about 20-23% of patients presenting at emergency department accounts for increasing mortality and morbidity world wide . Along with ECG and other clinical parameters, cardiac biomarkers do have an important role in the early diagnosis and management of patient with ACS. Ischemia modified albumin is one of the recently identified ischemic biomarker approved by U.S food and drug administration .

AIM AND OBJECTIVE To measure IMA and CKMB levels in the patient with ACS.The role of IMA as an early marker in diagnosis of ACS when compare with CKMB.

MATERIALS AND METHODS: Study group includes 50 patients with ACS and 50 age and sex matched healthy controls. Serum IMA levels measured by cobalt binding assay method measured colorimetrically.serum albumin and creatinine kinase (CK-MB) measured by bromocresol green , immune inhibition method respectively.

RESULTS: Serum IMA levels increased in early hours of ACS (mean =115.05±17.55) when compared to healthy controls.

CONCLUSION: Increased serum IMA levels in early hours of ACS can be used in the diagnosis of ACS along with ECG and other biomarker CKMB.

KEYWORDS

Acute coronary syndrome, Ischemia modified albumin,creatinine kinase -MB

INTRODUCTION

Ischemic heart disease is the greatest single cause of mortality and loss of disability-adjusted life years worldwide(Murray & Lopez, 1997) . Acute Coronary Syndrome comprises of about 20-23% of patients presenting at emergency department accounts for increasing mortality and morbidity worldwide(Braunwald et al., 2000). The traditional clinical approaches such as detailed history, careful physical examination and ECG findings are helpful in stratifying the patients but it seems to be inadequate in early definitive diagnosis in many of ACS cases. Along with ECG and other clinical parameters, cardiac biomarkers do have an important role in the early diagnosis and management of patient with ACS(Dekker, Mosterd, van't Hof, & Hoes, 2010). Although currently available biomarkers such as CK-MB, CK-MB mass trop-I , etc are useful in the diagnosis of ACS, they don't seem to increase before necrosis of myocytes and are time dependent. Moreover these markers to increase in the serum require cell death and leakage of proteins out of the myocytes which takes longer time for about 4 -6 hours. Ischemia Modified Albumin is one of the recently idendified ischemic biomarker approved by U.S Food and Drug Admnistration. N-terminus part of albumin which is either damaged or replaced by copper ion is termed as ischemia modified albumin (IMA)(Sinha, Roy, Gaze, Collinson, & Kaski, 2004) . The N terminus of albumin is damaged when exposed to ischemic conditions, making it unable to bind metals thus enabling it to be measured using albumin cobalt binding test.The levels of IMA increase within minutes of onset of ischemia- implicating it in the early detection of acute ischemia before the onset of necrosis. Conditions necessary for altering the metal binding site of Human Serum Albumin are known to occur in vivo and probably occur within minutes after the onset of myocardial ischemia. As a result of hypoxia, acidosis, free-radical injury and energy- dependent membrane disruption which occurs during ischemia, the N-terminus of albumin is transformed reducing its binding capacity for metals(Bar-Or et al., 2001). The metal binding property of HSA has been vastly researched on. It has been found that metallic ions bind to different sites on HSA. Extensive studies of HSA have revealed multiple metal binding properties and the metal ions bind to a extensive range of sites. The binding comprising of the amino acid sequence N-Asp-Ala-His-Lys is very typical(Plantier, Duretz, Devos, Urbain, & Jorieux, 2016). First three residues have been shown to be necessary for metal ion binding whereas the fourth residue (lysine) not. These sites have high affinity particularly for copper and nickel. The α-amino group, the δ-imidazole nitrogen from His3, the two intervening peptide nitrogen atoms, and the side-chain carboxyl group of Asp1 are specifically involved in this binding property. N terminal- binds metal ions like cobalt, nickel, copper. Although, few studies have been done on IMA as a biomarker in ACS patients, this study focus on the role of IMA as an early diagnosis of ACS and to compare with CKMB.

MATERIALS AND METHODS

This cross sectional study was conducted in KAPV government Medical College Hospital Trichy .The study was approved by the ethical committe and also written informed consent from the participants was obtained. 50 patients of aged 30 to 65 years with symptoms of acute coronary syndrome presented within 6 hours of onset of pain in the causality with ECG findings correlated were taken as subjects. 50 age and sex matched healthy individuals were taken as control group .The exclusion criteria considered in the study population includes Presence of renal diseases. Cirrhosis ,Presence of stroke, skeletal muscle injury, malignancy, trauma, Critically ill patients and Any infectious diseases. patients having Serum albumin < 2 gms/dl and Serum creatinine > 3 mgs/dl were also excluded.

5ml of Venous blood from the control and patients were collected by vene puncture under strict aseptic precaution. It was done as soon as the subjects got admitted as per the inclusion criteria. All the blood samples were centrifuged at 3000 rpm and serum separated. One part of serum sample was taken for analysis of serum CK-MB and serum Albumin. serum CK-MB measurement was done by kinetic immune inhibition (Modified IFCC) method and serum albumin was measured by bromo cresol green method in erba 360 fully automated analyser . Remaining part of the sample was kept at -20°C for measurement of Ischemia Modified Albumin.

Estimation of ischemia modified albumin- The tests were performed by chemical method using Cobalt chloride (hexa hydrate form) Dithiothreitol and Sodium chloride.

Principle - Free Cobalt that does not bind to the Ischemia modified albumin in serum gives a brown coloured complex with Chromogen dithiothreitol which is measured spectrophotometrically at 470 nm .Intensity of the colour is directly proportional to Ischemia modified

albumin in serum. Add 50µl of cobalt chloride to the serum sample, mix vigorously and after ten minutes of incubation add 50 µl of Dithiothreitol. Wait for 2 minutes and then add 1ml of 0.9 % sodium chloride. Read the absorbance at 470 nm after 1 minute. The reference units for IMA is 6-80U/ml

STATISTICALANALYSIS

Students t –test was employed for the statistical analysis of data.the data were expressed in the terms of mean and standard deviation.p<0.05 was taken as significant.mann whitnney U score was applied for the comparison of Ischemia modified albumin ,CKMB between the study and control group using SPSS software.

RESULTS

A total of 100 participants were included in the study. Patients with ACS n=5 , healthy individuals n=50 as control group. Both in study and control group males n=37 and females n=13 were included. The serum levels of albumin, ischemia modified albumin and CK-MB were measured both in the patients and in the controls. In table 1 clinical and labarotary characteristics of blood pressure,Body mass index,serum albumin, Ischemia modified albumin ,CKMB are shown with the mean and standard deviation for study and control group.

TABLE -1 clinical and labarotary characteristic of study and control group

VARIABLES	MEAN	STD. DEVIATION
Weight		
study n=50	73.78	11.07
Control n=50	70.46	9.01
Height		
study n=50	1.62	.08
Control n=50	1.61	.08
BMI		
study n=50	28.25	5.38
Control n=50	27.24	4.02
SBP		
study n=50	148.28	14.26
Control n=50	126.92	8.19
DBP		
study n=50	94.28	8.21
Control n=50	79.76	4.17
IMA		
study n=50	115.07	17.55
Control n=50	37.60	14.74
S,Albumin		
study n=50	3.80	.27
Control n=50	3.79	.26
CKMB		
study n=50	67.87	31.85
Control n=50	12.40	2.79

The mean and standard deviation for ischemia modified albumin in the patients with ACS was 115.07 ± is more than 37.60±14.74 in the controls.

Table:2 Ischemia modified albumin in control and study group

IMA	Mean	SD	Mean rank	Sum of rank	Mann Whitney U score	*p* value
Control	37.61	14.74	25.5	1275	.000	.000
Study	115.07	17.55	75.5	3775		< 0.01 statistically significant

In table 2 the Mann whitnney U score for IMA clearly shows in the patients the sum of rank was 3775 > than 1275 in controls.Thus the score was .000<.01 which was significant.

Table:3 CK-MB in control and study group

CKMB	Mean	SD	Mean rank	Sum of rank	Mann Whitney U score	*p* value
Control	12.40	2.79	25.56	1278.00	3.000	.000
Study	67.87	31.85	75.44	3772.00		

Frequency table for duration after onset of ACS and serum levels of IMA and CK-MB shows in the early hours that is between 2-4hrs more number of patients had elevated serum levels of IMA compared to CK-MB

frequency table for duration after onset of ACS and serum levels of IMA and CK-MB

		Hrs				Total	
		2 to 4 hours		2 to 4 hours			
		count	Col %	count	Col %	count	Col %
IMA (U/L)	Below 85	2	6.4	1	5.2	3	6
	Above 85	29	93.6	18	94.8	48	94
CK-MB(U/L)	Below 24	12	38.7	1	5.2	13	26
	Above 24	19	62.8	18	94.8	37	74

DISCUSSION

Many studies have proposed that combined use of more than one cardiac biomarkers along with clinical findings and ECG can be applied in the diagnosis of ACS(MEMBERS et al., 2007).IMA is an early marker of myocardial ischemia related to vascular disorder(Quiles et al., 2003). Elevated serum levels of IMA in ACS occurs due to the following proposed mechanism. Ischemia induces Hypoxia acidosis increases free radical damage membrane dependent sodium and calcium pump discharge free iron and copper ion exposure all of which involves damage of amino terminal of human serum albumin In patients presenting to emergency department with chest pain(Bar–Or, Lau, & Winkler, 2000). IMA has been shown to have negative predictive value for excluding the diagnosis of ACS.IMA levels in serum become positive within minutes of ischemia and remains elevated up to several hours favours the early detection before the development of necrosis. bar-or 2001 reported high IMA levels during transient ischemia that returned to baseline value by 6 hrs after percutaneous transluminal angioplasty. In accordance with the above studies, the present study demonstrate Ischemia Modified Albumin was increased earlier than CK-MB. The mean CK-MB level in the study group was (75.44±31.85) which is significantly higher than in the control group (25.56 ± 2.79) and found to be increased only after 4 hours of onset of chest pain. The results of our study clearly demonstrate the high level of serum IMA in early hours of ACS. The mean and standard deviation for ischemia modified albumin in the patients with ACS was 115.07 ± is more than 37.60±14.74 in the controls.The strength of this study includes the homogenecity of the study group with respect to exclusion of possible confounding clinical conditions and proper timing of blood sampling.

CONCLUSION

Increased serum IMA levels in early hours of ACS can be used in the diagnosis of ACS along with ECG and other biomarker CK-MB.

Limitations of the study

The data provided here is the only one time measurement for each patient, in the small-sized study population.

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