Prognostic significance of Ischemia Modified Albumin and role of high sensitive C-reactive protein levels in acute ischemic stroke patients

Arun Kumar[1,*], Vishal Kalasker[2], K. Pratibha[3], K. Srinivas Rao[4], Harish Bhat[5]

[1,5]Assistant Professor, [2]Professor, [4]Associate Professor, Navodaya Medical College Raichur, [3]Professor & Head ESIC MC & PGIMSR Rajajinagara, Bangalore.

***Corresponding Author:**
Email: arunmd26@gmail.com

Abstract

Introduction: Acute ischemic stroke (AIS) is one of the leading cause of death worldwide and the main causes of long-term disability. Brain CT shows no abnormality in the early event of AIS and the infarct may not be seen reliably for 24-48 hours. Oxidative stress is proposed as a fundamental mechanism of brain damage in ischemic stroke. Earlier it was reported that free radicals alters the N-terminus of the albumin which decreases its binding capacity for metals and is termed as Ischemia Modified Albumin (IMA). Recently it was found that IMA is increased in cerebrovascular diseases and may serve as biomarker for early identification of acute stroke. There is little information regarding the use of IMA for the prognosis of AIS. There is growing evidence of the importance of high sensitive C-reactive protein (hs-CRP) in Acute Ischemic Stroke. Therefore, the current study aims to determine the prognostic evaluation of time course of serum level of IMA and hs-CRP in Acute ischemic Stroke patients.

Material and Method: 56 AIS patients diagnosed (clinically/ radiologically) of either sex and >18 years of age were taken as cases. 56 age and sex matched healthy subjects were taken as controls. Serum IMA levels were estimated by spectrophotometric method and hs-CRP levels were estimated by Auto-analyzer.

Results: There was a significant increase in IMA levels in AIS patients at the time of admission (488.82±24.84) and on 3rd day (397.17±32.44) when compared to control (324.27±36.45) group. It was found to be statistically significant ($P < 0.001$). There was a significant increase in Hs-CRP levels in AIS patients at the time of admission (9.55±1.63) than in control (0.95±0.40) group. It was found to be statistically significant ($P < 0.001$).

Conclusion: Estimation of serum IMA in AIS patients has both diagnostic and prognostic application. Routine hs-CRP measurement will be a useful tool for identifying AIS patients, in order to plan aggressive diagnostic protocols and prevention therapies. Diagnosis of AIS can be made very early then the available routine investigation & the cost of the test is less, can be used in Primary health care & remote places where CT & MRI are far from their reach.

Keywords: Ischemia Modified Albumin(IMA), High Sensitive C Reactive Protein (hs-CRP), Acute ischemic stroke (AIS), Albumin Cobalt Binding test

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Introduction

Stroke is defined by W.H.O. (World Health Organization) as clinical syndrome consisting of "Rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin". A Transient Ischemic Attack (TIA) is defined as stroke symptoms that resolve within 24 hours. A non-disabling stroke is defined as a stroke with symptoms that lasts for more than 24 hours but later resolve, leaving no permanent disability.

Acute Ischemic Stroke (AIS) is one of the leading cause of death worldwide and one of the main causes of long-term disability [1,2]. Brain CT scans obtained in the first several hours after an Infarction generally show no abnormality, and the infarct may not be seen reliably for 24–48 hours. MRI is less sensitive for acute blood products than CT and is more expensive and time consuming and less readily available. Claustrophobia also limits its application[3].

Biomarkers which help in outcome prediction and therapeutic decision makings are very important in the management of AIS patients and reducing mortality rates[4]. Oxidative stress is proposed as a fundamental mechanism of brain damage in ischemic stroke. Earlier it was reported that free radicals alters the N-terminus of the albumin which decreases its binding capacity for metals and is termed as Ischemia Modified Albumin (IMA)[5]. IMA was reported to be a sensitive marker of ischemic events[6]. Recently it was found that IMA is increased in cerebrovascular diseases and may serve as biomarker for early identification of acute ischemic stroke. Despite all the available information, there is little information regarding the use of IMA for the prognosis of AIS.

There is growing evidence of the importance of high sensitive C-reactive protein (hs-CRP) in Acute Ischemic Stroke[7]. Also the independent value of hs-CRP in acute ischemic stroke has not been established.Therefore the

current study aims to determine evaluation of serum level of hs-CRP in Acute ischemic Stroke patients.

Objective of this study was to estimate IMA and hs-CRP levels in acute ischemic stroke patients and controls andto determine the prognostic significance of IMA and the role of hs-CRP in patients with acute ischemic stroke.

Materials and Methods

The study entitled "Prognostic significance of Ischemia Modified Albumin and High sensitive C-Reactive Protein in patients with Acute Ischemic Stroke" was conducted during the period from November 2011 to April 2013 at ESIC –Medical College and Post Graduate Institute of Medical Science and Research, Bangalore. The subjects were selected based on the following inclusion and exclusion criteria. All the patients of age group >18 years of either sex who are attending casualty/ICU Department of Neurology clinic of ESICMH, Rajajinagar, Bangalore with clinical and radiological evidence of acute ischemic stroke were included in the study. Patients with the evidence of ongoing cardiac ischemia, acute coronary syndrome, with known peripheral vascular disease, Severe hypoalbuminemia, anemia, chronic renal disease, liver disease, bleeding disorders, cerebral haemorrhage of any etiology, autoimmune disorders, CNS problems like hemiplegic migraine, subdural hematoma, abscess, intracranial tumours were excluded from the study.

Subjects

Selection of subjects for the study was done as follows:

Study group: The blood samples of 56 cases (46 males and 10 females) diagnosed (clinically/radiologically) Acute Ischemic Stroke patients attending ESIC-Medical College & Post Graduate Institute of Medical Science and Research, Rajajinagar, Bangalore were the source of data for the study.

Control group: The blood samples of 56 (46 males and 10 females) age and sex matched healthy subjects > 18 years from the blood bank donors & healthy volunteers were the control group.

Sampling: Under strict aseptic precautions, 5 ml of venous blood was collected into plain vacutainer tubes and were centrifuged at 1000G speed for 3 min and samples were analyzed in clinical Biochemistry for hs-CRP by turbidimetric method with COBAS integra 400 plus and Ischemia modified albumin was estimated manually by albumin cobalt binding test in Post graduate Research Lab.

Methods

Ischemia Modified Albumin estimation: Ischemia modified albumin is measured by albumin cobalt binding test according to colorimetric method described by Bar Or-et al[6]. The assay is based on the premise that cerebral ischemia causes changes in human serum albumin (HSA) that are determined by reduced exogenous cobalt(II) binding. The concentration of ischemia modified serum albumin can be determined by addition of a known amount of cobalt(II) to a serum specimen and the measurement of the unbound cobalt (II) by colorimetric assay using dithiothreitol. An inverse relation thus exists between the level of albumin bound cobalt and the intensity of the colour formation[6].

Serum High sensitive C – Reactive Protein estimation: hs-CRP estimation was carried out in an autoanalyzer ROCHE-COBAS INTEGRA 400® clinical chemistry which employs the particle enhanced turbidimetric assay. Human CRP agglutinates the latex particles coated with monoclonal antibodies. This method is accordance with the recommendation Price CP et al for autoanalyzer. Particle enhanced turbidimetric assay Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimetrically at 552 nm. **Normal range: ≤ 5 mg/l for adults.**

Table 1: Showing the mean values of ischemia modified albumin in cases and controls

	Cases at admission	Cases on 3rd day	Controls
IMA (ABSU) Mean ±SD	488.82 ±24.84	397.17±32.44	324.27±36.45

Table 2: Showing Mean, Standard deviation, minimum & maximum values of IMA in cases at admission, on 3rd day and in controls

	IMA in ABSU at admission	IMA in ABSU on 3rd day after the onset of stroke	IMA in ABSU in control group
Mean	488.82	397.17	324.27
Std. Deviation	24.84	32.44	36.45
Minimum	398	336	236
Maximum	544	498	406

Table 3: Showing the mean value of hs-CRP levels mg/L in cases and controls

hs-CRP (mg/L) Mean±SD	Case	Control
	9.54±1.63	0.95±0.40

Table 4: Comparison of hs-CRP values among cases and control

Parameters	Cases n=56 Mean ±SD	Controls n=56 Mean ±SD	Comparison P value
hs-CRP (mg/L)	9.55±1.63	0.95±0.40	< 0.001

Table 5: Paired t test between IMA levels in AIS patients at admission and on 3rd day

	Mean	N	Std. Deviation	*P* value
IMA at admission in ABSU	488.82	56	24.844	<0.001
IMA on 3rd day in ABSU	397.17	56	32.44	

After applying Paired t test between IMA levels in patients at admission and on 3rd day it was found to be statistically significant ($p < 0.001$).

Table 6: Independent sample t test for IMA in ABSU among cases and controls

	Groups	N	Mean	Std. Deviation	P value
IMA in ABSU	Case	56	488.82	24.844	<0.001
	Control	56	324.27	36.454	

After applying independent sample t test for IMA levels between cases and control it was found to be statistically significant (P <0.001)

Table 7: Independent sample t test for hs-CRP in mg/L among cases and controls

	Groups	N	Mean	Std. Deviation	t	df	P value
hs CRP in mg/litre	Case	56	9.548	1.6362	38.133	110	<0.001
	Control	56	.954	.4094			

After applying independent sample t test for hs-CRP levels between cases and control it was found to be statistically significant (P <0.001).

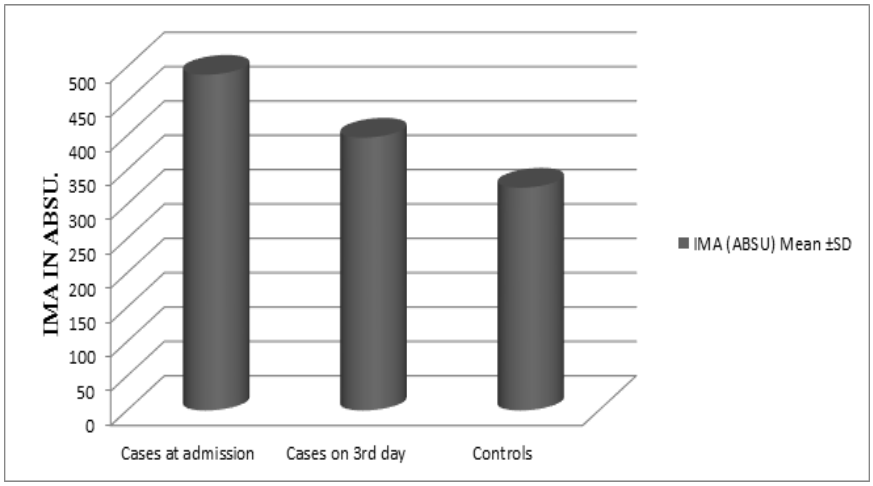

Fig. 1: Bar diagram showing the mean value of ischemia modified albumin in cases at admission, on 3rd day and control

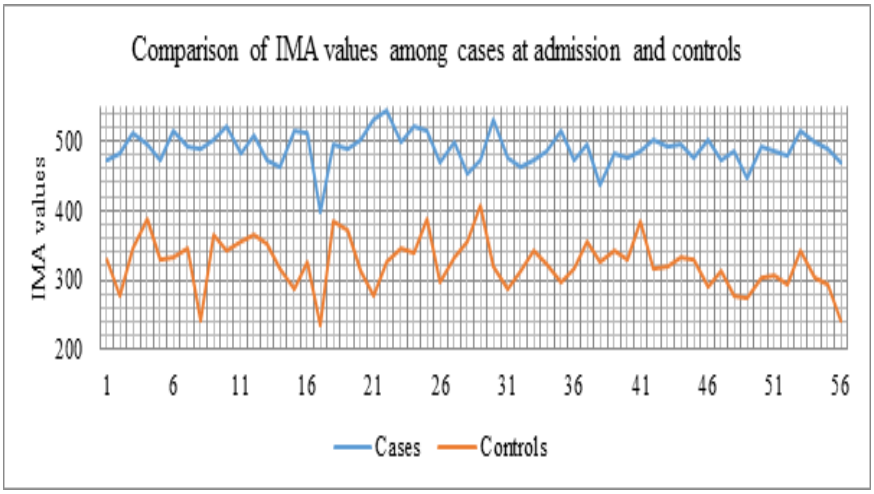

Fig. 2: Line graph showing the comparison of IMA in cases and controls

[Above graph explains there was a significant increase in the IMA levels in cases as compared to the values of the control group and was found to be statistically significant (p<0.001)].

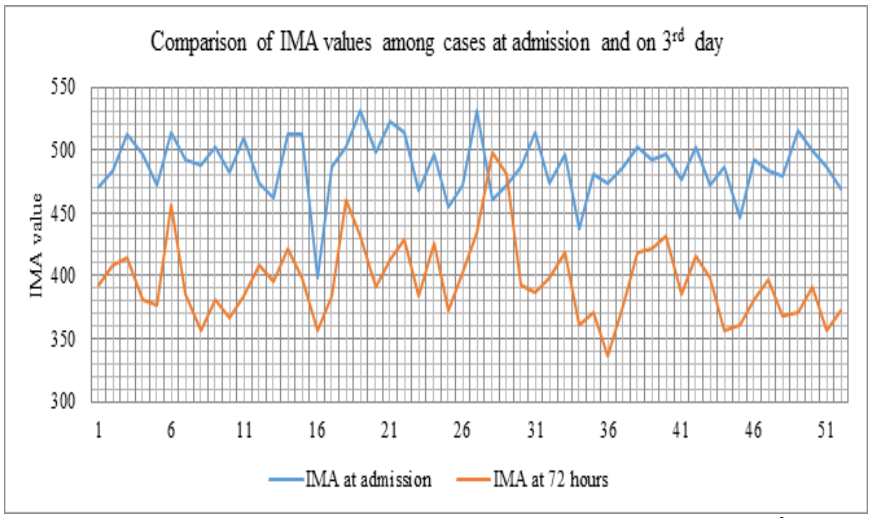

Fig. 3: Line graph showing the comparison of IMA in cases at admission and on 3rd day after the onset of stroke

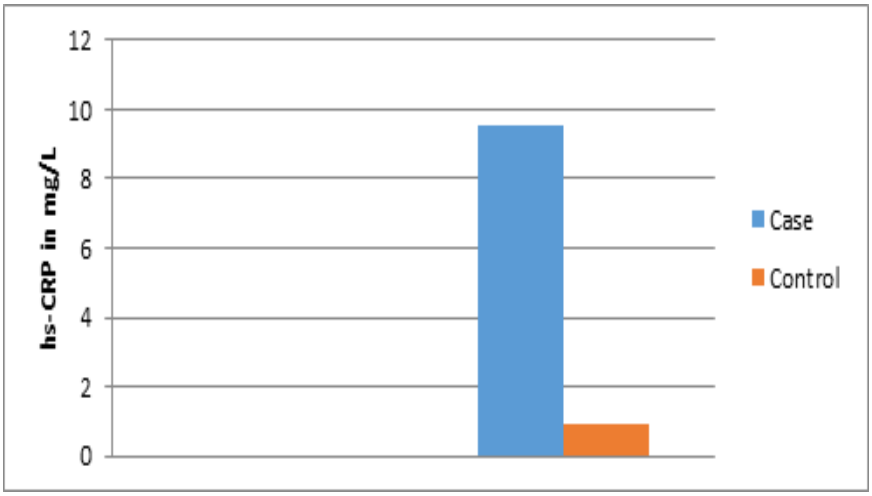

Fig. 4: Bar Diagram showing the mean value of hs-CRP in cases and control

Discussion

In the current study we have evaluated the time course of serum level of IMA in AIS Patients. We found that serum IMA level increased in AIS patients as compared to controls. Significant increases in IMA level were observed at the time of admission mean (488.82±24.84) and on 3rd day (397.17±32.44) when compared with control (324.27±36.45). Our results are in agreement with the earlier studies that IMA level increases in stroke patients[8].

Albumin is a hemodiluting agent and is found to increase cerebral blood flow both in normal and ischemic brain[9]. It may be possible that protective function of albumin is associated with the N-terminal of the albumin which gets modified by reactive oxygen species generated in response to ischemic event that leads to a loss in its protective ability and thereby an increase in an increase in the IMA in AIS patients.

It is reported that IMA levels may be reversible and return to normal level within a few hours (12 to 24 hours) with the removal of free radicals[10].We have also observed that the IMA levels decreases in the follow-up AIS patients sample on 3rd day as compared to the admission value. The treatment regimens given to the AIS patients like antiplatelet and anti-edema agents also act as antioxidant[11]. However, we observe further increase in IMA level in few cases that suggest further deterioration in the clinical status of AIS patients after initial improvement. Our study shows that follow-up estimation of IMA in AIS may help in the prediction of clinical status and outcome in AIS patients.

There is growing evidence of the importance of high sensitive C-reactive protein (hs-CRP) in Acute Ischemic Stroke In the current study we have evaluated the hs-CRP levels is AIS patients. We found that serum hs-CRP level increased in AIS patients as compared to controls. Significant increases in hs-CRP level were observed in AIS patients mean (9.55±1.63) when compared with control hs-CRP mean (0.95±0.40). Our results are in agreement with the earlier studies that hs-CRP level increases in AIS patients[12]. Routine hs-CRP measurement might be a useful tool for identifying AIS patients in order to plan aggressive diagnostic protocols and prevention therapies.

Conclusion

On the basis of present study, we conclude that estimation of serum IMA in AIS patients has both diagnostic and prognostic application. Routine hs-CRP measurement might be a useful tool for identifying AIS patients, in order to plan aggressive diagnostic protocols and prevention therapies. Diagnosis of AIS can be made very early than the available routine investigations& the cost of the test is less, can be used in Primary health care &remote places where CT & MRI are far from their reach.

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