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A Study of Diagnostic Utility of Ischemia Modified Albumin in Cerebrovascular Accidents

KEYWORDS: Ischemia Modified Albumin, Cerebro-vascular accident

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ABSTRACT *Background: The absence of a widely available and sensitive diagnostic test, acute cerebral ischemia remains a significant limitation in the diagnosis and management of stroke. Computed Tomography (CT) scanning and MRI are may be normal in early phase or not feasible every time in developing country like India. Ischemia Modified Albumin (IMA) is a marker for ischemia. Pathophysiology of stroke also involved ischemia. Hence objective of this study is to evaluate diagnostic utility of IMA in cerebro-vascular stroke.*

Method: This cross sectional type of study consists of 100 subjects, 35 ischemic stroke, 15 hemorrhagic stroke (definitive diagnosis based on radiological images) and 50 as control. Blood samples obtained within 6 hours of presentation were analysed for IMA by albumin cobalt binding assay.

Result: IMA concentrations were 0.410 ± 0.0478 absorbance unit (ABSU) in ischemic stroke, 0.319 ± 0.0632 ABSU in hemorrhagic stroke and 0.240 ± 0.0363 ABSU in control group. IMA concentrations were statistically higher ($p < 0.0001$) among stroke group as compare to control and there was also statistical difference ($p < 0.001$) of IMA concentrations between ischemic stroke and hemorrhagic stroke. At cut off value of 0.297 ABSU (by ROC curve), IMA have diagnostic sensitivity of 94% and specificity of 90%.

Conclusion: It is found that IMA has potential role in diagnosis of acute ischemia in cerebrovascular accidents as well as it also differentiates types of stroke. So, Clinical diagnosis when supplemented by IMA estimation may be useful for confirmation of the diagnosis.

Introduction:
Stroke is one of the leading causes of death and disability in the world. According to WHO, stroke is second leading cause of death after Ischemic heart disease in high and middle income countries while sixth leading cause of death in low income countries [1]. About 85% of all stroke deaths are registered in low and middle income countries, which also account for 87% of total losses due to stroke in terms of disability adjusted life year (DALY), calculated 72 million per year [2]. Direct as well as indirect cost for stroke is also high. So, stroke has high economical burden on society [3].

The absence of a widely available and sensitive diagnostic test for acute cerebral ischemia remains a significant limitation in the diagnosis and management of stroke. In the absence of such test the diagnosis is mainly based on history and clinical examination and radiological images. Unfortunately, radiological imaging are often not useful during early stage of acute stroke, as well as such facilities are not available widely, time consuming, and very costly. Another approach for diagnosis of acute stroke would be use of biochemical markers. A candidate marker for the detection of ischemia is ischemia modified albumin (IMA). Human serum albumin is modified by ischemia at N-terminal which is a binding site for transitional metal such as cobalt, copper and nickel [4]. Because of this modification N-terminal undergoes a decrease in binding capacity in the presence of ischemia. This can be measured from patient serum by albumin cobalt binding test [5]. IMA has a short half-life returning to normal in 6–12 hours, as shown in patients undergoing elective per-cutaneous coronary intervention [6]. U.S. food and drug administration approved IMA as candidate marker for myocardial ischemia. After this, utility of IMA in various diseases has been studied. As pathophysiology of stroke also involve ischemic cascade, IMA level may be increase in such condition. This study is undertaken to evaluate a utility of IMA level for diagnosis of stroke.

Material and Methodology:
The study was carried out by biochemistry department at Shree Krishna Hospital and H M Patel Centre for Medical Care and Education, 550 bedded rural based tertiary care hospital. A study protocol was set before undertaking this study and it was approved by institutional Human Research Ethical Committee. This study includes 100 subjects with 50 cases and 50 controls, informed and written consent had been taken from each subject.

Study group: 50 patients of age >18 years (36 male and 14 female) admitted in medical / surgical ICU within 6 hours of clinical and/or radiological evidence of Cerebrovascular accident, were recruited in the study. Definitive diagnosis of stroke and its classification is based on radiological study (CT scan or MRI) and 15 hemorrhagic strokes and 35 ischemic strokes were confirmed.

Control group: 50 age and sex matched normal individuals, who don't have any evidence of ischemic disease per se clinical examination, come to the hospital for routine whole body health check-up were included in control group.

Exclusion criteria: Any patient with history suggestive of other ischemic diseases like acute coronary syndrome, acute myocardial infraction, pulmonary embolism or peripheral vascular diseases was excluded from this study. Patient with liver diseases (serum albumin level <3.5 or >5.5gm/dl) and/or renal failure (serum creatinine level > 1.7mg/dl) was also excluded.

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Sample collection: Samples were collected in plain vacutainer and centrifuged within 30 minutes of collection for 10 minutes at 1000g. After centrifugation serum was separated and used for estimation of serum Creatinine, Albumin, Total Protein. Remaining serum was stored at -20°C for estimation of IMA later on.

Procedure: Frozen samples were thaw and mixed thoroughly before analysis only once. And ischemia modified albumin was measured by albumin cobalt binding test as described by Bar Or at al. All reactions were carried out in 1.5-mL Eppendorf tubes at standard room temperature and in duplicate. Preparations for the Co^{+2}–albumin binding protocol involved the addition of 200 µL of patient serum to 50 µL of a solution of 1 g/L cobalt chloride, followed by vigorous mixing, and a 10 min incubation. 50 µL Diathiotreitol (of a 1.5 g/L solution) was then added and mixed. After two min incubation, 1.0 mL of phenobarbitone buffer (pH-8.6) was added. The absorbance of assay mixtures was read at 500 nm on UV Spectrophotometer. The blank was prepared similarly with the exclusion of Diathiotreitol and absorbance was read at 500 nm on the spectrophotometer. Results are reported as absorbance unit. Within run CV% was 5.04% and between day CV % was 7.88%.

Results: 100 subjects were enrolled in the study according to inclusion and exclusion criteria. Demographic data of all subjects were:

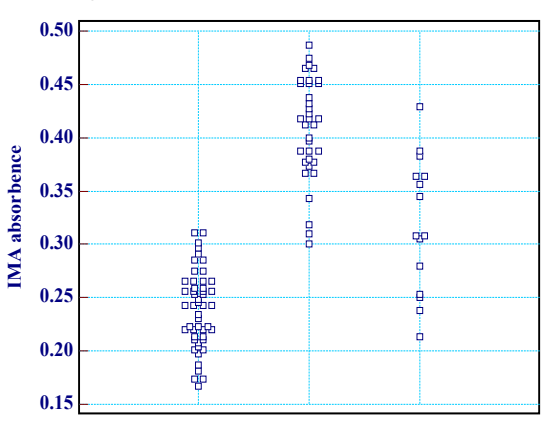
Table No.1 Demographic data and Basic test results

	Hemorrhagic stroke (n=15)	Ischemic stroke (n=35)	Control (n=50)
Age (Mean ± SD)	62.6 ± 12.8	62.5 ± 14.6	51.8 ± 11.1
Gender (M/F)	10/5	26/9	27/23
Albumin(gm/dL)	4.05 ± 0.54	3.97 ± 0.62	4.06 ± 0.55
S.Creatinine (mg/dL)	0.866 ± 0.22	1.08 ± 0.55	1.01 ± 0.44
S. Total Protein (gm/dL)	6.42 ± 0.49	6.37 ± 0.71	6.63 ± 0.69

IMA value (mean ± SD) were 0.410 ± 0.0478 absorbance unit (ABSU) in ischemic stroke, 0.319 ± 0.0632 ABSU in hemorrhagic stroke and 0.240 ± 0.0363 ABSU in control group. When these groups were compared by student t-test, there was statistically significant difference of IMA value between control group and stroke group (p value <0.0001). There was also statistical difference of IMA value between ischemic stroke and hemorrhagic stroke group (p value =0.0001).

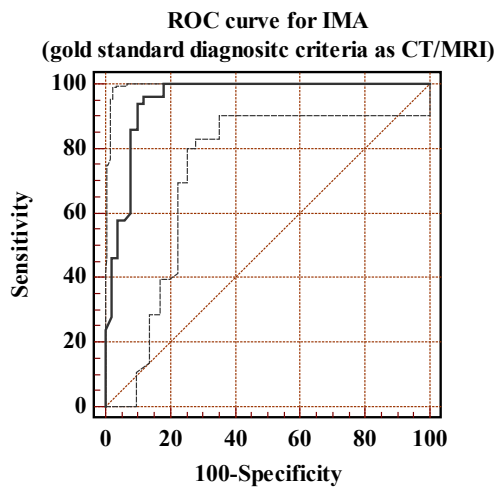
Distributions of IMA value among different groups were shown in figure 1.

Figure 1 Dot chart shows distribution of IMA value among different groups



ROC curve (figure 2) evaluating the value of IMA with respect to CT/MRI scan report. With cut off value of 0.297 absorbance unit, derived from ROC curve with area under curve is 0.951 (95% CI 0.889-0.984) has 94% sensitivity (95% CI83.4 - 98.7), 90% specificity (95% CI78.2 - 96.6), 90.38% Positive predictive value and 93.75% Negative predictive value.

Figure 2: ROC curve for all patients.



Discussion:

One of the markers for ischemia is Ischemia Modified Albumin. Human serum albumin is modified by ischemia at N-terminal which is a binding site for transitional metal such as a cobalt, copper and nickel [4].[4] Mechanism of Ischemia induced changes to albumin possibly as a result of hypoxia, acidosis, free-radical injury, membrane energy dependent sodium and calcium pump disruption, and free iron and copper ion exposure [7,8,9].

IMA is approximately 1% to 2% of the total albumin concentration and increases to 6% to 8% in patients experiencing ischemia. IMA rises within six to ten minutes, seems to be produced continually during the acute phase of vascular injury and remains elevated during an ischemic event. IMA has a short half-life returning to normal in 6–12 hours, as shown in patients undergoing elective percutaneous coronary intervention [6].

IMA have been increases in various diseases like myocardial ischemia, percutaneous coronary intervention, skeletal muscles ischemia, mesenteric ischemia, pulmonary embolism, aortic dissection, acute phase reaction and stroke. IMA level in stroke were studied by two group, Abboud H et al [10] and Abdulkadir Gunduz et al study [6]. Abdulkadir Gunduz et al study, IMA level was 0.280 ± 0.045 ABSU for ischemic stroke patients, 0.259 ± 0.053 for ICH patients and 0.243 ± 0.061 for SAH patients. The mean serum IMA level for the control patients was 0.172 ± 0.045. The mean serum IMA level for the control patients was 0.172 ± 0.045. There was a statistically significant difference between the mean BI, ICH, and SAH patient group and mean control patient IMA levels (P <0.0001).

Abboud H et al.[10] study, median IMA level (bootstrap 95% confidence interval, CI) was 83 U/ml (79-86) and 86 U/ml (75-90) in patients with BI and ICH, respectively (p = 0.76), and was 73 U/ml (58-79) in others (p = 0.003 compared with BI, and p = 0.017 with ICH). Result of this study is comparable to above studies.

For effective management in emergency department, NPV is most essential. Negative IMA value helps to rule out ischemia.

Conclusion:

It is found that IMA has potential role in diagnosis of acute

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ischemia in cerebro-vascular accidents as well as it also differentiates types of strokes. So, Clinical diagnosis when supplemented by IMA estimation may be useful for confirmation of the diagnosis.

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