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Pattern of change of serum uric acid level during acute ischemic stroke and their prognostic significance

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Abstract
In Acute ischemic stroke (AIS) there is cascade of inflammatory reaction, and uric acid exert beneficial role in AIS due to its strong antioxidant property.
Aim: *Aim was to study the pattern of change in serum uric acid (SUA) level and the association between SUA level at presentation and the clinical outcome in AIS patient.*
Methodology: *Single centre prospective cross sectional analytical hospital based time bound study. 100 consecutive patients admitted with AIS in medicine emergency were enrolled for study after considering the inclusion and exclusion criteria. Prognostic significance of SUA were analysed in term of NIHSS (national institute of health stroke scale) score (at admission, discharge, 90 days), hospital stay, and survival (at 90 days). Student t test and χ^2 test was used to compare continuous and categorical variables respectively. Kaplain Meier survival plot was used for survival analysis.*
Results: *Mean SUA was (6.23mg/dl, SD±1.2) at admission, (5.64mg/dl, SD±0.98) discharge, (5.28mg/dl, SD±0.82) 90 days. Mean SUA shows significant inverse correlation with NIHSS score (p <0.0001, 0.001, 0.004 with r = -0.382,-0.403,-0.357) at admission, discharge and 90 days respectively. SUA shows significant negative correlation with hospital stay (p= 0.004, r= -0.342). The odds ratio of SUA at admission (cut off < 5.5 mg/dL) was 5.962 (2.08-17.09; CI 95%) showing more survival for SUA at admission > 5.5 mg/dL. The mortality rate, hospital stay, NIHSS score was found to be more in patient having diabetes or metabolic syndrome.*
Conclusions: *SUA is consumed during AIS. Higher SUA level is associated with low NIHSS score, reduced hospital stay, more survival and may act as good prognostic marker.*
Keyword: *AIS (acute ischemic stroke); SUA (serum uric acid); NIHSS (national institute of health stroke scale).*

Introduction

Among the neurological diseases of adult life, cerebrovascular accident ones clearly rank the first in frequency and importance. At least 50% of the neurological disorders in a general hospital are of this type. Stroke, after heart disease and cancer is one of the most common causes of death. Many epidemiological studies identified high SUA level as an important risk marker for stroke. Furthermore, raised SUA concentrations are associated with increased risk of stroke in high risk groups, like patient with hypertension or type

2 diabetes mellitus[1]. However, these relationships remains subject to considerable debate. Both in vitro and in vivo studies have shown that SUA act as powerful free radical scavenger in human paradoxically, this antioxidant properties offer a number of benefits in AIS[2]. Emerging evidence suggests that UA plays beneficial role in AIS, because of its antioxidant properties. Therefore this study was conducted to evaluate the role of SUA in AIS. Reference range: Men: 2.5-8 mg/dL; Women: 1.9–7.5 mg/dL

Materials and Methods

Study design and population selection

A single centre, cross sectional, prospective, analytical, hospital based, time bound study was conducted from 1 December 2012 to 30 October 2013 in department of medicine GMC Bhopal, India. The study was approved by institute Ethical Committee for human research. A total of 134 patients with acute ischemic stroke presenting to medicine emergency meeting the inclusion and exclusion criteria were enrolled. Of these, 119 patients gave informed consent to participate in the study, 100 patients could complete study protocol and their clinical data were analyzed.

All patients with first episode of ischemic stroke as evident on either CT or MRI brain were screened for recruitment in the study. Patients with evidence of intracranial haemorrhage, onset of symptoms >48 hours, previous history or Transient ischemic stroke (TIA) or vascular disease (stroke, myocardial infarction, revascularizations, peripheral artery disease), past history of gout, excessive alcohol consumption and taking drugs known to affect SUA levels (diuretics, losartan, allopurinol, probenecid, atorvastatin, fenofibrate) were excluded. The primary objective was to study the association between Serum uric acid at presentation and clinical outcome among acute ischemic stroke patients

Demographic, clinical, biochemical was collected at enrolment, discharge and at end of the study. The study duration was for 90 days. Detailed history was obtained at enrollment, clinical examination and battery of investigations were done on admission, discharge and at completion of study. Blood was drawn after 8 hour of overnight fasting to measure serum parameters such as albumin, creatinine, hemoglobin, C-reactive protein (CRP), total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride. Serum uric acid was measured using Uricase method. Blood pressure was recorded with standard mercury sphygmomanometer with cuff adapted to arm circumference after the subject had rested in the supine position for 15 minutes. NIHSS scoring system was used objectively quantify the impairment caused by stroke. All 11 parameters were individually scored and were summed to calculate total NIHSS score [3,4].

Statistical Analysis:

Statistical analysis was performed with the help of SPSS 16.0 software. It included the usual descriptive and univariate analysis. Student t test was used to compare continuous variables and χ^2 test used to compare categorical variable.Unadjusted odds ratio with 95% confidence interval and P value was calculated. P value less than 0.05 was taken as significant. Kaplain meier survival plot was used for survival analysis with serum uric acid.

Results

Table 1 lists baseline characteristics of all 100 acute ischemic stroke patients at enrolment. The mean age was 57.12 yrs, systolic blood pressure was 158 mmHg, Serum uric acid level at the time of admission, at discharge and at 90 days were 6.23 mg/dL, 5.64 mg/dL and 5.28 mg/dL respectively.

Table no: 1. Demographic and clinical characteristics of patients

Baseline characteristics	Mean ± Std. Deviation
Age (yr)	57.12 ± 14.81
SBP (mmHg)	158.04 ± 25.52
DBP (mmHg)	96.8 ± 15.00
NIHSS admission score	15.66 ± 10.69
NIHSS discharge score	11.29 ± 6.46
NIHSS day 90 score	10.13 ± 5.27
SUA admission (mg/dL)	6.23 ± 1.20
SUA discharge (mg/dL)	5.64 ± 0.98
SUA day 90 (mg/dL)	5.28 ± 0.82
Hospital stay (days)	6.78 ± 2.55
Total Cholesterol (mg/dL)	180.49 ± 18.52
LDL (mg/dL)	108.09 ± 19.43
S. Creatinine (mg/dL)	1.04 ± 0.82
Sex (M/F)	53 / 47
Diabetes (Y/N)	35 /65
Metabolic syndrome (Y/N)	42/58
Tobacco use (Y/N)	40 / 60

57% were male. Metabolic syndrome was identified in 42% of the participants. There was more non-diabetic and non-tobacco user in our present study. The average hospital stay was 6.78 days. In our study, out of 100 patients, 11 patients died before discharge and 79 patients could complete 90 day follow up. The mean SUA level was significantly higher in the patients who were alive at discharge as compared to those who died (6.3± 0.96 vs 5.61 ± 1.24 mg/dl). In our study around 48.1% patients had <5 days of hospital stay and their mean uric acid level was 6.59mg/dl (maximum uric acid level in any class) showing significant weak negative correlation with hospital stay (p= 0.004, r= -0.342) as shown in table 2.

Table 2: Co-relation between serum uric acid level and hospital Stay

Hospital stay (Days)	SUA admission (mg/dL)		P	R
	N	Mean ± SD		
1—5	44	6.59 ± 1.2	0.004	-0.342
5—9	38	6.05 ± 1.19		
≥10	18	5.72 ± 1.21		
Total	100	6.23 ± 1.2		

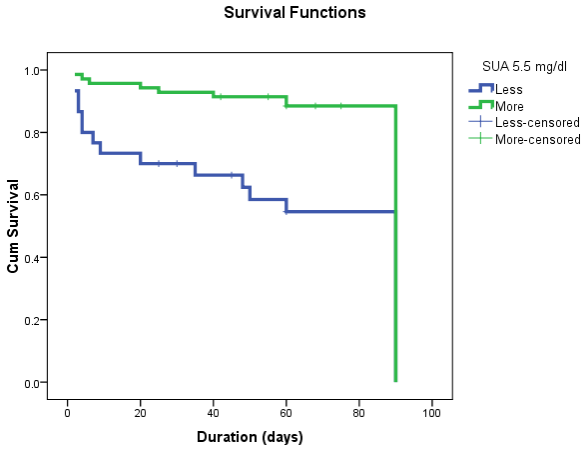
52%, 58.4%, 59.4% patients were having NIHSS score between 5-15 at the time of admission, discharge and 90 days respectively. Mean serum uric acid level shows significant weak negative correlation with NIHSS score with p value <0.0001, 0.001, 0.004 with r = -0.382,-0.403,-0.357 at the time of admission, discharge and 90 days respectively as depicted in table 3.

Table 3: Distribution of serum uric acid in different NIHSS class

NIHSS SCORE	SUA admission (mg/dL)		SUA discharge (mg/dL)		SUA day 90 (mg/dL)	
	N	Mean±SD	N	Mean±SD	N	Mean±SD
1—4	16	7.3±1.16	16	6.44±0.98	15	5.91±0.79
5—15	52	6.18±0.95	52	5.60±0.83	47	5.21±0.69
16—20	16	5.96±1.14	16	5.21±0.81	13	4.90±0.71
21—42	16	5.56±1.44	5	4.96±1.60	4	4.92±1.57
Total	100	6.23±1.20	89	5.64±0.98	79	5.28±0.82
P	<.0001		.001		0.004	
R	-0.382		-0.403		-0.357	

The kaplain meier survival graph with serum uric acid at admission as baseline parameter clearly shows that values >5.5mg/dL at admission is associated with cumulative improved patient survival at discharge and at 90 days. (Figure 1)

Figure: 1 Kaplain Meier survival graph of serum uric acid at admission



This study calculates the odds ratio in terms of binary survival outcome in reference with SUA at admission (cut off value < 5.5 mg/dL), odds ratio of 5.962 (2.08-17.09; CI 95%) showing more survival for SUA at admission > 5.5 mg/dL syndrome than patients without diabetes or metabolic syndrome despite of higher serum uric acid level in them, but this finding is insignificant (p<0.05).

Discussion

Our current study was a cross sectional prospective analytical hospital based study conducted with 100 acute ischemic stroke patients to know the prognostic significance of serum uric acid, and their prognosis is assessed in term of survival, days of hospital stay and NIHSS score.

Uric acid may act as an important prognostic marker in acute ischemic stroke patients. Higher serum uric acid (>5.5 mg/dL) level at admission were associated with good 90 day outcome in term of survival, reduced hospital stay and decreased NIHSS score.

Uric acid has proven antioxidant property and it has protective role in many neurological illnesses like multiple sclerosis, acute ischemic stroke. Cerebral infarction initiates a complex cascade of metabolic events in the surrounding tissue, and free-radical-mediated oxidative damage[5]. Free radicals are liberated from a variety of sources, including inflammatory cells, dysfunctional mitochondria and excitotoxic mechanisms stimulated by increased glutamate and aspartate concentrations[6]. Hydroxyl radicals peroxynitrite and superoxide are powerful radicals that can cause lipid peroxidation, a self-propagating chain reaction, that irreversibly damages plasma and mitochondrial membranes[7]. Plasma concentrations of cholesterol ester hydro peroxides (CEOOH) are sensitive and specific markers of lipid peroxidation, and correlate positively with infarct volume calculated by CT, and clinical severity, determined by the National Institute of Health Stroke Scale. These observations have stimulated interest in the possibility that antioxidant treatments could offer benefits in acute ischaemic stroke, through their ability to defend against excess free radical activity. Chamorro A et al[1] found that neurological impairment on admission (p=0.001) and infarction size on CT (P=0.001) were inversely associated with uric acid and concluded that 12% increase in odds of good clinical outcome for each mg/dL increase of serum uric acid. Our study concluded that NIHSS score at admission shows significant inverse correlation with serum uric (p <.0001; r = -0.382). Antonio Cherubini et al[2] studied that mean antioxidant levels and activities in patients on admission were lower than those of controls and showed a gradual increase over time and concluded that the majority of antioxidants are reduced immediately after an acute ischemic stroke. Current study shows that persistent decrease in serum uric acid level from the time of admission to discharge (p=.004). This was also associated with decrease in NIHSS score with time and correlated with better survival at 90 days. This finding suggesting that uric acid may utilized during the process of stroke.

Janne S. Leinonen et al[4] et al studied antioxidant activity of blood plasma and cerebrospinal fluid in patients with cerebral hemisphere infarction that was verified and quantified by MRI, shows that patient with higher antioxidant level having decrease infarct size, reduced neurological impairment. Our study, concluded that patient with higher serum uric acid at admission have good survival, low NIHSS score and reduced hospital stay. Emilio Tayag et al[8] found that following traumatic brain injury, cortical uric acid was elevated by ten-fold at 24 and 48 h, but not at 1 h post-TBI. In our study Serum uric acid level was measured at admission, discharge and at day 90 and found that uric acid level decreased as compared to time of admission implying utilization of serum uric acid in oxidative stress of acute ischemia.

However, some studies reported that the decreases in serum UA during the first week after onset of stroke correlates with more severe stroke, unfavourable stroke evolution, and poor long-term stroke outcome[9,10]. The findings of Premier study also suggests that a low SUA concentration is modestly associated with a very good short-term outcome and is more a marker of magnitude of cerebral infarction[11]. Serum uric acid is one of the major aqueous antioxidant in human beings. It is therefore prudent to expect that serum uric acid should have a protective role in stroke but review of literature suggests otherwise. Wang et al have also concluded that a higher levels of serum uric acid is neuro-protective in stroke patients[12]. An explanation to this comes from the study which concluded that serum uric acid can work as pro-oxidant under certain circumstances, particularly if the levels of other antioxidants like ascorbic acid are low[13].

Our present study has some advantage as the timing of estimation of serum uric acid is known to affect the results so patient presenting >48 hrs after the onset of symptoms were excluded from the study. A detailed history of drugs taken by the patient was made in order to exclude those were taking medicines known to affect serum uric acid levels. There were some limitations in our study. Our study was a single centre study with small sample size. Sizable participants were diabetes which is known to interfere with serum uric acid estimation. There is lack of data on exercise pre- and post- stroke of the patient.

Conclusion

Higher Serum uric acid level was associated with low NIHSS score (direct marker of stroke severity) and reduced hospital stay (indirect marker of stroke severity) with good outcome at the end of the study of 90 days and showing that it may act as an anti-oxidant in patients with acute ischemic stroke but similar finding was not obtained from group of patients having diabetes and metabolic syndrome suggesting that suppression of antioxidant property in presence of co morbid condition like diabetes and metabolic syndrome.

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