Original Article

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Effect of Serum Uric Acid Level on Acute Ischaemic Stroke Patients in South Indian Population: A Prospective Cohort Study

Internal Medicine Section

KARRI VIJAYA PHANI VARDHAN REDDY[1], SUBRAMANIAM MURUGESAN[2], THANGAVELU ARUN PRAKASH[3], BALASUBRAMANI SOORYA NARAYANAN[4]

ABSTRACT

Introduction: Stroke is one of the most common causes of morbidity and mortality in the world. Various studies have shown the correlation between the uric acid levels and acute ischaemic stroke. There are several studies which project the cerebro-protective effect of uric acid in acute ischaemic stroke patients by its antioxidant effect. However, still it is a wide area of controversy.

Aim: To assess the short term (14 days) clinical outcomes in acute ischaemic stroke patients with reference to their serum uric acid levels on day of admission day.

Materials and Methods: This prospective cohort study, which included a total of 74 acute ischaemic stroke patients who presented to Emergency Department in a Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth University, Pondicherry (a tertiary care hospital in South India) within 48 hours from the month of April 2018 and June 2019. The severity of stroke was quantified in all patients using National Institute of Health Stroke Scale (NIHSS) during admission and serum uric acid levels and other routine investigations were measured in all cases. All patients were managed as per American Heart Association (AHA) guidelines and at the end of 14 days their outcome was reassessed by modified Rankin Scale (mRS). The correlation between severity of stroke and the clinical outcome on 14 days with reference to admission day serum uric acid was analysed.

Results: A total of 74 patients were analysed, 51 were male and 23 were females and mean serum uric acid was 6.07±0.78 (mg/dL), and mean NIHSS score at admission was 18.32±3.8. Severity assessment by NIHSS scoring system showed majority percentage of population in elevated serum uric acid group were in moderate and severe categories (73.7%, 62.9%, respectively) in adjunct with normal uric acid group. Outcome assessment by mRS showed major percentage population in elevated uric acid group with score 2,3 (score 2-89.3%, score 3-80%) in relation to normal uric acid group.

Conclusion: The present study supported the hypothesis that acute ischaemic stroke patients with elevated serum uric acid levels at the time of admission had reduced severity and favourable short term clinical outcome due to its neuroprotective effect secondary to antioxidant property.

Keywords: Antioxidant, Hyperuricaemia, Modified rankin scaling

INTRODUCTION

The cerebrovascular accident is one of the most common and leading causes of morbidity and mortality worldwide and it is only second to myocardial infarction accounting for up to 165,000 death per year in the United States [1]. The collective incidence of stroke ranges from 105 to 152/100,000 persons per year in India [2].

Uric acid proved to be a free radicle scavenger, which scavenges the hydroxyl radicle, Superoxide Dismutase (SOD) anion, hydrogen peroxide, and peroxyl nitrate groups [3]. Uric acid is one of the most potent antioxidants in the human body. Their levels rapidly decrease following acute ischaemic stroke and reduced uric acid levels further worsen the clinical outcomes.

There were a number of studies that highlight the safety and clinical efficacy of uric acid therapy in acute ischaemic stroke especially patients with hyperglycaemia, mechanical thrombectomy and thrombolysis [4-6]. Hence, there is a need to study the severity and clinical outcome of stroke patients with respect to their uric acid levels in the blood. Hence the present study has been undertaken to analyse the severity and clinical outcome of stroke patients with respect to their serum uric acid levels at the time of admission.

MATERIALS AND METHODS

This prospective cohort study was conducted in a Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth University, Pondicherry (a tertiary care hospital in South India). This study was conducted from the month of January 2018 to June 2019. A written and informed consent was obtained from all participants. The Institutional Medical Ethics Committee approval was obtained on 22-12-2017 (IHEC: PG DISSERTATION/12/2017/119).

Sample size calculation: The prevalence of ischaemic stroke was taken as 0.2 from review of literature [7] sample size is 74. Simple random sampling type was followed for selection of patient in the study.

Inclusion and Exclusion criteria: Patients who presented within 48 hours of onset of stroke (as per WHO definition [8]) and then who gave consent (74 patients) were included in the study as subjects. Patient with Gout, Tumourlysis Syndrome, Drugs (Diuretics, Salicylates, Pyrazinamide, Ethambutol, Levodopa) for more than two weeks duration, patients on chemotherapy, sepsis, malignancy, haemorrhagic stroke, space occupying lesion, previous history of cerebrovascular accident/transient ischaemic attack, cardio embolic stroke, seizure from onset of stroke to 14 days, known congenital anomalies in brain, chronic renal failure, any case requiring interventional/surgical procedure were excluded (20 patients) from the study.

Study Procedure

A total of 74 patients were included, detailed history and physical examination was done for all stroke cases and patients were assigned into two groups based on serum uric acid levels (normal serum uric acid group and elevated serum uric acid group). Serum

uric acid levels were measured using blood samples taken using a 2 mL of blood taken in EDTA tube, uric acid was analysed using an auto-analyser using urate oxidase reagent on a Dax analyser on the day of admission and based on the levels they were further divided broadly into following two groups:

1. Normal serum uric acid group (Males-upto 6.2 mg/dL, Females-upto 5.7 mg/dL).
2. Elevated serum uric acid group (Males- >6.2 mg/dL, Females->5.7 mg/dL).

The severity of stroke was assessed in all cases with National Institute of Health Stroke Scale (NIHSS) [9]. As per standard operating protocol all patients were subjected to all routine investigations and neuroimaging {Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) brain}. All the cases were managed conservatively according to standard Stroke guidelines [10]. Finally, by the end of 14 days once again severity of stroke was assessed using NIHSS and the clinical outcome was assessed using the mRS [11].

STATISTICAL ANALYSIS

All data was entered into a Data Collection Performa Sheet [Appendix-1] and were entered into Excel spread sheet sequentially (MS Excel 2011). Statistical analysis was carried out with Statistical Package for the Social Sciences (SPSS) version 19.0. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Chi-square/Fisher-Exact test/Independent t-test was used to find the significance of study parameters on categorical scale and continuous scale between two groups. The p-value <0.05 is suggestive of statistical significance.

RESULTS

In the present study total of 74 cases were included, majority of the population were male (68%) and 32% was female. The mean age group of the population in the present study was around 58 years.

[Table/Fig-1] shows basic demographic details and [Table/Fig-2] shows the distribution of the demographic and risk factors among the acute stroke patients with normal serum uric acid group and elevated serum uric acid group i.e., the percentage of population in both normal and elevated serum uric acid groups based on different variables like gender, diabetes, hypertension, smoking, dyslipidaemia were almost similar as there was no statistical difference between normal and elevated serum uric acid groups.

Variables	Total subjects n (%)
Gender	
Male	51 (69)
Female	23 (31)
Medical hisotry	
Diabetes	51 (69)
Hypertension	50 (68)
Smoking	33 (45)
Alcohol	32 (43)
Dyslipedemia	20 (27)

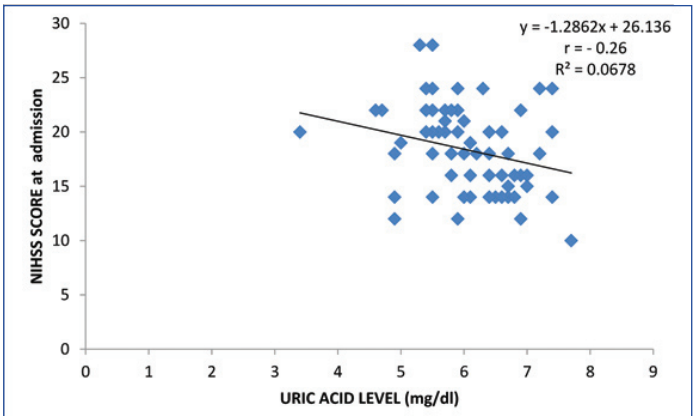
[Table/Fig-1]: Showing the baseline demographic data.

[Table/Fig-2] also depicts the mean values of continuous variables in both normal and elevated serum uric acid groups based on different variables like age, lipid profile, Glycated hemoglobin (HbA1c) and renal parameters were found to have only slight difference among them.

In the present study, the Spearman correlation between NIHSS score of the patients during admission and serum uric acid levels [Table/Fig-3] depicts a negative correlation with r value (r=-0.26) and significant R^2 (R^2=0.067).

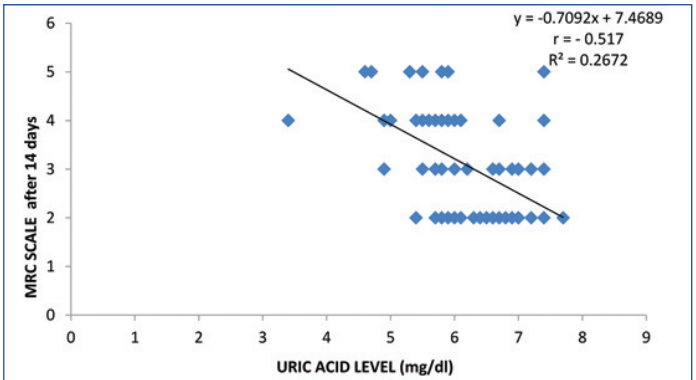
Variable (categorical)	Normal uric acid group n (%)	Elevated uric acid group n (%)	p-value (Chi-square test)
Female	11 (47.8)	12 (52.2)	0.70
Male	22 (43.1)	29 (56.9)	
Diabetes	23 (44.2)	29 (55.8)	0.92
Hypertension	22 (43.1)	29 (56.9)	0.71
Smoking	16 (47.1)	18 (52.9)	0.69
Alcohol	14 (42.4)	19 (57.6)	0.74
Dyslipedemia	12 (57.1)	9 (42.9)	0.17
Variables (continuous)	**Normal uric acid group (Mean±SD)**	**Elevated uric acid group (Mean±SD)**	**p-value (Independent T test)**
Age (years)	57.76 (13.24)	61.51(11.09)	0.19
Total cholesterol (mg/dL)	178.03 (40.72)	183.83(33.57)	0.50
TGL (mg/dL)	108.76 (59.31)	104.46 (42.30)	0.72
HDL (mg/dL)	43.94 (10.04)	47.63 (9.36)	0.11
LDL (mg/dL)	132.67 (46.4)	138.29 (57.07)	0.65
VLDL (mg/dL)	25.33 (13.31)	25.20 (9.73)	0.96
HBA1C (mg/dL)	7.8121(1.7)	7.51 (1.5)	0.44
Urea (mg/dL)	20.97 (5.99)	20.66 (6.4)	0.83
Serum creatinine (mg/dL)	1.16 (0.38)	1.08 (0.37)	0.34

[Table/Fig-2]: Distribution of the risk factors in the patients with normal serum uric acid group and patients with high serum uric acid group among acute stroke patients.
TGL: Triglyceride levels; HDL: High density lipoprotein; LDL: Low density lipoprotein; VDLD: Very low density lipoprotein; HbA1c: Glycated hemoglobin



[Table/Fig-3]: Correlation between NIHSS score at admission and uric acid level (Pearson coefficient).

[Table/Fig-4] shows the mRS of stroke at the end of 14 days in each group and its correlation with serum uric acid levels by Pearson correlation coefficient showed a negative correlation with r value (r=-0.517) and significant R^2 (R^2=0.267).



[Table/Fig-4]: Correlation between mRS scale after 14 days and uric acid level (Spearman coefficient).

[Table/Fig-5] shows the multilinear regression for NIHSS and mRS scoring and regression model was adjusted for uric acid, age and gender showed statistically significant values in NIHSS score and mRS scale (p-value=0.005 and 0.001, respectively).

Variables	β co-efficient	Confidence interval	Test value	p-value (Chi-square test)
Model 1 (NIHSS)				
Constant	31.48	21.44- 41.45	6.27	0.001*
Uric acid level	-1.81	-0.57- -3.04	-2.29	0.005*
Age	0.007	0.07- -0.065	0.19	0.84
Gender	-1.97	-0.10- -4.05	-1.8	0.06
Model 2 (mRS)				
Constant	9.24	6.8-11.63	7.71	0.001*
Uric acid level	-0.89	-0.6- -1.19	-6.06	0.001*
Age	0.004	0.02- -0.01	0.51	0.61
Gender	-0.69	-0.19- -1.18	-2.7	0.007*

[Table/Fig-5]: Multilinear regression for NIHSS score and mRS scale in study groups.
(*p-value <0.05 is statistically significant)

Comparison of both groups based on severity and outcome was done in [Table/Fig-6]. Severity assessment by NIHSS scoring system showed majority percentage of population in elevated serum uric acid group were in moderate and severe categories (73.7%, 62.9%, respectively) in adjunct with normal uric acid group. Likewise, outcome assessment by mRS scaling system showed major percentage population in elevated uric acid group with score 2,3 (score 2-89.3%, score 3-80%) in relation to normal uric acid group.

Variables	Elevated uric acid group n (%)	Normal uric acid group n (%)	Adjusted odds ratio (adjusted for age and gender)	p-value
NIHSS score				
Moderate	14 (73.7)	5 (26.3)	0.10 (0.02-0.44)	0.003
Severe	22 (62.9)	13 (37.1)	0.13 (0.03-0.51)	0.004
Very severe	5 (25)	15 (75.0)	Ref	
mRS score				
Score 2	25 (89.3)	3 (10.7)	0.009 (0.001-0.12)	0.001
Score 3	12 (80.0)	3 (20.0)	0.02 (0.001-0.26)	0.003
Score 4	3 (13.6)	19 (86.4)	0.56 (0.05-6.64)	0.64
Score 5	1 (11.1)	8 (88.9)	Ref	

[Table/Fig-6]: Comparision of both groups based on severity and outcome.
n=frequency; *p-value <0.05 is statistically significant

DISCUSSION

The incidence and the prevalence of the stroke are on the rise worldwide with maximum predominance in developing countries like India. The estimated incidence rate of stroke in India was 119-145/100,000 based on the recent population-based studies [12,13].

In the present study, the gender distribution [Table/Fig-1], 68% of the study population were males and 32% of them were female, a similar study done by Chiquete E et al., showed a gender distribution of 52% males and 48% females [14]. The present study had a male predominance, this can be attributed to the presence of additional risk factors for stroke like smoking, and alcohols {smokers- normal uric acid group: 16 (47.1%), elevated uric acid group: 18 (52.1%) and alcoholics- normal uric acid group: 14 (42.4%), elevated uric acid group: 19 (57.6%)}.

In the present study, the mean age included was 59.84±12.15 (years), a similar study done by Balaji B and Srinivas B the mean age of the study population was 60.58±13.27, respectively [15]. This increased incidence of stroke in elderly can be attributed to the fact that the age acts as an independent risk factor for ischaemic stroke.

In the present study the mean serum uric acid levels during admission was 6.07±0.78, in a similar study conducted by Mapoure YN et al., mean serum uric acid levels was 7.10±2.56 [16]. The mean serum uric acid levels were comparatively on the lower range when compared to other study, this lower range in the present study population can be attributed to the exclusion of most of the causes of hyperuricaemia in the study population. The mean uric acid levels were comparatively higher in males than females and this difference can be due to the effect of oestrogen in uric acid which is still to be proved by further studies.

In this study, the mean NIHSS score during admission was 18.32±3.8. In a similar study done by Mapoure YN et al., the mean NIHSS score at presentation among ischaemic stroke was 10.42±7.837 [16]. The present study had an increased severity of stroke when compared to other study. This increase in severity can be explained with the fact that the major risk factors like pre-existing diabetes, hypertension, and dyslipidaemia were not being controlled adequately because they are treated elsewhere or lost follow-up and most of the patients admitted with stroke were newly diagnosed hypertensive and diabetic.

[Table/Fig-5] also showed that patients with higher uric acid has a less severe stroke on admission and they also had less hospital admission days and faced less complications when compared to the patients with lower uric acid group, this was attributed to the anti-oxidant property of uric acid (uric acid itself is an anti-oxidant. No other anti-oxidant has been analysed in present study).

[Table/Fig-4] showed that in this study, there was a negative correlation between the serum uric acid levels and the mRD scale and most of the people with high uric acid had a score level between 1-3 and patients with low level uric acid had a score of 4-6 at the end of 14 days, there by proving that patients with high uric acid had a favourable clinical outcome when compared to the other group and this difference was also significant. This result can be hypothesised, that serum uric acid had a significant neuroprotective effect there by reducing the neuronal damage and promoting a better clinical outcome.

In the present study, there was a negative correlation between the admission day serum uric acid levels and clinical outcome by mRS, there by saying that increased serum uric acid was associated with a better clinical outcome by the end of 14 days. In addition to it, this study also showed increased serum uric acid levels were associated with a less severe stroke on the onset. Similar results were seen in a study conducted by Chamorro A et al., which concluded by saying that there was a 12% increase in the odds of good clinical outcome for every 1 mg/dL increase of serum uric acid levels [5]. In the above study, stepwise logistic regression was done to confirm the independent relationship between higher uric acid levels on admission and good outcome at hospital discharge. This was further supported by two southern Chinese clinical studies, both the study concluded that, increased serum uric acid levels were associated with good clinical outcome in younger adults and also younger adults with diabetes [17] this conclusion was attributed to the fact that uric acid reserve were more in the younger population than the older patients and hence the antioxidant effect was more pronounced.

A study conducted by Seet RCS et al., from Singapore which included both acute ischaemic stroke and transient ischaemic of total 881 patients found that serum uric acid levels of both the extremes that is elevated and low levels were associated with poor clinical outcome instead, uric acid level within the reference range was associated with a better clinical outcome [18]. The present study done showed contradictory finding i.e., elevated uric acid group had better clinical outcome compared to normal uric acid group.

There are some studies that showed an acute decline in the serum uric acid after the onset of stroke, this decline was mainly attributed to the utility of the uric acid as an antioxidant in acute stress state [19,20]. The series of changes in the serum uric acid in acute ischaemic stroke patients was mainly determined by the amount of oxidative stress and severity of stroke. Iranmanesh F et al., had found that reduction in the uric acid levels during the first week of the stroke was associated with a bad clinical outcome and a more severe stroke [21]. The present study also supportively showed similar finding of better outcome with elevated uric acid group. But, in future extensive studies are needed on the present topic to get a confirmatory evidence and correlation.

In the present study, [Table/Fig-3], there is a negative association (r=-0.26) between the NIHSS scale and serum uric acid and hence can hypothesise that uric acid was neuroprotective. But still, there are other factors that may influence the poor clinical outcome or better clinical outcome in study group, which needs further research. In recent days many research articles were published and supporting the data that administration of intravenous uric acid along with intravenous thrombolysis and mechanical thrombectomy to an acute stroke patient was associated with a statistically significant better clinical prognosis [3,5,6]. But in this study, none of the patients were treated with reperfusion strategies. Even in the present study, there was a better clinical outcome in patients with increased uric acid levels and also a less severe stroke during the onset.

Limitation(s)

The limitations of the study were, uric acid was measured only once, and hence the change in the trend of the uric acid and its effect in the stroke outcome were not being evaluated. Only ischaemic stroke was included, no case of Haemorrhagic stroke was included and hence the effect of uric acid in haemorrhagic stroke was also not evaluated. All the patients included in the study were managed conservatively and hence the effect of uric acid in thrombolysed patients and patients who underwent other interventional procedure were not known, this was mainly because of unavailability of resources in the hospital.

CONCLUSION(S)

The correlation of serum uric acid levels and regarding the significance in acute ischaemic stroke patients was a wide controversy. At this juncture, this study is in favour of the beneficial effect of serum uric acid both in severity and their recovery from the acute phase that is patients with high uric had a better clinical outcome and a less severe stroke during admission. Probably a multicentric study with sequential follow up of serum uric acid levels may throw more light in this research area. The present study can be concluded by stating that increased uric acid had a positive beneficial effect in ischaemic stroke that is by having a less severe stroke during onset and also a favourable clinical outcome at the end of 14 days.

Scope for further study: The correlation of serum uric acid levels regarding the prognostic significance in acute ischaemic stroke patients is a wide controversy. The group which favours the beneficial effect of uric acid by its neuroprotective effect as an antioxidant therapy argues serum uric acid can be used as a marker to access the severity of stroke at the time of onset and prognostic outcome of the patient in acute ischaemic stroke patients. This group also favours the the idea of giving uric acid to acute ischaemic stroke patients either along with thrombolysis and interventional procedure like thrombectomy or also as an individual drug for its neuroprotective effect.

But the other group which argues against the beneficial effect of uric acid doubt the above beneficial hypothesis and argues about the deleterious effect of uric acid in a stroke patient.

Serum Uric acid levels solely cannot be used as prognostic indicator for acute ischaemic stroke it also requires other supportive laboratory tests. More further studies including the measurement of Brain Natriuretic Peptide (BNP) etc., are required along with serum uric acid required in this context in future to get into exact conclusion of present topic.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of General Medicine, Mahatma Gandhi Medical College and Research Institute, Puducherry, India.
2. Associate Professor, Department of Neurology, Mahatma Gandhi Medical College and Research Institute, Puducherry, India.
3. Assistant Professor, Department of Neurology, Mahatma Gandhi Medical College and Research Institute, Puducherry, India.
4. Junior Resident, Department of Cardiology, Institute of Cardiology, Madras Medical College, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Thangavelu Arun Prakash,
No. 234, Anugraha Satellite Township, Cuddalore District,
Periyakattupalayam-605007, Tamil Nadu, India.
E-mail: drarunt@gmail.com

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