CORRELATION OF SERUM URIC ACID LEVELS WITH MODIFIED RANKIN SCORE IN PATIENTS WITH ACUTE ISCHEMIC STROKE

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ABSTRACT

Objective: To determine the correlation of mean serum levels of uric acid with mean modified Rankin score at 72 hours in patients with acute ischemic stroke.

Study Design: Correlational study.

Place and Duration of Study: Department of Medicine, Benazir Bhutto Hospital Rawalpindi, from Oct 2016 to Apr 2017.

Methodology: Total of 40 ischemic stroke patients, aged 15 to 85 years were selected after fulfilling the inclusion criteria. Serum uric acid levels were obtained within 24 hours of admission. Functional outcome was measured after 72 hours by modified Rankin Scale. The data was analyzed by SPSS version 23. Pearson correlation coefficient was calculated between mean SUA levels and mean MRS. *p*-value of ≤0.05 was considered significant.

Results: Mean age was 66.53 ± 12.20 years. 19 (47.5%) patients were males. The SUA was 4.78 ± 1.46 mg/dl while MRS was 3.15 ± 1.72. Poor outcome (MRS ≥3) was noted in 22 (55%) patients. Out of these, five patients (12.5%) died. The Pearson correlation between SUA and MRS was 0.511 (*p*=0.001). The correlation was statistically significant for all age and gender groups except female (r=0.363, *p*=0.106).

Conclusion: Our study results yielded that Serum Uric acid (SUA) levels are correlated with the severity of ischemic stroke.

Keywords: Ischemia, Prognosis, Stroke, Uric acid.

INTRODUCTION

Stroke ranks third commonest disease and a major source of disability all over the world. It has several risk factors e.g. Diabetes, hypertension, hyperlipidemia etc. The mortality of acute stroke ranges up to 20%[1]. Factors contributing to this early mortality may be non-modifiable, which may be responsible for about two-thirds of early deaths[2]. The main modifiable factors are increased intracranial pressure (ICP), pneumonia, or other early complications; treatment and prevention of these can improve the prognosis of acute stroke[3]. As such, the identification of prognostic factors may help to predict stroke outcomes and improve the prognosis by early intervention of these prognostic factors[3].

In stroke the oxidative stress caused by free radicals and cellular calcium overload are the major cause of neuronal injury and death, effect of which can be mitigated by anti-oxidants[4].

Uric acid (UA) is produced by the break-down of purine bases[5]. It is a neuroprotective anti oxidant[5] found mainly in plasma where its levels are 10 times higher than other anti-oxidants like vitamin C and E. Its plasma levels are determined by dietary protein intake, endogenous purine break down and renal clearance, as well as age, gender[6].

It is a predisposing factor for many metabolic conditions and its levels increase after oxidative stress situations such as stroke[7]. Its connection with stroke has been debated for quite long, but is still controversial and remains to be elucidated further. Several studies have evaluated its role in acute stroke, but have contrasting and conflicting results[8, 3].

Research is being done to find out inexpensive, reliable, easily available prognostic factors

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for stroke like uric acid. There is limited local data available in this area of research. This study was conducted to evaluate the role of Uric acid as a predictor of stroke outcome.

METHODOLOGY

This correlational study was performed in department of medicine, Benazir Bhutto Hospital Rawalpindi from October 2016 to April 2017. We enrolled patients 15-85 years of age, admitted with acute ischemic stroke, who presented within 24 hrs of symptom onset and had MRS of ≥3 at the time of admission. Consecutive non probability technique was used for patient recruitment.

The sample size of 40 was calculated by using Correlation Coefficient of 0.465 as reported in literature[8], confidence interval of 95%, margin of error 5%, power of test 80%. We excluded the patients with previous history of stroke, patients having intracranial hemorrhage on CT scan brain, gout, chronic renal failure with GFR <30 ml/min, patients taking alcohol, xanthine oxidase inhibitors, diuretics, low dose aspirin or other drugs that can affect serum uric acid levels.

Ischemic stroke was defined as hypo dense area/absence of intracranial hemorrhage on CT scan, in a patient with focal deficit lasting beyond 24 hours. Serum Uric acid (SUA) level was used as independent variable. It was measured within 24 hours of admission, by standard liquid chromatography method. Dependent variable was functional outcome of stroke, which was measured by modified Rankin score (MRS) at 72 hours after admission. MRS of <3 was labeled as good functional outcome. MRS of 3 or more, or death of the patient was considered poor outcome.

The scoring scheme was as follows; 0 means asymptomatic; 1 if there was no significant disability and patient can carry out daily activities, with some symptoms; 2 indicated slight disability and patient can look after himself without assistance, but cannot carry out all previous activities; 3 denoted moderate disability, when patient required some assistance, but able to walk without support; a score of 4meant moderately severe disability, characterized by inability to attend to bodily needs without help, and unable to walk without support; 5 meant severe disability, where patient needed constant nursing care and is bedridden and/or incontinent; 6 depicted the patient's death.

After obtaining informed consent, detailed history and examination of the patients were done including demographic profile, history of risk factors, medications used and other co-morbid conditions. Blood samples were taken for baseline chemistry including CBC, urea, creatinine and SUA levels within 24 hours of admission. MRS was calculated at admission and after 72 hours. All patients were givens standard treatment as per hospital protocols. Ethical approval was taken from institutional review board; letter No. R-15/ RMC.

Data was analyzed using SPSS version 23. Mean and standard deviation were calculated for age, MRS, SUA. Frequency and percentages were calculated for qualitative data. Pearson Coefficient was calculated between mean SUA levels and mean MRS. Chi square test was applied to compare outcome between gender and age groups. Possible confounders like age and gender were managed with Stratification. Post- stratification correlation coefficient was analyzed and *p*-value ≤0.05 was considered significant.

RESULTS

22 (55%) patients had poor outcome (MRS ≥3). Out of poor outcome group, five patients (12.5%) died due to ischemic stroke. The age of the patients was 66.53 ± 12.20 years. The age was divided into two categories, 19 (47.5%) patients were aged <65 years and 21 (52.5%) >65 years. Out of 40 patients, 19 (47.5%) were males while the 21 (52.5%) were females. Table-I shows the demographic characteristics of study population. The age groups were compared with each other in terms of outcome. The analysis showed that there was no significant distinction between age groups (table-II). The male and female patients were compared with each other in terms of outcome or prognosis (table-III). The Pearson correlation between SUA and MRS was calculated and the

value was 0.511 (p=0.001). The data was stratified according to age and gender. The results showed that the correlation was insignificant only for the female gender with p-value of 0.106 (table-IV).

Receiver operating characteristic (ROC) curve was used to determine efficacy of SUA in predicting the stroke outcome, as shown in (figure). Area under curve (AUC) for SUA was fairly good at 0.793 with confidence interval of 95% ranging from 0.631 to 0.955. The cutoff value for SUA was ≥4.5 mg/dl with sensitivity of 77.3% and specificity of 88.9%, with p-value of 0.002.

Table-I: Demographic characteristics of the study population.

Characteristic	Descriptive Statistics
Age (years) Mean ± SD	66.52 ± 12.20
Gender	**n(%)**
Male	19 (47.5)
Female	21 (52.5)
SUA levels (mg/dl) Mean ± SD	4.78 ± 1.46
MRS (Mean ± SD)	3.15 ± 1.72
Outcome	**n(%)**
Good	18 (45)
Poor	22 (55)
Death: n(%)	5 (12.5)

Table-II: Comparison of stroke outcome between age groups.

Parameter		Outcome		p-value
		Good n (%)	Poor n (%)	
Age	<65 years	08 (20)	11 (27.5)	0.726
	>65 years	10 (25)	11 (27.5)	

Table-III: Comparison of stroke outcome between gender groups.

Parameter		Outcome		p-value
		Good n (%)	Poor n (%)	
Gender	Male	9 (22.5)	10 (25)	0.775
	Female	9 (22.5)	12 (30)	

Table-IV: Correlation between SUA and MRS after stratification for age and gender.

Parameter		Frequency (n)	Pearson correlation coefficient (r)	p-value
Age	<65 years	19	0.561	0.012
	>65 years	21	0.455	0.038
Gender	Male	19	0.688	0.001
	Female	21	0.363	0.106

DISCUSSION

In animal studies, UA proved neuroprotective but in early human trials, this claim proved to be debatable[9]. Anyhow, recent studies proved the role of UA as neuroprotective in many conditions[10].

The role of UA in acute stroke has been established in many studies; study by Wang *et al*. Stated that higher levels of serum UA heralded better prognosis[3], while Zhang *et al*. Reported that deviation of UA, in any direction from normal is marker of poor outcome in stroke. Studies by Miedema *et al*. Found no association between high SUA and functional outcome (OR 1.09, 95% CI 0.72-1.65, p=0.690); and Saadat *et al*. have shown no interrelationship of SUA with any stroke type, neither with severity of ischemic stroke[11,12]. Kawase and team reported that lower SUA was predictor of poorer stroke outcomes in both genders[13].

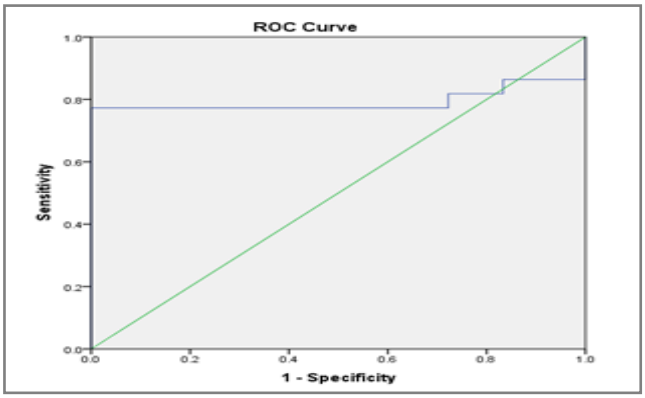

Figure: ROC curve showing AUC for SUA levels in determining the functional outcome of ischemic stroke.

Due to this proposed association, some studies focused the controversial therapeutic role of UA in stroke patients and some even showed the encouraging result. Amaro *et al*. Reported that UA administration with alteplase treatment had prevented post thrombolysis decrease in serum UA levels, but this study did not evaluate any outcome measures[14]. Whereas, study by Llull *et al*.

Concluded that UA treatment improved fun ctional outcome and prevented infarct expansion in females stroke patients undergoing thrombolysis[15]. Therefore, in hyperuricemia patients the allopurinol may improve the outcome as suggested by the work of Taheraghdam *et al*[16]. While in hypouricemic patients the UA does the same, as too low or too high UA levels are associated with poor outcomes[17]. A recent meta-analysis by Wang *et al*. Stated that UA confers neuroprotection after acute ischemic stroke, and high UA level at the stroke onset forecasts a better clinical outcome[3].

Moreover, the contribution of UA as predictor of ischemic stroke is evident in high-risk groups like in patients with hemodialysis[18]. Whether high UA is predictor of ischemic stroke sequelae or it is biomarker for the cerebral infarction is debatable[7]. A review article in 2008 urged the need for large trials in order to confirm, validate these clinical findings and to review the role of hypouricemic treatment in high risk individuals or during an acute vascular event e.g. stroke[19]. The ischemic form of stroke is reported to be associated with the UA levels, while the hemorrhagic form shows no association[20]. The ischemic stroke caused by the cardio embolic events has also strong association between the UA and severity of stroke[21]. A study by Bandyopadhyay *et al*. Showed that serum UA are negatively connected with the prognosis of ischemic stroke, higher the UA poorer is the functional outcome (r=0.456, $p<0.001$)[8]. The correlation in our study was to some extent similar to their results with r=0.511 and *p*-value of 0.001.

The changes in the UA levels during the progression of the disease may be more sensitive than the baseline levels. Brouns *et al* measured UA at admission day 1, 3, 7 and then at 1 and 3 months post stroke. They concluded that decrease in UA during the first week post stroke correlates with higher severity, poor evolution, and adverse long-term outcomes of stroke[9]. Our study is limited in that we performed single UA level measurement.

After the acute ischemic stroke, the patients are at increased risk of mortality in the early period. The dose-response relationship exists between UA levels and ischemic stroke related mortality[22]. The main reasons for mortality are increased intracranial pressure and septic complications like pneumonia[2]. In our study, 12.5% of patients died after ischemic stroke, in these patients mean serum UA level was 5.05 mg/dl. Behera *et al*. Reported that UA has strong association with the mortality in ischemic stroke patients[5]. These figures vary greatly from our results.

The UA association with the ischemic stroke in perspective of gender is arguable. Some research data claimed that increase in UA contributed to mortality and severity in men with ischemicstroke[23]. While a study by Jiménez *et al*. reported equal association in both genders[24]. A recent study by Zhang *et al*. Showed that males with high UA levels had 6 times higher likelihood of poor prognosis and probability was seven times higher in females in comparison to the baseline study group. This study concluded that the relation of UA to prognosis of ischemic stroke is different in each gender, which emphasizes the need of gender stratification in the investigation of cerebrovascular risk factors[17]. Study by Chen *et al*. Reported that higher UA predicted better outcome in males[23], while Kawase *et al*. Stated that lower UA was related to worse functional outcome in either gender[13]. Our observations conflicted with both of these studies. We noted that the female gender had non-significant correlation between serum UA and MRS (r=0.363, *p*-value= 0.106). Male patients had a significant correlation (r=0.688, $p=0.01$).

A study by Mehrpour *et al*[1]. Showed that hyperuricemia is associated with the ischemic stroke severity but this association is confounded by the triglyceride and low-density lipoprotein levels. Moreover, this study showed higher UA levels in males as compared to females ($p=0.03$). The mean age in their study was 67 ± 14 years, which was very close to our results (66.53 ± 12.20 years).

CONCLUSION

The serum UA is positively correlated with the severity of ischemic stroke with a fairly good sensitivity and specificity. This correlation was statistically significant for the all age groups. The female gender had non-significant correlation. Further studies on larger scale are needed to ascertain and evaluate these results.

CONFLICT OF INTEREST

This study has no conflictof interest to be declared by any author.

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