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Original Research Article

The study of hyponatremia in the prognosis of acute ischemic stroke

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ABSTRACT

Background: Stroke is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Acute ischemic stroke is the fourth leading cause of death and most common cause of long-term disability worldwide. Hyponatremia is the commonest electrolyte disturbance encountered in the neurological intensive care units. This study investigated to evaluate hyponatremia in acute ischemic stroke patients as a reliable prognostic marker on admission to ICU.
Methods: A total of 150 patients admitted to M S Ramaiah Hospitals during the period of October 2014 to September 2016 who fulfilled the inclusion criteria were considered in the study. All patients were evaluated by neurologist/ physician and the diagnosis of Acute ischemic stroke was made by Clinical examination and confirmed by Computed Tomography (CT) and/ Magnetic resonance imaging (MRI) brain. Hyponatremia was defined as serum sodium level <135 mmol/L and recorded on admission. Outcome was assessed by National Institute of Health Stroke Scale (NIHSS) score at admission, day 5 and at discharge, duration of ICU stay, duration of hospital stay and in-patient mortality.
Results: Among the 150 patients admitted with acute ischemic stroke, mean age was 60 years, 68% were males and 36% patients had hyponatremia. Baseline characteristics were similar between groups except for gender distribution (p=0.037). Hyponatremic patients had higher NIHSS score on admission, on day 5 and at discharge (p=<0.001). Hyponatremic patients had a longer duration of ICU stay (p=<0.001) and in hospital stay (p=<0.001). Hyponatremia was associated with higher mortality in hospital (p=0.026).
Conclusions: Study demonstrates that hyponatremia at admission in acute ischemic stroke patients is associated with acute mortality, worse NIHSS score at admission and at discharge, and longer duration of ICU and hospital stay.

Keywords: Acute ischemic stroke, Hyponatremia, mortality, NIHSS Score, Prognosis

INTRODUCTION

Acute ischemic stroke is the fourth leading cause of death and most common cause of long-term disability worldwide. Hyponatremia is the commonest electrolyte disturbance encountered in the neurological intensive care units. About 16% of acute ischemic stroke patients will have hyponatremia at presentation.[1] A study done previously has shown that patients with hyponatremia have worse National institute of health stroke scale (NIHSS) scores on admission and their NIHSS Score worsens during hospitalization. Study also shows that patients with hyponatremia have higher acute mortality rates and poorer discharge dispositions.[1]

Hyponatremia in neurological disorders is usually of the hypo-osmolar type caused either due to the Syndrome of Inappropriate Secretion of Anti Diuretic Hormone

(SIADH) or Cerebral Salt Wasting Syndrome (CSWS). It is important to distinguish between these two disorders, as the treatment of the two differs to a large extent. In SIADH, the fluid intake is restricted, whereas in CSWS the treatment involves fluid and salt replacement.[2,3] Low serum sodium levels are also seen as a complication of cerebrovascular disease, especially after subarachnoid hemorrhage.[3,4] Hyponatremia has long been described as a risk factor for stroke and cardiovascular disease.[3-5] Even mild hyponatremia is a factor for poor prognosis in the general population, and low sodium levels on admission were associated with increased 30-day mortality after a myocardial infarction and acute ischemic stroke.[5,6] A recent study demonstrated higher 3-year mortality in hyponatremic patients with first ever ischemic stroke.[6]

METHODS

This was prospective study in which consecutive patients admitted with acute ischemic STROKE during the study period who fulfilled the inclusion criteria. All patients were evaluated by a neurologist/ attending physician and the diagnosis of an acute ischemic stroke was made by Clinical examination and confirmed by head Computed Tomography and/or by brain magnetic resonance imaging. Clinical Assessment of stroke was done by NIH stroke scale. The duration of the study was two years (October 2014-September 2016).

Investigations done

- Serum sodium level (by ion selective electrode method)
- Imaging-computed tomography/magnetic resonance imaging of brain.

Inclusion criteria

- Patients with Acute ischemic stroke.
- Patients aged above 18 years.

Exclusion criteria

- All patients with hemorrhagic stroke (subarachnoid, subdural, epidural, parenchymal hemorrhages) were excluded.
- Ischemic stroke with hemorrhagic transformation.
- Recurrent stroke.
- Venous stroke.
- Posterior circulation stroke.

Sample size

Based on study conducted by Rodrigues B, Staff I, Fortunato G et al, "Hyponatremia in the Prognosis of Acute Ischemic Stroke" in the journal of stroke and cerebrovascular disease. For a confidence level of 95% with 6% relative precision it was estimated that a minimum of 143 subjects were required for the present study.

Statistical analysis

Data was entered in MS excel and analysed using SPSS version 17. All quantitative variables like serum sodium levels were expressed in terms of mean and standard deviation. Students 'T' test/Mann Whitney test was used to find the mean difference between serum sodium levels in normal and hyponatremic group. Chi-square test/ Fischer exact test was applied to compare the categorical variables.

RESULTS

In the present study mean age was 60 years with 22 years as the youngest and 85 years as the eldest. 68% of the patients were males. In our study 66% of the patients had pre-existing hypertension.

Authors observed that in this study mean SBP was 144mm hg, with majority of patients had their SBP between 121 to 160mm hg and 48% patients had pre-existing Type 2 DM. In this study, mean RBS at admission was 187 with highest RBS being 543 and lowest being 67 mg/dl.

Table 1: RBS at admission.

RBS	No. of patients	Percentage
<70	2	1.3
70-100	33	22
100-150	44	29.3
151-200	21	14
201-250	17	11.3
251-300	11	7.3
301-400	14	9.3
401-500	6	4
>501	2	1.3
Total	150	100

In the present study, 102 patients had HbA1c level, out of which 29 patients had an HbA1c >9. There were 8.7% of the patients who had hyponatremia and 46% patients had dyslipidemia. Majority of the patients had serum cholesterol <200 mg/dl (54%) and serum LDL <130 (60%).

Table 2: HbA1c level.

HbA1c	No. of patients	Percentage
<6.5	32	21.3
6.5-7.2	16	10.7
7.3-9	25	16.7
>9	29	19.3
Missing	48	32

Authors observed that in this study systemic hypertension (66%) was the most common comorbidity then followed by type 2 dm (48%) and Dyslipidemia (46%). Majority of

patients had infarct in left MCA territory (36%), then followed by right MCA territory (22.7%).

In the present study, 36% of the patients had thrombocytopenia. In hyponatremic patients the NIHS score at admission was higher when compared to normonatremic patients. This reached a statistical significance. In hyponatremic patients the NIHS score at day 5 was higher when compared to normonatremic patients. This reached a statistical significance. In hyponatremic patients the NIHS score at discharge was much higher when compared to normonatremic patients. In patients with normonatremia 18% had an NIHS score between 1 to 4, whereas in patients with hyponatremia only 1.3% had a score between 1 to 4. This reached a statistical significance.

Table 3: Comparison of characteristics between hyponatremic and normonatremic patients.

Characteristics	Hyponatremia	Normal	p value
Age	59.52+14.46	61.14+11.87	0.467
Gender	Males-57.4	Males-74	0.037
	Females - 42.6	Females - 26	
Hypertension	61.1	68.8	0.346
Type 2 Diabetes mellitus	42.6	51	0.323
Dyslipidemia	51.9	42.7	0.672
Smoking	31.5	26	0.677
Alcohol consumption	9.3	4.2	0.378
CCF	16.7	13.5	0.606
CKD	9.3	7.3	0.672
Hypothyroidism	7.4	9.4	0.683
IHD	13	8.3	0.368
Diuretics	20.4	15.6	0.464
RBS	185±111.62	188±108.26	0.711
HbA1c	8.15±2.54	7.75±2.15	0.721
Serum cholesterol	207±47.85	200.92±44.03	0.372
LDL	127.63±39.65	124.54±38.137	0.64
TSH	4.997±3.72	3.61±2.91	0.318
NIHSS score at admission	16.04±5.158	10.19±3.966	<0.001
NIHSS score at day 5	12.61±5.17	6.67±3.514	<0.001
NIHSS score at discharge	10.35±3.48	6.16±2.90	<0.001
Duration of ICU stay	6.43±7.218	2.44±3.803	<0.001
Duration of hospitalization	12.63±8.44	7.299±5.657	<0.001

Hyponatremia was associated with higher mortality. This reached a statistical significance. P value=0.026. Patients with hyponatremia had a longer duration of ICU stay and prolonged hospitalization when compared to normonatremic patients. Both of which achieved statistical significance p value <0.001. Patients with hyponatremia tend to have delayed in hospital recovery when compared to normonatremic patients. On comparison of the characteristics between normonatremic and hyponatremic group, patients with hyponatremia had worse NIHS score at admission, day 5, at discharge and also, they had longer duration of ICU stay and prolonged hospitalization. Multivariate analysis, hyponatremia remains an independent predictor of in hospital mortality rates. There is negative correlation between serum sodium level at admission with NIHS score at admission, day 5 and at discharge. (p <0.001). There is a negative correlation between serum sodium level at admission with duration of ICU stay and hospitalization (p <0.001).

Table 4: Distribution of serum sodium level at admission.

Serum sodium	Frequency	Percentage
111-120	3	2
121-130	23	15.3
131-134	28	18.7
135-145	93	62
>146	3	2
Total	150	100

DISCUSSION

A total of 150 patients with acute ischemic stroke were studied, all 150 patients had sodium levels documented on admission. In this study, mean age of distribution was 60.55±12.841, youngest patient was 22 years and the

eldest patient was 85 years. Out of 150 patients 68% were men and 32% women. Among the studied patients the highest incidence of AIS was found between the age group of 51 to 70 years comprising about 59.4%, in men the highest was between 51 to 60 years and then followed by 61 to 70 years comprising about 28.43% and 26.47% respectively whereas in females majority of the patients were in the age group between 61 to 70 years comprising about 45.85% and the next group with highest incidence was between the age group of 51 to 60 years comprising about 22.92%.

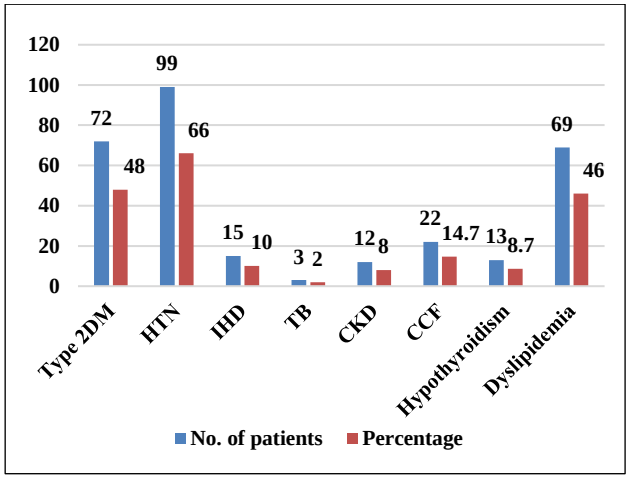

Figure 1: Comorbidities.

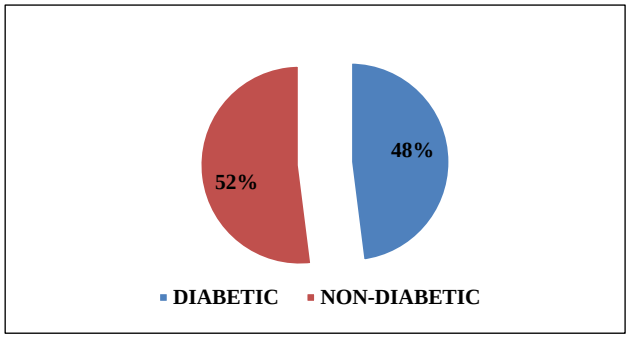

Figure 2: Distribution of type 2 DM.

In this study, systemic hypertension (66%) was the most common comorbidity then followed by type 2 DM (48%) and dyslipidemia (46%). Majority of the infarcts were in the MCA territory comprising about left MCA territory (36%), then followed by right MCA territory (22.7%). Baseline clinical characteristics and risk factors for stroke were similar between groups except for higher gender distribution (*p*=0.037).

Hyponatremia was observed in 54 (36%) patients in our study, which was similar to the study by S Saleem et al which had a prevalence of 35.3%. Whereas Prevalence of hyponatremia on hospital admission was 15.6% and 16% in studies done by J B Kuramatsu et al, and B Rodriguez et al, respectively. Patients with hyponatremia had worse NIHSS scores at admission. The comparison of ranked scores shows a trend for this effect (p=<0.001) with significant differences found when the scores are classified into 4 severity groups (p=<0.001), which was similar to the study by B Rodriguez et al. Better NIHSS score at discharge was observed in 18% of the patients with normonatremia when compared to only 1.3% in the patients with hyponatremia (p=<0.001), which was similar to the study by B Rodriguez et al (p=0.02).

Patients with hyponatremia on admission have significantly higher rates of short-term mortality defined as either expiring during the initial hospital stay or a composite of in-hospital death, (p=0.026) which was similar to the study by B Rodriguez et al. (p=0.039) and J B Kuramatsu et al. Also, Patients with hyponatremia tend to have delayed in hospital recovery when compared to normonatremic patients. Patients with hyponatremia had a longer duration of ICU stay and prolonged hospitalization when compared to normonatremic patients. Both of which achieved statistical significance (p=<0.001).

A history of malignancy, and heart failure were also documented in the study and it was analyzed using the univariate analysis. These are conditions commonly associated with hyponatremia and are often associated with SIADH and cerebral salt-wasting syndrome. Other conditions associated with hyponatremia, such as hypothyroidism, CKD and diabetes, did not differ in our sample. Patients with these comorbidities are commonly associated with hyponatremia, the possible confounding factors were statistically evaluated in the multivariate logistic regression, which confirmed hyponatremia as an independent predictor of poor outcome. The level at which hyponatremia is defined is critical to our findings and hyponatremia is defined as a sodium level below 135mmol/L. It was noted that out of 36% patients with hyponatremia, 18.7% of the patients had serum sodium between 131-134mmol/L and 17.3% patients had <131 mmol/L. Majority of the studies on hyponatremia in western population indicates that overall prevalence of hyponatremia in hospital to be around 15 to 20%.[1,5,6] Whereas the prevalence of hyponatremia in Indian studies show much higher incidence 32-36% which was very similar to our study.[2] By this we would suggest that a lesser threshold be used to diagnose hyponatremia in Indian population when compared to western population.
Low serum levels of sodium have been associated with a variety of neurologic symptoms, including seizures, encephalopathy, and diffuse cerebral edema.[3] The mechanisms underlying the poorer outcomes in patients with hyponatremia are not clear. These findings have also been demonstrated in cardiovascular patients and even in the general population.[4,5] Cerebral edema could be a part of the process resulting in extension of the vascular injury. AIS initiates a cascade of events that eventually lead to cell death; including depletion of adenosine triphosphate (ATP), changes in ionic concentrations of sodium, potassium, and calcium; increased lactate; acidosis, accumulation of oxygen free radicals;

intracellular accumulation of water; and activation of proteolytic processes on cerebral perfusion. Stroke has been associated with a wide range of systemic inflammatory conditions. It may be associated with primary vasculitis, like giant cell arteritis, primary angitis of CNS, Takayasu's arteritis, vasculitis secondary to SLE, progressive systemic sclerosis, rheumatoid arthritis; and other inflammatory conditions like inflammatory bowel disease (IBD) and sarcoidosis.[7] Osmotic changes at the cell membrane level, which cannot be seen with current imaging techniques, could also be responsible for enhances in cellular dysfunction and death. Hypertonic saline is widely used in other types of strokes (subarachnoid hemorrhage, subdural hemorrhage) to improve these outcomes and diminish cerebral edema, but it has never been studied in ischemic injury. Brain injury following stroke results from the complex interplay of multiple pathways including excitotoxicity, acidotoxicity, ionic imbalance, peri-infarct depolarization, oxidative and nitrative stress, inflammation and apoptosis.[8]

A comparison between premorbid and admission sodium levels could establish how quickly the hyponatremia developed and determine if this resulted in enhanced neurologic deficits. Unfortunately, this design would be difficult because stroke onset is not always easy to predict. Early initiation of treatments for secondary stroke prevention is associated with an 80% reduction in risk of early recurrent stroke.[9]

New predictors for stroke after MI were identified, including history of hypertension, diabetes, and peripheral vascular disease. These predictors are generally accepted as risk factors for ischemic stroke.[10]

The proportion of isolated transient ischemic attacks increased significantly over the 30 years studied, yielding an apparent and significant decline in case-fatality rates in men only.[11] Major advances have occurred in secondary prevention during the past three decades, which demonstrate the broader potential to prevent stroke.[12] Insulin-dependent diabetics have both an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors, notably hypertension, obesity, and abnormal blood lipids. In the low-mortality regions, the health situation is much worse for men than for women. The life expectancy at birth is substantially longer for women than for men, as is disability-adjusted life expectancy at birth, and the percentage of the lifespan lived with disability is higher for men than women.[13] The 5-year adjusted incidence rates for cardiovascular disease were 4.6 (95% CI 4.4-4.9) per 100 women aged 50-69 in non-smokers with diabetes, 5.9 (95% CI 4.6-7.6) in smokers with diabetes not using insulin and 11.0 (95% CI 8.3-14.7) in smokers with diabetes using insulin.[14] Evidence-based recommendations are provided for control of risk factors, intervention for vascular obstruction, antithrombotic therapy for cardioembolism, and antiplatelet therapy for noncardioembolic stroke. Recommendations are also provided for the prevention of recurrent stroke in a variety of specific circumstances, including aortic arch atherosclerosis, arterial dissection, patent foramen ovale, hyperhomocysteinemia, hypercoagulable states, antiphospholipid antibody syndrome, sickle cell disease, cerebral venous sinus thrombosis, and pregnancy.[15]

Strength of the study is all comorbidities and confounding factors for hyponatremia and poorer outcomes were analyzed. Also, stringent monitoring of NIHS score was done at admission, day 5 and at discharge. Drawbacks of the study was, only short-term morbidity and mortality were assessed, long-term morbidity and mortality is also high in these patients as seen in studies by B Rodriguez et al, and Kuramatsu JB et al.

CONCLUSION

From this study, author concluded that hyponatremia at admission in acute ischemic stroke patients is associated with acute mortality. Author also conclude that hyponatremia at admission was associated with higher NIHSS score at admission, day 5 and at discharge.

Longer duration of ICU stay and prolonged hospital stay was also noted in patients with hyponatremia. Hyponatremia had negative correlation with NIHS stroke score, duration of ICU, and hospital stay.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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