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ORIGINAL RESEARCH

Hyponatremia as an Independent Indicator of Grave Prognosis in Patients with Spontaneous Intracerebral Haemorrhage

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Abstract

Background: Hyponatremia an electrolytic imbalance is most commonly found in all types of stroke patients especially in haemorrhagic stroke and is associated with increased mortality. Stroke severity, comorbid conditions associated with hyponatremia and type of haemorrhage worsens the morbidity and mortality.

Objective: To determine hyponatremia as an independent indicator of grave prognosis in patients with spontaneous intra cerebral haemorrhage.

Methods: A cross sectional study of 100 patients of haemorrhagic stroke confirmed by CT scan or MRI at SCB Medical College &Hospital, was done with ethical clearance. The risk factors were evaluated for correlation with hyponatremia and mortality rate, The patients with or without neurological deficits were followed for 2 months and hyponatremia as independent risk factor was analysed by multivariable cox regression model.

Observations: Hyponatremia was found in 54% of cases and mortality rate 31% in hyponatremic patients compared to 10% in non-hyponatremic patients. Hyponatremia as a risk factor for mortality in stroke patients with RR 3.63 (2.008-6.594) p=0.0001. Odds ratio of hospital death and 60 days death rate were 9.093(3.614-22.881) p=0.0001 and 7.368(0.768-70.7090 P=0.041. The hazards ratio for 60 days death rate related to hyponatremia was 3.03(1.705-5.419) P= <0.001 and significant when compared to mortality related to age, ICH score >1, comorbidity, rebleeding and normonatretremic patients.

Conclusion: Hyponatremia due to any cause influence the mortality rate and and an independent predictor of prognosis in patients with haemorrhagic stroke. Correction of hyponatremia along with other medications may decrease the death rate but not up to mark as desired.

Keywords: Cerebrovascular accident, Intracerebral haemorrhage, Hyponatremia, Cerebral salt wasting syndrome, SIADH.

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Introduction

Stroke is abrupt onset of neurological deficit that is attributable to a focal vascular cause. It is the second most common cause of death in the world which accounts for approximately 12% of all deaths[1]. Electrolytic imbalance such as hyponatremia is most common in all types of stroke patients especially in haemorrhagic stroke and is associated with increased mortality. There are different types of hyponatremia based on the volume status of the individual. They are Euvolemic, Hypervolemic and Hypovolemic hyponatremia. The restoration of the volume depletion remains the cornerstone of treatment in hypovolemic hyponatremia[2]. Hyponatremiais encountered in patients of neurological disorders due to cerebral salt wasting syndrome and inappropriate secretion of antidiuretic hormone which is also associated with ischemic stroke. Acute ischemic stroke patients need thrombolytic therapy complicate to haemorrhagic stroke also lower the serum sodium level which worsen the clinical outcome and increase mortality [3]. Inhyponatremic patients with haemorrhagic stroke, most common sites of haemorrhage are putamen ,thalamus in patients with SIADH and cerebral salt wasting syndrome[4]. Subarachnoid haemorrhage probably due to rupture aneurysm is also associated hyponatremia which worsens the morbidity and mortality [5]. Hyponatremia is a risk factor for stroke and cardio vascular disease which is associated with increased risk of mortality [6]. Comorbidities associated with stroke patients are also associated with hyponatremia. The scale of clinical assessment of stroke severity, the size and location of the stroke and 30 days mortality are assessed for analysis of association with hyponatremia. hyponatremia is frequently observed in patients with haemorrhagic stroke [7]. In patients with acute non traumatic haemorrhagic stroke, hyponatremia determines its impact on hospital mortality. The outcomes such as motor or sensor deficit and in hospital mortality are high in patients with cerebral salt wasting syndrome and SIADH. Hyponatremia is an independent predictor of short-term mortality in patients with acute haemorrhagic stroke [8]. The serum concentration of electrolytes such as sodium, potassium and chlorides are less in haemorrhagic stroke [9]. Patients coming to emergency with stroke should be screened immediately for dyselectrolytemia. Early diagnosis of electrolytic imbalance and prompt medical interventions can improve outcomes in stroke patients [10]. Antidiuretic hormone secretion (SIADH) and cerebral salt wasting syndrome (CSW) are two common aetiologies of hyponatremia with brain injury [11]. Hyponatremia is also associated traumatic brain haemorrhage and post traumatic vasospasm [12] Cerebral infarction and cerebral salt wasting syndrome in the course of haemorrhagic stroke should be assessed for fluid replacement and electrolytic management. The observation led to the description of CSW as separate entity occurring in the setting of stroke worsen the prognosis of stroke, increased morbidity, short- and long-term mortality [13].

Objectives

To determine the influence of hyponatremia on mortality and functional outcome in patients with spontaneous intracerebral haemorrhage.

Materials & methods

This was a cross sectional study of 100 cases of Spontaneous intracerebral haemorrhage admitted in the medical ward of SCB Medical College Hospital. All the tests were done with the Ethical clearance from institutional ethical committee IEC NO 705 dated 10.03.2021 at SCB Medical College &Hospital, Cuttack, Odisha India and informed consents from the subjects. Age, sex, history of patients and thoroughly examination with blood pressure record for systolic and diastolic blood pressure, Glasgow coma score (GCS) which scores from minimum 3 to maximum 15. serum sodium sugar and osmolality of serum and urine were recorded. Urine sodium excretion was recorded. MRI was done in all cases and case

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with finding of all types of brain haemorrhage were included for study. There was follow up period for two months for any rebleeding and mortality, all patients aged above 18 years, Radiologically proven and diagnosed case of spontaneous intracerebral haemorrhage were included. ICH secondary to anticoagulation, Trauma, A V Malformations Thrombocytopenia and patients on diuretics were excluded.

Statistical analysis

Clinical demographic characteristics and the outcomes were categorised into two groups of Hyponatremia and no Hyponatremia. The continuous variables were described as mean and the difference was analysed by independent t test. The Categorical variables were described as percentage and were compared for significance by Fischer exact test. The predictors remained significant between two groups were subjected for multivariable analysis for the strong association of hospital mortality in terms of relative risk, 95% CI and p-value. Odds ratio for hospital mortality for hyponatremia compared to no hyponatremia was calculated by logistic regression method. The events are followed for two months of discharge, The hazards ratio for outcomes of 60 days mortality rate related to Age, rebleeding, comorbidity, low GCS score were compared between hyponatremia and non-hyponatremia by Cox regression method and analysed by Kaplan Meir analysis. Statistical analysis was with the help of SPSS22.

Results

Hyponatremia was the most electrolytic abnormality seen among the ICH patients in 54% of cases as compared to 46% in non-hyponatremia patients. But there was no significance difference between the two groups. Mean age of the patients developed to hyponatremia were 64.8 $\pm$ SD 8.3 years. There was no age group significantly related to hyponatremia (Table-1) but those cases developed hyponatremia were significantly related to hospital mortality with odds ratio and 95% confidence interval was 9.093(3.614-22.881). Hospital mortality in hyponatremic patients was 31% whereas hospital mortality in non-hyponatremic patients was 10%. Hyponatremia related death rate was 3.1 times of normotremia death rate, translating the risk ratio into 3.63-fold with p-value 0.00001. Mean GCS score was 9.7 with SD 2.04 in all case of hyponatremia whereas 9.25 with SD 2.25 in cases not developed hyponatremia but there was no significance difference between them. Increased systolic and diastolic blood pressure were significantly related to hyponatremia and hospital death. Similarly decreased serum osmolality, increased urinary osmolality and increased urinary sodium excretion significantly related to hyponatremia and hospital mortality. Increased urinary osmolality and urinary sodium excretion were highly associated with hospital death. Hyponatremia was independent associated with mortality RR 3.63, 95% CI (2.008-6.594; P=0.0001) controlling for its related factors SBP, DBP, Serum and urinary osmolality. was identified by multivariable analysis and logistic regression (Table-2)

Clinical Pathological Characteristics	**Hyponatremia**	**(54)54%**		**NoHyponatremia**	**46(46%)**	**Significance p=0.05**
	Mean	SD		Mean	SD	P value
Age	64.8	8.3		63.5	8	0.427
SBP	180.56	28.56		160.2	25.6	<0.001
DBP	102.86	15		92.3	10.7	<0.001
GCS	9.7	2.04		9.25	2.2	0.29
comorbidities	32%	-		21%	-	0.356
Hypertensive	15%		-	21%	-	0.2

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(ECG)						
Brain Haemorrhage (MRI)	54%		-	46%	-	0.44
Serum Osmolality (Decrease)	39%		-	0	-	<0.001
Urine Osmolality (increased)	39%		-	0	-	<0.001
Urinary Sodium Excretion (Increase)	39%		-	0	-	<0.001
Sugar Level (RBS)	46%		-	56%	-	0.42
Hospital Mortality	31%		-	10%	-	<0.001

Table 1: Comparison of clinical pathological characteristics between Hyponatremia and No-Hyponatremia

Relative risk (risk ratio), 95% confidence interval and P-value for relative risk.

Hyponatremia (YES/NO)	3.63 (2.008-6.594)	<0.001
SBP>150	4.80 (2.043-11.276)	<0.001
DBP>100	6.64(2.843-15.537)	<0.001
Serum osmolality(decreased)	7.59(3.745-15.411)	0.0
Urine osmolality (increased)	19.81(6.565-59.792)	0.0
Urine sod excretion(increase)	14.46(5.595-37.414)	0.0

Table 2- Association Between Clinico pathological Characteristics and Hospital Mortality by multi variable regression method

Outcome	95% CI	p- Value
Hospital death	9.093 (3.614-22.881)	P<0.001
60 days death rate	7.368(0.768-70.709)	0.041

Table 3- Logistic Regression to Estimate the Odds Ratio of Hospital Death and mortality within 60 days follow up for Hyponatremia compared to No Hyponatremia

Odds for hospital mortality rate and 60days mortality rate after follow up were similar and significant when compared between hyponatremia and non-hyponatremia.

Outcomes	**HR and 95%CI**	**P-Value**
Mortality related to age more than 60	0.56(0.24-1.33)	0.133
Comorbidity related mortality	0.57(0.235-1.431)	0.176
ICH With midline shift	1.32(0.488-3.587)	0.610
ICH Score >1	0.72(0.280-1.862)	0.462
Hyponatremia, sod <135meq/l	3.03(1.705-5.419)	<0.001

Table 4- Hyponatremia as an independent prognostic factor by Cox regression hazard method

Mean hospital stay with or without neurological deficit was recorded and each survival patients was followed for 2 months, Rebleeding and death was recorded in every 7 days, Further investigation and physiotherapy along with appropriate medication was required.

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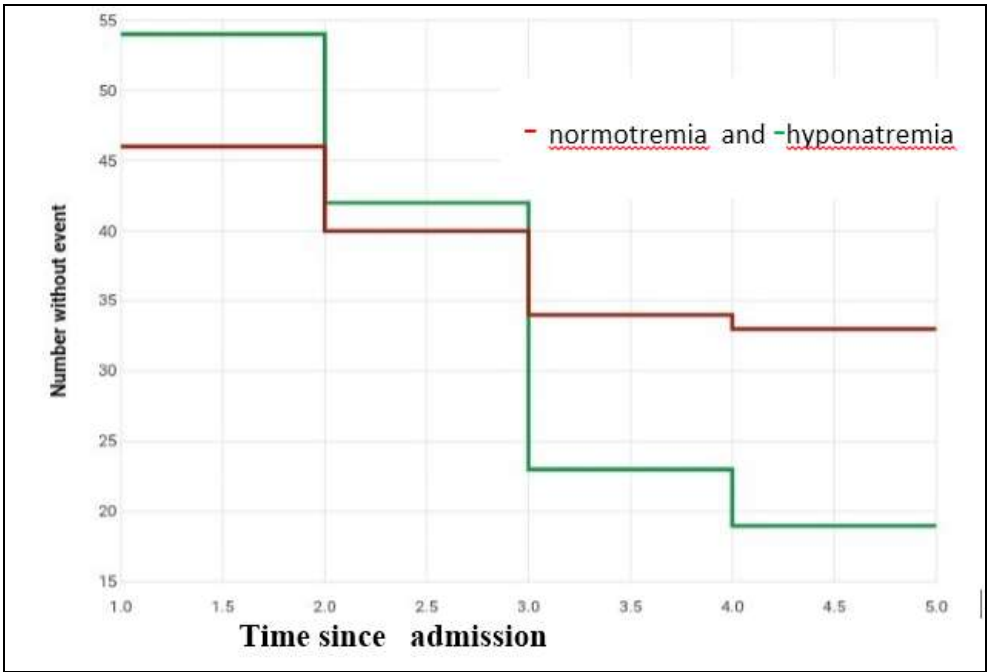

Graph1- Time to event(death) curve for hyponatremia compared to normotremia

Hyponatremia was found to be independent prognostic factor by Cox hazard regression analysis. The outcome of death for hyponatremia compared to non-hyponatremic on different times by Kaplan Meir analysis/Time event graph. Median survival time was more in non-hyponatremic group than hyponatremic patients.

Discussion

A total of 100 cases were included in this study. Of these majority of cases were in the age group 60-69 years. Among them males were 46 and female were 54, F:M=1.17. The mean systolic blood pressure was 180.56 among the hyponatremic patients and was 160.2 among the normonatremic patients. The mean diastolic blood pressure was 102.86 among the hyponatremic patients and was 92.3 among the normonatremic patients. Elevated blood pressure is common acutely after ICH, even in patients without a prior history of hypertension. In most cases, blood pressure spontaneously declines over 7- 10 days, and the maximal decline occurs over the first 24 hours. Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998 showed a stronger association of usual diastolic blood pressure with haemorrhagic stroke than with non-haemorrhagic stroke [14]. The systolic Hypertension in the Elderly Programme (SHEP) Study determines the effects, on stroke, of treating isolated systolic hypertension in 4736 elderly patients. Antihypertensive treatment appears to be more protective against haemorrhagic stroke than ischemic stroke, the relative risk for reduction of haemorrhagic stroke being 0.46(95%CI:0.21-1.02) [15]. High BP has also been shown to be an important risk factor for the recurrence of ICH. In prospective study of 74 patients with hypertensive brain haemorrhage, high diastolic BP was related to an increased rate of rebleeding. The Glasgow coma scoring used for assessing the consciousness level in our study patients, was not significantly associated with hyponatremia. Similarly Random blood sugar of the study was not significantly associated with hyponatremia and outcome. The presence of multiple comorbid conditions like diabetes, coronary artery disease, COPD were not significantly associated with hyponatremia. Decreased serum osmolality seen both in CEREBRAL SALT WASTING SYNDROME and SIADH has significantly association with hyponatremia and increases the mortality rate [16]. Increased

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urine osmolality seen in both cerebral salt wasting syndrome and in syndrome of inappropriate antidiuretic hormone has significant association with hyponatremia hence by correcting urine osmolality by drugs like vaptans reduces the mortality rate [17]. Urinary sodium excretion seen both in cerebral salt wasting syndrome and syndrome of inappropriate antidiuretic hormone hence correction or prevention of urinary sodium loss reduce mortality rate [18]. Hyponatremia was found in 15.6% of patients admitted for intracerebral haemorrhage [19]. Correcting hyponatremia could not prevent hospital mortality and is not proved by any study [20]. There was no correlation between sodium level and the time of cerebral haemorrhage symptoms onset to admission.

Our study was single cantered, prospective follow up till the discharge of the patients or hospital death could not answer the increase of hospital mortality in hyponatremic patients in stroke patients. Pre-existing hyponatremia probably due to previous comorbid conditions and polymedications and its relation to outcome may not have sufficiently achieved. The prevalence of hyponatremia in haemorrhagic stroke patients and its association with increased mortality have been analysed by multivariable regression analysis.

Conclusion

Hyponatremia is commonly found in haemorrhagic stroke patients and more hospital mortality is found in those patients. Hence hyponatremia due to any cause influence the mortality rate and an independent predictor of hospital mortality.

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