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Hyponatremia as an early marker of poor outcome of stroke - results of a prospective cohort study

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Abstract

Background & Objective: Hyponatremia is a frequently found complication of stroke. However, its impact on stroke outcome is poorly understood. Hence, the purpose of this study was to determine the outcome of strokes in association with hyponatremia. *Methods:* This was a prospective cohort study conducted at a tertiary referral center in Sri Lanka. The study subjects consisted of 246 patients with confirmed stroke. Patient characteristics, mortality, length of hospital stay and functional outcome by Modified Rankin Scale (MRS) score were assessed to evaluate the effect of hyponatremia (<131mmol/l) on stroke. Early mortality was defined as the total number of deaths occurred by 70 days. The "not favorable" MRS score was defined from 4 to 6. *Results:* Out of 246 patients, 47 patients (19.1%) developed hyponatremia (95% confidence interval (CI): 14.39, 24.58). The mean day of development of hyponatremia was 1.81days (SD=1.73). Hyponatremia was associated with early mortality (OR=2.08; 95% CI: 1.05, 4.1; P=0.034), increased length of hospital stay (β=2.37; 95% CI: 1.51, 3.23; P= <0.001) and "not favourable" functional outcome at discharge (OR=2.59; 95% CI: 1.33, 5.05; P=0.005). Kaplan Meier survival curve analysis showed better chance of survival in non-hyponatremic group compared to hyponatremic group (P =0.02).
Conclusion: Hyponatremia is associated with early mortality, increased length of hospital stay and unfavorable functional outcome at discharge following stroke. Early detection and correction of hyponatremia may improve stroke outcome.

Keywords: Functional outcome, hyponatremia, length of hospital stay, mortality, stroke

INTRODUCTION

Stroke is considered as the most prevalent neurological emergency.[1] According to World Health Organization, stroke is defined as the sudden deterioration of brain function due to interrupted blood supply which lasts more than 24 hours.[2] Epidemiological data on stroke has revealed a shift of stroke burden from high income countries to low and middle income countries.[3] In addition, stroke is associated with a number of complications of which hyponatremia is frequently seen.[4] One study has reported the prevalence of stroke in Sri Lanka as 10.4 per 1,000.[5]

Hyponatremia is defined as the serum Na^+ concentration of less than 135mmo/l.[6] However, one review done by a panel of experts has recommended that hyponatremia should be further investigated and treated if the serum Na^+ level is less than 131mmol/l.[7] Even though there are many aetiologies for hyponatremia, syndrome of inappropriate anti diuretic hormone secretion (SIADH) and cerebral salt wasting syndrome (CSWS) are the main aetiological causes in neurological patients.[8]

The impact of hyponatremia on stroke is depicted in two ways. It acts as both a risk factor and a complication in strokes. Further, hyponatremia has a negative prognostic effect on both the short and long term mortality risk in stroke patients.[9] Hyponatremia can cause cerebral edema which results in increased intracranial pressure. This could result in further cerebral ischaemia worsening the neurological status of the patient.[10] On the other hand, there is a possibility

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of fatal outcomes from the rapid correction of hyponatremia as it could result in central pontine myelinosis. However, the exact mechanism of hyponatremia that results in mortality is still not known.[4]

Apart from mortality, hyponatremia could result in lower discharge rates in hospitals increasing the hospital burden.[11] A study based on 202 stroke patients concluded that the length of hospital stay is increased in the hyponatremic group by 11 days compared to the non-hyponatremic group. [12]

Our aim of this study is to investigate the outcome of hyponatremia on mortality, duration of hospital stay and functional outcome assessed by the Modified Ranking Score (MRS score), thereby emphasizing the strong need for the close observation of hyponatremia in stroke patients.

METHODS

Design and setting

This was a prospective cohort study carried out on 246 stroke patients admitted consecutively to Teaching Hospital Peradeniya, located in the central province of Sri Lanka. Ethical clearance to this study was obtained from the Ethics Review Committee, Faculty of Medicine, University of Peradeniya, Sri Lanka (2018/EC/44). Written informed consent was obtained from the patient or, in the instances where the patient was not clinically fit to do so, from the next of kin.

Data collection

The study patients of stroke were recruited prospectively from 1st of June 2019 to 12th of February 2021. The diagnosis of stroke was established on the clinical history, examination and neuroimaging. Hyponatremia was defined as serum Na^+ less than 131mmo/l.[7]

Patients with known pre-event hyponatremia were excluded from the study based on the clinical records. On admission serum sodium level was recorded. Thereafter serial serum sodium levels were performed in all stroke patients. Even a single value of serum Na^+ level less than 131mmol/l during the hospital stay was considered as hyponatremia. All the patients with low Na^+ levels were assessed for their serum osmolality levels. Mortality was recorded during the hospital stay and up to 70 days following hospital discharge. MRS score was recorded at the discharge and 70 days after discharge. Altogether 58 patients were lost to follow up. Early mortality was defined as the total number of deaths that occurred by 70 days. The "favorable" MRS score was defined from 0 to 3. In contrast, the "not favorable" MRS score was defined from 4 to 6. [13]

Statistical analysis

Fisher's exact test or Pearson chi square test for categorical variables and student t-test or Mann Whitney u test for continuous variables were used to compare the characteristics between hyponatremic and non hyponatremic groups. Logistic regression analysis was performed to investigate the effect of hyponatremia on in-hospital mortality, early mortality and functional outcome. Further, the log rank test visualized by the Kaplan-Meier curve was done to evaluate the relationship between hyponatremia and mortality. In the analysis, time variable or survival time was defined as the days a stroke patient survived after admission to the hospital. Univariate Cox regression analysis was performed to investigate the hazard of hyponatremic group compared to non-hyponatremic group. Finally a linear regression analysis was performed to evaluate the effect of hyponatremia on length of hospital stay. A P value of 0.05 or less than that is considered to be significant. Statistical analysis was performed by using STATA Version 16 (StataCorp. 2019. *Stata Statistical Software*. College Station, TX: StataCorp LLC.).

RESULTS

Study participant characteristics

The study sample comprised of 246 proven cases of stroke patients. The mean age of the study participants was 68.14 years (SD=12.71). The percentage of males was 48.7% and their mean age was 68.25 years (SD=12.25). The mean age of the females was 67.8 years (SD=12.65) and there was no statistical difference between age of males and females (P= 0.778). Most of the patients (57.32%) belonged to the age group of 60-79 years. Among the study group, 27.2% were smokers and 35.7% were abusers of alcohol. In the study sample, 56.09% patients were on treatment for hypertension. Diabetes mellitus comprised of 30.8% of patients and 13% of patients on lipid lowering drugs.

Of the 246 stroke patients, 79.7% had ischaemic stroke and 20.3% had haemorrhagic stroke. In the stroke patient sample the prevalence of left sided stroke was 39.02%, 41.8% had right sided stroke and 19.1% had bilateral changes.

Hyponatremia evaluation

Out of 246 patients, 47 patients (19.1%) developed hyponatremia (95% confidence interval (CI): 14.39, 24.58). The mean day of development of hyponatremia was 1.81days (SD=1.73). The mean of the serum Na^+ was 130.1mmol/l (SD =3.46) in the hyponatremic group and it was 136.72mmol/l (SD=3.3) in non-hyponatremic group (P= <0.001). There was a statistical difference of age and admission Glasgow Coma Scale (GCS) score between the hyponatremic and non-hyponatremic group (Table 1).

Outcome evaluation

Mortality

In-hospital deaths were 29 (11.7%) out of the total population. Out of 29 there were 8 deaths with hyponatremia. There was a total of 66 (26.8%) deaths at the end of the 70 days follow up period. It comprised of 19 deaths with hyponatremia. There was no association between the presence of hyponatremia and in-hospital mortality (Odds Ratio (OR) =1.73; 95% CI: 0.71, 4.21; P = 0.22). However, there was a significant two fold increase in early mortality in the hyponatremic group compared to the non-hyponatremic group (OR= 2.08; 95% CI: 1.05, 4.1; P = 0.034).

Kaplan Meier survival curve analysis showed better chance of survival in the non-hyponatremic group compared to the hyponatremic group (Figure 1). Log rank test reveals a significant difference regarding the survival between the hyponatremic and the non-hyponatremic groups (P = 0.02). Further, the cox-regression analysis indicates a hazards ratio of 1.91 in patients with hyponatremia compared to the non-hyponatremic group (95% CI: 1.12, 3.27; P = 0.02).

Table 1: Comparison of the characteristics of the hyponatremic and non hyponatremic group

Stroke Patients (*n*-246)	**Hyponatremia (*n*-47)**	**Non- hyponatremia (*n*-199)**	**P**
Age (mean)	71.65 (SD=11.00)	67.16 (SD =12.80)	**0.03**
Gender			
Male	25(10.16%)	95(38.62%)	0.52
Female	22(8.94%)	104(42.28%)	
Alcohol abuse	17(6.91%)	71(28.86%)	0.95
Smoking	13(5.28%)	54(21.95%)	0.94
Comorbidities			
Hypertension	29(11.79%)	110(44.72%)	0.42
Diabetes mellitus	14(5.69%)	62(25.20%)	0.86
Dyslipidemia	7(2.85%)	25(10.16%)	0.64
Hypothyroidism	3(1.22%)	6(2.44%)	0.38
Stroke type			
Ischaemic	36(14.63%)	160(65.04%)	0.55
Haemorrhagic	11(4.47%)	39(15.85%)	
Side of stroke			
Left	18(7.32%)	78(31.71%)	
Right	16(6.5%)	87(35.37%)	0.21
Bilateral	13 5.28%)	34(13.82%)	
Admission GCS[a]	12.82 (SD =2.32)	13.76 (SD =2.32)	**0.01**
Systolic blood pressure mmHg	153.46 (SD=31.91)	158.9 (SD =33.77)	0.39
Diastolic blood pressure mmHg	88.61 (SD =19.20)	91.66 (SD =19.25)	0.16

[a]Glasgow coma scale score, [b]Fisher's exact test or Pearson chi square test and student t-test or Mann Whitney u test were performed to obtain the results, [c]Bold indicates statistical significance

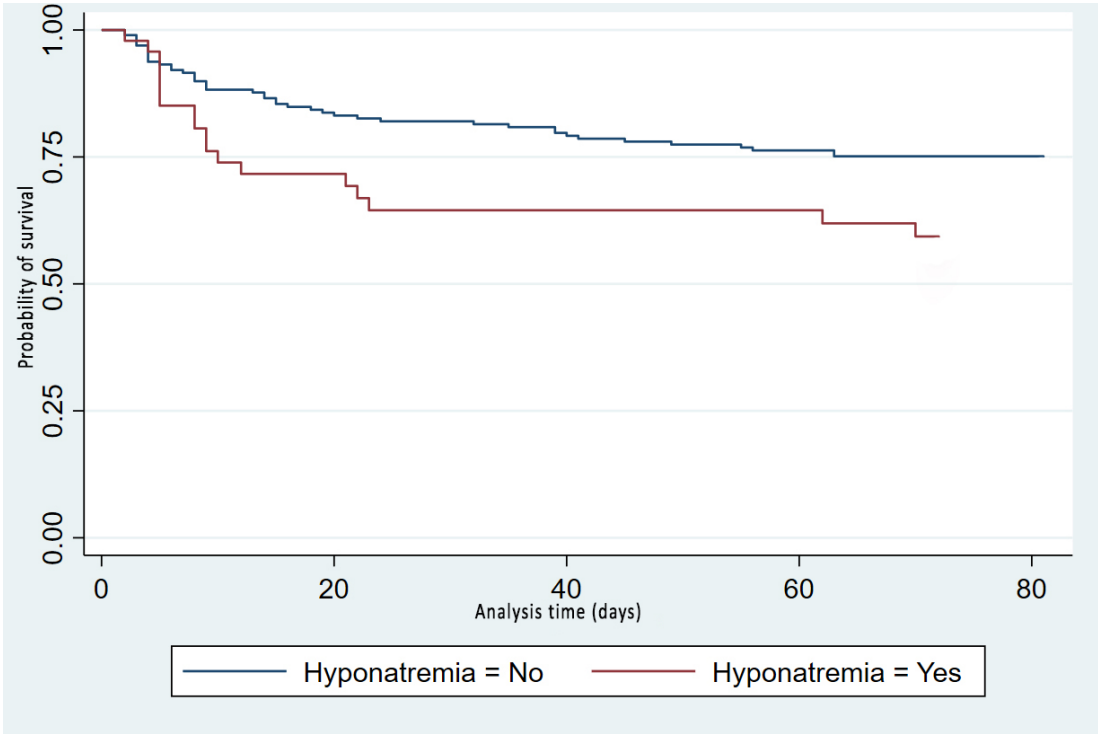

Figure. 1 Kaplan- Meier survival curve in patients with hyponatremia and non-hyponatremia

Length of hospital stay

The mean day of hospital duration in the hyponatremia group was 5.6 days (SD =3.76: Min-1, Max-16 days). In contrast, the mean of length of hospital stay of the non hyponatremic group was 3.2 days (SD=2.09; Min-1, Max-15 days). Thus, the linear regression analysis revealed a significant association between the presence of hyponatremia and the length of hospital stay in stroke patients (β= 2.37; 95% CI: 1.51, 3.23; P= <0.001).

Functional outcome

Majority of the hyponatremic patients ended up having "not favorable" functional outcome at the discharge and at the end of 70 day follow up period (Table 2). There was a significant association between the presence of hyponatremia and the functional outcome at discharge. Thus hyponatremic patients were more vulnerable to end up with "not favorable" functional outcome at discharge (OR=2.59; 95% CI: 1.33, 5.05; P=0.005). This was the same when considering the functional outcome at 70 days even though that association was not significant (OR= 1.69; 95% CI: 0.81, 3.53; P=0.16).

DISCUSSION

The evaluation of outcome of hyponatremia patients was performed based on all types of stroke patients. The majority of patients (79.7%) presented with ischaemic stroke. Of the 246 patients, 47 developed hyponatremia. Patients with advanced age and low GCS are more susceptible to develop hyponatremia. The incidence of in-hospital mortality was 11.7% and an additional 15.1% of patients died during the follow up at 70 days post discharge. The length of hospital stay was longer (mean-5.6 days) in the hyponatremic group compared to the non-hyponatremic group which was mean 3.2 days. Of the 47 hyponatremic patients 31 presented with "not favourable" functional outcome at discharge (P=0.04). However, at the end of 70 days there was no difference between the two groups.

The incidence of hyponatremia in our study group was 19.1%. This finding is consistent with Natarajan *et al*, which reported incidence of hyponatremia as 20%.[14] However some studies showed a higher hyponatremia incidence as high as 54%.[15] In our study majority of hyponatremic patients had ischaemic stroke (76.6%). This finding is supported by a previous study which concluded that the incidence of ischaemic stroke is higher among stroke patients.[16]

Table 2: Association between hyponatremia and functional outcome

Presence of hyponatremia	Functional outcome (MRS score)[a]							
	Functional outcome at discharge (*n*-246)				Functional outcome after 70 days (*n*-188)			
	Favourable		Not Favourable		Favourable		Not Favourable	
YES	16	6.5%	31	12.6%	16	8.5%	22	11.7%
NO	114	46.3%	85	34.5%	45	24%	105	55.9%

[a] Modified Rankin Score

We could not find a significant association between the presence of hyponatremia and in hospital mortality even though hyponatremic patients are more susceptible to death which is depicted by an OR of 1.73. However, a study done on 464 spontaneous intracerebral haemorrhage patients has shown that hyponatremia acts as an independent predictor of in-hospital mortality.[13]Furthermore, when evaluating the association of hyponatremia and early mortality, it turned out be a significant association with an OR of 2.08 (P=0.034). This is supported by another study done on 224 stroke patients which revealed that hyponatremia is significantly associated with early mortality (mortality after 30 days).[15] Moreover it concluded that hyponatremia is an independent predictor of early mortality (OR=7.282; 95% CI: 3.211, 16.513; P =<0.001). A similar association between hyponatremia and short term mortality was found in a study done using on 234 haemorrhagic stroke patients. [17]

Kaplan Meier survival analysis has shown that the hyponatremic group had poor survival compared to non-hyponatremic group. According to the curve, most deaths occur between day 5 and day 20 in the hyponatremic group. However, the mean day of the length of hospital stay in the hyponatremic group was 5.6 days. Therefore, it seems that most of the hyponatremic deaths occur soon after they were discharged from the hospital. Hence, it is recommended to closely observe the hyponatremic patients during the high risk period by increasing the frequency of hospital clinic visits.

According to our results, patients who developed hyponatremia stayed longer in hospitals compared to the non hyponatremic group. There is enough evidence in the literature that is consistent with this finding. One such study was done on spontaneous intracerebral haemorrhagic patients which revealed that the mean of the hospital stay in the hyponatremic group was 14 days whereas it was 6 days in non hyponatremic group (p=<0.001).[18] Another study on ischaemic stroke patients also concluded that hyponatremic patients had delayed discharge compared with non hyponatremic group (p= 0.004). [11]

One study that investigated the dyselectrolytemia in stroke patients has reported that the electrolyte status is not associated with the functional outcome of the patients.[19] However, our study showed that hyponatremic patients were more vulnerable to result in unfavorable functional outcome. However, there is an improvement of the functional outcome at the end of 70 days and it may be due to the gradual improvement of the patient with time.

Undoubtedly, hyponatremia is associated with adverse outcomes. Therefore, all the stroke patients should have their electrolyte value evaluated. Every effort should be made to identify the aetiology of hyponatremia and appropriate management commenced.[20] Taking in consideration the age of the patients, steps should be taken to correct the electrolyte levels at the onset of stroke. [21]

In conclusion, hyponatremia is associated with early mortality in stroke patients. Therefore, hyponatremia should be detected without any delay and corrective management given promptly. Hyponatremia is associated with increased length of hospital stay and unfavorable functional outcome at discharge. Most patients seem to succumb after they have been discharged from the hospital and thus a system to monitor their wellbeing after discharge is required.

DISCLOSURE

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