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Comparative Study of Syndrome of Inappropriate Antidiuretic Hormone Secretion and Cerebral Salt Wasting Syndrome in Stroke Patients

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Abstract:

Background: *Hyponatremia is a common finding after stroke and can be caused by either cerebral salt-wasting syndrome (CSWS) or syndrome of inappropriate antidiuretic hormone secretion (SIADH). Distinguishing between these two entities can be difficult because they have similar manifestations, including hyponatremia, serum hypo-osmolality, and high urine osmolality.* ***Objectives:*** *The study aimed to determine the differences in frequency, clinical profile, and outcome of CSWS and SIADH among stroke patients with hyponatremia admitted to a Neurology department of a tertiary teaching hospital in Bangladesh.* ***Methods:*** *One hundred and three patients with stroke having hyponatremia from the Department of Neurology of Chittagong Medical College Hospital were included in the study. Based on the clinical and laboratory parameters the type of hyponatremia (CSWS or SIADH) was determined. In-hospital and 30-day outcome were compared between patients with CSWS and SIADH.* ***Results:*** *Out of 103 patients, 65 (63.1%) had SIADH and 38 (36.9%) had CSWS. The proportion of patients with ischemic stroke was higher in the SIADH group than in the CSW group (90.8% versus 60.5%, p<0.001). The median (IQR) GCS was comparatively lower in patients with CSWS [10 (8-12)] than the patients with SIADH [11 (9-13)] (p=0.044). The median (IQR) stay in the hospital for the patients with SIADH was shorter [5.0 (4.0-9.0) days] than the in the patients with CSWS [8.0 (6.8-12.3) days] (p=0.001). At 30 days, out of 97 assessed patients, the mortality rate was 6.6% and 38.9%, respectively, in patients with SIADH and CSWS (p<0.001). Patients with CSWS were 8.67 times more likely to die within 30-days than the patients who had hyponatremia due to SIADH (OR: 8.67, 95% CI:2.22-33.75, p=0.002).* ***Conclusions:*** *Hyponatremia have impact on stroke outcome, mainly when caused by CSWS. Therefore, it requires close monitoring, accurate diagnosis, and prompt treatment.*

Keywords: *Hyponatremia, Syndrome of Inappropriate Anti-Diuretic Hormone, Cerebral Salt Wasting, stroke, outcome.*

Introduction

Hyponatremia is frequently observed in patients with stroke either on admission (3.9- 45.3%) or during their hospital stay (40-45%), which may increase the risk of brain edema, thereby seizure, mass effect, and death.1 Hyponatremia may result

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from medications given for the associated comorbidities in stroke patients, inappropriate administration of intravenous fluids, poor solute intake, vomiting, and infections, or stroke-related therapies like an osmotic agent.1,2 Stroke-related causes of hyponatremia are conditions related to strokes, such as secondary adrenal insufficiency due to pituitary ischemia or hemorrhage, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and cerebral salt-wasting syndrome (CSWS).[2]

Making the distinction between SIADH and CSWS is vital as the treatment for the two conditions is different. SIADH is treated by restricting fluids and drugs such as the oral vasopressin antagonist tolvaptan. CSWS is managed by treating the underlying cause, replacing the volume with normal or hypertonic saline, administering sodium, and taking medications like fludrocorti- sone.[1] The frequency of CSWS and SIADH varies among studies, but the influence of CSWS on stroke outcomes is significant- ly worse than SIADH.[3-7]

However, the diagnoses of SIADH and CSWS are still confusing due to overlapping clinical symptoms and laboratory findings.8.9 There is a scarcity of prospective studies that have evaluated the frequency and severity of SIADH and CSWS and their outcomes on stroke patients from Bangladesh, especially from public tertiary healthcare settings where many stroke patients are managed routinely. Therefore, the present study aimed to observe the frequency of SIADH versus CSWS and to study the short-term mortality, morbidity, and discharge disposition among the two entities in patients with newly diagnosed stroke admitted to a tertiary hospital in Bangladesh.

Methods

This prospective analytic study was conducted in the Department of Neurology and Neurosurgery, Chattogram Medical College Hospital (CMCH), Chattogram, Bangladesh, from June 2021 to May 2022. The study protocol was approved by the ethical review committee of Chittagong Medical College, and written informed consent was taken from the caregivers of the patients prior to the commencement of the study. Stroke patients admitted within seven days of stroke onset having serum sodium level <135 mmol/l were included in the study. Patients with vomiting, diarrhea, pneumonia, renal impairment, thyroid dysfunction and features suggestive of adrenal insufficiency, on Diuretics, Mannitol, SSRI, TCA, Antipsychotic, NSAID, Carbamazepine were excluded.

All selected patients were examined and investigated for the assessment of extracellular fluid volume status in order to differen- tiate SIADH from CSW syndrome. CSWS was diagnosed on the basis of clinical (dry mucous membrane, tachycardia, hypoten- sion, negative fluid balance, high urine output) and laboratory evidence (raised hematocrit, hemoglobin or blood urea) of hypo-volemia.9,10 SIADH was considered on the absence of above mentioned clinical and laboratory evidence of hypovolemia.[10,11]

Upon evaluation of the cause of hyponatremia patients were treated as per the standard protocol, that is, fluid restriction in case of SIADH and intravenous normal saline and sodium administration in case of suspected CSWS. Then alternate day serum sodium was measured until normalization. Short-term follow-up of the patient's outcome till discharge/ death and after 30-day (by telephonic interview) was done to see whether the type of hyponatremia could significantly affect the outcome of the patient.

Data were analyzed using SPSS 23.0. Continuous data were expressed as mean ± standard deviation (SD) for normally distrib- uted data or median and 25%–75% interquartile range (IQR) for non-normally distributed data. Categorical variables were presented as frequency (percentages) or proportions. The Independent t-test was used to analyze normally distributed continu- ous variables, while Mann–Whitney U- test was used for non-normally distributed continuous variables. Categorical variables were compared using the Chi-square test/ Fishers exact test. The independent factor for 30-days mortality was determined by binary logistic regression analysis, and the results were expressed as odds ratio (OR) and 95% confidence interval (CI) of OR. $P < 0.05$ was considered statistically significant.

Results

During the study period, 103 hospitalized patients with stroke having hyponatremia were included in the study. The mean age of the patients was 65.8 (±11.4) years, and more than two-thirds were male (67%). The stroke type was predominantly ischemic (78.6%). SIADH was a more common cause of hyponatremia (63.1%) in the study. Table I compared different clinical and biochemical parameters of stroke patients with SIADH and those with CSWS. It shows that the mean age of the CSWS group patients was higher than those in the SIADH group without any statistical significance. Males outnumbered females in both groups. The proportion of patients with ischemic stroke was significantly higher in the SIADH group than in the CSW group. The median GCS was comparatively lower in patients with CSWS than with SIADH. Serum and urinary sodium levels were similar in SIADH and CSWS groups (Table I).

Thirty-day mortality data were missing for six patients due to loss of follow-up. The median length of hospital stay was 7 (4-10) days. The in-hospital mortality rate was 2.9%, and the 30-days mortality rate was 18.6%. The median (IQR) stay in the hospital for the patients with SIADH was 5.0 (4.0-9.0) days, and for the patients with CSWS, it was 8.0 (6.8-12.3) days. The difference was highly significant statistically (p=0.001). The in-hospital mortality rate was 1.5% and 5.3%, respectively, in patients with SIADH and CSWS, and the difference was not significant statistically (p=0.535). At 30 days, out of 97 assessed patients, the mortality rate was 6.6% and 38.9%, respectively, in patients with SIADH and CSWS, and the difference was highly significant statistically (p<0.001) (Figure 1).

Table I

Clinical and biochemical characteristics of the patients stratified by the type of hyponatremia (n=103)

Variables	Hyponatremia due to		P value
	SIADH (n=65)	CSWS (n=38)	
Age, years	64.7±11.9	67.5±10.3	0.244†
Sex			
Male	40 (61.5)	29 (76.3)	0.124*
Female	25 (38.5)	9 (23.7)	
Type of stroke			
Ischemic	59 (90.8)	23 (60.5)	<0.001*
Hemorrhagic	6 (9.2)	15 (39.5)	
Clinical features			
Dehydration	0 (0)	33(86)	<0.001*
Hypotension	2 (3.1)	11 (28.9)	<0.001*
Tachycardia	3 (4.6)	28 (73.7)	<0.001*
High urine output	0 (0)	12 (31.6)	<0.001*
Negative fluid balance	0 (0)	31(81)	<0.001*
Glasgow coma scale	11 (9-13)	10 (8-12)	0.044‡
Biochemical parameters			
Hematocrit, %	35.7±5.5	38.3±4.6	0.017†
Haemoglobin, gm/dl	12.1±1.9	12.8±1.7	0.081†
S. sodium, mmol/L	125.2±5.9	123.1±20.6	0.444†
Blood urea, mg/dl	27.7±8.2	61.6±15.9	<0.001†
S. creatinine, mg/dl	1.0±0.2	1.2±0.2	0.001†
S. osmolality,	262.9±11.4	270.0±8.3	<0.001†
U osmolality	408.4±117.8	573.1±144.2	<0.001†
U sodium, meq/L	61.0 (42.0-84.5)	65.0 (44.8-78.5)	0.218‡

Data were expressed as either mean±SD, n (%), or median (Interquartile range);
†Independent sample t-test; ‡Mann-Whitney U test. *Chi-square test;

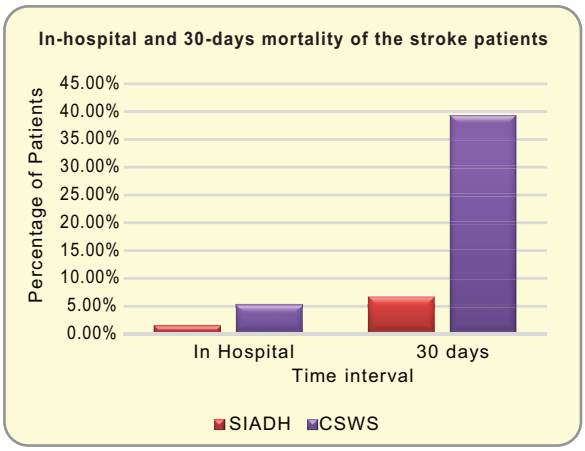

Figure 1: *In-hospital and 30-days mortality of the stroke patients stratified by type of hyponatremi*

In univariate analysis, dehydration, tachycardia, high urine output, negative fluid balance, GCS, blood urea, and urine osmolality were significantly associated with 30- days mortality in the study (Table II). The proportion of patients with dehydration, tachycardia, high urine output, and negative fluid balance was higher in the expired group than the survived group. The median GCS was lower and blood urea on admission was higher among the expired than the survived patients. Table III shows that, after adjusting for age, sex, stroke type, GCS, and serum sodium level, type of hyponatremia had an independent association with 30-days mortality. Stroke patients who had hyponatremia due to CSWS were 8.67 times more likely to die within 30-days than those who had hyponatremia due to SIADH (OR: 8.67, 95% CI:2.22-33.75, p=0.002).

Table II

Association between the clinical and biochemical factors and 30-day mortality in the studied patients (n=97)

Variables	30-day mortality		P value
	Survived (n=79)	Expired (n=18)	
Age, years	65.1±11.7	67.5±11.1	0.425†
Sex	50 (63.3)	15 (83.3)	
Male	29 (36.7)	3 (16.7)	0.103*
FemaleStroke type			
Ischemic	63 (79.7)	13 (72.2)	0.484*
Hemorrhagic	16 (20.3)	5 (27.8)	
Dehydration	20 (25.31)	11 (61.11)	<0.001*
Hypotension	9 (11.4)	3 (16.7)	0.540*
Tachycardia	17 (21.5)	11 (61.1)	<0.001*
High urine output	5 (6.3)	7 (38.9)	<0.001*
Negative fluid balance	18 (22.78)	11(61.1)	<0.001*
Glasgow coma scale	11 (9-13)	9 (7-13)	<0.001‡
Hematocrit, %	36.6±5.6	38.2±4.2	0.242†
Haemoglobin, mg/dl	12.3±1.9	12.9±1.6	0.237†
Serum sodium, meq/L	123.9±14.9	125.5±5.2	0.652†
Blood urea, mg/dl	36.5±18.9	57.8±17.9	0.001†
S. creatinine, mg/dl	1.0±0.2	1.1±0.2	0.210†
S. osmolality, mOsmol/kg	264.9±11.2	266.9±10.9	0.499†
U. osmolality, mOsmol/kg	457.3±153.8	544.0±133.2	0.030†
U. sodium, meq/L	63.0 (45.0-80.0)	61.5 (44.0-98.3)	0.218‡

Data were expressed as frequency (%), or mean±SD or median (Interquartile range); †Independent sample t-test;
‡Mann-Whitney U test; *Chi-square test

Table III

Factors associated with 30-day mortality in multivariate binary logistic regression analysis

Variables	B	S.E.	Wald	OR	95% CI for OR		P-value
					Lower	Upper	
CSWS vs SIADH	2.160	.693	9.710	8.67	2.22	33.75	0.002
Age, years	-.005	.029	0.025	0.99	0.94	1.05	0.875
Male vs female	-.703	.735	0.915	0.49	0.12	2.09	0.339
Ischemic vs hemorrhagic	-.536	.730	0.539	0.58	0.14	2.45	0.463
GCS	-.144	.123	1.372	0.86	0.68	1.10	0.241
Serum Na, meq/L	.014	.026	0.309	1.01	0.96	1.07	0.578

OR: Odds ratio; CI: Conndence interval

Discussion:

In the present study, SIADH was a more common cause of hyponatremia (63.1%). Previous studies found that SIADH may be the predominant cause of stroke-associated hyponatremia, especially in hemorrhagic stroke patients.[5,7] However, two recent studies showed the opposite result; where CSWS was the most common cause of hyponatremia.[3,12]

The proportion of patients with ischemic stroke was significantly higher in the SIADH group than in the CSWS group. In the previous study from Bangladesh frequency of CSWS was relatively higher in hemorrhagic stroke and SIADH in ischemic stroke but did not reach the level of statistical significance.4 In the study by Babuanand et al. 83% had an ischemic stroke among SIADH patients, and 17% had an intracerebral haemorrhage.[13] Another study demonstrated an equal prevalence of SIADH among ischemic and hemorrhagic stroke patients (69.8% and 68.6%, respectively).5 Bade and his colleague reported that stroke was the most common cause of SIADH, and intracerebral bleeding was found to be the most common cause of CSWS.6 Still others reported a higher incidence of SIADH (58.5%) as compared to CSWS (41.5%) in patients with hemorrhagic stroke.[14] The variability in the frequency may reflect different types of hospitals and the clinical diversity of the patients in other studies.

As expected, the present study demonstrated significant differences in the clinical presentation between patients with SIADH and CSWS. Patients with SIADH were typically euvolemic, as evident by the absence of dehydration, hypotension, and tachycardia, whereas patients with CSWS are hypovolemic and appear dehydrated (86%). Most of the patients in the CSWS group had tachycardia and negative fluid balance. The median GCS was comparatively lower in patients with CSWS than the patients with SIADH (p=0.044). As SIADH is a volume-expanded state and CSWS is a volume-depleted state, these differences in clinical presentations were noticeable.[15]

Different laboratory parameters were used to differentiate between SIADH and CSWS.9 The present study demonstrated that serum and urinary sodium levels were similar in SIADH and CSWS groups. In contrast, the mean hematocrit, blood urea, serum creatinine, serum and urinary osmolality were significantly higher in the CSWS group than in the SIADH group. There was a statistically significant difference in urinary Na + levels, serum osmolality and urinary osmolality between the etiologies of hyponatremia in the study.12 Another study has shown a significant difference (P = 0.001) in urinary Na + between SIADH and CSWS.16 However, most of the literature suggests that these parameters could not differentiate the etiologies of hyponatremia and proper evaluation of the extracellular volume is mandatory.[17]

The present study demonstrated that, at 30 days, out of 97 assessed patients, the mortality rate was 6.6% and 38.9%, respectively, in patients with SIADH and CSWS, and the difference was highly significant statistically. Stroke patients who had hyponatremia due to CSWS were 8.67 times more likely to die within 30 days than those who had hyponatremia due to SIADH (OR: 8.67, 95% CI:2.22-33.75, p=0.002). Previous studies consistently reported that CSWS was significantly associated with a higher death rate.5,13,14 In the present study, stroke types had no significant

association with 30-day mortality. Like the mortality rate, stroke patients with CSWS had an unfavorable outcome in terms of length of hospital stay in the present study.

Conclusion

In conclusion, the frequency of SIADH was higher than the CSWS. CSWS was an independent predictor of short-term mortality in stroke. It also predisposes to a longer duration of hospital stay. It can be recommended from this study that in limited resource setting, clinical parameters like dehydration and negative fluid balance as well as laboratory measurement of blood urea would be valuable in differentiating SIADH and CSWS in stroke patients.

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