

Hyponatremia In Ischemic Stroke Patients And Its Relationship To Clinical Outcomes In Such Patients

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Abstract

Objective: To quantify the frequency of hyponatremia in patients with ischemic stroke, and to compare patient outcomes according to the frequency and severity of hyponatremia.

Methods: A descriptive cross-sectional study was carried out for a period of six months (11-12-2020 to 10-06-2021) at the department of Medicine and Neurology, PIMS, Islamabad. A total of one hundred and seventy-nine (n=179) acute ischemic stroke patients of either gender between age 16-80 years were enrolled. Stroke severity was measured through the National Institute of Health stroke scale score and serum sodium was measured at the time of admission in all patients to diagnose hyponatremia. All patients with hemorrhagic stroke, having previous history of stroke, recent head injury, CNS infection, already using sodium lowering diuretics, or with end-stage diseases like Heart failure, chronic kidney disease and decompensated liver diseases were excluded from the study. Primary outcome measures were in-hospital mortality and duration of hospital stay (LOS).

Results: Hyponatremia was found in 30.1% (n=54/179) patients at the time of admission. Overall, in-hospital mortality in the study population was 11.7% (n=21/179) and the mean length of hospital stay was 6.9 days $\pm$ 2.5 SD. Mortality was significantly higher in patients with severe stroke (based on NIHSS score) (P=0.010) and severe hyponatremia (serum Na levels below 120 mEq/litre) (P=0.001). Mean hospital stay was also significantly longer in patients with severe stroke based on NIHSS score (P=0.001) and severe hyponatremia (P=0.048).

Conclusions: A remarkable proportion (30.1%) of acute ischemic stroke patients had hyponatremia. In-hospital mortality was significantly higher and the length of hospital stay LOS was significantly longer in patients with severe stroke and severe hyponatremia.

Keywords: Hyponatremia, Ischemic stroke.

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1. Introduction

Stroke is a significant healthcare issue in the regions of South, East, and South-East Asia. The Asian area, being home to a major proportion of the global population residing in developing nations, is expected to bear the greatest burden of stroke on a worldwide scale.¹ Stroke is the second most common cause of death and the third most common cause of death and disability worldwide.² Pakistan shares a significant weight of this debilitating illness contributing towards an exponential consumption of assets, finances, well-being administrations and the economy overall.³ There are many risk factors associated with the occurrence of stroke and death, including hypertension, cigarette smoking, electrolyte imbalance, hyperlipidemia, and diabetes.^{4,5} The condition of hyponatremia is of significant concern because of its high prevalence among patients with acute stroke and its association with unfavourable outcomes.⁶ Hyponatremia is defined as a medical

condition in which the concentration of sodium in the blood falls below the threshold of 135 mEq/L. Hyponatremia in the stroke is often characterized by hypo osmolality and may be attributed to either the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or cerebral salt wasting syndrome. SIADH is characterized by euvolemia or increased ECF volume with normal hematocrit and decreased BUN/ creatinine ratio.⁷ Cerebral salt wasting (CSW) syndrome is less often seen compared to a syndrome of inappropriate antidiuretic hormone secretion (SIADH). The other potential causes of hyponatremia may include adherence to a low-sodium diet as a means of managing hypertension, the use of anti-hypertensive medications such as diuretics, and the presence of infections. This phenomenon induces alterations in the patient's sensorium and may also render them susceptible to experiencing seizures.⁸ In CSW compared to SIADH there is decreased ECF volume and increased hematocrit and BUN.⁷



Several studies have revealed that hyponatremia might have an impact on the outcome in stroke patients. In a study conducted by Kidwai A et.al, it was observed that patients exhibited varying degrees of hyponatremia, with mild, moderate, and severe cases accounting for 60%, 29.1%, and 10.9% of the patient population, respectively. Additionally, the study found that 63 patients (57.2%) displayed symptoms consistent with the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), while 38 patients (34.5%) exhibited characteristics indicative of Cerebral Salt Wasting (CSW) among those with hyponatremia. The overall mortality rate among the patients was recorded as 14.5%.⁶ In a study conducted by Saleem S et al., it was shown that the presence of hyponatremia was associated with an elevated risk of death due to stroke.⁷ According to the research conducted by Ehtesham M et.al, the incidence of hyponatremia in stroke has been seen to range from 11% to 35%.⁸ Meta-analysis by Chen Z concludes that hyponatremia has a significant prognostic value for short- and long-term prognosis to stroke patients.⁹

This research aims to measure the extent of hyponatremia among stroke patients and evaluate its impact on patient outcomes, specifically in terms of hospital time and fatality rates. The gathered information if comes out to be significant would help in devising our local guidelines to identify and manage these patients at an earlier stage. This would ultimately result in improved outcomes for these patients.

The main objective was to quantify the prevalence of hyponatremia in patients with ischemic stroke and to compare patient outcomes in terms of hospital stay and fatality according to the frequency and severity of hyponatremia.

2. Materials & Methods

In a descriptive cross-sectional study conducted for six months between December 2020 and May 2021 the sample size was calculated by WHO standards and 179 patients were included, keeping a confidence level of 95%, an anticipated population proportion of 35%, and an absolute precision of 7%. Non-probability Consecutive sampling was done to include patients in the study. Newly diagnosed cases of Ischemic stroke, aged, 16-80 years of both genders were included in the study. Ischemic stroke was defined as individuals who

sought medical attention within a 72-hour timeframe after the initiation of observable indications, such as facial, arm, or leg numbness or weakness, particularly on a unilateral side of the body. The manifestation of abrupt cognitive disarray, impaired verbal articulation, or challenges in comprehending spoken language. The sudden onset of visual impairment in either one or both eyes. The presence of sudden difficulties in walking, dizziness, loss of balance, or impaired coordination, accompanied by indications of ischemia, can be observed through the examination of brain CT and MRI scans. These scans reveal the existence of lesions as hyper-intense areas on Diffusion Weighted Images (DWI) and hypointense areas on Apparent Diffusion Coefficient (ADC) maps. Alternatively, evidence of ischemia can also be identified through CT scans of the brain, which may exhibit wedge-shaped hypodensity, loss of grey-white matter, and effacement of sulci and gyri.

All patients with hemorrhagic stroke, having a previous history of stroke, recent head injury CNS infection, already using sodium lowering drugs like diuretics or with end-stage diseases like Heart failure, chronic kidney disease or decompensated liver disease were excluded from the sample.

After obtaining ethical approval from the hospital and obtaining informed consent, 179 patients fulfilling the selection criteria were enrolled after taking informed consent. Detailed history and clinical examination were carried out by the researchers. Stroke severity was determined by NIHSS score. NIHSS is a comprehensive assessment tool consisting of 15 questions that are used to evaluate the extent of damage caused by a stroke. The summation of item ratings resulted in a total score that ranged from 0 to 42, with higher numbers indicating greater severity of the stroke. The stroke was classified as severe if the score was more than 16, moderate if the score ranged from 5 to 16, and mild if the score was between 0 and 4. Blood samples for serum sodium were obtained at admission in a sterile manner and were sent to the hospital laboratory. Hyponatremia was measured at the time of admission and labelled if Serum sodium came out to be <135mEq/L. Mild hyponatremia: Serum Sodium levels between 130 -134 mEq/L Moderate Hyponatremia: Serum Sodium between 120-129 mEq/L Severe Hyponatremia: Serum Sodium less than 120 mEq/L. Outcomes in terms of hospital stay and death during the hospital stay were noted. All this information was recorded on Performa.

Data was analyzed by SPSS version 23. In-hospital mortality was described as frequency and percentages. NIHSS score, serum sodium levels and length of hospital stay were described as mean and standard deviation. P value was used to know statistical significance.

3. Results

A total of 179 patients were included. Out of which 103(57.5%) were males and 76(42.5%) were females. 30.2% of patients were diabetics and 27.4% had hypertension. The mean age was 62.3 ± 13.3 years. 90(50.3%) patients duration of symptoms was less than 12 hours and 89(49.7%) duration of symptoms was of more than 12 hours. Mean sodium levels were 134.3 ± 5.4 mEq/L in the study population. 13.4% of patients had a mild stroke; 65.9% had moderate stroke and 20.7% had severe stroke based on NIHSS score. Hyponatremia was found in 30.1% of patients at the time of admission. Of which 16.2% had mild hyponatremia; 9.5% and 4.5% had moderate and severe hyponatremia respectively. (Table 1).

Table 1: Variables distribution in the study population

		Frequency	Percent
Gender	Males	103	57.5
	Females	76	42.5
Age	16-50 Years	35	19.6
	51-80 Years	144	80.4
DM	Present	54	30.2
	Absent	125	69.8
HTN	Present	49	27.4
	Absent	130	72.6
IHD	Present	23	12.8
	Absent	156	87.2
Duration	≤ 12 Hours	90	50.3
	> 12 Hours	89	49.7
Severity Of Stroke	Mild	24	13.4
	Moderate	118	65.9
	Severe	37	20.7
Severity Of Hyponatremia	None	125	69.8
	Mild Hyponatremia	29	16.2
	Moderate Hyponatremia	17	9.5
	Severe Hyponatremia	8	4.5
In-Hospital Mortality	Present	21	11.7
	Absent	158	88.3

Mortality was significantly higher in patients with severe stroke ($P=0.010$) and severe hyponatremia ($P=0.001$). No significant difference was observed in

mortality rate across all other strata ($P>0.05$ in all cases). Table 2

Table 2: Mortality in different effect modifiers groups

Variables		Mortality		P-Value
		Present	Absent	
Age Groups	16-50 Years	6	29	0.267
		17.1%	82.9%	
	51-80 Years	15	129	
		10.4%	89.6%	
DM	Present	4	50	0.237
		7.4%	92.6%	
	Absent	17	108	
		13.6%	86.4%	
HTN	Present	9	40	0.090
		18.4%	81.6%	
	Absent	12	118	
		9.2%	90.8%	
Symptom Duration	≤ 12 Hours	10	80	0.795
		11.1%	88.9%	
	>12 Hours	11	78	
		12.4%	87.6%	
Severity Of Stroke	Mild	0	24	0.010
		0.0%	100.0%	
	Moderate	12	106	
		10.2%	89.8%	
Severity Of Hyponatremia	Severe	9	28	0.001
		24.3%	75.7%	
	None	3	122	
		2.4%	97.6%	
	Mild	3	26	
		10.3%	89.7%	
	Moderate	8	9	
		47.1%	52.9%	
	Severe	7	1	
		87.5%	12.5%	

The mean length of hospital stay (LOS) was 6.9 ± 2.5 days. Mean LOS was significantly longer in patients with severe stroke ($P=0.001$) with severe hyponatremia ($P=0.048$). No significant difference was observed in mortality rate across all other strata ($P>0.05$ in all cases). Table 3.

Table 3: Mean length of hospital stay in different effect modifiers groups

VARIABLES		N	MEAN LOS (DAYS)	P-Value
Age Groups	16-50 Years	35	7.54 ± 2.54	0.112
	51-80 Years	144	6.78 ± 2.52	
Gender	Males	103	7.13 ± 2.59	0.236
	Females	76	6.67 ± 2.44	
DM	Present	54	6.29 ± 2.57	0.203
	Absent	125	7.21 ± 2.48	
HTN	Present	49	7.49 ± 2.59	0.071
	Absent	130	6.72 ± 2.49	
IHD	Present	23	7.57 ± 3.17	0.200
	Absent	156	6.84 ± 2.42	
Symptom Duration	≤12 Hours	90	6.66 ± 2.47	0.141
	>12 Hours	89	7.21 ± 2.57	
Stroke Severity	Mild	24	2.46 ± 0.72	0.001
	Moderate	118	6.89 ± 1.04	
	Severe	37	9.97 ± 2.24	
Hyponatremia	None	125	6.6 ± 2.47	0.048
	Mild	29	7.59 ± 2.42	
	Moderate	17	7.93 ± 2.87	
	Severe	8	8.13 ± 2.34	

4. Discussion

The prevalence of hyponatremia in patients with acute central nervous system disorders is notably high, making it the predominant electrolyte abnormality seen in neurological critical care units. The condition may manifest with clinical manifestations that resemble those of a neurological disorder and may exacerbate pre-existing neurological impairments. At now, there exists a dearth of evidence about the correlation between hyponatremia and the prognosis of acute ischemic stroke in Pakistan. The objective of this research was to investigate the occurrence of hyponatremia and its potential correlation with in-hospital mortality and duration of hospitalisation among individuals diagnosed with acute ischemic stroke. A total of one hundred and seventy-nine (n=179) acute ischemic stroke patients of either gender between age 16-80 years were enrolled. Stroke severity was measured through NHISS score and serum sodium was measured in all patients to diagnose hyponatremia. Primary outcome measures were in-hospital mortality and duration of hospital stay. Our study results showed that Mean serum sodium was 134.3 ± 5.4 mEq/L in the study population. Hyponatremia was found in 30.1% (n=54/179) patients at the time of admission. Overall, in-hospital mortality in the study population was 11.7% (n=21/179) and the mean length of hospital stay was 6.9 days $\pm$ 2.5 SD. Mortality was significantly higher in patients with severe stroke

(P=0.010) and severe hyponatremia (P=0.001). Mean LOS was also significantly longer in patients with severe stroke (P=0.001) and severe hyponatremia (P=0.048).

A study found that although hyponatremia was present in 35% of stroke patients, 67.5% of those people had SIADH and 32.5 had CSWS. Sixty-seven per cent of those with a hemorrhagic stroke had SIADH, but only 33 per cent of those with a CSWS. Ischemic stroke patients were more likely to have SIADH (68.5%) and CSWS (31.5%).¹⁰ In a research conducted in Iraq including patients with hyponatremic stroke, it was shown that 82% of the participants exhibited syndrome of inappropriate antidiuretic hormone secretion (SIADH), whereas the remaining 18% presented with cerebral salt-wasting syndrome (CSWS).¹¹ A study conducted in a tertiary care hospital in Karachi showed mild hyponatremia in 25% of patients 9.8% had moderate hyponatremia only 3.8% had severe hyponatremia.¹²

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is certainly the most relevant, mainly in oncological and hospitalized patients.¹³ One study showed the prevalence rate of stroke patients with hyponatremia was 7.0-59.2%.¹⁴ Karunanandham et al. emphasize that the Syndrome of Inappropriate Antidiuretic Hormone Secretion (21.28%) is the most common cause of hyponatremia in patients with stroke. In addition, he also found that the mean hospital stay was prolonged in the patient with hyponatremia (21 $\pm$ 8.51) vs normonatremia (10 $\pm$ 3.8), P=0.04.¹⁵ Previous studies have also shown that SIADH is a more prevalent cause of hyponatremia when compared to CSWS. Ehtisham et al. (year) conducted research in the local community, wherein they observed that hyponatremia was identified in 34.2% of individuals diagnosed with acute stroke. The research observed a mean blood sodium level of 130.4 ± 3.5 (mEq/L). The most prevalent cause of hyponatremia was SIADH, accounting for 71.1% of cases. These findings align closely with the results of our investigation. Our findings demonstrate a similar trend to that seen by Saleem et al., who conducted a study including 1,000 stroke patients, of whom 353 (35%) had hyponatremia. Among a cohort of 353 patients diagnosed with hyponatremia in the context of stroke, a total of 197 individuals were found to have survived, while 156 people unfortunately succumbed to their condition. Among a cohort of 647 patients who did not present with hyponatremia, a total of 553 patients

were found to have survived whereas 94 patients unfortunately succumbed to their condition.⁸

Rodrigues et al. conducted a comprehensive analysis of 3585 stroke patients, whereby they noticed the occurrence of hyponatremia in 565 individuals or 16% of the overall sample. Patients with hyponatremia had significantly higher scores on the National Institutes of Health Stroke Scale (NIHSS) upon admission ($P = .032$) and at the time of release ($P = .02$).¹⁶ Furthermore, the presence of hyponatremia was shown to be linked with increased death rates during hospitalization ($P = .039$), as well as at the 3-month ($P = .001$) and 12-month follow-up assessments ($P = .001$).

In summary, based on current study results and review of literature on the subject it is evident that hyponatremia is frequently encountered electrolyte imbalance in stroke patients. The primary aetiology of hyponatremia in stroke patients is a syndrome of inappropriate antidiuretic hormone secretion (SIADH), with cerebral salt wasting syndrome (CSWS) being the subsequent leading cause. It is crucial to differentiate between the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and Cerebral Salt Wasting Syndrome (CSWS) since the therapeutic approaches for these two disorders vary. Present study results and several other studies cited in the literature demonstrate that the severity of hyponatremia is associated with early mortality in ischemic stroke patients. The present study has some limitations. Firstly, in the present study, we did not categorize the causes of hyponatremia. We suggest future studies in this regard. Secondly, we only took serum sodium levels at admission as the predictor of mortality and did not take into account further falls in sodium levels during hospital stay. Some studies showed an association between changing serum sodium values during hospital stay with mortality. We suggest future studies in this regard. Lastly, we only measured in-hospital mortality and did not measure the association of hyponatremia with 30-day mortality and neurological deficits. We suggest future studies in this regard.

5. Conclusion

This study results showed a remarkable proportion (30.1%) of acute ischemic stroke patients had hyponatremia. In-hospital mortality was significantly higher and duration of hospital stay was significantly longer in patients with severe stroke and severe hyponatremia.

Institutional Review Board Approval

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Contributions:

M.Z, A.J - Conception of study

- Experimentation/Study Conduction

M.Z, A.J, A.G, M.Y, S.B -

Analysis/Interpretation/Discussion

M.Z, A.J, M.Y - Manuscript Writing

M.Z, A.J, A.G, M.Y, S.B - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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