Original Article

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Internal Medicine Section

Hyponatremia in Patients Admitted with Stroke

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ABSTRACT

Introduction: Many studies have focused on association of serum electrolytes with hypertension. In recent years status of serum sodium have established an important role in the distinguishing the two entities of hyponatremia in Cerebrovascular Accidents (CVA).

Aim: To estimate the serum sodium levels and to determine the incidence and aetiology of electrolyte disturbances in patients with newly diagnosed CVA.

Materials and Methods: This was the cross-sectional study conducted at the tertiary care teaching hospital, Trichy. 202 diagnosed stroke patients were evaluated for presence of hyponatremia. The data was analysed using independent t test using SPSS software 21.

Results: Among the 202 CVA patients, 78 patients (38.61%) presented with hyponatremia. Among the 78 patients, 43 (21.28%) were ascertained as Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH), in which ischemic stroke and haemorrhagic stroke were diagnosed in 31 and 12 patients respectively. Fifteen patients (7.42%) had Cerebral Salt Wasting Syndrome (CSWS), in which 5 patients had ischemic stroke and 10 patients had haemorrhagic stroke. A total of 20 (9.90%) cases had hyponatremia with unknown aetiology. The hospital stay of patients with hyponatremic CVA was more than patients with normal serum sodium level (mean 21 days).

Conclusion: This study shows that hyponatremia was observed in 38.61% of stroke patients. Among hyponatremia stroke cases, 21.28 % had SIADH and 7.42% had CSWS. The hospital stay of hyponatremic CVA patients was longer, hence monitoring of serum sodium is absolutely essential in patients admitted with stroke. Close observation and prompt diagnosis are needed to identify the cause of electrolyte disturbance, because their treatments are completely dissimilar.

Keywords: Cerebral salt wasting syndrome, Cerebro vascular accident, Hyponatremia, Stroke, Syndrome of Inappro

INTRODUCTION

Stroke, also known as cerebrovascular accident is defined as abrupt onset of neurologic deficit that is dogmatic to focal vascular origin [1]. Stroke causes perpetual neurological illness and it is one of the foremost causes of lifelong, incurable disability and fatality. In India, the incidence of stroke is more when compared to western countries [2]. The estimated adjusted prevalence rate of stroke range was 84-262/100,000 in rural and 334-424/100,000 in urban areas [3]. In neurological disorders like stroke, hyponatremia is frequently faced electrolyte disturbance and customarily linked with SIADH and CSWS [4,5].

The inappropriate secretion of Antidiuretic Hormone (ADH) causes hyponatremia in SIADH due to water retention. ADH regulates the water permeability of the collecting tubules and ascending limb of loop of Henle and allows the kidney to reabsorb water or an increase in serum osmolality [6]. In SIADH, ADH is constantly produced despite of the hypotonicity of body fluid. The negative feedback mechanism is lost; hence it is unable to control the ADH secretion and it results in an unsuppressed ADH release into the blood stream. The hypo-osmolality occurs due to dilution of solutes in plasma and results in hyponatremia. CSWS is described by the occurrence of excessive sodium excretion in urine, dehydration and resultant hyponatremia, in patients with intracranial disease, trauma and cerebral lesions [4]. Depletion of blood volume occurs in CSWS instead of volume expansion. The most common cause of CSWS is Subarachnoid Haemorrhage (SAH) [7]. The hyponatremia and decrease in plasma osmolality causes movement of water into the brain causing cerebral oedema which is said to be the adaptive mechanism of osmotic gradient.

The decrease in the serum sodium level in CVA patients warrants the other underlying investigations to pinpoint the diagnosis before the treatment modality is initiated. Some patients may experience the symptoms of hyponatremia much earlier because the hypoosmolality occurs at a faster rate than the brain adaptive mechanism to the electrolyte loss. A differentiation must be done among hypervolemia with normal total body sodium (SIADH) and hypovolemia with disproportionately low total body sodium like CSWS [8]. This differentiation is essential because the therapeutics of these two disorders are dissimilar. There is a scarcity of data and only limited studies had been done regarding the electrolyte disturbances in acute stroke, especially from rural population. The objective of this study was to estimate the serum sodium levels and to determine the incidence and aetiology of hyponatremia in patients with newly diagnosed cerebro-vascular accidents.

MATERIALS AND METHODS

This was the descriptive type of cross-sectional study conducted in the tertiary care teaching hospital, Trichy. The study period was 6 months (January 2017-June 2017). A total of 216 CVA patients were enrolled in the study and 14 patients were excluded due to residual paralysis, patients with head injury, renal failure and liver failure, congested cardiac failure, meningitis, encephalitis, chronic kidney disease, malignancy, gastroenteritis and patients on drugs which affect the electrolyte levels (diuretic or steroid therapy). Hence, 202 patients were included in the study. Diabetic patients presenting with severe hyperglycemia (>300 mg/dl) and hypertriglyceridemia (> 400 mg/dl) were also excluded from the study to avoid the chance of pseudohyponatraemia [9]. Blood pressure was recorded and urine output was measured. A detailed history was elicited for time of the stroke, clinical manifestations, co-morbid diseases, concomitant drug intake and treatment before hospitalization. Patients admitted within 48 hours of the onset of stroke which includes Haemorrhagic CVA, Ischemic CVA and Transient Ischemic Attack (TIA) diagnosed by appropriate imaging, either Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) were included in the study.

Under strict aseptic precautions, 3 mL of venous blood was collected from the CVA patients for the estimation of serum electrolytes. Laboratory assistants were blinded to sample sources and clinical information until the end of the study. Calibration of instruments and reagents had been done daily before the analysis. Serum sodium levels were measured in ion selective electrode (Roche, 9180 Electrolyte analyser). The reference range for serum sodium is 135-145mEq/L. Serum osmolality, urinary sodium and urine osmolality were also measured. The serum osmolality was calculated using the formula: 2(Na)+Glu/18+BUN/2.8. Blood glucose was estimated by Glucose oxidase-Peroxidase (GOD-POD) method. Blood urea was estimated by Glutamate Dehydrogenase (GLDH) method. Blood Urea Nitrogen in mg/dl (BUN) was calculated using the formula, Urea (mg/dl)/2.14. Serum osmolality was measured to differentiate between true and pseudo-hyponatremia in hyponatremia patients. True hyponatremia is defined as those patients with a sodium level of 130 meq/L and Serum osmolality less 275 mosm/kg. The reference range of serum osmolality is 275-295mosm/kg. Serum uric acid was also measured using uricase method. Urine sodium was measured using Ion selective method. Urine sodium >18 mmol/L is diagnostic of SIADH. Urine Specific gravity was also measured. The reference range of specific gravity of urine is 1.005-1.030. Urine osmolality was measured on the random urine specimen. The reference range of urine osmolality is 300-900 mosm/kg. Hyponatremia were categorized as SIADH/CSWS and treated as per the standard protocol. The diagnostic criteria of CSWS are hyponatremia (serum sodium ≤130 mEq/L), urine output ≥3 ml/kg/hr, urine specific gravity ≥1020 and urinary sodium≥100 mEq/L. The definition of SIADH were hyponatremia (serum sodium ≤130 mEq/L), urine output < 3 ml/kg/hr, urine specific gravity≥1020 and urinary sodium concentration > 20 mEq/L [10].

Before entering the study, informed written consent was obtained from the patient/ attenders. Ethical clearance was obtained from Institutional ethical committee. Continuous variables were expressed as mean±standard deviation using Statistical Package for the Social Sciences (SPSS) version 20. The differences between categorical variables among study group were analysed by student t-test. For all analyses, p-values < 0.05 were considered as significant.

RESULTS

Among the study group, 86.64 % were males and 13.36 % were females. Mean age of the study group was 57.5 ranging from 40 to 78 years. Patients with ischemic CVA were significantly older than patients with TIA and haemorrhagic CVA as given in [Table/Fig-1].

Patients with CVA				
Characteristics	Total (n = 202)	Ischemic (n =163)	Haemorrhagic (n = 24)	TIA (n =15)
Sex Male, n *(%)* Female, n *(%)*	 175 (86.63) 27 (13.36)	 151 (92.63) 12 (7.37)	 20 (83.33) 4 (16.66)	 14(93.33) 1(6.67)
Age in years, mean(SD)	57.5 (4.5)	64.8 (5.6)	58.5 (4.9)	49.2 (3.8)
Smokers	119(58.91)	93(44.78)	15(62.5)	11(73.33)
Alcoholic	108(53.46)	79(48.46)	16(66.66)	13(86.66)

[Table/Fig-1]: Demographic characteristics of the study population (n=202).

In our study, among stroke patients, hypertension as a pre-morbid condition was present in 41.08% (n=83) and diabetes in 35.64% (n=71). Serum sodium levels in patients with TIA, ischemic CVA, and haemorrhagic CVA were summarized in [Table/Fig-2]. Among the 202 CVA patients, 78 patients (38.61%) presented with hyponatremia. Among the 78 patients, 43 (21.28%) were ascertained as SIADH, in which ischemic stroke and haemorrhagic stroke were diagnosed in 31 and 12 patients respectively. Fifteen (7.42%) had CSWS, in which 5 patients had ischemic stroke and 10 patients had haemorrhagic stroke. Twenty (9.90%) patients had hyponatremia of unknown aetiology [Table/Fig-3]. Laboratory Characteristics of stroke patients with hyponatremia were given in [Table/Fig-4]. Mean hospital stay of the CVA patients with hyponatremia was more than patients with normal sodium level with significant p-value [Table/Fig-5]. The artery affected in stroke is given in [Table/Fig-6].

Parameters	Total	Ischemic	Haemorrhagic	TIA
Sodium mEq/L (mean±SD)	130±4.9	129±3.3	129±3.9	132±3.7
Potassium mEq/L (mean±SD)	4±0.71	4±0.62	3.9±0.73	4.1±0.52

[Table/Fig-2]: Serum electrolytes of the CVA patients.

	Hyponatremia		
Type of stroke	SIADH (n) (%)	CSWS (n)(%)	Unknown aetiology
Haemorrhagic	12 (5.9)	10 (4.95)	7(3.46)
Ischemic	31 (15.34)	5 (2.47)	13(6.43)

[Table/Fig-3]: Causes of hyponatremia in stroke patients.

Characteristics	SIADH	CSWS	p-value
Serum Sodium mEq/L	125±1.7	124±1.6	0.10
Serum uric acid mg/dL	3.8±0.92	5.2±0.76	0.02
Serum Osmolality (mOsmol/kg)	249±7.3	248±8.2	0.14
Urine Osmolality (mOsmol/kg)	1035±33	980±24	0.06
Urine sodium mEq/L	64±15.4	192.6±26.2	0.001
Urine Specific gravity	1024.46±2.4	1027±3.2	0.11
Urine Volume (ml/kg/hr)	4.1±1.1	2.8±0.61	0.02

[Table/Fig-4]: Laboratory Characteristics of stroke patients with hyponatremia.
p-value was calculated using student t-test. p-value <0.05 was considered significant

Serum sodium status	Mean duration of hospital stay	
	Days (Mean±SD)	p-value
With hyponatremia	21±8.51	0.04
Without hyponatremia	10±3.82	

[Table/Fig-5]: Duration of hospital stay of stroke patients.
p-value was calculated using student t-test. p-value<0.05 was considered significant

Artery affected	SIADH (n)	CSWS(n)
Anterior cerebral artery	13	4
Middle cerebral artery	27	9
Posterior cerebral artery	3	2

[Table/Fig-6]: Artery affected in Ischemic stroke.
SIADH: Syndrome of Inappropriate Secretion of Antidiuretic Hormone; CSWS: Cerebral Salt Wasting Syndrome

DISCUSSION

The present was study conducted in newly diagnosed CVA patients to identify the causes of hyponatremia, whether it is due to SIADH or CSWS.

Among 202 stroke patients, 163 patients had ischemic stroke and their mean age was 64.8 years. Twenty four patients were suffering from haemorrhagic stroke. The incidence of stroke was more in males than females, but there were no gender and age specific differences in the incidence of hyponatremia. In the present study, the incidence of hyponatremia in CVA patients was 38.6%.

In the study conducted by Saleem S et al., the incidence of hyponatremia was 35 % which is consistent with our study [4]. In the studies by Hoorn EJ et al., the prevalence of hyponatremia in hospital care setting ranges from 11% to 21% and increases to 28.2% in acutely hospitalized patients [11]. Hyponatremia causes cerebral oedema which attenuates neurological dysfunction which results in altered sensorium, seizures, drowsiness and coma [4].

Hyponatremia is quite common in stroke patients and is highly important to differentiate the causes of hyponatremia (SIADH, CSWS) because the pathophysiology and management are

different. In this present study, 21.28% and 7.42% cases were diagnosed with SIADH and CSWS respectively, whereas in the study by Saleem S et al., 7% and 33% had SIADH and CSWS respectively [4]. The urine osmolality and specific gravity was high in both disorders. Increased urine sodium excretion was observed in both disorders, but it was higher in CSWS when compared to SIADH (64±15.4; 192.6±26.2). Hyponatremia in SIADH is due to increased volume overload and hyponatremia is dilutional in nature. In CSWS, natriuresis is due to disruption of sympathetic neural input signal to kidney and it is also induced by natriuretic peptides like Arterial Natriuretic Peptide (ANP), Brain Natriuretic Factor (BNP), C-Type Natriuretic factor (CNP) and Dendroaspis Natriuretic Peptide (DNP) [10,12,13]. Depression of the sympathetic system of kidney results in decreased resorption of sodium in the proximal tubule. This further leads to a decrease in the effective arterial blood volume which in turn triggers the baroreceptors to release ADH in order to maintain intravascular volume. A depressed sympathetic drive is also associated with decrease in renin and aldosterone levels which further inhibits sodium retention [12]. Battery of laboratory tests is needed to distinguish SIADH and CSWS.

Singh S et al., reported that CSWS is less common than SIADH, which is similar with our study, in which incidence of SIADH was more than CSWS, as shown in [Table/Fig-3] [14]. In the present study, hyponatremia due to CSWS was 7.4%, SIADH was 21.24% and unknown causes were 9.89%. In another study, hyponatremia due to CSWS was 44.2%, SIADH was 7% and miscellaneous causes were 32.6% [15] which was inconsistent with this present study. In the present study, patients with hyponatremia stayed a mean of 21 days which was more than non-hyponatremia patients. In the study of Sherlock M et al., hyponatremic patients had a significantly longer hospital stay median 19 days [interquartile range (IQR) 12-28] [16]. Two hyponatremic patients had hospital stay that extended to 31 days. The patients with hyponatremia had substantially longer hospital stay period than the patients with normal serum sodium level. Even though the SIADH and CSWS patients had decreased serum sodium level, the pathophysiology and treatment of these two entities are different. Hyponatremia due to CSWS improves with fluid replacement and treatment with Fludrocortisone, but hyponatremia due to SIADH improves with fluid restriction and vasopressin-2 receptor antagonists [17-19]. Thus, the exact aetiology of hyponatremia must be identified before starting appropriate therapy. In patients with SIADH, hyponatremia was cured in 76% and 24% was capitulated. In CSWS individuals, hyponatremia were cured in 68% and 32% was perished.

LIMITATION

The limitation of this study is that we enrolled patients from a single center and small numbers of subjects were studied; data from a multicenter study would be more useful. Larger studies are needed to confirm the findings, to understand the mechanisms associated with hyponatremia, and to explore the benefit of correction of hyponatremia after stroke.

CONCLUSION

This study shows that hyponatremia was observed in 38.61% of stroke patients. Hence, hyponatremia should be suspected to any stroke patients admitted in the Intensive care unit in order to achieve prompt diagnosis, to provide appropriate treatment, to reduce the hospital stay and to reduce the mortality. Laboratory estimation of serum sodium levels must be done to all stroke patients. Among hyponatremia stroke cases, 21.28% had SIADH and 7.4% had CSWS. Hence, careful attention has to be paid in distinguishing the aetiology of hyponatremia and while in applying the treatment strategies.

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