FREQUENCY OF HYPONATREMIA IN PATIENTS WITH ACUTE CEREBROVASCULAR ACCIDENTS PRESENTING AT COMBINED MILITARY HOSPITAL PESHAWAR

Muhammad Saleem, Abdul Latif Khattak*, Saeed Bin Ayaz, Qasim Raza***, Naveed Anjum****, Syed Ahmed Raza*****

142 Medical Battalion, Gujranwala Pakistan, *Quetta Institute of Medical Sciences, Quetta Pakistan, **Combined Military Hospital Jhelum Pakistan, ***Quaid-e-Azam International Hospital, Islamabad Pakistan, ****78 Medical Battalion, Okara Pakistan, *****136 Medical Battalion, Jumber Pakistan

ABSTRACT

Objective: To determine the frequency of hyponatremia in acute cerebrovascular accidents and explore the relationship of hyponatremia with age, gender, type, and duration of cerebrovascular accidents.
Study Design: Cross-sectional analytical study.
Place and Duration of Study: Department of Internal Medicine, Combined Military Hospital Peshawar, from Dec 2016 to Jun 2017.
Methodology: In this study, a total of 127 patients with acute cerebrovascular accidents i.e. within 12 hours of onset were enrolled. Serum sodium levels were evaluated at the initial presentation of the patient at the emergency department after confirmation of cerebrovascular accidents following clinical evaluation and computed tomography scan of brain without contrast.
Results: In this study, the mean age was 46 ± 8.7 years. Seventy-four (58%) patients were males while 53 (42%) patients were females. Eighty-six (68%) patients had ischemic cerebrovascular accidents while 41 (32%) patients had hemorrhagic cerebrovascular accidents. Thirty-eight (30%) patients had hyponatremia. Stratification of hyponatremia with age, gender, duration of cerebrovascular accidents, and the type of cerebrovascular accidents showed statistically insignificant correlation with *p*-value >0.05.
Conclusion: The frequency of hyponatremia in our cohort of acute cerebrovascular accidents patients was 30%. There was no association between hyponatremia and age, gender, type, or duration of cerebrovascular accidents. Monitoring of serum sodium levels must be done in all patients who are admitted with a cerebrovascular accidents.

Keywords: Age, Cerebrovascular accidents, Epidemiology, Hyponatremia.

INTRODUCTION

Stroke or cerebrovascular accident (CVA) is characterized as the unexpected beginning of a neurological deficiency, which is owing to a central vascular etiology[1]. Stroke is a global health issue and it is the second most frequent reason for death on the planet leading to 6.7 million deaths every year[2]. There are many factors that contribute towards mortality in CVAs and electrolyte disturbances are among these factors, which contribute to mortality unless corrected urgently[3]. Hyponatremia is the most frequent electrolyte abnormality seen in acute CVA patients with frequency ranging from 30-35%[4,5].

Hyponatremia is defined as serum sodium level less than 135 mEq/L. The consequences of salt depletion were first described by McCance in 1936. In acute CVA i.e. within 24 hours of onset[6], hyponatremia may be either due to Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion or due to Cerebral Salt Wasting Syndrome (CSW). Low serum sodium levels in the setting of abnormally concentrated urine with high urinary sodium concentration, and confirmation of normal or slightly increased intravascular volume describe SIADH while CSW is defined as renal loss of sodium due to intracranial disease leading to hyponatremia and hypovolemia[7].

Correspondence: Dr Muhammad Saleem, Graded Medical Specialist, Combined Military Hospital Gujranwala Pakistan
Email: drbangashamc@gmail.com
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Recently, hyponatremia has been perceived as a factor being related with negative prospects in acute CVA though not many investigations have led to similar conclusion. Based on these studies, the mortality in acute CVAs ranges from 14-44% in patients with hyponatremia[7,8]. Hyponatremia might be an important cause of altered level of consciousness in patients who present with CVA and it can also lead to seizures, which would further add to the insult and deteriorate the level of consciousness and the prognosis. There are various factors that can lead to development of hyponatremia in acute CVA. The commonly identified factors are: severe hyperglycemia (>300 mg/dl) and hypertriglyceridemia (>400 mg/dl), renal failure, infections, head injuries, recent surgery, central nervous system tumors, subdural and epidural hematomas, and drugs such as diuretics, steroids, selective serotonin reuptake inhibitors, tricyclic antidepressants, narcotics, non-steroidal anti-inflammatory drugs, antipsychotics, carbamazepine, cyclophosphamide, and clofibrate.

So far, there is deficiency in relevant data about prevalence and associations of hyponatremia among CVA patients in Pakistan. The objectives of this study were to evaluate the frequency of hyponatremia in patients presenting with acute CVA at a Pakistani tertiary care hospital i.e. Combined Military Hospital Peshawar and explore the relationship of hyponatremia with age, gender, type, and duration of CVA.

METHODOLOGY

It was a cross-sectional analytical study conducted at the department of Internal Medicine, Combined Military Hospital Peshawar from December 2016 to June 2017. After permission from the hospital ethical committee, a sample size of 81 was estimated via Epi Tools Epidemiological Calculator[9] while keeping confidence level 95%, estimated true proportion 30%[4], and 10% of absolute precision. Through non-probability consecutive sampling, we included patients of both gender, presenting with acute CVA i.e. within 24 hours of onset[6]. Patients with severe hyperglycemia (>300mg/dl) and hypertriglyceridemia (>400 mg/dl), renal failure, documented infections, head injuries, recent surgery, central nervous system tumors, and on therapy with diuretics, steroids, selective serotonin reuptake inhibitors, tricyclic antidepressants, narcotics, non-steroidal anti-inflammatory drugs, antipsychotics, carbamazepine, cyclophosphamide, or clofibrate were excluded as these could have contributed towards hyponatremia even in the absence of CVA.

Written informed consent was taken from all patients prior to inclusion. Serum sodium levels were evaluated at the initial presentation of the patient using Mindray BS-400 chemical analyzer by photometric technique having normal reference range of 135-145 mEq/L. All the reports were verified by a consultant chemical pathologist before entering the data in the proforma. The computed tomography (CT) scan of the brain without contrast was performed in the emergency department at the first presentation as recommended by Ihsan *et al*[10] using CT scan machine Brilliance CT 16 slice – DS. The scans were verified by a consultant radiologist before entering the data in the proforma.

Data analysis was performed using Statistical Package for Social Sciences version 20.0 for windows. Means and standard deviations were calculated for quantitative variables like age, duration of CVA, and serum sodium levels. Qualitative variables like gender, type of CVA, and hyponatremia were described as numbers and percentages. After stratification, Pearson's chi-square test was used for analysis. The significance was set at p-value of ≤0.05.

RESULTS

A total of 127 patients were enrolled with a mean age of 46 ± 8.7 years. Twenty-nine (23%) patients were in the age-range of 35-45 years, 45 (35%) patients were in the age-range of 46-55 years, and 53 (42%) patients were in the age-range of 56-70 years. Seventy-four (58%) patients were males while 53 (42%) patients were females.

Eighty-six (68%) patients had ischemic CVA while 41 (32%) patients had hemorrhagic CVA.

Mean duration of the CVA was 5 ± 3.5 hours. Fifty-one (40%) patients had a CVA for the past <5 hours while 76 (60%) patients had a CVA for the past ≥5 hours. Mean serum sodium level was 169 ± 12.11 mEq/L. Thirty-eight (30%) patients had hyponatremia while 89 (70%) patients had normal serum sodium levels. Statistical analysis using Pearson's chi-square analysis showed that the frequency of hyponatremia at sub-levels for different investigation variables had statistically insignificant correlation with age, gender, duration of CVA, and the type of CVA (p-value>0.05) (table).

Table: Comparison of sublevels of different variables for hyponatremia and normal levels..

Variables and sub-variables	Hyponatremia	Normal levels	p-value
Age group			
35-45 years	8	21	0.898
46-55 years	13	32	
56-70 years	17	36	
Gender			
Male	22	52	0.956
Female	16	37	
Type of cerebrovascular accident			
Ischemic	26	60	0.912
Hemorrhagic	12	29	
Duration of cerebrovascular accident			
<5 hours	15	36	0.918
≥5 hours	23	53	

DISCUSSION

In this study, 30% patients had hyponatremia while 70% patients didn't have hyponatremia. The prevalence of hyponatremia in CVA patients varies considerably. Saleem *et al*[5] in a study done in Jammu and Kashmir, included 1000 patients of CVA out of which 353 patients were having hyponatremia, giving an incidence of 35.3%. Similar results were observed in another study conducted by Bhattacharjee *et al*[7] in which frequency of hyponatremia was found to be 30% in patients presenting with acute CVA. Siddiqui *et al*[11]. showed that 32% of the patients with acute CVA had hyponatremia.

Karunanandham *et al*[12] found an incidence of 38.6% in 202 South Indian CVA patients. Metwally *et al*[13] observed a frequency of 30.6% in 85 Egyptian patients. Wali and Patel observed a frequency of 32.9% in ischemic and a frequency of 25.7% in hemorrhagic CVAs[14]. Saleem *et al*[5] found percentages of 34% and 66% for hyponatremia in acute ischemic CVA and intracerebral hemorrhage respectively. Most of other studies have found a lower incidence of hyponatremia in CVA patients. Soiza *et al*[15] observed a prevalence of 13.8% of hyponatremia on admission, in a sample of 8540 CVA patients. Similarly, Rodrigues *et al*[16], Al-Khazraji[17], Huang *et al*[8], Kembuan and Sekeon[18], Kuramatsu *et al*[19], and Hoyle *et al*[20] found lower incidences of 16%, 17%, 12%, 7.1%, 15.6%, and 18% respectively. Some studies, on the contrary, have found higher percentages of 45%[21] and 54%[22] for hyponatremia in acute CVA patients. This may be related to ethnical differences, as most researches from the Indian subcontinent have yielded higher incidences of hyponatremia than studies from other areas.

We could not find statistically significant effect of age, gender, type, and duration of CVA on hyponatremia frequency (p> 0.05). Other studies investigating the same query had come up with varied results. Koivunen *et al*[21] and Kuramatsu *et al*[19] found no correlation between hyponatremia and age or gender. Soiza *et al*[15] noted that sodium abnormalities were more common in women and older-aged CVA patients. Hoyle *et al*[20] and Metwally *et al*[13] inferred that the rate of sodium irregularities particularly hyponatremia increased with increased age of the patients. Kuramatsu et al[19] did not discover a relationship of serum sodium levels with the time since beginning of symptoms. Al-Khazraji[17] found a significantly higher percentage (p<0.001) of hyponatremia in hemorrhagic CVA patients as compared with ischemic CVA patients. Maniram *et al*[22], Roy *et al*[3], Wali and Patel[14], Alam *et al*[23], and Nemade et al[24] did not find any significant difference in the prevalence of hyponatremia in different types of CVAs.

Hyponatremia, independent of all other affecting factors, is a contributor towards mortality after CVA. Maniram *et al*[22] found a statistically significant correlation between hyponatremia and early mortality (i.e. within 30 days) in CVA patients. Kuramatsu *et al*[19] observed that the patients of CVA with hyponatremia had 2.5 times more chances of dying in the hospital than those patients of CVA who had a normal serum sodium levels (40.9% vs 21.1%; $p<0.001$). Huang *et al*[8]. studied 925 ischemic CVA patients with the very first CVA and followed them for 3 years for mortality. They identified hyponatremia as a predictor of mortality independent to any other factor affecting adverse outcome. Rodriguez *et al*[16] recognized hyponatremia as an independent factor associated with increased mortality at 3 to 12 months after ischemic CVA and poor health status on hospital discharge. Probably the biggest investigations to date was completed in Scotland to research the relationship between sodium levels and mortality after CVA and it additionally affirmed that hyponatremia was an autonomous indicator of poor prognosis after CVA both in the short and the longer term[15]. Metwally *et al*[13] observed a rise in the mortality rate by 34.6% among patients with hyponatremia. Similarly, Saleem *et al*[5] and Bhatta-charjee *et al*[7] observed higher rates of mortality by 44.2% and 24% in hyponatremic patients in CVA. The mechanism of this association remains unclear. One possible explanation is that severe ischemic CVA in patients with hyponatremia results in a reduction in plasma osmolality, which secondarily may increase the risk of cerebral edema and increased intracranial pressure[25]. Cerebral edema consequently attenuates neurological functions leading to altered sensorium, seizures, drowsiness, and coma[5]. Notwithstanding these theoretical pathophysiological contemplations of hyponatremia-mediated effects on outcome, it stays uncertain whether hyponatremia simply represents a by stander of CVA, that is, it is a pre-existing comorbidity or the effect of polymedication reflecting poorer overall status.

One of the major demographic factors affecting survival in hyponatremic patients suffering from CVA, is age of the patient[15]. Strikingly, younger patients with hyponatremia are at a higher risk of death. There are various potential clarifications for this startling observation. One of the reasonable explanations is that in older patients age-related cerebral atrophy might be protective against fatal coning due to raised intracranial pressure as compared to younger patients who don't have enough intracranial space to accommodate the cerebral edema secondary to hyponatremia[15]. Also, older people have increased susceptibility to dyshomeostasis e.g. regarding serum sodium levels. So, they may become hyponatremic because of less extreme and/or potentially more effectively remediable causes than younger individuals[15]. These elderly people, generally develop hyponatremia of mild and chronic (i.e. >48 hours) nature that gets settled easily. Whereas, younger patients require a major imbalance in homeostasis to have hyponatremia and therefore are not cured by simple treatment strategies.

Uptill now, there is no evidence across various studies that correcting hyponatremia could result in better outcome in terms of clinical parameters and survival in patients with CVA. Rather, the correction of hyponatremia could even be deleterious in light of the fact that cerebral adaptive mechanisms are damaged after neurological injury and neurons may lose their myelin even at normal serum sodium levels[18]. The other way around, recent studies inspecting evolution of cerebral edema suggest that continuous hypertonic saline infusions with upper limit of the sodium levels are safe and even beneficial in hemorrhagic CVAs[18].

In the nutshell, we end the discussion by saying that hyponatremia affects the outcome of CVA especially in terms of mortality. Therefore, serum sodium must be monitored in all patients who present with CVA and the cause of hyponatremia must be sorted out, in order to manage such patients optimally thereby decreasing the mortality rate.

LIMITATION OF STUDY

Our study had some limitations that should be considered. Firstly, it was a single center study; thus, the results could not be generalized. Secondly, we used only the sodium measurements at admission and did not use the mean levels for the whole duration of stay in hospital though sodium levels are reported to alter quite frequently during early post CVA phase. Thirdly, we did not measure the severity of CVA and thus, could not relate hyponatremia with CVA severity. Fourthly, as in any observational study, it was possible that there were unmeasured confounders.

CONCLUSION

The frequency of hyponatremia in our cohort of acute cerebrovascular accidents patients was 30%. There was no association between hyponatremia and age, gender, type, or duration of cerebrovascular accidents. Monitoring of serum sodium levels must be done in all patients who are admitted with a cerebrovascular accidents.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44(7): 2064-89.
2. World Health Organization. The top 10 causes of death. [Online] Updated May 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death [Accessed 3rd July 2019].
3. Roy K, Bandyopadhyay R, Paul R, Chakraborty S, Ray D, Mitra S, et al. Study on serum and urinary electrolyte changes in cerebrovascular accident. J Indian Acad Clin Med 2014; 15(2): 91-95.
4. Hassan MK, Hasan AB, Rubaiyat KA. Electrolyte disturbances in acute phase of stroke patients. Dinajpur Med Coll J 2013; 6(1):12-6
5. Saleem S, Yousuf I, Gul A, Gupta S, Verma S. Hyponatremia in stroke. Ann Indian Acad Neurol 2014; 17(1): 55-57.
6. Birenbaum D, Bancroft LW, Felsberg GJ. Imaging in acute stroke. West J Emerg Med 2011; 12(1): 67-76.
7. Bhattacharjee K, Das D, Kalwar A, Debnath B, Kar G. Relationship of Hyponatremia with immediate mortality in acute stroke. J Evid Based Med Health Care 2015; 2(38): 6119-24.
8. Huang WY, Weng WC, Peng TI, Chien YY, Wu CL, Lee M, et al. Association of hyponatremia in acute stroke stage with three-year mortality in patients with first-ever ischemic stroke. Cerebrovasc Dis 2012; 34(1): 55–62.
9. Ausvet. Epi Tools. Available from: https://epitools.ausvet.io/oneproportion. [Accessed 29 August 2019].
10. Ihsan HR, Ahmad S, Ayaz SB. The spectrum of radiological findings in patients presenting with different clinical indications for cranial computed tomographic scan. Pak Armed Forces Med J 2019; 69(1): 170-74.
11. Siddiqui MR, Islam QT, Haque MA, Iqbal MJ, Hossain A, Rahman YU, et al. Electrolytes status in different type of acute stroke patients and their correlation with some common clinical presentation. J Med 2012; 13(2): 133-37.
12. Karunanandham S, Rajappa T, Selvaraju K. Hyponatremia in patients admitted with stroke. J Clin Diagn Res 2018; 12(8): 34-36.
13. Metwally H, Hablas W, Fawzy E, Seddeek M, Meshref M. Acute stroke and serum sodium level among a sample of Egyptian patients. Nat Sci 2016; 14(12): 245-49.
14. Wali VV, Patil SS. A comparative study of serum electrolytes and lipid levels in ischaemic and haemorrhagic stroke. Int J Res Med Sci 2016; 4(11): 4838-42.
15. Soiza RL, Cumming K, Clark AB, Bettencourt-Silva JH, Metcalf AK, Bowles KM, et al. Hyponatremia predicts mortality after stroke. Int J Stroke 2015; A100 (Suppl-10): 50-55.
16. Rodrigues B, Staff I, Fortunato G, McCullough LD. Hyponatremia in the prognosis of acute ischemic stroke. J Stroke Cerebrovasc Dis 2014; 23(5): 850-54.
17. Al-Khazraji AKK. Hyponatremia in a group of iraqi patients with stroke. Iraqi J Med Sci 2016; 14(2): 191-96.
18. Kembuan MAHN, Sekeon SAS. Electrolyte disturbances among acute stroke patients in Manado, Indonesia. Global J Med Public Health 2014; 3(1): 1-9.
19. Kuramatsu JB, Bobinger T, Volbers B, Staykov D, Lücking H, Kloska SP, et al. Hyponatremia is an independent predictor of in-hospital mortality in spontaneous intracerebral hemorrhage. Stroke 2014; 45(5): 1285-91.
20. Hoyle GE, Chua M, Soiza RL. Prevalence of hyponatremia in elderly patients. J Am Geriatr Soc 2006; 54(9): 1473-74.
21. Koivunen RJ, Haapaniemi E, Satopää J, Niemelä M, Tatlisumak T, Putaala J. Medical acute complications of intracerebral hemorrhage in young adults. Stroke Res Treat 2015; 2015: 357696.
22. Maniram R, Patel L, Kaware K. Hyponatremia in stroke patients and its association with early mortality. J Evol Med Dent Sci 2015; 4(54): 9485-91.
23. Alam MN, Uddin MJ, Rahman KM, Ahmed S, Akhtar M, Nahar N, et al. Electrolyte changes in stroke. Mymensingh Med J 2012; 21(4): 594–99.
24. Nemade ST, Patil MS, Chaudhari RA, Vankudre AJ. Comparative assessment of severity of dyselectrolytaemia (sodium and potassium) in cerebral infarction and cerebral hemorrhage. MVP J Med Sci 2016; 3(1): 25-27.
25. Kret B, Lasek-Bal A, Holecki M, Hawrot-Kawecka A, Wilczyński K, Duława J. Prognostic relevance of hyponatremia after first-ever ischemic stroke. Ann Acad Med Siles 2016; 70(1): 127–32.