International Journal of Research in Medical Sciences
Ahmed J et al. Int J Res Med Sci. 2023 Oct;11(10):3744-3749
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20233030

Original Research Article

Clinical and biochemical profile of hyponatremia and the role of vaptans in comparison to other standard modalities of therapy

Jalal Ahmed[1]*, Mohammed Fahad Khan[1], Shashikiran Umakanth[2], Seema Shetty[2]

[1]Department of Nephrology, Manipal Hospitals, Bangalore, Karnataka, India
[2]Department of Medicine, TMA Pai Hospital, Udupi, Karnataka, India

Received: 05 August 2023
Revised: 07 September 2023
Accepted: 15 September 2023

***Correspondence:**
Dr. Jalal Ahmed,
E-mail: drjalal7@gmail.com

ABSTRACT

Background: This study, conducted from August 2014 to August 2015, investigated hyponatremia in 228 in-hospital patients, aiming to discern its clinical and biochemical features and compare the efficacy of vaptans against standard treatments. The null hypothesis assumed no significant disparity in outcomes, while the alternate hypothesis posited otherwise.
Methods: Using an open-label, non-blinded, observational, prospective comparative design, we assessed 228 hyponatremia patients. We scrutinized their clinical and biochemical profiles and made comparisons between moderate and profound hyponatremia cases, along with different treatment approaches.
Results: Our findings revealed that patients aged 61-80, primarily females, dominated the cohort. Moderate hyponatremia occurred in 56.6% of cases, with severe hyponatremia in 43.4%. Common symptoms included drowsiness, nausea, and vomiting. Euvolemic hyponatremia was predominantly due to SIADH, while heart failure led to most hypervolemic cases. Various treatments were employed, with fluid restriction and normal saline being common. Tolvaptan and 1.6% hypertonic saline significantly increased serum sodium levels at 24 and 48 hours. Hospital stay duration didn't significantly differ, and no osmotic demyelination cases emerged. Mortality stood at 10.5%, notably higher in profound hyponatremia cases.
Conclusions: This study provides insights into hyponatremia's clinical and biochemical aspects and compares vaptans to standard treatments. Tolvaptan and hypertonic saline displayed promise in raising serum sodium levels. Nevertheless, further research is warranted to validate these findings and explore additional factors impacting hyponatremia treatment outcomes.

Keywords: Hyponatremia, Saline, Tolvaptan

INTRODUCTION

Sodium (Na) is the sixth in abundance among elements of the earth's crust, constituting 2.8% of its weight. It has a single stable isotope of atomic weight 22.991.[1]

Humans have a total body sodium content of 3000-4000 mmol, 60% of which is exchangeable and rest being found in bone. It constitutes of 90 percent of total solute in extracellular fluid. It is the principal osmotically active solute responsible for maintenance of intravascular and interstitial volumes.[2]

Fluid balance is maintained both between the body and the environment i.e., external balance and also between internal body fluid compartments. Diseases may affect this balance or steady state. Hyponatremia is one such disorder where there is relative excess of water to body's sodium.

Hyponatremia is a common clinical entity that may occur during course of variety of medical illnesses. It is the most common electrolyte abnormality in the general population.[3] It is defined as a serum sodium concentration of less than 135 mEq/l.[4,5] Most patients have mild hyponatremia and recent studies have shown that they have subtle neuromotor and neurocognitive changes and hence it needs to be treated.[6,7] Serum sodium concentrations below 120 mEq per litre are more frequently associated with serious clinical symptoms. The search for the cause of hyponatremia is guided by the clinical circumstances, time of development and patients' state of hydration.[3] Hyponatremia is generally a secondary manifestation of another primary disease state, and may occur in association with hypovolemia, euvolemia and hypervolemia. Symptoms of low serum sodium are merged with those of the underlying disease state.[8] Severe hyponatremia is a disorder with high mortality. Most studies suggest that mortality in patients with hyponatremia is due to progression of the underlying disease. Hyponatremia is an indicator of severe disease and poor prognosis.[3,8] Despite advances hyponatremia remains a grey area in the field of research as there is no consensus regarding its management. As data on hyponatremia from the Indian subcontinent is scarce, this study has been undertaken to evaluate the clinical profile of hyponatremia in our population. The objective of the study was to study the clinical features and biochemical profile of hyponatremia in hospitalized subjects and to compare the response to vaptans with other modalities of therapy.

METHODS

Study type

This study employed an open-label, non-blinded, observational, prospective comparative design.

Study place and period

The research was conducted at TMA Pai Hospital, Udupi from September 2014 to October 2015.

Selection criteria of patients

Subjects were exclusively selected as inpatients, meeting the criteria of having hyponatremia, defined as serum sodium levels below 130 mmol/l. Inclusion criteria encompassed both male and female individuals aged 18 years or older who were eligible for the study. Exclusion criteria comprised participants who did not provide informed consent, those with serum sodium levels exceeding 130 mmol/l, pregnant or lactating women, and subjects with multifactorial etiology for hyponatremia.

Procedure

Upon obtaining informed consent, a comprehensive patient history was documented, encompassing symptoms, signs at presentation, volume status assessments, and past drug history, using a pretested proforma. Venous blood samples were collected to estimate electrolytes, urine osmolality, random blood sugar, and conduct thyroid and renal function tests. Repeat estimations were performed as necessitated by the treating physician, depending on clinical circumstances. Serum sodium was quantified via autoanalyzers using ion-sensitive electrodes, while serum potassium, urea, creatinine, urine osmolality, and random blood sugars were also analyzed by autoanalyzers. Subgroup classification was conducted based on clinical and biochemical data, categorizing subjects into pseudohyponatremia, hypertonic, isotonic, and hypotonic hyponatremia. Further stratification was based on volume status, differentiating subjects into hypovolemic, hypervolemic, and euvolemic categories according to clinical and laboratory data. Euvolemic subjects meeting Schwartz and Bartter criteria were classified as having SIADH. Etiological classification was also undertaken. Subjects with moderate hyponatremia (125-129 mEq/l) were compared with those exhibiting profound hyponatremia (<125 mEq/l) concerning morbidity and mortality, as assessed by hospital stay duration and death. Patients with mild hyponatremia (130-134 mEq/l) were not included in the study. Among subjects with SIADH and hypervolemia, two subgroups were established: one treated with hypertonic saline and the other receiving both hypertonic saline and tolvaptan 15 mg/day. Sodium level improvement was compared between these subgroups.

Ethical approval

The study adhered to ethical principles in accordance with the declaration of Helsinki and obtained approval from the institutional ethics committee of Manipal University.

Statistical methods

The study followed an open-label, non-blinded, observational, prospective comparative design from August 2014 to August 2015. The sample size consisted of 228 subjects with hyponatremia who met the eligibility criteria. Data analysis involved calculating means, standard deviations, frequencies, and percentages. Repeated measures ANOVA was used to compare changes from baseline among different groups. Statistical analysis employed SPSS® (version 16.0) and Microsoft Excel®.

RESULTS

228 patients were included in the study. As depicted in Figure 1, most patients were in the age category of 61-70 and 71-80 years. In this study 52.6% (120) of females had hyponatremia while 47.4% (108) of males had hyponatremia out of 228 subjects studied.

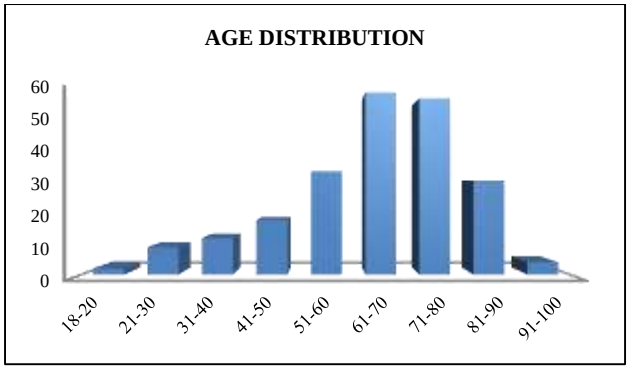

Figure 1: Age distribution of the study population.

In our study, 129 (56.6%) subjects had moderate hyponatremia (serum Na- 125-129) while 99 (43.4%) subjects had severe hyponatremia (serum Na<124). Moreover, 129 (56.6%) subjects were symptomatic while 99 (43.4%) were asymptomatic.

Drowsiness, nausea and vomiting were the most common symptoms encountered in our patients with their frequencies being 29.4%, 22.8% and 17.5% respectively. Confusion was seen in 14% patients and headache in another 7.9%.

217 (95.17%) out of total 228 cases were due to hypotonic hyponatremia. 11 (4.8%) cases were due to nonhypotonic hyponatremia.

Amongst the 217 patients with hypotonic hyponatremia after ruling out pseudohyponatremia, 85 patients were identified to be euvolumic and 78 patients were hypovolemic.

Table 1: Euvolemic hyponatremia.

Causes	Frequency	Percentage
Pneumonia	33	38.8
Malaria	11	12.9
Hypothyroidism	2	2.4
Quetipine	2	2.4
SSRI use	8	9.4
Carbamazepine	6	7.1
Cerebrovascular accident	7	8.2
CNS malignancy	1	1.2
Pulmonary tuberculosis	2	2.4
Lung carcinoma	4	4.7
Cholangiocarcinoma	2	2.4
Renal carcinoma	1	1.2
Gastric carcinoma'	1	1.2
HIV	2	2.4
Esophageal malignancy	1	1.2
Beer potomania	1	1.2
Lymphoma	1	1.2
Total	85	100.0

In this study gastrointestinal loss, diuretics and third space fluid loss due to sepsis were prime causes of hypovolemic hyponatremia. SIADH was the major cause of euvolemic hyponatremia. In hypervolemic category cardiac failure was major cause of hyponatremia followed by renal failure and liver failure.

Table 1: Incidence of different types of asterion.

Gender	Type I	Type II
	N (%)	N (%)
Male (n=54)	14 (25.9)	40 (74.1)
Female (n=46)	13 (28.2)	33 (71.7)

Predominant cause of euvolemic hyponatremia was due to SIADH with 82 of 85 cases with euvolemic hyponatremia (Table 1). 2 cases (2.4%) were due to hypothyroidism. 1 case was due to beer potomania (1.2%). In this study pneumonia (40%), drugs (20%) and malaria (13%) were the prime causes of SIADH. Among CNS causes CVA was the most common cause. Among causes originating from respiratory system, pneumonia was the predominant followed by lung carcinoma (4.9%) and pulmonary tuberculosis (2.4%). Among drugs causing hyponatremia SSRIs were predominant cause followed by carbamazepine. Two cases of retroviral illness had hyponatremia. Other causes were malignancies like gastric carcinoma, renal carcinoma and cholangiocarcinoma.

In our study, heart failure accounted for majority of cases of hypervolemic hyponatremia 32 (59.3%) while renal failure was seen in 15 subjects (27.8%) and liver failure in 7 subjects (13%).

Table 2: Treatment of hyponatremia.

Treatment modality	Frequency	Percentage
Fluid restriction	60	26.3
Normal saline	79	34.6
1.6% saline	22	9.6
3% saline	4	1.8
Tolvaptan	16	7.0
Diuretics	25	11.0
Cause-specific treatment	22	9.6
Total	228	100

Normal saline (34.6%) and fluid restriction (26.3%) were the predominant treatment modalities used. In 22 subjects 1.6% saline infusion was used while 16 subjects received tolvaptan. 3% hypertonic saline was used in 4 subjects. In 22 (9.6%) subjects cause-specific treatment was the modality of management (Table 2).

Tolvaptan 15 mg per day and 1.6% hypertonic saline had significant effects on rising serum sodium level in hyponatremic subjects at both 24 hours and 48 hours ($p<0.001$) (Table 3). This increase was about 3.85±0.86 and 9.11±0.45 for 1.6% hypertonic saline and 5.5±0.51

and 10.57±0.44 for tolvaptan, after 24 hours and 48 hours respectively (p<0.001) (Table 4).

Table 3: Comparison of vaptans with 1.6% saline.

Serum Na	1.6% saline (n=19)	Tolvaptan (n=16)	Total
	mean±SD	mean±SD	
baseline	109.42±6.077	114.81±5.969	111.89
24 hours	113.05±5.911	120.31±5.57	116.37
48 hours	118.53±6.257	125.38±4.349	121.66

Table 4: Increase in sodium level from baseline.

Increase in sodium level from baseline	1.6% saline	Tolvaptan
After 24 hours	3.85±0.86	5.5±0.51
After 48 hours	9.11±0.45	10.57±0.44
P value	<0.001	<0.001

Duration of hospital stay was compared between moderate hyponatremia and profound hyponatremia and median duration of stay was found to be 7 days in both the groups. p value obtained from Mann Whitney U test was 0.063 and was not statistically significant. No case of osmotic demyelination was found during the course of the study. In this study out of 228 subjects studied 24 subjects expired (10.5%) while 204 (89.5%) subjects improved. 7.75% of the subjects having moderate hyponatremia expired while 16.4% of those with profound hyponatremia expired during hospital stay. Although clinically significant it was not statistically significant with a p value of 0.119.

DISCUSSION

This study was done with a total number of subjects of 228, the subjects with a Na level <130 mEq/l were included in the study. Those with multifactorial etiology were excluded from the study. In this study majority of subjects were in the age group of 60-80 years (Figure 1). Elderly subjects had higher predisposition for hyponatremia. In an analysis by Upadhyay et al, it was inferred that the geriatric population is susceptible to hyponatremia because of the aging-related impaired water-excretory capacity, and an increased exposure to drugs and diseases associated with hyponatremia.[4] Hawkins et al noted that increasing age was independently associated with hyponatremia.[9] In this study 51.75% subjects who had hyponatremia were between the age group of 60-80 years.

In a prospective study by Clayton et al, 60% of subjects were females. Studies have also shown that female gender is an important risk factor for development of complications.[10] In our study there was a slight female preponderance with 52.6% subjects being females. It was difficult to assess the duration of hyponatremia prior to admission. However, 56.6% subjects presented with symptoms attributable to hyponatremia but a significant proportion (43.4%) did not have symptoms attributable to hyponatremia. This is probably since in chronic mild hyponatremia patients remains asymptomatic due to cerebral adaptation, however recent studies have shown that mild cognitive disturbances and falls are more common in them. In our study, drowsiness (29%) and nausea (22.8%) were the predominant symptoms. In a study by Rao et al, drowsiness (33%), lethargy (29%) were common presenting symptoms while few had seizures (4%), and headache (8%).[11] In our study, 11 subjects (4.8%) had non hypotonic hyponatremia while the rest had hypotonic hyponatremia. Most of the cases were due to hyperglycemia (8 subjects, hypertonic) or multiple myeloma (3 subjects, pseudohyponatremia).

The subjects were again divided on the basis of volume status. Majority of them had euvolemic hyponatremia (42%) followed by hypovolemic hyponatremia (34%) and hypervolemic hyponatremia (24%) (Figure 2).

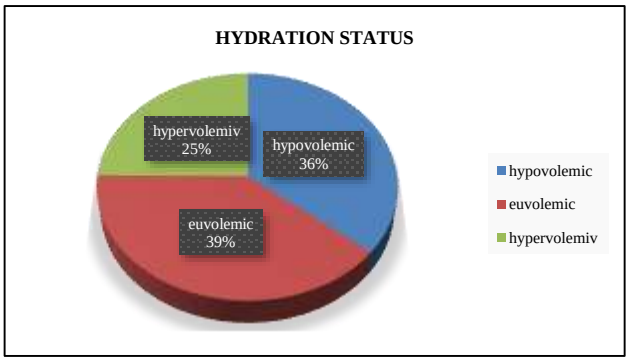

Figure 2: Hydration status in hypotonic hyponatremia.

In this study, most cases of hypovolemic hyponatremia resulted from diuretics (22 cases), GI losses (31 cases) and third space fluid loss mainly resulting from sepsis (25 cases). In a study by Padhi et al, SIADH was the most common cause followed by severe sepsis which usually results from third space fluid loss.[12] In this study, Infections like dengue, typhoid fever, leptospirosis, urosepsis were major causes of third space fluid loss. Diuretics use was also a major cause of hyponatremia in our study, majority of which were caused by thiazides and rest by spironolactone. In a study by Sonnenblik et al, almost all cases of diuretic induced hyponatremia resulted from use of thiazide diuretics.[13] In our study 19 of 22 cases resulted from thiazide diuretic use, and they as a whole accounted for 8.3% of 228 cases.

In this study SIADH as a whole accounted for 36% of the cases. Pneumonia was the single most important cause of SIADH causing 40.2% cases of SIADH. Drugs were the next common cause accounting for 19.51% of the cases. SSRIs and carbamazepine were prime causes of drug induced SIADH. In study by clayton et al 11.1% cases had hyponatremia due to SSRI.[10] In our study, malaria

was also a significant cause of SIADH probably due to endemicity of the disease in the coastal belt. In a study by Ewout J Hoorn, Malaria was an important cause of SIADH.[14,15] Among respiratory causes, pneumonia was the predominant (40.2%) followed by lung carcinoma (4.9%) and pulmonary tuberculosis (2.4%). Two subjects of retroviral illness in this study had hyponatremia (Table 1).

In this study 24% cases were due to hypovolemic hyponatremia. Heart failure accounted for majority of cases of hypervolemic hyponatremia 32 (59.3%) while renal failure was seen in 15 subjects (27.8%) and liver failure in 7 subjects (13%). In an Indian study by Padhi et al, 26.29% accounted for hypervolemic hyponatremia.[12]

In this study treatment was given as decided clinical judgment of treating physician. Subjects were treated after analyzing symptoms and volume status, rapidity of development and the underlying cause. In our study 34.6% of the subjects received normal saline, 26.3% of subjects were managed with fluid restriction, 9.6% subjects received cause specific treatment. 9.6% subjects received 1.6% saline, 7% received tolvaptan 15 mg/day and 11% of the subjects received diuretics (for management of hypervolemic hyponatremia). As there is no consensus on management of hyponatremia, there are considerable variations in the treatment strategies of hyponatremia (Table 2).

In a recent landmark randomized clinical trial called SALT (SALT-1 and SALT-2) enrolling 205 and 243 subjects respectively, efficacy of tolvaptan was studied in subjects with euvolemic and hypervolemic hyponatremia. The effect of tolvaptan was compared with placebo by comparing rise in sodium levels on day 4 and day 30 as primary end points. Tolvaptan was found superior to placebo in rising and maintaining sodium levels.[16]

In our study, response of vaptans was studied in the group of hypervolemic and euvolemic subjects and was compared with the standard therapy used i.e., 1.6% hypertonic saline.

Both vaptans and hypertonic saline resulted in statistically significant rise in serum Na levels, both with a p value of <0.001. Vaptans had a better response when compared to 1.6% saline, with a rise of sodium 5.5±0.51 mEq/l and 10.57±0.44 mEq/l, after 24 hours and 48 hours respectively (p<0.001). Rise of sodium was also significant with 1.6% saline with Na rising by 3.85±0.86 and 9.11±0.45 for 1.6% at 24 hours and 48 hours respectively (p<0.001).

Tolvaptan had statistically significant efficacy over 1.6% saline in rising Na concentration at both 24 hours and 48 hours (p<0.001) (Table 3 and Table 4).

A prospective study by Vilapurathu and Rajarajan also yielded similar results however in that study 3% hypertonic saline had a slightly superior efficacy in rising serum Na concentration.[17] Another study showed that Tolvaptan and 3% hypertonic saline solution had significant effects in raising serum sodium level in hyponatremic patients at both 24 hours and 48 hours (p<0.0001). This increase was about 8.030±0.6507 mEq/l and 12.33±0.6489 mEq/l for 3% hypertonic saline and about 5.111±0.6616 mEq/l and 10.11±0.6230 mEq/l for tolvaptan, after 24 hours and 48 hours, respectively.[18]

Duration of hospital stay was compared between moderate hyponatremia and profound hyponatremia and median duration of stay was found to be 7 days in both the groups and was not statistically significant (p<0.063 by Man Whitney U test). In one study it was shown that oral tolvaptan and 3% hypertonic saline were equally effective in correcting hyponatraemia at 48 hours, but serum sodium levels were higher at 72 hours after oral tolvaptan.[19] Yet, in another study the efficacy of 3% HTS for the correction of hyponatraemia is well documented. It had shown a slightly superior efficacy in raising the serum sodium concentration at both 24-hours and 48-hour periods in hyponatraemic patients as compared with oral tolvaptan 15-30 mg daily.[17]

Influence of hyponatremia on mortality was a matter of debate as studies have different conclusions on the same. According to a study by Chatterjee et al, 13.5% hyponatremic subjects died during the hospital stay, while the mortality in corresponding normonatremic subjects was 8.5%.[20] Similarly in a study by Rao et al, mortality rate was 20%.[11] In the present study, hyponatremic subjects had a mortality rate of 10.5%. According to most studies mortality is related to primary etiology than the serum Na levels. In our study, heart failure (10 cases) followed by liver failure (4 cases) and pneumonia (3 cases) accounted for most cases of mortality.

This study was carried out in a small representative local population. Though the results are statistically significant, we recommend larger population studies to further validate these results.

CONCLUSION

We conclude that hyponatremia is a condition that is more commonly observed in the elderly age group. Our study found that the predominant cause of hyponatremia was the euvolemic hypotonic type, with SIADH being the main contributing factor. The most prevalent symptoms experienced by patients were drowsiness, followed by nausea. The study also revealed that hyponatremia was associated with an overall mortality rate of 10.5%. However, the severity of the biochemical imbalance did not have a significant influence on the duration of hospitalization or mortality. Interestingly, the administration of both tolvaptan and 1.6% hypertonic saline resulted in a statistically significant rise in sodium

levels among hyponatremic subjects. However, tolvaptan exhibited slightly superior efficacy in increasing sodium concentration at both the 24-hour and 48-hour time points.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Simpson FO. Sodium intake, body sodium, and sodium excretion. Lancet. 1988;2(8601):25-9.
2. King A. Basic concepts of fluid and electrolyte therapy. Clin Med. 2013;13(5):524.
3. Turner N, Lameire N, Goldsmith DJ, Winearls CG, Himmelfarb J, Remuzzi G, eds. Oxford Textbook of Clinical Nephrology. 4th edn. Oxford University Press; 2016.
4. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med. 2006;119(7 Suppl 1):S30-5.
5. Hoorn EJ, Lindemans J, Zietse R. Development of severe hyponatraemia inhospitalized patients: treatment-related risk factors and inadequate management. Nephrol Dial Transplant. 2006;21(1):70-6.
6. Pillai BP, Unnikrishnan AG, Pavithran PV. Syndrome of inappropriate antidiuretic hormone secretion: Revisiting a classical endocrine disorder. Indian J Endocrinol Metab. 2011;15(Suppl3):S208-15.
7. Tachi T, Yokoi T, Goto C, Umeda M, Noguchi Y, Yasuda M, et al. Hyponatremia and hypokalemia as risk factors for falls. Eur J Clin Nutr. 2015;69(2):205-10.
8. Taal MW, Alan SL, Luyckx V. Brenner and Rector's the kidney. Skorecki K, Chertow GM, Marsden PA, eds. Philadelphia, PA: Elsevier; 2016.
9. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. Clin Chim Acta. 2003;337(1-2):169-72.
10. Clayton JA, Le Jeune IR, Hall IP. Severe hyponatraemia in medical in-patients: aetiology, assessment and outcome. QJM. 2006;99(8):505-11.
11. Rao MY, Sudhir U, Anil Kumar T, Saravanan S, Mahesh E, Punith K. Hospital-based descriptive study of symptomatic hyponatremia in elderly patients. J Assoc Phys India. 2010;58:667-9.
12. Padhi R, Panda B, Jagati S, Patra S. Hyponatremia in critically ill patients YR- 2014/2/1. Indian J Crit Care Med. 2014;18(2):83.
13. Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic-induced severe hyponatremia. Review and analysis of 129 reported patients. Chest. 1993;103(2):601-6.
14. Hoorn EJ, van Wolfswinkel ME, Hesselink DA, de Rijke YB, Koelewijn R, vanHellemond JJ, et al. Hyponatremia in imported malaria: the pathophysiological role of vasopressin. Malar J. 2012;11:26.
15. Mishra SK, Mohanty S, Mohanty A, Das BS. Management of severe and complicated malaria. J Postgrad Med. 2006;52(4):281-7.
16. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med. 2006;355(20):2099-112.
17. Vilapurathu JK, Rajarajan S. A prospective study to compare the clinical efficacy of Tolvaptan with 3% hypertonic saline solution in hospitalized patients having hyponatremia. J Res Pharm Pract. 2014;3(1):34-6.
18. Rajan S, Tosh P, Kadapamannil D, Srikumar S, Paul J, Kumar L. Efficacy of vaptans for correction of postoperative hyponatremia: a comparison between single intravenous bolus conivaptan versus oral tolvaptan. J Anaesthesiol Clin Pharmacol. 2018;34(2):193-7.
19. Tosh P, Rajan S, Kadapamannil D, Joseph N, Kumar L. Efficacy of oral tolvaptan versus 3% hypertonic saline for correction of hyponatraemia in post-operative patients. Indian J Anaesth. 2017;61(12):996-1001.
20. Chatterjee N, Sengupta N, Das C, Chowdhuri AR, Basu AK, Pal SK. A descriptive study of hyponatremia in a tertiary care hospital of Eastern India. Indian J Endocrinol Metab. 2012;16(2):288-91.

Cite this article as: Ahmed J, Khan MF, Umakanth S, Shetty S. Clinical and biochemical profile of hyponatremia and the role of vaptans in comparison to other standard modalities of therapy. Int J Res Med Sci 2023;11:3744-9.