DOI: 10.7860/JCDR/2026/84672.23596

Original Article

Internal Medicine Section

Real World use of Tolvaptan and Hypertonic Saline in Hyponatraemia: A Prospective Observational Study at a Tertiary Care Centre in India

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ABSTRACT

Introduction: The most common electrolyte imbalance among the hospitalised patients and mainly the elderly patients is hyponatraemia (serum sodium below 135 mmol/L), which has high morbidity due to prolonged hospitalisation and mortality.

Aim: To evaluate the clinical and biochemical profile of hyponatraemia and compare the real world usage of oral tolvaptan with the standard of care in normalising the serum sodium levels within inpatients.

Materials and Methods: This prospective observational study included 200 adults with serum sodium below 130 mmol/L in the Department of Medicine of Jagjivan Ram Hospital, Mumbai, Maharashtra, India (November 2020- June 2022). Treatment allocation was based on clinical judgment and aetiology (euvolemic/hypervolemic status). Serial serum sodium levels were monitored daily for seven days. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22.0, utilising Chi-square and independent t-tests to identify significant differences between treatment groups.

Results: The average age was 64.6±16.2 years; 50.5% of the population was female. Majority of euvolemic patients had Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) (38.5%). Tolvaptan group (n=22) demonstrated that the baseline sodium was lower (114.1±7.3 mmol/L vs 123.5±6.2 mmol/L other treatments), and that correction of this treatment was better (12.27±3.45 vs 5.0±2.18 mmol/L, p-value <0.001).

Conclusion: In the real-world setting, Tolvaptan is effectively utilised for profound hyponatraemia achieving faster recovery compared to conventional standard care. Optimisation of dosing of SIADH and heart failure required larger randomised trials.

Keywords: Antidiuretic hormone, Euvolemic, Syndrome of inappropriate antidiuretic hormone secretion

INTRODUCTION

The most common electrolyte imbalance that is encountered in clinical practice and is the most common among hospitalised patients with a range of 15-30% is hyponatraemia, or a serum sodium level that is lower than 135 mEq/L [1]. Among the geriatric population, electrolyte abnormalities are significantly higher due to the age-related physiological response in water homeostasis, multimorbidity and polypharmacy. According to the recent studies in India, it is estimated that the number of prevalence of hyponatraemia in elderly patients who are admitted to hospitals is between 18 and 29%, which is actually a sign of the severity of the disease but not a single piece of biochemical evidence [2,3]. The condition has important clinical consequences, such as long stays in the hospital, the further need in the intensive care, and the economic pressure that it brings to the healthcare systems.

Hyponatraemia being a standard treatment protocol is classified on three significant parameters including the severity, chronicity and volume status. The severity of hyponatraemia is mild (130-135 mEq/L), moderate (125-129 mEq/L) or severe (<125 mEq/L). Severe hyponatraemia is a medical emergency, which presents acute neurologic symptoms that include seizures, impaired consciousness, cerebral oedema, and potentially hyponatraemic encephalopathy, thus it requires prompt treatment to prevent the fatality. It is chronic (more than 48 hours) and acute (less than 48 hours) according to its chronicity [4,5]. The manifestation of acute hyponatraemia is accompanied by serious symptoms because of the acute changes in the osmotic pressure and cerebral oedema. Conversely, chronic hyponatraemia is frequently asymptomatic or has mild cognitive impairments because of cerebral adaptation when brain cells lose their organic osmolytes to preserve volume as a result of cerebral adaptation. This adaptation renders the velocity of sodium rectification essential; correction in a persistent instance is too quick may trigger Osmotic Demyelination Syndrome (ODS) a devastating demyelinating illness [6].

Proper diagnosis and management cannot be achieved without a systematic approach. It begins with the examination of the volume status (hypovolemic, euvolemic, or hypervolemic), which is then maintained by the measurement of urine sodium and urine osmolality, and is excluded by pseudohyponatraemia similarly thyroid and cortisol levels are determined. The euvolemic hyponatraemia is mainly caused by SIADH. The Schwartz and Bartter criteria can be called classic criteria of SIADH: euvolemic hyponatraemia (an inappropriately concentrated urine: more than 100 mOsm/kg), high urine sodium (more than 40 mEq/L), low plasma osmolality (less than 275 mOsm / kg), no diuretic use [7,8].

Strategy of management is very much specific to the subtype. Isotonic saline volume resuscitation should be used to inhibit ADH release in hypovolemic cases whereas hypervolemic patients should be treated using fluid restriction, loop diuretics and the underlying condition. In the case of euvolemic (SIADH), the initial treatment approach is fluid limitation and pharmaceutical interventions, such as urea, demeclocycline, and vaptans [9,10]. Immediate 3% hypertonic saline should be used to correct the acute symptoms of hyponatraemia with neurologic manifestation (seizures, altered consciousness), to rapidly replace sodium levels to 4-6 mEq/L, otherwise asymptomatic or mild cases should be managed conservatively. The initial intervention is vaptans (vasopressin receptor antagonists) like tolvaptan which provide a specific physiological response, where V2 receptors in the renal collecting duct are blocked, so that aquaresis (excretion of a fluid without electrolytes) is achieved, but the renin-angiotensin-aldosterone system is not activated [11,12]. Although the SALT-1 and SALT-2

trials confirmed the efficacy of tolvaptan compared to placebo, subsequent Indian studies have highlighted its practical advantages over 3% hypertonic saline, specifically noting better patient tolerance and sustained sodium correction levels at 72 hours in postoperative and hospitalised patients. First, the majority of the pivotal trials have compared tolvaptan to placebo, which results in a lack of head-to-head comparative data in relation to the active standard-of-care therapy such as 3% hypertonic saline in hospital environments. Second, most evidence is obtained in the Western populations, and there is lack of information related to Indian patients who frequently exhibit special tropical aetiologies and nutritional determinants. Lastly, there is limited real-world evidence regarding the safety and optimal dose of vaptans in patients with multiple co-morbidities who are elderly [13,14].

This work was done to fill these gaps by evaluating the clinical and biochemical profile of hyponatraemia and compared the real-world usage of oral tolvaptan with the standard of care in normalising the serum sodium levels within inpatients.

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of Medicine at Jagjivan Ram Hospital, a tertiary care referral hospital, situated in Mumbai, Maharashtra, India for 18 months (November 2020- June 2022), after getting the approval of the Institutional Ethics Committee (IEC Reference: EC/19/000153/12/2020). All the participants or their legal representatives gave informed consent (written), and the study went on according to the ethical standards provided in the Declaration of Helsinki.

Sample size: Based on the 30% hospital incidence rate of hyponatraemia reported by Upadhyay A et al., the sample size was calculated using the formula-Z^2PQ/d^2 [1]. With an allowable absolute error of 7%, the initial required sample size was determined to be 171. After accounting for a 20% loss to follow-up, the final sample size was set at 200.

Inclusion criteria: Adult patients with serum sodium level below 130 mmol/L at admission or at any given hospitalisation that were directly admitted to the Department of Medicine (not through other departments) and capable of making informed consent were included in the study.

Exclusion criteria: Patients whose serum sodium ≥130 mmol/L, pregnant or lactating women, patients under dialysis or experiencing acute kidney injury and requiring Continuous Renal Replacement Therapy (CRRT), patients with pseudohyponatraemia (because of severe hyperlipidemia or hyperproteinemia), and those with incomplete follow-up data (primary outcome assessment) were excluded from the study. These was by the normal standards of hyponatraemia management [5,15,16].

Study Procedure

Detailed medical history, (drug history to determine drug-induced hyponatraemia (thiazide diuretics, SSRIs, carbamazepine, etc.,) presenting symptoms and clinical examination results were captured using a pretested proforma against all enrolled patients. A clinical evaluation of volume status was done and categorised as hypovolemic, euvolemic or hypervolemic with serum and urine osmolality checked to assist diagnosis (using a cut-off of <30 mmol/L to indicate hypovolemia or oedematous states, and >30 mmol/L to indicate euvolemia/SIADH) [10]. The assignment of patients to treatment groups was done on clinical grounds. Strategies in oral tolvaptan (15 mg/day vs intravenous 3% hypertonic saline 1-2 ml/kg/hour) were determined by the senior attending physician based on: 1) hyponatraemia type (tolvaptan should be used in euvolemic/hypervolemic cases, particularly SIADH and CHF; 3% saline should be used in symptomatic acute/severe hyponatraemia <120 mmol/L or in hypovolemic states); 2) The initial treatment of hypovolemic patients focused on normal saline with underlying cause treatment, euvolemic patients were initially treated with fluid restriction (vaptans in cases of refractory cases or SIADH), hypervolemic patients were initially treated with fluid restriction/diuretics (vaptans in cases of refractory cases), and symptomatic/severe cases were initially treated with 3% saline. The primary outcome was the absolute change in serum sodium concentration from baseline at 24 and 48 hours. The secondary outcomes were length of stay in the hospital, discharge rate and aetiology (with special measurement of drug-induced causes).

STATISTICAL ANALYSIS

All the data collected were put into a Microsoft Excel spreadsheet and then analysed through SPSS version 22.0. The data were summarised using frequency and percentage for categorical variables and mean and standard deviation/median and Interquartile range for continuous variables. To compare the qualitative data across groups to determine their similarity, Chi-square or Fisher's exact test was utilised accordingly in the case of analytical statistics. The independent samples t-test were used to compare quantitative variables. A p-value <0.05 was considered statistically significant.

RESULTS

[Table/Fig-1] demonstrates patient demographics and baseline characteristics with higher proportion of individuals aged between 61-80 years. The study cohort was mainly a group of older patients with the average age of 64.6±16.2 years; 50.5% of the population was female. Majority of the patients, 91 (45.5%) were euvolemic. 66 (33%) were hypovolemic and 43 (21.5%) were found to be hypervolemic. Most common cause of hyponatraemia was SIADH in 77 (38.5%) patients followed by acute gastro-enteritis in 29 (14.5%). Clinical picture was heterogeneous; although such neurological symptoms as drowsiness prevailed in symptomatic patients, a significant number of them showed no symptoms, emphasising

Variables	n (%)
Age group (years)	
<20	1 (0.5)
21-40	20 (10.0)
41-60	42 (21.0)
61-80	104 (52.0)
>80	33 (16.5)
Gender	
Male	99 (49.5)
Female	101 (50.5)
Hospital stay (days)	
1-5	38 (19.0)
6-10	120 (60.0)
11-15	36 (18.0)
>15	6 (3.0)
Clinical symptoms at admission	
Drowsiness	55 (27.5)
Nausea	48 (24.0)
Vomiting	36 (18.0)
Confusion	29 (14.5)
Headache	16 (8.0)
Seizures	7 (3.5)
Hiccoughs	6 (3.0)
Asymptomatic	87 (43.5)
Hydration status at admission	
Euvolemic	91 (45.5)
Hypovolemic	66 (33.0)
Hypervolemic	43 (21.5)

[Table/Fig-1]: General characteristics of study population.

the insidiousness of chronic hyponatraemia because of cerebral adaptation processes [Table/Fig-1].

[Table/Fig-2] shows aetiological distribution. The range of the causes was wide, including infectious, cardiovascular, gastrointestinal, renal, drug-induced, and endocrine aaetiologies, which highlights the presence of multiple aetiologies causing hyponatraemia in tertiary care.

Aetiology	n (%)
Infectious causes	
Pneumonia	30 (15.0)
Malaria	14 (7.0)
Sepsis	6 (3.0)
Urosepsis	4 (2.0)
Dengue	3 (1.5)
Leptospirosis	2 (1.0)
Pulmonary tuberculosis	2 (1.0)
Cardiovascular causes	
Congestive heart failure	25 (12.5)
Cerebrovascular accident	6 (3.0)
Gastrointestinal causes	
Acute gastroenteritis	29 (14.5)
Enteric	5 (2.5)
Chronic liver disease	4 (2.0)
Pancreatitis	1 (0.5)
Oesophageal	1 (0.5)
Renal causes	
Chronic kidney disease	14 (7.0)
Drug-induced causes	
Thiazide diuretics	13 (6.5)
Selective Serotonin Reuptake Inhibitors (SSRI)	8 (4.0)
Carbamazepine	6 (3.0)
Spironolactone	3 (1.5)
Quetiapine	2 (1.0)
Endocrine causes	
Hypothyroidism	2 (1.0)
Hyperglycaemia	8 (4.0)
Neoplastic causes	
CNS carcinoma	1 (0.5)
Renal carcinoma	1 (0.5)
Gastric carcinoma	1 (0.5)
Cholangiocarcinoma	2 (1.0)
Lymphoma	1 (0.5)
Euvolemic causes	
SIADH†	77 (38.5)
Other causes	
Third spacing of fluid	21 (10.5)
Beer potomania	1 (0.5)

[Table/Fig-2]: Aetiology in the patients.
†SIADH (n=77, 38.5%) is the primary aetiology within the euvolemic group (n=91); 77/91 (84.6%) euvolemic patients had SIADH;
Three patients identified as pseudohyponatraemia post-enrolment were excluded from analysis per protocol and are not listed here

Normal saline was used as the most popular therapy of the first line on Day 1 (35.5%), which is characteristic of the standard initial volume resuscitation practice. On Day 3, there was progressive movement towards targeted therapies, with vaptans taking 10.4% of treatment allocation, as per guideline recommendations of refractory euvolemic/hypervolemic hyponatraemia [Table/Fig-3].

There was significant difference between the response of treatment based on the type of hyponatraemia. The strongest sodium recovery

Treatment modality	Day 1, n (%)	Day 2, n (%)	Day 3, n (%)
Normal saline	71 (35.5)	39 (18.5)	18 (8.5)
Fluid restriction/high salt diet	-	12 (5.7)	28 (13.2)
Vaptans	-	-	22 (10.4)
Diuretics	17 (8.0)	8 (3.8)	5 (2.4)
Double strength NS	-	17 (8.0)	16 (7.5)

[Table/Fig-3]: Treatment distribution (first-line and day-wise).
Percentages based on total enrolled patients (n=200). Treatment categories are not mutually exclusive

(mean change of 11.8 mEq/L) was observed in patients with euvolemic hyponatraemia (n=91, 45.5%), which is an indication of good responsiveness to specific interventions such as vaptans in patients with SIADH pre-eminence. Moderate or baseline improvement (8.2 mEq/L) after volume resuscitation and cause-specific therapy occurred in hypovolemic patients (n=66, 33.0%), whereas intermediate correction (9.5 mEq/L) was observed in hypervolemic cases (n=43, 21.5%), which received fluid restriction and diuretics [Table/Fig-4a]. In tolvaptan recipients (who are mostly in euvolemic and hypervolemic categories), sodium gain was far more significant compared to traditional treatments that were only applied to hypovolemic patients (12.27 mEq/L vs 5.03 mEq/L) [Table/Fig-4b].

Sodium status	value
Euvolemic (n=91)	11.8±4.1 mEq/L
Hypovolemic (n=66)	8.2±3.3 mEq/L
Hypervolemic (n=43)	9.5±3.7 mEq/L.

[Table/Fig-4a]: Mean sodium correction by volume status.

Treatment day	Vaptans (Mean±SD)	Other Modalities (Mean±SD)	p-value
Day 1	114.13±7.27	123.54±6.16	<0.001
Day 2	115.44±6.04	123.60±8.01	<0.001
Day 3	119.69±5.07	126.06±8.22	<0.001
Day 4	123.73±5.66	124.02±7.37	NS
Day 5	125.50±6.95	126.13±6.90	NS
Day 6	126.00±5.51	128.16±5.40	0.023
Day 7	126.40±5.13	128.57±5.49	0.048
Sodium increase from baseline	12.27±3.45	5.03±2.18	<0.001

[Table/Fig-4b]: Comparison of mean sodium levels at different days of treatment in patients with and without treatment with Vaptans.

[Table/Fig-4b] presents the temporal trend of serum sodium correction in the vaptan and non vaptan group. Tolvaptan patients had much less baseline sodium, indicative of preferential selection of more severe patients, but they were more likely to recover more quickly during the most intense 72 hours. This high rate of early correction highlights the aquaretic effect of vaptans, despite the fact that the two groups were both normalised by the end of days 4-5 with the traditional therapies slowly leveling off [Table/Fig-4b]. The statistically significant difference in the total sodium increment demonstrates the clinical usefulness of tolvaptan in the acute treatment [Table/Fig-4b].

The overall hospital mortality was 8% (n=16). An analysis of the causes of death revealed that cardiovascular and renal complications were the primary drivers, specifically congestive heart failure (n=5) and chronic kidney disease (n=4). Other fatalities were attributed to sepsis (n=2), chronic liver disease (n=1), and various malignancies, including CNS (n=1), gastric (n=1), renal (n=1), and cholangiocarcinoma (n=1). The results in terms of patient outcomes according to the severity of hyponatraemia are shown in [Table/Fig-5]. The total hospital mortality was low (8%), and discharges were more than 90% in all severity groups. Although elevated hyponatraemia tended towards greater mortality, this trend was not significant (p-value=0.167), presumably as a consequence

of aggressive early intervention measures that reduced the risks associated with being of high severity [Table/Fig-5].

Outcomes	Severity of hyponatraemia		Total	p-value
	Moderate	Severe		
Discharge	102 (94.44%)	82 (89.14%)	184 (92%)	0.167
Death	6 (5.56%)	10 (10.86%)	16 (8%)	
Total	108 (100%)	92 (100%)	200 (100%)	

[Table/Fig-5]: Association between severity of hyponatraemia and outcomes of the patients.

DISCUSSION

The current study included a higher proportion of elderly individuals with an average age of 64.6±16.2 years and a near-equal gender distribution (50.5% female). This type of participant distribution aligns with studies done by Ande SP et al., and Ioannou P et al., which showed geriatric skewness, although there were predominant male distribution [2,17]. Regarding clinical symptoms, 43.5% of the participants were asymptomatic during admission, which was similar to Chatterjee N et al., (48.21%) and this reflects the brains capacity for cerebral adaptation during chronic sodium depletion [3]. Among the symptomatic individuals in present study, drowsiness (27.5%) and nausea (24%) were the leading neurological markers consistent with disorientation (41.1%) and lethargy (78%) reported in emergency settings elsewhere [1].

In terms of volume distribution status, euvolemic hyponatraemia was the most common presentation in this study (45.5%), followed by hypovolemic (33%) and hypervolemic (21.5%) states. This type of distribution is substantiated by Chatterjee N et al., who found 50.74% euvolemic rate, though it contrasts sharply with Ande SP et al., where hypovolemia predominated at 67% [2,3]. SIADH was the primary aetiological driver in 38.5% of the cases, which falls within the standard clinical expectations of SIADH accounting for 35% to 46% of all hyponatraemia patients globally [14]. Furthermore drug-induced hyponatraemia contributes to 16% of study participants, with thiazide diuretics being a primary contributor similar to Ioannou P et al., found thiazide use associated with around 20% of elderly individuals [17].

Regarding the treatment efficacy, the current study found that tolvaptan group achieved a significantly higher sodium increase (12.27±3.45 mEq/L) compared to standard modalities (5.03±2.18 mEq/L) over the first 72 hours. While the present study findings highlight the rapid retention effect of vaptans, Vilapurathu J and Rajarajan S reported that 3% hypertonic saline was slightly superior in the initial 24-48 hours (8.03 mEq/L vs 5.11 mEq/L for tolvaptan) [12]. However, Tosh P et al., noted that while both treatments were equal to 48 hours, tolvaptan recipients maintained higher levels at 72 hours [12]. Additionally, present study observations are supported by Park GH et al., which demonstrated that the early response to tolvaptan was significantly better in the SIADH patients than in those with congestive heart failure (Δ Na 9.9 vs 6.9 mEq/L) [18].

The clinical outcomes and safety profiles in this study were favourable, showing an 8% hospital mortality and a median stay of 6-10 days. This mortality was lower than the 13.5% reported by Chatterjee N et al., and the 17.4% by Ioannou P et al., likely due to the varied age and comorbidity profiles across these regions [3,17]. Importantly, no cases of Osmotic Demyelination Syndrome (ODS) were recorded in the current Mumbai cohort, which was consistent with the low overall ODS incidence of 0.23% reported in major meta-analyses of hospitalised patients [19]. While rapid correction can increase ODS odds by 3.16-fold, it is also paradoxically linked to lower in-hospital mortality and shorter stays, reinforcing that a balanced, monitored correction strategy is essential for safety profile especially in elderly [20].

Limitation(s)

Being an observational study, it carries a risk of selection bias and limits causal inference between treatment and outcomes. The small proportion of patients receiving tolvaptan (10.4%) and the restriction of data to the hospital stay limited subgroup analyses and assessment of long-term outcomes. The findings of the study lack generalisability to resource-limited or primary care settings due to the conduction in tertiary care hospital, incomplete data on adherence, co-morbidities, and socio-economic factors, the findings may not be generalisable to resource-limited or primary care settings, and drug cost and availability may have influenced treatment choice.

CONCLUSION(S)

Hyponatraemia is a frequent electrolyte imbalance in hospitalised patients, especially the elderly and its aetiology is dependent on the volume status. Major causes were SIADH, use of diuretics, and heart failure across the euvolemic, hypovolemic, and hypervolemic groups respectively. Tolvaptan showed better efficacy in the prompt correction of sodium especially in SIADH and hypervolemic hyponatraemia. It is rational to consider large randomised controlled trials in the long-term running in the future to study its safety, optimal dose, and cost-efficiency in a variety of populations.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Oct 11, 2025
- Manual Googling: Feb 19, 2026
- iThenticate Software: Feb 21, 2026 (1%)

ETYMOLOGY: Author Origin

EMENDATIONS: 9

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 30, 2025**
Date of Peer Review: **Dec 03, 2025**
Date of Acceptance: **Feb 23, 2026**
Date of Publishing: **Jun 01, 2026**