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Effectiveness and hepatic safety of short-term low-dose tolvaptan for severe hyponatremia

A retrospective comparative study

Seyit Uyar, MD[a], Müberra Kaplan Çayır, MD[a], Nizameddin Koca, MD[b,*]

Abstract

Tolvaptan is an effective treatment for hyponatremia, but concerns about hepatotoxicity, mainly from high-dose, long-term use in autosomal dominant polycystic kidney disease, have limited its widespread application. This study aimed to assess the efficacy and hepatic safety of short-term, low-dose tolvaptan in hospitalized patients with severe hyponatremia, in comparison with 3% hypertonic saline. We retrospectively evaluated 236 hospitalized adults with severe hyponatremia (serum sodium < 125 mEq/L). A total of 118 patients received oral tolvaptan (15 mg/day for ≥ 4 days), while 118 received only 3% hypertonic saline. Changes in serum sodium, potassium, blood urea nitrogen, creatinine, and liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin) were analyzed over time. Liver enzymes were evaluated separately in subgroups with normal and elevated baseline values. Both treatment groups exhibited significant increases in serum sodium over time ($P < .001$). At the 24th and 72nd hours, sodium levels were higher in the tolvaptan group ($P = .042$). Among patients with normal liver enzymes at baseline, transient fluctuations in AST and ALT were observed, without clinically significant elevations. In those with elevated baseline values, AST and bilirubin levels showed improvement, while ALT remained stable. No cases of clinically apparent hepatotoxicity were reported. Short-term, low-dose tolvaptan is effective in correcting severe hyponatremia and does not appear to adversely affect liver function, even in patients with preexisting liver enzyme elevations. These findings support its use as a safe and practical therapeutic alternative in select hospitalized patients. Further prospective studies are warranted to confirm these observations.

Abbreviations: ADH = antidiuretic hormone, ALT = alanine aminotransferase, AST = aspartate aminotransferase.

Keywords: hepatotoxicity, hypertonic saline, hyponatremia, liver enzymes, low-dose, tolvaptan

1. Introduction

The most prevalent electrolyte disorder leading to hospitalization is hyponatremia, with the non-osmotic secretion of antidiuretic hormone (ADH) being accountable for its pathogenesis in 95% of cases.[1] Patients undergo assessment based on the etiology of hyponatremia, clinical characteristics, and laboratory parameters, and treatment strategies are devised, incorporating fluid restriction, isotonic or 3% hypertonic sodium replacement, and ADH receptor antagonists. The syndrome of inappropriate antidiuresis stands as one of the prevalent manifestations of hyponatremia. It represents an imbalance in sodium and water regulation, marked by compromised urine dilution and hypotonic hyponatremia. Notably, it occurs without underlying kidney pathology or any discernible non-osmotic trigger for ADH release, and its diagnosis relies on an exclusionary algorithm.[2,3]

Vasopressin receptor antagonists inhibit the action of ADH in the collecting duct, leading to water diuresis. These agents prove beneficial in managing hyponatremia, particularly in cases characterized by elevated urine osmolality and ADH levels.[3] Tolvaptan is an orally administered, selective, non-peptide vasopressin receptor antagonist.[4]

Following the SALT studies, which affirmed the efficacy and safety of tolvaptan in addressing hyponatremia, it has been employed for managing both euvolemic and hypervolemic cases of hyponatremia.[5] However, the elevation of liver enzymes observed in patients taking tolvaptan during the TEMPO study published in 2012 raised safety concerns.[6] Consequently, the U.S. Food and Drug Administration issued a safety warning regarding the long-term use of tolvaptan and its use in patients with liver disease.[7] The TEMPO study focused on patients with polycystic kidney disease and

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study adheres to the Declaration of Helsinki and the principles of good clinical practice. The Antalya Training and Research Hospital Clinical Research Ethics Committee approved the study, with the decision dated March 03, 2022 and numbered 5/14.

[a] Department of Internal Medicine, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey, [b] Department of Internal Medicine, University of Health Sciences, Bursa Faculty of Medicine, Bursa City Training & Research Hospital, Bursa, Turkey.

** Correspondence: Nizameddin Koca, Department of Internal Medicine, University of Health Sciences, Bursa Training & Research Hospital, Bursa 16280, Turkey (e-mail: nkoca@yahoo.com).*

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involved the prolonged and high-dose administration of tolvaptan. Thus, while monitoring alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels is advised for high-dose and long-term use of tolvaptan, monitoring of these tests is not required for low-dose and short-term use.[8]

Although numerous studies have focused on the high-dose use of tolvaptan, there is a scarcity of data in the literature regarding its low-dose and short-term use in patients hospitalized with hyponatremia. In this study, we retrospectively compared patients admitted to our clinic with a diagnosis of hyponatremia who were treated with tolvaptan to those who received 3% hypertonic saline. Our objective was to investigate the impact of low-dose, short-term tolvaptan administration on ALT, AST, and bilirubin levels and to evaluate its effectiveness by comparing it with 3% hypertonic saline.

2. Methods

2.1. Study design and ethical approval

This retrospective observational study was conducted at the Antalya Training and Research Hospital, analyzing medical records from patients hospitalized with a diagnosis of hyponatremia between 2017 and 2022.

The study was approved by the Antalya Training and Research Hospital Clinical Research Ethics Committee (Decision No: 5/14, Date: March 03, 2022), and it adhered to the Declaration of Helsinki and principles of good clinical practice. The need for informed consent was waived due to the retrospective design.

2.2. Patient selection

Inclusion criteria were:

- Age ≥ 18 years,
- Documented severe hyponatremia (serum sodium < 125 mEq/L) on admission, and
- Availability of daily laboratory data for at least 3 consecutive days during treatment and follow-up.

Exclusion criteria included pseudo-hyponatremia, hypovolemic hyponatremia, liver cirrhosis, or insufficient laboratory records.

Based on these criteria, 236 patients were included and categorized into 2 groups: 118 patients treated with oral tolvaptan (15 mg/day for a minimum of 4 days) and 118 patients who received only 3% hypertonic saline.

2.3. Treatment protocol

The tolvaptan group received 15 mg once daily for at least 4 consecutive days during hospitalization. The control group received 3% hypertonic saline infusion at individualized doses based on clinical judgment and sodium monitoring. No patient in either group received combination therapy. Standard supportive care was provided to all patients.

2.4. Outcomes and laboratory measures

The primary effectiveness outcome was change in serum sodium levels over time. The secondary safety outcome was the change in liver function tests (AST, ALT, and total bilirubin) evaluated at baseline, on the fourth day of treatment, and the third day post-treatment.

Patients in the tolvaptan group were further subcategorized based on baseline liver enzyme levels into (a) normal and (b) elevated groups, using the following cutoffs: AST > 50 U/L, ALT > 50 U/L, and total bilirubin > 1.5 mg/dL.

Additional laboratory parameters analyzed included serum potassium, blood urea nitrogen, and creatinine. Clinical variables such as age, gender, type of hyponatremia (euvolemic vs hypervolemic), and length of hospital stay were also recorded.

2.5. Statistical analysis

All analyses were performed using IBM Statistical Package for the Social Sciences Statistics, version 26.0 (IBM Corp., Armonk). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Data were presented as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables were summarized as counts and percentages.

Group comparisons for continuous variables were performed using the Independent Samples *t* test or the Mann–Whitney *U* test, based on data distribution. Categorical variables were compared using the Chi-square test or Fisher exact test. Within-group changes over time were analyzed using the Friedman test for non-parametric data. Between-group repeated measures were compared using two-way repeated measures ANOVA. Statistical significance was defined as a *P*-value < .05.

3. Results

The median age of 236 patients was 74 (range 65–82) years, and the median length of stay was 9 (range 7–11) days. The percentage of women participants was 53.4%. Among the patients, 30.5% had hypervolemic hyponatremia, while 69.5% had euvolemic hyponatremia. The length of hospital stay was significantly longer in patients receiving tolvaptan treatment (9 [8–15] days compared to 8 [7–9] days; $P < .001$). Median age values were similar between the 2 groups ($P = .127$). The proportion of female patients was significantly higher in the 3% hypertonic saline treatment group than in the tolvaptan group ($P = .037$) (Table 1).

It was observed that the sodium levels of patients receiving both tolvaptan and 3% hypertonic treatment increased

Table 1

Demographical characteristics and types of hyponatremias of all patients according to the treatment of hyponatremia.

Variables, (n = 236)			
Median age (min–max), *years*			74 (65–82)
Median hospital stay (min–max), *days*			9 (7–11)
Gender			
Male, n(%)			110 (46.6)
Female, n(%)			126 (53.4)
Type of hyponatremia			
Hypervolemic, n(%)			72 (30.5)
Euvolemic, n(%)			164 (69.5)
	Tolvaptan (n = 118)	**3% hypertonic (n = 118)**	***P***
Median age, (min–max), *years*	74 (62–82)	75 (67–82)	.127*
Median hospital stay (min–max), *days*	9 (8–15)	8 (7–9)	**<.001***
Gender			**.037†**
Male, n(%)	63 (53.4)	47 (39.8)	
Female, n(%)	55 (46.6)	71 (60.2)	
Type of hyponatremia			**<.001†**
Hypervolemic, n(%)	56 (47.5)	16 (13.6)	
Euvolemic, n(%)	62 (52.5)	102 (86.4)	

Bold values indicate statistical significance.

*Mann Whitney *U* test, *Med*(*IQR*).

†Pearson Chi-square test, Yates correction, Fisher Exact test, n(%).

significantly over time ($P < .001$). Meanwhile, potassium levels showed a statistically significant increase during treatment for the group receiving the 3% hypertonic solution ($P = .009$) (Table 2).

Analysis of the changes in laboratory findings over time according to treatment groups highlighted a significant decrease in sodium levels ($P = .042$). The sodium values on the 24th hour and the 72nd-hour post-treatment were higher in the tolvaptan group, while they remained lower on other days. No significant differences were found in the changes in potassium, blood urea nitrogen, and creatinine levels over time between the treatment groups (Table 3).

When the changes in AST, ALT, and total bilirubin values over time were examined in patients using tolvaptan who had normal liver function tests before treatment, significant changes were observed in AST ($P = .005$) and ALT ($P = .031$) values, while total bilirubin values remained unchanged ($P = .364$). In patients with elevated initial test results, significant changes were identified in AST ($P < .001$) and total bilirubin ($P = .049$) levels, but no significant change was observed in ALT levels ($P = .123$) (Table 4).

4. Discussion

In our study, both tolvaptan and 3% hypertonic saline effectively increased serum sodium levels in hospitalized patients with severe hyponatremia. The subgroup receiving low-dose, short-term tolvaptan demonstrated comparable, and in some timepoints superior, sodium correction compared to 3% saline, particularly at the 24th and 72nd hours of treatment. This observation aligns with previous findings supporting the efficacy of tolvaptan in correcting hyponatremia through aquaresis, particularly in syndrome of inappropriate antidiuretic hormone and euvolemic states.[9–11]

Although both treatments resulted in significant sodium elevation over time, our between-group comparison revealed an interaction effect ($P = .042$), indicating a differing trajectory of sodium correction rather than a treatment-associated decline. This distinction may reflect transient fluctuations in sodium kinetics related to pharmacodynamics and patient-specific volume status.[12]

Tolvaptan's hepatotoxicity profile, particularly with prolonged and high-dose administration, remains a central concern. The TEMPO trial revealed elevations in liver enzymes in up to 11% of patients receiving tolvaptan long-term, leading to regulatory warnings and restrictions on use in individuals with liver disease.[13,14] In contrast, our study provides supportive data regarding the hepatic safety of short-term, low-dose tolvaptan in an acute inpatient setting. Among patients with normal baseline liver function tests, AST and ALT fluctuations remained within reference ranges. For those with elevated initial AST, ALT, or bilirubin levels, follow-up values demonstrated stabilization or mild improvement, particularly for AST and bilirubin.[15]

Importantly, these biochemical fluctuations did not translate into clinical hepatotoxicity. This observation is consistent with a recent meta-analysis of randomized controlled trials in cirrhotic patients with diuretic-refractory ascites, which reported no significant hepatotoxic events associated with short-term tolvaptan use.[16]

This reinforces the concept that hepatic safety concerns are likely dose- and duration-dependent, and may not apply to the short-term, low-dose protocols evaluated in our study.[17]

Nonetheless, these findings must be interpreted with caution due to potential baseline imbalances between treatment groups. The tolvaptan group had a significantly longer hospital stay, which may reflect higher disease severity or more complex clinical scenarios. Additionally, there was a gender imbalance, with a greater proportion of female patients in the 3% hypertonic saline group. Since liver enzyme profiles and pharmacokinetics can differ by sex and clinical burden, these unadjusted differences could confound the interpretation of treatment-related effects. A lack of multivariable regression analysis to adjust for these confounders is a limitation of our study design.

From a clinical perspective, our findings suggest that short-term use of low-dose tolvaptan represents a viable therapeutic alternative for correcting severe hyponatremia in selected hospitalized patients (particularly when fluid overload or rapid correction is a concern). Unlike hypertonic saline, tolvaptan offers oral administration and aquaretic action, which may be advantageous in certain settings such as syndrome of inappropriate antidiuretic hormone.[13]

Future prospective studies should be designed to include adjustment for key confounders such as comorbidities, sex, and hospital stay duration. Moreover, randomized controlled trials comparing fixed-duration, low-dose tolvaptan with standard treatments would be valuable in defining its optimal clinical use and hepatic safety profile.

5. Conclusion

While our study represents the first investigation into tolvaptan's side effects based on AST, ALT, and bilirubin values, it is constrained by its retrospective design, omission of patients' accompanying comorbidities, lack of analysis regarding mortality associations, and absence of post-discharge follow-up. We have demonstrated that tolvaptan effectively corrects hyponatremia when used alone or compared to 3% hypertonic saline. Importantly, our findings indicate that using tolvaptan for short durations and at low doses does not adversely affect AST, ALT, and bilirubin levels, regardless of comorbidities.

Table 2

Variations of the serum sodium, potassium, BUN, and creatinine values of the patients were measured pretreatment, on the third day of treatment, and on the third day post-treatment.

Laboratories, median (min–max)		Pretreatment	24th hour	48th hour	72nd hour	Post-treatment 72nd hour	P*
Sodium (mEq/L)	Tolvaptan	122 (118–124)	124 (120–127)	126.5 (122–129)	129 (127–133)	131 (130–135)	**<.001**
	3% hypertonic	120 (117–124)	124 (120–128)	127 (123–130)	130 (126–133)	132 (129–134)	**<.001**
Potassium (mEq/L)	Tolvaptan	4.3 (3.75–4.9)	4.25 (3.9–4.8)	4.4 (3.9–4.8)	4.3 (3.9–4.8)	4.4 (3.9–4.7)	.606
	3% hypertonic	3.96 (3.4–4.5)	3.9 (3.5–4.4)	4 (3.5–4.4)	4 (3.6–4.5)	4.1 (3.6–4.5)	**.009**
BUN (mg/dL)	Tolvaptan	26 (15–45)	26 (14–49)	24 (14–46)	25 (15–43)	24.5 (15–38)	.221
	3% hypertonic	17.5 (11–31)	17 (11–31)	16 (10–30)	16 (11–30)	16.5 (11–27)	.656
Creatinine (mg/dL)	Tolvaptan	1.2 (0.82–1.54)	1.13 (0.84–1.54)	1.11 (0.83–1.58)	1.11 (0.88–1.56)	1.12 (0.88–1.51)	.684
	3% hypertonic	0.99 (0.74–1.4)	1 (0.8–1.32)	1.01 (0.77–1.34)	0.98 (0.74–1.3)	1 (0.74–1.24)	.059

Bold values indicate statistical significance.

BUN = blood urea nitrogen.

*Friedman test.

Table 3

Comparison of the changes in serum sodium, potassium, BUN, and creatinine values over time according to treatment groups.

Variables	Pretreatment	24th hour	48th hour	72nd hour	Post-treatment 72nd hour	*P**
Sodium (mEq/L)						
Tolvaptan	120.5678 ± 5.57387	123.6186 ± 5.32679	126.161 ± 5.28984	129.7542 ± 5.0161	132.3559 ± 4.61237	**.042**
3% hypertonic	119.6102 ± 5.87627	124.2203 ± 5.57947	127.2712 ± 6.14867	129.8136 ± 5.38905	132.1186 ± 4.23895	
Potassium (mEq/L)						
Tolvaptan	4.3451 ± 0.78367	4.7696 ± 4.70868	4.3478 ± 0.76389	4.2912 ± 0.6521	4.3465 ± 0.63007	.191
3% hypertonic	3.9521 ± 0.71334	3.8899 ± 0.69378	3.9292 ± 0.62527	4.0625 ± 0.55166	4.0642 ± 0.57953	
BUN (mg/dL)						
Tolvaptan	33.6271 ± 24.76136	33.0593 ± 23.32318	31.7966 ± 22.08165	32.9407 ± 31.80531	31.2873 ± 22.79561	.598
3% hypertonic	24.6017 ± 19.3493	23.7373 ± 19.41381	23.4745 ± 20.43331	22.2034 ± 17.48042	22.6186 ± 18.19877	
Creatinine (mg/dL)						
Tolvaptan	1.3204 ± 0.68819	1.3464 ± 0.89863	1.2831 ± 0.64507	1.6014 ± 3.0984	1.3097 ± 0.67255	.296
3% hypertonic	1.1847 ± 0.65028	1.2458 ± 1.0306	1.7728 ± 6.45896	1.1502 ± 0.60594	1.3178 ± 2.18135	

Bold values indicate statistical significance.

BUN = blood urea nitrogen.

*Between-subjects repeated measures ANOVA, mean ± SD.

Table 4

Comparison of the effect of tolvaptan on the serum ALT, AST, and total bilirubin values in the patient groups (patients with normal and elevated levels).

Normal	Pretreatment	72nd hour	Post-treatment 72nd hour	*P**
AST (U/L)	23 (17–31)	23 (17–27)	19 (15–24)	**.005**
ALT (U/L)	14 (11–20)	16 (11–23)	14 (11–22)	**.031**
Total bilirubin (mg/dL)	0.7 (0.58–1)	0.7 (0.5–0.9)	0.7 (0.6–0.9)	.364
Elevated				
AST (U/L)	80 (48–126)	49 (34–94)	53 (33–106)	**<.001**
ALT (U/L)	54 (23–101)	41 (24–73)	36 (20–72)	.123
Total bilirubin (mg/dL)	2.71 (1.49–6.4)	2.4 (1–5.3)	2.1 (1–4.9)	**.049**

Bold values indicate statistical significance.

ALT = alanine aminotransferase, AST = aspartate aminotransferase.

*Friedman test.

Author contributions

Conceptualization: Seyit Uyar, Müberra Kaplan Çayır.
Data curation: Seyit Uyar, Müberra Kaplan Çayır.
Formal analysis: Seyit Uyar, Nizameddin Koca.
Investigation: Müberra Kaplan Çayır.
Methodology: Seyit Uyar.
Resources: Müberra Kaplan Çayır.
Supervision: Seyit Uyar.
Writing – original draft: Seyit Uyar, Müberra Kaplan Çayır.
Writing – review & editing: Seyit Uyar, Nizameddin Koca.

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