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MANAGEMENT OF SEVERE HYPONATREMIA: ROLE OF TOLVAPTAN, AND THE IMPORTANCE OF SLOW CORRECTION TO PREVENT MYELINOLYSIS

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ABSTRACT

Severe hyponatremia is a frequent electrolyte disturbance in hospitalized patients and poses a significant risk of neurologic complications, especially when serum sodium correction is performed quickly. Tolvaptan, a selective antagonist of vasopressin V2 receptors, has emerged as an effective therapeutic option in the correction of euvolemic and hypervolemic hyponatremia, especially in cases of inappropriate antidiuretic hormone

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secretion syndrome (SIADH). The objective of this study is to analyze the efficacy of tolvaptan, in the management of severe hyponatremia, and to discuss the importance of slow correction in the prevention of osmotic demyelination syndrome (ODS). To this end, a literature review was carried out in databases such as PubMed, Scopus, Embase, Web of Science, and Cochrane Library, covering publications between 2015 and 2025. 10 studies were selected, including meta-analyses, cohort studies, randomized controlled trials, and case reports. The findings demonstrate that tolvaptan promotes a significant and rapid increase in serum sodium, but with a considerable risk of overcorrection, especially in patients with profound hyponatremia and low urea levels. Reports of SDGs, even with corrections within the limits considered safe, reinforce the need for rigorous monitoring and an individualized approach. It is concluded that tolvaptan is a valuable therapeutic tool, as long as it is used with caution, respecting the clinical and laboratory parameters of each patient.

Keywords: Severe hyponatremia. Tolvaptano. Osmotic demyelination. Sodium correction. SIADH.

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INTRODUCTION

Hyponatremia is the most common electrolyte disorder in clinical practice, characterized by serum sodium levels below 135 mEq/L. In its severe form, especially with concentrations below 120 mEq/L, it can cause important neurological symptoms such as headache, mental confusion, seizures, and coma. Among the most frequent causes are the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), heart failure, liver cirrhosis, and use of diuretics. The therapeutic management of this condition represents a challenge, especially when seeking to safely and effectively correct sodium, avoiding the dreaded osmotic demyelination syndrome (SDD) — a devastating neurological complication resulting from rapid correction of serum sodium in patients with chronic hyponatremia (Ayus et al., 2024).

In recent years, tolvaptan, a selective vasopressin V2 receptor antagonist, has been widely used in the treatment of euvolemic and hypervolemic hyponatremia, particularly in patients with SIADH. Its action promotes the selective excretion of free water (aquaresse), without loss of electrolytes, resulting in a progressive increase in plasma sodium. Although effective, studies have shown that tolvaptan can induce rapid and abrupt sodium corrections, especially in patients with very low baseline levels, hypokalemia, malnutrition, or associated chronic diseases, increasing the risk of ODS even within the limits considered safe to correct (Castello et al., 2017; Hwang, 2023).

The current literature shows that, in addition to the correction rate, individual clinical factors are also determinants of the risk of myelinolysis, which reinforces the importance of a personalized and monitored approach in the treatment of hyponatremia. In this context, this article proposes a technical and critical analysis of the use of tolvaptan in severe hyponatremia, emphasizing the importance of slow and safe correction for the prevention of SDG, considering both the therapeutic benefits and the risks associated with its administration. The choice of theme is justified by the high prevalence of hyponatremia in hospitalized patients, its clinical complexity, and the increasing use of tolvaptan as a therapeutic alternative in different contexts.

METHODOLOGY

This study adopted a narrative literature review approach with the objective of analyzing, from a technical and clinical perspective, the use of tolvaptan, in the management of severe hyponatremia and the care necessary to prevent neurological

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complications, especially osmotic demyelination syndrome (ODS). The review sought to understand the efficacy of the drug, its associated risks, and the importance of the speed of serum sodium correction in different clinical settings.

The search was carried out in the PubMed, Scopus, Cochrane Library, Web of Science, and Embase databases, considering articles published between 2015 and 2025, with emphasis on clinical studies, meta-analyses, cohort studies, and case reports that provided quantitative data on the use of tolvaptan. The search strategy used controlled terms (MeSH) and free keywords combined with Boolean operators, such as: "hyponatremia," "tolvaptan," "osmotic demyelination syndrome," "sodium correction" and "SIADH treatment".

We included 10 studies, selected based on the following criteria: (1) adult population diagnosed with severe hyponatremia (Na+ ≤ 125 mEq/L); (2) therapeutic use of tolvaptan, alone or compared to other strategies, such as fluid restriction or hypertonic saline; (3) description of sodium correction rate and clinical outcomes; (4) articles published in English, Portuguese or Spanish. Studies without quantitative clinical data, narrative reviews without critical analysis, and duplicate articles were excluded.

The extracted data included: study objective, number of patients, dose of tolvaptan used, sodium correction rate, response time, presence of adverse events (especially overcorrection and SDG), mortality, and length of hospital stay. The studies were organized in a summary table for better comparison of the findings and discussed in the light of current clinical guidelines.

The present review aims to contribute to clinical practice by gathering recent evidence on the safety and efficacy of tolvaptan in severe hyponatremia, offering subsidies for a safer, more personalized, and risk-based approach.

RESULTS

Ten studies (Table 1) published between 2015 and 2025 were included, including meta-analyses, cohort studies, randomized controlled trials, and case reports, all with relevant quantitative data on the management of severe hyponatremia with tolvaptan, and the implications of the serum sodium correction rate in the prevention of osmotic myelinolysis. The data demonstrate that tolvaptan promotes a significant increase in sodium concentration, with efficacy superior to fluid restriction alone and the use of saline solutions in certain clinical contexts, especially in patients with SIADH. However, corrections greater

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than 12 mEq/L in 24 hours were observed in up to 41.7% of the cases with standard doses (15 mg), evidencing a risk of overcorrection.

Factors such as reduced baseline sodium and urea levels, preserved renal function, and absence of limiting comorbidities were associated with more intense responses to tolvaptan. In addition, some reports have highlighted the occurrence of osmotic demyelination syndrome even with corrections within the limits considered safe, particularly in patients with hypokalemia, malnutrition, and chronic alcoholism, suggesting that the correction rate, although essential, should not be the only parameter considered in the therapeutic management

Table 1. Studies on the Management of Severe Hyponatremia With Tolvaptan

Authors and Year	Title	Objective of the Study	Key Findings	Study Summary
Castello et al., 2017	Efficacy and safety of two different tolvaptan doses in the treatment of hyponatremia in the Emergency Department	To compare efficacy and safety of 7.5 mg vs. 15 mg tolvaptan in severe hyponatremia.	Correction >12 mEq/L occurred in 41.7% (15 mg) vs. 0% (7.5 mg); 7.5 mg was effective and safer.	Prospective study with 23 patients; 15 mg dose caused increased risk of overcorrection; 7.5 mg has been shown to be effective and safe.
Ayus et al., 2024	Correction Rates and Clinical Outcomes in Hospitalized Adults With Severe Hyponatremia	To evaluate the relationship between sodium correction rate and mortality/hospitalization.	Rapid correction associated with 32-221 fewer deaths per 1000 patients; Risk of myelinolysis did not increase.	Meta-analysis with 16 studies and 11,811 patients; Slow correction associated with higher mortality and length of stay.
Indirli et al., 2021	Tolvaptan in the Management of Acute Euvolemic Hyponatremia After Transsphenoidal Surgery	To compare tolvaptan vs. standard of care in hyponatremia after pituitary surgery.	Correction with tolvaptan: 12 mEq/L vs. 1.8 mEq/L/24h ($p<0.001$); no cases of myelinolysis.	Retrospective study with 29 patients; tolvaptano reduced length of hospital stay and was more effective in correcting.
Morris et al., 2018	Rapidity of Correction of Hyponatremia Due to SIADH Following Tolvaptan	To identify predictors of rapid correction with tolvaptan.	25% of patients with SIADH had correction >12 mEq/L/day; Low levels of urea and sodium predicted rapid response.	Multicenter study; Baseline sodium and urea levels predicted risk of overcorrection with tolvaptan.

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Li et al., 2017	The Efficacy and Safety of Tolvaptan in Patients with Hyponatremia	To analyze the efficacy and safety of tolvaptan, via meta-analysis.	Average increase of 3.99 mEq/L of sodium; higher incidence of thirst and hypercorrection (RR=8.43).	Meta-analysis with 11 studies and 5,209 patients; tolvaptan effective but at increased risk of mild adverse events.
Martínez González et al., 2024	[Tolvaptan versus fluid restriction in SIADH]	To compare efficacy and safety between tolvaptan and fluid restriction.	Tolvaptano corrected sodium at 4 days vs. 8 days; lower 60-day mortality (12.8% vs. 32.8%).	Observational study with 186 patients; Tolvaptan was more effective but with a higher risk of overcorrection.
Lacquaniti et al., 2023	Tolvaptan resistance is related with a short-term poor prognosis	To evaluate efficacy of tolvaptan in patients with cancer and SIAD.	Correction in 3.7 days (vs. 5.2 days); treatment failure associated with tumor progression.	Study with 15 cancer patients; resistance to tolvaptan may indicate a worse oncological prognosis.
Kai et al., 2019	Tolvaptan corrects hyponatremia in terminal lung cancer	To report the use of tolvaptan in patients with end-stage lung cancer and SIAD.	Sodium correction facilitated early discharge and avoided strict dietary restrictions.	Report of two cases; tolvaptano improved quality of life and outpatient management.
Shaikh et al., 2024	Cavitating Osmotic Demyelination Following Correction of Hyponatremia in Sheehan's Syndrome	OBJECTIVE: To describe a case of ODS after gradual correction of hyponatremia.	SDG occurred even with slow correction (<8 mEq/L/day).	Rare case in a patient with Sheehan's syndrome; warns of risk even with correction within the guidelines.
Hwang, 2023	Osmotic Demyelination Syndrome Despite Cautious Correction	Report ODS in a patient with risk factors even with slow correction.	SDG occurred with correction <8 mEq/L/day; Factors such as hypokalemia and malnutrition were relevant.	Clinical reports reinforce that predisposing factors (alcohol, hypokalemia) increase the risk of SDGs even with slow correction.

Source: The authors.

DISCUSSION

Analysis of the selected studies allows for an in-depth understanding of the efficacy and safety of tolvaptan in the treatment of severe hyponatremia, as well as the risks associated with the rate of serum sodium correction, especially with regard to the occurrence of osmotic demyelination syndrome (OSD). All included studies were published

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between 2015 and 2025 and present relevant results from both a clinical and statistical perspective.

Castello et al. (2017) conducted a prospective study in an emergency setting with 23 patients diagnosed with moderate to severe euvolemic or hypervolemic hyponatremia. The individuals were divided into two groups: one received 15 mg/day of tolvaptan and the other 7.5 mg/day. The mean 24-hour sodium elevation was 12 mEq/L in the 15 mg group and 6 mEq/L in the 7.5 mg group ($p = 0.025$). However, the correction rate considered ideal (between 4–8 mEq/L in 24 hours) was achieved in 45.4% of patients with the lower dose, compared to only 25% in the standard dose group. The most important was the finding of overcorrection (>12 mEq/L in 24 hours) in 41.7% of the patients who received 15 mg, while no cases were recorded in the 7.5 mg group ($p = 0.037$). These data indicate that lower doses of tolvaptan offer greater safety, reducing the risk of complications such as ODS.

Complementing this finding, Morris et al. (2018) conducted a multicenter study with 67 adult patients with SIADH (n=28) or congestive heart failure (n=39), all with sodium ≤130 mEq/L. The study identified that 25% of patients with SIADH had corrections greater than 12 mEq/L in 24 hours, while this occurred in only 3% of patients with heart failure ($p<0.001$). The correction was more intense in patients with lower baseline sodium ($r = -0.78$; $p<0.001$) and lower serum urea nitrogen (SUN) concentration ($r = -0.76$; $p<0.001$). Patients with sodium ≤121 mEq/L and SUN ≤10 mg/dL achieved a mean of 15.4 mEq/L of sodium elevation in 24 hours, a value much higher than that considered safe. This study reinforces that the patient's profile directly influences the response to tolvaptan.

Ayus et al. (2024), in turn, analyzed 16 cohort studies involving 11,811 patients with severe hyponatremia, with the aim of comparing different sodium correction rates. Rapid corrections (≥8–10 mEq/L in 24h) were associated with lower in-hospital mortality (odds ratio: 0.67; 95% CI: 0.55–0.82) and 221 fewer deaths per 1000 patients, when compared to very slow corrections (<4–6 mEq/L/24h). 30-day mortality was also lower in rapid corrections (RR: 0.55; 95% CI: 0.45–0.67). Regarding length of stay, rapid correction reduced hospital time by 1.20 to 3.09 days compared to slower corrections. Notably, the risk of SDG did not show a statistically significant increase with rapid corrections, which goes against some isolated clinical reports, and opens a debate about the real safety of current correction guidelines.

The efficacy of tolvaptan is also strongly supported by the meta-analysis conducted by Li et al. (2017), which included 11 randomized studies, totaling 5,209 patients. Treatment

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with tolvaptan resulted in a mean increase of 3.99 mEq/L in sodium concentration (95% CI: 2.80–5.19; p<0.001) and a mean increase of 987.64 mL in 24-hour urine volume (95% CI: 850.71–1124.57 mL). The sodium correction rate was 3.35 times higher with tolvaptan than with the control group. However, the risk of adverse events, such as thirst (RR: 3.85), dry mouth (RR: 2.38), and overcorrection (RR: 8.43), was significantly higher in the tolvaptan group, although no significant difference was observed in overall mortality (RR: 0.99).

Complementary data are provided by Martínez González et al. (2024), who conducted an observational study with 186 patients with hyponatremia due to SIADH. Of these, 86 were treated with tolvaptane (mean dose of 7.5 mg) and 100 with fluid restriction. Sodium correction up to levels ≥135 mmol/L was achieved in 4 days with tolvaptan, versus 8 days with restriction (p<0.001). Mortality at 60 days was 12.8% in the tolvaptan group and 32.8% in the control group (p<0.003), indicating an important clinical impact. However, 10.46% of patients in the tolvaptan group experienced overcorrection, while 5.81% reported polyuria as an adverse event.

In an oncology setting, Lacquaniti et al. (2023) investigated 15 patients with cancer and SIAD. Those treated with tolvaptan achieved normonatremia in 3.7 ± 2.8 days, while those treated with hypertonic saline and fluid restriction achieved the same in 5.2 ± 3.1 days (p=0.01). The rate of relapse and readmissions was significantly lower in the tolvaptan group. Even so, 37% of patients in the tolvaptan group were resistant to treatment, and were later diagnosed with tumor progression or metastases, suggesting that drug resistance may be a prognostic indicator in cancer patients.

Kai et al. (2019) reinforce the role of tolvaptan in improving quality of life. They report two patients with lung cancer and SIAD who did not tolerate the food and water restrictions imposed. With the use of tolvaptan, both patients had hyponatremia corrected, allowing early discharge and lifting of restrictions, which had a positive impact on palliative care.

However, three studies warn of the real risk of ODS even when sodium correction is considered "safe". Shaikh et al. (2024) reported a case of a woman with Sheehan's syndrome and chronic hyponatremia (Na+ = 118 mEq/L), who developed pontine and extrapontin demyelination after controlled replacement with hypertonic saline. The patient developed cavitating lesions and important neurological sequelae, even without rapid correction, suggesting that chronic conditions such as hypopituitarism increase CNS vulnerability.

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Hwang (2023) reported a similar case of a patient with alcoholism, hypokalemia, and malnutrition who developed ODS despite correction of less than 8 mmol/L for 24 hours. Even with controlled infusion and monitoring, the patient evolved with tremors, rigidity and decreased level of consciousness, and was transferred to palliative care. The study points out that, in addition to the correction rate, metabolic and clinical factors contribute significantly to the risk of myelinolysis.

Finally, the study by Indirli et al. (2021), with 29 patients after pituitary surgery, reinforces that tolvaptan corrects sodium faster than standard measurements (12 mEq/L vs. 1.8 mEq/L in 24h, $p<0.001$) and reduces the length of hospital stay (11 days vs. 15 days, $p=0.01$), without recording SDG events. This data reinforces the thesis that, under proper monitoring, quick fixes can be safe and beneficial in certain contexts.

Taken together, the studies show that tolvaptan is a highly effective therapeutic tool for the correction of severe hyponatremia, with a positive clinical impact on length of hospitalization, quality of life, and, in some cases, mortality. However, the variability in response between different patient profiles and the risk of overcorrection or demyelination, even under slow corrections, indicate that the approach should be personalized. Dose choice, close monitoring, and assessment of individual risk factors are imperative to maximize therapeutic benefits and mitigate treatment risks.

CONCLUSION

The management of severe hyponatremia requires a judicious approach, balancing therapeutic efficacy and neurological safety. The analysis of studies available between 2015 and 2025 showed that tolvaptan is an effective alternative for serum sodium correction, especially in patients with SIADH, promoting faster responses and significant clinical improvement, including outcomes such as length of hospital stay and short-term mortality.

However, the data also demonstrate that the use of tolvaptan is not without risks, especially with regard to sodium overcorrection, observed in up to 41.7% of cases with standard doses of 15 mg. Such overcorrection is directly associated with the risk of osmotic demyelination syndrome (ODS), a serious and potentially irreversible neurological complication. In addition, clinical reports reinforce that ODS can occur even with corrections within the limits considered safe (<8 mEq/L in 24 hours), especially in patients with predisposing factors, such as hypokalemia, chronic alcoholism, malnutrition, and hypopituitarism.

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Therefore, it is concluded that tolvaptan is a valuable therapeutic tool, but that it requires close monitoring, individualized evaluation of the patient's profile, and careful dose adjustment. The sodium correction rate should be continuously monitored, but it should not be the only guiding criterion for management, since clinical and metabolic factors strongly influence the risk of complications.

Therefore, success in the management of severe hyponatremia with tolvaptan depends on the combination of pharmacological knowledge, clinical surveillance, and individual risk stratification, which reinforces the need for personalized protocols and centers prepared for the safe use of this medication.

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