

Tolvaptan vs Fluid Restriction in Moderate-Profound Hyponatremia: An Open-Label Randomized Clinical Trial

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Abstract

Context: Current first-line therapy for hyponatremia, fluid restriction (FR), is often unsuccessful. Tolvaptan, an arginine vasopressin V2-receptor antagonist, is effective; however, concerns about plasma sodium (pNa) overcorrection risk have limited its uptake.

Objective: This work aimed to compare the efficacy of tolvaptan and FR, with a prespecified protocol for dextrose 5% intervention if sodium correction targets were exceeded.

Methods: An open-label, randomized trial was conducted at a single-center tertiary hospital, Austin Health, in Melbourne, Australia. Fifty-four hospitalized patients with pNa 115 to 130 mmol/L (mean 124 mmol/L) were enrolled and randomized to tolvaptan 7.5 mg oral daily or FR less than 1000 mL/day (1:1) for 3 days, with daily titration according to pNa response. Main outcome measures included plasma sodium change from day 1 to 4, requirement for intravenous 5% dextrose to prevent or treat overcorrection, symptom measures, and length of hospital stay.

Results: Plasma sodium concentrations increased more in the tolvaptan group, compared to FR, over 3 days ($P_{\text{overall}} < .001$). The mean adjusted difference in pNa between groups at days 2, 3, and 4 was 3.2 (95% CI, 1.6–4.7), 3.5 (95% CI, 1.9–5.2), and 2.5 mmol/L (95% CI, 0.8–4.2), respectively. Five tolvaptan recipients (19%) required dextrose 5% to treat rapid sodium increase. With this intervention, no patient had an Na increase more than 10 mmol/L at 24 hours. There was no difference in length of stay or symptoms.

Conclusion: Tolvaptan was superior to FR at raising pNa over 3 days. However, intervention was required to prevent overcorrection in some, with no benefit in secondary outcomes. This is the first prospectively validated protocol to detect and prevent tolvaptan-related overcorrection.

Key Words: hyponatremia, hyponatraemia, syndrome of inappropriate antidiuresis (SIAD), SIADH, tolvaptan, fluid restriction

Abbreviations: AUC, area under the curve; AVP, arginine vasopressin; CAM-S, Confusion Assessment Method-Shortform; ECOG, Eastern Cooperative Oncology Group; FR, fluid restriction; IQR, interquartile range; ITT, intention-to-treat; IV, intravenous; MAD, mean adjusted difference; pNa, plasma sodium; SIAD, syndrome of inappropriate antidiuresis; TUG, Timed Up and Go Test.

Hyponatremia is the most common electrolyte disorder in hospital patients, affecting more than 15% (1, 2). Severe symptoms including seizure, decreased conscious state, and vomiting require urgent intervention. Even without severe symptoms, hyponatremia can cause confusion and nausea, and it is associated with falls, fractures, prolonged length of hospital stay, and increased mortality (3, 4).

Hyponatremia can be classified biochemically by plasma sodium (pNa) concentration as mild 130 to 134 mmol/L, moderate 125 to 129 mmol/L, or profound less than 125 mmol/L (3). The most common cause of hyponatremia in the hospital is the syndrome of inappropriate antidiuresis (SIAD), accounting for 40% of cases (5, 6). SIAD is characterized by osmotically inappropriate production of arginine vasopressin (AVP), leading to retention of free water. SIAD can be caused by malignancy, lung pathology, central nervous system pathology, medication, pain, nausea, or be idiopathic (1).

Hyponatremia can correct (or overcorrect) spontaneously if the cause of SIAD improves, hence observational data can be unreliable in evaluating therapies.

Recommended first-line therapy for SIAD is fluid restriction (FR) below 1000 mL per day (3, 7); however, approximately half of patients do not respond (8, 9). FR is low cost and accessible, but limitations include adherence, conflict with prescribed fluids, thirst, and reduced quality of life (10).

Tolvaptan, an AVP V2 receptor antagonist, is an alternative treatment for hyponatremia. There is disagreement between current guidelines as to whether tolvaptan should be recommended in moderate-profound hyponatremia due to the risk of excessively rapid pNa increase (“overcorrection”) (3, 7, 11). The efficacy of tolvaptan 15 mg compared to placebo was established in the SALT trial in mild-moderate hyponatremia (mean pNa 129 mmol/L) (12, 13). Tolvaptan was approved in 2009 for “clinically significant hyponatremia,

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defined as serum sodium <125 mmol/L,” a threshold based on expert opinion not trial data (14). Postapproval observational studies have reported rates of overcorrection (>12 mmol/L/24 hours) of 10% to 25%, even with lower-dose tolvaptan, 7.5 mg (8, 15-18).

Tolvaptan has not undergone controlled trials in hospitalized patients with lower pNa concentrations compared to standard first-line care, FR. There are no prospectively validated recommendations for frequency of monitoring post tolvaptan, or management of overcorrection risk.

We aimed to compare the efficacy of tolvaptan vs a rigorous FR to raise pNa in acute hospital patients with moderate-profound hyponatremia. Our protocol included prespecified thresholds for intervention with intravenous (IV) dextrose 5% if pNa targets were exceeded, to prevent or reverse overcorrection (Table 1) (19).

We hypothesized that tolvaptan would more effectively raise pNa, reduce length of stay, and improve associated symptoms without significant adverse effects—but that it would require higher rates of 5% dextrose administration to prevent overcorrection.

Materials and Methods

Study Design

This investigator-initiated, 3-day, randomized, open-label trial occurred at a single tertiary hospital, Austin Health, in Melbourne, Australia. The trial received ethics approval from the Austin Health Human Research Ethics Committee (HREC/48055/Austin-2019) and was prospectively registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12619001683123). The protocol was previously published (19).

We included hospitalized patients with pNa 115 to 130 mmol/L, age 18 years or older, providing informed consent (self, or designated decision-maker). Exclusion criteria included hypovolemia (clinical assessment, and/or urine Na <20 mmol/L), severe symptoms of hyponatremia (seizure, coma, respiratory arrest, vomiting without other cause), polydipsia, recent thiazide or thiazide-like diuretic, cirrhosis, malnutrition, alcohol excess, increase in pNa greater than 10 mmol/L within 24 hours, hypokalemia of 3.0 mmol/L or less, untreated glucocorticoid deficiency, untreated hypothyroidism, chronic kidney disease stage 5, systolic blood pressure less than 100 mm Hg, marked hyperglycemia (glucose $\geq$ 30 mmol/L), inability to drink, or contraindication to FR.

Recruitment was by screening the electronic medical record for pNa less than 130 mmol/L. Potentially eligible patients were evaluated by a trial physician and invited to enroll if appropriate.

Randomization was stratified according to pNa (<123 mmol/L or $\geq$ 123 mmol/L) and volume state (euvolemic or hypervolemic), resulting in 4 strata. Four randomization sequences based on computer-generated random numbers with varying block size (2-6) were generated by Austin Health Clinical Trials Pharmacy, independent of study personnel. Sequential sealed envelopes revealed the allocation. This trial was open-label due to differing fluid intake instructions in each arm.

Procedures

Enrolled participants were randomly assigned 1:1 to tolvaptan or FR. Tolvaptan-assigned patients were initially

Table 1. Protocol for monitoring and intervention with intravenous dextrose 5% in response to plasma sodium increase following tolvaptan

Increase in serum sodium	Time post-tolvaptan	Action
>6 mmol/L	Within 6 h	Commence IV dextrose 5% at rate equivalent to urine output, continue to monitor frequently and cease when sodium back within target range
>8 mmol/L	Within 12 h	
>10 mmol/L	Within 24 h	Relower with bolus hypotonic fluid (eg, dextrose 5% 10 mL/kg over 1 h), continue to monitor pNa and repeat bolus if necessary

Abbreviations: IV, intravenous; pNa, plasma sodium.

prescribed 7.5 mg oral tolvaptan day 1 and counseled to drink freely according to thirst. Participants allocated to FR were advised to restrict their fluid intake initially below 1000 mL per day. IV infusions were included in fluid intake, but the water content of food was not accounted for.

Titration of interventions occurred daily based on pNa at 6 AM via direct measurement (venous blood gas, Radiometer ABL800) (19). If the 24-hour change in pNa rose within the target range 5 to 8 mmol/L/24 hours, the intervention was continued. If pNa rose more than 8 mmol/L/24 hours, the intervention was paused with free fluid intake allowed. If change in pNa was less than or equal to 4 mmol/L/24 hours, the intervention was escalated (tolvaptan dose increased (eg, 7.5 to 15 mg, 15 to 30 mg), or FR limit lowered (eg, 1000 mL to 750 mL, 750 mL to 500 mL).

Demographic data, blood and urine biochemistry, fluid balance, weight, and vital signs were recorded. Participants were examined daily, including the Confusion Assessment Method-Shortform (CAM-S) (20); a composite Hyponatremia Symptom Questionnaire (visual analog scales of nausea, headache, unsteadiness plus the Hyponatremia Disease-Specific Survey) (21); and the Timed Up and Go Test (TUG) (22).

Repeat direct pNa was taken at a minimum 6 and 12 hours post intervention to monitor rate of change. There was a pre-specified protocol for IV 5% dextrose if pNa targets were exceeded (see Table 1). If pNa rose more than 6 mmol/L within 6 hours, or more than 8 mmol/L within 12 hours, IV 5% dextrose matched to rate of urine output was commenced, aiming to prevent further pNa increase. If pNa rose more than 10 mmol/L from baseline within 24 hours at any point, a weight-based bolus of 5% dextrose (10 mL/kg) was administered over 1 hour to relower pNa within the target range, as per European hyponatremia guidelines (3). These measures were repeated as many times as necessary to achieve a net pNa increase less than 10 mmol/L in 24 hours. Our protocol did not include desmopressin (DDAVP) due to receptor blockade by tolvaptan, hence lack of efficacy. A data safety and monitoring committee of 3 external expert clinicians was established prospectively.

Outcomes

The primary end point was change in pNa between groups over time, from day 1 (baseline) to day 4. Secondary end

points included difference in area under the curve (AUC) of serial pNa; pNa increment in the first 24 and 48 hours; proportion of patients with normalized pNa (≥ 135 mmol/L); requirement for hypotonic fluid to relower pNa; length of hospital stay; change in symptom scores; 30-day readmission rate; and pNa 30 days after discharge.

Statistical Analysis

Power calculation was based on the SALT trials, which showed SD in day 4 sodium concentrations approximately 4.9 (effect size 0.8) (19). We estimated a minimum of 26 participants per group would be required to detect a 4-mmol/L difference in pNa based on a *t* test with 80% power and a 2-sided *P* value of .05.

Baseline data are reported as mean (SD) except for highly skewed data or frequencies (%). Crude differences between 2 groups were tested using the Welch *t* test, 2-sample Wilcoxon rank sum test, and chi square test or, in case of low numbers, Fisher exact test or Barnard test for 2×2 tables. No interim analysis was performed.

The main analysis of the treatment effect of tolvaptan compared to FR from day 1 to day 4 followed the intention-to-treat (ITT) principle. We estimated the between-group difference over time as a mean adjusted difference (MAD), using repeated-measures linear mixed-effects models based on restricted maximum likelihood. The models included fixed effects of the randomization strata, variable baselines, treatment group, study time points or real time (hours), the interaction of time with the treatment group, and random effects at the subject level.

The treatment effect is reported as the MAD between the tolvaptan and FR groups over the trial period, with 95% profiled CIs. The statistical significance level was tested as a single *P* value over all time points and the entire trial period. The AUC of serial pNa was assessed as an integral effect measure for each patient according to the trapezoid method and compared between groups. Mixed models are inherently robust against some observations missing at random, thereby allowing ITT analysis. Sensitivity analyses included sex and age adjustment, and per protocol analysis.

A 2-sided *P*-value of less than .05 was considered indicative of statistical significance. Variables other than main effects were considered exploratory. All statistical analyses were performed in the R statistical environment (version 4.4.0 for Mac) (23) and the additional packages lme4 1.1-35.3, effects 4.2-2, and gcplyr 1.9 .0 (24-26).

Results

Between May 21, 2021, and April 9, 2024, 54 participants were enrolled and randomly assigned to either tolvaptan (*n* = 28) or FR (*n* = 26) (Fig. 1). Two participants discontinued tolvaptan, and 3 discontinued FR, but all were included in ITT analysis. The trial ended when the recruitment target was met.

The average participant age was 79 years (SD 11.4) and 54% were women (Table 2). Most participants were of White (European) ethnicity (85%), with the remainder Asian (11%) or multiracial (3%). The mean baseline pNa was 124 mmol/L (SD 3.6) in both groups.

SIAD was the most common cause of hyponatremia (47/54, 87%), with the underlying causes of SIAD idiopathic (33%),

central nervous system (22%), malignancy (19%), then lung pathology (nonmalignant) (13%). Our cohort was frail, with a high-risk Charlson comorbidity score in 80%, and Eastern Cooperative Oncology Group (ECOG) status 3 to 4 in 63%. The majority were euvolemic (50/54, 93%) with the remainder hypervolemic.

Results for the primary outcome showed a greater increase in pNa from day 1 to day 4 in the tolvaptan group compared to FR ($P_{\text{overall}} < .001$) (Fig. 2 and Table 3). The mean adjusted difference in pNa between groups at day 2 was 3.16 mmol/L (95% CI, 1.59-4.73), day 3 3.60 mmol/L (95% CI, 1.98-5.20), and day 4 2.54 mmol/L (95% CI, 0.81-4.25), in favor of tolvaptan.

Change in pNa was most marked within the first 24 hours, then the groups improved in parallel. The difference in the AUC for pNa increment over 72 hours was 114.6 mmol/L (95% CI, 29.4-199.8; *P* = .009). There was no statistically significant difference in the proportion of participants who achieved a normal pNa of 135 mmol/L or greater (*P* = .35).

Five tolvaptan-treated participants required additional fluid to prevent or treat overcorrection, vs zero participants with FR (*P* = .04). All 5 episodes occurred following the initial 7.5-mg tolvaptan dose (Fig. 3). In 4 of these patients, IV dextrose 5% was administered according to the protocol. The average volume of dextrose required to maintain pNa within the target range was 2237 mL (range, 2000-2600 mL). The remaining patient had difficult IV access, so oral fluid was encouraged instead. With these interventions, all participants maintained a pNa increase within the recommended 10 mmol/L or less at 24 hours.

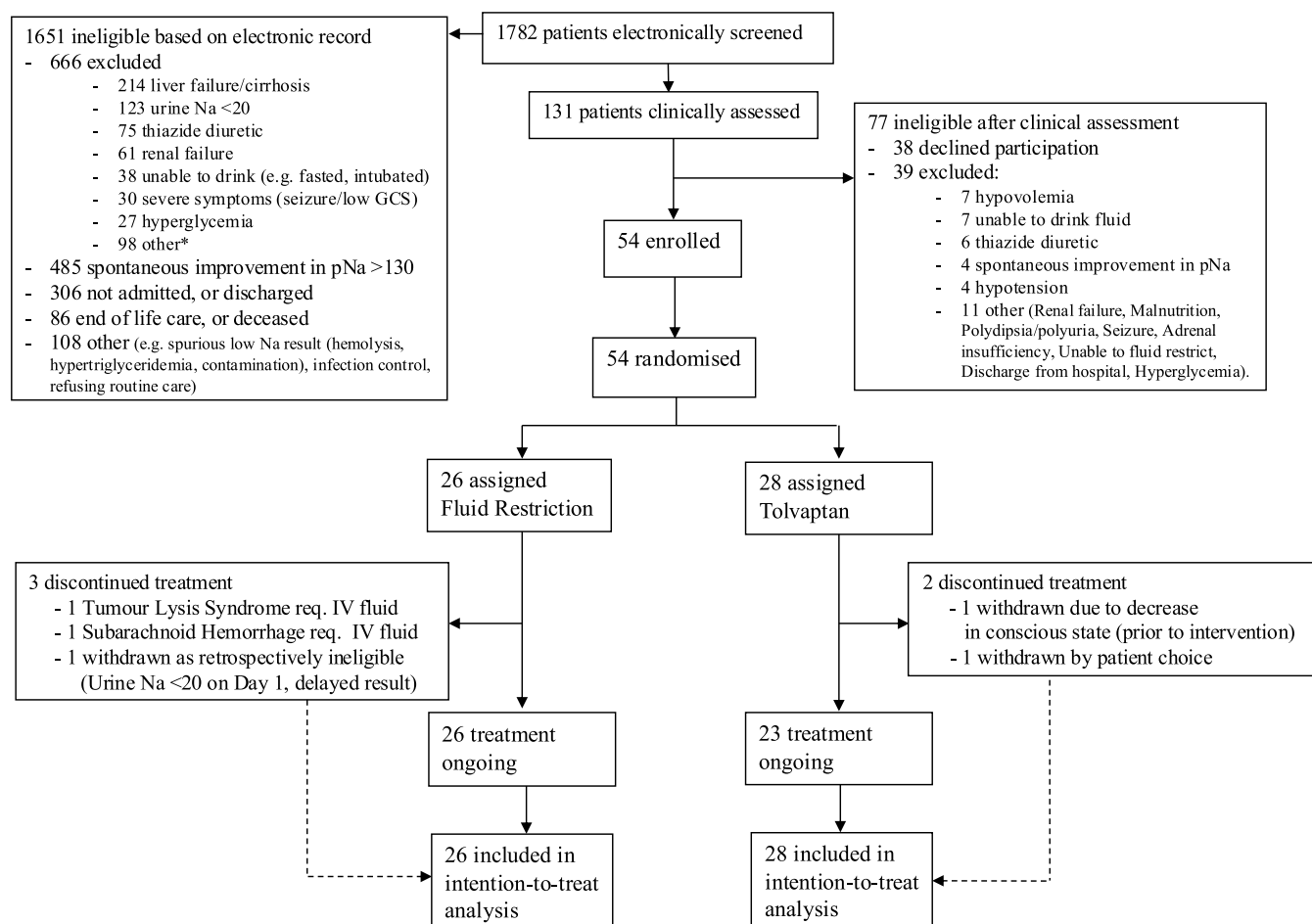
The 5 patients with an above-target pNa increase after tolvaptan had a lower baseline pNa (median 121 mmol/L [interquartile range (IQR) 118-122]) compared to tolvaptan-treated patients, in whom pNa rose at target (median 125 [IQR 121-127]; *P* = .010).

Length of hospital stay did not significantly differ between groups (*P* = .39). There were substantial outliers, with the longest length of stay 155 days. Post hoc exploratory analysis in the subset of participants with a length of stay less than 10 days (*N* = 20) showed a trend toward reduced length of stay with tolvaptan (5.0 days [IQR 4.3-5.8] vs 6.5 days [IQR 5.3-7.0]; *P* = .06).

There was no significant difference in pNa 30 days post discharge. In fact, there was a trend toward higher pNa following FR (136 mmol/L [SD 4.1] vs 133 mmol/L [SD 5.1]; *P* = .06). There was no difference in 30-day hospital readmission between groups (*P* = .21).

Tolvaptan was not associated with a statistically significant change in symptom scores, assessed by the CAM-S (*P* = .92), Hyponatremia Symptom Score (*P* = .55), or TUG test (*P* = .47). There were missing data; for example, only 18 of 54 participants were able to walk 3 m for the TUG.

Tolvaptan increased serum osmolality (*P* < .001) and decreased urine osmolality (*P* = .010), compared to FR. There was no difference between groups in renal function, serum glucose, or liver function tests during the trial. Prior to enrollment, daily fluid intake was even between the groups, around 1000 mL per day. After 24 hours, the FR group had a mean intake of 849 mL per day (SD = 353), indicating good initial adherence to FR. As expected, fluid intake was significantly higher in the tolvaptan group at 1413 mL per day (SD = 542) (mean difference 620 mL/24 h [95% CI, 195-1045]; *P* = .008). Mean fluid output also increased with



IV = intravenous, pNa = plasma sodium concentration, req. = requiring.

*other exclusions: overcorrection of pNa, documented clinical hypovolaemia, adrenal insufficiency, hypotension, unable to fluid restrict, malnutrition, AVP deficiency (excess DDAVP), unable to consent with no medical treatment decision maker.

Figure 1. Trial profile.

tolvaptan compared to FR (mean difference 739 mL/24 h [95% CI, 240-1233]; $P = .01$), where accurately recorded. There was a trend toward reduced body weight in the tolvaptan group ($P = .057$), though these data were incomplete.

No serious adverse events were observed in either group during the trial period. Two participants in the FR group developed complications unrelated to the intervention and discontinued to receive therapeutic IV fluid. One participant discontinued tolvaptan due to perceived lack of benefit.

There was a trend toward differing outcomes 30 days post discharge, led by higher deaths with tolvaptan ($P = .06$), which was not anticipated. Five participants who received tolvaptan (19%) died either in-hospital or within 30 days of discharge, compared to zero patients with FR. The causes of death were 3 progressive metastatic cancer (2 non-small cell lung carcinoma, 1 renal cell carcinoma), 1 respiratory failure, and 1 massive gastrointestinal bleed. All deaths were reviewed by the data safety and monitoring board and deemed unrelated to the trial.

Sensitivity analysis, with additional adjustment for age and sex, confirmed the result of the primary outcome. Per-protocol analysis of only those participants who completed the trial as intended also maintained significance.

Discussion

This randomized trial of 54 inpatients with moderate-profound hyponatremia showed greater improvement in pNa over 3 days with tolvaptan compared to FR (~3 mmol/L), with a high degree of statistical significance. Without our protocol to prevent overcorrection, there may have been a larger difference in pNa between groups; however, this would be contrary to treatment goals.

The effect of tolvaptan was greatest during the first 24 hours. There was limited benefit to escalating doses of tolvaptan beyond the initial 7.5 mg in those with little response.

There was no significant difference in the proportion who achieved a normal pNa of 135 mmol/L or greater within 3 days. Contrary to our hypothesis, we did not observe any difference in hyponatremia symptoms nor length of hospital stay.

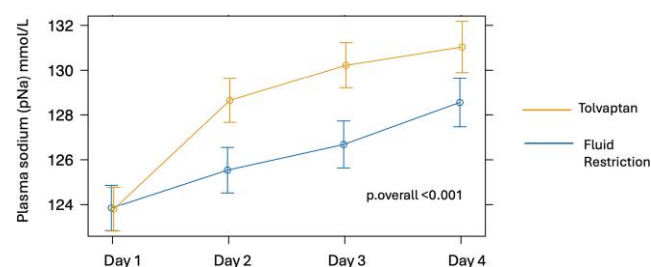
Our trial is the first prospective randomized comparison of tolvaptan with the current first-line standard of care, FR, in real-world hospitalized patients, replicating conditions of greatest potential utility. Our cohort of acutely hospitalized patients had a mean baseline pNa of 124 mmol/L, in contrast to the SALT trials in electively admitted ambulatory patients with a mean pNa of 129 mmol/L (12). This is the first published randomized trial evaluating the lower 7.5-mg dose of tolvaptan.

Table 2. Baseline characteristics of the intention-to-treat population (N [%] OR mean [SD])

	Fluid restriction (N = 26)	Tolvaptan (N = 28)	All (N = 54)
Age, y	82.2 (11.3)	76.5 (11.0)	79.2 (11.4)
Sex			
Female	15 (58%)	14 (50%)	29 (54%)
Male	11 (42%)	14 (50%)	25 (46%)
Ethnic origin			
White	21 (81%)	25 (89%)	46 (85%)
Asian	3 (12%)	3 (11%)	6 (11%)
Multiracial/Other	2 (8%)	0	2 (4%)
Weight, kg ^a	63.6 (13.1)	67.4 (14.8)	65.8 (14.1)
Baseline plasma Na, mmol/L	124 (3.6)	124 (3.5)	123.8 (3.5)
Hyponatremia duration			
<1 mo	16 (62%)	8 (29%)	24 (44%)
>1 mo	7 (27%)	12 (43%)	19 (35%)
Unknown	3 (12%)	8 (29%)	11 (20%)
Cause of hyponatremia			
SIAD-idiopathic	5 (19%)	13 (46%)	18 (33%)
SIAD-CNS pathology	7 (27%)	5 (18%)	12 (22%)
SIAD-malignancy	4 (15%)	6 (21%)	10 (19%)
SIAD-lung pathology	6 (23%)	1 (4%)	7 (13%)
Heart failure	1 (4%)	1 (4%)	2 (4%)
Unknown	3 (12%)	2 (7%)	5 (9%)
Fluid status			
Euvolemic	25 (96%)	25 (89%)	50 (93%)
Hypervolemic	1 (4%)	3 (11%)	4 (7%)
Charlson Comorbidity Index			
0-4 (lower risk)	7 (27%)	4 (14%)	11 (20%)
≥5 (higher risk)	19 (73%)	24 (86%)	43 (80%)
ECOG score			
0-2	13 (50%)	7 (25%)	20 (37%)
3-4	13 (50%)	21 (75%)	34 (63%)

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group performance status score; ECOG 3, “capable of only limited self-care; confined to bed or chair more than 50% of waking hours”; ECOG 4, “completely disabled, totally confined to bed or chair”; Na, sodium; SIAD, syndrome of inappropriate antidiuresis.

^aData available for 41 of 54 participants.

**Figure 2.** Primary end point: effect of tolvaptan vs fluid restriction on plasma sodium in hospital patients with baseline Na 115-130 mmol/L.

The frequency of above-target pNa increase following tolvaptan, 19%, matches existing observational data—however, our protocol successfully prevented or reversed overcorrection in all participants. Our participants were closely monitored with repeat pNa levels 6 and 12 hours post tolvaptan at minimum. The 5 participants who did require additional hypotonic fluid to prevent tolvaptan-related overcorrection needed a significant volume, more than 2000 mL, with the therapy frequently occurring overnight. Lower baseline pNa was the only factor predictive of above-target Na increase; we did not observe other previously identified risk factors such as low body mass index, higher renal function, and history of cancer (1).

Tolvaptan did not reduce length of stay, in contrast to our hypothesis and some observational data (8). In our frail multimorbid cohort, length of stay was often determined by factors other than hyponatremia correction, such as resolution of underlying illness, or post-acute care arrangements. Post hoc analysis of participants discharged less than 10 days after enrollment showed a trend toward reduced length of stay with tolvaptan, but this missed the threshold of significance.

Our composite symptom scores did not show any significant difference between groups. Our symptom assessments were potentially limited due to missing data. This would bias toward the null as the most symptomatic participants were less able to participate in surveys and mobility evaluation. Some previous studies report improvement in symptoms with correction of hyponatremia (12), but our findings align with the INSIGHT randomized trial of tolvaptan vs placebo in 57 older adults with mild-moderate hyponatremia with a primary cognitive end point, which did not show short-term benefit (27).

We unexpectedly observed higher short-term mortality among tolvaptan-assigned participants: Four died during their posttrial hospital admission, and 1 died within 30 days of discharge. Review of these cases found no evidence that tolvaptan was implicated. Hyponatremia is known to be associated with increased mortality, and our cohort's overall in-hospital mortality of 9.2% aligns with comparable cohorts (28). The uneven distribution of deaths between groups may be explained by differing mortality risk profiles at baseline, despite randomization. More tolvaptan-assigned participants had a high-risk Charlson Comorbidity Index score (29) and a lower ECOG score. Nevertheless, vigilance is advised in future studies.

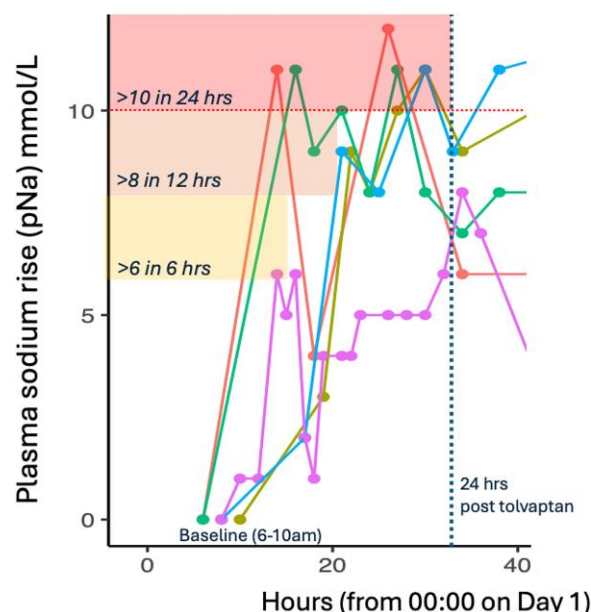
Thirty days after discharge, pNa was not significantly different, in keeping with tolvaptan's short duration of action. The mean pNa was slightly higher in the FR group, which may reflect some ongoing FR. There were no significant adverse events and no significant difference in renal function, serum glucose, or liver function between groups, despite a previously identified risk of liver injury with higher doses of tolvaptan (30).

A strength of our trial was rigorous selection of hospitalized patients with nonmild and persistent hyponatremia. Assessment for enrollment effectively excluded patients with spontaneous sodium correction, which allows more accurate characterization of above-target sodium increase risk. Unlike the SALT trials, which recruited a large proportion of participants with cirrhosis and heart failure, most of our participants had SIAD. Our mean pNa of less than 125 mmol/L replicates the real-world context in which hyponatremia intervention is potentially indicated.

Table 3. Change in plasma sodium during study period (mean [SD])

	Fluid restriction (n = 26)	Tolvaptan (N = 28)	Mean adjusted difference (95% CI)	P
Primary end point				
Plasma sodium, mmol/L				<.001 ^a
Day 1, baseline)	124 (3.61)	124 (3.54)	—	
Day 2	126 (3.99)	129 (4.02)	3.16 (1.59-4.73)	
Day 3	127 (3.44)	130 (4.27)	3.60 (1.98-5.20)	
Day 4	128 (4.11)	131 (4.66)	2.54 (.81-4.25)	
Area under curve of pNa concentration increments from day 1 to day 4	199 (160)	313 (152)	114.6 (29.4-199.8)	.009 ^a

Abbreviation: pNa, plasma sodium.

^aP less than .05.**Figure 3.** Trajectory of plasma sodium increase from baseline in 5/27 tolvaptan-treated participants with above-target sodium increase who received additional fluid to prevent or reverse overcorrection.

Limitations included the open-label design, which was by necessity due to the interventions. We selected participants at low risk of osmotic demyelination syndrome, so risks may differ if our protocols were to be applied more broadly. This trial was conducted by a single-investigator endocrinologist closely monitoring serial sodium assessments, including after hours and overnight, which may not be a replicable level of oversight in routine settings.

Although in our trial tolvaptan was superior to FR at raising pNa, FR is likely to remain first-line therapy. Previous comparisons of cost between the two interventions rely on reduced length of hospital stay with tolvaptan to offset its initial expense (31, 32). Given that we did not observe a reduction in length of stay overall, the cost of tolvaptan may not be as easy to justify when combined with the additional resource utilization associated with more intensive monitoring and intervention to achieve the desired sodium outcome. However, there is likely to remain a select cohort of patients with persistently low sodium despite FR, particularly where

eventual resolution of the underlying driver of SIAD is likely (postpituitary surgery, pneumonia, etc) and who would otherwise be fit for discharge, where the superior efficacy of tolvaptan may support its use with appropriate safeguards in place.

Future research to conduct randomized trials comparing other hyponatremia therapies, in particular urea, would be beneficial. Large-scale studies to assess whether hyponatremia treatment improves symptoms and clinical outcomes will clarify treatment goals.

Conclusion

In this randomized trial tolvaptan was superior to FR in raising plasma sodium over 3 days in inpatients with pNa 115 to 130 mmol/L, but there was no difference in other patient-centered end points such as length of stay or symptoms. We offer the first prospectively validated protocol to detect and prevent overcorrection following tolvaptan.

Based on our findings, we conclude that FR should remain first-line treatment for moderate-profound hyponatremia, due to lower cost and resource intensity. With close monitoring and administration of 5% dextrose if needed, we see a role for tolvaptan in refractory cases of hyponatremia, or where low sodium is the primary barrier to hospital discharge.

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Author Contributions

This trial was conceptualized by N.R. and M.G. A.M.W. and R.H. refined the study design and protocol. A.M.W. performed all recruitment, participant consent, clinical assessments, and data collection. Clinical management decisions were made by A.M.W. with input from N.R. or M.G. R.L. assisted with recruitment and data processing. Data analysis was performed by A.M.W. and R.H. The original draft of this paper was written by A.M.W. with revisions by M.G., N.R., R.H., R.L., and J.D.Z.

Disclosures

A.M.W., M.G., and N.R. have received a grant-in-aid from Otsuka Pharmaceutical Australia for this trial. Unrelated to this work, M.G. has received research funding from Bayer Pharma, Novartis, Weight Watchers, and Lilly and speaker honoraria from Bayer Pharma and Besins Healthcare.

Data Availability

Deidentified individual-level data may be shared on reasonable request following completion of a signed data agreement.

Clinical Trial Information

Trial registration number ACTRN12619001683123 (registered 2 December 2019).

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To the Selection Committee
ESA Young Investigator Scientific Article Award
13 June 2026

Re: Letter in Support for Dr. Annabelle Warren - ESA Young Investigator Scientific Article Award

It is a pleasure to unreservedly and enthusiastically support Dr. Annabelle Warren's application for the ESA Young Investigator Scientific Article Award. The article, published in the Journal of Clinical Endocrinology and Metabolism, presents findings of a randomised clinical trial (RCT) comparing fluid restriction and tolvaptan for the treatment of hyponatraemia in hospitalised patients. The RCT reports that while tolvaptan is superior to fluid restriction in raising serum sodium, its use requires careful monitoring to avoid overly rapid serum sodium correction. This RCT is impacting clinical practise internationally and has been featured in a presentation of upcoming European Endocrine Society Hyponatraemia Guidelines given at the 2026 European Society of Endocrinology Meeting in Prague, Czechoslovakia.

During her PhD, Annabelle has been extremely dedicated and productive, and has shown initiative, creativity and capacity of independent thought, way beyond what would be expected at her level. As a testimony to her grit and determination, recruitment for her RCT progressed, despite the difficulties in conducting research during the COVID-19 pandemic.

Annabelle has my strongest support.

Sincerely,



Professor Mathis Grossmann, MD, PhD, FRACP
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Statement of Contributions

Tolvaptan vs Fluid Restriction in Moderate-Profound
Hyponatremia: An Open-Label Randomized Clinical Trial

Annabelle M. Warren, Mathis Grossmann, Rudolf Hoermann, Rose Lin, Jeffrey D. Zajac
and Nicholas Russell.

The Journal of Clinical Endocrinology and Metabolism, 111(2):341-347. February 2026.

DOI: [10.1210/clinem/dgaf428](https://doi.org/10.1210/clinem/dgaf428)

This randomised trial was conceptualized by NR and MG. **AW** made substantial updates to the trial protocol, particularly the addition of a standardised approach to prevention/treatment of sodium overcorrection. **AW** finalised ethics approval.

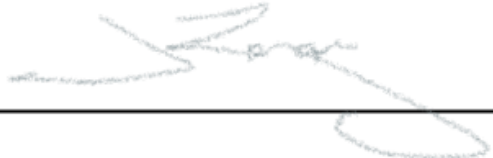
AW performed all recruitment, participant consent, clinical assessments, and data collection. Clinical management decisions were made by **AW**, with input from NR or MG in certain cases. RL assisted with data processing. Data analysis was performed by RH and **AW**.

AW wrote the first draft of the manuscript. All authors contributed to revising the manuscript.

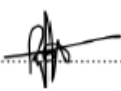
Dr Annabelle Warren _____  Date, 4/6/26

Prof Mathis Grossmann _____  Date, 4/6/26

Dr Rudolf Hoermann _____  Date, 4/6/26

Prof Jeffrey Zajac _____  Date, 4/6/26

Dr Nicholas Russell _____  Date, 4/6/26

Dr Rose Lin _____  Date, 4/6/26