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Clinical Research Article

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Fluid Restriction Therapy for Chronic SIAD; Results of a Prospective Randomized Controlled Trial

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Abbreviations: AKI, acute kidney injury; FR, fluid restriction; IQR, interquartile range; NoTx, no specific hyponatremia treatment; pNa, plasma sodium concentration; RR, risk ratio; SALT, Studies of Ascending Levels of Tolvaptan in Hyponatremia; SIAD, syndrome of inappropriate antidiuresis; UNa, urinary sodium concentration; UOsm, urine osmolality.

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Abstract

Context: Fluid restriction (FR) is the recommended first-line treatment for syndrome of inappropriate antidiuresis (SIAD), despite the lack of prospective data to support its efficacy.

Design: A prospective nonblinded randomized controlled trial of FR versus no treatment in chronic SIAD.

Interventions and Outcome: A total of 46 patients with chronic asymptomatic SIAD were randomized to either FR (1 liter/day) or no specific hyponatremia treatment (NoTx) for 1 month. The primary endpoints were change in plasma sodium concentration (pNa) at days 4 and 30.

Results: Median baseline pNa was similar in the 2 groups [127 mmol/L (interquartile range [IQR] 126-129) FR and 128 mmol/L (IQR 126–129) NoTx, $P = 0.36$]. PNa rose by 3 mmol/L (IQR 2-4) after 3 days FR, compared with 1 mmol/L (IQR 0-3) NoTx, $P = 0.005$. There was minimal additional rise in pNa by day 30; median pNa increased from baseline by 4 mmol/L (IQR 2-6) in FR, compared with 1 mmol/L (IQR 0-1) NoTx, $P = 0.04$. After 3 days, 17% of FR had a rise in pNa of ≥5 mmol/L, compared with 4% NoTx, RR 4.0 (95% CI 0.66-25.69), $P = 0.35$. After 3 days, 61% of FR corrected pNa to ≥130 mmol/L, compared with 39% of NoTx, RR 1.56 (95% CI 0.87-2.94), $P = 0.24$.

Conclusion: FR induces a modest early rise in pNa in patients with chronic SIAD, with minimal additional rise thereafter, and it is well-tolerated. More than one-third of patients fail to reach a pNa ≥130 mmol/L after 3 days of FR, emphasizing the clinical need for additional therapies for SIAD in some patients.

Key Words: Hyponatremia, fluid restriction, syndrome of inappropriate antidiuresis.

Hyponatremia is the commonest electrolyte abnormality in clinical practice (1, 2), and the syndrome of inappropriate antidiuresis (SIAD) is the most frequent cause of hyponatremia (3). Chronic mild to moderate hyponatremia is associated with subtle cognitive effects, poor attention, unsteady gait (4, 5) leading to increased

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falls (6), osteoporosis (7), and an increased fracture rate (8). Recent data have suggested that effective treatment of hyponatremia can improve cognitive function (9) and reduce mortality (10). Despite this, hyponatremia has traditionally been underinvestigated and undertreated (11).

Fluid restriction (FR) is recommended by international guidelines as first-line treatment for SIAD (12, 13). There is, however, no evidence base which proves the efficacy of FR in SIAD. In the observational Hyponatremia Registry, the median rate of change in plasma sodium concentration (pNa) in patients treated with FR was only 1 mmol/L/day over the initial 3 days, and most patients required additional treatment to reach treatment targets (11). A drawback of the Hyponatremia Registry, and subsequent studies of FR in SIAD, is that they did not distinguish between chronic SIAD and acute SIAD, where the underlying cause of hyponatremia may be transient. This is an important distinction, as acute SIAD due to a treatable cause will self-correct with treatment of the underlying disease (14), falsely exaggerating the benefit of FR.

We have therefore prospectively tested the effect of FR on plasma sodium concentration in a cohort of patients with confirmed chronic SIAD, a clinical scenario where elevation in pNa in response to FR would reflect an independent effect of FR, rather than treatment of coexisting conditions. Our hypothesis, based on the results of the Hyponatremia Registry, was that in chronic SIAD, the elevation in pNa produced by FR would not be different from that seen when no specific treatment of SIAD was administered.

Methods

Patients and setting

This was a single-center study conducted in Beaumont Hospital, a 600-bed university teaching hospital, which is an acute general hospital and is the National Centre for Neurosurgery. Patients were recruited from the medical, surgical and oncology wards, and from the Endocrinology outpatient clinic. Key inclusion criteria were designed to ensure a robust diagnosis of SIAD (13):

1. Euvolemia [assessed clinically (13)].
2. PNa 120 to 130 mmol/L, ≥48 hours duration.
3. Urinary sodium concentration (UNa) ≥30 mmol/L.
4. Urine osmolality (UOsm) ≥100 mOsm/kg.
5. Serum cortisol at 8:00 AM ≥300 nmol/L (10.9 µg/dL), or 30-minute value ≥500 nmol/L (18.1 µg/dL, pre-2019) or ≥430 nmol/L (15.6 µg/dL, January 2019 onwards) on short Synacthen testing (15-17). The 8:00 AM cutoff of 300 nmol/L was chosen based on our published normative data in neurosurgical conditions (18, 19) and all-cause hyponatremia (20).
6. Normal thyroid function.

Subjects were excluded from the study if any of the following criteria were met:

1. Hyponatremia with symptoms of cerebral irritation (headaches, confusion, seizures, drowsiness).
2. An underlying cause of SIAD was recognized which was reversible with treatment of the underlying condition, eg, postoperative SIAD, pneumonia.
3. Hyponatremia-causing medications which had been discontinued.
4. Subject required intravenous fluids.
5. Alcohol excess.
6. Diuretic therapy.
7. Renal, liver, or cardiac failure.
8. Subarachnoid hemorrhage.
9. Subject already on fluid restriction.
10. Patients who had previously failed to respond to fluid restriction.

Randomization and masking

The study protocol was agreed upon after consultation with the departments of statistics and therapeutics. Patients were randomized, using a computer-generated randomization table in random permutated blocks of 4, in a 1:1 ratio to either FR or to no specific hyponatremia treatment (NoTx) for 1 month. The study was unblinded to the treating clinicians and the patients.

Study protocol

Patients randomized to FR were instructed to limit total daily fluid intake to 1 liter. Patients were evaluated at baseline, Day 4 (after 3 days of treatment), 11, 18, and 30. Blood pressure, volume status, and daily fluid intake were recorded, blood was drawn for measurement of plasma osmolality, electrolytes, urea, creatinine, and a urine sample was analyzed for urinary sodium (UNa), urinary potassium concentration, and urinary osmolality (UOsm) at each time-point.

The primary endpoints were the change in pNa at Day 4 and Day 30, time-points specifically chosen to allow comparison of our study results with those derived from the Studies of Ascending Levels of Tolvaptan in Hyponatremia (SALT) trial (21). Response to FR was defined as an

increase in pNa at Day 4 of ≥3 mmol/L (22). Predictors of nonresponse (UOsm >500 mOsm, Fürst equation >1) were identified from baseline data (13). The Fürst equation is calculated by dividing the sum of urinary sodium and potassium concentrations by pNa (23). A Fürst equation >1 has been shown to suggest a low likelihood of effectiveness of fluid restriction (24).

Patients were withdrawn from the study if pNa fell by ≥5 mmol/L from baseline, or to <120 mmol/L. Acute kidney injury was defined by serum creatinine concentration according to KDIGO guideline recommendations (25) and hypotension was defined as blood pressure <90/60 mmHg on bedside measurement. Other hyponatremia treatments were not allowed during the course of the study. The study was approved by the Beaumont Hospital Research Ethics Committee and registered on the ISRCTN Registry (ISRCTN34822127). All patients provided written informed consent.

Laboratory analysis

PNa and UNa were measured using an ion selective electrode (Olympus AU2700, Tokyo, Japan). Normal pNa reference range is 133 to 146 mmol/L. For a mean pNa of 121 mmol/L, the between-day coefficient of variation is 1.4%, and for a mean pNa of 125 mmol/L, it is 1.6%. Plasma and urine osmolality were measured by the depression of freezing point method (2400 Osmometer; Fiske, Norwood, MA, USA).

Statistics

Power calculations indicated that a sample of 17 patients per treatment arm was required for a power of 80% to show noninferiority at the 5% level of significance, and a sample of 23 patients per group for a power of 90%. Therefore, we aimed to recruit 46 patients, to allow for a dropout rate of 20% to maintain power at 80%. Data from all participants were included in the study. Continuous data are expressed as median (interquartile range) and categorial data are expressed as number (percentage). The Mann-Whitney U test was used to compare continuous data (nonparametric) and the Fisher exact test to compare categorical data across 2 groups. Repeated measures analysis of variance (ANOVA) was used to test the significance of changes in pNa, UNa, and UOsm over study time-points. A P value of < 0.05 was considered as statistically significant. Statistical analysis was performed using GraphPad Prism 8 (GraphPad Software, La Jolla, California, USA) and STATA Version 13SE (StataCorp LP, College Station, TX, USA).

Results

A total of 56 patients were suitable for inclusion and 46 were subsequently recruited between May 2018 and January 2020 (Fig. 1). Twenty-three patients were assigned to FR and 23 to NoTx. All 46 patients reached the first study endpoint of Day 4 assessment; 17 FR patients (74%) completed the 30-day study period, while 15 NoTx patients (65%) completed the study. The reasons for withdrawal from the study are outlined in Fig. 1. Four patients who had biochemical confirmation of SIAD at initial screening had UNa concentration ranging from 22 to 27 mmol/L at the Day 1 assessment. In 3 of these cases, UNa was ≥30 mmol/L at Day 4 and they remained in the trial. In the fourth case, UNa remained <30 mmol/L at Day 4. This patient, randomized to NoTx, had chronic SIAD due to head and neck cancer and was felt to be solute-deficient. He was subsequently withdrawn from the study after Day 4 when pNa dropped to 116 mmol/L in the setting of excessive alcohol intake. He was followed up in the Endocrine Service, and pNa rose with fluid restriction. Patients in the 2 randomized groups were well matched for age, gender, baseline pNa, and cause of hyponatremia. In patients with medication-induced SIAD, the dosage of the offending medication was not tapered during the course of the study. Median duration of hyponatremia in patients treated with FR was 19 months (interquartile range [IQR] 9-132), compared with 71 months (8-146) in the NoTx group, $P = 0.48$ (Table 1). Median self-reported daily fluid intake was significantly less in the FR group than in NoTx at each time-point (Fig. 2d). The median fluid intake in the FR group did not change throughout the study ($P = 0.1$). The number of patients in the FR group with self-reported daily fluid intake exceeding 1000 mL at Day 4, 11, 18, and 30 was 1, 2, 5, and 0, respectively.

Fluid restriction resulted in greater increase in pNa compared with no treatment, at both Day 4 and Day 30. PNa rose by 3 mmol/L (IQR 2-4) by Day 4 in the FR group, compared with 1 mmol/L (IQR 0-3) in the NoTx group ($P = 0.005$) (Table 2, Fig. 2a). Seventeen percent of subjects treated with FR had a pNa rise of ≥5 mmol/L by Day 4, compared with 4% in the NoTx group (risk ratio [RR] 4.0; 95% CI, 0.66-25.69; $P = 0.35$). Fifty-seven percent of subjects treated with FR had a rise in pNa ≥3 mmol/L by Day 4, compared with 26% of the NoTx group (RR 2.17; 95% CI, 1.05–4.8; $P = 0.07$). Overall, 61% of patients treated with FR corrected pNa to ≥130 mmol/L by Day 4, compared with 39% of the NoTx group (RR 1.56; 95% CI, 0.87-2.94; $P = 0.24$).

By Day 30, pNa rose by 4 mmol/L (IQR 2-6) in those treated with FR, compared with 1 mmol/L (IQR 0-3) in the NoTx group ($P = 0.04$). Among patients treated with

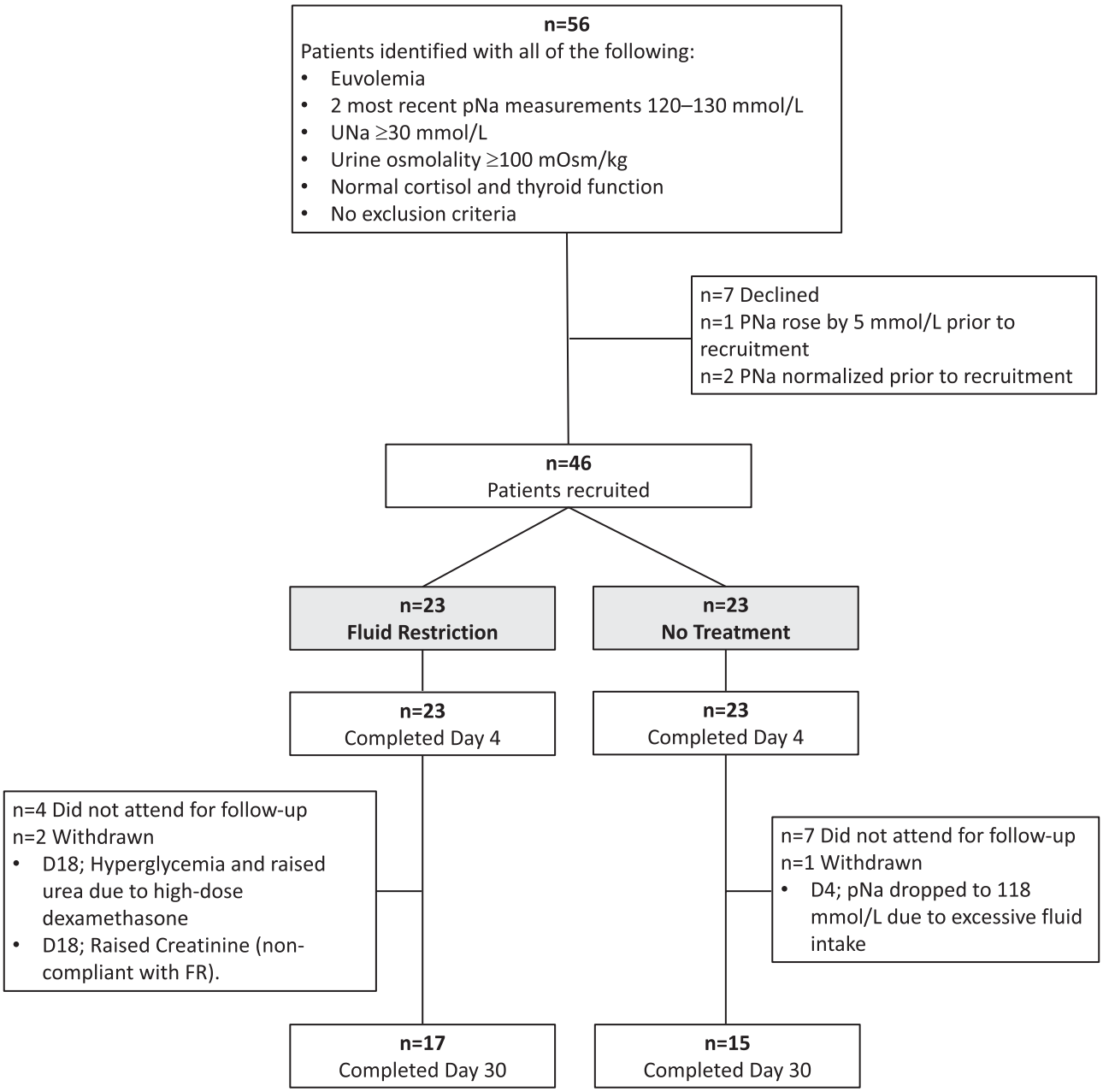

Figure 1. Study flow diagram. Abbreviations: D, day; pNa, plasma sodium concentration; UNa, urinary sodium concentration; UOsm, urinary osmolality.

FR who completed 30 days, 47% had a rise in pNa of ≥5 mmol/L, compared with 6.7% of the NoTx group (RR 7.06; 95% CI, 1.4-41.42; P = 0.02). Fifty-nine percent of patients treated with FR had a rise in pNa ≥3 mmol/L, compared with 27% of the NoTx group (RR 2.2; 95% CI, 0.95-5.75; P = 0.09). Seventy-one percent of patients treated with FR finished the study at Day 30 with pNa ≥130 mmol/L, compared with 40% of the NoTx group (RR 1.77; 95% CI, 0.93-3.73; P = 0.15). The change in pNa from baseline is shown in Fig. 2a; there were significant differences between the 2 groups in the change from baseline pNa at Day 4, Day 11, and Day 30. The corresponding change in UOsm, UNa, and fluid intake is illustrated in Fig. 2b-2d.

There was no significant correlation between baseline pNa, UOsm, or estimated pre-trial fluid intake in those treated with FR and change in pNa at Day 4 or Day 30. Change in pNa was similar across the different SIAD etiologies (Fig. 3).

Patients who had been randomized to FR were analyzed according to baseline urine osmolality (UOsm > or < 500 mOsm/kg) and Fürst equation results (< or > 1), and response was defined as increase in pNa of ≥3 mmol/L. Baseline UOsm or Fürst ratio did not predict treatment

response to FR, although the study was not specifically powered to investigate this. Half (4/8) of patients with baseline UOsm >500 mOsm/kg treated with FR had a rise in pNa ≥3 mmol/L at Day 4, compared with 60% (9/15) of those with UOsm <500 mOsm/kg (P = 0.69). In addition, 25% (1/4) of patients with Fürst equation >1 treated with FR had a rise in pNa of ≥3 mmol/L at Day 4,

Table 1. Baseline Demographics

	Fluid Restriction n = 23	No Treatment n = 23
Age, years	74 (68-80)	72 (54-80)
Male/Female	12/11	12/11
Baseline pNa (mmol/L)	127 (126-129)	128 (126-129)
Urinary Na (mmol/L)	53 (42-68)	51 (35-68)
Urinary osmolality (mOsm/kg)	459 (345-604)	457 (287-556)
Duration of HN (months)	19 (9-132)	71 (8-146)
Cause of SIAD		
Medications	7 (30%)	6 (26%)
Antiepileptic drugs	*4*	*3*
Proton pump inhibitors	*3*	*2*
Selective serotonin reuptake inhibitors	*0*	*1*
Respiratory	5 (22%)	3 (13%)
Bronchiectasis	3	2
Pleural plaques/COPD	1	0
Pulmondary fibrosis	1	0
Other	0	1
CNS	0	3 (13%)
Stroke		*1*
Glioma		*1*
Traumatic brain injury		*1*
Malignancy	2 (9%)	5 (22%)
Lung	*2*	*1*
Bladder	*0*	*2*
Pharyngeal	*0*	*1*
Colorectal	*0*	*1*
Idiopathic	9 (39%)	6 (26%)

Abbreviations: CNS, central nervous system; COPD, chronic obstructive airway disease; FR, fluid restriction; HN, hyponatremia; pNa, plasma sodium concentration; SIAD, syndrome of inappropriate antidiuresis.

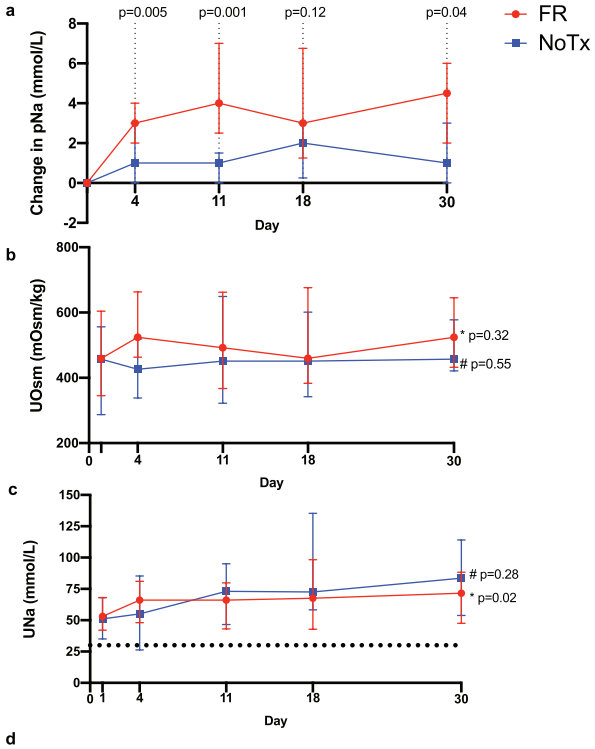

Figure 2. 2a: Change in plasma sodium concentration (pNa) from baseline, **2b:** UOsm at each study visit, **2c:** UNa at each study visit, **2d:** daily self-reported fluid intake. Data expressed as median (IQR). The dashed line in Fig. 2c marks UNa of 30 mmol/L. Abbreviations: UNa, urinary sodium concentration; UOsm, urinary osmolality. * P value for change over time in FR group. # P value for change over time in NoTx group.

Table 2. Change in Plasma Sodium Concentration in Patients Randomized to Fluid Restriction and No Treatment

Day 4	Fluid Restriction n = 23	No Treatment n = 23	P
Change in pNa (mmol/L) median and IQR	3 (2-4)	1 (0-3)	0.005
≥3 mmol/L increase	13 (56.5%)	6 (26%)	0.07
≥5 mmol/L increase	4 (17%)	1 (4%)	0.35
≥130 mmol/L achieved	14 (61%)	9 (39%)	0.24
Day 30	**Fluid Restriction n = 17**	**No Treatment n = 15**	P
Change in pNa (mmol/L) median and IQR	4 (2-6)	1 (0-3)	0.04
≥3 mmol/L increase	10 (59%)	4 (27%)	0.09
≥5 mmol/L increase	8 (47%)	1 (6.7%)	0.02
≥130 mmol/L achieved	12 (71%)	6 (40%)	0.15

Abbreviations: IQR, interquartile range; pNa, plasma sodium concentration.

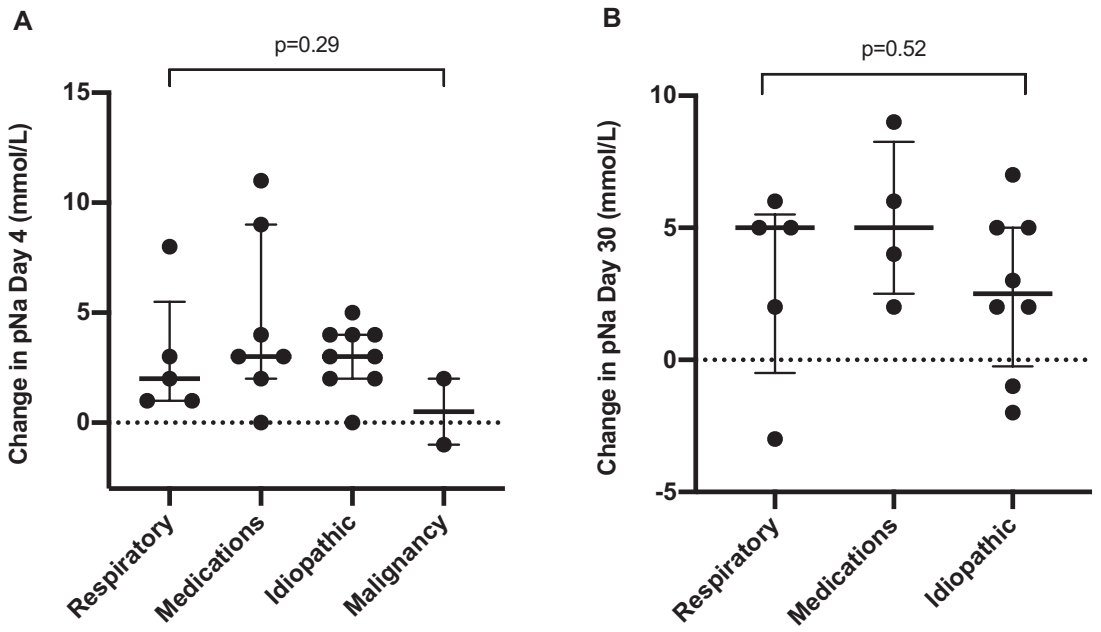

Figure 3. Change in plasma sodium concentration (pNa) at Day 4 (panel A, n = 23) and Day 30 (panel B, n = 17) in patients treated with FR, according to etiology of SIAD.

compared with 61% (11/18) of those with Fürst equation <1 (P = 0.29). The proportion of patients achieving a rise in pNa ≥5 mmol/L or to ≥130 mmol/L according to baseline UOsm and Fürst ratio is outlined in Table 3.

In the FR cohort, there was no significant difference in median self-reported daily fluid intake in responders versus nonresponders (900 mL [IQR 800-1000] vs 1000 mL [IQR 925-1000]; P = 0.2). Level of supervision did not significantly affect treatment response; 50% (9/18) of hospital inpatients had a rise in pNa ≥3 mmol/L after 3 days of FR, compared with 80% of outpatients (4/5) (P = 0.34).

Two patients were withdrawn from the FR group. One patient, with metastatic small cell lung cancer, developed hyperglycemia and elevated serum urea due to high dose dexamethasone therapy, and was withdrawn at Day 18. The second patient was withdrawn from the study at Day 18 due to a rise in serum creatinine in the context of recent angioplasty and IV antibiotics for lower limb ulceration; this patient had not been compliant with fluid restriction. There were no cases of hypotension (BP <90/60 mmHg).

Discussion

Fluid restriction is the recommended first-line treatment choice for chronic SIAD in international guidelines (12, 13, 26, 27), despite the absence of prospective randomized clinical data. We have demonstrated, in a prospective randomized trial conducted in patients with well-defined, chronic SIAD, that fluid restriction is modestly effective in treating hyponatremia, producing a median rise in pNa of 3 mmol/L over 3 days. Fewer than 1 in 5 patients achieved a rise in pNa ≥5 mmol/L after 3 days FR, with less than half of patients meeting this correction endpoint after 30 days. The results of this prospective randomized trial are similar to the retrospective observations of clinical practice from the Hyponatremia Registry (n = 1524 SIAD), which showed a mean daily rise of pNa of 1 mmol/L compared with 0.4 mmol/L in patients who were untreated (median follow-up of 7 days) (28). The registry also showed that 44% of FR patients failed to correct pNa by ≥5mmol/L after 3 days, which were similar to our results (28).

The association between chronic hyponatremia and unsteady gait (4, 5), falls (29), osteoporosis (7), fractures (8), and mortality (30) is well-established. Improvement in all-cause hyponatremia is associated with improvements in gait and reaction time (4), and a reduction in mortality (10). While these data support the rationale for treatment of chronic hyponatremia, there is no consensus on the exact threshold for pNa correction at which there is a clear clinical benefit. A recent large observational study by Brinkkoetter et al demonstrated that an increase in pNa ≥5 mmol/L is associated with improvements in activities of daily living and cognition scores in patients with SIAD, with no improvements noted in patients in whom pNa rose by <5 mmol/L (9). Relatively few patients achieved this level of pNa correction in our study,

Table 3. Change in Plasma Sodium Concentration and Rate of Correction ≥3 mmol/L, ≥5 mmol/L and to ≥130 mmol/L According to Predictors of Nonresponse

Urine Osmolality	UOsm >500 mOsm/kg	UOsm <500 mOsm/kg	*P*
Day 4	**n = 8**	**n = 15**	
Change in pNa (mmol/L)	3 (1-4)	3 (2-5)	0.45
≥3 mmol/L	4 (50%)	9 (60%)	0.69
≥5 mmol/L	0	4 (26.7%)	0.26
≥130 mmol/L	5 (62.5%)	9 (60%)	>0.99
Day 30	**n = 5**	**n = 12**	
Change in pNa (mmol/L)	3 (-1-6)	5 (2-6)	0.67
≥5 mmol/L	2 (40%)	6 (50%)	>0.99
≥130 mmol/L	4 (80%)	8 (66.7%)	>0.99
Fürst Equation	**Urine Na+K/PNa >1**	**Urine Na+K/PNa <1**	***P***
Day 4	**n = 4**	**n = 18**	
Change in pNa (mmol/L)	1 (0-3)	3 (2-4)	0.1
≥3 mmol/L	1 (25%)	11 (61%)	0.29
≥5 mmol/L	0	4 (22.2%)	0.55
≥130 mmol/L	1 (25%)	12 (66.7%)	0.26
Day 30	**n = 4**	**n = 12**	
Change in pNa (mmol/L)	3 (–2-4)	5 (2-7)	0.16
≥5 mmol/L	0	7 (58.3%)	0.09
≥130 mmol/L	2 (50%)	9 (75%)	0.55

Abbreviations: pNa, plasma sodium concentration; UOsm, urine osmolality.

which suggests that FR alone is insufficient to reverse cognitive decline in a significant proportion of patients. A rise in pNa of <5 mmol/L may still be clinically significant, but the data to support this suggestion is not available. Correction of pNa to ≥130 mmol/L is an alternative target which is commonly applied in clinical practice; more than half of patients did reach this biochemical threshold after 3 days of FR, and 70% after 30 days.

Although the rise in pNa produced by FR in this study was modest, the safety profile of FR was favorable. The 2 patients who were withdrawn from FR had conditions unlikely to be causatively associated with FR. The low rate of acute kidney injury (AKI) directly attributable to FR, and the absence of hypotension in our study are findings which are in contrast with the results reported in a recent trial comparing FR and FR plus furosemide with or without oral sodium chloride (31). In that study (n = 90), 10% of patients treated with FR developed AKI, with 1 in 5 patients developing hypotension. Rates of AKI were even higher in those who also received furosemide and oral sodium chloride (17% and 32%, respectively). There are a number of possible explanations for the higher rate of AKI in the study by Krispanan et al (31). Fluid intake was more restrictive in that study (<500 mL in 43% of patients), and this in itself could have led to volume depletion and diminished renal blood flow. Treatment of the underlying etiology of SIAD in that study may have led to resolution of SIAD, leaving patients vulnerable to hypovolemia with prolonged FR (30 days). Finally, the effects of furosemide in 2 arms of the study would have increased the likelihood of AKI. The high rate of AKI in the Krispanan study does support our decision to aim for a modest FR of 1 liter, which we felt was more attainable anyway in an outpatient, clinical practice setting.

Aside from FR, many of the treatment options for chronic asymptomatic SIAD are limited by high cost or lack of randomized prospective data. The first randomized prospective data on the treatment of SIAD was a subgroup analysis of the SALT studies (21). Tolvaptan was shown to induce a mean rise in pNa of 5 mmol/L at Day 4, and 8 mmol/L at Day 30 (21). We specifically chose the change in pNa at Day 4 and Day 30 as primary endpoints for our study, so that the effects of FR in our study protocol could be compared with those produced by tolvaptan in the SALT studies. Based on clinical experience, as well as the observations of the Hyponatremia Registry, we were not surprised to find that the pNa rise in response to FR was less than the rise in pNa reported in response to tolvaptan in the SALT studies (28). Although tolvaptan is very effective, it remains expensive, and it is not universally available or reimbursable. Recent observational data shows favorable efficacy and tolerability of urea (32), but there is little data from prospective randomized studies. Although urea has not been available in a commercially prescribable form, a commercial formulation, "Ure-Na," was recently made available in the United

States, and a retrospective review of its use in 58 hospitalized patients has shown it to be effective, producing a median rise in plasma sodium concentration of 6 mmol/L over 4 days, without overcorrection or other adverse events (33). Prospective data are awaited. The use of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, was recently tested in a prospective randomized controlled trial. Empagliflozin, in combination with FR, produced a rise in pNa of 10 mmol/L after 3 days, compared with 7 mmol/L in those on FR alone (34). However, a significant proportion of patients included in this study had transient causes of hyponatremia, including nausea/pain, postoperative status, and infectious diseases. In the absence of an untreated control group, therefore, it is unclear whether pNa would have corrected with treatment of the underlying cause. The inclusion of patients with reversible causes of SIAD may explain why the rise in pNa with FR alone was higher than that reported in the Hyponatremia Registry and in our study. Additional studies examining the effects of this drug on pNa in well-defined chronic SIAD are therefore required.

The significant strengths of this study are the prospective, randomized design and the strict SIAD inclusion criteria; all of our patients had 100% ascertainment of published diagnostic criteria. We recruited only patients who had no reversible etiology, which is critical, as SIAD often resolves with treatment of pneumonia (14), withdrawal of a causative medication (28), or other specific therapies. Because of this, and the exclusion of patients with any symptoms of cerebral irritation, our study population had a relatively long duration of hyponatremia, 19 and 71 months in the FR and NoTx groups, respectively. Therefore, the data in the study apply to patients with stable chronic SIAD, and not to those with a transient dynamic underlying cause of SIAD. Other studies of FR in SIAD have not differentiated between acute and chronic SIAD, or elaborated on the treatment of the underlying cause of hyponatremia; it is therefore difficult to be certain whether the increases in pNa are due to FR, or the natural history of hyponatremia as the causative process is treated. In contrast, we can be certain that changes in pNa in our study reflected genuine treatment effects. In addition, we did not recruit patients who had failed treatment with FR previously, to avoid bias toward treatment failure.

The level of supervision and the frequency of reinforcement in this prospective study may have encouraged better compliance with FR than what is expected in routine practice. Only patients who were agreeable to FR were recruited to the study, which may have introduced a selection bias toward motivated patients. Our compliance rates are higher than those reported in previous studies (31); however, they are self-reported and thus should be interpreted with caution. Certainly, the dip in median urine osmolality at Day 18 (Fig. 2b) would suggest a fall-off in compliance. The limitation of self-reported fluid intake also exists when we prescribe FR outside of clinical trials; our results are thus reflective of real-life practice. Interestingly, we found no difference in pNa rise in those patients whose FR was supervised in-hospital compared with those who completed the protocol at home, suggesting that day-to-day supervision of FR did not unduly influence outcome. The withdrawal rate of 25% was higher than predicted by our sample size calculation; nevertheless, there were significant differences in both primary endpoints between the groups.

We applied a 1-liter fluid restriction to all patients, rather than adjusting fluid target according to urine output. This could be a considered a limitation of the study. In our clinical experience, however, patients with chronic SIAD find it difficult to tolerate stricter FR targets in the medium–long-term, due to resetting of the thirst threshold (35). Furthermore, accurate 24-hour urine measurement is not practical in chronic SIAD. We selected 1-liter FR, which is our standard clinical practice, as we felt it was an achievable clinical goal, with a low rate of poor compliance to bias the study results. Finally, although our study was not powered to test the whether UOsm >500mOsm/kg and Fürst ratio >1 predicted nonresponse to FR, none of the 12 patients who met one or both of these criteria responded to FR with a rise in pNa ≥5 mmol/L at Day 4. Larger cohort studies would be needed to test the predictive power of UOsm and Fürst ratio >1.

Conclusion

We have disproved our hypothesis that FR produces a similar rise in pNa to no treatment in patients with chronic SIAD. The modest rise in plasma sodium concentration, coupled with the favorable safety profile of FR, justifies its position as first-line therapy for mild chronic SIAD. Although FR produced a statistically higher pNa, fewer than 20% patients elevated pNa by ≥5 mmol/L after 3 days FR, and fewer than 50% achieved this clinical endpoint after 30 days of FR. Our data challenge the effectiveness of the guideline-recommended first-line treatment for SIAD in a significant proportion of patients, which highlights the need for effective, affordable treatments for chronic SIAD, if clinically significant reduction in morbidity is to be targeted.

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Data Availability: Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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