Efficacy of Furosemide, Oral Sodium Chloride, and Fluid Restriction for Treatment of Syndrome of Inappropriate Antidiuresis (SIAD): An Open-label Randomized Controlled Study (The EFFUSE-FLUID Trial)

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Rationale & Objective: First-line therapy for syndrome of inappropriate antidiuresis (SIAD) is fluid restriction. Additional treatment for patients who do not respond to fluid restriction are water restriction with furosemide or water restriction with furosemide and salt supplementation. However, the efficacy of these treatments has never been tested in a randomized controlled study. The objective of this study was to investigate whether, combined with fluid restriction, furosemide with or without sodium chloride (NaCl) supplementation was more effective than fluid restriction alone in the treatment of hyponatremia in SIAD.

Study Design: Open-label randomized controlled study.

Setting & Participants: Patients with serum sodium concentrations ($[Na^+]$) ≤ 130 mmol/L due to SIAD.

Intervention(s): Random assignment to 1 of 3 groups: fluid restriction alone (FR), fluid restriction and furosemide (FR+FM), or fluid restriction, furosemide, and NaCl (FR+FM+NaCl). Strictness of fluid restriction (<1,000 or <500 mL/d) was guided by the urine to serum electrolyte ratio. Furosemide dosage was 20 to 40 mg/d. NaCl supplements were 3 g/d. All treatments were continued for 28 days.

Outcomes: The primary outcome was change in $[Na^+]$ at days 4, 7, 14, and 28 after randomization.

Results: 92 patients were recruited (FR, n = 31; FR+FM, n = 30; FR+FM+NaCl, n = 31). Baseline $[Na^+]$ was 125 ± 4 mmol/L, and there were no significant differences between groups. Mean $[Na^+]$ on day 4 in all treatment groups was significantly increased from baseline by 5 mmol/L ($P < 0.001$); however, the change in $[Na^+]$ was not significantly different across groups ($P = 0.7$). There was no significant difference in percentage of patients or time to reach $[Na^+]$ ≥ 130 or ≥135 mmol/L across the 3 groups. Acute kidney injury and hypokalemia (potassium ≤ 3.0 mmol/L) were more common in patients receiving furosemide.

Limitations: Open-label treatment.

Conclusions: In patients with SIAD, furosemide with NaCl supplement in combination with fluid restriction did not show benefits in correction of $[Na^+]$ compared with treatment with fluid restriction alone. Incidences of acute kidney injury and hypokalemia were increased in patients receiving furosemide.

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Hyponatremia, defined as serum sodium concentration ($[Na^+]$) < 135 mmol/L, is the most common electrolyte abnormality in clinical practice. The prevalence of hyponatremia reported in hospitalized patients is between 30% and 42%.[1-3] It is well documented that hyponatremia is associated with increased mortality and morbidity.[4] Also, chronic hyponatremia is associated with impaired mental status, gait disturbance, falls, osteoporosis, and increased fracture rates.[5-10] There are many recommendations for the management of hyponatremia.[4,11] However, most of the evidence in these recommendations is from noncontrolled studies.

Syndrome of inappropriate antidiuresis (SIAD) is the most common cause of hyponatremia in hospitalized patients.[12-14] It is caused by an inappropriate release of antidiuretic hormone or an increased renal response to antidiuretic hormone.[15,16] First-line treatment of SIAD is fluid restriction.[4] However, it is difficult to adhere to and may not be effective in patients with severe hyponatremia.[4,16] Furthermore, there have been no randomized controlled trials (RCTs) proving the efficacy or safety of fluid restriction in this clinical setting.

There is a paucity of evidence of an appropriate method for $[Na^+]$ correction in SIAD and uncertainty surrounding the efficacy of fluid restriction. Increasing oral solute intake in combination with loop diuretics makes sound physiologic sense.[4,17] However the physiologic principle behind using loop diuretics in SIAD is that loop diuretics can induce natriuresis and aquaresis, whereas oral sodium chloride (NaCl) supplementation can increase renal water excretion. To our knowledge, there have only been small case series using oral NaCl and furosemide in patients with SIAD. However, there is no documented controlled study to support the efficacy and safety of loop diuretics in its treatment.[18] The objective of this study is to investigate whether the combination of furosemide and/or NaCl

supplement with fluid restriction is more effective than fluid restriction alone in the treatment of SIAD.

Methods

Study Population

Eligible patients were hospitalized patients who were 18 years or older with a serum $[Na^+] \leq 130$ mmol/L due to SIAD. For a firm diagnosis of SIAD, all the following criteria had to have been met: (1) serum osmolality < 275 mOsm/kg, (2) urine osmolality > 100 mOsm/kg, (3) clinical euvolemia diagnosed from the history and physical examination, (4) urine $[Na^+] > 30$ mmol/L, and (5) absence of hypothyroidism, glucocorticoid deficiency, estimated glomerular filtration rate < 60 mL/min/1.73 m^2 or diagnosed acute kidney injury (AKI), and diuretic therapy.[4,11] A complete list of inclusion and exclusion criteria is shown in Table S1.

Study Design

This single center, open-label, randomized, controlled study was conducted at Chiang Mai University Hospital from May 2017 to January 2018. The Institutional Review Board of the Faculty of Medicine, Chiang Mai University, approved the study protocol (study code: MED-2560-04547). Written informed consent was obtained from all eligible patients.

Randomization

A permuted block-of-6 randomization was done by computer-generated random number prepared by an investigator who was not involved with the patients. Randomization was stratified by severity of hyponatremia: mild ($[Na^+]$ of 126-130 mmol/L, inclusive), moderate ($[Na^+]$ of 121-125 mmol/L, inclusive), and severe ($[Na^+] \leq 120$ mmol/L). Patients were randomized in a 1:1:1 ratio to receive the following interventions: fluid restriction alone (FR group); fluid restriction and furosemide (FR+FM group); fluid restriction, furosemide, and oral NaCl supplement (FR+FM+NaCl group). The randomized assignments were concealed until all eligibility criteria had been met; however, blinding was not maintained. After the investigators had obtained the patient's consent, they telephoned a contact who was independent of the recruitment process for allocation assignment.

Intervention and Study Procedures

Fluid restriction was applied to all patients at the time of enrollment. The amount of fluid restriction was directed by urine to serum electrolyte ratio, which is the sum of urinary sodium and potassium concentrations divided by serum sodium.[19] If the electrolyte ratio was ≤1 or >1, the goals of fluid restriction would be <1 L/d or <500 mL/d, respectively. Furosemide treatment was started at a dose of 20 mg orally once daily and adjusted to a maximum of 40 mg daily with the aim of keeping a negative fluid balance of >500 mL/d. The NaCl dose was 3 g (51 mmol) orally daily divided into 3 separate doses (ten 300-mg tablets per day because this preparation is available in our institution). All patients were advised to keep dietary sodium intake as normal. All treatments including fluid restriction were continued until day 28 after randomization.

Adherence to fluid restriction was defined as the patient following the prescribed fluid restriction for >80% of the period. Fluid restriction was assessed by recording all types of fluid intake during the hospital stay or at home. Medication adherence was identified by direct observation during hospitalization and pill count in an outpatient setting. More than 80% of medication taken was defined as medication adherence. Details of rescue therapy and overly rapid correction of $[Na^+]$ can be found in Item S1.

Study Outcomes

The primary outcome was change in $[Na^+]$ on days 4, 7, 14, and 28 from baseline; the primary objective was change in $[Na^+]$ on day 4 and secondary objectives were change in [Na+] on days 7 and 28 from baseline. Secondary outcomes included the percentage of patients who achieve $[Na^+] \geq 130$ or ≥135 mmol/L on day 4 and time to achievement of $[Na^+] \geq 130$ or ≥135 mmol/L. Routine clinical measurements of $[Na^+]$ were also used to determine the time to the correction of $[Na^+]$. We selected $[Na^+]$ at days 4 and 28 as an outcome measurement owing to 4 days being a reasonable target to increase $[Na^+]$ back to normal and to be consistent with other reports in the literature, and 28 days to assess the durability of the response. $[Na^+]$ was measured using an ion-selective electrode system (Cobas 6000/8000 analyzer series; Roche Diagnostics).

Outcome Assessments

Clinical conditions and $[Na^+]$ were evaluated daily from randomization to day 4 to ensure patient safety and prevent overcorrection. Patients were scheduled for follow-up at days 7, 14, and 28 after randomization. Evaluations at follow-up visits included patient clinical and volume status, amount of fluid intake, blood and urine chemistry, and adverse events. Adverse events were spontaneously reported or ascertained by nonleading questions. AKI was defined in accordance with KDIGO guideline recommendations using serum creatinine criteria.[20]

Statistical Analyses

Based on previous observational and uncontrolled studies for the treatment of SIAD,[21,22] we estimated that $[Na^+]$ would increase by 5, 8, and 12 mmol/L on day 4 after randomization in the FR group, FR+FM group, and FR+FM+NaCl group, respectively. Changes in $[Na^+]$ between groups were compared using an analysis of repeated-measures model with assumed within-group variance of 64 and a 5% drop-out rate. A sample size of at least 30 patients per group was defined as giving 80% power and a 2-sided alpha level of 5%.

Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR) and were compared using 1-way analysis of variance or Kruskal-Wallis test, as appropriate. Categorical variables were expressed as frequency and proportion and compared using χ^2 test or Fisher exact test, as appropriate. An extension of the Wilcoxon rank sum test for trend was used for trend analysis.[23] We performed an intention-to-treat analysis for both efficacy and harms among patients who underwent randomization. A repeated-measures linear mixed-effects model was used to test the change in $[Na^+]$ on days 4, 7, 14, and 28 between intervention groups. Times to $[Na^+] \geq 130$ or ≥135 mmol/L were compared using Gray test and presented as cumulative incidence probabilities estimated by the cumulative incidence function method in the presence of the competing event of death. No interim analysis was done. All *P* values were 2 sided and were not adjusted for multiple testing. $P < 0.05$ was considered statistical significance. All statistical analyses were performed using Stata software, version 15.0 (StataCorp), and R, version 3.6.1 (R Foundation), using the cmprsk package, version 2.2-9.

Results

Study Population

A total of 289 patients were screened. Of those, 92 patients underwent randomization (31 in the FR group, 30 in the FR+FM group, and 31 in the FR+FM+NaCl group; Fig 1). Two patients withdrew consent after randomization; however, both were included in outcome analyses. Overall, 66 (72%) patients completed a final visit and 10 (11%) patients died during the follow-up period; 87 (95%) of the participants had data relating to the primary objective. The percentage of patients receiving the trial regimen was 97% in the FR group, 97% in the FR+FM group, and 100% in the FR+FM+NaCl group.

Clinical characteristics and laboratory values of the patients were similar among the 3 groups (Table 1). Overall, 63% were men, with a mean age of 59.5 ± 16.6 years. The causes of SIAD were identified in 93% of patients. Malignancies were the most common cause (51%), followed by drug-associated (37%), neuropsychiatric disorders (37%), and pulmonary disease (33%). There were 59 (64%) patients who had more than 1 identifiable cause of SIAD. Specific diseases or drugs in each category are shown in Table S2. Mean $[Na^+]$ and severity of hyponatremia were no different between groups. Median values for serum uric acid and fractional excretion of uric acid were 3.1 (IQR, 2.0-4.1) mg/dL and 13.1% (IQR, 9.2%-19.2%), respectively. Median urine to serum electrolyte ratio was 0.95 (IQR, 0.82-1.29). All these parameters were not significantly different between groups. Assignment for oral fluid restriction was not different between groups because the proportions of patients who had electrolyte ratios ≤ 1 or >1 were similar between the 3 groups ($P = 0.5$). Overall, 57% were assigned to restrict oral fluid to <1 L/d, while 43% of patients were assigned to restrict oral fluid to <500 mL/d.

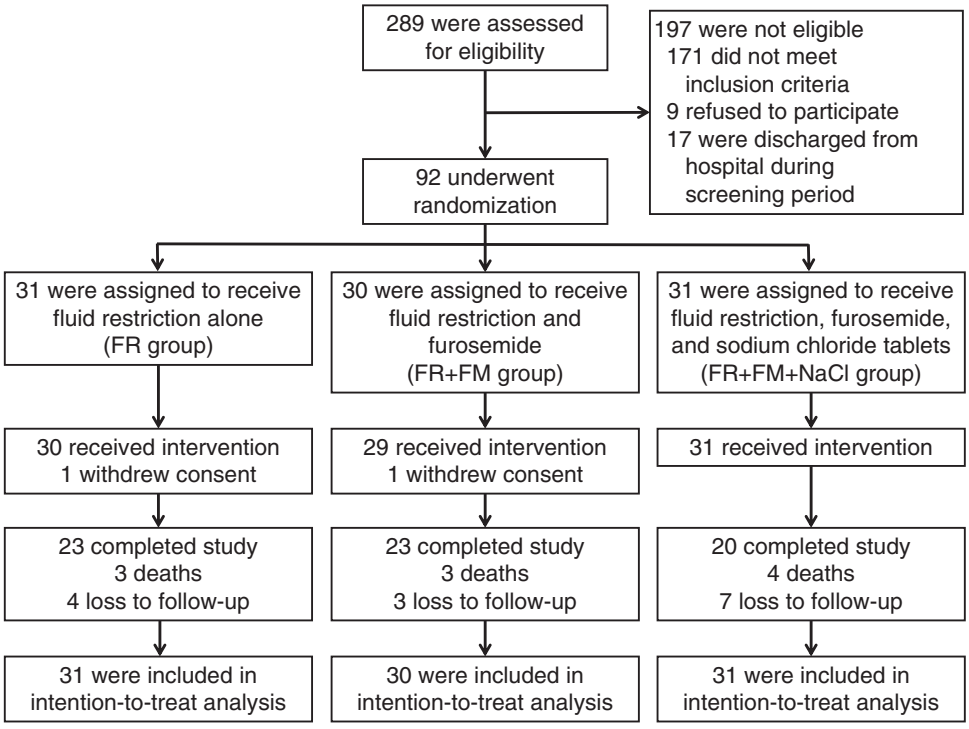

Figure 1. Enrollment, randomization, and analysis. Abbreviations: FM, furosemide; FR, fluid restriction; NaCl, sodium chloride.

Table 1. Baseline Characteristics of the Patients

Characteristic	FR Group (n = 31)	FR+FM Group (n = 30)	FR+FM+NaCl Group (n = 31)	Total (N = 92)
Age, y	60.1 ± 14.7	54.6 ± 17.3	63.5 ± 17	59.5 ± 16.6
Male sex	18 (58%)	19 (63%)	21 (68%)	58 (63%)
Body weight, kg	48.6 ± 10.3	51.4 ± 10.8	52.0 ± 14.9	50.6 ± 12.1
Admission department				
Medical ward	24 (77%)	20 (67%)	20 (65%)	64 (70%)
Surgical ward	7 (23%)	10 (33%)	11 (35%)	28 (30%)
Symptoms of hyponatremia				
Nausea/vomiting	14 (45%)	6 (20%)	7 (23%)	27 (30%)
Impaired consciousness	7 (23%)	3 (10%)	5 (16%)	15 (16%)
Fatigue	2 (6%)	5 (17%)	3 (10%)	10 (11%)
Other	1 (3%)	0 (0%)	1 (3%)	2 (2%)
Causes of SIAD[a]				
Malignancy	12 (39%)	17 (57%)	18 (58%)	47 (51%)
Drug associated	10 (32%)	11 (37%)	13 (42%)	34 (37%)
Neuropsychiatric disorders	14 (45%)	10 (33%)	10 (32%)	34 (37%)
Pulmonary diseases	7 (23%)	12 (40%)	11 (35%)	30 (33%)
HIV infection	2 (6%)	5 (17%)	3 (10%)	10 (11%)
Idiopathic	2 (6%)	2 (7%)	2 (6%)	6 (7%)
Serum sodium, mmol/L	125 ± 4	125 ± 3	125 ± 4	125 ± 4
Severity of hyponatremia				
Mild	15 (48%)	14 (47%)	16 (52%)	45 (49%)
Moderate	11 (35%)	12 (40%)	11 (35%)	34 (37%)
Severe	5 (16%)	4 (13%)	4 (13%)	13 (14%)
Serum TSH, IU/mL	1.70 [0.99-2.87]	2.11 [1.26-2.96]	1.74 [1.06-3.00]	1.87 [1.04-2.96]
Serum cortisol, μg/dL	17.0 [15.5-19.0]	18.5 [15.3-21.6]	16.0 [13.6-19.8]	17.0 [14.7-19.8]
eGFR,[b] mL/min/1.73 m^2	106 [95-115]	108 [88-117]	98 [87-112]	103 [90-116]
Serum urea nitrogen, mg/dL	9 [7-13]	11 [7-15]	10 [7-14]	10 [7-14]
Serum potassium, mmol/L	3.7 [3.4-3.9]	3.8 [3.5-4.0]	3.6 [3.3-4.2]	3.7 [3.4-4.1]
Serum uric acid, mg/dL	2.8 [1.8-3.6]	2.8 [2.0-4.2]	3.2 [2.4-4.6]	3.1 [2.0-4.1]
Serum magnesium, mEq/L	1.49 [1.28-1.67]	1.64 [1.44-1.70]	1.50 [1.24-1.67]	1.52 [1.34-1.67]
Serum osmolality, mOsm/kg	269 [261-275]	271 [262-276]	269 [262-275]	269 [262-275]
Urine osmolality, mOsm/kg	397 [353-540]	426 [353-545]	397 [307-501]	414 [333-529]
Urine sodium, mmol/L	107 [68-131]	87 [59-119]	99 [65-120]	100 [66-127]
Urine potassium, mmol/L	26 [18-41]	25 [14-43]	22 [14-36]	25 [15-41]
24-h urine				
Volume, mL/d	1,350 [900-2,010]	1,300 [700-2,100]	1,357 [950-1,900]	1,325 [825-1,975]
Sodium excretion rate, mmol/d	125 [91-182]	92 [43-178]	128 [75-233]	119 [74-205]
Potassium excretion rate, mmol/d	42 [21-65]	30 [13-70]	25 [18-53]	30 [18-62]
Solute excretion rate,[c] mmol/d	179 [110-242]	153 [70-293]	161 [96-289]	165 [105-280]
FE of uric acid, %	13.6 [9.2-21.0]	11.9 [8.8-22.7]	13.1 [9.9-16.4]	13.1 [9.2-19.2]
Urine-serum electrolyte ratio[d]	1.01 [0.84-1.31]	0.91 [0.83-1.61]	0.93 [0.74-1.30]	0.95 [0.82-1.29]
Urine-serum electrolyte ratio category				
≤1	15 (48%)	18 (60%)	19 (61%)	52 (57%)
>1	16 (52%)	12 (40%)	12 (39%)	40 (43%)

Note: Data are mean ± standard deviation, median [interquartile range], or number (percent). Percentages may not total 100 because of rounding.
Abbreviations: eGFR, estimated glomerular filtration rate; FE, fractional excretion; FM, furosemide; FR, fluid restriction; HIV, human immunodeficiency virus; NaCl, sodium chloride; SIAD, syndrome of inappropriate antidiuresis; TSH, thyroid-stimulating hormone.
[a]Total percentage of SIAD causes may be more than 100 because some patients have more than 1 cause.
[b]Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.
[c]Solute denotes the combination of sodium and potassium.
[d]Calculated as the sum of the urinary concentrations of sodium and potassium divided by serum sodium.

Efficacy

For change in $[Na^+]$ at day 4 from baseline, there were no significant differences between the 3 groups ($P = 0.7$; Table 2; Fig 2). Generally, mean $[Na^+]$ on day 4 in all treatment groups were significantly increased from baseline by 5 (95% confidence interval, 4-6) mmol/L ($P < 0.001$). On day 7, change in $[Na^+]$ in the FR+FM+NaCl group was significantly larger than the change in the other 2 groups

Table 2. Baseline Serum Sodium Levels and Clinical Outcomes

Variable	FR Group (n = 31)	FR+FM Group (n = 30)	FR+FM+NaCl Group (n = 31)	*P*
Baseline serum sodium, mmol/L	125 ± 4	125 ± 3	125 ± 4	0.9
Primary outcome: Δ[Na+] from baseline				
At d 4, mmol/L (n = 87)	4.9 ± 4.7	4.3 ± 4.4	6.3 ± 8.7	0.7
At d 7, mmol/L (n = 61)	4.8 ± 4.5	3.8 ± 4.6	7.5 ± 5.9	0.03
At d 28, mmol/L (n = 67)	5.7 ± 4.7	7.8 ± 7.2	8.6 ± 7.8	0.8
Secondary outcomes				
Percentage of patients with [Na+] ≥ 130 mmol/L				
At d 4 (n = 89)	15 (48%)	16 (53%)	20 (65%)	0.4
At d 7 (n = 82)	22 (71%)	20 (67%)	27 (87%)	0.2
At d 28 (n = 83)	23 (74%)	24 (80%)	25 (81%)	0.8
Percentage of patients with [Na+] ≥ 135 mmol/L				
At d 4 (n = 87)	6 (19%)	4 (13%)	8 (26%)	0.5
At d 7 (n = 69)	13 (42%)	10 (33%)	15 (48%)	0.5
At d 28 (n = 71)	16 (52%)	15 (50%)	18 (58%)	0.8

Note: Data are mean ± standard deviation or number (percent). *P* value for baseline serum [Na^+] is from analysis of variance. *P* values for change in serum [Na^+] at days 4, 7, and 28 from baseline are from a linear mixed-effects model. *P* values for percentage of patients with serum [Na^+] ≥ 130 and ≥135 mmol/L are from Fischer exact tests.
Abbreviations: Δ, change; FM, furosemide; FR, fluid restriction; [Na+], serum sodium concentration; NaCl, sodium chloride.

(P = 0.03). However, changes in [Na^+] from baseline in the 3 groups were not significantly different on days 14 and 28 (Fig 2). Change in [Na^+] at day 4 from baseline in the subgroup of patients with electrolyte ratios ≤ 1 or >1 were not significantly different between the 3 groups (P = 0.7 and P = 0.6, respectively).

The percentage of patients for whom [Na^+] ≥ 130 mmol/L or ≥135 mmol/L was recorded at days 7, 14, and 28 after randomization were not significantly different between the 3 groups (Table 2). Time to reach [Na^+] ≥ 130 mmol/L or ≥135 mmol/L was not significantly different between groups when cumulative incidence functions using death as a competing risk were compared (Fig 3A and B). Median time to achievement of [Na^+] ≥ 130 mmol/L was 4 days in all treatment groups (P = 0.8). Median time to achievement of [Na^+] ≥ 135 mmol/L in the FR+FM+NaCl group was nominally shorter than in the other 2 groups (14 vs 28 days), but this was not statistically significant (P = 0.5).

Fluid intake and urine output during the first 4 days were not significantly different between groups (Fig 4), except that urine output on day 4 in the FR+FM+NaCl group was significantly higher than in the other 2 groups (P = 0.03).

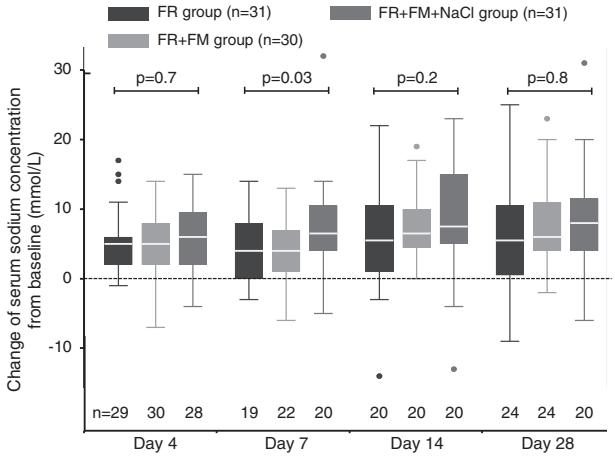

Figure 2. Change in serum sodium concentration from baseline by treatment group during study period. *P* values are from linear mixed-effects models. Abbreviations: FM, furosemide; FR, fluid restriction; NaCl, sodium chloride.

Fluid Restriction, Medication, and Treatment Adherence

The overall adherence rate for fluid restriction was 63%. Specifically, 55% of the FR group, 63% of the FR+FM group, and 71% of the FR+FM+NaCl group adhered to fluid restriction; these levels were not statistically different between groups (P = 0.4). Nevertheless, although 79% of patients assigned to restrict oral fluid to <1 L/d adhered to the fluid restriction protocol throughout the study period, only 43% of patients assigned to restrict oral fluid to <500 mL/d adhered to the fluid restriction protocol.

Overall adherence to furosemide and/or oral NaCl treatment was 90%, which did not differ significantly between groups (P = 0.4). All patients in the FR+FM+NaCl group received oral NaCl at the dose of 3 g/d, while 87% of the FR+FM group and 84% of the FR+FM+NaCl group received furosemide at a dose of 20 mg/d (P = 0.8). The rest received furosemide at 40 mg/d.

Adverse Events

Ten (11%) patients died during the follow-up period. Of those, 9 had malignancy as an underlying cause of SIAD. The numbers of deaths in each group were not statistically different (P = 0.9) and none of the deaths were related to study treatments (Table 3). The incidence of any adverse

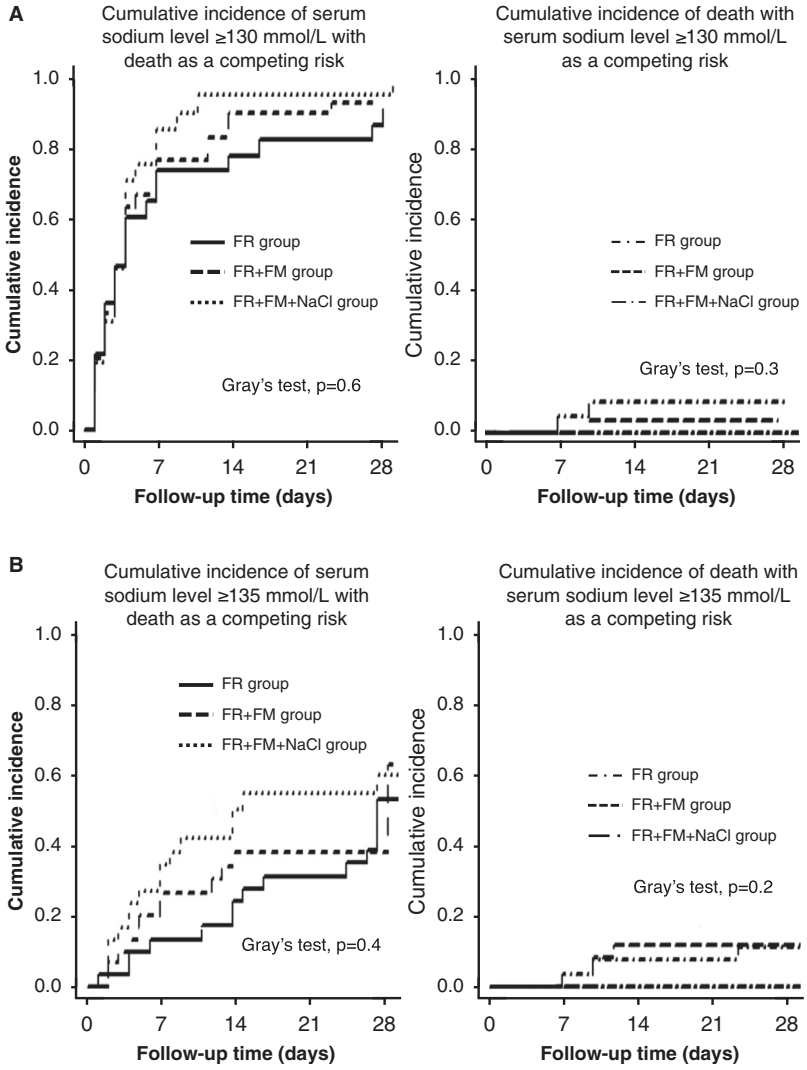

Figure 3. Cumulative incidence of achieving serum sodium levels (A) ≥130 mmol/L and (B) ≥135 mmol/L with death as a competing risk. Abbreviations: FM, furosemide; FR, fluid restriction; NaCl, sodium chloride.

events was not statistically different between groups. These occurred in 61% of the FR group, 53% of the FR+FM group, and 71% of the FR+FM+NaCl group ($P = 0.4$). Fourteen patients were withdrawn from the study due to adverse events, 11 of these were withdrawn due to AKI, and 1 patient each was withdrawn due to hypotension, hypovolemia, and hypernatremia. Of note, the proportion of patients withdrawn from the study was higher in the FR+FM+NaCl group ($P = 0.03$).

The incidence of AKI was nominally higher in the FR+FM+NaCl group. Specifically, 32% of patients in the FR+FM+NaCl group developed AKI compared with 17% in the FR+FM group and 10% in the FR group. However, this was not significantly significant ($P = 0.07$). The risk for significant hypokalemia, defined as serum potassium level ≤ 3.0 mmol/L, was highest in the FR+FM+NaCl group, followed by the FR+FM and FR groups (P for trend = 0.01; Table 3). Other adverse events were comparable between groups; however, the number of patients with overly rapid correction of $[Na^+]$ was numerically higher in the FR+FM+NaCl group. No patients developed severe symptomatic hyponatremia requiring rescue therapy during the study period.

Discussion

We conducted this study because to our knowledge there has never been an RCT comparing the efficacy of fluid restriction versus furosemide and/or use of an NaCl supplement in the treatment of patients with SIAD. Our findings have shown that among patients with hyponatremia due to SIAD, there was no evidence that treatments with once-daily furosemide and/or a 3-g NaCl supplement add-on to fluid restriction resulted in a greater change in $[Na^+]$ in comparison to fluid restriction alone on day 4 after treatment. Although the change in $[Na^+]$ on day 7 was higher in the FR+FM+NaCl group, the change in $[Na^+]$ on day 28 was similar in all treatment groups. Also,

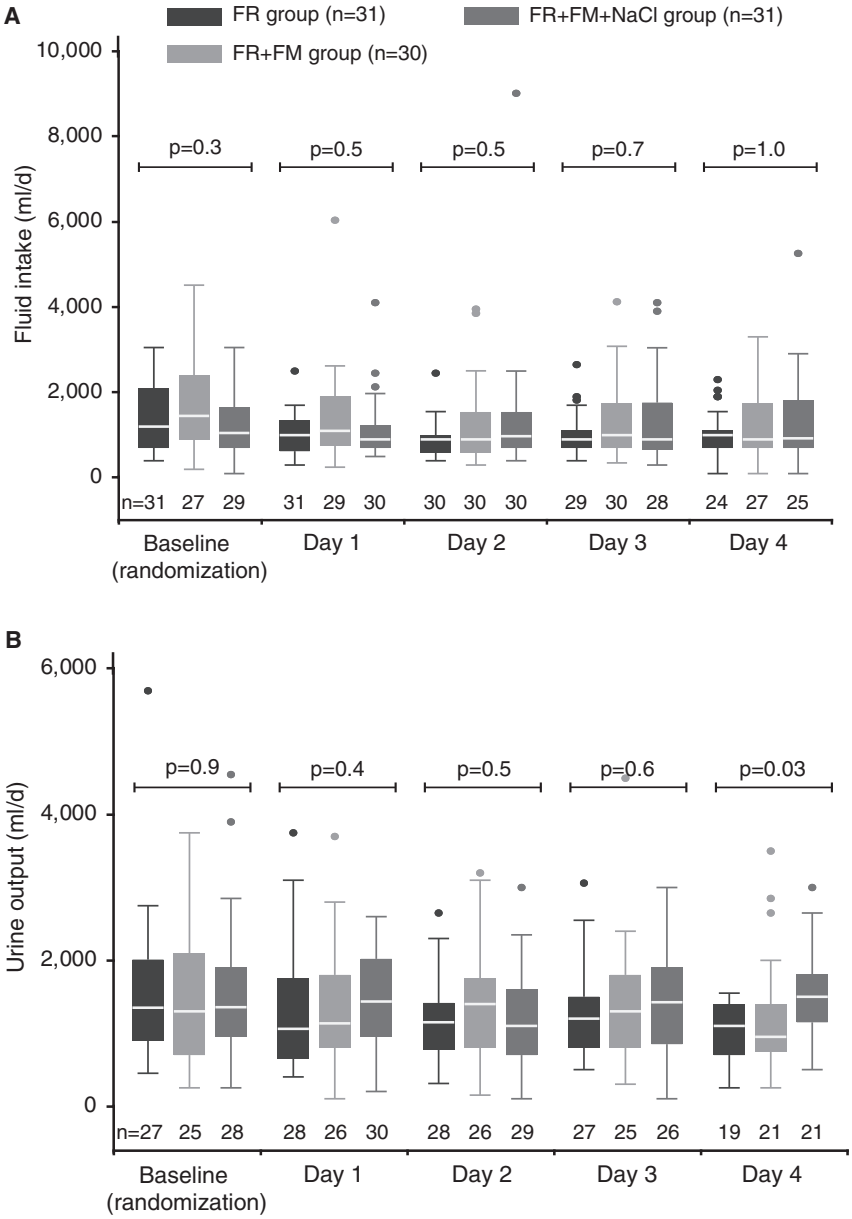

Figure 4. (A) Fluid intake and (B) urine outputs at randomization and during the first 4 days after randomization. Abbreviations: FM, furosemide; FR, fluid restriction; NaCl, sodium chloride.

the percentage of patients and time to reach $[Na^+]$ ≥ 130 mmol/L (which is accepted as being a safe level) and ≥135 mmol/L (which is a normal level) were similar between the 3 treatment groups.

Most guidelines recommend fluid restriction as a first-line therapy for patients with SIAD[4] and recommend low-dose loop diuretics and an NaCl supplement as a second-line therapy in patients in whom treatment with fluid restriction failed.[4,11] Evidence of the use of furosemide or an NaCl supplement for the treatment of SIAD as recommended by major guidelines is based on uncontrolled studies with very small sample sizes. Hantman et al[24] showed that furosemide was effective in correcting $[Na^+]$ in patients with SIAD; however, the study included only 5 patients, all of whom received hypertonic saline solution. Additionally, the investigators adjusted the furosemide dose to keep urine output > 2 L/d. It is likely that the efficacy of furosemide is correlated with urine volume because we found that a group of patients who received furosemide, an NaCl supplement, and underwent a fluid restriction combination had a higher $[Na^+]$ on day 7, whereas they started to have higher urine volume in comparison to the other groups on day 4.

We found that $[Na^+]$ in all treatment groups increased by 5 mmol/L in 4 days and by 7 to 8 mmol/L in 28 days. These findings indicate a lack of evidence for a beneficial effect of once-daily furosemide and/or a 3-g NaCl supplement in patients who could adhere to fluid restriction. Decaux et al[18,21] reported a small case series involving 9 and 12

Table 3. Patients With Adverse Events

Variable	FR Group (n = 31)	FR+FM Group (n = 30)	FR+FM+NaCl Group (n = 31)	*P*
Death from any cause	3 (10%)	3 (10%)	4 (13%)	0.9
All adverse events	19 (61%)	16 (53%)	22 (71%)	0.4
Withdrawn from study due to adverse events	2 (6%)	3 (10%)	9 (20%)	0.03
Acute kidney injury	3 (10%)	5 (17%)	10 (32%)	0.07
Hypotension (BP ≤ 90/60 mm Hg)	6 (19%)	4 (13%)	6 (19%)	0.8
Hypovolemia	1 (3%)	1 (3%)	0 (0%)	0.8
Thirst	7 (23%)	4 (13%)	7 (23%)	0.6
Significant hypokalemia (serum potassium ≤ 3.0 mmol/L)	4 (13%)	7 (23%)	13 (42%)	0.01
Severe hypomagnesemia (serum magnesium ≤ 1.0 mEq/L)	0 (0%)	1 (3%)	2 (6%)	0.5
Hypercalcemia (serum calcium ≥ 10.5 mg/dL)	0 (0%)	1 (3%)	0 (0%)	0.3
Fatigue	2 (6%)	1 (3%)	4 (13%)	0.5
Nausea/vomiting	1 (3%)	0 (0%)	2 (6%)	0.8
Decreased level of consciousness	1 (3%)	0 (0%)	2 (6%)	0.8
Overly rapid correction of serum sodium	2 (6%)	2 (7%)	4 (13%)	0.7

Note: All *P* values are from Fischer exact tests except a *P* value for significant hypokalemia is from an extension of the Wilcoxon rank sum test for trend.[23]
Abbreviations: BP, blood pressure; FM, furosemide; FR, fluid restriction; NaCl, sodium chloride.

patients with SIAD, again without a control group, and showed that 40 mg of furosemide and 3 to 6 g of NaCl per day were very effective in the correction of $[Na^+]$. However, all participants in these studies did not adhere to the prescribed fluid restriction (500 mL/d), all of them being allowed to take oral fluid of 2 L/d. It appears that the efficacy of furosemide and an NaCl supplement may be observed only if patients do not adhere to fluid restriction.

There are various regimens of fluid restriction advocated by experts, for example, 500 to 1,000 mL/d[25] or 500 mL less than the 24-hour urine output.[26] In this study, we limited fluid intake for our patients to <500 mL/d or <1 L/d according to the urine to serum electrolyte ratio as described by Furst et al.[19] Previous evidence showed that the ability of the kidneys to excrete water is a crucial factor in the determination of an individual's response to fluid restriction as a treatment of hyponatremia.[27,28] This approach may be more effective and more acceptable for patients because 63% of our participants could adhere to the fluid restriction protocol throughout the study period. The other explanation for the success of fluid restriction without furosemide and/or an NaCl supplement in this study could be the urine osmolality of the patients. One of the predictors for the likely failure of fluid restriction is urine osmolality > 500 mOsm/kg,[11] and the median urine osmolality of patients in this study was 414 (IQR, 333-529) mOsm/kg. Furthermore, patients with urine osmolality < 500 mOsm/kg are unlikely to experience much benefit from furosemide due to a limitation to decrease urine osmolality.[29]

Consistent with the findings of our study, that $[Na^+]$ increased by 5 mmol/L in 4 days in all treatment groups, a registry that assessed the treatment of hyponatremia in 1,524 patients with SIAD showed that fluid restriction alone or fluid restriction in combination with an NaCl supplement can increase $[Na^+]$ by a median rate of 1 mmol/L per day.[22] Unfortunately, this registry did not include patients who received furosemide for the treatment of SIAD. The registry also showed that only 28% of patients who received furosemide alone and 42% of patients who received furosemide and an NaCl supplement had $[Na^+] \geq 130$ mmol/L, and only 9% of patients who received furosemide alone and 11% of patients who received furosemide and an NaCl supplement had $[Na^+] \geq 135$ mmol/L at a median time of 7 days. These findings are a remarkable contrast to our results because 71% and 42% of our patients in the fluid restriction group had $[Na^+] \geq 130$ and ≥ 135 mmol/L on day 7 after treatment, respectively. These differences may result from the nature of the 2 studies. In the registry report, the treatment regimen, adherence monitoring, and follow-up schedule all depended on the treating physician. In contrast, our study was a controlled study; the treatment regimen was systematically assigned, adherence was closely monitored, and regular follow-up was scheduled by a closely briefed team. That said, although an RCT is a reference standard for demonstrating the efficacy of a particular intervention, patients enrolled in RCTs tend to have higher treatment adherence than those in real-world clinical practice.[30]

We found that adverse events were fairly balanced among the 3 treatment groups. However, adverse events leading to withdrawal from the study were higher in the group treated with furosemide. The most important reason was a higher incidence of AKI in these groups. It is not surprising that patients receiving furosemide would have a higher risk for AKI because furosemide can induce intravascular volume depletion.[31] Although there is evidence that using furosemide in combination with an NaCl supplement may prevent deterioration of kidney function,[32] only 3 g (51 mmol) of the NaCl supplement was prescribed in this study. This amount of NaCl may not be sufficient to replace renal sodium loss induced by furosemide and prevent intravascular volume depletion, but there is no solid evidence to make a recommendation as

regards the dose of NaCl used in the treatment of SIAD,[4,11,16] although a dose up to 6 g/d had been used in some studies.[21]

The mortality rate of the patients in our study is high, that is, 11% during a 28-day period, which is higher than that in other reports citing a 6% value in hospitalized hyponatremic patients.[33] One possible explanation was the high proportion (51%) of patients with malignancies in our study. We think it likely that the nature of the underlying illness rather than the severity of hyponatremia accounted for the higher mortality associated with hyponatremia.[33]

We observed that the incidence of significant hypokalemia (serum potassium ≤ 3.0 mmol/L) was considerably higher in patients who received furosemide, especially in those who received an NaCl supplement. It is widely accepted that furosemide increases urinary potassium excretion, and an increase in sodium delivery to distal nephrons can potentiate renal potassium excretion.[34] Our results were consistent with a previous study that showed an incidence of hypokalemia as high as 58.3% in patients with SIAD treated with loop diuretics.[21] Also, the risk for severe hypomagnesemia (serum magnesium ≤ 1.0 mEq/L) was numerically higher in patients who received furosemide; however, this finding did not reach statistical significance, possibly due to a low incidence of severe hypomagnesemia in the study.

The strength of our study is the randomized controlled design with an adequate sample size and high adherence rate to the treatment regimens. Thus, selection bias should be minimized.

However, our study also has several limitations. First, it is an open-label study, which may create bias in treatment adherence because the patients know what treatments they were assigned. However, we worked successfully to encourage our patients to adhere to the treatment regimens throughout the study period; thus, high adherence rates were achieved and did not significantly differ between the 3 intervention groups. Second, information about urine electrolyte-free water clearance during the first 4 days after randomization is not available. Because we used urine volume and urine to serum electrolyte ratio to guide the intensity of treatment, changes in these parameters over time might affect treatment outcomes. Finally, the treatment regimens used in this study was somewhat inflexible. Furosemide was given once daily, whereas its action might last only 6 to 8 hours. The NaCl dosage was in the lower range (3 g/d) and was not allowed to increase during the study, which may differ from clinical practice. Also, no potassium supplements were given concurrent with the furosemide and NaCl supplement to prevent hypokalemia, although it could be anticipated that these regimens might cause hypokalemia. Additional studies using twice-daily furosemide or torsemide, higher NaCl doses, and potassium supplements are warranted to elucidate the efficacy of these treatment regimens in patients with SIAD. Also, urea has been described as an alternative to loop diuretics and NaCl for the treatment of SIAD. Although several uncontrolled studies have shown that oral urea is effective in the treatment of hyponatremia, it has never been tested in a controlled trial. Thus, oral urea may merit for future investigations in patients with SIAD.

This study has demonstrated that the addition of 20 to 40 mg of furosemide once daily and/or a 3-g NaCl supplement to fluid restriction does not increase serum $[Na^+]$ correction rate in patients with SIAD but increases the risk for adverse events compared with treatment with fluid restriction alone. However, the protocol regarding fluid restriction should be guided by urine electrolyte concentration and patient adherence to the regimen and should be closely monitored and appropriately adjusted by the patient care team to improve outcomes.

Supplementary Material

Supplementary File (PDF)

Item S1: Supplementary methods.

Table S1: Inclusion and exclusion criteria.

Table S2: Additional baseline characteristics of patients.

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