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Risk of Overcorrection in Rapid Intermittent Bolus vs Slow Continuous Infusion Therapies of Hypertonic Saline for Patients With Symptomatic Hyponatremia
The SALSA Randomized Clinical Trial

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IMPORTANCE Few high-quality studies have clarified whether hypertonic saline is best administered as slow continuous infusion (SCI) therapy or rapid intermittent bolus (RIB) therapy for symptomatic severe hyponatremia.

OBJECTIVE To compare the risk of overcorrection in RIB and SCI with hypertonic saline in patients with symptomatic hyponatremia.

DESIGN, SETTING, AND PARTICIPANTS This prospective, investigator-initiated, multicenter, open-label, randomized clinical trial enrolled 178 patients older than 18 years with moderately severe to severe hyponatremia and glucose-corrected serum sodium (sNa) levels of 125 mmol/L or less. Recruitment took place from August 24, 2016, until August 21, 2019, across emergency departments and wards of 3 general hospitals in the Republic of Korea.

INTERVENTIONS Either RIB or SCI of hypertonic saline, 3%, for 24 to 48 hours stratified by the severity of clinical symptoms.

MAIN OUTCOME AND MEASURES The primary outcome was overcorrection at any given period, defined as increase in the sNa level by greater than 12 or 18 mmol/L within 24 or 48 hours, respectively. Secondary and post hoc outcomes included efficacy and safety of the treatment approaches. The sNa concentrations were measured every 6 hours for 2 days.

RESULTS The 178 patients (mean [SD] age, 73.1 [12.2] years; 80 (44.9%) male; mean [SD] sNa concentrations, 118.2 [5.0] mmol/L) were randomly assigned to the RIB group (n = 87) or the SCI group (n = 91). Overcorrection occurred in 15 of 87 (17.2%) and 22 of 91 (24.2%) patients in the RIB and SCI groups, respectively (absolute risk difference, −6.9% [95% CI, −18.8% to 4.9%]; *P* = .26). The RIB group showed lower incidence of relowering treatment than the SCI group (36 of 87 [41.4%] vs 52 of 91 [57.1%] patients, respectively; absolute risk difference, −15.8% [95% CI, −30.3% to −1.3%]; *P* = .04; number needed to treat, 6.3). Groups did not differ in terms of efficacy in increasing sNa concentrations nor improving symptoms, but RIB, when compared with SCI, showed better efficacy in achieving target correction rate within 1 hour (intention-to-treat analysis: 28 of 87 (32.2%) vs 16 of 91 (17.6%) patients, respectively; absolute risk difference, 14.6% [95% CI, 2%-27.2%]; *P* = .02; number needed to treat, 6.8; per-protocol analysis: 21 of 72 (29.2%) vs 12 of 73 (16.4%) patients, respectively; absolute risk difference, 12.7% [95% CI, −0.8% to 26.2%]; *P* = .07). The statistical significance of the intention-to-treat and per-protocol analyses were similar for all outcomes except for achieving the target correction rate within 1 hour.

CONCLUSIONS AND RELEVANCE This randomized clinical trial found that both RIB and SIC therapies of hypertonic saline for treating hyponatremia were effective and safe, with no difference in the overcorrection risk. However, RIB had a lower incidence of therapeutic relowering treatment and tended to have a better efficacy in achieving sNa within 1 hour than SCI. RIB could be suggested as the preferred treatment of symptomatic hyponatremia, which is consistent with the current consensus guidelines.

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Visual Abstract

Supplemental content

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Hyponatremia is the most common electrolyte imbalance encountered in clinical practice. It occurs in 14% to 42% of hospitalized patients and is associated with higher mortality.[1-3] Hypertonic saline is an effective treatment for symptomatic hyponatremia.[4-11] Undercorrection of hyponatremia may be insufficient to prevent life-threatening manifestations of cerebral edema, whereas overcorrection from indiscriminate prolonged use of hypertonic saline may result in permanent neurologic disability from osmotic demyelination syndrome (ODS).[12-19] Owing to this concern, the concept of intermittent use of a bolus of hypertonic saline was introduced in 2005 for the treatment of hyponatremia in marathon runners.[20-22] Recent American and European guidelines have recommended administering hypertonic saline as small, fixed boluses[3,23] based on results of small randomized trials,[24] case reports with small numbers of patients,[20,25] and expert opinions.[21,26-28] The appealing aspects of a fixed bolus therapy are[29]: (1) efficacy: reaches rapid partial correction of serum sodium (sNa); (2) safety: limits risk of overcorrection that occurs commonly with continuous infusion of hypertonic saline[30]; and (3) user friendly: omits need for calculations. However, few high-quality evidences have clarified whether hypertonic saline is best administered as a slow continuous infusion (SCI) therapy, which is preferred by most, or as a rapid intermittent bolus (RIB) therapy. We compared the efficacy and safety of RIB and SCI with hypertonic saline in patients with moderately severe to severe symptomatic hyponatremia.

Key Points

Question What are the risks of overcorrection in rapid intermittent bolus (RIB) and slow continuous infusion (SCI) therapies in patients with symptomatic hyponatremia?

Findings In this randomized clinical trial of 178 patients who received either RIB or SCI of hypertonic saline, 3%, for 48 hours, overcorrection occurred in 17.2% in the RIB group and 24.2% in the SCI group.

Meaning Both RIB and SCI therapies of hypertonic saline for treating symptomatic hyponatremia are effective and safe, with no difference in the overcorrection risk; however, RIB could be suggested as the preferred treatment of symptomatic hyponatremia, which is consistent with the current consensus guidelines.

Methods

Study Design and Participants

The SALSA (Efficacy and Safety of Rapid Intermittent Correction Compared With Slow Continuous Correction With Hypertonic Saline in Patients With Moderately Severe or Severe Symptomatic Severe Hyponatremia) trial is a prospective, investigator-initiated, multicenter, open-label, randomized clinical trial that was performed in 3 general hospitals in Korea (Seoul National University Bundang Hospital, Seoul National University Boramae Medical Center, and Hallym University Dongtan Sacred Heart Hospital). The study specifics have been previously described in more detail[31] (trial protocol in Supplement 1). This study was approved by the institutional review boards of the Seoul National University Bundang Hospital, Seoul National University Boramae Medical Center, and Hallym University Dongtan Sacred Heart Hospital. Written informed consent was obtained from all participants or a legal guardian, when applicable. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

atients older than 18 years with moderately severe to severe symptoms and glucose-corrected sNa[32] of 125 mmol/L or less were included. Moderate symptoms include nausea, headache, drowsiness, general weakness, and malaise.[3,33,34] Severe symptoms include vomiting, stupor, seizure, and coma (Glasgow Coma Scale [GCS] score ≤8). Patients were allowed to check multiple times for symptoms of hyponatremia. Patients were excluded if they had primary polydipsia (urine osmolality ≤100 mOsm/kg); were pregnant or breastfeeding; had anuria, arterial hypotension (systolic blood pressure <90 mm Hg and mean arterial pressure <70 mm Hg), liver disease (transaminase levels >3 times the upper limit of normal, known decompensated liver cirrhosis with ascites or diuretic use, hepatic encephalopathy, and varices), uncontrolled diabetes mellitus (glycated hemoglobin >9%); or had a history of cardiac surgery, acute myocardial infarction, sustained ventricular tachycardia, ventricular fibrillation, acute coronary syndrome, cerebral trauma, and increased intracranial pressure within 3 months prior to randomization. Although we excluded patients with pseudohyponatremia (serum osmolality >275 mOsm/kg), if serum osmolality was greater than 275 mOsm/kg but blood urea nitrogen was 30 mg/dL or greater, the patients were included if the calculated serum osmolality (2 × plasma [Na] + [glucose]/18) was less than 275 mOsm/kg.[34]

From August 2016 to October 2018, patients in emergency departments were included, as per previously published trial protocol.[31] After September 2018, patients in wards were included to increase patient enrollment. After July 2017, eligible patients from Hallym University Dongtan Sacred Heart Hospital were also included to increase the number of participants.

By an independent statistician, the randomization sequence was created using a computer-generated list of random numbers and was stratified by centers with a 1:1 allocation using random block sizes of 2, 4, 6, and 8. Study coordinators who were independent persons and responsible for screening and enrolling the participants allocated each patient to a group based on the randomized sequence. The allocation sequence was concealed from the researchers but not from the study coordinators. Eligible participants were randomly allocated in a 1:1 manner to either the SCI or RIB group in accordance with the predefined list. Patients were stratified based on hyponatremia symptom severity (moderately severe or severe) (**Figure 1**). Whereas patients and physicians were aware of the intervention received, the analysts were blinded to the intervention.

We assessed comorbidities based on *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code. Comorbidities were determined by a self-reported history or medical record review. The presence of hypertension, diabetes mellitus, and hypothyroidism was also

confirmed by preexisting use of antihypertensive medications, antihyperglycemic agents, and levothyroxine, respectively. Hypothyroidism was defined as thyroid-stimulating hormone concentrations above 0.4 to 4.0 mIU/L and free thyroxine concentration below reference range. Adrenal insufficiency was defined by basal cortisol less than 3 µg/dL or plasma cortisol at 30 to 60 minutes after 250-µg cosyntropin administration of less than 18 µg/dL.

The determination of the underlying cause of hyponatremia was accomplished by a structured diagnostic approach based on history, physical examination, and laboratory test. All patients were classified into the following 5 categories: (1) decreased extracellular fluid volume due to renal sodium loss (eg, use of diuretics, especially thiazides); (2) decreased extracellular fluid volume due to nonrenal sodium loss (eg, gastrointestinal sodium loss or third spacing); (3) increased extracellular fluid volume (eg, heart failure, liver cirrhosis, nephrotic syndrome); (4) normal extracellular fluid volume with adrenal insufficiency; and (5) normal extracellular fluid volume fulfilling the essential criteria for syndrome of inappropriate antidiuresis.[3,35]

Outcome Measures

The primary outcome was the incidence of overcorrection (overcorrection rate is the number of individuals who develop overcorrection among the total number of participants) at any given period, which was defined as increase in sNa by greater than 12 mmol/L within the first 24 hours or increase in sNa by greater than 18 mmol/L within 48 hours. The secondary outcomes included efficacy and safety; whether symptoms remained at 24 and 48 hours after treatment with hypertonic saline, 3%; first time to an increase in sNa of 5 mmol/L or greater after treatment initiation; time from treatment initiation to achievement of sNa greater than 130 mmol/L; incidence of target correction rate, defined as achieving sNa of 5 to 9 mmol/L within 24 hours and sNa of 10 to 17 mmol/L or 130 mmol/L or greater within 48 hours; length of hospital stay; incidence of additional treatment; incidence of ODS confirmed by *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes or magnetic resonance imaging; incidence of relowering treatment; and change in GCS between pretreatment and 24 and 48 hours after treatment.

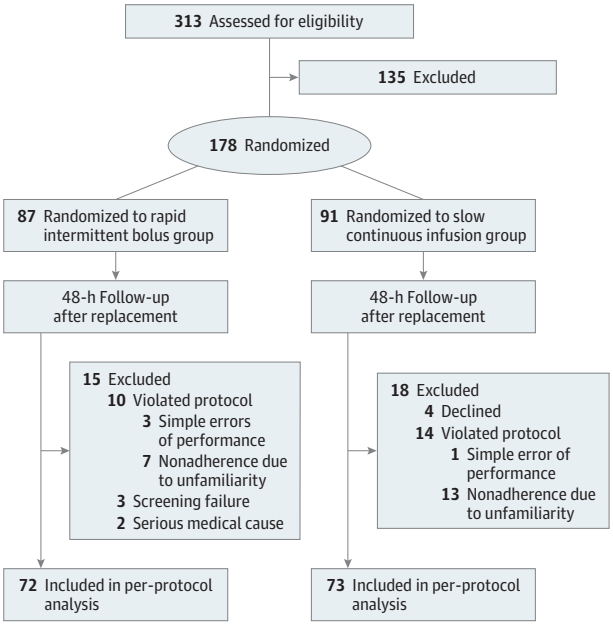
Post Hoc Analysis

In addition to the definition of the existing target correction rate, we added 4 target correction rates specified by the time frame. These were defined as achieving sNa of 5 to 9 mmol/L within 1, 6, and 24 hours, and achieving sNa of 10 to 17 mmol/L or 130 mmol/L or greater within 48 hours.

Practical Treatment Guidelines According to sNa Level

The initial infusion rate of hypertonic saline, 3%, was based on hyponatremia symptom severity. Treatment in the RIB group complied with the European guidelines published in 2014,[3] and the SCI group was guided by widely accepted methods.[23,25,36,37] Treatment guidelines for each group are detailed in eFigure 1 and eMethods in Supplement 2. The treatment goals were to increase sNa level by 5 to 9 mmol/L and to achieve symptom relief within the first 24 hours, and to increase sNa level by 10 to 17mmol/L or 130 mmol/L or greater and to achieve symptom relief during the 48 hours.[7,30,38] Symptom relief was assessed as either no (symptom resolution) or persistent symptoms of hyponatremia, which were somewhat different from the definitions of the recent European guideline (symptom improvement).[3] We checked for overcorrection at every sample time point and conducted a relowering treatment (dextrose, 5%, infusion of 10 mL/kg over 1 hour and/or intravenous desmopressin 2 µg if sNa level increase was ≥10 mmol/L within the first 24 hours or ≥18 mmol/L within 48 hours).[3,23] The treatment goal, relowering treatment strategy, and cause-specific treatment of hyponatremia were equally applied to each group.

Figure 1. Flowchart of SALSA Study



Clinical and Laboratory Evaluations

Acute and chronic hyponatremia were defined according to whether the symptoms of hyponatremia developed in less than or more than 48 hours. Hospital-acquired hyponatremia was defined as a persistent hyponatremia for 48 hours as assessed by serologic tests during hospital stay. The sNa concentrations were measured every 6 hours for 2 days. The sNa was measured by using indirect ion-selective electrodes in the following 3 centers: Seoul University Bundang Hospital (AU5800 [Beckman Coulter] and Dimension Vista 1500 [Siemens Healthineers]); Seoul National University Boramae Medical Center (Modular DP [Roche Diagnostics] and Unicel DxC 800 [Beckman Coulter]); and Hallym University Dongtan Sacred Heart Hospital (AU5800 [Beckman Coulter]). The GCS was assessed before treatment and at 24 and 48 hours of treatment. All types and volumes of administered fluid during the 48 hours were monitored.

Sample Size Calculation

Even though ODS is a critically important hard outcome, its incidence is very low.[3,23] Therefore, as one of the main causes of ODS, the rate of overcorrection of greater than 12 mmol/L within 24 hours or greater than 18 mmol/L within 48 hours was calculated as a primary outcome. A previous study reported an overcorrection rate of 10% to 16% with SCI.[30] We observed that the overcorrection rate was 32% with SCI during a recent 1-year period on a preliminary examination. However, there was no information for estimating the rate of overcorrection with intermittent bolus infusion. We therefore assumed that rate of overcorrection was 5% and as high as 20% in patients treated with RIB and SCI, respectively. We calculated the required sample size for an estimated dropout rate of 15%, a 2-sided level of significance of α = .05, and a power of 80%, and found that 89 participants are required in each group (178 participants total) to find a significant difference using a χ^2 test. We deemed in our 1 interim analysis at that time that half of the participants completed the study. O'Brien-Fleming alpha spending function was used to test the first interim, and the critical value was 2.8 (P = .003). However, intention to treat (ITT) and per protocol (PP) did not pass the threshold. The trial was not stopped.

Statistical Analyses

Statistical analyses (Supplement 3) were performed on the basis of both ITT and PP, because the dropout rate was expected to be high owing to the sophisticated hypertonic saline infusion protocol. The ITT population was defined as all participants in whom the primary end point was available, and participants were analyzed according to the groups in which they were randomly allocated, regardless of deviation from the protocol. In the ITT analysis, all outcomes, including the overcorrection, were counted until the infusion protocol had been well adhered to; the time was defined as the time of dropout if violated protocol or serious medical conditions developed or the time just before dropout if consents were withdrawn. All outcomes, except for remaining symptom at 24 and 48 hours and GCS at 24 and 48, were counted in all ITT patients whose sNa was measured more than once after the initiation of hypertonic saline owing to the special time point and outcomes occurring repeatedly.

Screening failure occurred in 2 patients with elevated liver function (no history of previous liver disease, transaminase levels 4-6 times the upper limit of normal) and 1 patient who did not achieve the glucose-corrected sNa level (124 mmol/L of sodium in the arterial blood gas analysis; 126 mmol/L of glucose-corrected sNa level in the chemistry analysis). For the ITT analysis, we used the outcomes of 3 participants with screening failure prior to unblinding and analysis in the independent safety board. This decision was intended to maintain the internal validity of randomization. Moreover, these patients did not differ significantly from those patients who met the inclusion criteria. The outcomes were also counted until the infusion protocol had been well complied, similar to the other participants.

The baseline characteristics and laboratory data were presented as means and standard deviations for continuous variables, as well as frequencies and percentages for categorical variables. The incidence of overcorrection, remaining symptoms, target correction rate (achieved sNa <10 mmol/L within the first 24 hours and sNa <18 mmol/L within 48 hours), incidence of additional treatment, ODS, and relowering treatment were compared using χ^2 and Fisher exact tests. For these binary outcomes, absolute risk differences and 95% CIs were calculated using a Poisson regression with robust error variance. The differences in changes in GCS between pretreatment and 24 and 48 hours, time to achieved sNa 5 mmol/L or greater or sNa greater than 130 mmol/L for the first time, and length of hospital stay were analyzed using t test or Mann-Whitney U test. For these continuous outcomes, mean difference was calculated using a linear regression. We used a linear mixed model to analyze the effect of repeated sNa and overall change of sNa from baseline with fixed effects of time, group, and interactions between time and group. Marginal effect of a sNa and overall change of sNa from baseline according to groups was plotted. For the prespecified subgroup analyses, we performed the analysis of primary, secondary, and post hoc outcomes according to the initial hyponatremia symptoms (moderately severe vs severe) using the same method implemented in the main analysis and assessed the heterogeneity of treatment effects among subgroup pairs by fitting an interaction between a treatment and a subgroup.

Two-sided P value of less than .05 was considered statistically significant. Adjustment for multiple comparisons are not shown herein; therefore, secondary outcomes should be interpreted as exploratory because of potential inflation for type I error due to multiple comparisons. Adjustment for multiple tests for secondary outcomes is shown in Supplement 2 using the Bonferroni and Benjamini-Hochberg procedures. All analyses were performed using SPSS Statistics software, version 24.0 (IBM Corporation), STATA, version 14.0 (StataCorp LP), and R, version 3.5.3 (R Foundation for Statistical Computing). The trial was overseen by an independent data-monitoring committee.

Results

Recruitment was conducted from August 24, 2016, to August 21, 2019. Written informed consent was obtained from 178 patients who underwent randomization. Their mean (SD) age and sNa concentration were 73.1 (12.2) years and 118.2 (5.0) mmol/L, respectively, and 80 (44.9%) patients were men. Two individuals presented with a seizure activity, 5 were in a stuporous state, and 38 had vomiting. The causes of hyponatremia were use of thiazide diuretics (n = 53 [29.8%]), syndrome of inappropriate antidiuresis (n = 52 [29.2%]), adrenal insufficiency (n = 29 [16.3%]), decreased extracellular cellular fluid volume due to nonrenal sodium loss (n = 25 [14.0%]), and increased extracellular fluid volume (n = 19 [10.7%]). Five individuals had a history of alcoholism. The proportions of acute or chronic hyponatremia and community-acquired or hospital-acquired hyponatremia were 37.5% and 62.5% and 82.6% and 17.4%, respectively. Among the 178 patients, hypertonic saline was initiated in the emergency department and general

ward in 131 (73.6%) and 46 (25.8%) of the patients, respectively. Altogether, 175 patients (98.3%) received hypertonic saline through a peripheral intravenous line. Forty-six (25.8%) and 12 patients (6.7%) underwent brain computed tomography and/or brain magnetic resonance imaging, respectively, at admission.

Eighty-seven and 91 patients of the RIB and SCI groups, respectively, were included in the ITT analysis. The 2 groups had similar baseline characteristics (**Table 1** and eTable 1 in Supplement 2). Seventy-two and 73 patients from the RIB and SCI groups, respectively, completed the study (eTable 2 in Supplement 2). The analysis was completed by original assigned groups. The cohort flowchart (Figure 1) shows why patients dropped out from the study, and there was no difference in the characteristics between these patients and enrolled patients except for a history of liver cirrhosis and serum albumin levels (eTable 3 in Supplement 2). The main reasons for protocol violation were 4 simple errors in performing instructions by nurses and 20 events of physician's nonadherence owing to the unfamiliarity with the protocol.

Primary Outcome: The Incidence of Overcorrection

The 2 groups did not differ in baseline mean (SD) sNa concentrations (118.2 [5.0] vs 118.2 [5.0]; $P = .94$). For ITT analysis, overcorrection occurred in 15 of 87 (17.2%) patients in the RIB group and 22 of 91 (24.2%) patients in the SCI group (absolute risk difference, −6.9% [95% CI, −18.8% to 4.9%]; $P = .26$) (**Table 2** and **Figure 2**A). For PP analysis, overcorrection occurred in 14 of 72 (19.4%) patients in the RIB group and 19 of 73 (26.0%) patients in the SCI group (absolute risk difference, −6.6% [95% CI, −20.2% to 7.0%]; $P = .35$) (eTable 4 in Supplement 2 and Figure 2B).

Secondary Outcomes

No significant differences between the groups were observed in symptoms at 24 and 48 hours after treatment initiation; first time to an increase in sNa 5 mmol/L or greater after treatment initiation; incidence of target correction rate; time from treatment initiation to achievement of sNa greater than 130 mmol/L; and length of hospital stay. Additional treatment was provided in 79 of 87 (90.8%) patients in the RIB group and 68 of 91 (74.7%) patients in SCI group (absolute risk difference, 16.1% [95% CI, 5.3%-26.9%]; $P = .005$; number needed to treat [NNT], 6.2). The RIB group had higher mean (SD) of additional treatments than the SCI group (3.4 [1.8] vs 1.8 [1.7], respectively; mean difference, 1.6 [95% CI, 1.0-2.3]; $P < .001$). In terms of safety outcomes, there were no events of ODS in both groups. The RIB group showed a lower incidence of relowering treatment than the SCI group (36 of 87 [41.4%] vs 52 of 91 [57.1%] patients; absolute risk difference, −15.8% [95% CI, −30.3% to −1.3%]; $P = .04$; NNT, 6.3) (Figure 2C and D). Other secondary outcomes among safety end points did not differ between the 2 groups. The statistical significance was similar between the RIB and SCI groups for all secondary outcomes in the ITT and PP analyses. Adjustment for multiple comparisons for secondary outcomes is presented in eTable 5 in Supplement 2 using the Bonferroni and Benjamini-Hochberg procedures.

Post Hoc End Points

In ITT analysis, the proportion of patients achieving target correction rate within 1 hour was higher in the RIB group than the SCI group (28 of 87 [32.2%] vs 16 of 91 [17.6%] patients; absolute risk difference, 14.6% [95% CI, 2%-27.2%]; $P = .02$; NNT, 6.8) (Table 2). In PP analysis, statistical significance of achieving target correction rate within 1 hour was lost (21 of 72 [29.2%] vs 12 of 73 [16.4%] patients; absolute risk difference, 12.7% [95% CI, −0.8% to 26.2%]; $P = .07$) (eTable 4 in Supplement 2). No significant differences between the groups were observed in the incidence of target correction rate in 6, 24, or 48 hours.

Cointerventions and Adverse Events

There were no significant differences regarding fluid types (hypotonics or isotonics), total amount of fluid and oral intake, use of furosemide for volume overload, and urine volume for 48 hours. The RIB group had a higher cumulative amount of hypertonic saline, 3%, administered within 1 and 6 hours than the SCI group (1 hour: 220.4 mL vs 38.6 mL; $P < .001$; 6 hours: 273.9 mL vs 210.4 mL; $P < .001$), but there were no differences in the cumulative amount of hypertonic saline administered within 24 and 48 hours (24 hours: 362.6 mL vs 440.6 mL; $P = .22$; 48 hours: 535.4 mL vs 572.8 mL; $P = .57$). After correction of hyponatremia, of the 178 patients, 3 (1.7%) and 12 (6.7%) underwent brain tomography and magnetic resonance imaging, respectively. No difference was observed in the distribution of neuroimage followed according to the interventions. The statistical significance was similar between the RIB and SCI groups for cointerventions in the ITT and PP analyses (Table 2 and eTable 4 in Supplement 2).

One patient experienced pulmonary edema and pleural effusion, and another patient experienced oliguria in the RIB group. Only 2 patients in the SCI group had phlebitis related to the infusion. Five of the 178 (2.8%) individuals died during admission (Table 2).

Subgroup Analysis

In both ITT and PP analyses, there was no significant heterogeneity in the effect of treatment on primary, secondary, and post hoc outcomes in the predefined subgroups according to the severity of the initial hyponatremic symptoms (eTables 6 and 7 in Supplement 2).

Discussion

In this randomized clinical trial, no significant difference in the incidence of overcorrection between the 2 groups was observed. The RIB group showed a lower incidence of relowering treatment than the SCI group, and the magnitude of the difference between RIB vs SCI (15.8%) translates into a NNT of 6.3 to prevent relowering treatment. Moreover, RIB tended to have a higher target correction rate (defined as achieving sNa of 5-9 mmol/L) within 1 hour than SCI, and the magnitude of the

Table 1. Baseline Characteristics of Intention-to-Treat Population

Characteristics	Patients, No. (%)		*P* value
	Rapid intermittent bolus (n = 87)	Slow continuous infusion (n = 91)	
Demographics			
Male	42 (48.3)	38 (41.8)	.38
Age, mean (SD), y	72.9 (12.4)	73.2 (12.1)	.85
Weight, mean (SD), kg	56.6 (10.9)	57.5 (12.2)	.52
Body mass index, mean (SD)	22.2 (4.3)	22.9 (4.2)	.09
Causes of hyponatremia			
Thiazide use	21 (24.2)	32 (35.2)	.34
Decreased extracellular fluid due to nonrenal sodium loss	15 (17.2)	10 (11.0)	
Increased extracellular fluid	8 (9.2)	11 (12.1)	
Adrenal insufficiency	17 (19.5)	12 (13.2)	
Syndrome of inappropriate antidiuresis	26 (29.9)	26 (28.6)	
Comorbidity			
Diabetes mellitus	31 (35.6)	28 (30.8)	.53
Hypertension	62 (71.3)	61 (67.0)	.63
Congestive heart failure	14 (16.1)	17 (18.7)	.70
Liver cirrhosis	5 (5.7)	6 (6.6)	.82
Nephrotic syndrome	2 (2.3)	2 (2.2)	>.99
Adrenal insufficiency	27 (31.0)	17 (18.7)	.08
Hypothyroidism	8 (9.2)	10 (11.0)	.81
Malignant tumor	23 (26.4)	19 (20.9)	.48
Chronic alcoholism	2 (2.3)	3 (3.3)	>.99
Dropout	15 (17.2)	18 (19.8)	.66
Hyponatremic symptom			
Moderate	66 (75.9)	68 (74.7)	.86
Severe	21 (24.1)	23 (25.3)	
Nausea	29 (33.3)	27 (29.7)	.60
Headache	7 (8.0)	4 (4.4)	.31
Dizziness	3 (3.4)	7 (7.7)	.33
General weakness	39 (44.8)	44 (48.4)	.64
Drowsiness	6 (6.9)	2 (2.2)	.16
Vomiting	18 (20.7)	20 (22.0)	.83
Stupor	2 (2.3)	3 (3.3)	>.99
Seizure	2 (2.3)	0	.24
Bone fracture	1 (1.1)	2 (2.2)	>.99
Fall	1 (1.1)	1 (1.1)	>.99
Site to initiate hypertonic saline			
Emergency department	67 (77.0)	64 (70.3)	.41
General ward	20 (23.0)	26 (28.6)	
Intensive care unit	0	1 (1.1)	
IV route			
Peripheral	85 (97.7)	90 (98.9)	.59
Central	1 (1.1)	0	
Mixed	1 (1.1)	1 (1.1)	
Blood pressure, mean (SD), mmHg			
Systolic	141.6 (25.6)	136.9 (42.9)	.20
Diastolic	75.6 (12.3)	75.7 (15.2)	.97
Glasgow Coma Scale score, mean (SD)			
Pretreatment (n = 146)	14.3 (1.5)	14.0 (2.5)	.64

(continued)

Table 1. Baseline Characteristics of Intention-to-Treat Population (continued)

Characteristics	Patients, No. (%)		*P* value
	Rapid intermittent bolus (n = 87)	Slow continuous infusion (n = 91)	
Laboratory values			
Sodium, mean (SD), mmol/L	118.2 (5.0)	118.2 (5.0)	.94
Serum osmolality, mean (SD), mOsm/kg	251.8 (27.0)	250.3 (14.7)	.69
Creatinine, mean (SD), mg/dL	0.98 (0.8)	0.92 (0.9)	.23
Potassium, mean (SD), mmol/L	4.1 (0.8)	3.9 (0.7)	.10
Total carbon dioxide, mean (SD), mmol/L	22.7 (3.7)	23.7 (6.0)	.58
Urine, mean (SD)			
Osmolality, mOsm/kg	442.7 (170.7)	406.8 (156.9)	.19
Sodium, mmol/L	74.5 (50.7)	69.7 (48.1)	.63
Potassium, mmol/L	36.5 (23.9)	32.8 (21.1)	.22

Conversion factors: to convert creatinine to µmol/L, multiply by 88.4; to convert serum and urine osmolality to mmol/L, multiply by 1.

difference between RIB and SCI (14.6%) translates into a NNT of 6.8 to achieve the target correction rate within 1 hour. The 2 therapies did not differ in terms of efficacy in increasing sNa concentrations after 6 hours of treatment or improving symptoms.

Recent American and European guidelines recommend providing prompt infusion of small, fixed boluses of hypertonic saline to patients with symptomatic hyponatremia.[3,23] This regimen can lead to rapid partial corrections in sNa concentrations and improvement of hyponatremia-related symptoms.[29] In the present study, baseline sNa concentrations were similar (mean [SD], 118.2 [5.0] mmol/L), but sNa concentrations at 1 hour after treatment were significantly higher in the RIB group than in the SCI group (mean [SD], 122.0 [4.9] mmol/L vs 120.1 [5.0] mmol/L, respectively; *P* = .001) (**Figure 3** and eFigure 2 in Supplement 2). Furthermore, the proportion of patients reaching a target correction rate within 1 hour tended to be higher in the RIB group. Given that the RIB group had a higher amount of hypertonic saline, 3%, administered within 1 and 6 hours than the SCI group, RIB therapy might be considered as having better efficacy for 1 hour. RIB therapy is considered to have a lower risk of overcorrection without sufficient verification,[21,29] although it is well known that SCI using Adrogue-Madias formula has a risk of inadvertent overcorrection (10%-16%).[30]

According to unpublished retrospective data in the study design phase, overcorrection in the SCI group occurred in approximately 32% of 129 patients with hyponatremia during the 1-year period. In this trial, overcorrection occurred in 17.2% to 19.4% and 24.2% to 26.0% of patients in the RIB and SCI groups, respectively. Incidence of overcorrection was shown higher for each group than those we assumed in the study design phase.[31] Given that the 95% CI for absolute risk difference of overcorrection was somewhat wide (ITT: absolute risk difference, −6.9% [95% CI, −18.8% to 4.9%]; PP: absolute risk difference, −6.6% [95% CI, −20.2% to 7%]), reflecting imprecision and uncertainty as to the true effect, further studies with a larger sample sizes are needed. However, RIB showed a reduced incidence of relowering treatment compared with SCI in the present trial. There were no differences in the cumulative amount of hypertonic saline, 3%, administered within 24 and 48 hours between the 2 groups (RIB vs SCI in 24 hours: 362.6 mL vs 440.6 mL; 48 hours: 535.4 mL vs 572.8), which is similar to the total amount recommended in the European guideline[3] and previous report[9]; nevertheless, RIB therapy showed a reduced incidence of relowering treatment. RIB therapy tends to be more effective in achieving the target correction rate in the first hour, does not increase the risk of overcorrection, and is a user-friendly method because it does not require calculations, compared with SCI. Furthermore, despite the rapid correction of sodium, none of the patients developed ODS. For this reason, RIB therapy could be recommended as the treatment of choice in patients with hyponatremia.

Expected cointerventions, such as concomitant intravenous fluid except for hypertonic saline or oral fluid intake, would have an influence on the overcorrection. We did not limit the concomitant intravenous injection and oral fluid intake and left it to the physician's discretion to make the research realistically adaptable in clinical practice. The type and amount of intravenous fluid administered and oral intake during the treatment were not significantly different between both groups (Table 2 and eTable 4 in Supplement 2). However, participants receiving SCI of hypertonic saline concomitantly were less likely to receive isotonic fluid and more likely to receive hypotonic fluids. Moreover, the relowering treatment could be adhered to more strictly in the trial than in the actual clinical practice. These may have contributed to the reduction of the risk of overcorrection. It implies that, with less stringent protocol adherence in reality, the risk of overcorrection could be much higher than that estimated in the trial (eTable 8 in Supplement 2). The development of unexpected substantial water diuresis is a well-known reason for overcorrection.[39,40] We monitored the urine volume of the participants during the study period. We could not differentiate between water and solute diuresis, because regular evaluations of urine electrolyte and osmolality were not included in the present trial protocol. However, there were no differences in the urine volume during the study period; thus, there was no difference in the overcorrection risk owing to the development of diuresis in both groups.

The characteristics of the hypertonic saline, 3%, treatment protocol were as follows: (1) weight-based approach rather than fixed 100- to 150-mL infusion volumes of hypertonic saline, 3%, because Koreans tend to have smaller physique than Americans or Europeans; the weight-based approach might

Table 2. Outcomes and Progressions in Intention-to-Treat Population

Variable	Patients, No. (%)		Absolute difference (95% CI)	*P* value
	Rapid intermittent bolus (n = 87)	Slow continuous infusion (n = 91)		
Dropout	15 (17.2)	18 (19.8)	NA	.66
Primary outcome				
Overcorrection rate	15 (17.2)	22 (24.2)	−6.9 (−18.8 to 4.9)[a]	.26
Secondary outcome				
Efficacy				
Remaining symptoms				
At 24 h	11 (13.1)	15 (16.9)	−3.8 (−14.4 to 6.8)[a]	.49
At 48 h	7 (8.8)	5 (6.5)	2.3 (−6.0 to 10.5)[a]	.60
Time to increase of sNa ≥5 mmol/L, mean (SD), h	8.2 (8.7)	8.6 (6.9)	−0.4 (−2.7 to 2.0)[b]	.21
Incidence of target correction rate	57 (65.5)	60 (65.9)	−0.4 (−14.4 to 13.5)[a]	.85
Time to sNa >130 mmol/L, mean (SD), h (n = 96)	23.6 (12.4)	22.3 (13.4)	1.3 (−3.9 to 6.6)[b]	.56
Length of hospital stay, mean (SD), d	11.3 (18.6)	7.5 (6.5)	3.8 (−0.3 to 7.9)[b]	.50
Incidence of additional treatment	79 (90.8)	68 (74.7)	16.1 (5.3 to 26.9)[a]	.005
No. of additional treatment, mean (SD)	3.4 (1.8)	1.8 (1.7)	1.6 (1.0 to 2.3)[b]	<.001
Safety				
Incidence of osmotic demyelination syndrome	0	0	0	NA
Incidence of relowering treatment	36 (41.4)	52 (57.1)	−15.8 (−30.3 to −1.3)[a]	.04
Glasgow Coma Scale score, mean (SD)				
At 24 h (n = 131)	14.6 (1.2)	14.1 (2.4)	0.5 (−0.1 to 1.1)[b]	.50
At 48 h (n = 123)	14.6 (1.2)	14.2 (2.2)	0.4 (−0.2 to 1.1)[b]	.74
Post hoc analysis (efficacy as incidence of target correction rate by the time frame)				
sNa 5-9 mmol/L				
Within 1 h	28 (32.2)	16 (17.6)	14.6 (2 to 27.2)[a]	.02
Within 6 h	50 (57.5)	54 (59.3)	−1.9 (−16.4 to 12.6)[a]	.80
Within 24 h	78 (89.7)	79 (86.8)	2.8 (−6.6 to 12.3)[a]	.56
sNa 10-17 mmol/L or ≥130 mmol/L within 48 h	60 (69)	67 (73.6)	−4.7 (−17.9 to 8.6)[a]	.49
Fluid type within 24 h except for saline, 3%				
Isotonics only	31 (35.6)	28 (30.8)	NA	.40
Hypotonics only	52 (59.8)	62 (68.1)	NA	
Isotonics and hypotonics	3 (3.4)	1 (1.1)	NA	
None	1 (1.1)	0	NA	
Fluid amount within 24 h except for saline, 3%, mean (SD), mL	1563 (1160)	1641 (2165)	NA	.76
Fluid type within 24-48 h except for saline, 3%				
Isotonics only	28 (32.2)	18 (19.8)	NA	.15
Hypotonics only	23 (26.4)	26 (28.6)	NA	
Isotonics and hypotonics	22 (25.3)	22 (24.2)	NA	
None	14 (16.1)	25 (27.5)	NA	
Fluid amount within 24-48 h except for saline, 3%, mean (SD), mL	1077 (895)	1152 (884)	NA	.54
Oral intake during 48 h, mean (SD), mL	1852 (1298)	1961 (1262)	NA	.40
Cumulative amount of hypertonic saline, 3%, mean (SD), mL				
Within 1 h	220.4 (76.3)	38.6 (29.2)	NA	<.001
Within 6 h	273.9 (102.3)	210.4 (119.2)	NA	<.001
Within 24 h	362.6 (183.3)	440.6 (308.4)	NA	.22
Within 48 h (total amount)	535.4 (322.1)	572.8 (371.8)	NA	.57
Urine volume during 48 h, mean (SD), mL	3611 (2763)	4108 (2889)	NA	.27
Neuroimage after correction of hyponatremia	5 (5.7)	10 (11.0)	NA	.21
Phlebitis	0	2 (2.2)	NA	.50

(continued)

Table 2. Outcomes and Progressions in Intention-to-Treat Population (continued)

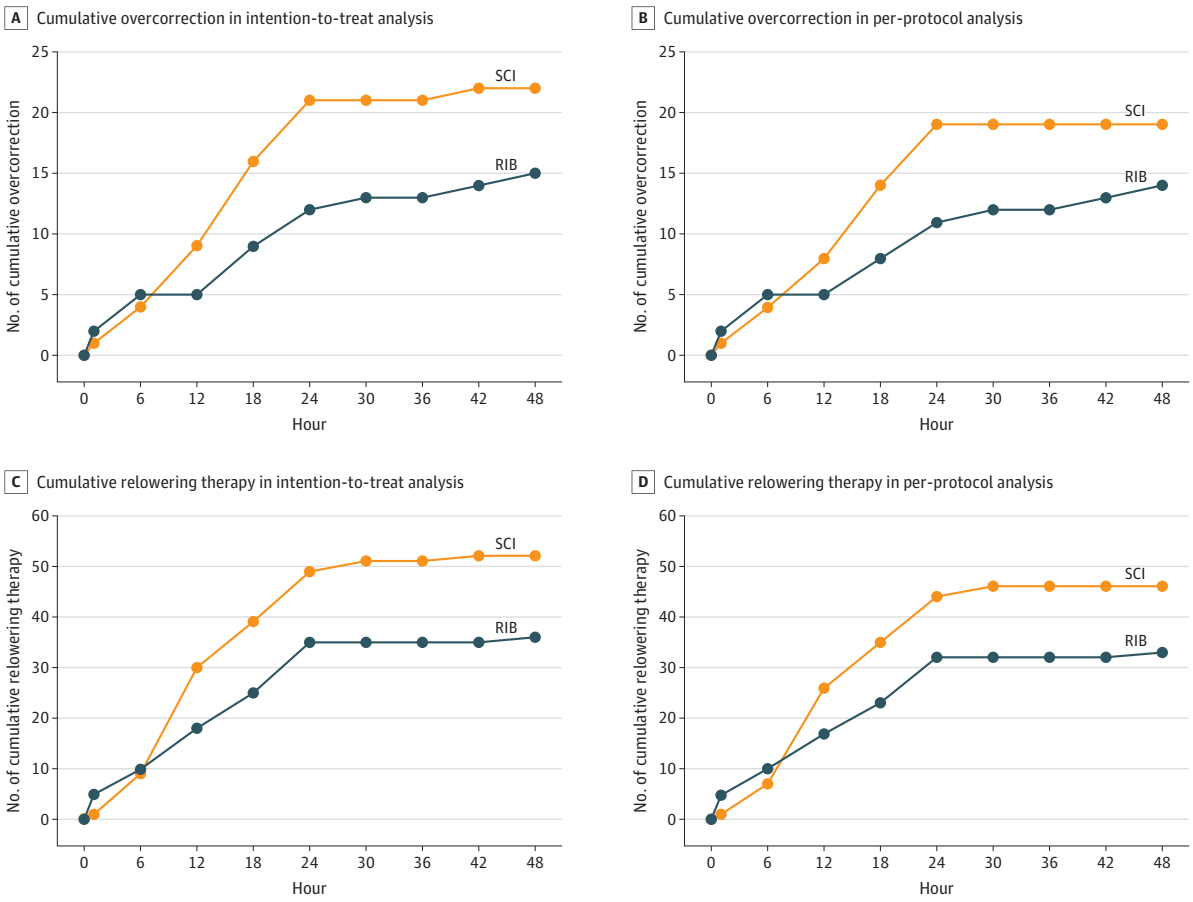
Variable	Patients, No. (%)		Absolute difference (95% CI)	*P* value
	Rapid intermittent bolus (n = 87)	Slow continuous infusion (n = 91)		
Mortality				
During admission	4 (4.6)	1 (1.1)	NA	.20
At 30 d	3 (3.4)	1 (1.1)	NA	.36

Abbreviations: NA, not applicable; sNa, serum sodium.

[a] This value is risk difference.

[b] This value is the mean difference.

Figure 2. Cumulative Overcorrection and Relowering Treatment



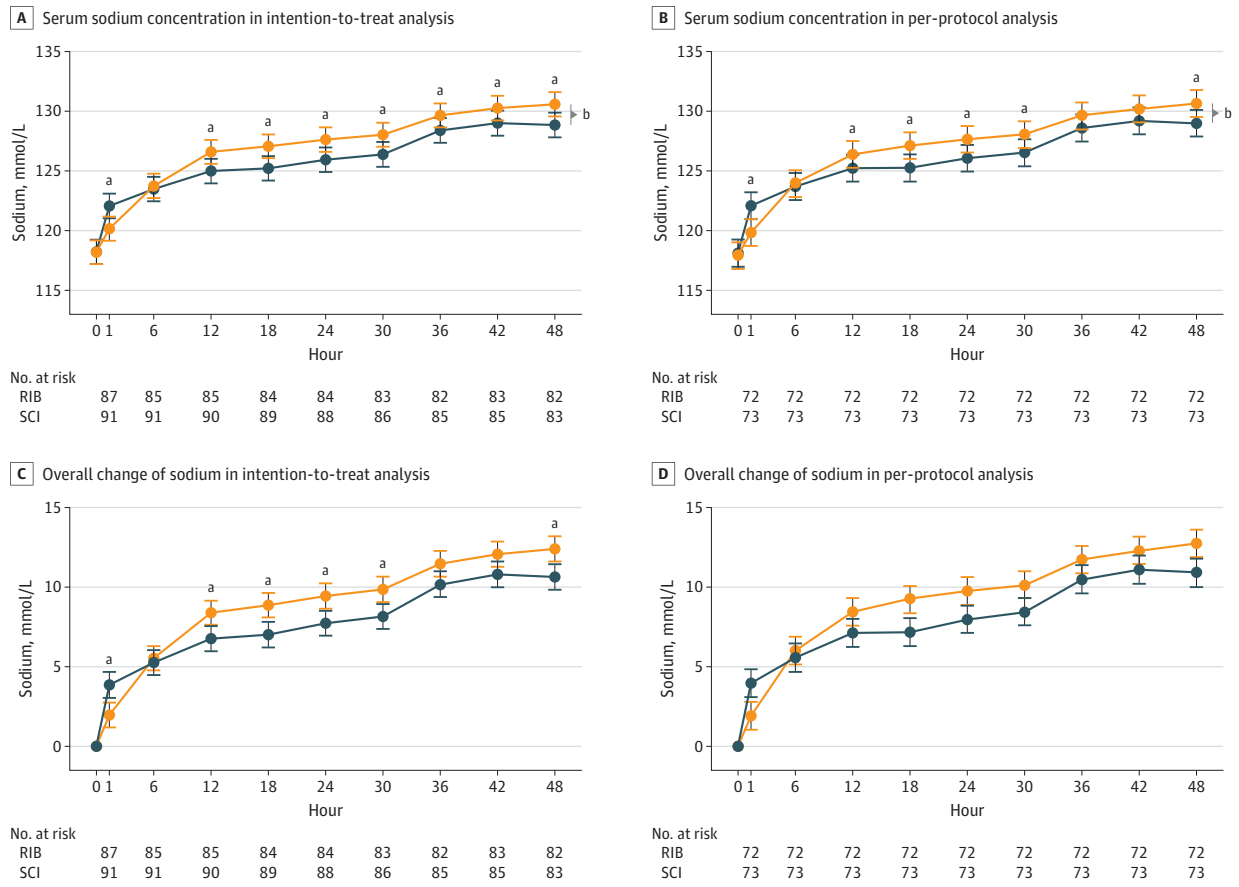
RIB indicates rapid intermittent bolus; SCI, slow continuous infusion.

help prevent overcorrection and also effectively increase sNa concentrations; and (2) recent guideline recommended stopping hypertonic saline infusion in patients with improvement of symptoms after a 5-mmol/L increase in sNa concentrations and commencing a diagnosis-specific treatment.[3] The present trial protocol to decrease or not change the sNa concentrations during the diagnosis of hyponatremia and initiation of cause-specific treatment was established to maintain hypertonic saline by RIB or SCI every 6 hours until sNa level gradually increased to target level and symptoms improved. Moreover, we assessed symptom relief as symptom resolution, which was different from the definition of the recent European guideline.[3] Thus, a higher incidence of overcorrection may be observed in the present study than in previously published studies.

Strengths and Limitations

To our knowledge, no large-scale randomized clinical trials comparing the efficacy and safety of RIB and SCI with hypertonic saline have been conducted, and this was the first clinical trial to provide physicians with adequate quality evidence regarding treatment with hypertonic saline in

Figure 3. Serum Sodium Concentration and Overall Change of Sodium After Hypertonic Saline Treatment in Total Patients



RIB indicates rapid intermittent bolus; SCI, slow continuous infusion. Error bars indicate 95% CIs.

[a] $P < .05$ using marginal effect of serum sodium and overall change of serum sodium according to groups.

[b] $P < .05$ using a linear mixed model to analyze the effect of repeated serum sodium with fixed effects of time, group, and interactions between time and group.

symptomatic hyponatremia. These findings are applicable to the larger population because we have included adult patients from emergency departments and wards of 3 general hospitals, and they are representative of the population who develop hyponatremia.

This trial has some limitations. First, the number of patients who dropped out was higher than expected. The main reason for this was protocol violation. Given that bolus treatment was not yet widely used in Korea, it has taken longer training periods to educate physicians and nurses about the protocol. Dropouts owing to protocol violations occurred mostly in the early period and gradually decreased as the study proceeded (eFigure 3 in Supplement 2). Second, we used the incidence of overcorrection as the primary outcome. It could be argued that the overcorrection was adequate as a primary outcome. Although the incidence of overcorrection was considerably higher than expected in this study, there was no incidence of ODS, the true outcome of interest, in patients who experienced overcorrection. In this study, we regularly checked the sNa concentrations and performed relowering treatment whenever overcorrection occurred, which may be the reason why no patients developed ODS. We acknowledge that ODS is multifactorial and can also occur in other settings, including liver disease, chronic alcoholism, malnutrition, and hypoxia in the absence of overcorrection.[7,33,41-45] However, several studies reported that overcorrection may be 1 of the main causes of ODS.[13,15,17-19,33,46] Overcorrection is a good laboratory outcome that can be monitored in patients with hyponatremia who are treated with hypertonic saline and a correctable factor through relowering treatment in clinical practice.[47] It is the reason why we chose overcorrection as a primary outcome. The European guideline has defined the hierarchy of outcomes involved in hyponatremia treatment.[3] It is inevitable to use a surrogate marker as an outcome because of the rare incidence of critically important outcomes, such as patient survival or ODS.[46-48] Third, we did not adjust for secondary and post hoc outcomes as mentioned in the Methods section because the exploration of clinically meaningful variables was thought to be valuable. In this case, the probability of false positive findings can be a concern. We presented the adjusted P value for secondary and post hoc end points in eTable 5 in Supplement 2. Fourth, the allocation sequence was not concealed

from the study coordinators, and it may have influenced recruitment. The study coordinators were independent persons from the researchers; thus, there might be little room for selection bias. Moreover, baseline characteristics were similar enough to suggest this may not have occurred.

Conclusions

To our knowledge, the SALSA trial is the first prospective, multicenter, randomized, open-label clinical trial to compare the efficacy and safety between RIB and SCI with hypertonic saline in patients with moderately severe or severe symptomatic hyponatremia. Both RIB and SIC therapies of hypertonic saline for treating hyponatremia were effective and safe, with no difference in the overcorrection risk. However, RIB therapy had a lower incidence of therapeutic relowering of sNa and tended to have a better efficacy in achieving sNa within 1 hour than SCI. RIB therapy could be suggested as the preferred treatment of symptomatic hyponatremia, which is consistent with the current consensus guidelines.

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