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Original Research

Overcorrection and undercorrection with fixed dosing of bolus hypertonic saline for symptomatic hyponatremia

Anissa Pelouto,[1] Julie C. Refardt,[2,3] Mirjam Christ-Crain,[2,3] Adrienne A.M. Zandbergen,[1] and Ewout J. Hoorn[1,*]

[1]Department of Internal Medicine, Erasmus Medical Center, University Medical Center Rotterdam, PO Box 2040, Room Ns403, 3000 CA Rotterdam, The Netherlands
[2]Departments of Endocrinology, Diabetology and Metabolism University Hospital Basel, Basel, Switzerland
[3]Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland

***Corresponding author:** Department of Internal Medicine, Erasmus Medical Center, University Medical Center Rotterdam, PO Box 2040, Room Ns403, 3000 CA Rotterdam, The Netherlands. Email: e.j.hoorn@erasmusmc.nl

Abstract

Objective: Current guidelines recommend treating symptomatic hyponatremia with rapid bolus-wise infusion of fixed volumes of hypertonic saline regardless of body weight. We hypothesize that this approach is associated with overcorrection and undercorrection in patients with low and high body weight.

Design: Single-center, retrospective cohort study.

Methods: Data were collected on patients treated with ≥1 bolus 100 or 150 mL 3% NaCl for symptomatic hyponatremia between 2017 and 2021. Outcomes were overcorrection (plasma sodium rise > 10 mmol/L/24 h, > 18 mmol/L/48 h, or relowering therapy) and undercorrection (plasma sodium rise < 5 mmol/L/24 h). Low body weight and high body weight were defined according to the lowest (≤60 kg) and highest (≥80 kg) quartiles.

Results: Hypertonic saline was administered to 180 patients and caused plasma sodium to rise from 120 mmol/L to 126.4 mmol/L (24 h) and 130.4 mmol/L (48 h). Overcorrection occurred in 32 patients (18%) and was independently associated with lower body weight, weight ≤ 60 kg, lower baseline plasma sodium, volume depletion, hypokalemia, and less boluses. In patients without rapidly reversible causes of hyponatremia, overcorrection still occurred more often in patients ≤ 60 kg. Undercorrection occurred in 52 patients (29%) and was not associated with body weight or weight ≥ 80 kg but was associated with weight ≥ 100 kg and lean body weight in patients with obesity.

Conclusion: Our real-world data suggest that fixed dosing of bolus hypertonic saline may expose patients with low and high body weight to more overcorrection and undercorrection, respectively. Prospective studies are needed to develop and validate individualized dosing models.

Keywords: hyponatremia, hypertonic saline, overcorrection, undercorrection, body weight

Significance

Clinical guidelines recommend bolus-wise infusion of fixed volumes of hypertonic saline for symptomatic hyponatremia. However, overcorrection is still common with bolus hypertonic saline, while the risk of undercorrection is unknown. In this retrospective study, we report the largest cohort of patients treated with bolus hypertonic saline and show for the first time that body weight is independently associated with more overcorrection and undercorrection. Specifically, body weights of ≤60 kg and ≥100 kg were associated with overcorrection and undercorrection, respectively. Our data indicate that prospective studies are needed to develop and validate individualized dosing models for hypertonic saline that are both safe and effective.

Introduction

Hyponatremia (plasma sodium < 136 mmol/L) is one the most common electrolyte disorders encountered in clinical practice.[1] When hyponatremia develops acutely (<48 h), it may cause cerebral edema with symptoms such as vomiting, seizures, or coma.[2-4] Cerebral edema secondary to acute hyponatremia can be treated with the infusion of hypertonic saline,[5-7] which introduces an effective osmole that will shift water out of cells. In clinical practice, the exact duration of hyponatremia is usually unknown. Consequently, the differentiation between acute and chronic hyponatremia is based on the presence and severity of symptoms. Although acute hyponatremia typically produces more severe symptoms,[8] chronic hyponatremia may also be symptomatic. Therefore, symptoms of acute and chronic hyponatremia may overlap.[9,10] Furthermore, patients may present with "acute-on-chronic" hyponatremia. To navigate these different scenarios, current guidelines recommend treatment with hypertonic saline in patients with moderate or severe symptoms and to avoid overcorrection in all forms of hyponatremia.[10,11] Overcorrection

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of chronic hyponatremia can result in the osmotic demyelination syndrome (ODS), a rare but devastating disorder that can result in permanent brain injury.[10,12,13]

The aim of hypertonic saline therapy is to increase plasma sodium by at least 5 mmol/L, which is considered sufficient to effectively decrease intracranial pressure due to cerebral edema.[10,14] Hypertonic saline can be administered as slow continuous infusion or rapid intermittent bolus. Two studies have compared these two approaches and found that the rapid intermittent bolus results in a faster initial rise in plasma sodium,[15,16] which is also accompanied by faster neurological recovery.[15] In addition, the need for relowering therapy to reverse overcorrection after rapid intermittent bolus appears to be lower.[16] However, both studies also showed that overcorrection remains a problem of hypertonic saline therapy. In one of the studies, rapid intermittent bolus was delivered with fixed volumes of 150 mL hypertonic saline,[15] whereas the other study applied a weight-based approach.[16] Hyponatremia guidelines recommend rapid bolus-wise correction with fixed volumes of 100 mL[11] or 150 mL[10] hypertonic saline regardless of body weight.

Here, we hypothesize that low and high body weight may be additional risk factors for hyponatremia overcorrection and undercorrection, respectively, following fixed dosing of bolus hypertonic saline. To address our hypothesis, we performed a retrospective study including real-world data on rapid intermittent bolus therapy with fixed volumes.

Methods

Study design

This single-center, retrospective cohort study was conducted at the Erasmus Medical Center in Rotterdam, the Netherlands. Medical ethics approval (MEC-2020-0965) was obtained prior to initiation of this study, and informed consent was not required, given the observational and retrospective design reflecting routine clinical care. This study was conducted in accordance with the Declaration of Helsinki (version 2013).[17] The electronic records of all patients who received an intravenous bolus hypertonic saline for hyponatremia between July 2017 and July 2021 were reviewed. Inclusion criteria included age ≥ 18 years and the administration of 100 or 150 mL bolus hypertonic saline (3% NaCl) in the emergency department or medical ward via a peripheral venous catheter with hypotonic hyponatremia as treatment indication. Our national guidelines leave the choice whether to use 100 or 150 mL up to the treating physician. In the Netherlands, intravenous hypertonic saline can be administered in the emergency department and medical wards and does not require monitoring in a critical care setting. Patients treated with any other bolus volume and patients without follow-up plasma sodium measurements were excluded. We also excluded patients who were treated with hypertonic saline in the intensive care unit. The reason to do so is that our intensive care unit is a tertiary referral center for patients with multi-organ failure who are often treated with vasoactive medications (including vasopressin) and kidney replacement therapy, which affect the plasma sodium trajectory.

Data collection

Data collection included patient demographics, medical history, vital signs, body weight and height, hyponatremia onset and etiology, symptom severity, baseline biochemical parameters, treatment details, and relevant clinical outcomes. Follow-up plasma sodium measurements were collected up to 48 h after the last bolus. Because intra-individual plasma sodium levels are known to differ depending on measurement with direct or indirect ion selective electrode (ISE),[18] only follow-up plasma sodium measurements determined with the same technique as the baseline measurement were included in the analysis. Symptoms of hyponatremia were classified as moderately severe (nausea, headache, and confusion) or severe (vomiting, somnolence, seizures, and coma) according to the European hyponatremia guideline.[10] Hyponatremia etiology was based on the documented diagnosis by the treating physicians. If unavailable, we determined the most probable cause using clinical and biochemical data. The syndrome of inappropriate antidiuresis (SIAD) was defined by clinical euvolemia, plasma osmolality < 280 mOsm/kg, urine osmolality ≥ 100 mOsm/kg, urine sodium > 30 mmol/L, and normal TSH and cortisol levels.[19] As primary body size measure, we used body weight. The cut-off for low and high body weight was based on the lowest and highest quartile of the cohort, resulting in a cut-off of 60 and 80 kg, respectively. In patients with obesity (BMI ≥ 30 kg/m^2), we also estimated lean body weight using Janmahasatian's formula.[20,21]

Outcomes

The primary outcome was the risk of overcorrection, which was defined as the increase in plasma sodium > 10 mmol/L/24 h, > 18 mmol/L/48 h, or the use of relowering therapy (hypotonic fluids and/or desmopressin). The secondary outcome was the risk of undercorrection (defined as increase < 5 mmol/L within the first 24 h, unless a plasma sodium level of ≥ 130 mmol/L is reached).[10,22,23] Other outcome measures included duration of hospitalization, the incidence of ODS, and in-hospital mortality.

Statistical analysis

Normally distributed continuous data are presented as means ± standard deviation and non-normal data as median with interquartile range (IQR). Differences were analyzed using the Mann–Whitney *U*, Kruskal–Wallis, or χ^2 test (categorical data). Repeated plasma sodium measurements were analyzed with a linear mixed model with age, sex, and time to the first bolus as fixed and patient as random effect. Natural cubic splines were fitted into the model to account for possible non-linearity. Furthermore, we performed stratification analyses by bolus volume, number of boluses, concurrent intervention, and body weight group to explore different trends among subgroups. Linear regression was used to analyze correlations between maximum plasma sodium change in 24 h and body weight. Multivariable logistic regression was used to analyze whether body weight (continuous and categorized low and high) was associated with overcorrection and undercorrection, respectively. Additional variables for overcorrection were selected based on previous literature, including baseline plasma sodium, volume depletion, hypokalemia, and number of boluses.[7,15,24-29] Because risk factors for undercorrection have not been analyzed previously, the selection of additional variables was based on clinical rationale and included baseline plasma sodium, time to the first bolus, and number of boluses. For both multivariable analyses, multicollinearity was ruled out. Missingness for all covariates was ≤3%, except for baseline Glasgow Coma Scale score (34%), plasma osmolality (22%), plasma glucose (9%), and urine biochemical values (6%). Missing values were not imputed. All tests were two-tailed, and *P* values of <.05 were considered statistically

significant. Statistical analysis was performed using SPSS version 28.01.1 and R version 4.1.2 (R Foundation for Statistical Computing).

Results

Patient characteristics

We identified 240 patients who were treated with bolus hypertonic saline for symptomatic hyponatremia (Figure 1A). After excluding patients who received a bolus in the intensive care unit ($n = 49$), patients treated with any other bolus volume than 100 or 150 mL ($n = 10$), and patients without follow-up plasma sodium measurements ($n = 1$), 180 patients were included for further analysis. One hundred and fifty-four patients (86%) presented with hyponatremia, while 26 patients (14%) had hospital-acquired hyponatremia. The most common cause of hyponatremia was SIAD ($n = 82$, 46%, most frequently malignancy induced: $n = 31$, 38%), followed by volume depletion ($n = 35$, 19%) (Figure 1B). The median age was 63 years (IQR 55–71), and 78 patients (43%) were

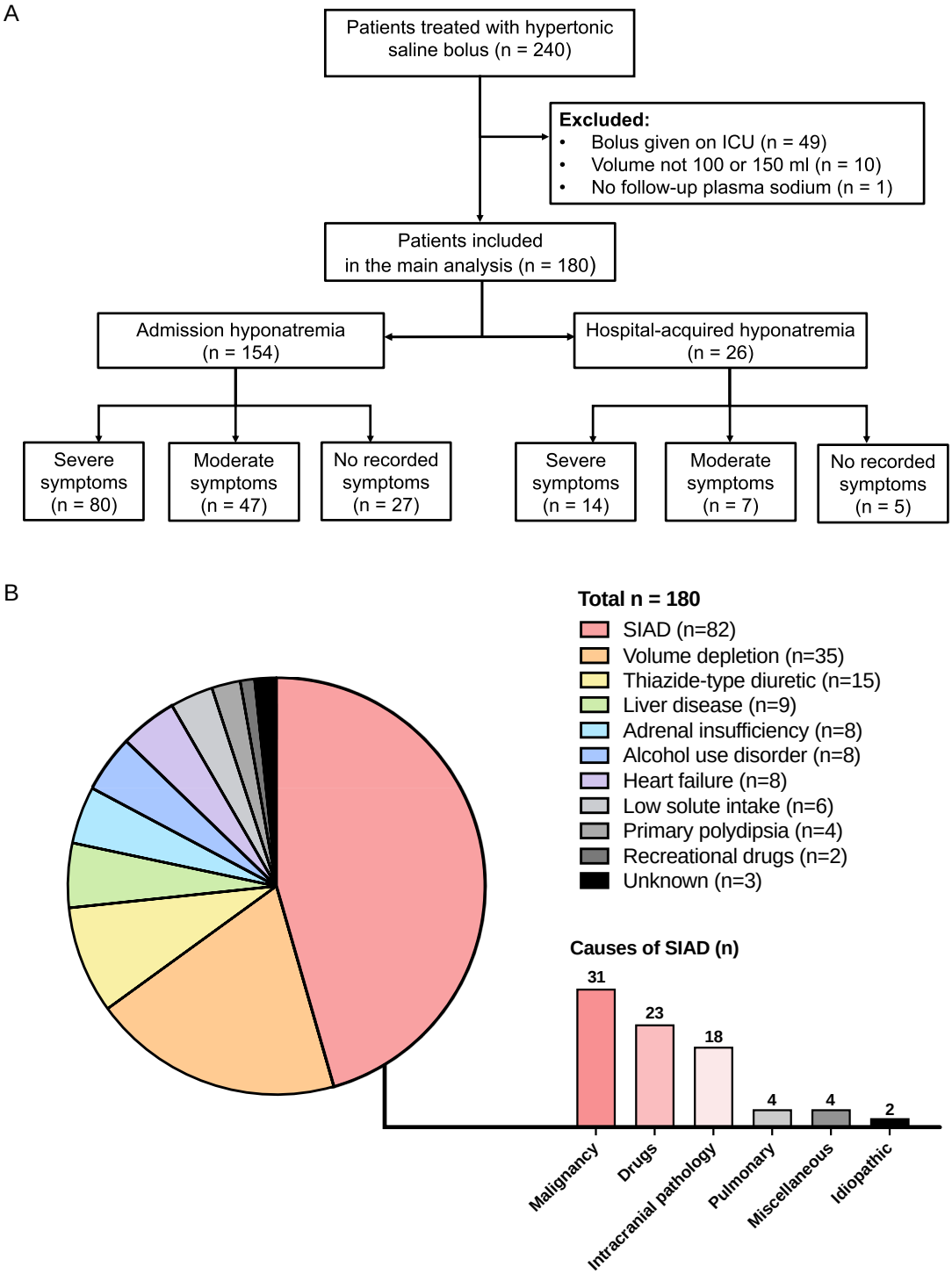

Figure 1. Selection of the study population flowchart (A) and etiology of hyponatremia (B). Total $n = 180$.

Table 1. Baseline characteristics.

Parameter[a]	Values ($n = 180$)
Demographic data and vital signs	
Male, *n* (%)	78 (43)
Age, years	63 (55, 71)
Total body weight, kg	70.0 (60.0, 80.0)
Body mass index, kg/m^2	24.2 (21.3, 27.2)
Lean body weight, kg	47.3 (40.6, 56.9)
Systolic blood pressure, mmHg	139 ± 27
Diastolic blood pressure, mmHg	80 ± 18
Heart rate, beats/minute	85 ± 18
Glasgow Coma Scale	15 (14, 15)
Symptoms, *n* (%)	
No recorded symptoms	32 (18)
Moderately severe	54 (30)
Nausea	84 (47)
Headache	36 (20)
Confusion	78 (43)
Severe	94 (52)
Vomiting	62 (34)
Seizures	20 (11)
Somnolence	33 (18)
Coma	4 (2)
Biochemical parameters	
Plasma osmolality, mOsm/kg	254 (244, 263)
Indirect plasma sodium, mmol/L	120 (116, 122)
Direct plasma sodium, mmol/L	118 (113, 122)
Plasma glucose, mmol/L	7.0 (5.6, 8.8)
Plasma potassium, mmol/L	4.1 (3.6, 4.7)
eGFR, mL/min per 1.73 m^2	90 (70, 99)
Urine osmolality, mOsm/kg	484 (307, 643)
Urine sodium, mmol/L	41 (21, 80)

[a]Missingness for all covariates was ≤3%, except for baseline the Glasgow Coma Scale score (34%), plasma osmolality (22%), plasma glucose (9%), and urine biochemical values (6%).

male (Table 1). The median body weight was 70 kg (IQR 60–80; see Figure S1 for the distribution). Ninety-four patients (52%) had severe symptoms, 54 patients (30%) had moderately severe symptoms, and 32 patients (18%) had no recorded symptoms (Table 1). Hyponatremia time of onset was unknown in 108 patients (60%), while hyponatremia was documented as chronic in 59 patients (33%) and as acute in 13 patients (7%).

Plasma sodium and hypertonic saline

Baseline plasma sodium was determined by indirect ISE in 175 patients (97%, median 120 mmol/L, IQR 116–122 mmol/L) and by direct ISE in 5 patients (3%, median 119 mmol/L, IQR 118–123 mmol/L). In 79 patients (44%), the baseline plasma sodium was determined by both methods resulting in an indirect plasma sodium of 119 mmol/L (IQR 114–122 mmol/L) and a direct plasma sodium of 118 mmol/L (IQR 113–122 mmol/L, median difference 1.0 mmol/L, $P < .001$). The majority of patients received a single bolus (58%) with a fixed volume of 100 mL (87%, Table 2). The median time to first bolus was 02:20 (hh:mm) (Table 2) and was positively correlated with the baseline plasma sodium concentration (standardized $\beta = .23$, 95% CI 0.08–0.37, $P = .002$). The most used concurrent interventions were fluid restriction ($n = 77$, 43%) and isotonic saline ($n = 65$, 36%).

Effect of hypertonic saline on plasma sodium

A total of 1107 plasma sodium measurements were analyzed. After hypertonic saline, the plasma sodium rose by 6.4 mmol/L (95% CI 5.7–7.0 mmol/L) after 24 h and 10.4 mmol/L (95% CI 9.3–11.5 mmol/L) after 48 h (Figure 2A). The change of plasma sodium during the full observation period is shown in Figure 2B. The overall time to reach an increase in plasma sodium of 5 mmol/L was 9.3 h. Stratification analyses were used to further explore plasma sodium trajectories depending on bolus volume (Figure 2C), number of boluses (Figure 2D), concurrent treatment (Figure 2E), and low and high body weight groups (Figure 2F). These trajectories suggested that patients treated with bolus volume of 150 mL, concurrent treatment with isotonic saline, and body weight ≤ 60 kg had a more rapid increase in plasma sodium concentration, whereas a higher number of boluses showed a lower increase. We further assessed the relationship with body weight and the plasma sodium increase and found a significant association between these two variables (standardized $\beta = -.19$, 95% CI −0.34 to −0.04, $P = .01$, Figure 3).

Table 2. Treatment characteristics.

Number of boluses, *n* (%)	
1	104 (58)
2	53 (29)
3	20 (11)
4	3 (2)
Fixed bolus volume, *n* (%)	
100 mL	156 (87)
150 mL	24 (13)
Treatment initiation (in hh:mm)	
Time to first bolus	02:20 (01:05, 04:17)
Time between first and second bolus	04:59 (02:50, 09:29)
Time between second and third bolus	10:18 (03:36, 14:34)
Concurrent interventions, *n* (%)	
Fluid restriction	77 (43)
Isotonic saline infusion	65 (36)
Loop diuretics	6 (3)
Glucocorticoids	9 (5)
Oral urea	8 (4)
Thiazide diuretic stopped	11 (6)
None	25 (14)

Overcorrection

Overcorrection occurred in 32 patients (18%), including 26 patients (14%) in whom the plasma sodium rise exceeded the limits and 20 patients (11%) who received relowering therapy. Relowering therapy was used as "rescue" in 14 patients (ie, after overcorrection had already occurred) and in 6 patients "reactive" (ie, in response to a worrisomely rapid plasma sodium rise and impending overcorrection).[30] The degree of overcorrection was 13 ± 2 mmol/L in the first 24 h and 22 ± 2 mmol/L in the first 48 h. Plasma sodium was relowered either with hypotonic fluids ($n = 15$), with desmopressin ($n = 2$), or with a combination of both ($n = 3$). Overcorrection occurred most frequently in patients with low-solute intake, alcohol use disorder, and/or primary polydipsia (50%), followed by volume depletion (31%) (Figure S2A). Of the 8 patients with adrenal insufficiency, 2 patients (25%) had overcorrection including one newly diagnosed patient who initially (ie, during the first 24 h) received only hypertonic saline and one patient with a history of adrenal insufficiency who received both hypertonic saline and hydrocortisone upon presentation. In patients with low body weight (≤60 kg), the cumulative rate of overcorrection was significantly higher compared to patients without low body weight (33% vs

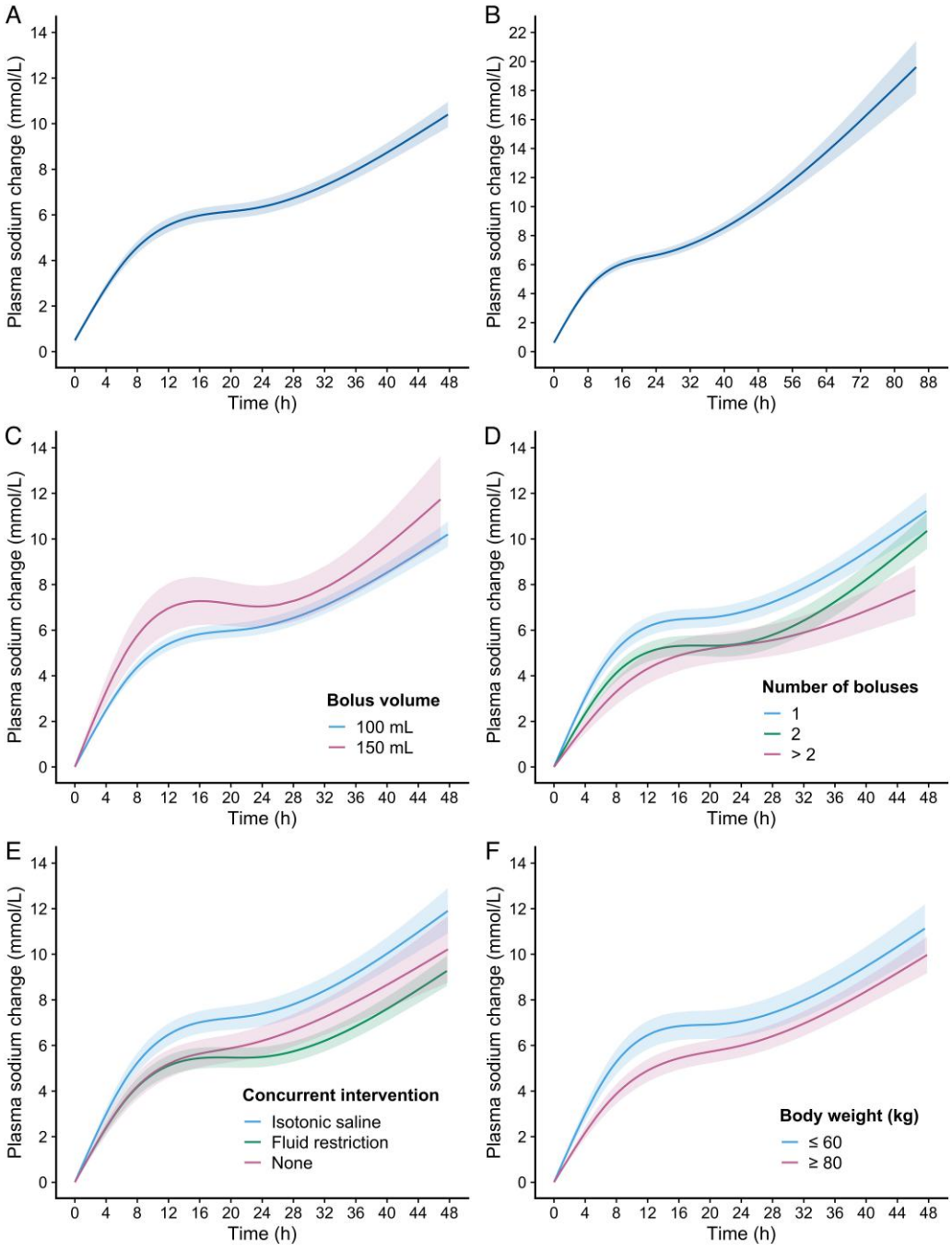

Figure 2. Plasma sodium change over time after bolus hypertonic saline therapy. The panels show the trajectories of the overall cohort during the first 48 h (A), during the full observation period (B), stratified by bolus volume (C), number of boluses (D), concurrent intervention (E), and body weight group (F). The analyses were performed using a linear mixed model, and natural cubic splines were fitted into the model to account for possible nonlinearity. The bands indicate standard errors.

11%, relative risk 3.03, 95% CI 1.59–5.78, $P < .001$, Figure 4A). The increased risk for overcorrection in patients with low body weight (≤60 kg) persisted after excluding patients treated with 150 mL boluses (33% vs 10%, relative risk 3.39, 95% CI 1.68–6.87, $P < .001$). In a subgroup of patients ($n = 103$, 57%) without rapidly reversible causes of hyponatremia (SIAD, liver disease, and heart failure), patients with low body weight (≤60 kg) also had a significantly higher risk of overcorrection (17% vs 4%, relative risk 4.64, 95% CI 1.12–19.25, $P = .04$). In multivariable regression analysis, lower body weight was independently associated with overcorrection (Table 3). Similarly, categorized low body weight (≤60 kg) was independently associated with overcorrection [odds ratio (OR) 3.22, 95% CI 1.24–8.31, $P = .02$, Table S1]. Subgroup analysis in patients with a baseline plasma sodium < 125 mmol/L ($n = 160$, 89%) showed similar results (Table S2). In addition to low body weight, we identified lower baseline plasma sodium, volume depletion, and hypokalemia as independent risk factors for overcorrection. Finally, an increasing number of boluses was associated with a lower risk for overcorrection (Table 3). Patients receiving multiple boluses of hypertonic saline had a lower baseline

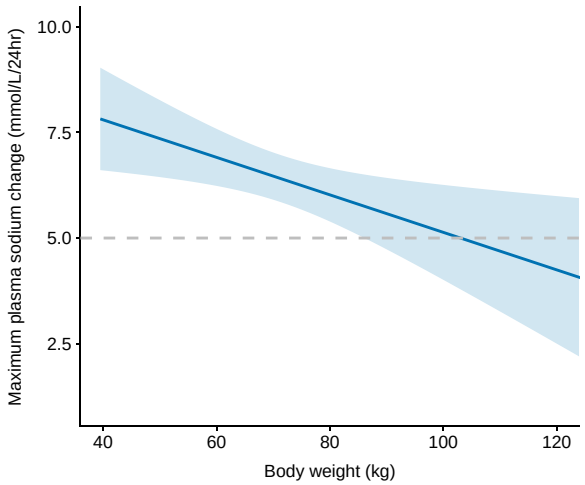

Figure 3. Relationship of the maximum change in plasma sodium in the first 24 h after bolus hypertonic saline therapy and body weight. The band indicates the 95% confidence interval. The dashed line marks the 5 mmol/L threshold. The analysis was performed using a linear regression analysis (standardized $\beta = -0.19$, 95% CI −0.34; −0.04, $P = .01$).

plasma sodium, higher baseline urine osmolality, and more often SIAD (Table S3).

Undercorrection

In 52 patients (29%), plasma sodium was undercorrected (−1 to 4 mmol/L during the first 24 h). The cumulative rate of reaching a minimum of 5 mmol/L/24 h plasma sodium rise did not significantly differ between patients with a body weight < 80 kg and ≥ 80 kg (71% vs 70%, relative risk 1.00, 95% 0.80–1.24, $P = .97$, Figure 4B). In multivariable analysis, a higher baseline plasma sodium, but not continuous body weight, time to first bolus, or higher number of boluses, was associated with undercorrection (Table 4). Similarly, categorized high body weight (≥80 kg) was not associated with undercorrection (OR 0.97, 95% CI 0.45–2.09, $P = .95$, Table S4A). However, visual inspection of the relationship between the 24-h maximum increase in plasma sodium and body weight suggested that a cut-off ≥ 100 kg may be associated with undercorrection (Figure 3). Undercorrection occurred in 7 out of 11 patients (64%) with a body weight ≥ 100 kg. A post hoc analysis indicated that body weight ≥ 100 kg was indeed independently associated with undercorrection (OR 5.11, 95% CI 1.35–19.29, $P = .02$, Table S4B). Although obesity itself (BMI ≥ 30 kg/m^2) was not a risk factor for undercorrection (OR 1.78, 95% CI 0.65–4.85, $P = .26$, Table S5A), higher lean body weight was independently associated with undercorrection in patients with obesity (OR 1.22, 95% CI 1.01–1.47, $P = .04$, Table S5B). The etiology of hyponatremia was not different in the subgroup of patients with obesity (data not shown).

Other outcomes

The length of hospitalization did not differ significantly between patients whose plasma sodium was corrected within the treatment targets, overcorrected or undercorrected patients (7 days, IQR 4–11; 8 days, IQR 4–12; and 8 days, IQR 4–16 days, respectively, $P = .34$). Twenty patients died in the hospital (11%). Osmotic demyelination syndrome was suspected in one patient who presented with confusion, headache, and a plasma sodium of 125 mmol/L due to drug-induced SIAD. She received 150 mL hypertonic saline once after which plasma sodium rose to 134 mmol/L in 15 h. She was discharged but presented to the emergency department again 2 days later with symptoms of vertigo, weakness, and seizures. A CT scan showed no intracranial pathology, but an MRI scan was not performed. In the following 24 h, the symptoms resolved spontaneously.

Discussion

In this retrospective study, we assessed the impact of body weight on the risk of overcorrection and undercorrection with fixed dosing of bolus hypertonic saline. Our real-world data show that patients weighing ≤ 60 kg and ≥ 100 kg had a significantly higher risk of overcorrection and undercorrection, respectively. Although a fixed-dose regimen is convenient, timesaving and eliminates the risk of calculation errors, our data suggest that these practical benefits may compromise effective and safe correction rates in patients without average body weight.

In our study, the risk of overcorrection was increased more than 3-fold in patients with low body weight. Although low body weight may be only one of many factors contributing to overcorrection in patients treated with hypertonic saline (eg, concurrent correction of volume depletion), the increased risk of overcorrection in patients with low body weight persisted in a subgroup of patients with more resistant hyponatremia. The impact of body weight on the risk of overcorrection after bolus hypertonic saline has not been investigated previously. In a large general cohort of patients with hyponatremia, George et al.[24] did show that patients who experienced overcorrection had a lower baseline BMI (26 vs 28 kg/m^2). In the recent study by Arshad and Iqbal et al.,[31] mean body weight was also lower in patients who experienced overcorrection after hypertonic saline, although this did not reach statistical significance. In the SALSA trial, the investigators applied a weight-based infusion protocol to avoid overcorrection, assuming that people from South Korea generally have lower body weight.[16,32] However, the risk of overcorrection in the present study (14% exceeding correction limits, 11% relowering therapy) was lower than that in the SALSA trial (17% overcorrection, 41% relowering therapy).[16] Inherent to the clinical trial setting, hyponatremia correction and relowering in the case of overcorrection were more actively implemented than in real-world practice. The volume of hypertonic saline may also have played a role, as the mean cumulative volume in the SALSA trial (535 mL) was relatively high. Furthermore, in the observational studies by Chifu et al.[28] (use of 150 mL 3% NaCl boluses) and Arshad and Iqbal et al.[31] (use of 170 mL 2.7% NaCl boluses), the overcorrection rates (28% and 45% in 24 h, respectively) were considerably higher than those in our study, in which 100 mL 3% NaCl boluses were mostly used. Other risk factors for overcorrection in our study were lower baseline plasma sodium, volume depletion, and hypokalemia, which is in line with previous studies.[24-27] Of note, treatment with multiple boluses was associated with a *lower* rather than a *higher* risk of overcorrection. This is in contrast to a previous prospective study in which especially a third bolus of hypertonic saline was associated with overcorrection.[15] The number of administered boluses primarily reflects the treating physician's response to the

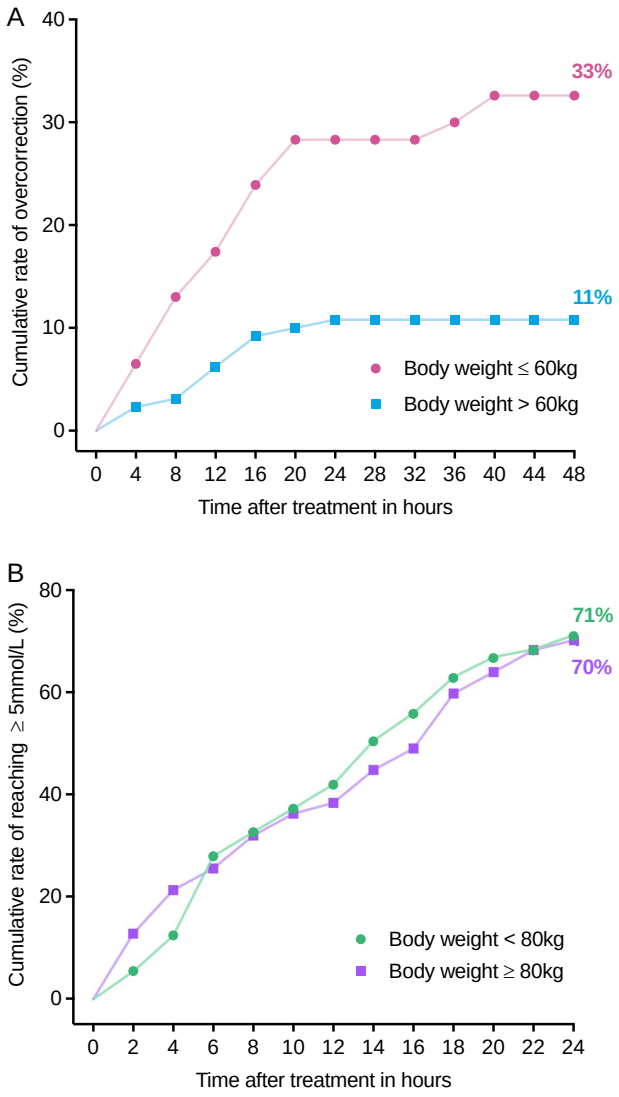

Figure 4. Cumulative rate of overcorrection and of reaching a correction of ≥5 mmol/L/24 h. The cumulative rate of overcorrection in patients with a body weight of ≤60 kg and >60 kg is shown (A). The cumulative rate of reaching ≥5 mmol/L plasma sodium correction in patients with a body weight of <80 kg and ≥80 kg is depicted (B).

plasma sodium trajectory. Because we observed that patients with multiple boluses more often had SIAD and a higher urine osmolality, it is possible that these patients had more resistant hyponatremia and therefore received more boluses. Another observation was that the time to a subsequent bolus was relatively long, which could have allowed plasma sodium to decrease again. This also suggests that the decision to administer a subsequent bolus was often driven by a lack of biochemical response rather than persisting symptomatology, which has also been reported in a previous study.[28]

Body weight was not associated with undercorrection when analyzed as a continuous parameter or using the highest quartile cut-off of 80 kg. However, when analyzing the relationship between body weight and the maximum rise in plasma sodium after hypertonic saline, a higher cut-off of 100 kg appeared to be associated with undercorrection. Indeed, when this cut-off was tested statistically, a body weight ≥ 100 kg was independently associated with undercorrection. A similar finding was that lean body weight was associated with undercorrection but only in patients with obesity. This may be explained by the fact that in people with obesity, the plasma volume is also increased, which will increase the volume of distribution for hypertonic saline.[33] Another independent risk factor for undercorrection was a higher baseline plasma sodium. This is in agreement with the recent study by Chifu et al. which observed a significantly increased risk for undercorrection in patients with baseline plasma sodium > 120 mmol/L.[28] It remains unclear why a higher baseline sodium was associated with undercorrection. Speculatively, a higher baseline plasma sodium led to a treatment delay which allowed plasma sodium to further decrease. The time to the first bolus was indeed longer in patients with higher baseline plasma sodium concentration.

Based on our data and previous studies, we consider the appropriate use of bolus hypertonic saline to be safe.[10,11,16,34,35] We do recommend adhering to the correction limits based on the study of George et al.[24] In their cohort of 1490 patients with plasma sodium < 120 mmol/L, ODS was rare (0.5%), but 3 out of 8 patients with MRI-confirmed ODS had experienced overcorrection with the use of hypertonic saline. Of

Table 3. Risk factors for overcorrection.

	Odds ratio (95% CI)	
	Univariable	Multivariable
Body weight (per kg)	0.95 (0.92–0.98)	0.96 (0.92–0.99)
Baseline plasma sodium (mmol/L)	0.88 (0.82–0.95)	0.86 (0.79–0.94)
Volume depletion	2.71 (1.16–6.33)	3.07 (1.06–8.83)
Hypokalemia[a]	3.70 (1.53–8.92)	4.40 (1.45–13.35)
Number of boluses	0.45 (0.23–0.89)	0.34 (0.13–0.88)

[a]Plasma potassium < 3.5 mmol/L.

Table 4. Risk factors for undercorrection.

	Odds ratio (95% CI)	
	Univariable	Multivariable
Body weight (per kg)	1.02 (1.00–1.04)	1.01 (0.99–1.04)
Baseline plasma sodium (mmol/L)	1.17 (1.08–1.28)	1.18 (1.07–1.30)
Time to first bolus (per hour)	1.11 (0.99–1.24)	1.05 (0.93–1.19)
Number of boluses	0.98 (0.64–1.50)	1.26 (0.78–2.02)

note, some patients in our study had no recorded symptoms of hyponatremia, which suggests that hypertonic saline was administered because conventional treatments were deemed insufficient to increase plasma sodium promptly or to prevent further worsening, while cause-specific treatment was initiated. Similar observations were made in a previous study.[7] Only a minority of the patients in our study presented with overt signs of cerebral irritation such as seizures, somnolence, and coma. In the European hyponatremia guideline, a bolus hypertonic saline is also recommended for patients who present with moderately severe symptoms (nausea, headache, and confusion) as these may be early signs of increased intracranial pressure.[10] Our data show that the consequence of this recommendation is that patients with mild hyponatremia and mild symptoms are sometimes treated with hypertonic saline, while their symptoms may have been due to the underlying disease or may even have been the cause of hyponatremia (eg, nausea or pain causing vasopressin release). This raises a benefit vs harm question: does the potential harm of withholding hypertonic saline in a patient with moderately severe symptoms outweigh the risk of possible overcorrection when treating with hypertonic saline? Although this decision should be individualized, our data suggest that it is important to monitor for overcorrection after giving hypertonic saline, especially in patients with risk factors such as hypovolemia, hypokalemia, or low baseline plasma sodium. Monitoring for overcorrection can be achieved by follow-up measurements of plasma sodium but also by monitoring the urine output with a brisk increase in diuresis being a warning sign for impeding overcorrection.

To the best of our knowledge, this study describes the largest patient cohort treated with bolus hypertonic saline for symptomatic hyponatremia. Another strength is the real-world setting, which enhances the generalizability of our findings and offers a reflection of routine clinical practice. In this regard, we found that the guidelines were not always followed in terms of monitoring the response in plasma sodium to the first bolus of hypertonic saline and active relowering in the case of overcorrection. The limitations of this study are primarily related to the retrospective study design. Our study was not designed or powered to analyze the clinical consequences of overcorrection or undercorrection. As for undercorrection, our study was unable to differentiate whether undercorrection represented insufficient treatment of hyponatremia, symptom resolution, or an alternative explanation for the presenting symptoms.

In conclusion, although a fixed-dose hypertonic saline regimen has practical advantages, it exposes patients with low and high body weight to more overcorrection and undercorrection, respectively. Our retrospective data suggest that patients weighing ≤ 60 kg and ≥ 100 kg may therefore benefit from weight-based volume adjustments. Prospective studies are needed to validate these cut-offs or investigate a weight-based infusion protocol of bolus hypertonic saline. Individualized dosing models based on readily available body size measures may improve bolus hypertonic saline therapy towards an approach that is both effective and safe.

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Supplementary material

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Data availability

The data are not publicly available due to restrictions based on patient privacy regulations. Data are however available from the authors upon reasonable request.

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