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Original Article

ORIGINAL ARTICLE

Correction of profound hyponatraemia following rapid bolus therapy: effectiveness of the Barsoum–Levine formula based on the Edelman equation

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ABSTRACT

Background. The optimal treatment for profound hyponatraemia remains uncertain. Recent clinical studies have demonstrated that a standardized bolus of hypertonic saline is effective, but relying solely on this approach may not fully address the individual variability of hyponatraemia among patients. We evaluated the effectiveness of rapid bolus (RB) administration of hypertonic saline followed by predictive correction (PC) using an infusate and fluid loss formula identical to the Barsoum–Levine formula based on the Edelman equation (RB-PC) for managing profound hyponatraemia.
Methods. In this retrospective observational cohort study, we evaluated 276 patients aged >18 years with s[Na] levels ≤120 mEq/L (January 2014–December 2023). Using propensity score matching (PSM), we assessed s[Na] elevations at 6 h post-treatment initiation and the rate of appropriate hyponatraemia correction between the RB-PC and PC groups. We defined the appropriate correction as a change in s[Na] in the range of 4–10 mEq/L within the first 24 h and ≤18 mEq/L within the first 48 h following corrective treatment initiation.
Results. Among 276 patients with profound hyponatraemia (s[Na] ≤120 mEq/L), 49 and 108 underwent treatment with RB-PC therapy and with PC therapy without RB, respectively. Post-PSM, 84 patients were selected and allocated to the RB-PC ($n = 42$) or PC group ($n = 42$). In PSM analysis, patients with RB-PC experienced a higher elevation in s[Na] at 6 h after treatment initiation than PC (4.0 vs 2.4 mEq/L, $P < 0.001$). The rate of appropriate correction was similar between the RB-PC and PC groups (90.5% vs 90.5%, $P = 1$).
Conclusions. RB-PC can quickly elevate s[Na] levels and achieve appropriate correction of s[Na] in patients with profound hyponatraemia.

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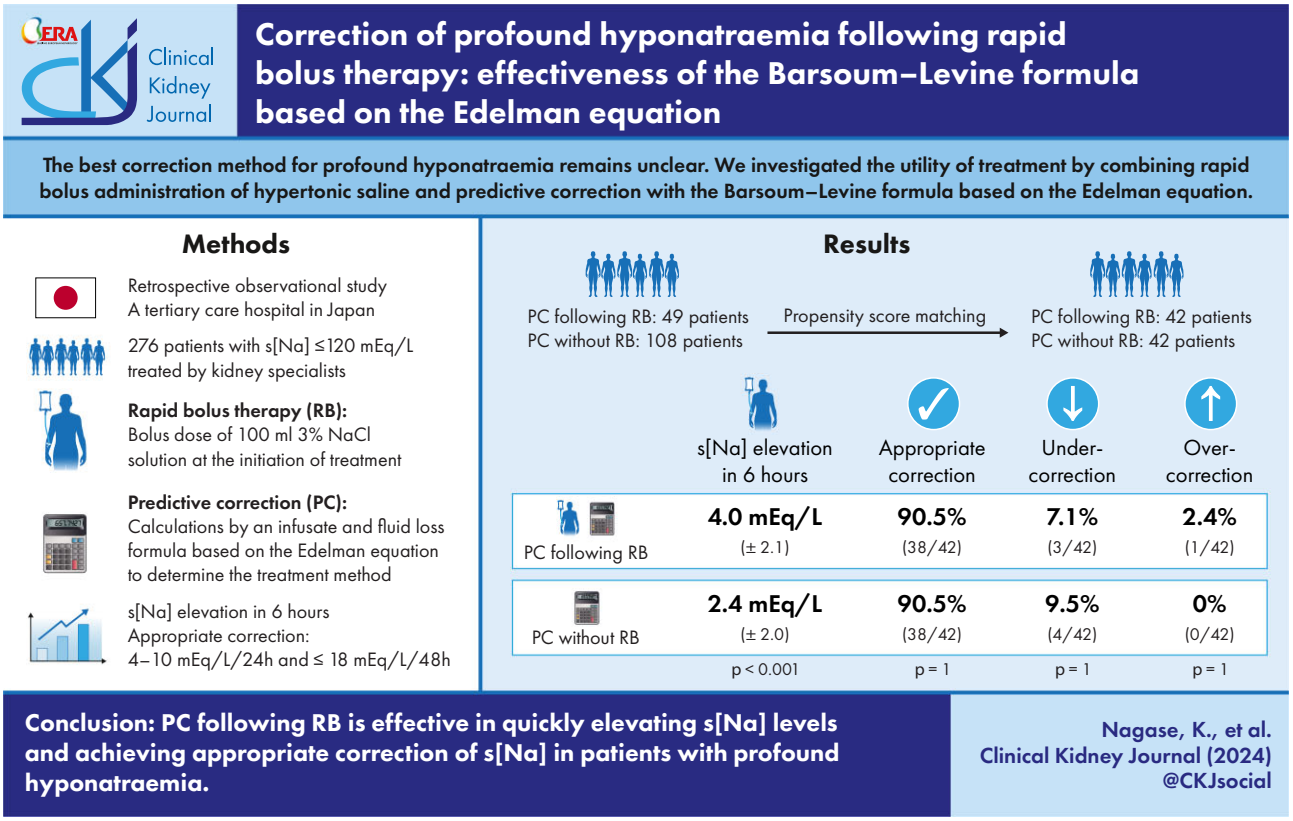
GRAPHICAL ABSTRACT



Keywords: Barsoum–Levine formula, Edelman's equation, hyponatraemia, predictive correction, rapid bolus therapy of hypertonic saline

KEY LEARNING POINTS

What was known:

- The safest and most effective approach to management for profound hyponatraemia remains a challenge.
- Rapid bolus (RB) administration of hypertonic saline effectively increases s[Na] by 4–6 mEq/L within a few hours, reduces intracranial pressure, and reverses imminent brain herniation.

This study adds:

- The combined therapy of RB and a predictive correction (PC) approach, using an infusate and fluid loss formula identical to the Barsoum–Levine formula based on the Edelman equation (RB-PC), facilitated a rapid increase in s[Na] and allowed subsequent fine-tuning of s[Na] within an appropriate correction range.

Potential impact:

- RB-PC quickly elevates s[Na] levels and achieves appropriate correction in patients with profound hyponatraemia.
- Applying RB-PC may offer flexibility in adhering to any treatment recommendation and enable precise adjustment of s[Na] to fall within the desired ranges.

INTRODUCTION

Hyponatraemia, defined as serum sodium (s[Na]) concentration <135 mEq/L, affects 30%–42% of hospitalized patients [1, 2]. Profound hyponatraemia (s[Na] ≤120 mEq/L) can lead to life-threatening cerebral oedema and mortality, necessitating prompt intervention to elevate s[Na] [3–6]. Evidence suggests that increasing s[Na] by <3–4 mEq/L within 24 h might be linked to higher mortality in acute or postoperative hyponatraemia [7, 8], leading expert guidelines to recommend a minimum increase of ≥4 mEq/L within the first 24 h, even in chronic cases [9]. However, excessively rapid correction can result in osmotic demyelination syndrome (ODS), a serious neurological condition [10–13]. Consequently, the guidelines advise limiting s[Na] increases to 10–12 and 18 mEq/L within the first 24 and 48 h, respectively [9, 14].

In treating hyponatraemia with moderate and severe symptoms, the guidelines recommended rapid bolus (RB) infusion of hypertonic saline to increase s[Na] by 4–6 mEq/L within a few hours to reduce intracranial pressure and reverse imminent brain herniation [9, 14, 15]. However, when RB was administered for the treatment of symptomatic hyponatraemia, overcorrection occurred in 17.2%, and re-lowering therapy for s[Na] was required in 28.0%–41.4% of cases [16, 17]. Thus, determining the safest and most effective approach for profound hyponatraemia treatment remains challenging.

Recently, our retrospective observational study demonstrated the effectiveness of using an infusate and fluid loss formula based on the Edelman equation [predictive correction (PC)] to correct s[Na] levels predictively in managing profound hyponatraemia [18]. This approach utilizes Equation (1) to forecast future s[Na] (serum $[Na]_2$):

$$\text{serum}[Na]_2 = (\text{serum}[Na]_1 \times TBW_1 + \Delta\,[Na + K])/\,(TBW_1 + \Delta TBW) \quad (1)$$

where serum $[Na]_1$ is current s[Na], TBW_1 is current total body water, and K is potassium.

This formula is based on the original Edelman formula (2) [19], and a simplified version of the formula is proposed for more convenient use in clinical practice (3) [20]. Nae and Ke represent exchangeble Na and K, respectively.

$$[Na]\,\text{in plasma water} = 1.11\,(Nae + Ke)\,/TBW – 25.6 \quad (2)$$

$$\text{serum}\,[Na] = (Nae + Ke)\,/TBW \quad (3)$$

We applied Equation (1), incorporating a broad range of data on Na, K, and water inputs and outputs to optimize the accuracy of serum$[Na]_2$ predictions. This formula is identical to the Barsoum–Levine formula and is considered helpful for managing significant fluid losses during hyponatraemia treatment [5, 18, 21, 22].

Considering the above, we hypothesized that combining RB with a PC using an infusate and fluid loss formula based on the Edelman equation (RB-PC) could theoretically facilitate a rapid increase in s[Na] and allow subsequent fine-tuning within an appropriate correction range. We aimed to evaluate the effectiveness of the RB-PC approach in managing profound hyponatraemia.

MATERIALS AND METHODS

Inclusion criteria, definition of appropriate correction, and outcome

This was a single-centre, retrospective study conducted at a tertiary hospital in Nagoya, Japan, from January 2014 to December 2023. The study protocol was designed following the Helsinki Declaration and approved by the Clinical Research Ethics Committee of Chubu Rosai Hospital (reference no. 202401-01, approved on 8 January 2024). As the study data were anonymized before use and did not lead to patient identification, the requirement for informed consent was waived by the ethics committee.

We included adults aged >18 years with a s[Na] level ≤120 mEq/L treated by kidney specialists. We excluded individuals with no available data pertaining to s[Na] within 12 h of the 24- and/or 48-h time points after corrective treatment initiation because the appropriateness of s[Na] correction could not be determined for these patients. Furthermore, we excluded patients with apparent acute hyponatraemia (onset within 48 h of admission), patients with serum glucose levels >400 mg/dL on admission, and those with hypertriglyceridaemia presenting with pseudohyponatraemia. Following previous guidelines, we defined appropriate correction as a change in s[Na] in the 4–10 mEq/L range in the first 24 h and within 18 mEq/L in the first 48 h after corrective treatment initiation [9, 14]. Overcorrection was defined as an increase in s[Na] levels >10 mEq/L within 24 h or >18 mEq/L within 48 h. Undercorrection was defined as an increase in s[Na] levels <4 mEq/L within the first 24 h.

The primary analysis compared the rate of elevation of s[Na] at 6 h after corrective treatment initiation in patients with s[Na] level ≤120 mEq/L between the RB-PC and PC groups. Another primary analysis compared the achievement of the appropriate correction of s[Na] in patients with s[Na] level ≤120 mEq/L between the two treatment groups.

Infusion protocols

Predictive correction using an infusate and fluid loss formula based on the Edelman equation

At our institution, although the final choice of treatment was at the discretion of each kidney specialist, many patients with profound hyponatraemia were treated using PC (Equation 1) (Supplementary Fig. S1) [18].

In Equation (1), serum$[Na]_1$ represents the current s[Na], while serum$[Na]_2$ represents the future s[Na]. We collected data on the input and output of Na, K, and water (including infusion, urine, food, and drink [Na and water], electrolyte repletion [Na and K], insensible evaporation [water], and drainage [Na and water]) to optimize the accuracy of serum$[Na]_2$ predictions via Equation 1. Total body water (in litres) was estimated as a fraction of body weight: 0.6 for non-elderly men, 0.5 for non-elderly women, 0.5 for elderly men, and 0.45 for elderly women [14]. To predict the future urine output of Na, K, and water, we used data from the most recent time point for urine Na (u[Na]), urine K (u[K]), and the amount of urine flow, as we also concurrently performed spot urine tests for each blood test. In cases of sudden and substantial diuresis or rapid increase in s[Na], hypotonic solution and/or desmopressin were administered at the physicians' discretion to prevent overcorrection. For fluid infusion treatment, we administered various solutions, including 3% sodium chloride solution, saline, and 5% dextrose solution, aiming to achieve the targeted correction range of s[Na] based on predictive calculations (Supplementary Fig. S1).

Rapid bolus with a predictive correction using an infusate and fluid loss formula based on the Edelman equation

First, patients underwent more than one 100-mL bolus infusion of 3% sodium chloride solution over 15 min to achieve a target rapid increase in s[Na] of 4–6 mEq/L. After administering RB of 3% sodium chloride solution, a PC protocol was conducted for future s[Na] predictions (Supplementary Fig. S1) (Equation 1). To clarify the exact procedure, we provided a detailed example of an individual patient, outlining the specific measurements, calculations, and treatments administered throughout the intervention for profound hyponatraemia (Supplementary Fig. S2). We administered hypertonic sodium chloride solutions in both protocols through a peripheral intravenous cannula.

Data collection

Patient data were collected by reviewing electronic medical records. Demographic data included age, sex, onset setting

of profound hyponatraemia (community-onset or otherwise), BMI, body weight, blood pressure, and comorbidities (congestive heart failure, cerebrovascular disease, dementia, diabetes, chronic kidney disease, chronic liver disease, alcohol abuse, depression, schizophrenia, and solid tumour). Additionally, the analysis encompassed the cause of hyponatraemia (primary polydipsia, hypovolaemia, syndrome of inappropriate antidiuresis, adrenal insufficiency, drug-induced hyponatraemia, heart failure, and unknown reason), daily medication usage (thiazide and loop diuretics, aldosterone antagonists, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, antiseizure drugs, and antipsychotic drugs), and the location within the in-patient ward. We diagnosed the syndrome of inappropriate antidiuresis based on the criteria described in previous studies [9, 16]. Comorbidity severity was recorded according to the Charlson Comorbidity Index (CCI) [23]. Upon admission, the patient's laboratory evaluations included s[Na], s[K], creatinine levels, estimated glomerular filtration rate, uric acid concentration, albumin levels, and glucose levels; both serum and urine osmolality, u[Na], and u[K] were meticulously analysed. Symptomatic or asymptomatic status was recorded. Symptoms of hyponatraemia were further categorized as moderate (nausea without vomiting, headache, drowsiness, confusion, general weakness, and malaise) or severe [vomiting, seizure, and coma (Glasgow Coma Scale score ≤8 points)] following previous studies and guidelines [9, 16, 18]. We also collected data regarding the correction methods (isotonic saline, hypertonic saline continuous infusion, number of RB administrations, electrolyte repletion [sodium and potassium], loop diuretics, vaptans, desmopressin, re-lowering treatment of s[Na] when the correction limits were exceeded, and number of measurements of u[Na] during the first 48 h) and outcomes (appropriate correction, undercorrection, overcorrection, the rate of s[Na] elevations at 6, 24, or 48 h after treatment initiation, development of abrupt diuresis (>2 mL/kg/h), u[Na]+u[K] levels during abrupt diuresis (categorized as <50, 50–100, or >100 mEq/L), length of hospital stay, incidence of ODS, and mortality in the hospital). If there was no exact value of s[Na] at 6, 24, or 48 h, we estimated the s[Na] levels as the extrapolation numbers using the formula utilized in a previous study [18]. We could not present the data for abrupt diuresis and increase of s[Na] at 6 h in the patients managed by non-kidney specialists due to missing >80% of the data.

Statistical analysis

Categorical data are presented as total numbers (percentages) and were analysed using the χ^2 test or Fisher's exact test, as appropriate. Continuous data are presented as means (standard deviations) and were analysed using the Mann–Whitney *U* test.

As the allocation to RB-PC or PC was not random, we developed multinomial propensity scores for the probability of any patient receiving each treatment. Variables used to develop the propensity score model were age, sex, CCI, symptoms associated with hyponatraemia, severity of symptoms due to hyponatraemia (severe or moderate), s[Na], and u[Na]. The predicted probability of preprocedural RB-PC was calculated by fitting a logistic regression model. Confounders were chosen based on clinical knowledge for their potential association with the outcome of interest. We performed one-to-one propensity score matching (PSM) comparing the RB-PC and PC groups. The matching was accomplished through nearest-neighbour matching without replacement, relying on each patient's estimated propensity scores [24]. Propensity scores were matched with a calliper width set at 0.15 logit of standard deviation, ensuring a refined alignment of comparable cases. After matching, standardized differences in covariate imbalances were presented to assess the effectiveness and adequacy of the matching process. Subsequently, matched patient demographics were displayed and compared between the RB-PC and PC groups using the Mann–Whitney *U* test for continuous variables and the χ^2 or Fisher's exact test for categorical variables. For further confirmation of the treatment effect of RB-PC, we conducted a multiple linear regression analysis (forced entry model) to evaluate the association of RB-PC with s[Na] elevation at 6 h post-treatment, with adjustment for propensity scores based on the same covariates as those used in the PSM analysis. We also conducted a logistic regression analysis to evaluate the effect of RB-PC on the rate of appropriate correction, with an adjustment for propensity scores based on the same covariates as those used in the PSM analysis.

Assuming non-linear trajectories, we employed a mixed-effects model with an unstructured variance–covariance matrix, patient-level random effects, and spline time terms to examine the elevation in s[Na] over time in the RB-PC and PC groups. All statistical analyses were performed using SPSS Statistics (version 22; IBM Japan, Tokyo, Japan) and Stata 18.0 BE (Stata Corp., College Station, TX, USA).

RESULTS

Patient characteristics of RB-PC and PC groups

Among 383 patients with profound hyponatraemia (s[Na] ≤120 mEq/L) admitted between 2014 and 2023, 276 (72%) were treated by kidney specialists. Within this cohort, 49 underwent treatment with RB-PC therapy, whereas 108 received PC therapy without RB for their hyponatraemia; these patients were included in the primary analysis (Fig. 1).

Table 1 shows the baseline characteristics of all patients undergoing RB-PC and PC. Post-PSM, 84 patients were selected and allocated to either the RB-PC ($n = 42$) or PC group ($n = 42$) (Table 1). After PSM, baseline covariates were relatively comparable between the two groups (Supplementary Table S1) and the groups exhibited similar baseline characteristics (Table 1).

Treatment outcomes of RB-PC and PC groups

In PSM analysis, patients who underwent RB-PC experienced a higher elevation in s[Na] at 6 h after treatment initiation than did those who underwent PC (4.0 vs 2.4 mEq/L, $P < 0.001$) (Table 2, Fig. 2a). The rate of appropriate correction, undercorrection, and overcorrection of profound hyponatraemia in patients with RB-PC was compatible with those for PC (90.5% vs 90.5%, $P = 1$ for appropriate correction; 7.1% vs 9.5%, $P = 1$ for undercorrection; 2.4% vs 0%, $P = 1$ for overcorrection) (Table 2, Fig. 2b). Restricted cubic spline models for s[Na] elevation from baseline indicated the rapid elevation of s[Na] in the early stages of treatment in the RB-PC group compared with the PC group, and a gradual and steady rise succeeded this initial increase in s[Na] levels in both groups (Fig. 2c). The mean frequency of hypertonic saline infusions in the RB-PC group was 1.1 times. The RB-PC group more often received desmopressin treatment (54.8% vs 26.2%, $P = 0.01$) and underwent measurements of u[Na] during the initial 48-h period (9.1 vs 7.7 times, $P = 0.01$) (Table 3). The exact cumulative amount of infusion administered could not be determined from the medical records in either group. Although the frequency of re-lowering treatment was higher in the RB-PC group than in the PC group, the difference was not statistically significant (14.3%

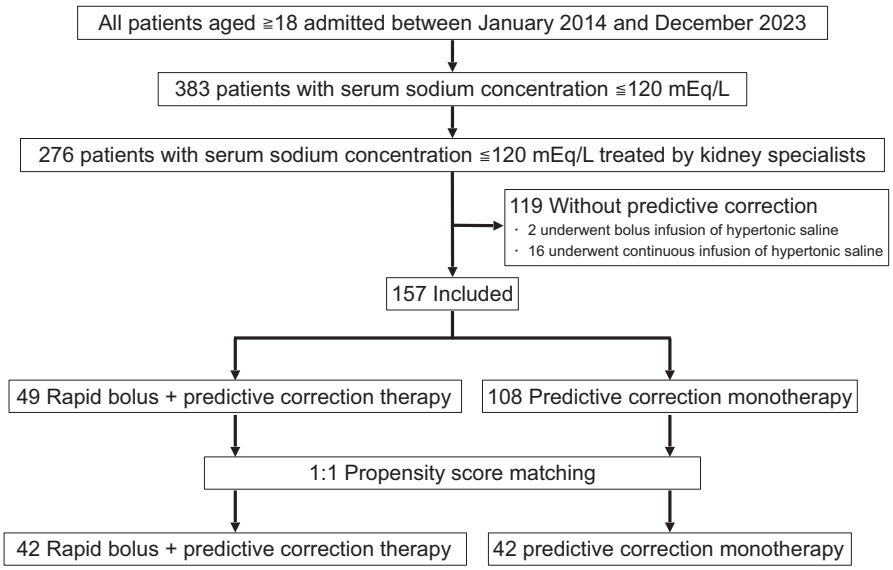


Figure 1: Patient selection process and the subsequent categorization.

vs 2.4%, $P = 0.11$). In the PSM pairs, abrupt diuresis was observed in 31 (73.8%) and 30 (71.4%) patients who underwent RB-PC and PC, respectively.

Using multiple linear regression analysis, we confirmed that the application of RB-PC was a significant predictor of an elevation in s[Na] at 6 h after treatment initiation (β=1.68 mEq/L; 95% confidence interval 0.86–2.50; $P < 0.001$) (Table 3). Conversely, achievement of appropriate correction was comparable between the two groups (odds ratio 1.20; 95% confidence interval 0.39–3.74; $P = 0.58$).

Patient characteristics and treatment outcomes of groups not receiving RB-PC or PC therapy

Supplementary Table S2 presents the patient characteristics and treatment outcomes for the entire cohort in this study. The patient characteristics of the RB-PC and PC groups showed baseline differences compared with patients who were managed by kidney specialists with no PC and all patients under the care of non-kidney specialists, particularly in terms of the severity of hyponatraemia and CCI scores (Supplementary Table S2). Additionally, the rate of appropriate correction for hyponatraemia was higher in the RB-PC and PC groups compared with patients managed by kidney specialists with no PC and those managed by non-kidney specialists. Conversely, in-hospital mortality rates were lower in the RB-PC and PC groups.

DISCUSSION

This retrospective, exploratory study was the first to assess the effectiveness of a combined treatment approach using RB-PC for swiftly elevating s[Na] and achieving appropriate correction in patients with profound hyponatraemia. In the group undergoing RB-PC therapy, the increase in s[Na] levels at 6 h post-treatment initiation was significantly higher than that in the PC group (4.0 vs 2.4 mEq/L, $P < 0.001$). The incidence of appropriate corrections (90.5%) was comparable to that of the group receiving only PC (90.5%), as determined through PSM.

In our study, 6 h after initiating treatment for profound hyponatraemia, the mean s[Na] increase was 4.0 mEq/L in the RB-PC group, which was significantly higher than that in the PC group. This extent of s[Na] elevation with RB-PC fell within the target increase of 4–6 mEq/L, as recommended by American and European guidelines [9, 14]. However, we could not track changes in symptoms and Glasgow Coma Scale scores during s[Na] elevation, leaving the adequacy of our RB therapy (mean of 1.1 administrations) for hyponatraemia treatment unresolved [15, 25, 26]. Additionally, our study's patient cohort had a mean weight of 48.1 kg, notably less than the 57–73 kg range of patients in prior studies on the treatment of hyponatraemia [16, 27]. The variation in weight among individuals could potentially surpass the initial target range of 4–6 mEq/L elevation in s[Na], especially within our patient cohort if additional RB therapy were introduced. Subsequent investigations should focus on determining the optimal dosage of RB for the initial treatment of profound hyponatraemia.

The strength of our treatment protocol is that there was only one overcorrection in the RB-PC group. The PC method is advantageous in incorporating a fluid loss formula, monitoring urine volume, and facilitating a quick response to the development of substantial diuresis. In developing marked diuresis, we can adjust the volume and concentration of fluid with the PC formula to achieve the desired s[Na] in the future while administering hypotonic fluid and/or desmopressin. Intriguingly, abrupt diuresis (>2 mL/kg/h) was observed in 73.8% of patients in the RB-PC group and 71.4% of those in the PC group in the PSM pairs within 48 h after treatment initiation for hyponatraemia. Additionally, we observed a broad range in u[Na] + u[K] concentrations (42.9% of patients with <50 mEq/L, 19.0% of patients with 50–100 mEq/L, and 11.9% of patients with >100 mEq/L in the RB-PC group), during the episodes of abrupt diuresis. While abrupt diuresis could occur due to antidiuretic hormone suppression following infusion therapy for profound hyponatraemia, our findings indicate that abrupt diuresis does not necessarily equate to 'water diuresis'. Therefore, we should consider urine volume and composition when devising infusion strategies. Although the applications of desmopressin and frequent measurements of u[Na]

Table 1: Baseline characteristics of predictive correction following rapid bolus infusion of hypertonic saline and predictive correction monotherapy groups with s[Na] ≤120 mEq/L in the entire cohort of patients and the propensity score-matched pairs.

	Entire patients		Propensity score matching pairs		
Parameter	Rapid bolus + predictive correction, *n* = 49	Predictive correction, *n* = 108	Rapid bolus + predictive correction, *n* = 42	Predictive correction, *n* = 42	*P* value
Age, years, mean (SD)	75.8 (11.4)	76.9 (12.0)	76.6 (11.1)	76.9 (13.4)	0.69
Women, *n* (%)	25 (51.0)	54 (50.0)	22 (52.4)	24 (57.1)	0.66
Community onset, *n* (%)	38 (77.6)	74 (68.5)	34 (81.0)	31 (73.8)	0.43
Body mass index, kg/m^2, mean (SD)	18.8 (6.5)	19.6 (3.5)	19.4 (4.1)	19.6 (6.2)	0.85
Body weight, kg, mean (SD)	47.8 (12.0)	47.6 (9.9)	48.0 (12.3)	46.4 (10.3)	0.81
Systolic BP, mmHg mean (SD)	145.3 (31.6)	141.4 (27.4)	146.7 (32.8)	139.8 (30.5)	0.32
Diastolic BP, mmHg mean (SD)	81.0 (20.3)	78.3 (17.4)	83.2 (20.2)	75.5 (14.6)	0.07
Symptomatic (%)	45 (91.8)	79 (73.1)	38 (90.5)	37 (88.1)	1
Severe symptoms (%)	26 (53.1)	27 (25.0)	20 (47.6)	20 (47.6)	1
Moderate symptoms (%)	19 (38.8)	51 (47.2)	18 (42.9)	17 (40.5)	0.83
Comorbidities, *n* (%)					
Congestive heart failure	4 (8.2)	14 (13.0)	4 (9.5)	5 (11.9)	1
Cerebrovascular disease	0 (0)	8 (7.4)	0 (0)	2 (4.8)	0.15
Dementia	4 (8.2)	9 (8.3)	3 (7.1)	4 (9.5)	1
Diabetes	10 (20.4)	26 (24.1)	9 (21.4)	9 (21.4)	1
Chronic kidney disease	7 (14.3)	12 (11.1)	6 (14.3)	4 (9.5)	0.74
Chronic liver disease	3 (6.1)	2 (1.9)	1 (2.4)	1 (2.4)	1
Solid tumour	9 (18.4)	16 (14.8)	9 (21.4)	4 (9.5)	0.23
Alcohol abuse	3 (6.1)	2 (1.9)	2 (4.8)	0 (0)	0.49
Depression	7 (14.3)	3 (2.8)	7 (16.7)	2 (4.8)	0.16
Schizophrenia	1 (2.0)	3 (2.8)	1 (2.4)	1 (2.4)	1
Charlson comorbidity index					
Score, mean (SD)	1.2 (1.6)	1.6 (1.8)	1.3 (1.7)	1.0 (1.3)	0.75
0, *n* (%)	22 (44.9)	38 (35.2)	19 (45.2)	19 (45.2)	1
1, *n* (%)	11 (22.4)	23 (21.3)	9 (21.4)	10 (23.8)	0.79
2, *n* (%)	8 (16.3)	23 (21.3)	6 (14.3)	8 (19.0)	0.56
≧3, *n* (%)	8 (16.3)	24 (22.2)	8 (19.0)	5 (11.9)	0.55
Cause of hyponatraemia, *n* (%)					
Primary polydipsia	2 (4.1)	6 (5.6)	1 (2.4)	4 (9.5)	0.30
Hypovolaemic	5 (10.2)	38 (35.2)	5 (11.9)	13 (31.0)	0.06
SIAD	19 (38.8)	53 (49.1)	16 (38.1)	21 (50.0)	0.27
Adrenal insufficiency	1 (2.0)	3 (1.9)	1 (2.4)	1 (2.4)	1
Drug-induced	10 (20.4)	18 (16.7)	9 (21.4)	5 (11.9)	0.38
Heart failure	4 (8.2)	7 (6.4)	4 (9.5)	3 (7.1)	1
Unidentified cause	5 (10.2)	3 (1.9)	5 (11.9)	1 (2.4)	0.20
Daily use of medication, *n* (%)					
Thiazide diuretics	10 (20.4)	23 (21.3)	8 (19.0)	7 (16.7)	0.78
Loop diuretics	4 (8.2)	13 (12.0)	4 (9.5)	1 (2.4)	0.36
Aldosterone antagonists	7 (14.3)	6 (5.6)	6 (14.3)	4 (9.5)	0.74
NSAIDs	2 (4.1)	16 (14.8)	2 (4.8)	4 (9.5)	0.68
SSRIs	5 (10.2)	3 (2.8)	5 (11.9)	1 (2.4)	0.20
Antiseizure medication	2 (4.1)	2 (1.9)	1 (2.4)	1 (2.4)	1
Antipsychotic medication	1 (2.0)	4 (3.7)	0 (0)	3 (7.1)	0.24
Laboratory values at bottom sodium level, mean (SD)					
Sodium, mEq/L	112.7 (5.0)	115.1 (4.1)	113.2 (5.1)	113.1 (4.7)	0.84
Potassium, mEq/L	4.2 (0.7)	4.1 (0.8)	4.0 (0.9)	4.1 (0.7)	0.48
Creatinine, mg/dL	0.74 (0.54)	0.77 (0.57)	0.76 (0.57)	0.71 (0.42)	0.87
eGFR, ml/min/1.73 m^2	98.0 (66.8)	94.0 (59.2)	93.2 (64.4)	92.1 (58.5)	0.92
Uric acid, mg/dL	4.1 (5.3)	3.7 (2.2)	4.0 (5.6)	3.3 (2.0)	0.95
Serum osmolarity, mOsm/kg	241.9 (25.0)	246.3 (47.8)	239.0 (14.2)	237.6 (11.0)	0.54
Albumin, g/dL	3.5 (0.8)	3.5 (0.7)	3.5 (0.8)	3.6 (0.7)	0.74
Glucose, mg/dL	138.6 (45.9)	126.8 (40.2)	135.2 (38.5)	127.9 (41.6)	0.37
Urine sodium, mEq/L	72.6 (43.7)	68.9 (45.5)	68.0 (37.4)	69.2 (51.4)	0.75
Urine potassium, mEq/L	34.9 (17.8)	32.2 (18.8)	34.9 (18.6)	31.5 (18.9)	0.38
Urine osmolality, mEq/L	408.1 (135.4)	399.3 (155.3)	401.2 (141.1)	399.0 (153.2)	0.92
Location within in-patient ward					
General ward	23 (46.9)	80 (74.1)	21 (50.0)	26 (61.9)	0.27
Intensive care unit	26 (53.1)	28 (25.9)	21 (50.0)	16 (38.1)	0.27

All data are expressed as the mean value (SD) for continuous variables or *n* (percentage) for categorical variables.

Missingness for all covariates was ≤3%, except for baseline of the body mass index (5.7%), uric acid (10.8%), serum osmolarity (4.5%), and urine osmolality (3.8%).

Rapid bolus + predictive correction indicates the predictive correction following rapid bolus of hypertonic saline group. Predictive correction indicates the predictive correction monotherapy group.

BP, blood pressure; SIAD; syndrome of inappropriate antidiuresis; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

Table 2: Correction methods and outcome of predictive correction following rapid bolus infusion of hypertonic saline and predictive correction monotherapy groups with s[Na] ≤120 mEq/L in the entire cohort of patients and the propensity score-matched pairs.

	Entire patients		Propensity score matching pairs		
Parameter	Rapid bolus + predictive correction, *n* = 49	Predictive correction, *n* = 108	Rapid bolus + predictive correction, n = 42	Predictive correction, *n* = 42	*P* value
Correction method					
Isotonic saline, *n* (%)	15 (30.6)	34 (31.5)	13 (31.0)	11 (26.2)	0.63
Hypertonic saline continuous infusion, *n* (%)	36 (73.5)	65 (60.2)	32 (76.2)	24 (57.1)	0.06
Number of RBs, mean (SD)	1.1 (0.3)	0 (0)	1.1 (0.3)	0 (0)	<0.001
Electrolyte repletion, *n* (%)	12 (24.5)	13 (12.0)	11 (26.2)	6 (14.3)	0.18
Loop diuretics, *n* (%)	1 (2.0)	4 (3.7)	1 (2.4)	1 (2.4)	1
Vaptans, *n* (%)	0 (0)	2 (1.9)	0 (0)	0 (0)	N/A
Desmopressin, *n* (%)	25 (51.0)	26 (24.1)	23 (54.8)	11 (26.2)	0.01
Re-lowering treatment, *n* (%)	7 (14.3)	3 (2.8)	6 (14.3)	1 (2.4)	0.11
Number of measurements of u[Na] level during the first 48 h, mean (SD)	9.1 (2.4)	7.1 (2.2)	9.1 (2.3)	7.7 (2.3)	0.01
Outcome					
Appropriate correction, *n* (%)	44 (89.8)	87 (80.6)	38 (90.5)	38 (90.5)	1
Undercorrection, n (%)	4 (8.2)	21 (19.4)	3 (7.1)	4 (9.5)	1
Overcorrection, *n* (%)	1 (2.0)	0 (0)	1 (2.4)	0 (0)	1
Increases in s[Na], mean (SD), mEq/L					
at 6 h	3.9 (1.9)	2.1 (2.2)	4.0 (2.1)	2.4 (2.0)	<0.001
at 24 h	6.7 (2.0)	5.4 (2.2)	7.0 (2.2)	6.1 (2.0)	0.06
at 48 h	12.3 (2.9)	9.9 (2.8)	11.9 (3.0)	10.5 (2.7)	0.01
Abrupt diuresis, *n* (%)	35 (71.4)	72 (66.7)	31 (73.8)	30 (71.4)	0.81
u[Na] + u[K] level during abrupt diuresis, *n* (%), mEq/L					
<50	20 (40.8)	36 (33.3)	18 (42.9)	17 (40.5)	0.83
50–100	9 (18.4)	16 (14.8)	8 (19.0)	4 (9.5)	0.35
>100	6 (12.2)	20 (18.5)	5 (11.9)	9 (21.4)	0.38
Length of hospital stay, mean (SD)	24.7 (25.4)	37.6 (40.5)	24.3 (26.7)	38.7 (48.3)	0.03
ODS, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	N/A
In-hospital mortality, *n* (%)	3 (6.1)	6 (5.6)	3 (7.1)	1 (2.4)	0.31

All data are expressed as the mean value (SD) for continuous variables or *n* (percentage) for categorical variables.
Rapid bolus + predictive correction indicates the predictive correction following rapid bolus of hypertonic saline group. Predictive correction indicates the predictive correction monotherapy group.

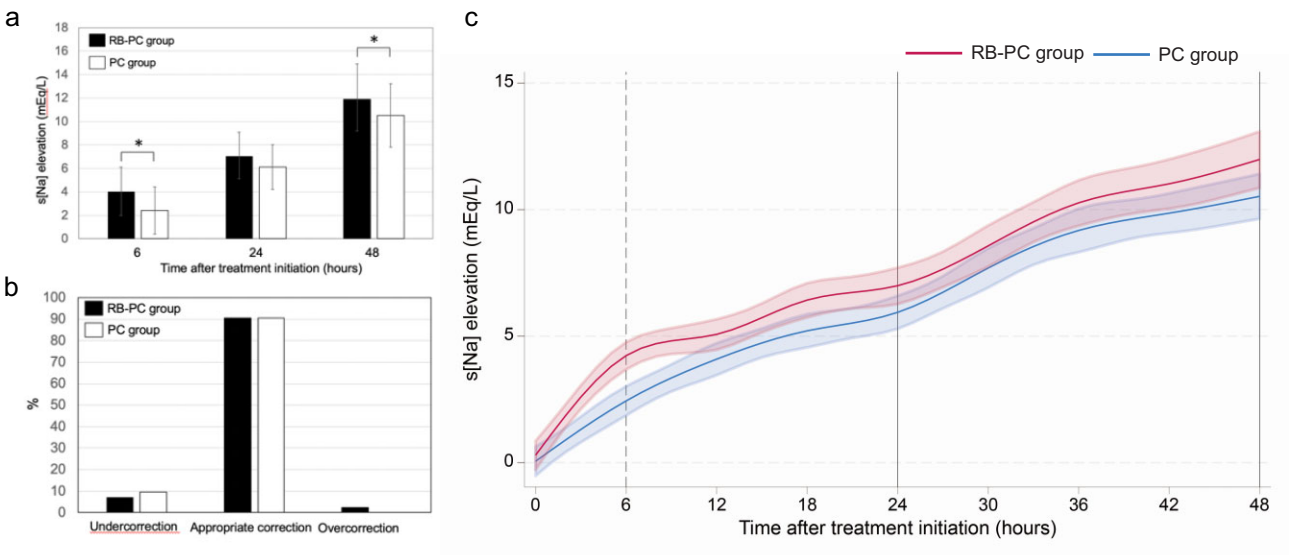


Figure 2: Comparison of treatment effects between the RB-PC and PC groups in the propensity score-matched pairs. **(a)** Changes of s[Na] at 6, 24, and 48 h after treatment initiation. Data are expressed as means and standard deviations. Asterisks indicate *P*-values <0.05. **(b)** Percentages of undercorrection, appropriate correction, and overcorrection. **(c)** Restricted cubic spline models for depicting s[Na] changes over time after treatment initiation. Shaded bands indicate the 95% confidence interval.

Table 3: Results of logistic regression analysis for the elevation of s[Na] at 6 h after treatment initiation and multiple linear regression analysis for achievement of the appropriate correction in patients with s[Na] concentration ≤120 mEq/L.

	Elevation of s[Na] at 6 h after treatment initiation (mEq/L)			
	B	95% CI for *B* (lower, upper)	*P* value	*β*
Rapid bolus + predictive correction	1.68	(0.86, 2.50)	<0.001	0.33
	Achievement of appropriate correction			
	Odds ratio	95% CI for odds ratio (lower, upper)	*P* value	
Rapid bolus + predictive correction	1.20	(0.39, 3.74)	0.58	

Rapid bolus + predictive correction indicates the predictive correction following rapid bolus of hypertonic saline group.
CI, confidence interval.

may also contribute to the appropriate correction in the RB-PC group [28, 29], given the diverse variations in urinary properties during the development of abrupt diuresis, we speculate that the PC method, when applied following RB therapy, is effective in tuning s[Na] for the appropriate range without overcorrection.

In the PSM pairs, we noted undercorrection rates of 7.1% and 9.5% in patients who received RB-PC and PC, respectively. These rates are assumed to be lower than those reported in prior studies, where undercorrection in patients with hyponatraemia was estimated to be ∼20%–30% [30, 31]. Although undercorrection is reportedly linked to increased mortality and more extended hospital stays [8, 32], it has been infrequently evaluated as an outcome of treating profound hyponatraemia in prior studies. Our treatment strategy, utilizing PC, can potentially reduce the incidence of undercorrection in patients with hyponatraemia. Further validation in a larger-scale study is warranted to assess whether decreasing undercorrection through RB-PC contributes to the rapid reduction of symptoms due to hyponatraemia and shortening of hospitalization durations.

Our study has some limitations. First, although we used the PSM method to balance the major confounders, we could not remove all the potential confounders affecting the results due to the study's retrospective nature. Second, this was a single-centre study with a small sample size. Therefore, caution should be exercised when generalizing the results to other geographic regions or patients in the community. Third, we only included patients with profound hyponatraemia treated by kidney specialists with RB-PC and PC therapies; thus, the results may not be generalizable to patients managed by kidney specialists with no PC and all patients managed by non-kidney specialists. Patients managed by kidney specialists with no PC and patients managed by non-kidney specialists had higher CCI scores and lower rates of severe hyponatraemia symptoms. Additionally, the rate of appropriate correction in those groups was lower than in the RB-PC and PC groups. This implies that physicians might have prioritized other severe illnesses over hyponatraemia or that intense treatment for hyponatraemia was not pursued due to the severity of underlying conditions in both groups. On the other hand, patients managed by kidney specialists with RB-PC and PC had higher severity of hyponatraemia and lower CCI scores. This might enable kidney specialists to focus on treating hyponatraemia rather than other underlying illnesses, which may have resulted in better outcomes for correcting hyponatraemia. However, our study does not statistically establish a causal relationship between patient backgrounds, treatment approaches, and prognoses in each group, which will be the focus of future research. Fourth, although applying the predictive equation has its merits in managing hyponatraemia, some studies have indicated that predictive formulas derived from Edelman's equation might not accurately forecast s[Na] changes in hospitalized patients with hyponatraemia over 12–24 h [33]. Moreover, subsequent *post hoc* analysis of data from the original Edelman's study has shown that coefficients in Edelman's equation are significantly affected by patient-specific factors, such as weight, oedema, and plasma sodium levels, suggesting variable tissue sodium accumulation capacities [34]. Thus, diligent monitoring of s[Na], u[Na], u[K], and urine output may remain essential in treating profound hyponatraemia. Fifth, although we excluded patients with serum glucose levels >400 mg/dL on admission and confirmed the comparable blood glucose value at baseline between the two groups, we did not correct plasma sodium concentration for glucose values due to the lack of blood glucose tests for each s[Na] measurement during the treatment course. Finally, although the final choice of treatment was at the discretion of each physician, users of RB-PC therapy may be better prepared to treat patients with hyponatraemia because they measured u[Na] more frequently.

In conclusion, we highlighted the effectiveness of rapid bolus administration of hypertonic saline, followed by predictive correction using an infusate and fluid loss formula identical to the Barsoum–Levine formula based on the Edelman equation in quickly elevating s[Na] levels and achieving appropriate correction in patients with profound hyponatraemia. The optimal therapeutic range for treating profound hyponatraemia remains a subject of debate [32, 35, 36]. However, applying RB-PC may offer flexibility in adhering to any treatment recommendation and enable precise adjustment of s[Na] to fall within the desired ranges. Future research with this treatment protocol should include prospective, large-scale clinical studies to validate its role in the critical outcomes, such as swiftly alleviating symptoms, improving activities of daily living, and reducing hospital stay by elevating s[Na].

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

K.N. and T.W. designed the protocol and collected the data. K.N., T.I., Y.F., and T.W. analysed and interpreted the patient data. K.N. and T.W. wrote the original draft. W.Y.K., N.T., H.S., and Y.F. supervised this study. K.N., T.I., A.Y., Y.H., M.K., Yun.K., Yuk.K., Yo.K., F.N.N., K.I., Y.I., H.I., M.Y., Y.M., and T.W. reviewed and edited the manuscript. All authors read and approved the manuscript.

DATA AVAILABILITY STATEMENT

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, we did not use AI and AI-assisted technologies.

CONFLICT OF INTEREST STATEMENT

None declared.

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