Hypertonic saline use in severe hyponatraemia

RESEARCH

Hypertonic saline for severe symptomatic hyponatraemia: real-world findings from the UK

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Abstract

Objective: To evaluate ‘real-world’ safety and efficacy of the European Society of Endocrinology guidelines for the treatment of severe symptomatic hyponatraemia using hypertonic saline (HTS).

Design: Retrospective, observational, cohort study, examining the use of HTS for severe symptomatic hyponatraemia at Sheffield Teaching Hospitals between 2017 and 2020.

Methods: Patients were identified from pharmacy records and demographic, clinical, and treatment data extracted.

Results: Out of 112 patients (females:males = 61:51), the mean age ± s.d. was 66.3± 16.0 years and mean pre-treatment serum sodium ± s.d. was 113.8 ± 6.4 mmol/L. Overall, overcorrection rates at 24 and 48 h (>10 and >18 mmol/L) were 44.9 and 19.6%, respectively, while 19.6% of patients were treated for overcorrection. Above-target rise in sodium (>5 mmol/L) after first and second boluses was noted in 22.6 and 34.6% of patients, respectively. In-hospital and 12-month mortality was 7.1 and 18.7%, respectively, with no cases of osmotic demyelination. The mean venous blood gas (VBG) sodium was 1.9 mmol/L lower than paired serum sodium (n = 36) (113.6 ± 6.6 vs 115.7 ± 7.8 mmol/L).

Conclusion: We report real-world data demonstrating that a significant number of patients overcorrected using current guidelines. Also, several patients had above-target rise in sodium after one bolus of HTS, and sodium measurement should be considered before the second bolus unless ongoing severe symptoms persist. A point of care VBG sodium concentration was useful for this purpose. In addition to careful monitoring, a cautious but anticipatory overcorrection prevention strategy should be considered in the first 24 h.

Introduction

Hyponatraemia (serum sodium concentration <135 mmol/L) is the most frequently encountered electrolyte abnormality in clinical practice, occurring in up to one-third of all hospitalised patients (1). While hyponatraemia is driven by multiple causes, several studies have consistently demonstrated an association between hyponatraemia and adverse patient outcomes irrespective of the aetiology (2, 3, 4).

Clinical manifestations of hyponatraemia are on a clinical spectrum, ranging from being asymptomatic to seizures (5). Symptoms of hyponatraemia are typically more striking when the fall of serum sodium is acute (over hours) or is large (5, 6). Awareness of the chronicity of change can be essential. Rapid correction of serum sodium is required when hyponatraemia causes severe symptoms as the latter can indicate cerebral oedema. Here, expeditious treatment
is required to prevent progression to cerebral herniation and death (7, 8). This has to be balanced against the risk of overcorrection which increases the possibility of osmotic demyelination syndrome (ODS). This highlights the importance of rapid yet controlled correction of sodium to mitigate the deleterious effects of overcorrection on the CNS (1).

Hypertonic saline (HTS) has been used in marathon runners who develop acute exercise-associated hyponatraemia (9, 10, 11). It is also an effective treatment for severe symptomatic hyponatraemia of any other aetiology (12). Several clinical treatment guidelines published in the last few years have aimed to standardise the administration of HTS in severe symptomatic hyponatraemia (1, 13, 14, 15). A common aim of these guidelines has been to achieve a quicker (or rapid) initial rise in sodium and the need to monitor and avoid overcorrection is also emphasised. Most recommend the use of small, frequent boluses of HTS to achieve the desired quicker rise in sodium as opposed to the more steady rise in sodium seen with continuous infusion of HTS (16). The evidence for a dose-response relationship underpinning these guidelines is, however, limited. Recently, an observational study from Germany compared the use of conventional treatment with HTS in severe and moderately symptomatic hyponatraemia (n = 62 total; n = 36 HTS and n = 26 conventional) (17). They found that with 150 mL boluses of 3% HTS, the rate of overcorrection at 24 h in severely symptomatic hyponatraemia was as high as 38%. Another single-centre, retrospective study, examined the use of 150 mL aliquots of 3% HTS for the treatment of acute decompensated heart failure and measured serum sodium levels as a safety parameter (18). In 40 patients with diuretic-resistant heart failure, 3% HTS use resulted in a median serum sodium rise of 2 mmol/L at 24 h with no reported adverse neurological outcomes.

The European Society of Endocrinology (ESE) published guidelines for the management of hyponatraemia (2014), and these are now in routine clinical use (1). For the first-hour management of severe symptomatic hyponatraemia, ESE guidelines recommend an intravenous infusion of two boluses of 150 mL 3% HTS with an aim to raise serum sodium concentration by 5 mmol/L. These guidelines also recommend checking the serum sodium in between the first two boluses, however, not waiting for this result before administering the second bolus. As acknowledged by the authors, the evidence base for these recommendations is limited to case reports and series, and to small observational studies with fewer than 100 participants (1). The ESE guidelines were adopted at Sheffield Teaching Hospitals in 2017 to harmonise the use of HTS for the treatment of severe symptomatic hyponatraemia. The aim of this study was to evaluate the safety and efficacy of the ESE guidelines in a ‘real-world’ setting.

Materials and methods

We conducted a retrospective, observational, cohort study that examined the use of HTS for severe symptomatic hyponatraemia at Sheffield Teaching Hospitals (Northern General Hospital & Royal Hallamshire Hospital) United Kingdom between January 2017 and March 2020. The study was registered with Sheffield Teaching Hospitals Clinical Effectiveness Unit (reference number 9757) as a service improvement project. Thus, all data collected as part of this observational study reflect routine clinical care, and ethical approval was not required.

Patients who were issued with a prescription for HTS were identified using centralised pharmacy electronic records (JAC Medicines Management version 2016). Inclusion criteria were age of 18 years or more and evidence of at least one bolus of HTS for hyponatraemia. This was confirmed by a review of the electronic and/or paper notes and biochemical results.

Exclusion criteria were administration of HTS for reasons other than hyponatraemia and lack of clear documentation to confirm HTS administration. For those who met the inclusion criteria, demographic, clinical and laboratory data were extracted from electronic and paper case notes. This was recorded in a password-protected Excel spreadsheet and stored securely on a Trust computer in line with national governance protocols. Data extraction was performed by one team of investigators using a standard operating procedure with quality checks to minimise missing data and ensure accuracy.

A history of alcohol excess was defined as a documented diagnosis of active or past alcohol excess. Being underweight was defined as having a BMI of <18.0 kg/m². Sodium levels were considered to be post-HTS only if blood was drawn within one hour of the initiation of the bolus. Serum sodium concentrations were analysed using a fully automated system (Cobas® system, Roche Diagnostics). The intermediate precision coefficients of variation (CV) for this system at mean sodium concentrations of 88.7, 120.6, and 175.8 mmol/L were 1.1, 0.7, and 0.6%, respectively. Heparinised venous blood gas (VBG) sodium concentrations were analysed on point of care test machines (Siemens RAPIDPoint®500 Blood Gas Analyser). The intermediate precision CV at a mean
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sodium concentration of 114 mmol/L was 0.3% and at 153 mmol/L it was 0.6%.

Overcorrection at 24 and 48 h was defined as a rise in serum sodium levels of >10 and >18 mmol/L respectively, as defined in the ESE guidelines (1). An above-target rise after first and second HTS boluses was defined as an increase in serum sodium of >5 mmol/L from baseline. The primary outcome was to establish the incidence of overcorrection rates at 24- and 48-h post-HTS. Early time points were the rate of above-target rise in sodium after the first and second HTS boluses. Secondary outcomes were incidence of ODS and early (same admission) and late all-cause mortality at 12 months follow-up. This was performed by a review of death certificates. While more stringent cut-offs for overcorrection may be used by clinicians when treating those at particularly high risk of ODS for example in individuals underweight or those consuming excess alcohol, these cut-offs were not analysed in this study. This was because ESE guidelines do not make a distinction in overcorrection cut-offs for these groups and our aim was to evaluate the guidelines in the real world. ODS was defined as new neurological findings on clinical examination confirmed by MRI post-HTS in-hospital or within 12 months follow-up. We also conducted further analyses to determine if there was a relationship between admission demographic (age and sex), anthropometric, and clinical variables with the risk of sodium overcorrection post-HTS.

The ESE guidelines recommend the use of HTS for both severe symptoms (vomiting, cardiorespiratory distress, seizures, Glasgow coma scale ≤8, and deep somnolence) and moderately severe symptoms (nausea, confusion, and headache). However, as a matter of policy, our local guidelines recommend HTS only for severely symptomatic patients as defined in the ESE guidelines as non-specific symptoms such as nausea, chronic confusion, and headache are extremely common and likely to be benign when hyponatraemia develops insidiously (19). Also, our local guidelines recommend using 2.7% saline infusion bottles (Fresenius Kabi Ltd, Runcorn, UK) as the 3% preparation is unavailable locally. However, to keep the sodium chloride dose equivalent to the ESE guidelines (77 mEq), the infusion volume for each bolus was increased to 170 mL providing 78 mEq sodium chloride.

Continuous variables are represented as mean and s.d. while categorical variables are represented by the number of cases (n) and a percentage (%) of the total. Categorical variables were analysed using the chi-squared ($\chi^2$) test. Possible predictive variables for sodium overcorrection post first HTS bolus were explored using bivariate regression analysis incorporating the following at admission variables: age, sex, BMI, pre-treatment baseline serum sodium, history of alcohol excess, and being underweight. Analyses were conducted in SPSS version 26 and in all analyses, a $P$-value of <0.05 was considered statistically significant.

Results

The total number of patients identified was 134. Of these, 4 patients had a duplicate entry, 17 patients were identified as having been issued HTS from the pharmacy, however, this was not administered later on clinical grounds, and one patient’s notes could not be located to confirm inclusion/exclusion criteria. Thus, a total of 112 patients met the inclusion criteria and were included in the final analysis (Fig. 1).

Baseline characteristics

The mean age was 66.3 ± 16.0 years with a mean BMI of 24.8 ± 5.6 kg/m$^2$. Mean sodium at baseline was 113.8 ± 6.4 mmol/L and on average, there were 3.7 ± 1.8 serum sodium measurements after administration of any number of HTS boluses in the first 24 h. The most common cause of hyponatraemia in our cohort was syndrome of inappropriate antidiuresis (SIAD), either in combination with offending drugs (32.1%) or alone (26.8%). Other commonly reported aetiologies were hypovolaemia (20.5%), drug-induced only (8.9%), and others (1.8%). Histories of alcohol excess or being underweight were noted in 29.5 and 8.0%, respectively. The most common symptom was acute confusion (49.1%), while a significant proportion of patients presented with signs of severe hyponatraemia including seizures or vomiting (24.1% each). The decision to administer HTS was solely based on the biochemical severity of hyponatraemia in 17.9% of our cohort, not in line with hospital guidelines. In these patients, the mean baseline sodium was comparable to the overall cohort (113.3 ± 6.5 mmol/L vs 113.8 ± 6.4 mmol/L), however, in most of these cases, sodium levels were on a downward trajectory despite the initiation of aetiology-specific treatment. They did not have severe symptoms per se but their onset was anticipated given the sodium trajectory, so treatment with HTS was commenced based on clinical judgement.

Table 1 summarises baseline characteristics for the study population. The majority of patients had either one (37.5%) or two (38.4%) boluses of HTS, but, 24.1% received ≥3 boluses. HTS was administered most frequently...
in a general ward (67%), followed by the accident and emergency department (20.5%), and intensive/high dependency care units (12.5%). Re-lowering treatments for sodium overcorrection were used in 19.6% ($n = 22$) of the total cohort (i.e. dextrose = 17, desmopressin = 2, both = 3). These were mostly provided outside of general wards, especially desmopressin which was given exclusively in high dependency/intensive care units. Details of the patients who received dextrose infusion and/or desmopressin are summarised in Supplementary Table 1 (see section on supplementary materials given at the end of this article). HTS administration, except within high dependency areas, was only via peripheral intravenous cannulae with no reported major extravasation injury.

**Sodium overcorrection**

The number of patients who had overcorrection at 24 and 48 h was 48/107 (44.9%) and 22/97 (19.6%), respectively with mean increases in sodium of $10.0 \pm 5.5$ at 24 h and $13.4 \pm 7.0$ mmol/L at 48 h (Fig. 2). Data were available for 53 patients who had serum sodium checked within 1 h of starting the first bolus of HTS infusion; of these, 12 patients (22.6%) had a rise of >5 mmol/L from the pre-treatment baseline. For the second bolus, data were available for 26 patients who had serum sodium checked within 1 h of starting the second bolus of HTS; of these nine patients (34.6%) had above-target rise (Fig. 3). Likewise, 5/12 patients (41.7%) breached the 5 mmol/L threshold after the third bolus with a mean sodium increase of $5.17 \pm 2.25$ mmol/L. We further analysed the relative contribution of those overshooting the desired initial 5 mmol/L target after first and second boluses to those who overcorrected at 24 and 48 h. Our analyses showed that overshooting after first and second boluses was associated with overcorrection at 24 hours ($P = 0.024$ and 0.009, respectively), but not at 48 h ($P = 0.264$ and 0.066, respectively).

Table 2 compares the characteristics of patients that achieved target at 24 h that is, responders ($n = 44$) with non-responders ($n = 15$) and those who overcorrected ($n = 48$). Our analyses were unable to delineate any significant demographic or biochemical characteristics at baseline that distinguish non-responders from responders. None of the non-responders had a reduced consciousness at baseline compared to 25% of those who did respond to HTS ($P = 0.028$). Numbers in the non-responder sub-group were low ($n = 15$) limiting statistical power to robustly explore sub-group differences. On the other hand, patients who overcorrected had a significantly shorter hospital length of stay compared to responders (11.4 days vs 18.4 days; $P = 0.022$). We speculate this was on account of a more rapid resolution of hyponatraemia facilitating earlier discharge in those who overcorrected. Overcorrectors had a more severe clinical phenotype on admission with a greater proportion presenting with seizures (overcorrector seizures 37.5% vs responder seizures 15.9%; $P = 0.020$) despite comparable baseline sodium (mean overcorrector Na$^+$ at baseline 112.3 vs responder Na$^+$ at baseline 113.7; $P = 0.381$). Further, those with overcorrection were more

**Figure 1**

Flow diagram listing the total number of patients identified from pharmacy records and all exclusions to arrive at the final number of patients in the analysis (created with BioRender. com).
Table 1  Baseline clinical characteristics of 112 patients treated for severe symptomatic hyponatraemia using HTS.

| Characteristic                                      | Mean ± s.d.           | n  |
|-----------------------------------------------------|-----------------------|----|
| Mean age ± s.d. (years)                             | 66.38 ± 16.04         | 112|
| Weight ± s.d. (kg)                                  | 68.88 ± 16.30         | 105|
| Height ± s.d. (m²)                                  | 1.67 ± 0.09           | 102|
| BMI ± s.d. (kg/m²)                                  | 24.80 ± 5.62          | 102|
| Sex                                                 |                       |    |
| Females                                             | 61; males =51         |    |
| Mean Na⁺ at baseline ± s.d. (mmol/L)                | 113.82 ± 6.41         | 112|
| Mean number of Na⁺ readings in first 24 h after infusion ± s.d. | 3.71 ± 1.84 | 112|
| Aetiology                                           |                       |    |
| SIAD                                                | 30 (26.8%)            |    |
| SIAD and drug-induced                               | 36 (32.1%)            |    |
| Hypovolemia                                         | 12 (10.7%)            |    |
| Hypovolemia and drug-induced                        | 11 (9.8%)             |    |
| Drug-induced only                                   | 10 (8.9%)             |    |
| Hypervolemia                                        | 6 (5.4%)              |    |
| Others                                              | 2 (1.8%)              |    |
| Unknown                                             | 5 (4.5%)              |    |
| Symptoms                                            |                       |    |
| Acute confusion (%)                                 | 55 (49.1%)            | 112|
| Seizures (%)                                        | 27 (24.1%)            | 112|
| Reduced consciousness (%)                           | 26 (23.2%)            | 112|
| Vomiting (%)                                        | 27 (24.1%)            | 112|
| Biochemical severity of hyponatraemia only (%)      | 20 (17.9%)            | 112|
| Location                                            |                       |    |
| Ward (%)                                            | 72 (67%)              | 112|
| High dependency or intensive care units (%)         | 14 (12.5%)            | 112|
| A&E (%)                                             | 23 (20.5%)            | 112|
| Number of boluses                                   |                       |    |
| 1 (%)                                               | 42 (37.5%)            | 112|
| 2 (%)                                               | 43 (38.4%)            | 112|
| 3 or more (%)                                       | 27 (24.1%)            | 112|
| History of alcohol excess (%)                       | 33 (29.5%)            | 112|
| Underweight (%)                                     | 9 (8.0%)              | 112|
| Length of stay (days)                               | 15.7 ± 14.7           | 112|
| Overcorrection treatment                            |                       |    |
| Use of desmopressin (%)                             | 5 (4.5%)              | 112|
| Use of dextrose (%)                                 | 20 (17.9%)            | 112|
| Investigations                                      |                       |    |
| Serum osmolality (%)                                | 110 (98.2%)           | 112|
| Urine osmolality and Na (%)                         | 103 (92%)             | 112|
| Cortisol (%)                                        | 97 (86.6%)            | 112|
| TSH (%)                                             | 103 (92%)             | 112|
| Aetiology-specific treatment (%)                    | 110 (98.2%)           | 112|
| Type of specific treatment                          |                       |    |
| Fluid restriction (%)                                | 75 (67.0%)            | 112|
| Intravenous normal saline (%)                       | 38 (33.9%)            | 112|
| Hold-offending drugs (%)                            | 57 (50.9%)            | 112|
| Tolvaptan (%)                                       | 1 (0.9%)              | 112|
| Demeclocycline (%)                                  | 4 (3.6%)              | 112|
| Slow sodium tablets (%)                             | 12 (10.7%)            | 112|
| Specialist endocrine opinion (%)                    | 92 (82.1%)            | 112|
| Type of hypertonic saline                           |                       |    |
| 2.7% (%)                                            | 109 (97.3%)           | 112|
| 1.8% (%)                                            | 3 (2.7%)              | 112|

A&E, Accident and Emergency department; BMI, body mass index; SIAD, syndrome of inappropriate antidiuresis; TSH, thyroid-stimulating hormone.
likely to need treatment with desmopressin or dextrose and were more likely to require a specialist endocrine opinion.

Mortality and osmotic demyelination syndrome

In-hospital mortality in this cohort was 7.1% (n = 8). Causes of death as reported on the death certificates were as follows: pneumonia/chest infection n = 3, congestive cardiac failure n = 2, cancer n = 2, and pulmonary hypertension due to congenital heart disease n = 1. The patients who died during the same admission were older than the cohort average (mean age 69.9 years vs 66.3 years) and had several co-morbidities. Mean baseline serum sodium in these patients was higher than the cohort average (116.7 mmol/L vs 113.8 mmol/L) and rates of overcorrection at 24 h were lower (14.3% vs 44.9% for the whole cohort). Total mortality (death due to any cause) at 12 months was 18.7% (n = 21). No case of ODS was reported during the in-hospital stay or at 12 months follow-up.

Admission factors associated with sodium overshooting post first HTS bolus

As a significant number of patients (22.6%) were noted to have exceeded the 5 mmol/L target cut-off, an exploratory bivariate regression analysis including age, sex, BMI, pre-treatment baseline serum sodium, history of alcohol excess, and being underweight was performed to potentially identify those at higher risk of overshooting (Table 3). While younger age appeared to be linked with an above-target rise in the univariate analysis, a multivariate analysis was unable to statistically stratify a high-risk group.
Table 2  Characteristics of responders vs overcorrectors and non-responders at 24 h. (responders = achieving sodium rise between 5 and 10 mmol/L at 24 h, overcorrectors= achieving sodium rise >10 mmol/L at 24 h, and non-responder= achieving sodium rise <5 mmol/L at 24 h).

|                          | Responders (n = 44) (A) | Overcorrectors (n = 48) (B) | P value (A and B) | Non-responders n=15 (C) | P value (A and C) |
|--------------------------|-------------------------|----------------------------|-------------------|--------------------------|------------------|
| Mean age ± s.d. (years)  | 72.23 ± 15.24           | 60.17 ± 13.47              | 0.237             | 70.02 ± 16.64           | 0.637            |
| Weight ± s.d. (kg)       | 71.28 ± 15.64           | 67.23 ± 17.72              | 0.179             | 67.34 ± 15.36           | 0.414            |
| Height ± s.d. (m²)       | 1.66 ± 0.08             | 1.68 ± 0.10                | 0.090             | 1.66 ± 0.10             | 0.415            |
| BMI ± s.d. (kg/m²)       | 26.17 ± 5.62            | 23.79 ± 5.58               | 0.741             | 24.45 ± 6.03            | 0.336            |
| Sex                      | Females= 26             | Females= 24                | 0.382             | Females= 9              | 0.951            |
|                          | Males= 18               | Males= 24                  |                   | Males= 6                |                   |
| Mean Na⁺ at baseline ± s.d. (mmol/L) | 113.7 ± 5.82 | 112.31 ± 6.37              | 0.381             | 116.27 ± 5.63           | 0.143            |
| Mean number of Na⁺ readings in first 24 h after infusion ± s.d. | 3.68 ± 1.57 | 3.94 ± 1.77                | 0.918             | 3.53 ± 2.56             | 0.790            |
| Aetiology                |                         |                            |                   |                          |                   |
| SIAD                     | 14 (31.8%)              | 12 (25%)                   | 0.206             | 4 (26.7%)               | 0.384            |
| SIAD and drug-induced    | 16 (36.4%)              | 13 (27.1%)                 | 0.020             | 7 (46.7%)               | 0.161            |
| Hypovolemia              | 3 (6.8%)                | 5 (10.4%)                  | 0.090             | 2 (13.3%)               | 0.161            |
| Hypovolemia and drug-induced | 5 (11.4%)       | 6 (12.5%)                  | 0.090             | 0 (0%)                  | 0.028            |
| Drug-induced only        | 2 (4.5%)                | 6 (12.5%)                  | 0.090             | 0 (0%)                  | 0.028            |
| Hypervolemia             | 4 (9.1%)                | 1 (2.1%)                   | 0.090             | 1 (6.7%)                | 0.028            |
| Others                   | 0 (0%)                  | 2 (4.2%)                   | 0.090             | 0 (0%)                  | 0.028            |
| Unknown                  | 0 (0%)                  | 3 (6.3%)                   | 0.090             | 1 (6.7%)                | 0.028            |
| Length of stay (days)    | 18.4 ± 15.4             | 11.4 ± 9.1                 | 0.022             | 21.53 ± 19.95           | 0.527            |
| Symptoms                 |                         |                            |                   |                          |                   |
| Acute confusion (%)      | 22 (50%)                | 24 (50%)                   | 1.000             | 6 (40%)                 | 0.203            |
| Seizures (%)             | 7 (15.9%)               | 18 (37.5%)                 | 0.020             | 1 (6.7%)                | 0.161            |
| Reduced consciousness (%)| 11 (25%)                | 13 (27.1%)                 | 0.820             | 0 (0%)                  | 0.028            |
| Vomiting (%)             | 11 (25%)                | 10 (20.8%)                 | 0.634             | 5 (33%)                 | 0.168            |
| Biochemical severity of hyponatraemia only (%) | 10 (22.7%) | 8 (16.7%)                  | 0.464             | 2 (13.3%)               | 0.180            |
| Location                 |                         |                            |                   |                          |                   |
| Ward (%)                 | 29 (65.9%)              | 28 (58.4%)                 | 0.426             | 14 (93.3%)              | 0.136            |
| High dependency or intensive care units (%) | 4 (9.1%) | 10 (20.8%)               | 0.090             | 0 (0%)                  | 0.028            |
| A&E (%)                  | 11 (25%)                | 10 (20.8%)                 | 1.000             | 1 (6.7%)                | 0.161            |
| Number of boluses        |                         |                            |                   |                          |                   |
| 1 (%)                    | 12 (27.3%)              | 21 (43.8%)                 | 0.461             | 5 (33.3%)               | 0.518            |
| 2 (%)                    | 20 (45.5%)              | 18 (37.5%)                 | 0.461             | 5 (33.3%)               | 0.518            |
| 3 or more (%)            | 12 (31.9%)              | 9 (18.8%)                  | 0.461             | 5 (33.3%)               | 0.518            |
| History of alcohol excess (%) | 10 (22.7%) | 18 (37.5%) | 0.461 | 3 (20%) | 0.826 |
| Underweight (%)          | 2 (4.5%)                | 5 (10.4%)                  | 0.289             | 2 (13.3%)               | 0.242            |
| Overcorrection treatment |                         |                            |                   |                          |                   |
| Use of desmopressin (%)  | 0 (0%)                  | 5 (10.4%)                  | 0.028             | 0 (0%)                  | N/A              |
| Use of dextrose (%)      | 5 (11.4%)               | 15 (31.3%)                 | 0.021             | 0 (0%)                  | 0.172            |
| Specialist endocrine opinion (%) | 34 (77.3%) | 45 (93.8%) | 0.023 | 11 (73.3%) | 0.757 |
| Death during same admission | 2 (4.5%) | 1 (2.1%) | 0.507 | 3 (20%) | 0.063 |
| 12-month mortality       | 8 (18.2%)               | 8 (16.7%)                  | 0.848             | 3 (20%)                 | 0.876            |

A&E, accident and emergency department; SIAD, syndrome of inappropriate antidiuresis; TSH, thyroid-stimulating hormone.
Bold indicates statistical significance, \( P < 0.05 \).

Comparison of post-HTS laboratory serum sodium with VBG sodium

We assessed point of care VBG sodium concentrations vs formal laboratory serum sodium concentrations to determine whether VBG sodium can be reliably used to guide further HTS boluses in severe symptomatic hyponatraemia. We compared all available (\( n = 36 \)) simultaneous VBG and serum sodium data post-HTS bolus. We found that mean sodium in VBG samples was, on average, 1.9 mmol/L lower than for serum (VBG sodium 113.6 ± 6.6 vs serum sodium 115.7 ± 7.8 mmol/L).
### Table 3  Impact of admission variables on overshooting after first HTS bolus (>5 mmol/L) by univariate and multivariate logistic regression analyses.

| Parameters                        | Univariate |           | Multivariate |           |
|-----------------------------------|------------|-----------|--------------|-----------|
|                                   | OR (95% CI)| P value   | OR (95% CI)  | P value   |
| Age                               | 0.95 (0.90–0.99) | 0.02       | 0.98 (0.91–1.06) | 0.68 |
| BMI                               | 0.88 (0.74–1.06) | 0.19       | 0.70 (0.41–1.11) | 0.13 |
| Female sex                        | 0.29 (0.07–1.12) | 0.07       | 0.67 (0.12–3.85) | 0.66 |
| History of alcohol excess         | 0.51 (0.13–1.96) | 0.33       | 0.43 (0.07–2.63) | 0.36 |
| Underweight                       | 0.87 (0.08–9.20) | 0.91       | 4.03 (0.077–213.84) | 0.49 |
| Baseline Na*                      | 1.06 (0.95–1.18) | 0.31       | 1.20 (1.00–1.44) | 0.06 |

OR, odds ratio.

### Discussion

In this largest real-world study to date, we aimed to evaluate the safety, response to treatment, and clinical outcomes in 112 patients treated with HTS for severe symptomatic hyponatraemia as recommended by ESE guidelines. We have shown that the use of these guidelines in a busy tertiary hospital resulted in significant overcorrection at 24 and 48 h, despite adequate monitoring. While the majority of patients in this study were administered HTS on a general ward compared to higher-level care areas, it must be noted that overcorrection rates were not lower among those in intensive/high-dependency care units. The study results demonstrate that the administration of one bolus of HTS can raise serum sodium by more than 5 mmol/L in more than one in five patients. Thus, in adopting ESE guidelines, a significant proportion of patients would receive a second bolus despite achieving the initially intended improvement in sodium level. We were not able to identify patient-specific risk factors for overshooting after the first bolus of HTS. Our findings support recently published observational data from Germany where 150 ml 3% HTS boluses were used for the treatment of symptomatic hyponatraemia (17). Here, key findings were that patients treated with even a single bolus of HTS were susceptible to overcorrection, HTS use resulting in overcorrection rates between 28 and 38% at 24 h. They also report higher overcorrection in those with severe symptoms, but there were no reported cases of ODS. We have extended their findings in a larger cohort (n = 112 in our study vs n = 36), demonstrating safety more robustly by means of a longer follow-up period. Additionally, we detailed causes of in-hospital mortality using death certificate data and have included practically useful data by comparing VBG sodium to serum sodium when using HTS.

There is a dearth of prospective studies evaluating the safety and efficacy of HTS for the treatment of severe symptomatic hyponatraemia. Only two such studies comparing the use of bolus vs continuous infusion of HTS were identified. The largest of these, a multi-centre, randomised trial, was an open-label study recently published from South Korea (n = 178). In this Efficacy and Safety of Rapid Intermittent Correction Compared With Slow Continuous Correction With Hypertonic Saline in Patients With Moderately Severe or Severe Symptomatic Hyponatremia (SALSA) trial (20, 21), investigators reported a similar rate of overcorrection in both groups (17.2% rapid intermittent bolus vs 24.2% slow continuous infusion). However, in this study, the overcorrection at 24 h was defined as a rise in sodium of >12 mmol/L. The overcorrection rates in the SALSA trial were lower than our cohort despite the study regimen being more aggressive than recommended in ESE guidelines for which there are several possible explanations. First, in addition to a more relaxed cut-off at 24 h, aggressive use of overcorrection treatments (41% for bolus and 52% for continuous infusion vs 19.6% in our cohort) and a strict clinical trial protocol-driven approach compared to our real-world data may explain the difference in overcorrection rates. Secondly, compared to SALSA, our cohort had factors associated with more overcorrection including lower baseline sodium (mean 113.8 mmol/L vs 118 mmol/L), a higher burden of severe symptoms (27 patients with seizures vs 2 with seizures), and a higher proportion with a history of alcohol excess (33 vs 5). The second prospective study (n = 50) evaluated 100 ml 3% HTS bolus administration vs continuous HTS infusion in the treatment of symptomatic hyponatraemia due to SIAD (16). The reported rates of overcorrection are again lower compared to our study for similar reasons (overcorrection cut-off >12 mmol/L, more overcorrection treatment, higher sodium nadir, and fewer patients with alcohol excess) (16). However, in keeping with our data, there were no reported clinical cases of ODS in either of these studies. One explanation for this may be the use of overcorrection treatments (dextrose infusion or desmopressin) in overcorrectors who would have otherwise
developed ODS. However, in the absence of rigorous daily neurological examinations and formal MRI imaging of all patients with biochemical evidence of overcorrection post-HTS, some cases where there was subtle neurology or subclinical radiographic changes may have been missed in these studies and our cohort (19).

Despite adequate monitoring of sodium in our cohort (on average 3.7 readings in the first 24 h after initiation of treatment), there was a high rate of overcorrection at 24 h, especially in those treated outside high dependency areas. This, however, is manageable if a pre-emptive approach to either avoid overcorrection or to re-lowering is used. Our data suggest that once serum sodium is increased by the recommended 5 mmol/L with boluses, it is challenging to avoid exceeding the 10 mmol/L cut-off for 24 h. This is especially the case if overcorrection treatments are not employed, or where aetiology-specific treatment has also been started as was the case in 98.2% of our cohort. We postulate this is due to the attainment of a negative water balance given that fluid restriction was the single most commonly used aetiology-specific treatment, used for 67.0% of our cohort. The ESE 24-h correction target can only be realistically achieved if an anticipatory overcorrection prevention strategy is adopted. Such a strategy must incorporate a careful review of fluid balance including urine output, frequent sodium monitoring, and judicious use of re-lowering treatments. This will minimise the risk of adverse neurological events from rapid bidirectional fluxes in serum sodium.

At variance with ESE guidelines, our data indicate that an additional strategy that may prevent or slow down overcorrection, and reduce the need for re-lowering therapies would be to assess sodium concentrations immediately after the first bolus of HTS before proceeding to the second bolus unless the patient has ongoing seizures, coma or cardiorespiratory instability. This refined bolus strategy is also supported by the aforementioned data from Germany where ESE guidelines were in use (17). Other clinical guidelines including the ones published by Verbalis and colleagues from the United States (14) recommend treatment protocols for severe symptomatic hyponatraemia using HTS. It is challenging, however, to infer conclusions on overcorrection as reported in this study when using HTS as recommended by Verbalis et al. given differences in the volume of HTS boluses (100 ml. bolus of 3% HTS in American Verbalis et al guidelines vs 150 mL. bolus of 3% HTS in ESE guidelines) (1, 14). Physiologic principles governing the relationship between cerebral volume and intracranial pressure dictate that even a modest 5% increase in serum sodium concentration provides sufficient osmoses to substantially reduce intracranial pressure and herniation risk (19, 22). However, even on state-of-the-art automated biochemistry platforms, as used in our hospitals, serum sodium results are not immediately available to determine if a 5 mmol/L rise has been achieved after each bolus of HTS. VBG sodium may have utility in this scenario with results available within a few minutes at the point of clinical care. One caveat to using this method, however, is that VBG sodium appears to underestimate true serum sodium concentration and consequently osmotic ions delivered across the blood–brain barrier. In our platforms, VBG sodium concentration was on average 1.9 mmol/L lower than simultaneously-obtained serum sodium. One study from two European Hospitals compared sodium measurements ascertained via indirect (plasma/serum) vs direct (whole blood/VBG) methods in 231 participants undergoing HTS infusion (23). In agreement with our findings, sodium measured on blood gas platforms, was, on average, 1.9 mmol/L lower than serum/plasma. This phenomenon was also evident in other studies comparing arterial blood gas sodium concentrations with serum values (24, 25). One approach when using HTS would be to factor in this approximate 2 mmol/L difference between blood gas vs serum/plasma sodium concentrations. However, while this difference is within an acceptable range in absolute numerical terms, it is clinically significant in the context of HTS use (23). It is thus critical to use a consistent approach in obtaining sodium concentrations when using HTS as opposed to switching between serum/plasma and blood gas sodium. A logical approach would be to only use a quick turnaround test like VBG sodium to avoid under or over-estimation, due to differences in modalities used to quantify sodium (23).

One strength of our study is that it is the largest to comprehensively perform a real-world evaluation of the ESE guidelines and it is the first undertaken in a major UK University Hospital Trust. As well as examining outcomes over the entire length of hospital stay, we extended follow-up to 12 months post-discharge to robustly capture long-term neurological sequelae of sodium overcorrection. This study has limitations consequent to the retrospective observational design which makes it susceptible to selection bias and confounding. Our findings are, however, important for hypothesis generation and confirmation in prospective randomised clinical trials. Also, while our cohort is larger than all published observational studies (17, 24, 25, 26, 27, 28, 29) on HTS use informing the ESE guidelines, we are likely to be statistically underpowered in accurately delineating at admission patient characteristics that predict the risk of overcorrection post-HTS. Large, prospective, registry studies...
are urgently needed to develop admission risk stratification models based on robust clinical endpoints including overcorrection rates and ODS post-HTS. Further, despite a standardised approach to data extraction and meticulous review of available patient records, there was missing data at the source, specifically serum sodium data collected within the first hour after first and second boluses was available in only 53 (47%) and 26 (37%) participants, respectively. Further our findings were limited by whether symptoms resolved after one bolus of HTS and data on chronicity. In addition, a paucity of clinical assessment of volume status, urine output, and neurological symptoms and status infers a need for a bespoke educational package covering this acute emergency. Chronicity of hyponatraemia and urine output data in particular would have strengthened our analyses into identifying predictors of overcorrection post-HTS. Lastly, several in our cohort were treated solely on the basis of biochemical severity. Consequently, our group may be less representative than patients recruited in other studies, however, these patients were not excluded from the study as data on the dose–response relationship was still considered valid and insightful.

Conclusion

When applied to the real-world situation in busy large hospitals, the use of the ESE guidelines by a wide range of specialisms within medicine carries potential risk. Serum sodium level overcorrection is common. Data from our observational cohort suggest that a review of the ESE guidelines should be considered to specify a VBG sodium after the first bolus.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-22-0007.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Data availability

The data supporting these findings is available within the article. Raw data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contribution statement

M F A, A I, A M, and W M B, co-conceived this study. M F A and A I developed the protocol and study data collection tools with contributions from J W and I F. Data collection was performed by M F A, A I, and J W. Analysis was performed by M F A. The first draft of the manuscript was jointly prepared by M F A and A I with critical input on multiple versions of the manuscript from all authors. All authors approved the final submitted version. M F A and A I are the guarantors of this work, and as such had full access to all study data and thus take responsibility for data integrity and accuracy of data analysis.

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