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Case study

Serum sodium response to hypertonic saline infusion therapy in traumatic brain injury

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1. Introduction

Traumatic brain injury (TBI) affects 1.7 million individuals in the US annually, resulting in 275,000 hospitalizations and 52,000 deaths [1]. Traumatic brain injury is the leading cause of death in trauma, accounting for over 50% of all deaths [2]. Elevated intracranial pressure (ICP) in TBI patients is associated with increased odds of mortality, with 3.5 [95%CI: 1.7, 7.3] for ICPs 20–40 mmHg and 6.9 [95%CI 3.9, 12.4] for ICPs >40 mmHg relative to ICPs <20 mmHg [3].

Hyperosmolar therapy is an effective strategy for reduction of ICP in the setting of intracranial hypertension (IH) associated with TBI by counteracting the cerebral edema associated with TBI, thereby lowering the associated elevated ICP. Hypertonic saline (HTS) and mannitol are the two primary agents used for hyperosmolar therapy for elevated ICP [4]. While mannitol has been considered the gold standard hyperosmolar therapy in elevated ICP [5], evidence supporting the use of HTS for elevated ICP has increased over the past several years. An early report described two TBI patients who, after failing to respond to other therapies, had immediate decreases in ICP following a bolus of HTS [6]. Since this publication, others have reported on the effects of HTS for lowering ICP in TBI as bolus and continuous infusion administration strategies [7–12]. Hypertonic saline has been suggested as a more effective agent at reducing ICP than mannitol in small individual studies and in meta-analyses [13–17]. A more recent meta-analysis of 11 studies, however, concluded no mortality benefit was observed with HTS compared against other hyperosmolar therapies [5].

Reported dosing and administration strategies for HTS in TBI vary widely, and reported HTS concentrations range from 1.5% to 23.5% making it difficult to translate sNa response to HTS across studies. While HTS administration strategies of bolus dosing, continuous infusion or both have been reported as effective for lowering ICP, studies have not evaluated a standardized target serum sodium concentration (sNa) range for HTS therapy for lowering ICP, although a target range of 145–155 mEq/L has been reported [7,18,19], which correlates with a serum osmolality of 300–320 mOsm/L (assuming normal concentrations of other effective osmols, such as glucose and BUN) [18]. Reliably achieving and maintaining sNa at 145–155 mEq/L without hypernatremia (e.g. ≥160 mEq/L) or other adverse effects is important for efficacy and safety of HTS infusion, and yet there is no standardized dosing and monitoring protocol recommended for HTS infusions for TBI. As a result, recommendations for dosing, administration, and titration of HTS are lacking. Furthermore, there is limited guidance available for dosing HTS in TBI as few data characterizing the dose-response relationship of sNa to HTS infusion therapy exists [10,19]. There are also no data reporting on the effect, if any, of urine sodium (uNa) excretion on HTS infusion therapy. Our strategy has been to prescribe HTS as either a 3% NaCl or 7.5% NaCl: Acetate administered as a continuous infusion with a nurse driven titration of the infusion rate based on a sNa, and the infusion rate is adjusted up or down if the sNa is outside the target sNa range. This report characterizes our experience of sNa response to HTS infusion by evaluating this relationship in TBI patients who received HTS as either 3% NaCl or 7.5% NaCl:Acetate. Further, we evaluated whether there is a relationship between urine sodium (uNa) excretion and the change in serum sodium (sNa) after HTS discontinuation. We also evaluated the response of serum chloride (sCl), serum bicarbonate (sBicarb), and serum creatinine (sCr) during HTS.

2. Methods

This research was conducted at North Memorial Medical Center, an American College of Surgeons verified level one trauma center. Institutional Review Board approval was obtained for data collection and analysis. Patients ≥18 years who suffered TBI and were admitted to the trauma-neuro intensive care unit between January 2009 and October 2012 and received HTS infusion for ≥72 h were included. To best characterize the sNa response to HTS infusion,

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patients who received bolus doses of 23.4% NaCl or the HTS infusion for less than 72 h were excluded.

Medical records and the trauma registry of included patients were reviewed for demographics (age, gender, height, weight, mechanism of trauma, injury severity score (ISS), Glasgow Coma Scale (GCS) score, abbreviated injury scale-head (AIS-head), and baseline laboratory data. The HTS infusion start and stop date and time and infusion rates (ml/h, converted to mEq/h) were collected. Hypertonic saline infusion orders were reviewed and data collected included initial HTS infusion rate and minimum and maximum sNa goals and adjustments in the HTS infusion rate based on sNa results as ordered by providers, including orders to hold the HTS infusion at threshold maximum sNa concentrations, and instructions for infusion rates for minimum sNa concentrations. Serum sodium concentrations were ordered every 4 h and nurses adjusted the HTS infusion rate based on sNa results according to the providers order for adjusting HTS infusion based on those orders. Serum sodium during and post-HTS were collected and analyzed for changes over time. Since the actual sNa collection times within each 4 h window varied, all sNa were categorized into 4 h windows of time (e.g. 4–8 h). The sNa up to the 124–128 h time period for HTS infusion were included for analysis. Beyond this time, fewer than 50% of the originally included patients continued on HTS. Additionally, serum chloride (sCl) and serum bicarbonate (sBicarb) and serum creatinine (sCr) were collected. Serum electrolyte data were analyzed over time, with sNa data analyzed in 4 h time periods, sCl and sBicarb in 12 h time periods, and sCr in 24 h time periods. sNa post-HTS infusion was also analyzed from time 0 to 72–96 h post HTS.

Urine sodium (uNa) data was collected in patients in whom this was measured (at the providers discretion). For the uNa closest to HTS infusion discontinuation, we used this value and determined the change in sNa during the first 12–24 h following HTS discontinuation. From these data, we assessed whether there was a correlation between the uNa closest to HTS discontinuation to the change in sNa post-HTS therapy to evaluate the degree of sNa change in relation to the uNa excretion.

Data are reported as median [IQR (25th–75th)] for continuous variables. Statistical analysis for changes in sNa, sCl, sBicarb, and sCr over time included Kruskal-Wallis (K-W) for comparisons across all time periods presented and also by Wilcoxon Rank Sum (WRS) for pairwise comparisons between baseline and each individual time period when K-W was significant. Correlations between the last uNa collected prior to discontinuation of HTS and the change in sNa 12–24 h post-HTS were analyzed using Spearman's rho correlation coefficient. $p \leq .05$ was considered significant. For K-W comparisons, Bonferroni correction was applied for within group pairwise comparisons, as appropriate.

3. Results

3.1. Patient characteristics

Ninety-two patients received HTS infusion for TBI and did not receive bolus doses of NaCl. Of these, 37 patients received HTS for less than 72 h, leaving 55 patients included in the final analysis. Table 1 lists patient demographics and baseline laboratory data. The majority of the patients were male (80%), median age of 47 [IQR 27–57] years, 96% suffering blunt trauma with an ISS of 26 [IQR 24–36], GCS score of 7 [IQR 3–14], and AIS-head of 5 [IQR 4–5] (Table 1). Baseline laboratory data included sNa 138 [IQR 137–141] mEq/L, sCl 105 [IQR 102–108] mEq/L, sBicarb 25 [IQR 22–26] mEq/L, and sCr 0.9 [IQR 0.7–1.05] mg/dl. Table 2 lists HTS infusion characteristics and other interventions to manage elevated ICP. Patients received HTS infusion for 132:11 [IQR 96:36–217:36] hours. These patients had 1239 sNa measured (23/-patient). Other interventions to manage these patients included ICP monitoring (12.7%), mechanical ventilation (65.5%), and cranial decompression surgery (30.9%).

Table 1
Patient demographics and baseline laboratory data.

Demographics	
Age (years	47 [27–57]
Gender (male)	44 (80%)
Weight (kg)	76.3 [67.7–90.3]
Height (cm)	177.8 [170.2–182.9]
BMI (kg/m^2)	24.8 [22.8–27.8]
BSA (m^2)	1.92 [1.81–2.13]
Blunt Trauma	53 (96%)
ISS (n = 48)	26 [24–36]
AIS (Head) (n = 48)	5 [4–5]
GCS score (n = 52)	7 [3–14]
Baseline laboratory data	
Sodium (mEq/L)	138 [137–141]
Chloride (mEq/L)	105 [102–108]
Potassium (mEq/L)	3.7 [3.3–4.0]
Bicarbonate (mEq/L)	25 [22–26]
BUN (mg/dl)	9 [7–14]
sCr (mg/dl)	0.9 [0.7–1.05]
Glucose (mg/dl)	143 [116–175]
pH	7.32 [7.26–7.37]
pCO_2	48 [37–53]
Base excess	−2.6 [−5.6 to −0.38]

Data presented as Median [IQR] or n, %.
BMI: body mass index; BSA: body surface area; ISS: injury severity score; GCS: Glasgow coma scale; AIS: Abbreviated injury scale, BUN: blood urea nitrogen; sCr: serum creatinine.

Table 2
TBI treatment characteristics.

HTS infusion time (hours: minutes)	132:11 [96:36–217:26]
sNa measurements: total (per pt):	1239 (23)
ICP monitor placement:	7 (12.7%)
Mechanical Ventilation:	36 (65.5%)
Cranial decompression:	17 (30.9%)

Data presented as Median [IQR] or n, %.
HTS: hypertonic saline; sNa: serum sodium concentration; ICP: intracranial pressure.

3.2. Serum sodium concentrations response during and post-hypertonic saline infusion

Fig. 1A shows the change in sNa at baseline and following initiation of HTS infusion. Serum sodium increased to a median of 145 [IQR 141–149] mEq/L by 32–36 h and remained 145 mEq/L or greater for the duration of the follow-up period to 124–128 h, except for the 96–100 h time period, where the median sNa was 144 mEq/L. Compared to baseline, sNa were significantly elevated at 4–8 h and remained elevated until the 124–128 h ($p < .001$ for all and for each time point from 4–8 h to 124–128 h compared to baseline). Ten (18.2%) patients had one or more sNa > 155 mEq/L during HTS. Fig. 1B shows the change in sNa following discontinuation of HTS infusion. Serum sodium decreased compared to the last sNa prior to HTS discontinuation, and this decrease in sNa remained consistent through 72 h following discontinuation of the HTS infusion ($p < .001$ and all point from last-24 post HTS to last-72 h post-HTS). Hyponatremia (sNa < 135 mEq/L) following HTS occurred in 7 (12.7%) patients. One patient was hyponatremic at the time of HTS discontinuation and persisted following discontinuation of HTS. Six others had at least one hyponatremia

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