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Safety and Efficacy of Intravenous Hypotonic 0.225% Sodium Chloride Infusion for the Treatment of Hypernatremia in Critically Ill Patients

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Abstract

Background: The purpose of this study was to evaluate the safety and efficacy of central venous administration of a hypotonic 0.225% sodium chloride (one-quarter normal saline [¼ NS]) infusion for critically ill patients with hypernatremia. *Methods*: Critically ill, adult patients with traumatic injuries and hypernatremia (serum sodium [Na] >150 mEq/L) who were given ¼ NS were retrospectively studied. Serum sodium, fluid balance, free water intake, sodium intake, and plasma free hemoglobin concentration (fHgb) were assessed. *Results*: Twenty patients (age, 50 ± 18 years; Injury Severity Score, 29 ± 12) were evaluated. The ¼ NS infusion was given at 1.5 ± 1.0 L/d for 4.6 ± 1.6 days. Serum sodium concentration decreased from 156 ± 4 to 143 ± 6 mEq/L ($P < .001$) over 3–7 days. Total sodium intake was decreased from 210 ± 153 to 156 ± 112 mEq/d ($P < .05$). Daily net fluid balance was not significantly increased. Plasma fHgb increased from 4.9 ± 5.4 mg/dL preinfusion to 8.9 ± 7.4 mg/dL after 2.6 ± 1.3 days of continuous intravenous (IV) ¼ NS in 10 patients ($P = .055$). An additional 10 patients had a plasma fHgb of 10.2 ± 9.0 mg/dL during the infusion. Hematocrit and hemoglobin decreased (26% ± 3% to 24% ± 2%, $P < .001$ and 9.1 ± 1.1 to 8.2 ± 0.8 g/dL, $P < .001$, respectively). *Conclusions*: Although IV ¼ NS was effective for decreasing serum sodium concentration, evidence for minor hemolysis warrants further research to establish its safety before its routine use can be recommended. (*Nutr Clin Pract*. XXXX;xx:xx-xx)

Keywords

sodium; hypernatremia; water-electrolyte balance; critical care; hemolysis

Clinical Relevancy Statement

Intravenous 0.225% sodium chloride infusion is commonly employed for the management of moderate to severe hypernatremia in critically ill patients. Despite its widespread use in clinical practice, published work to support its safety and efficacy is lacking. Our data indicated that central venous administration of 0.225% sodium chloride solution was efficacious in reducing serum sodium concentrations. However, evidence of minor hemolysis during the infusion indicated that further study is warranted to ascertain its safety before its routine use can be recommended.

Introduction

Hypernatremia, acquired in the intensive care unit (ICU), has been associated with increased mortality.[1-3] Severe hypernatremia may cause brain shrinkage, which can induce vascular rupture with cerebral bleeding, subarachnoid hemorrhage, permanent neurologic damage, and death.[4] Patients with critical illness and traumatic injuries have multiple predisposing risk factors for the development of hypernatremia. First, critically ill trauma patients often require initial fluid resuscitation with intravenous (IV) crystalloid (0.9% sodium chloride or Lactated Ringer's) therapy. Concurrently, some neurosurgeons prescribe intermittent hypertonic sodium chloride for the therapeutic management of elevated intracranial pressure and avoidance of hyponatremia during traumatic brain injury. A limited number of patients with traumatic brain injury may also develop diabetes insipidus. For patients with muscle injuries and rhabdomyolysis, hydration with IV 0.9% sodium chloride or sodium bicarbonate solution is implemented for the prevention of myoglobin-induced acute kidney injury. In addition, it is common for patients with traumatic injuries to have gastric and other body fluid drainages, fever, hyperglycemia, diarrhea, replacement fluid therapy for body fluid losses, mechanical ventilation, nutrition therapy, and pharmacotherapy—all which can alter sodium and fluid homeostasis. These clinical events and therapies for the critically ill trauma patient can result in the

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development of a complicated form of hypernatremia that is not likely attributable to a single etiology such as simple dehydration.

It has been our clinical practice to administer a hypotonic 0.225% sodium chloride solution (also referred to as "one-quarter normal saline" or "¼ NS") by central venous administration when the euvolemic patient with hypernatremia is unresponsive to or unable to receive intragastric water boluses by the feeding tube or when it is inadvisable to receive near-isotonic, dextrose-containing, low-sodium solutions (eg, D5W or D5 ¼ NS) due to substantial preexisting hyperglycemia. One concern for the use of the IV ¼ NS solution is that red blood cells exposed to hypotonic solutions result in hemolysis in vitro.[5] Despite its extreme hypotonicity (~76 mOsm/kg), clinicians have assumed that central venous administration of ¼ NS is safe due to its rapid dispersal into the bloodstream analogous to the central venous administration of hypertonic parenteral nutrition (PN) solutions. Despite the common use of IV ¼ NS infusions for hypernatremia by numerous practitioners in clinical practice, we are unaware of any studies that have assessed its safety or efficacy. The purpose of this study was to evaluate the safety and efficacy of a continuous central venous infusion of a hypotonic ¼ NS solution for the treatment of moderate to severe hypernatremia (serum sodium concentration ≥150 mEq/L) in critically ill adult patients with traumatic injuries.

Materials and Methods

Adult patients at least 18 years of age who were admitted to the ICUs of the Presley Trauma Center at the Regional Medical Center at Memphis, were referred to the nutrition support service for PN or enteral nutrition (EN) therapy, received an IV hypotonic ¼ NS infusion for significant hypernatremia (serum sodium concentration ≥150 mEq/L), and had a plasma free hemoglobin concentration determination were retrospectively identified for potential inclusion into the study. Patients with acute kidney injury[6] or chronic kidney disease requiring hemodialysis, those with active bleeding, or patients who received blood products within 48 hours prior to the plasma free hemoglobin concentration determination were excluded from study entry. Patients with a known history of hemolytic anemia, sickle cell disease, or glucose-6-phosphate dehydrogenase deficiency were also excluded.

Our standard of practice at the time of this study was to consider continuous central venous administration of ¼ NS if the euvolemic patient with significant hypernatremia was (1) unresponsive to or intolerant to receive adequate volumes of water by the intragastric route of administration; (2) experiencing hyperglycemia where IV administration of near-isotonic, dextrose-containing, low-sodium solutions (eg, D5W or D5 ¼ NS) were restricted; or (3) unresponsive to IV therapy with ½ NS (0.45% NaCl). The patient was considered unresponsive to the current fluid therapy if the serum sodium concentration did not decrease after 24 to 48 hours of therapy for those with mild to moderate hypernatremia (serum sodium concentration <160 mEq/L). For those with severe hypernatremia (serum sodium concentration ≥160 mEq/L), the patient was considered unresponsive to the current therapy if the serum sodium concentration did not decrease within 24 hours of therapy. For patients who received gastric feeding, water boluses (200–300 mL every 4–6 hours) were prescribed if they could be tolerated as assessed by maintenance of gastric residual volumes ≤200 mL, absence of abdominal distension upon physical examination or abdominal discomfort as expressed by the patient, and without diarrhea.[7] Diarrhea was defined as >300 mL of stool volume per 24 hours collected per the fecal management system or ≥3 loose stools per day.[8] Patients who failed or could not receive intragastric water boluses and required a continuous IV regular human insulin (RHI) infusion, low carbohydrate enteral feeding formulation designed for diabetes or stress-induced hyperglycemia, or sliding scale coverage every 3–4 hours were also considered candidates for IV ¼ NS therapy. Sliding scale insulin therapy consisted of administering 3 units of IV RHI for every 25-mg/dL increase in blood glucose concentration above 125 mg/dL with a maximum individual dose of 24 units. All glycemic control efforts were designed in an effort to maintain blood glucose concentrations within 70–150 mg/dL[9] and not to exceed 180 mg/dL.

The ¼ NS infusion was prescribed by a member of the nutrition support service or the trauma service. The initial infusion rate was empirically chosen, usually within 50–100 mL/h, and adjusted once to twice daily thereafter based on the rate of fall in serum sodium concentration with a conservative target decrease of ~3–6 mEq/L/d. The infusion was continued until the serum sodium concentration was within 135–145 mEq/L. Serum sodium concentration was monitored 1–4 times daily depending on the severity of the hypernatremia and at the discretion of the prescribing clinical service. Sterile ¼ NS solution for IV use was prepared aseptically in the pharmacy by addition of 38 mEq of sodium chloride to 1 L of sterile water for injection and given a 24-hour expiration from the time of preparation.

Hypernatremic patients who were hypovolemic as evidenced by a combination of signs, including hypotension (mean arterial pressure <65 mm Hg), decreased urine output (0.5 mL/kg/d), rising serum urea nitrogen concentration with a stable serum creatinine concentration, negative net fluid balance upon review of nursing fluid intake and output records, tachycardia, or as assessed by Swan-Ganz catheter hemodynamic measurements, were given an IV infusion of 0.9% sodium chloride until intravascular volume status was restored. Intravascular volume-restored hypernatremic patients were then given an IV ¼ NS infusion. Exogenous sources of sodium chloride were eliminated from large-volume solutions, PN admixtures, and IV medications whenever possible.

The primary marker for assessing efficacy was evidence of a progressive decline in daily serum sodium concentration into

the normal range. The therapy was considered safe if the rate in decline of serum sodium concentration was ≤12 mEq/L/d and if the patient did not exhibit evidence of intravascular hemolysis. Intravascular hemolysis was assessed by measurement of plasma free hemoglobin concentration,[10-15] preferably prior to and during IV ¼ NS therapy. A rise in plasma free hemoglobin concentration above 4.9 mg/dL (the upper limit of the normal range) would indicate intravascular hemolysis. Other indirect markers of intravascular hemolysis, including serum bilirubin, lactate dehydrogenase, and haptoglobin concentrations, were also evaluated.[13-17] Serial daily blood hematocrit and hemoglobin concentrations and the requirement for blood transfusions during or within 2 days following discontinuation of the ¼ NS infusion were recorded.

Patients were preferentially given EN by a small-bore, nasoenteric feeding tube or nasogastric tube. PN was given when the patient was unable to tolerate EN despite prokinetic pharmacotherapy[7] or when EN was contraindicated. Patients were given enteral feeding formulations containing 38–57 mEq of sodium per liter of feeding. PN formulations were made sodium free by using potassium-based chloride, acetate, and phosphorus salts whenever possible until the hypernatremia was resolved.

Serum laboratories were obtained from each patient on a daily basis. The blood was obtained at approximately 2 AM via an indwelling central venous catheter while the patient lay supine in bed. Laboratory tests were ordered by the patient's primary service or the Nutrition Support Service and performed by the hospital laboratory as part of the patient's routine clinical care. Nonhemolyzed plasma samples were obtained for determination of plasma free hemoglobin concentrations by spectrophotometry using the tetramethylbenzidine reaction.[18] This assay technique has been previously cross-validated with the enzyme-linked immunosorbent assay methodology in critically ill patients.[19] The Injury Severity Score[20] (ISS) was obtained from the Trauma Registry at the Regional Medical Center at Memphis.

At the time of enrollment into the study, the patient's hospital chart, electronic medical records, and bedside clinical data were reviewed. Data were recorded for the day prior to starting ¼ NS and for a maximum of 7 days while receiving ¼ NS. Data recorded for day 1 were considered a partial day beginning when the IV ¼ NS infusion was initiated. All patients with enteral access were nil per os except for medications, enteral feeding, and free water flushes. Nursing fluid intake and output records were closely reviewed for estimation of daily fluid balance (total volume intake minus urine output, drainages, and liquid stool losses) and total daily Na intake (mEq) calculated from the sodium content of IV fluids, PN, and EN. Total daily free water intake was estimated by the following equation:

$$\text{Total free water intake (mL)} = \text{volume intake (mL)} - (\text{sodium intake [mEq] intake}/154 * 1000).$$

The study was approved and conducted in accordance with the guidelines established by the Institutional Review Board of the University of Tennessee Health Science Center and the Research Office of the Regional Medical Center at Memphis. Because all measurements for this observational study were performed as part of the routine clinical care of the patient and because confidentiality procedures for the patient were maintained, the requirement for informed consent was waived. Data were analyzed using SigmaPlot for Windows version 11.2 (Systat Software, Point Richmond, CA). Data were evaluated for normality of distribution by using the Shapiro-Wilk test. Variables obtained prior to and during ¼ NS infusion were compared by applying the *t* test for paired variables if the data were normally distributed or Wilcoxon signed rank test if not normally distributed. Differences between groups for nominal data were analyzed by either χ^2 analysis or Fisher exact test. One-way analysis of variance was used for comparing serial measurements of variables over time with post hoc, pairwise multiple comparisons performed by the Tukey test. Continuous data were expressed as mean ± SD. All statistical analyses were 2-tailed. A probability value (*P*) of .05 or less indicated statistical significance.

Results

Patient Characteristics

Twenty adult patients with traumatic injuries who were admitted to the trauma ICUs, were referred to the Nutrition Support Service, received an IV ¼ NS infusion for significant hypernatremia, and had a plasma free hemoglobin determination were evaluated. The majority of the patients were admitted to the hospital as a result of injuries from a motor vehicle collision, and most survived. Most were male, and one-third of the patients had a severe traumatic brain injury. Average ISS was 29 (range, 14–59); 16 patients (80% of the population) had an ISS >20. Nineteen patients were ventilator dependent during the observation period. None of the patients had Cushing syndrome or primary hyperaldosteronism. Two-thirds of the patients received intragastric EN, with the remaining requiring PN. Ten of the 14 patients who received EN received a fiber-containing, low-carbohydrate, high-fat formula for glycemic control, whereas the remaining patients received another disease-specific, fiber-containing enteral formula (eg, glutamine, arginine, ω-3 fatty acid diet [n = 3] or ω-3 fatty acid–enriched diet [n = 1]). Liquid protein supplements were given in addition to the enteral formula to achieve calorie and protein goals of 30–32 kcal/kg/d and 2–2.5 g/kg/d of protein.[21] Two patients received desmopressin for central diabetes insipidus. Overall length of hospital stay was 42 ± 23 days. Other characteristics of the patients are given in Table 1.

Table 1. Patient Characteristics.

Variable	Data
Total number of patients	20
Survived/died, No.	15/5
Sex, M/F, No.	17/3
Age, y, mean ± SD	50 ± 18
Weight, kg, mean ± SD	96 ± 20
Admit diagnosis, No.	
MVA	14
GSW	4
Fall	2
TBI, No. (%)	6 (30%)
ISS, mean ± SD	29 ± 12
Admit WBC, cells/mm^3, mean ± SD	14.1 ± 5.5
Admit serum albumin, g/dL, mean ± SD	3.1 ± 0.8
Tmax, °C at start of ¼ NS, mean ± SD	38.7 ± 0.6
EN/PN, No.	14/6

EN, enteral nutrition; F, female; GSW, gunshot wound; ISS, injury severity score; M, male; MVA, motor vehicle accident; ¼ NS, one-quarter normal saline; PN, parenteral nutrition; TBI, traumatic brain injury; Tmax, maximum daily temperature; WBC, white blood cell count.

Potential Etiologies for Hypernatremia

Patients had multiple potential etiologies for the development of hypernatremia, with a mean ± SD of 3.7 ± 1.1 concurrent etiologies present for each patient (Table 2). The most common etiology was substantial sodium intake from either the use of hypertonic saline (7.5% NaCl) or a continuous infusion of 0.9% sodium chloride or Lactated Ringer's solution. Fever, from sepsis or systemic inflammatory response syndrome, was the second most common potential etiology. Fever results in increased insensible losses[22] that were not accounted for in nursing intake and output volume records. Eighty-five percent of patients experienced a temperature >38°C; 4 patients had an average maximum daily body temperature of ≥39°C during the observation period. Inadequate fluid intake to maintain a net fluid balance of about 600 mL or more daily to account for estimated insensible losses[22] was also evident in about half of the patients (Table 2). Potential osmotic diuresis from increased ureagenesis[23] (serum urea nitrogen concentration to serum creatinine concentration ratio of >30:1) due to protein catabolism or aggressive protein intake occurred in half of the patients. Excessive body fluid loss from diarrhea (n = 8) or gastric fluid losses (n = 2) was also prevalent in half of the patients. Of those who experienced diarrhea, none received laxatives or sorbitol-containing liquid medications. One patient experienced a positive stool sample for *Clostridium difficile* toxin and was successfully treated with metronidazole; the others had negative toxin assay results. Two patients with diarrhea received a promotility agent (IV metoclopramide 10 mg every 6 hours) for gastric feeding intolerance. Older patients may have a decreased ability to adequately concentrate their urine[24]

Table 2. Potential Etiologies for the Development of Hypernatremia Prior to Hypotonic ¼ NS Infusion Therapy.

Potential Etiology	No. of Patients
Total number of patients	20
Increased sodium intake[a]	18
Temperature >38°C	17
Net fluid balance <600 mL/d	12
Increased ureagenesis[b]	11
Diarrhea or excessive gastric drainage[c]	10
Intermittent hyperglycemia[d]	4
Age >65 y	4

A mean of 3.7 ± 1.1 potential etiologies were concurrently present per patient. ¼ NS, one-quarter normal saline.
[a]Intermittent doses of hypertonic saline (7.5% NaCl) or a continuous infusion of 0.9% NaCl or Lactated Ringer's solution.
[b]Serum urea nitrogen to creatinine ratio >30 to 1.
[c]Diarrhea >300 mL/d (n = 8) or gastric drainage >1.5 L/d (n = 2).
[d]Serum glucose >180 mg/dL.

and are susceptible to dehydration and hypernatremia; however, only 4 patients were older than 65 years. None of the patients received diuretic pharmacotherapy.

Intermittent hyperglycemia >180 mg/dL, which may lead to glycosuria and diuresis, was evident in 4 patients prior to initiation of ¼ NS therapy. Five patients had a past medical history of diabetes, whereas the majority of patients experienced stress-induced hyperglycemia. Glycemic control with a target blood glucose concentration of 70–149 mg/dL was achieved, as evidenced by an average daily serum glucose concentration of 127 ± 16 mg/dL during the observation period. Four patients required a continuous regular human insulin infusion,[9] 3 received Neutral Protamine Hagedorn insulin therapy with intermittent sliding scale regular human insulin coverage,[25] and 13 were managed with intermittent sliding scale regular human insulin coverage. For those who received PN, regular human insulin was added to the PN solution to reduce reliance on intermittent sliding scale coverage if a continuous regular human insulin infusion was not required.

Efficacy of 0.225% Sodium Chloride Infusion

The central venous ¼ NS infusion was initiated for a serum Na concentration of 156 ± 4 mEq/L. An average volume of 1.5 ± 1.0 L/d was given for 4.6 ± 1.6 days (range, 2–7 days). Of the patients, 20, 19, 16, 10, 6, and 2 received the infusion for 2, 3, 4, 5, 6, and 7 days, respectively. The serum sodium concentration fell to 143 ± 6 mEq/L following completion of the ¼ NS infusion therapy (P = .001). Serum sodium concentration declined by an average of ~3 mEq/L/d. Hypernatremia was corrected to within 135–145 mEq/L for 13 patients (65% of the population) and was overcorrected to 131–133 mEq/L for 2 patients. Three patients had died before their hypernatremia could be fully corrected. The remaining 2 patients with hypernatremia achieved a

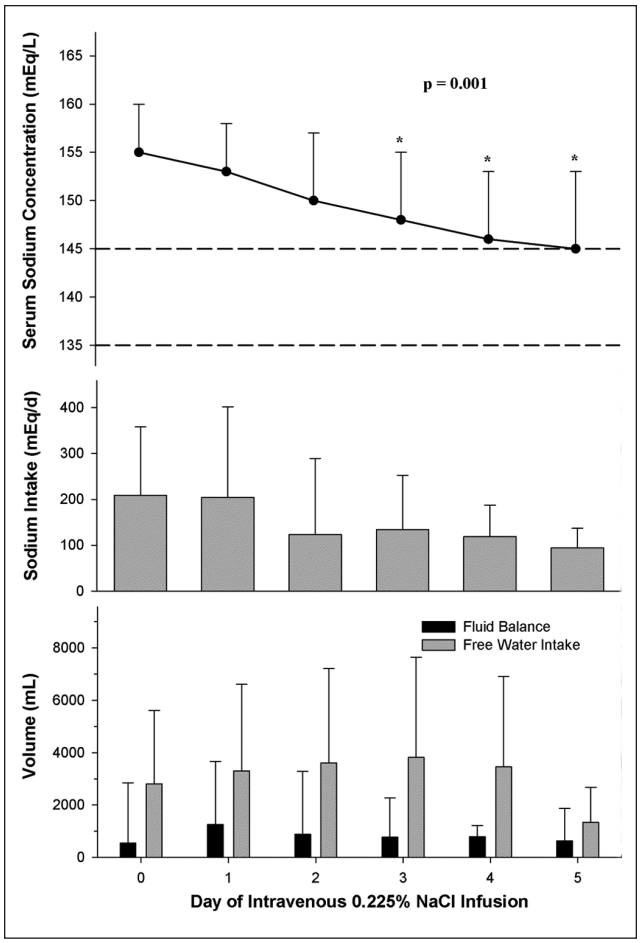

Figure 1. Serum sodium concentration, sodium intake, free water intake, and fluid balance prior to (day 0) and during intravenous one-quarter normal saline (¼ NS) infusion. Each day represents the results of 20, 20, 20, 19, 16, and 10 patients, respectively. *$P \leq .05$ from day 0.

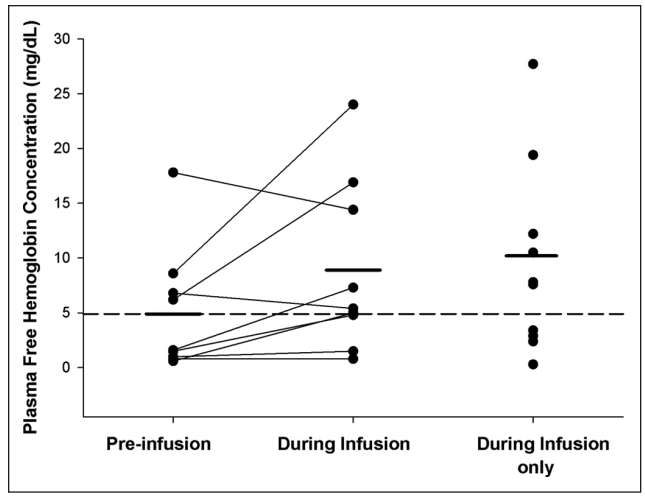

Figure 2. Plasma free hemoglobin concentrations before and during intravenous one-quarter normal saline (¼ NS) infusion. Plasma free hemoglobin increased from 4.9 ± 5.4 mg/dL prior to intravenous (IV) ¼ NS therapy to 8.9 mg ± 7.4 mg/dL (P = .055) during IV ¼ NS infusion therapy (n = 10). An additional 10 patients experienced a plasma free hemoglobin concentration of 10.2 ± 9.0 mg/dL during the infusion.

normal serum sodium concentration within 2 days following discontinuation of the ¼ NS as the infusion was substituted with either D5W or D5 ¼ NS since the patients' stress-induced hyperglycemia resolved necessitating less strict glycemic control interventions.

Fluid balance was 0.6 ± 2.3 L/d prior to starting ¼ NS and 1.2 ± 2.0 L/d ($P = NS$) thereafter during the observation period. Total sodium intake was reduced from 210 ± 153 mEq/d prior to ¼ NS to 156 ± 112 mEq/d during the ¼ NS infusion therapy ($P < .05$). Serial changes in serum sodium, sodium intake, fluid balance, and free water intake on the day prior to infusion of ¼ NS throughout the first 5 days of ¼ NS therapy are given in Figure 1. Although statistically insignificant between days, daily sodium intake tended to be less and calculated free water intake and fluid balance tended to be greater during hypotonic ¼ NS therapy compared with day 0 and most likely explains the success in significantly lowering serum sodium concentration by the third day of therapy (Figure 1). In addition, no significant changes were noted for serum urea nitrogen (37 ± 15 vs 33 ± 20 mg/dL), creatinine (1.3 ± 0.5 vs 1.3 ± 0.9 mg/dL), or glucose (118 ± 30 vs 117 ± 15 mg/dL) prior to the infusion compared with at the completion of ¼ NS therapy.

Safety of 0.225% Sodium Chloride Infusion

The rate in decline of serum sodium concentration averaged ~3 mEq/L/d. None of the patients' decline in serum sodium concentration exceeded 12 mEq/L/d. A trending increase in plasma free hemoglobin concentration from 4.9 ± 5.4 mg/dL preinfusion to 8.9 ± 7.4 mg/dL after 2.6 ± 1.3 days of IV ¼ NS infusion therapy, which nearly achieved statistical significance (P = .055), was observed in 10 patients (Figure 2). Four of the 10 patients who had determinations prior to and during ¼ NS infusion exhibited an increased plasma free hemoglobin concentration prior to initiation of the infusion. A separate group of 10 patients who had a plasma free hemoglobin concentration drawn only during the infusion exhibited an elevated concentration of 10.2 ± 9.0 mg/dL (Figure 2). With both groups combined together (n = 20), two-thirds of the patients had an increased plasma free hemoglobin concentration above normal (0–4.9 mg/dL) with a mean concentration of 9.1 ± 7.8 mg/dL during the infusion. The change in plasma free hemoglobin concentration (prior to vs during ¼ NS) or the concentration during the ¼ NS infusion was not related to the previous day's volume of ¼ NS received, cumulative volume, or either volume adjusted to body weight ($P = NS$). There was no difference in plasma free hemoglobin concentration during the infusion between those who died or survived (8.8 ± 6.7

mg/dL vs 9.3 ± 8.3 mg/dL, *P* = *NS*, respectively). None of the patients developed acute kidney injury following the IV ¼ NS infusion therapy.

Patients who were infected (n = 9) tended to experience a greater plasma free hemoglobin concentration during the infusion than those who were not infected (n = 11; 11.5 ± 9.2 mg/dL vs 7.2 ± 6.1 mg/dL, *P* = *NS*, respectively). Of the 10 patients who had determinations prior to and during the IV ¼ NS infusion, 4 were septic, whereas 6 were noninfected. Both septic and noninfected groups demonstrated an increased trend in plasma free hemoglobin concentration during the infusion; however, the infected group tended to have a higher baseline concentration prior to the infusion (8.1 ± 7.1 to 13.0 ± 8.4 mg/dL, *P* = *NS*, and 2.8 ± 2.9 to 6.2 ± 5.8 mg/dL, *P* = *NS*, respectively).

Hematocrit and hemoglobin both decreased (from 26% ± 3% to 24% ± 2%, *P* < .001, and from 9.1 ± 1.1 to 8.2 ± 0.8 g/dL, *P* < .001, respectively) postinfusion. Six patients received a transfusion of packed red blood cells 2 days prior to or after discontinuation of IV ¼ NS infusion therapy that was not related to the presence of overt bleeding or a concurrent surgical procedure. Plasma haptoglobin concentration, measured in 4 patients, fell from 424 ± 64 mg/dL to 369 ± 35 mg/dL (*P* = .06). Serum total bilirubin and lactate dehydrogenase concentrations were not significantly different before and after the ¼ NS infusion therapy (1.6 ± 1.5 to 2.3 ± 3.6 mg/dL, *P* = *NS*, and 575 ± 353 to 705 ± 917 IU/L, *P* = *NS*, respectively).

Discussion

Our data indicated that central venous administration of hypotonic ¼ NS solution for the treatment of moderate to severe hypernatremia resulted in a safe decline in serum sodium concentration by about 3 mEq/L/d, with achievement of normal serum sodium concentrations after 3–7 days of therapy. However, the safety of IV hypotonic ¼ NS was questionable due to evidence of mild intravascular hemolysis. Most patients had an elevated plasma free hemoglobin concentration above normal during the infusion that doubled from baseline prior to the infusion. Patients also experienced a mild decline in blood hematocrit and hemoglobin concentrations.

Although the incidence of hypernatremia is low for all hospitalized patients (~1%), an increased incidence (eg, 10%–26%) has been demonstrated for critically ill patients in the ICU.[26] More important, the development of moderate to severe hypernatremia (serum sodium concentration >150 mEq/L) in the ICU has been associated with increased mortality. In 1 large multicenter cohort study, 30% of patients with mild hypernatremia (serum Na concentration of 146–150 mEq/L) died compared with 46% of those with moderate to severe hypernatremia.[3] A 10% incidence of ICU-acquired hypernatremia in cardiac surgery patients has been associated with a 2-fold increase in mortality and nearly a 6-fold increase in length of stay in the ICU.[27] In a 5-year, retrospective analysis of the severity of hypernatremia and risk of death after traumatic brain injury in 1044 patients, Li and colleagues[28] demonstrated mortality rates for those who had a serum sodium concentration of 150–155 mEq/L, 155–160 mEq/L, and >160 mEq/L to be 21%, 42%, and 87%, respectively, compared with 2% for those whose serum sodium concentrations were kept <150 mEq/L. Collectively, these studies indicate an association between ICU-acquired hypernatremia and worsened clinical outcomes. However, it is important to note that patients with ICU-acquired hypernatremia are generally sicker upon admission to the ICU, and mortality may be related to their overall severity of illness rather than the presence of hypernatremia itself.[29] This observation may be reflective of our population as well since the mean ISS was 29, and 80% of our patients' scores were >20, which indicated the presence of severe injury for the majority of our patients.

The critically ill patient with severe traumatic injuries is at high risk for developing hypernatremia for multiple reasons. Most require crystalloid fluid resuscitation with 0.9% sodium chloride or Lactated Ringer's solution upon hospital admission. They also may be treated with hypertonic saline for management of elevated intracranial pressure from traumatic brain injury.[30] Some will receive substantial amounts of IV 0.9% sodium chloride or a sodium bicarbonate infusion in an effort to prevent acute kidney injury during rhabdomyolysis following muscle injury.[31] In addition to increased sodium intake, the critically ill patient with traumatic injuries often has numerous measurable hypotonic fluid losses (eg, body fluid drainages), unmeasurable hypotonic fluid losses (eg, fever[22]), and questionably measurable hypotonic fluid losses (eg, diarrhea). Others may experience osmotic diuresis due to glycosuria from hyperglycemia associated with insulin resistance[32] or from increased urinary urea excretion[21] due to increased protein catabolism or an aggressive protein intake. Occasionally, some patients will develop excessive urine output due to diabetes insipidus after traumatic brain injury.

Our patients averaged 4 etiologies per patient toward the development of moderate to severe hypernatremia; however, the summative effect for the majority of our patients was likely due to abundance in sodium intake and inadequate free water intake. This diagnostic conclusion was derived from calculation of daily sodium intake, free water intake, examination of daily fluid balance, lack of significant changes in serum urea nitrogen concentration and serum urea nitrogen to creatinine ratios, and omission of a significant increase in urine output during continuous IV ¼ NS infusion therapy. Others have described a similar pathogenesis for their hypernatremic ICU populations.[23,29] This clinical scenario is in contrast to hypernatremia due to simple dehydration, whereby an improvement in fluid balance, decrease in serum urea nitrogen concentration and serum urea nitrogen to creatinine ratio, and an increase in urine output during continuous ¼ NS infusion therapy would be anticipated.[4] Nevertheless, some of our patients may have experienced an inadequate free water intake due to numerous

measurable and nonmeasurable hypotonic fluid losses and experienced a net negative fluid balance prior to ¼ NS infusion therapy as a partial component to their development of hypernatremia (Table 2). Unfortunately, we could not or did not measure body water compartments, exchangeable sodium or potassium, plasma osmolality, urine osmolality, urine sodium concentration, fractional excretion of sodium, or electrolyte-free water clearance to facilitate a more informed assessment for the extracellular fluid volume or total hydration status of the patient and pathogenesis for the hypernatremia. The reader is referred elsewhere for a discussion on how to use these markers for the evaluation of dysnatremias.[33]

Common initial therapeutic interventions for our hypernatremic population prior to IV ¼ NS therapy included substituting lower sodium-containing solutions such as 0.45% sodium chloride for sodium-enriched IV solutions such as 0.9% sodium chloride or Lactated Ringer's solution and removal of sodium electrolyte additives from the PN solution or any sodium-containing electrolyte additives to the enteral feeding.[34] Isotonic, dextrose-containing, low-sodium solutions such as D5W or D5 ¼ NS were not prescribed as aggressive glycemic control interventions were being implemented at the time low-sodium fluid therapy was indicated. For patients who received gastric feeding, water boluses (200–300 mL every 4–6 hours) were prescribed if they could be tolerated.[7]

If the above interventions were not successful or possible, central venous administration of ¼ NS was initiated. Patients were empirically prescribed an initial rate within 50–100 mL/h with sequential monitoring of the serum sodium concentration every 6 hours daily to once daily at the discretion of the prescribing trauma or nutrition support service. The rate was adjusted thereafter with a conservative target for decline in serum sodium concentration of ~3–6 mEq/L/d. Our empiric approach to selection of the initial rate of the IV ¼ NS infusion was chosen in lieu of using predictive formulas to guide fluid therapy since they have been shown to be inaccurate for the individual patient, and their use could lead to severe electrolyte derangements.[35] Application of the Androgue-Madias, Baroum-Levin, and Kurtz-Nguyen formulas led to predicted vs measured sodium concentrations changes in excess of 5 mEq/L/d with only about 20% of the variability in measured serum sodium concentrations accountable by predicted values with use of these formulas.[35] Rapid correction of serum sodium concentration faster than 10–12 mEq/L/d has been associated with the development of cerebral edema.[36] Resultantly, some experts have suggested a more conservative approach for a maximal rate of decline of ~6 mEq/L/d.[26] Figure 1 demonstrates the efficacy of our empiric approach to lowering serum sodium concentrations by a mean of ~3 mEq/L/d. None of the patients in our study exceeded a 12-mEq/L/d decrease in serum sodium concentration. This rate in fall of the serum sodium concentration was accomplished by decreasing daily sodium intake as well as increasing free water volume intake with a resultant modest increase in daily fluid balance (Figure 1).

One concern for the use of an IV ¼ NS solution is that it is extremely hypotonic (~76 mOsm/kg) in contrast to a normal plasma osmolality within 270–300 mOsm/kg. Hemolysis occurs when erythrocytes are incubated with hypotonic sodium chloride solutions in vitro.[5] Clinicians have assumed that central venous administration of hypotonic ¼ NS is safe due to its rapid dispersal into the bloodstream, analogous to the central venous administration of hypertonic PN solutions. Despite common use of IV ¼ NS infusion therapy by numerous clinicians and recommendations for the use of hypotonic, low sodium-containing IV solutions from respected leaders in the field,[4] we could not find any published data to support its safety.

Unfortunately, conventional markers for detection of intravascular hemolysis, not attributable to hereditary, autoimmune, or drug-induced causes, is problematic for the critically ill patient as many are influenced by the presence of acute illness, infection, and injury. Serum haptoglobin is the classic marker for detection of intravascular hemolysis. Haptoglobin binds free hemoglobin released during hemolysis, forming a complex that is then rapidly removed by the reticuloendothelial system. This results in a reduction in serum haptoglobin concentration. A reduced concentration of serum haptoglobin <25 mg/dL has been reported as highly sensitive and specific for predicting a hemolytic state.[16] However, haptoglobin is also an acute-phase protein that will increase several fold in the event of an inflammatory stimulus such as infection, injury, or malignancy.[17] Serum haptoglobin concentrations substantially decreased during the IV ¼ NS infusion therapy in the 4 patients in whom it was measured in our study. However, it was unclear whether the decrease was related to recovery from the acute-phase stress response, binding to free hemoglobin, or a combination of both since the mean initial and final concentrations (464 mg/dL and 369 mg/dL) were still well above normal (34–200 mg/dL). After observing these initial results, we abandoned the use of serum haptoglobin as a potential marker of intravascular hemolysis for evaluating the safety of ¼ NS due to difficulty in its interpretation for our critically ill patients with traumatic injuries.

The availability of plasma free hemoglobin is increased during hemolysis, during sepsis, or following massive blood transfusions.[13,15,19] Free hemoglobin is a potent scavenger of nitric oxide and has been associated with decreased microcapillary bed perfusion, decreased organ perfusion, and increased organ injury.[13] Animal models indicate that an increase in free hemoglobin availability worsens the inflammatory response and increases mortality during endotoxemia and sepsis.[37,38] Exposure to large amounts of free hemoglobin from intraoperative blood cell salvage with auto-transfusion or from hemolysis and blood transfusions during cardiopulmonary bypass has resulted in hemoglobinuria-induced acute kidney injury and failure.[10,11,14] Our data indicated that plasma free hemoglobin concentrations tended to increase during central venous administration of ¼ NS, and two-thirds of

patients exhibited an increased plasma free hemoglobin concentration above normal (Figure 2).

The presence of sepsis may have also contributed to the observed elevations in plasma free hemoglobin concentration for our population.[19] Our preliminary data indicated that plasma free hemoglobin concentrations prior to IV ¼ NS infusion therapy were nearly 3 times higher in septic patients than in noninfected patients. However, both groups experienced a doubling in plasma free hemoglobin concentrations once continuous IV ¼ NS infusion therapy was undertaken. It is important to note that this increase in plasma free hemoglobin concentration was observed despite an increased haptoglobin concentration, whereby increased clearance of free hemoglobin and resultant decreased plasma concentrations of free hemoglobin would be anticipated. Impairment in nitric oxide activity does not occur until plasma free hemoglobin concentrations exceed 40 mg/dL.[39] Acute kidney injury and failure are not observed until concentrations exceed 70–90 mg/dL.[10,14] None of our patients exceeded a plasma free hemoglobin concentration >30 mg/dL, and none developed acute kidney injury or failure following IV ¼ NS infusion therapy.

A mild 2% decline in blood hematocrit and 0.9-g/dL decrease in hemoglobin concentration occurred over the course of IV ¼ NS infusion therapy. Six patients received blood products within 2 days prior to or after discontinuation of the IV hypotonic ¼ NS infusion. However, it is unknown whether the patients experienced impaired oxygen delivery necessitating a blood transfusion as none of the patients had a hemoglobin concentration <7 g/dL or a hematocrit <21%.[40] It is possible that this decline in hematocrit and hemoglobin concentration may have been partially explained by rehydration, multiple phlebotomies, and mild extravascular hemolysis for some patients. Serum bilirubin and lactate dehydrogenase were not helpful in assessing evidence of hemolysis as their concentrations were increased and equivocal between time periods likely due to traumatic injuries, abdominal surgeries, and sepsis.

This study has its limitations. It contains a limited number of patients and is retrospective in study design. Timing of the determination of the plasma free hemoglobin concentration after initiation of IV ¼ NS was not consistent among all patients. Baseline (pre) intravenous ¼ NS infusion plasma free hemoglobin determinations were lacking for half of the patients. Future study is warranted to provide better insight into the extent of hemolysis, adaptive processes, and potential physiologic ramifications of hemolysis caused by this therapy. Frequent and consistent evaluation of plasma free hemoglobin, serum haptoglobin, and reticulocytes; measurement of other endogenous scavengers and detoxification pathways (eg, hemopexin, α-hemoglobin stabilizing protein, heme oxygenase-1); expert microscopic evaluation of the blood smear; and evaluation of nitric oxide–dependent processes would provide a more definitive answer regarding the safety of IV ¼ NS infusion.

Conclusions

Our data indicate that central venous administration of hypotonic ¼ NS was effective in lowering serum sodium concentrations at a safe rate for critically ill patients with moderate to severe hypernatremia. However, it is concerning that some patients may have experienced minor hemolysis during this therapy. Therefore, we have abandoned the routine use of IV ¼ NS infusion and have substituted this therapy with near-isotonic, dextrose-containing, low-sodium solutions such as D5W or D5 ¼ NS when intragastric administration of free water is not effective or possible. If the patient experiences worsening hyperglycemia from the provision of additional dextrose, an adjustment in the nutrition regimen and more aggressive insulin therapy might be indicated. Further research is warranted to establish the safety of IV hypotonic ¼ NS infusion therapy before its routine use for critically ill patients with moderate to severe hypernatremia can be recommended.

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