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ORIGINAL ARTICLE

Performance Characteristics of a Sliding-Scale Hypertonic Saline Infusion Protocol for the Treatment of Acute Neurologic Hyponatremia

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Abstract
Background and Purpose Hypertonic saline (3% NaCl) infusions can be used to treat acute neurologic hyponatremia (ANH) in critically ill patients with neurological and neurosurgical disorders such as subarachnoid hemorrhage. Adjustments in the rate of hypertonic saline infusions to treat ANH are needed to achieve a goal sodium range and are usually made on an empiric basis. To date, no data are available to determine how reliably such adjustments achieve stable, normal serum sodium concentrations or how often iatrogenic hypernatremia occurs during the course of treatment with hypertonic saline.
Methods We have instituted a standardized sliding-scale hypertonic saline protocol to minimize patient-to-patient variability of hypertonic saline administration and to attempt to achieve safe rates of sodium correction and stable maintenance of serum sodium concentration with minimal overshoot. Here, we present a retrospective analysis of the performance characteristics of our standardized hypertonic saline protocol over a 1-year period, in 49 patients.
Results The mean rate of initial sodium correction was 0.44 ± 0.36 (mEq/l)/h. During the maintenance infusion phase, 84.3 ± 17.8% of the time was spent in goal range (Na 136–145 mEq/l), 14.9 ± 18.1% of the time was spent in mild undershoot (Na 130–135 mEq/l), and 0.7 ± 3.1% of the time was spent in overshoot (Na >145 mEq/l). No adverse events attributable to infusion of hypertonic saline were encountered.
Conclusion Our hypertonic saline sliding-scale protocol for treatment of ANH can be used reliably and achieves normal sodium concentrations in a safe manner with minimal overshoot.

Keywords Hyponatremia · Subarachnoid hemorrhage · Intracerebral hemorrhage · Cerebral salt wasting · Hypertonic saline

Introduction

Acute neurologic hyponatremia (ANH) is a common phenomenon in critically ill patients with neurological and neurosurgical diseases such as subarachnoid hemorrhage (SAH), traumatic brain injury, intracerebral hemorrhage, and ischemic stroke. ANH can lead to complications such as seizures or exacerbation of brain edema and raised intracranial pressure. The mechanisms behind the phenomenon of ANH remain controversial [1–3], with some authors arguing it is largely due to syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [4] and others arguing that the underlying mechanism is cerebral salt wasting (CSW) [5–8]. Because these two very different pathophysiological explanations can currently be distinguished in clinical practice only by assessment of volume status and fluid balance, the controversy about the underlying mechanism of ANH is likely to persist for the foreseeable future. Although both atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) have been proposed as a possible mediators of CSW in this context [9, 10], there are no clear standards at this time for using levels of these hormones to distinguish SIADH from CSW in patients with ANH. Calculation of electrolyte mass balance over time has been used to support the diagnosis of CSW

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[3, 11], but this has not been incorporated into routine clinical practice.

Irrespective of the pathophysiological mechanisms behind ANH, there is a general consensus that treatment of ANH with free-water restriction (as would be appropriate for treatment of SIADH in a general medical patient) is potentially deleterious, particularly in disease states such as SAH in which volume restriction may exacerbate or provoke delayed neurological deterioration from vasospasm. Instead of treating such patients with volume restriction, many centers now opt to maintain a goal of euvolemia and treat the acute hyponatremia with sodium repletion with enteral administration of sodium chloride and/or infusion of hypertonic saline (3% NaCl) [12]. Administration of hypertonic saline to treat ANH has been felt to carry with it a low risk of central pontine myelinolysis (CPM) or other adverse osmotic side effects because of the acute nature of the hyponatremia being treated, but this has not been rigorously examined. The largest risk of hypertonic saline therapy in this clinical context appears to be development of hypernatremia [13].

Acute neurologic hyponatremia is commonly encountered in SAH, and it is in this disease state that it has been most widely studied. Serum sodium values below 134 mEq/l have been reported in 34% of SAH patients [14]. The time course of ANH development in SAH is similar to that of the risk window for vasospasm [15, 16], which has led to the suggestion that ANH may be a harbinger of vasospasm [15], although this has not been firmly established. An interaction between ANH and symptomatic vasospasm (delayed cerebral ischemia in SAH) is suggested by the finding that there is a significantly higher rate of cerebral infarction in patients with hyponatremia than in patients without hyponatremia [16]. An interaction between hydrocephalus, intraventricular hemorrhage, and development of ANH also appears to exist: enlargement of the third ventricle and the extent of intraventricular hemorrhage are predictive of the development of hyponatremia in SAH, and treatment of hydrocephalus by external ventricular drainage correlates with resolution of hyponatremia [17]. Acute hyponatremia in general presents clinically with central nervous system manifestations, including seizures, altered mental status, cerebral edema, and raised intracranial pressure [18]. Although these effects of hyponatremia are typically seen in the general medical population with profound or very rapid onset of hyponatremia [2, 12, 18], pre-existing CNS pathology such as SAH, intracerebral hemorrhage, or traumatic brain injury may lead to a lowered threshold for such effects in more modest hyponatremic states [2, 12, 19].

Little data are available in the literature to establish standard practices regarding administration of hypertonic saline infusions in this clinical context. We have therefore developed and implemented a standardized sliding-scale hypertonic saline protocol at our institution. We present here a retrospective analysis over a 1-year period of the performance characteristics of this protocol to test the hypothesis that a standardized sliding-scale hypertonic saline protocol can treat hyponatremia safely and with appropriate control of serum sodium concentrations in a normal range.

Methods

Retrospective Review

Patients treated with 3% NaCl continuous infusion at Kaiser Permanente Medical Center, Redwood City were captured by a retrospective search of the pharmacy electronic record over a 1-year period (06/16/2007 to 06/15/2008). Patients were included in the analysis if they were admitted to the Neuroscience service with a diagnosis of SAH, intracerebral hemorrhage, hydrocephalus, brain tumor(s), subdural hemorrhage, intraventricular hemorrhage, meningitis, traumatic brain injury, or ischemic stroke and if the patient received the standardized hypertonic saline (3% NaCl) protocol (Table 1) for a clearly defined period of time greater than 24 h without interruption or modification of the parameters of the protocol. Patients receiving a 3% NaCl infusion without sliding-scale adjustment instructions or with a sliding-scale that differed from the standardized protocol described here were excluded from analysis. Other reasons for exclusion included administration of hypertonic saline at a fixed rate

Table 1 Standardized hypertonic saline (3% NaCl) protocol

Orders to start hypertonic saline infusion in neuroscience patients with acute hyponatremia
NaCl tabs 3 g PO/NGT every 6 h
Initiate 3% NaCl Infusion Protocol:
Start initial 3% NaCl infusion at 20 ml/h IV NOW
Check serum [Na+] every 6 h and follow sliding scale:
3% Sodium Chloride IV Infusion Instructions:
[Na+] less than 130:
Increase rate by 20 ml/h (max rate = 80 ml/h); if on hold at present, new rate = 20 ml/h
[Na+] 130–135:
Increase rate by 10 ml/h (max rate = 80 ml/h); if on hold at present, new rate = 10 ml/h
[Na+] 136–140:
No change
[Na+] greater than 140:
Hold infusion, check Na+ every 6 h, and follow sliding scale

without titration and administration of hypertonic saline as osmotherapy to treat raised intracranial pressure (using a different sliding-scale protocol with a hypernatremic target range). No patients during the time period under study received hypertonic saline with empiric physician-based titration. For the 1-year retrospective review period, 176 patients were identified as receiving any form of 3% NaCl infusion, and 49 patients met our inclusion criteria. Patients who received 3% NaCl infusions but were not included for analysis received 3% NaCl for different clinical reasons (such as osmotherapy for raised intracranial pressure) had multiple interruptions or changes in the protocol, or had changes made to the protocol (such as no administration of enteral NaCl). The present study was a retrospective chart review, and all decisions to start and discontinue the 3% NaCl infusion protocol were made by the treating physicians as part of routine clinical care. In general, the clinicians at our medical center commence the protocol when serum sodium levels drop by 6 mEq/l or more over a 24–48-hour period or if serum sodium levels drop to 133 mEq/l or lower over a similar time frame, but decisions regarding use of the protocol were up to the treating physician. On the other end of the protocol, decisions regarding when to discontinue the 3% infusion or modify it to a different protocol were also made by the clinician. The protocol is typically discontinued when the serum sodium is maintained in the goal range despite a decreasing rate of 3% NaCl administration over time. Patients treated with hypertonic saline infusion are treated in one of two monitored settings: a neurological intensive care unit (ICU) or a telemetry-capable neurological observation unit. Approval for retrospective chart review was obtained from the Kaiser Permanente Northern California Institutional Review Board.

Standardized Hypertonic Saline (3% NaCl) Protocol

Prior to 06/16/2007, the start of the study period, we introduced a standardized sliding-scale protocol for adjustment of 3% NaCl infusions in the setting of acute hyponatremia in neurological and neurosurgical patients at our institution. The protocol is reproduced in Table 1. All patients analyzed in the retrospective review received this standardized physician order.

Parameters for Analysis of Protocol Performance

For the purpose of analyzing performance of the standardized hypertonic saline infusion protocol, specific definitions of sodium ranges and times related to initiation, maintenance, and termination of the protocol were established a priori. The start of the protocol was determined from the date and time of the physician's order, determined from the pharmacy electronic record. During analysis of sodium values over time, time zero was always taken as the next sodium laboratory value after the start of the protocol. For comparison across patients and for purposes of averaging traces, the time domain for each data set was zeroed to time zero, such that times prior to the start of the protocol received negative time values and times after the start received positive time values. For the purpose of averaging serum sodium over time across patients, the time domain was normalized by tracking serum sodium across serial laboratory sodium checks (see Fig. 1b). The initial sodium correction phase was defined as the time from order initiation until the time that the serum sodium rose to at least 136 mEq/l. Maintenance phase was defined as the period from the time of the first serum sodium of at least 136 mEq/l to the last serum sodium measurement prior to the date/time of the physician's protocol discontinuation order. Analysis of time spent in the goal range and the degree of undershoot and overshoot was restricted to sodium values in the maintenance phase. For the purpose of analyzing undershoot and overshoot, the following sodium ranges were pre-specified: *profound undershoot* was defined as [Na] <130 mEq/l, *mild undershoot* was defined as [Na] 130–135 mEq/l, goal range was defined as [Na] 136–145 mEq/l (normal sodium concentration), and *overshoot* was defined as [Na] >145 mEq/l. The rate of initial sodium correction was determined by measuring the time from protocol start to the time of the first serum sodium laboratory measurement of at least 136 mEq/l and by rate of sodium correction from the last sodium measurement prior to protocol start to the first serum sodium laboratory measurement of at least 136 mEq/l, expressed in (mEq/l)/h.

Nursing Survey

To address the accuracy of interpretation of the standard hypertonic saline sliding-scale protocol, we administered an electronic survey of 46 full-time nurses in the ICU of the Kaiser Permanente Medical Center, Redwood City who had administered the hypertonic saline protocol in routine clinical practice prior to taking the survey. Survey responses were obtained anonymously via web-based survey software. Each respondent provided their nursing staff level (job position) and the number of years since nursing school graduation. Respondents then answered 10 questions in which the standardized protocol was displayed, a current 3% NaCl infusion rate was given, and the results of the most recent sodium laboratory determination were provided. The respondents chose one of 11 possible multiple-choice answers (hold infusion, or a new drip rate with options ranging from 10 to 100 ml/h) for each of the 10 questions.

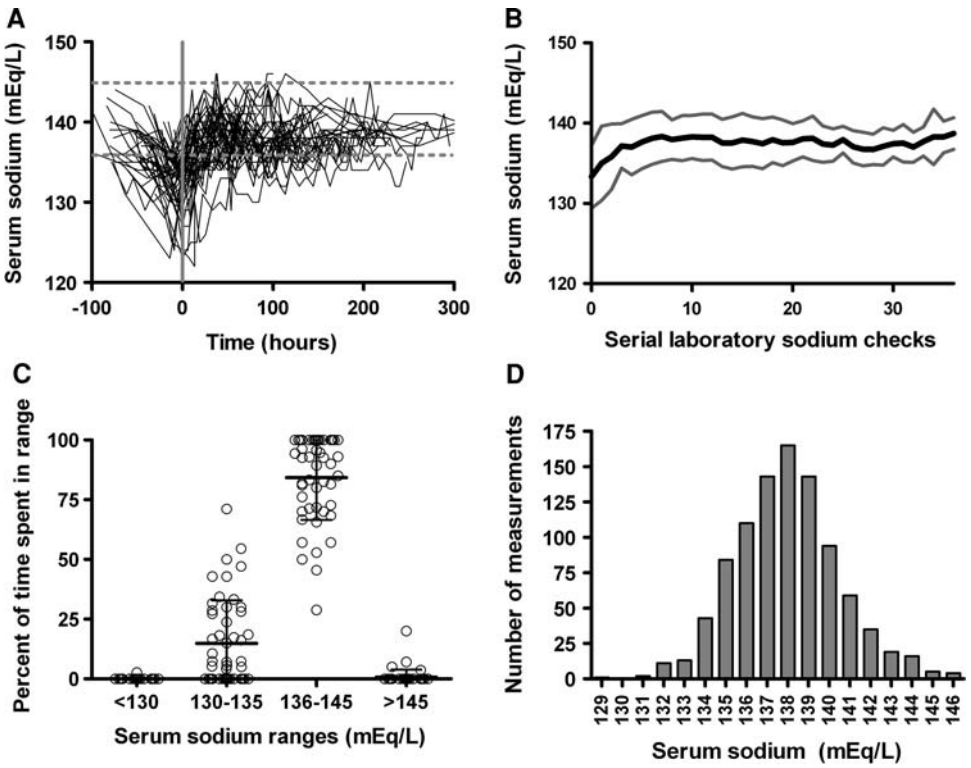

Fig. 1 Performance characteristics of the hypertonic saline infusion protocol during initial treatment and maintenance. **a** Individual graphs of all patients treated with the standardized hypertonic saline protocol. *Gray dashed horizontal lines* indicate the upper and lower limits of the normal serum sodium range (136–145 mEq/l). The *solid gray vertical line* indicates time zero for each tracing, the time of the first serum sodium value obtained after the physician order to start the standardized hypertonic saline protocol. **b** Plot of the mean serum sodium after initiation of the standardized hypertonic saline protocol. The *black line* shows the mean serum sodium, and the *gray lines* show ±standard deviation. Serial laboratory sodium checks (obtained approximately every 6 h) are displayed on the *x*-axis to allow for averaging. **c** Percentage of maintenance phase spent in specific serum sodium ranges (profound undershoot [<130], mild undershoot [130–135], goal range [136–145], and overshoot [>145]). Scatter plots show percentage of maintenance phase spent in each range of serum sodium for each patient treated (*open circles*). *Solid lines* indicate the mean (±standard deviation) amount of time spent in each range. **d** Histogram showing the distribution of serum sodium values across all sodium measurements in all patients during the maintenance phase

Statistics

Standard descriptive statistics were used for the performance analysis of the standardized hypertonic saline protocol. Averages are presented as mean ± standard deviation unless otherwise specified. For the Nursing survey, the relationship between nursing experience or staff level and accuracy in interpretation of the hypertonic saline sliding-scale protocol was explored using Fisher's exact test. The 95% confidence intervals were determined by the binomial exact method.

Results

Patient Characteristics

Over a 1-year period at our institution, 49 patients were treated with the standardized hypertonic saline infusion protocol shown in Table 1. Fifty-one percent of the patients were female, and mean patient age was 59 ± 15 years. Principal diagnoses were SAH (42.9%), intracerebral hemorrhage (20.4%), hydrocephalus (10.2%), brain tumor(s) (10.2%), subdural hematoma (6.1%), intraventricular hemorrhage (4.1%), meningitis (2%), cerebellar hemorrhage with hydrocephalus (2%), and both subarachnoid and intracerebral hemorrhage (2%). Of the 49 patients, 51% had hypertension, 12% had type 2 diabetes mellitus, and 2% had congestive heart failure. The average weight was 76.8 ± 18.6 kg, the average body mass index (BMI) was 27.2 ± 5.6, and the average body surface area (BSA) was 1.88 ± 0.27 m^2 [20].

Analysis of Protocol Performance

Graphical display of the serum sodium values over time for all 49 patients shows that patients demonstrated a rapid onset of hyponatremia prior to the start of the protocol

(Fig. 1a). Following the start of the protocol, sodium levels rose at variable rates, and then sodium values were largely maintained in the goal range (Fig. 1a, note dotted line showing the upper and lower limits of the normal sodium goal range). Some degree of mild undershoot can be appreciated, but little overshoot was seen. Analysis of the percentage of time spent in pre-specified sodium ranges across the patients showed that 0.06 ± 0.39% of the time was spent in profound undershoot (Na <130 mEq/l), 14.9 ± 18.1% of the time was spent in mild undershoot (Na 130–135 mEq/l), 84.3 ± 17.8% of the time was spent in goal range (Na 136–145 mEq/l), and 0.7 ± 3.1% of the time was spent in overshoot (Na >145 mEq/l) (Fig. 1c). Taking all laboratory values during maintenance phase together, 83.8% (95% confidence interval 81.3–86.1%) of sodium values (797/951 values) were in goal range (Na 136–145 mEq/l). The median sodium value during maintenance phase was 138 mEq/l and the distribution of sodium values was approximately normal (Fig. 1d). Average time on the protocol was 6.9 ± 4.1 days (range = 1–20 days).

The mean rate of initial sodium correction was 0.44 ± 0.36 (mEq/l)/h (Fig. 2a). The mean time from protocol start to goal sodium concentration (136 mEq/l or higher) was 19.7 ± 17.8 h (Fig. 2b). The time to reach goal sodium concentration was only modestly associated with the degree of hyponatremia prior to protocol initiation (Fig. 2c, $r2 = 0.27$). No relationship was found between rate of initial correction and measures of patient size (weight, BMI, or BSA).

No clinical adverse events attributable to infusion of hypertonic saline such as CPM or congestive heart failure exacerbation were encountered.

Nursing Survey

To determine the accuracy of order interpretation when clinical nurses in the ICU setting use our standardized hypertonic saline infusion protocol, we performed an anonymous web-based survey in which ICU nurses were asked 10 questions that assessed their understanding and interpretation of the standardized protocol given sample current 3% NaCl infusion rates and new sodium laboratory data. For the 46 respondents, across all 10 questions, the mean correct response rate was 95.9%. Scores for individual nurses ranged from 70% correct to 100% correct: 4.3% had a score of 70% correct, 4.3% had a score of 80% correct, 19.6% had a score of 90% correct, and 71.7% had a score of 100% correct. Neither nursing level (Staff Nurse, Levels I–III) ($P = 0.54$, Fisher's exact test) nor amount of time out of nursing school in 5-year increments ($P = 0.24$, Fisher's exact test) were associated with the aggregate score on the 10-question nursing survey.

Discussion

We present here the performance characteristics of a novel sliding-scale order set to initiate and maintain intravenous hypertonic saline (3% NaCl) infusion for the treatment of ANH. We find that use of this protocol allows for reliable correction and maintenance of serum sodium in the goal range 136–145 mEq/l with very low risk of overshoot into hypernatremia. Minimal mild undershoot into hyponatremia was encountered after the goal sodium concentration was achieved, and there was almost no profound undershoot. In clinical practice, the authors find that use of this protocol greatly simplifies the treatment of ANH: often the clinician writes the protocol order once, and the only further intervention required is to decide when to discontinue the protocol.

The rate of correction occurred over a clinically acceptable range for the treatment of ANH. Guidelines for maximal rates of sodium correction using hypertonic saline infusion in other clinical situations to avoid CPM apply specifically to the treatment of chronic hyponatremia or hyponatremia of unknown duration, as acute hyponatremia can be safely corrected more rapidly without danger of CPM. For this reason, we only use the protocol described here for patients in whom the time course of hyponatremia is known to be acute.

On the other side of the spectrum, the lack of significant problems with overshoot into hypernatremia with our protocol may be clinically important, as hypernatremia in SAH patients has been found to associate with poor cardiac and neurological outcomes [21]. Although our study was not designed to address this, it is possible that regulation of the hypertonic saline infusion rate by sliding-scale adjustment might have a lower risk of overshoot into hypernatremia than would be encountered with empiric physician adjustment. Consistent with this hypothesis, a recent study of hypertonic saline maintenance fluid use in the Neuro-ICU setting without a sliding-scale adjustment protocol found that 52.3% of patients developed hypernatremia with Na >155 mEq/l and 33.6% developed hypernatremia with Na >160 mEq/l [13]. In contrast, less than 1% of sodium values in our study were >145 mEq/l.

The accuracy of nursing interpretation of the order set as assayed by our anonymous survey was very good, but not 100%. Despite this imperfection in interpretation, the actual performance of the order set remains very reliable. This may be due to the fact that during use of the protocol, nurses can double-check their interpretation with their colleagues, a pharmacist, or the ordering physician. Alternatively, occasional errors in interpretation of how to change the drip rate may not translate into major swings in serum sodium concentration.

In addition to using hypertonic saline to correct ANH in the neurological and neurosurgical patient population,

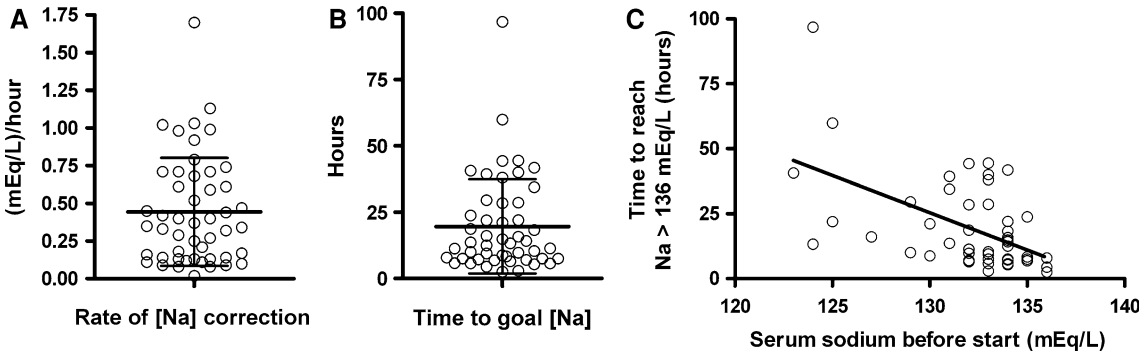

Fig. 2 Rate of initial sodium correction. **a** Scatter plot of initial sodium correction, expressed in (mEq/l)/h. *Open circles* are individual patient rates, and *solid black bars* show mean (±standard deviation). **b** Scatter plot of time to reach goal sodium (136 mEq/l or higher). *Open circles* are individual patient rates, and *solid black bars* show mean (±standard deviation). **c** Relationship between serum sodium before start of protocol and the time to reach goal sodium. *Open circles* are individual patient values, and the *solid black line* shows the linear regression of the data ($r2 = 0.27$)

many centers are now using bolus and continuous hypertonic saline administration as osmotherapy for raised intracranial pressure [22–25]. The present study does not address whether a sliding-scale protocol for hypertonic saline adjustment might prove useful in this setting, as our protocol is specific to treatment of hyponatremia with a goal of normal sodium concentration. It is possible that adjustment of the target ranges upward might prove useful to maintain supranormal sodium concentrations to reduce intracranial pressure, but our current data do not address this possibility. A separate analysis of such a protocol would be necessary to determine performance characteristics.

Our study has limitations. This is a retrospective analysis of performance characteristics of a single protocol, and does not have a comparator group. As this sliding-scale protocol was introduced at the onset of hypertonic saline use for ANH at our hospital, no historical control group exists for comparison. This analysis is not an attempt to examine the effects of a sliding-scale hypertonic saline protocol on clinical outcomes, and no conclusions can be drawn in this regard. MRI was not performed in all patients to exclude the possibility of subclinical CPM.

In summary, the protocol described here for the adjustment of intravenous 3% NaCl infusion appears to be safe and reliable for treating ANH.

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