Continuous Versus Bolus Infusion of Hypertonic Saline in the Treatment of Symptomatic Hyponatremia Caused by SIAD

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Background: Acute hyponatremia is a medical emergency that confers high mortality, attributed primarily to cerebral edema. Expert guidelines advocate the use of intravenous boluses of hypertonic saline rather than traditional continuous infusion to achieve a faster initial rise in plasma sodium (pNa) concentration. However, there is a limited evidence base for this recommended policy change.

Methods: We prospectively assessed the clinical and biochemical outcomes in patients treated for symptomatic hyponatremia caused by syndrome of inappropriate antidiuresis in response to intravenous bolus treatment with 3% saline (100 mL, repeated up to two more times) and compared the outcomes to retrospective data from patients treated with continuous intravenous infusion of low-dose (20 mL/h) 3% saline.

Results: Twenty-two patients were treated with bolus infusion and 28 with continuous infusion. Three percent saline bolus caused more rapid elevation of pNa at 6 hours [median (range) 6 (2 to11) vs 3 (1 to 4) mmol/L, $P < 0.0001$], with a concomitant improvement in Glasgow Coma Scale (GCS) [median (range) 3 (1 to 6) vs 1 (−2 to 2), $P < 0.0001$] at 6 hours. Median pNa concentration was similar at 24 hours in the two treatment groups. The administration of a third saline bolus was associated with greater need for dextrose/dDAVP to prevent overcorrection (OR 24; $P = 0.006$). There were no cases of osmotic demyelination in either group.

Conclusion: Three percent saline bolus produces faster initial elevation of pNa than continuous infusion with quicker restoration of GCS, and without osmotic demyelination. Frequent electrolyte monitoring, and judicious intervention with dDAVP is required to prevent overcorrection with bolus therapy. ***(J Clin Endocrinol Metab* 104: 3595–3602, 2019)**

Hyponatremia that presents with signs and symptoms of neurologic irritation is a medical emergency with high mortality (1). The presence of neurologic sequelae including headaches, diminished consciousness level, and seizures usually occurs when plasma sodium concentration decreases abruptly. If hyponatremia occurs in 48 hours or less, there is no time for cerebral adaptation, and the osmotic gradient between the brain and the relatively hyposmolar plasma facilitates the movement of water from the plasma into the brain, causing cerebral swelling, increased intracranial pressure, and the risk of death resulting from herniation of the brainstem through the foramen magnum (2). Neurosurgical patients are particularly vulnerable to developing symptomatic hyponatremia because of coexistence of other factors that may cause cerebral irritation (3). Treatment

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Abbreviations: dDAVP, desmopressin; GCS, Glasgow Coma Scale; pNa, plasma sodium; SIAD, syndrome of inappropriate antidiuresis.

strategies are aimed at reducing the osmotic gradient across the blood-brain barrier by elevation of the plasma sodium concentration. This must be carefully managed, because overcorrection of hyponatremia has the potential to cause the catastrophic development of osmotic demyelination syndrome, although this is much more likely when hyponatremia is chronic (4). To avoid the high rates of rise of plasma sodium concentration that increases vulnerability to osmotic demyelination, guidelines for management of hyponatremia have defined targets for safe elevation in plasma sodium concentration in chronic hyponatremia (5, 6). In cases of true acute hyponatremia (<24 to 48 hours), the US guidelines specify that the rate of correction need not be restricted, nor is there a need to relower sodium in cases of rapid correction (5); this distinction is less clear in European guidelines (6). In clinical practice, the duration of hyponatremia is often unknown and even though neurologic symptoms would suggest that the decrease in plasma sodium has been acute, hyponatremia is assumed to be chronic and the appropriate targets for correction are respected.

Recent guidelines have recommended changes to the management of acute symptomatic hyponatremia (5, 6). Traditionally, hyponatremia with neurologic sequelae has been managed by the slow intravenous infusion of hypertonic saline, with the aim of producing a gradual elevation in plasma sodium concentration over 24 hours. The guidelines have altered their recommendations, to aim for a rapid early increase in plasma sodium of 4 to 6 mmol/L over the initial 4 hours using bolus infusions of hypertonic saline (5, 6). This initial target is derived from neurosurgical data that demonstrated that an increment of 5 mmol/L reverses clinical signs of transtentorial herniation and reduces intracranial hypertension by nearly 50% within an hour of hypertonic saline administration in normonatremic neurosurgical patients (7). The target of the guidelines is to elevate plasma osmolality to shift water from the brain to the plasma, thereby reducing cerebral swelling and decreasing the risk of death caused by increased intracerebral pressure. Once the early plasma sodium targets are attained and the risk of cerebral herniation is reduced, plasma sodium can slowly be returned to normal without increasing the vulnerability to osmotic demyelination.There are few data in the literature examining the effects of the implementation of the guideline changes; most published data are specifically derived from experience in the management of acute exercise-associated hyponatremia (8). We present our data that compares the biochemical and clinical outcomes in patients with symptomatic hyponatremia treated with continuous and bolus infusion of hypertonic saline.

Aims

The aim was to compare the rate of increase of plasma sodium concentration in patients with symptomatic hyponatremia caused by syndrome of inappropriate antidiuresis (SIAD), using traditional continuous infusion of hypertonic (3%) sodium chloride and the rate of increase after using bolus injection of 3% sodium chloride, as recommended by recent guidelines (5). Secondary end points were improvements in consciousness level, as measured by the Glasgow Coma Scale (GCS), and the need for reversal of overcorrection of plasma sodium with intravenous dextrose or desmopressin (dDAVP; Ferring Pharmaceuticals, Dublin, Ireland).

Methods

Setting

Beaumont Hospital is a tertiary referral university hospital in Dublin with a catchment population of 250,000; patients were largely admitted via unselected call through the emergency department. Because Beaumont Hospital is the site of the National Neurosurgery Service, some patients with traumatic brain injury or subarachnoid hemorrhage were admitted by interhospital transfer.

Patients

Patients treated with bolus of 3% saline had prospective data collection. Patients treated with continuous saline infusion were identified via computerized laboratory records; all patients with plasma sodium concentration <125 mmol/L from 2000 to 2013 had case notes screened to examine whether they had symptomatic hyponatremia, and whether they were treated with hypertonic saline infusion by the endocrinology team using hospital protocol. Clinical data were downloaded from the case notes.

Patients were considered eligible for inclusion in the study by the following criteria. (i) An underlying diagnosis of SIAD, made by standard diagnostic criteria (plasma osmolality <280 mosm/kg, urine sodium >30 mmol/L, urine osmolality >100 mosm/kg, clinical euvolemia, and normal TSH and adrenal glucocorticoid secretion) (5). (ii) The presence of neurologic sequelae and including diminished consciousness level, as defined by the GCS of <15, confusion, coma, or seizures. (iii) Exclusion of glucocorticoid deficiency. Our published data has shown that a plasma cortisol concentration of greater than 300 nmol/L is sufficient to exclude glucocorticoid deficiency in hyponatremic patients (9, 10); if random plasma cortisol concentrations are <300 nmol/L, a response of plasma cortisol concentration to intramuscular Synacthen testing (250 μg; Alfasigma, Milan, Italy) of >500 nmol/L is regarded as normal. In neurosurgical conditions, in which acute pituitary injury may render the interpretation of the Synacthen test impossible, all patients with plasma cortisol <300 nmol/L were excluded from the analysis (9). (iv) There was a record of active intervention with either continuous hypertonic saline infusion, or bolus saline infusion, administered by the endocrine team, according to agreed protocols.

Only patients with SIAD were included because recent prospective data have shown that mortality is greater in both hypervolemic and hypovolemic hyponatremia than it is in SIAD (11); we therefore wanted our intervention groups to be as homogenous as possible.

Infusion protocols

Continuous hypertonic saline infusion

Prior to 2014, the established protocol in our hospital was for patients who were admitted to the endocrine unit with symptomatic hyponatremia to be treated with slow infusion of 500 mL of 3% sodium chloride solution over 24 hours at an initial rate of 20 mL/h. The rate of infusion of 3% saline was adjusted on the basis of two hourly plasma sodium estimations, increasing or decreasing by 10 mL/h, to achieve a steady increase in plasma sodium of 8 to 12 mmol/L over the first 24 hours of admission.

Although the risk of osmotic demyelination is relatively small in acute symptomatic hyponatremia, unit policy was to discontinue saline infusion if the rate of increase of plasma sodium concentration exceeded 0.5 mmol/L per hour (projected increase in plasma sodium concentration >12 mmol/L over the initial 24 hours). If plasma sodium continued to increase at above this rate despite discontinuation of therapy, intervention with infusion of intravenous dextrose to match urine output volume was recommended, plus administration of dDAVP 1 to 2 μg subcutaneously if urine osmolality at that time was <200 mosm/kg, as per published guidelines (5, 6).

GCS measurements were made every 6 hours for the first 24 hours. Careful neurologic observations were made by ward nursing staff; if plasma sodium targets were exceeded and patients developed new neurologic symptoms, brain MRI was obtained to screen for radiological evidence of demyelination.

Bolus hypertonic saline

A policy was adopted in 2014 to follow the recommendation of US guidelines for bolus hypertonic saline treatment of those patients with hyponatremia who exhibited signs and symptoms of cerebral irritation (5). Patients were treated with a 100-mL bolus infusion of 3% sodium chloride solution over 15 minutes. Plasma sodium concentration was remeasured after 1 hour, and the bolus repeated up to two more times, to reach an elevation in plasma sodium concentration of 4 to 6 mmol/L over 6 hours. If a normal consciousness level had been achieved at this time, no further treatment was given, other than fluid restriction of 1 L over 24 hours.

If the level of consciousness was still impaired after three boluses of 3% saline, a slow infusion of hypertonic saline of 500 mL over 24 hours was begun, aiming for a target total increase in plasma sodium of 8 to 10 mmol over 24 hours, not to exceed 12 mmol/L over 24 hours (5). If normal level of consciousness was restored or if the total increase in plasma sodium concentration exceeded 8 mmol/L within the first 24 hours, the infusion was stopped. The increase in plasma sodium concentration was only corrected in the first 6 hours if it exceeded 6 mmol/L; thereafter, it was corrected if the rate of increase over 24 hours was predicted to be >12 mmol/L, as per our original protocol outlined above. A maximum pNa target increase of 8 mmol/L in 24 hours was recommended in patients at increased risk of osmotic demyelination syndrome, including those with recent alcohol excess and hypokalemia (plasma potassium <3.5 mmol/L).

In both protocols, hypertonic saline was administered through a peripheral intravenous cannula (16 to 18 gauge).

Laboratory analyses

Plasma sodium and plasma potassium were measured every 2 hours for the first 12 hours, and then every 4 hours, using ion selective electrode. Normal plasma sodium reference range is 133 to 146 mmol/L, and plasma potassium 3.5 to 5.3 mmol/L. Plasma and urine osmolality were measured by the depression of freezing point method (2400 osmometer; Fiske, Norwood, MA). Plasma cortisol was measured using a chemiluminescent immunoassay with the Beckman Coulter Unicell DXI 800 (Fullerton, CA) with intraassay coefficients of variation (CV) of 8.3%, 5%, and 4.6% at serum cortisol concentrations of 76, 438, and 865 nmol/L, respectively. Serum free T4 and TSH were measured by chemiluminescent immunoassay on the Beckman Coulter UniCel DXI 800 Access Immunoassay system.

Statistics

Continuous data are expressed as median (range) and categorical data are expressed as number (percentage) unless otherwise stated. Mann-Whitney *U* test was used to compare continuous data (nonparametric), Fisher exact test was used to compare categorical data across two groups, and Kruskal Wallis test was used to compare continuous data across three groups. A correlation analysis of the absolute values of pNa and change in pNa was performed using the Spearman ρ method. A P value of < 0.05 was considered as statistically significant. Statistical analysis was performed using Prism GraphPad 7.0.

Results

Fifty patients who had been treated in the endocrine unit for hyponatremia caused by SIAD, which was complicated by signs or symptoms of cerebral edema, were identified. Twenty-two patients were treated with bolus infusion and 28 with continuous infusion. Baseline characteristics are outlined in Table 1. There were no differences in the proportion of patients with background of alcohol excess (9% vs 14%, $P = 0.68$), or hypokalemia (23% vs 21%, $P = 0.99$) in the two groups.

Change in plasma sodium concentration

A bolus of 3% saline caused more rapid elevation of pNa at 6 hours [median change in pNa 6 (2 to 11) vs 3 (1 to 4) mmol/L, $P < 0.0001$], and 12 hours [median change in pNa 8 (4 to 11) vs 5 (3 to 9) mmol/L, $P < 0.0001$] with no difference at 24 hours [median change in pNa 10 (6 to 13) vs 10 (6 to 12) mmol/L, $P = 0.9$] (Table 2 and Fig. 1). A lower baseline pNa was associated with higher increment in pNa at 24 hours (r −0.49; 95% CI, −0.69 to −0.22; $P = 0.0006$). There was no association between baseline urine osmolality and rate of change in pNa at 24 hours.

Change in GCS

The more rapid elevation in pNa seen in the bolus group was accompanied by a more favorable improvement in GCS at 6 hours [median (range) 3 (1 to 6) vs 1 (−2 to 2), $P < 0.0001$]), and 12 hours [median (range) 3 (1 to 6) vs 2 (−2 to 3), $P = 0.001$]. The results were similar when data from the four patients who died were removed from the analysis [median (range) 3 (1 to 6)

Table 1. Baseline Demographics and Initial Biochemical Test Results

	Bolus	Infusion	
	n = 22	n = 28	*P*
Age, y	56 (22–71)	57 (24–76)	0.68
Male/female	13/9	16/12	>0.99
Cause of SIAD, n			
Neurosurgical	5	8	
Respiratory	5	6	
Medications	4	6	
Malignancy	5	5	
Other	3	3	
Chronicity, n			
Acute	8	8	
Chronic	8	10	
Unknown	6	10	
Risk factors for ODS, n			
Alcohol excess	2	4	0.68
Serum K <3.5 mmol/L	5	6	0.99
Baseline pNa, mmol/L	119 (108–124)	121 (114–125)	0.3
Urine Na, mmol/L	46 (30–82)	51 (33–104)	0.36
Urine osmolality, mOsm/kg	415 (189–793)	499 (186–838)	0.41
0800 cortisol, nmol/L	572 (276–847)	475 (276–936)	0.69
TSH, mIU/L	1.1 (0.4–3.5)	1.1 (0.4–3.6)	0.93
Baseline GCS	12 (8–14)	12 (5–14)	0.66

Data are expressed as median (range).

Acute hyponatremia, <48-hour duration; chronic hyponatremia, >48-hour duration.

Abbreviations: K, potassium; Na, sodium; ODS, osmotic demyelination syndrome.

vs 1 (−1 to 2), $P = 0.0002$] at 6 hours and 3 (1 to 6) vs 2 (0 to 3) at 12 hours in patients treated with bolus and continuous infusion, respectively. The improvement in GCS was similar in the two groups at 24 hours [median (range) 3 (1 to 7) vs 3 (1 – 6), $P = 0.3$] (Table 2 and Fig. 2).

Overcorrection

Patients treated with boluses of 3% saline were more likely to require intravenous dextrose and/or dDAVP to offset overcorrection of pNa (5/22 vs 0/28, $P = 0.008$). Three patients in the bolus group (3/22, 14%) received dDAVP to halt a hypotonic aquaresis (urine osmolality <200 mosm/kg). Two patients received one dose (24-hour pNa increase 10 mmol/L in both patients) and a third received two doses (24-hour pNa increase 12 mmol/L). Despite an increased requirement for dextrose/dDAVP in the bolus group, however, there was no difference in 24-hour pNa increase between the two

Table 2. Biochemical and Clinical Outcomes in Patients Receiving 3% Hypertonic Bolus or Continuous Infusion

	Bolus	Infusion	
	n = 22	n = 28	*P*
Change pNa, mmol/L			
6 h	6 (2–11)	3 (1–4)	<0.0001
12 h	8 (4–11)	5 (3–-9)	<0.0001
24 h	10 (6–13)	10 (6–12)	NS
Change GCS			
6 h	3 (1–6)	1 (−2 to 2)	<0.0001
12 h	3 (1–6)	2 (−2 to 3)	0.0001
24 h	3 (1–7)	3 (1–6)	NS
Volume of 3% saline administered per 24 h, mL	200 (100–600)	500 (160–840)	<0.0001
pNa increase 8–12 mmol per 24 h, n	17	21	0.45
pNa increase >12 mmoL per 24 h, n	1	0	0.48
Need for dextrose and/or dDAVP, n	5	0	0.008
Mortality, n	0	4	0.12

Data are expressed as median (range).

Abbreviation: NS, not significant.

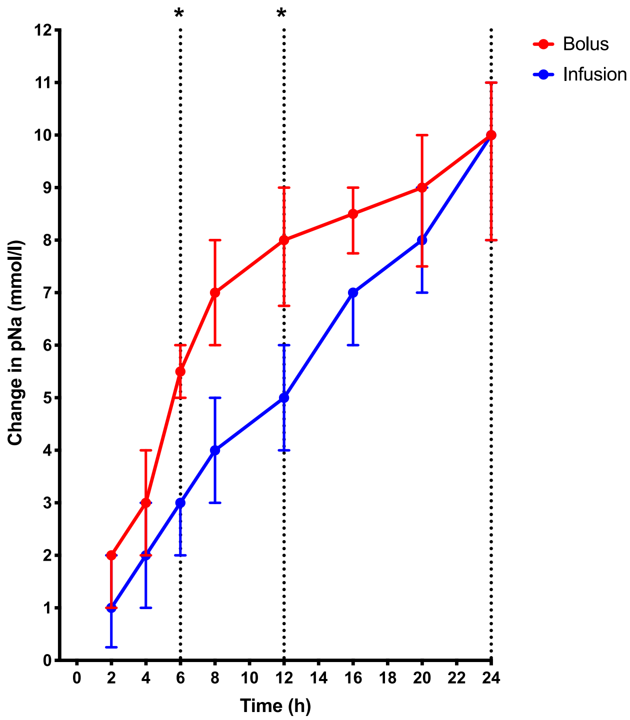

Figure 1. Change in pNa concentration from baseline at each time point. Data expressed as median and interquartile range (IQR). Asterisks indicate a *P* value of < 0.05.

groups or in the number of patients in whom pNa increased >12 mmol/L per 24 hours (1 vs 0 patients in the bolus and infusion groups respectively, $P = 0.48$) (Table 2).

Median (range) volume of hypertonic saline administered to patients treated with continuous infusion was 500 (100 to 840 mL) vs 200 (100 to 600 mL) in the bolus group ($P < 0.0001$); hypertonic saline was discontinued prior to 24 hours in 8 of 24 (33%) patients because of an increase in pNa >0.5 mmol/L per hour. Rate of increase exceeded 0.5 mmol/L per hour in 20 patients (71%) at some point over the first 24 hours, necessitating down-titration of rate of infusion, whereas the rate was up-titrated at some point in 17 patients (61%). There was no relationship between baseline plasma potassium concentration and subsequent overcorrection of pNa. There were no cases of osmotic demyelination in either group.

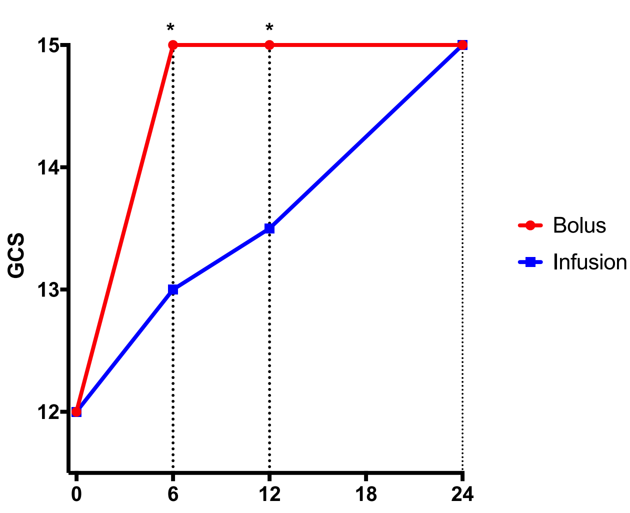

Figure 2. GCS at each time point. Data expressed as median. Asterisks indicate a *P* value of < 0.05.

Number of boluses

Six patients received one bolus, 12 patients received two boluses, and 4 patients received three boluses of 3% saline. Baseline pNa was similar across these three groups [median (range) 122 (114 to 124) mmol/L, 119 (112 to 122) mmol/L and 120 (108 to 124) mmol/L in those receiving 1, 2, and 3 boluses, respectively, $P = 0.37$].

Four of the five patients who were treated for overcorrection had received a third bolus of 3% saline; administration of a third bolus was associated with increased use of dextrose/dDAVP within the first 24 hours compared with those receiving only one or two boluses, OR 24 (95% CI, 2.1 to 322; $P = 0.006$). When changes in pNa were compared between those receiving one, two, or three boluses, there were no difference at 6, 12, or 24 hours (Table 3).

Mortality

Four patients died; all four had been treated with slow infusion. Three patients presented with seizures and one with out-of-hospital cardiac arrest; GCS on arrival ranged from 5 to 7. Median increase in pNa at six hours was 2 (2 to 4) mmol/L in these four patients, compared with a median increase of 4 (1 to 11) mmol/L in the group overall (P = NS). The etiology of hyponatremia, clinical presentation, and biochemistry for these four patients is summarized in Table 4.

Discussion

Hyponatremia complicated by neurologic symptoms is a medical emergency, with substantial associated mortality (12). In a major therapeutic policy change, bolus administration of 3% saline has been recommended to replace slow intravenous infusion in recent guidelines (5, 6). This study describes the performance of the two methods in a single center. Our data show that the newly recommended bolus treatment delivered faster elevation of pNa over the initial six hours; the quicker earlier elevation in plasma sodium concentration was associated with faster effective restoration of GCS without osmotic demyelination.

The reasoning behind the change in strategy for managing symptomatic severe hyponatremia was based on the hypothesis that early elevation in plasma sodium concentration might reduce cerebral edema. The median six-hour increase in plasma sodium in the bolus saline treatment group was 6 mmol/L, which is similar to that reported to

Table 3. Baseline and Change in Plasma Sodium in Patients Who Received One, Two, and Three Boluses of 3% Saline

	1 Bolus	2 Boluses	3 Boluses	
	n = 6	n = 12	n = 4	*P*
Baseline pNa, mmol/L	122 (114–124)	119 (112–122)	120 (108–124)	0.38
Change in pNa at 6 h, mmol/L	5 (4–6)	6 (4–8)	6 (2–11)	0.59
Change in pNa at 12 h, mmol/L	7 (4–8)	8 (6–9)	10 (5–11)	0.06
Change in pNa at 24 h, mmol/L	9 (6–11)	11 (7–13)	10 (7–12)	0.22

Data expressed as median (range).

cause 50% reduction in cerebral edema in neurologic studies (7). It also represented the upper target recommended by both the US and European guidelines (5, 6). The six-hour increase in plasma sodium concentration was greater in the bolus treatment group, compared with the infusion treatment group (6 vs 3 mmol/L, $P < 0.0001$)). The greater increase in plasma sodium concentration produced by bolus treatment was associated with improvement in conscious level, as measured by the GCS. The GCS offers a clinically relevant surrogate for intracranial pressure, and we would therefore contend that more rapid elevation in plasma sodium concentration was associated with demonstrable clinical improvement.

The most serious adverse event in the treatment of hyponatremia is the development of osmotic demyelination, which occurs when plasma sodium is reversed too quickly (4). Although this complication is uncommon in acute hyponatremia (13), we could not be certain in all cases that the onset of hyponatremia had occurred within the accepted time frame of <48 hours, which is by consensus used to define acute hyponatremia. Therefore, we were careful to avoid overcorrection of plasma sodium concentration by more than the maximum recommended increase of 12 mmol/L over 24 hours (5). The protocols for both treatment schedules therefore allowed for reversal of over-rapid correction with intravenous dextrose and/or dDAVP therapy if rate of increase exceeded 0.5 mmol/L per hour in patients treated with continuous infusion, or 6 mmol/L in the initial 6 hours in those treated with bolus infusion.

It is an important observation that patients receiving bolus hypertonic saline therapy were more likely to require rescue therapy with intravenous dextrose and/or dDAVP than those receiving continuous infusion. This could reflect greater caution in our application of the indications for intervention for overcorrection, with the use of an unfamiliar protocol. Certainly, the increase in plasma sodium concentration was similar in the two treatment protocols, other than the higher 6-hour plasma sodium increase, which was the specific target of the new regimen. However, the higher rate of intervention after the use of the third hypertonic saline bolus would prompt us to recommend particular caution after a third bolus is administered. In addition, despite careful monitoring of plasma sodium, one-third of all patients had an increase in pNa of >10 mmol/L in 24 hours, which indicates that even in experienced centers with expertise in hyponatremia management, dynamic control of plasma sodium concentration in the face of pronounced aquaresis can be challenging. Overcorrection of plasma sodium because of hypotonic aquaresis (urine osmolality <200 mosm/kg) was documented in three patients who were treated with bolus infusion (3/22, 14%) in our study. All three had presented with an acute decrease in plasma sodium, on a history of chronic SIAD caused either by bronchiectasis (n = 2) or lung cancer (n = 1), and all had received three boluses of hypertonic saline. They received dDAVP in addition to 5% dextrose to prevent overcorrection with good effect (maximum 24-hour pNa increase 12 mmol/L).

Although numbers are too small to comment statistically on mortality, we believe that an initial greater improvement in GCS at 6 hours could translate to better mortality outcome, if this was tested in a study powered to examine mortality rates. The first randomized clinical trial to investigate the efficacy and safety of these two therapeutic approaches is currently recruiting to answer this question. The Korean SALSA trial is a prospective, multicenter randomized controlled trial, which aims to recruit 178 patients with severe symptomatic hyponatremia caused by SIAD and randomly assign them to treatment with either rapid intermittent bolus or slow continuous infusion of hypertonic saline (14). Primary outcome will be overcorrection of plasma sodium during the first 48 hours; efficacy and safety will be secondary outcomes measures.

The nonrandomized design of this study is a limitation. The retrospective nature of the continuous infusion group meant that data collection was restricted to that available in clinical notes. However, because the unit decision was to change policy on the basis of new guidelines (5), prospective data collection on the new bolus treatment had to be compared with the retrospective data that was

Table 4. Clinical Information and Biochemical Test Results for Four Patients Who Died

Patient	Sex	Age (y)	Cause of SIAD	Clinical Presentation	pNa on Arrival (mmol/L)	GCS on Arrival	Interval From Arrival to Death (h)	pNa Prior to Death (mmol/L)	Volume of 3% Saline (mL)
1	M	24	TBI	Seizures	114	6	12	118	300
2	F	48	Chronic SIAD and alcohol	Excessive alcohol intake with seizures. CT scan: cerebral edema	114	7	6	116	160
3	F	44	SSRI	Out of hospital cardiac arrest. CT scan: cerebral edema	114	5	4	116	200
4	M	27	TBI and SDH	Seizures	119	7	12	126	400

Abbreviations: F, female; M, male; SDH, subdural hemorrhage; SSRI, selective serotonin uptake inhibitor; TBI, traumatic brain injury.

available. Accepting this limitation, however, the study provides more information on biochemical and clinical responses to hypertonic saline than is currently available in the literature.

A strength of our study is the use of two distinct protocols within the same unit. Administration of hypertonic saline was supervised by the senior author in all cases, plasma sodium concentration was monitored at identical time points, and a similar rationale was used for the initiation of rescue treatment of sodium overcorrection in all study patients. In contrast, previous retrospective studies on the treatment of symptomatic hyponatremia have examined the outcomes of dissimilar protocols, rendering analysis of outcomes more complex (15–18). In the only prospective study of hypertonic saline use in acute hyponatremia (19), 100 mL of hypertonic saline, administered over 4 hours, caused elevation in plasma sodium concentration, without an increment >12 mmol/L, at 24 hours. There was no need for dextrose or dDAVP administration, and 79% of patients showed marked clinical improvement at 24 hours, with recovery of level of consciousness and no cases of osmotic demyelination. The data from this study are reassuring with regard to safety of the protocol, but the 6-hour plasma sodium targets fell short of those recommended by modern guidelines (5). The slow rate of intravenous infusion caused a mean increase in plasma sodium concentration of only 2 mmol/L after the first 4 hours. Because 38% of patients had signs of cerebral irritation on presentation, modern guidelines dictate that the rate of change in plasma sodium concentration that they achieved was too slow to reverse cerebral edema.

Our data have demonstrated that the biochemical outcomes in patients treated with slow hypertonic saline infusion were similar to those reported by Bhaskar *et al.* (19), with a median increase in plasma sodium after four hours of only 2 mmol/L. In contrast, bolus hypertonic saline hit the higher recommended targets, and was associated with improved measurements of cerebral function. The objective assessment of neurologic status (GCS) at regular time points, which provided a clinical correlate to biochemical outcome, is a strength of our study.

Until recently, there was no uniform consensus on an appropriate infusion rate for hypertonic saline and the initial rate of continuous infusion, 20 mL/h, traditionally used in our unit pre-2014 is lower than that recommended in some guidelines (5, 6); this could be seen as a limitation of the study. However, the median increase in pNa in patients treated with continuous infusion at six hours was 3 mmol/L, against guideline recommendations at that time which advised a maximum rate of rise of 0.5 mmol/L per hour. It is possible that use of higher infusion rates (up to 2 mL/kg per hour) early, may result in pNa increase and GCS benefits closer to that demonstrated in the bolus group. However, if we had used higher initial rates of infusion, guideline limits at that time would have been exceeded, leading to greater rate of reduction of infusion rate, or even reversal of the rise in pNa with dextrose and/or dDAVP. Applying the Adrogue formula is an alternative strategy to determine initial infusion rate of 3% saline (20). However, from a practical perspective, accurate weight measurement is difficult in patients who present with acute neurologic disturbance, and the use of such formulas may delay initiation of treatment, thus, this is not an approach we use in our practice.

We deliberately selected a homogenous group of patients with clearly defined SIAD in order not to bias our results with groups of hyponatremic patients with different prognoses. Although we argue that this is a further strength of our study, our data cannot be extrapolated to patients with hypovolemic or hypervolemic hyponatremia, which have higher mortality (11). Further prospective studies are therefore needed.

Conclusion

Bolus intravenous injection of 3% sodium chloride solution delivers faster elevation of pNa, with more effective restoration of GCS within the first six hours of presentation of symptomatic severe hyponatremia caused by SIAD, than traditional continuous infusion of hypertonic saline. Plasma sodium concentration was similar at 24 hours with the two methods. Although neither group had osmotic demyelination as a complication of treatment, the use of dextrose/dDAVP to prevent overcorrection was more often required after bolus therapy. Larger prospective randomized studies are required to determine if this initial biochemical and neurologic benefit will translate into improved mortality; the results of the ongoing SALSA randomized controlled trial (14) may answer these questions.

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