HYponatremia in Neurosurgical Patients: Clinical Guidelines Development

OBJECTIVE: Neurosurgical patients have a high risk of hyponatremia and associated complications. We critically evaluated the existing literature to identify the determinants for the development of hyponatremia and which management strategies provided the best outcomes.

METHODS: A multidisciplinary panel in the areas of neurosurgery, nephrology, critical care medicine, endocrinology, pharmacy, and nursing summarized and classified hyponatremia literature scientific studies published in English from 1950 through 2008. The panel’s recommendations were used to create an evaluation and treatment protocol for hyponatremia in neurosurgical patients at the University of Florida.

RESULTS: Hyponatremia should be further investigated and treated when the serum sodium level is less than 131 mmol/L (class II). Evaluation of hyponatremia should include a combination of physical examination findings, basic laboratory studies, and invasive monitoring when available (class III). Obtaining levels of hormones such as antidiuretic hormone and natriuretic peptides is not supported by the literature (class III). Treatment of hyponatremia should be based on severity of symptoms (class III). The serum sodium level should not be corrected by more than 10 mmol/L/d (class III). Cerebral salt wasting should be treated with replacement of serum sodium and intravenous fluids (class III). Fludrocortisone may be considered in the treatment of hyponatremia in subarachnoid hemorrhage patients at risk of vasospasm (class I). Hydrocortisone may be used to prevent natriuresis in subarachnoid hemorrhage patients (class I). Hyponatremia in subarachnoid hemorrhage patients at risk of vasospasm should not be treated with fluid restriction (class II). Syndrome of inappropriate antidiuretic hormone may be treated with urea, diuretics, lithium, demeklocycline, and/or fluid restriction (class III).

CONCLUSION: The summarized literature on the evaluation and treatment of hyponatremia was used to develop practice management recommendations for hyponatremia in the neurosurgical population. However, the practice management recommendations relied heavily on expert opinion because of a paucity of class I evidence literature on hyponatremia.

KEY WORDS: Cerebral salt wasting, Evidence-based medicine, Hyponatremia, Syndrome of inappropriate antidiuretic hormone

Hyponatremia is the most common electrolyte disorder encountered in clinical medicine (25). Approximately 1 million hospitalizations per year in the United States are for a principal or secondary diagnosis of hyponatremia. The annual cost of managing patients with hyponatremia has been estimated at $3.6 billion (25). In addition to monetary costs, hyponatremia is associated with negative outcomes for patients. Specifically, the mortality rates are significantly higher in hyponatremic patients across a broad range of primary disorders (4, 22, 56). In some disease states, such as congestive heart failure, hyponatremia is an independent risk factor for increased mortality (18, 96).

ABBREVIATIONS: ANP, atrial natriuretic peptide; CSW, cerebral salt wasting; CVP, central venous pressure; ECF, extracellular fluid; Na, sodium; ODS, osmotic demyelinating syndrome; PE, physical examination; P\text{osmol}, plasma osmolality; SAH, subarachnoid hemorrhage; SIADH, syndrome of inappropriate antidiuretic hormone
The prevalence of hyponatremia in the neurosurgical population has been reported as high as 50% (26, 74, 107, 117, 120, 140, 153). Because of the cerebral effects of hyponatremia, neurosurgical patients are at increased risk of complications. Such complications include severe cerebral edema, mental status changes, seizures, vasospasm, and death. Unfortunately, these complications may also arise from the inappropriate treatment of hyponatremia. Correction of hyponatremia that is too slow or fast can lead to cerebral edema, seizures, osmotic demyelinating syndrome, or death (1, 42, 43, 138).

Despite the costs and complications associated with hyponatremia in the neurosurgical population, few randomized studies have been completed that describe when hyponatremia becomes clinically significant and how it should be treated. The evaluation and treatment of hyponatremia are left to the discretion of the individual health care provider or treatment team. This lack of a standardized treatment approach contributes to variable outcomes. Concern about the variability in the approach to hyponatremia treatment in neurosurgery patients prompted us to develop a standardized evaluation and treatment paradigm at the University of Florida.

The algorithm that we developed specifically addresses the most common causes of hyponatremia in neurosurgery patients: the syndrome of inappropriate antidiuretic hormone (SIADH) and cerebral salt wasting (CSW). Treatment of hyponatremia in subarachnoid hemorrhage (SAH) patients is also given special consideration. The evaluation and treatment algorithm for the treatment of hyponatremia in neurosurgery patients was instituted at the University of Florida in February 2008. The goal of the algorithm was to reduce the wide range of variation in treatment options.

PATIENTS AND METHODS

This paradigm was created by a multidisciplinary group represented by neurosurgery (2 physicians, 4 nurse practitioners), nephrology (2 physicians), critical care medicine (1 physician), endocrinology (1 physician), pharmacy (1 pharmacist), and nursing (4 nurses). The collaboration between these individuals ensured development of a comprehensive yet practical approach to the treatment of hyponatremia in neurosurgical patients. The multidisciplinary group met every other month for 8 months and agreed on the most pressing questions about hyponatremia. These questions were then examined by a detailed literature search. The panel developed 3 questions about the evaluation and treatment of hyponatremia in the neurosurgical setting: 1) When should hyponatremia be further evaluated and treated? 2) What is the optimal evaluation paradigm for hyponatremia in the neurosurgical setting? 3) What is the optimal treatment paradigm for hyponatremia in the neurosurgical setting?

The literature search was performed by one of the physicians from the Department of Neurosurgery. The search terms included “hyponatremia,” “hyponatremia and neurosurgery,” “osmotic demyelinating syndrome,” “cerebral salt wasting,” “syndrome of inappropriate antidiuretic hormone,” “CSW and neurosurgery,” and “SIADH and neurosurgery” using PubMed and the Cochrane Database. The literature published between 1940 and 2008 was reviewed in both databases. Additional references were obtained from publications found by the literature search. Relevant literature was graded on quality by the multidisciplinary group based on criteria developed by Walters (16) (Table 1).

RESULTS

For the first question about identifying the parameters for evaluation of hyponatremia, 16 of 38 studies were judged appropriate for the analysis. Retrospective studies were excluded from the analysis in accordance to the evidence classification system described by Walters (16) (Table 1). For the second question on optimal evaluation, 88 studies were reviewed and all were included in the analysis. For the third question regarding treatment, 71 studies were reviewed and all were included in the analysis. The grading system was then applied according to the methodology of Lohr et al. (80) to construct clinical practice guidelines for the evaluation and treatment of hyponatremia in neurosurgical patients at the University of Florida. The guidelines were developed by the physician participants of the panel and approved by the entire panel.

DISCUSSION

Question 1: When Should Hyponatremia Be Further Evaluated and Treated (What Laboratory Values and/or Clinical Symptoms Require Intervention)?

Review of the Literature

Although hyponatremia is classically defined as a serum sodium (Na) level less than 135 mmol/L, clinically significant hyponatremia has not been clearly defined (25, 69). Hyponatremia is associated with increased mortality (22, 56). In a prospective study of patients hospitalized for medical illnesses other than dysnatremia, a serum Na level less than 130 mmol/L was associated with a 60-fold increase in fatality (11.2% versus 0.19%). Patients with a serum Na level less than 120 mmol/L had a mortality rate of 25% compared with 9.3% in patients with a serum Na level greater than 120 mmol/L (4).

Another prospective study showed that hyponatremic patients (mean serum Na level of 125.3 mmol/L) were 7 times more likely to die in the hospital and more than twice as likely to die after discharge compared with normonatremic patients, even when controlling for underlying diagnoses (P < 0.0001) (137). In another study, hyponatremic patients with an improvement in the serum Na level (≥2 mmol/L) had a mortality rate of 11.1% at 60 days post-discharge compared with a 21.7% mortality rate in those showing no improvement (115). A change in the serum Na level was a significant predictor of 60-day mortality (hazard ratio, 0.736; 95% confidence interval, 0.569–0.952 for each 1 mmol/L increase from baseline).

Additional morbidity is associated with a serum Na level less than 130 mmol/L (9, 25, 52, 69). A case-control study of emergency department patients found 21% (26 of 122) of hyponatremic patients (serum Na level <135 mmol/L) presented with falls compared with 5% (13 of 244) of normonatremic patients matched in multiple comorbidities. The mean serum Na level of hyponatremic patients was 126 mmol/L (range, 115–132). The severity of the hyponatremia did not correlate with likelihood of presenting with falls (112). A frequently cited study by Arieff et al. (8) prospectively evaluated
65 patients with a serum Na level less than 128 mmol/L. The patients in whom hyponatremia developed over 48 hours or less were all symptomatic and had a mean serum Na level of 114 mmol/L. The mean serum Na level of chronic (>48 hours) hyponatremic patients was 115 mmol/L in symptomatic patients and 122 mmol/L in asymptomatic patients. All patients in whom seizures developed had a serum Na level less than 121 mmol/L.

In SAH patients in particular, hyponatremia has a clear association with increased morbidity. Hyponatremia in SAH patients is associated with increased rates of cerebral ischemia (61, 147). In one study, in patients who were not fluid restricted, 24% who were normonatremic and 12% who were hyponatremic (serum Na < 135 mmol/L) demonstrated cerebral ischemia compared to only 12% of normonatremic patients (61). Another prospective study of SAH patients demonstrated that hyponatremia was significantly associated with poor outcomes at 3 months (odds ratio, 2.7; 95% confidence interval, 1.2-6.1). Poor outcomes were classified according to the Glasgow Outcome Scale of death, vegetative state, or severe disability (109).

The panel reviewed many other studies that also showed increased morbidity and mortality associated with hyponatremia (1, 6, 10, 11, 13, 19, 28, 31, 36, 47, 65, 100, 101, 107, 108, 117, 119, 120, 135, 136, 140, 153). The serum Na value indicating clinically significant hyponatremia varied in the literature reviewed by the multidisciplinary panel. Therefore, the panel made the following recommendation based on the best evidence and expert opinion: **hyponatremia should be further investigated and treated when the serum Na level is less than 131 mmol/L (class II).**

**Question 2: What Is the Optimal Evaluation Paradigm, Clinical and Laboratory, for Hyponatremia in the Neurosurgical Setting?**

**Review of the Literature**

Causes of hyponatremia have traditionally been categorized by body fluid status. No standard reference test exists for the evaluation of hyponatremia. The lack of standard tests for the evaluation of hyponatremia often leads to inadequate evaluations of hyponatremic patients, such as failure to check plasma osmolality (Posm), urine Na level, and urine osmolality. In a retrospective study of 104 patients with a serum Na level of less than 125 mmol/L, osmolality was measured in only 26% of patients. Mortality was higher in the group with inadequate workup and management (41% versus 20%; \( P = 0.002 \)) (61, 66). Therefore, most experts proposed a combination of physical examination (PE) findings and laboratory tests to distinguish between the causes of hyponatremia (21, 34, 43, 53, 59, 62, 69, 73, 82, 92, 104, 110, 120, 138, 143). This approach is especially important to distinguish between SIADH and CSW.

Neurosurgery patients often develop hyponatremia in the setting of natriuresis. Hyponatremia with natriuresis is caused by either SIADH or CSW after diuretic use has been excluded (50).
128). Criteria for SIADH proposed by Janicic and Verbalis (69) include $P_{osm}$ less than 275 mOsm/kg, inappropriate urinary concentration (urine osmolality >100 mOsm/kg), clinical euvoolemia (absence of orthostasis, tachycardia, decreased skin turgor, dry mucous membranes, or edema and ascites), elevated urinary Na excretion with normal salt and water intake, and absence of other causes of euvolemic hypo-osmolality (hypothyroidism, hypocortisolism). However, these criteria have proven to be inadequate in distinguishing between SIADH and CSW. Ten of 12 neurosurgery patients in a prospective study who met the laboratory criteria for SIADH (serum Na level <135 mmol/L, $P_{osm}$ <280 mOsm/kg, urine Na >25 mmol/L, and urine osmolality >$P_{osm}$) had low blood cell mass, plasma volume, and total blood volume compared with controls (94). The authors suggested treating these patients with blood transfusions and replacement of volume. A retrospective study of 50 patients with a serum Na level less than 130 mmol/L and a diagnosis of SIADH showed an improvement in serum Na level with fluid restriction in only 68% of cases (64).

Extracellular fluid (ECF) status is the key to distinguishing between SIADH and CSW (2, 21, 43, 49, 53, 59, 62, 82, 84, 92, 104, 105, 110, 125, 138, 152). Determination of ECF status using PE alone has been shown to be inaccurate (31, 66, 83, 116). A prospective study of 35 patients with a serum Na level less than 130 mmol/L divided the patients into 4 groups (those who had received diuretics, polydipsic patients, saline responders, and saline nonresponders). Saline responders were patients who had a sustained increase in plasma Na of at least 5 mmol/L. All patients were initially determined to be hypo- or normovolemic based on PE findings (mucosal hydration, skin turgor, jugular vein distention), orthostatic changes in pulse (increase of 10% upright compared with supine), and systolic blood pressure (decrease of 10% upright compared with supine). The saline responders and those who had received diuretics were considered the true hypovolemic patients. Clinical determination of ECF status using PE finding parameters had a sensitivity of 41.1% and a specificity of 80%. This and other studies found that a low fractional excretion of Na and urea are associated with saline responsiveness (30, 91).

Based on several studies of the evaluation of hyponatremia, a urinary Na level less than 30 mmol/L has a positive predictive value of 71% to 100% for an infusion of 0.9% saline to increase the serum Na level (30, 91). Some authors propose an infusion of isotonic saline and measurement of urinary Na excretion to determine the cause of the hyponatremia (90). However, these recommendations targeted non-neurosurgical patients.

Uric acid has also been used to distinguish SIADH from other causes of hyponatremia. In the study of saline responsiveness in hyponatremic patients, the polydipsic and saline non-responsive patients tended to have lower plasma urea and uric acid compared with the other 2 groups (91). A serum uric acid level of less than 4 mg/dL (in the presence of hyponatremia) has been calculated to have a positive predictive value for SIADH of 73% to 100% (17, 48, 90, 106). However, the definitions for SIADH used in these studies were broad and most likely included patients with CSW.

To distinguish between SIADH and CSW, central venous pressure (CVP) can be used to determine intravascular volume status. Damaraju et al. (38) treated hyponatremia based on CVP values (<5 cm H$_2$O, 6–10 cm H$_2$O, >10 cm H$_2$O). Hypovolemic patients (CVP <5 cm H$_2$O) were given normal saline (50 mL/kg/d) and salt (12 g/d). Normovolemic patients (CVP 6–10 cm H$_2$O) were given normal saline with 12 g of salt per day. In addition, patients with anemia (hematocrit <27%) were administered whole blood. No patients were found to be hyper- volemic (CVP >10 cm H$_2$O). The serum Na level was corrected within 72 hours in 73% of patients and 12% more within the next 24 to 48 hours. The patients included 3 nonresponders, 2 of whom were found to have severe dehydration on blood volume measurements. Another prospective study used CVP to categorize 7 hyponatremic patients as SIADH (CVP 6–10 cm H$_2$O) and 4 patients as CSW (CVP <6 cm H$_2$O). The SIADH patients were treated with less than 800 mL/d of fluid restriction, and the CSW patients were treated with fluid replacement (50–100 mL/kg/d). Four patients achieved a normal serum Na level within 36 hours and the other 7 patients within 72 hours (46). Treatment of hyponatremia in SAH has generated controversy given the association of fluid restriction or dehydration with symptomatic vasospasm (61, 147). Traditionally, hyponatremia in SAH patients has been attributed to SIADH (120). However, more recent studies show that hyponatremic SAH patients often demonstrate a negative Na balance (loss of Na in urine is greater than Na intake per day) and lower ECF (74, 121). Peptides such as atrial natriuretic peptide (ANP), brain natriuretic peptide, C-type natriuretic peptide, and digoxin-like substance have been found in SAH patients. Some have suggested a correlation between the presence of these peptides and CSW causing delayed hyponatremia (20, 33, 45, 67, 74, 139, 148). In a prospective study of 8 SAH patients who met the criteria for SIADH proposed by Janicic and Verbalis (69), a linear relationship was found between ANP levels and urinary Na excretion. However, ADH levels did not correlate with Na loss (145).

The ANP level was found to be elevated in 14 SAH patients compared with controls in a study by Wijdicks et al. (146). Eight patients had a twofold increase in ANP above baseline and demonstrated natriuresis and a negative Na balance. Three of these patients had infarcts. Another study showed that cerebrospinal fluid adrenomedullin concentrations were significantly increased in hyponatremic patients (Na <135 mmol/L) and patients in whom delayed ischemic neurological deficits developed (72). Brain natriuretic peptide has also been shown to correlate with hyponatremia after SAH (20, 139).

Natriuretic peptides are associated with natriuresis but not always with hyponatremia. In a study of 21 SAH patients, increased ANP was present in all SAH patients compared with controls, regardless of the serum Na level (44).

ADH has also been shown to have limited diagnostic value in hyponatremia (29). The “appropriateness” of an ADH level has not been defined. SIADH has been documented in patients with no detectable ADH (71). A prospective study of severe head injury patients found that patients in whom hyponatremia developed within 3 days of injury had higher ADH levels com-
pared with patients who developed hyponatremia a week after the injury. However, ADH was detectable in all patients (143). Nevertheless, the available data on ADH and natriuretic peptides are conflicting (72, 77, 126).

The panel reviewed the full range of publications on the evaluation of hyponatremia (3–5, 14, 15, 19, 23, 24, 27, 34–37, 44, 51, 52, 58, 63, 81, 97, 99, 102, 114, 117, 122–124, 132, 136, 141, 144). Having reviewed the data, the panel recommended a general approach to the evaluation of hyponatremia (Fig. 1 and Table 2). Using the evaluation paradigm, a serum Na value less than 131 mmol/L should prompt a workup that includes measuring serum and urine osmolarity, urine electrolytes, uric acid, and an evaluation of ECF volume status. A normal or high serum osmolarity may result from laboratory error or pseudohyponatremia from hyperglycemia or hypertriglyceridemia. Hypotonic hyponatremia is categorized by ECF volume status. Volume status can be determined based on the criteria listed in Table 2. Hypovolemia results from extrarenal loss or intrarenal loss such as CSW, diuretics, or adrenal insufficiency. In normovolemic patients, thyroid disease, hypocortisolism, and polydypsia should be ruled out before a diagnosis of SIADH is given. Moreover, hypervolemic hyponatremia is less common in neurosurgical patients, and the treatment team should rule out cirrhosis, congestive heart failure, and renal failure.

Recommendation
- Evaluation of hyponatremia should include a combination of PE findings, basic laboratory study results, and invasive monitoring when available (class III).
- Obtaining levels of hormones such as ADH and natriuretic peptides is not supported by the literature (class III evidence).

Question 3: What Is the Optimal Treatment Paradigm for Hyponatremia in the Neurosurgical Setting?

Rate of Correction

Generally, the rate of correction of hyponatremia is determined by the severity of symptoms and rapidity of onset. Studies have shown that the severity of hyponatremia symptoms correlates with the magnitude of hyponatremia and the rate of onset (4, 8, 153). Given the significant morbidity/mortality associated with severely symptomatic hyponatremia, evidence exists to correct symptomatic severe hyponatremia aggressively with

TABLE 2. Diagnostic criteria for cerebral salt wasting and syndrome of inappropriate antidiuretic hormone

<table>
<thead>
<tr>
<th>CSW</th>
<th>SIADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium, mmol/L</td>
<td>&lt;135</td>
</tr>
<tr>
<td>Serum osmolarity, mOsm/kg</td>
<td>&lt;285</td>
</tr>
<tr>
<td>Urine osmolarity, mOsm/kg</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Urinary sodium, mmol/L</td>
<td>&gt;25</td>
</tr>
<tr>
<td>Weight</td>
<td>↓</td>
</tr>
<tr>
<td>Fluid balance</td>
<td>↓</td>
</tr>
<tr>
<td>Jugular venous distention</td>
<td>–</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>↑</td>
</tr>
<tr>
<td>Blood, urea, nitrogen</td>
<td>↑</td>
</tr>
<tr>
<td>Creatinine</td>
<td>↑</td>
</tr>
<tr>
<td>Uric acid</td>
<td>↓</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>↑</td>
</tr>
<tr>
<td>Central venous pressure, cm H2O</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Pulmonary wedge pressure, mm Hg</td>
<td>&lt;8</td>
</tr>
</tbody>
</table>

a CSW, cerebral salt wasting; SIADH, syndrome of inappropriate antidiuretic hormone.

b Must meet these criteria and at least 3 of the other criteria listed for a diagnosis.
developed in those whose level was corrected more slowly (134). Reinduction of hyponatremia has been reported for the treatment of ODS (103, 131).

A prospective study of 33 medical patients with symptomatic hyponatremia (mean serum Na level 108 mmol/L) showed no episodes of ODS despite an increase in mean serum Na level to 126 mmol/L within 48 hours (12). The authors evaluated retrospectively a group of 12 patients who all had evidence of cerebral demyelinating lesions at autopsy. The rate of correction of their hyponatremia was similar to the prospectively evaluated patients. However, they all had 1 of 4 characteristics: an increase in serum Na level to normal or hypertonic levels within 48 hours, a change in serum Na level of more than 25 mmol/L within 48 hours, a hypoxic episode, and/or hepatic encephalopathy (12). Based on case reports and animal data, the development of ODS is associated with the rate and magnitude of Na correction in chronic hyponatremia (48 hours), with hypokalemia, and with malnourished states (alcoholism, cirrhosis, burns) (32, 40, 57, 75, 76, 79, 127, 129).

Chronic hyponatremia should not be rapidly corrected. Generally, rapid correction at a rate of more than 1 mmol/L/h should be reserved for severely symptomatic and/or acute hyponatremia (<48 hours), with hypokalemia, and with malnourished states (alcoholism, cirrhosis, burns) (32, 40, 57, 75, 76, 79, 127, 129).

SIADH

The treatment of SIADH has been based on fluid restriction unless patients are severely symptomatic, in which case hypertonic saline is used (51, 89, 142). In a study of 55 hyponatremic patients after transsphenoidal pituitary tumor resection, all 44

![Figure 2. Treatment of cerebral salt wasting (CSW). After a diagnosis of CSW is confirmed, treatment is based on symptoms. Patients with severe symptoms should be treated in the intensive care unit (ICU) with hypertonic saline and fludrocortisone. Acute hyponatremia and/or severe symptoms should have 6 mmol/L corrected over 6 hours or until severe symptoms improve. The total correction of sodium (Na) should not exceed 8 mmol/L over 24 hours. Therefore, if 6 mmol/L is corrected in 6 hours, Na should not be increased more than 2 mmol/L in the following 18 hours. The total correction of Na is based on the Na deficit (def), which is calculated conservatively with the formula depicted. With improvement of symptoms, the patients can be moved to the less aggressive treatments in the algorithm until Na reaches 131 mmol/L. Subarachnoid hemorrhage (SAH) patients are an exception and receive treatment even for a serum Na level of 131 to 135 mmol/L. HHH, hypervolemia, hypertension, hemodilution; sx, symptoms; MS, mental status; sz, seizure; Ts, transfer; IMC, intermediate care unit; I/Os, in and out; vol, volume; wt, weight; N/V, nausea and vomiting; U, urine; CVL, central venous line; inc, increase; NS, normal saline; IVF, intravenous fluids.](image-url)
asymptomatic patients (80%) were treated as outpatients with fluid restriction and a high-salt diet. Six of these patients had follow-up and showed an improvement in the serum Na level. The 11 symptomatic patients were hospitalized. Three of these patients responded to fluid restriction and salt tablets, and 8 patients required hypertonic saline (153). The rationale for treatment with fluid restriction versus hypertonic saline was not given.

Other treatments for SIADH include diuretics and urea. A prospective study described use of furosemide and ethacrynic acid in 11 of 12 SIADH patients and 2 volunteers. Na supplements were necessary in 9 of 11 patients, and treatment of hypokalemia was required in 7 patients. Two of the patients required higher doses of diuretics (39). The use of urea in hyponatremia came from a study that showed that 20 hyponatremic patients who met the criteria for SIADH had a low blood urea level (41). In a retrospective study of hyponatremia in neurosurgical patients, 40 g of urea in 100 to 150 mL of normal saline was given every 8 hours in addition to a continuous infusion of normal saline at 60 to 100 mL/h for 1 to 2 days. Patients were not categorized as having SIADH or CSW because these

data were unavailable. The pretreatment mean Na level was 130 mmol/L (range, 119–134 mmol/L) and the posttreatment mean was 138 mmol/L (range, 129–148 mmol/L) (P < 0.001). In 85% of cases, only 1 day of treatment was necessary (111).

Traditionally, demeclocycline has been used in chronic SIADH (155). This approach may be replaced by a new class of drugs that block ADH receptors (54, 55, 87). Conivaptan has been approved for use in euvolemic hyponatremia based on improvement in hyponatremia in randomized, controlled trials (54, 55). These drugs may cause volume depletion (88, 130). ADH receptor blockers have been studied in patients with heart failure, but further human studies are necessary to determine their role in the treatment of hyponatremia in the neurosurgical population (53, 88, 98, 115, 118, 154).

CSW

Treatment of CSW has been studied mostly in the setting of SAH (59, 93). A retrospective analysis of 134 SAH patients demonstrated the risks associated with fluid restriction in the treatment of hyponatremia (147). Twenty-six of the 44 hyponatremic patients (serum Na level <135 mmol/L) were treated with fluid restriction (<1 L/24 h in normothermic patients). Cerebral infarction developed in 21 of the 26 fluid-restricted patients and in 27 of the 44 patients with a serum Na level less than 135 mEq/L compared with 19 of the 90 normonatremic patients (147). Another study of SAH patients demonstrated a negative Na balance in all patients regardless of the serum Na level between days 2 and 3 after SAH (74). Repletion of volume has become the standard treatment. A case report of a patient with CSW described a recurrence of hyponatremia when the intravenous fluids were stopped (44). A study of 21 hyponatremic (serum Na level <130 mmol/L) neurosurgical patients and 3 controls categorized patients into groups based on hematocrit, CVP, and total blood volume. Group A (hypovolemic and anemic) and group B (hypovolemic without anemia) were treated with isotonic saline and oral salt. Group A patients also received blood transfusions. No patients demonstrated hypervolemic hyponatremia. The endpoints were 72 hours after entry or 2

FIGURE 3. Treatment of the syndrome of inappropriate antidiuretic hormone (SIADH). Symptoms are used to guide the treatment of SIADH. Patients with severe symptoms or subarachnoid hemorrhage (SAH) at risk of vasospasm receive hypertonic saline; otherwise the cornerstone of SIADH treatment is fluid restriction. Acute hyponatremia and/or severe symptoms should have 6 mmol/L corrected over 6 hours or until severe symptoms improve. The total correction of sodium (Na) should not exceed 8 mmol/L over 24 hours. Therefore, if 6 mmol/L is corrected in 6 hours, Na should not be increased more than 2 mmol/L in the following 18 hours. The total correction of Na is based on the Na deficit (def), which is calculated conservatively with the formula depicted. With improvement of symptoms, the patients can be moved to the less aggressive treatments in the algorithm until Na reaches 131 mmol/L. MS, mental status; sx, symptoms; sz, seizure; tx, transfer; ICU, intensive care unit; I/Os, in and out; wt, weight; N/V, nausea and vomiting; IMC, intermediate care unit; CVL, central venous line; inc, increase.
consecutive serum Na values more than 130 mEq/L. All the patients had correction of their hyponatremia (serum Na level >130 mmol/L) within 72 hours (124). This study demonstrates that hyponatremia develops in many neurosurgical patients in the setting of volume depletion, and it responds to fluid and Na replacement.

The loss of fluid and Na can also be treated with fludrocortisone. Fludrocortisone is a synthetic adrenocortical steroid with mineralocorticoid properties. Mineralocorticoids act on the distal tubules of the kidney to enhance Na reabsorption. In the neurosurgical literature, this medication has mostly been studied in SAH patients (149, 150). A randomized, controlled trial in SAH patients showed that fludrocortisone reduced the frequency of a negative Na balance (63% versus 38%, P = 0.041). The treatment group did tend to have a higher plasma volume compared with controls, although this was not statistically significant. More patients in the control group developed cerebral ischemia (31% versus 22%; P = 0.349). Consequently, more control patients were treated with volume expanders, which may have masked the volume-expanding benefits of fludrocortisone (60). Another randomized, controlled trial in SAH patients showed that 0.1 mg fludrocortisone 3 times daily reduced the mean Na and water intake, urinary Na excretion, and urine volume (P < 0.01). The patients demonstrated a decrease in serum potassium that was easily corrected (85).

Similar studies demonstrated a benefit of the use of hydrocortisone in SAH patients. One study randomized 28 SAH patients to receive no hydrocortisone or 1200 mg/d of hydrocortisone for 10 days (86). All patients were treated with replacement of water and Na to prevent vasospasm. The treatment group never experienced a serum Na level less than 135 mmol/L compared with 43% of the control group in whom hyponatremia developed. The treatment group also had lower urine volume and lower infusion volume to maintain a CVP of 8 to 12 cm H2O. Both were statistically significant. Failure to maintain an adequate CVP was observed in 12 control patients (86%) compared with 3 treatment patients (21%) (P < 0.05). A randomized, controlled trial of hydrocortisone in 71 SAH patients failed to show a statistically significant difference in outcome between patients randomized to placebo and those receiving 1200 mg/d hydrocortisone for 10 days after surgery. Nevertheless, hydrocortisone did prevent excess Na excretion and urine volume. It also maintained the targeted serum Na level throughout the 14 days (70).

Numerous other smaller series or review papers were discussed by the panel (3, 14, 24, 46, 58, 68, 78, 95, 125). Having reviewed the data, the expert panel made recommendations for the treatment of SIADH and CSW. These recommendations were then used to create a paradigm for the treatment of hyponatremia in neurosurgical patients at the University of Florida (Figs. 2 and 3).

Treatment Paradigm at the University of Florida

The treatment paradigm includes patients with CSW and SIADH with special consideration for SAH patients.

**Recommendation**

- Treatment of hyponatremia should be based on severity of symptoms (class III).
- Na should not be corrected by more than 10 mmol/d (class III).
- CSW should be treated with replacement of Na and intravenous fluids (class III).
- Fludrocortisone may be considered in the treatment of hyponatremia in SAH patients at risk of vasospasm (class I).
- Hydrocortisone may be used to prevent natriuresis in SAH patients (class I).
- Hyponatremia in SAH patients at risk of vasospasm should not be treated with fluid restriction (class II).
- SIADH may be treated with urea, diuretics, lithium, demeclocycline, and/or fluid restriction (class III).

**CONCLUSION**

Hyponatremia in neurosurgical patients is a complex issue that requires a systematic approach for evaluation and treatment. Multiple measures are necessary to determine ECF status and thus the appropriate underlying diagnosis for hyponatremia. The appropriate diagnosis is critical for patient outcomes because the treatment varies widely depending on the diagnosis. A standardized approach by a multidisciplinary team will most likely result in improved management of hyponatremia in neurosurgical patients.

Using the best available evidence, we developed a diagnostic and treatment algorithm in an attempt to reduce variability among treating physicians and ensure the best possible outcomes. Further testing of the effectiveness of these recommendations is under way. Given the significant morbidity and mortality associated with hyponatremia, well-designed studies addressing the evaluation and treatment of hyponatremia are necessary.

**Disclosure**

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

**REFERENCES**

36. Cort JH: Cerebral salt wasting. 

15. Baylis PH: The syndrome of inappropriate antidiuretic hormone secretion. 


65. Hooren EL, Lindemans J, Zietse R: Development of severe hyponatraemia in hospitalized patients: Treatment-related risk factors and inadequate manage-
107. Peruzzi WT, Shapiro BA, Meyer PR Jr, Krumlovsky F, See BO: Hypo-
HYPONATREMIA IN NEUROSURGICAL PATIENTS


Acknowledgments

We especially thank Dr. Marian Limacher and Dr. Jane Douglas for assistance with manuscript revision and preparation.

COMMENTS

In this excellent review article, Rahman and Friedman summarize the current cumulative knowledge, as reported in the literature since 1950, on the nature, evaluation, and treatment of hyponatraemia attributable to the syndromes of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt wasting (CSW), with special emphasis on hyponatraemia occurring in patients with subarachnoid hemorrhage (SAH). On the basis of a review of the pertinent literature and experience with hyponatremic neurosurgical patients, a multidisciplinary panel at the University of Florida devised a set of guidelines for the evaluation and treatment of hyponatraemia at that institution.

The reader of this thoroughly researched article is informed as to the societal impact of managing patients with hyponatraemia (estimated annual cost, $3.6 billion), the prevalence of hyponatraemia in the neurosurgical patient population (estimated, in some series, to be 50%), the mortality and morbidity associated with hyponatraemia, and, finally, the evaluation and treatment of hyponatraemia in patients with SIADH and CSW.

For example, the authors cite reports from the literature showing that the mortality in patients with a serum Na level of less than 120 mmol/L was 25%, versus 9% mortality in patients with a serum Na level of greater than 120 mmol/L. As for morbidity, a reference cited by the authors was 25%, versus 9% mortality in patients with a serum Na level of greater than 120 mmol/L. As for morbidity, a reference cited by the authors 25%, versus 9%.
authors indicates that a Na level of 120 mmol/L is probably the critical level for development of seizures. As for the evaluation of hyponatremia, the authors suggest that the previously reported criteria for diagnosis of SIADH (plasma osmolality <275 mOsm/kg, urine osmolality >100 mOsm/Kg, clinical euvolemia, and absence of other causes of euvoletic hyponatremia, such as hypothyroidism and hypocortisolism) are inadequate to distinguish between SIADH and CSW. Instead, the authors feel that the key to distinguishing between these 2 syndromes is determination of the extracellular fluid level. To that end, they suggest a number of clinical and laboratory studies, including, as indicated, such invasive studies as placement of a central line to determine central venous pressure. Finally, the authors discuss the optimal treatment paradigm, including treatment of SIADH in patients with SAH.

On the basis of this critical review of the pertinent literature and their own experience, a multidisciplinary panel at the University of Florida developed several recommendations regarding the evaluation and treatment of hyponatremia in general and in patients with SAH in particular. Several of these recommendations struck this reviewer as important: 1) hyponatremia of 131 mmol/L merits evaluation and treatment; 2) hyponatremia should not be corrected more than 10 mmol/L/d, especially in patients with chronic hyponatremia. Failure to do so can lead to severe neurological complications, such as central pontine myelinosis and osmotic demyelinating syndrome; 3) CSW should be treated with replacement of Na and intravenously administered fluids; 4) corticosteroids may be used in hyponatremic SAH patients at risk for vasospasm (fludrocortisone) and to prevent natriuresis (hydrocortisone); 5) SAH patients with hyponatremia who are at risk for vasospasm should not be treated with fluid restriction. This article is recommended reading for neurosurgeons, critical care specialists, and endocrinologists.

Rahman and Friedman have provided an excellent review of the evaluation and management of hyponatremia in neurosurgical patients. In their review, they emphasize the importance of hyponatremia as a cause of excessive morbidity and mortality in neurosurgical patients. The fact that treatment of the electrolyte abnormality seems to improve prognosis indicates that hyponatremia itself is important in the pathogenesis of neurological impairment and is not just a related biomarker of severity of illness.

The section of the article dealing with evaluation emphasizes the differential diagnosis and the difficulty in making an easy diagnosis of SIADH versus CSW in many neurosurgical patients. It is disappointing that unambiguous laboratory studies, such as natriuretic peptide or vasopressin determinations, have not been helpful in this differential process, undoubtedly because of the complex interaction between mechanisms responsible for volume and osmoregulation.

Finally, the recommendations for managing hyponatremia in neurosurgical patients will be useful to clinicians dealing with this common problem. Some of the recommendations will be controversial to some, especially with regard to the use of hydrocortisone and fludrocortisone in management. Recommendations regarding the use of hypertonic saline solutions may also be somewhat controversial. Clearly, the use of hypertonic saline is an extremely effective therapy for many patients, but determining exactly when to use it and how to balance it with the alternative of fluid restriction in patients with SIADH requires the exercise of a great deal of judgment. Hopefully, newer agents such as conivaptan will further facilitate the management of this common condition. The authors have provided a scholarly review and systematically applied it to the care of patients at the University of Florida on the basis of their assessment of the available evidence.

Ivan S. Ciric
Evanston, Illinois

Ralph G. Dacey, Jr.
St. Louis, Missouri