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ORIGINAL ARTICLE

Treatment of Hyponatremia in Patients with Acute Neurological Injury

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Abstract

Background Little data exist regarding the practice of sodium management in acute neurologically injured patients. This study describes the practice variations, thresholds for treatment, and effectiveness of treatment in this population.

Methods This retrospective, multicenter, observational study identified 400 ICU patients, from 17 centers, admitted for ≥48 h with subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), intraparenchymal hemorrhage, or intracranial tumors between January 1, 2011 and July 31, 2012. Data collection included demographics, APACHE II, Glascow Coma Score (GCS), serum sodium (Na+), fluid rate and tonicity, use of sodium-altering therapies, intensive care unit (ICU) and hospital length of stay, and modified Rankin score upon discharge. Data were collected for the first 21 days of ICU admission or ICU discharge, whichever came first. Sodium trigger for treatment defined as the Na+ value prior to treatment with response defined as an increase of ≥4 mEq/L at 24 h.

Results Sodium-altering therapy was initiated in 34 % (137/400) of patients with 23 % (32/137) having Na^+ >135 mEq/L at time of treatment initiation. The most common indications for treatment were declining serum Na^+ (68/116, 59 %) and cerebral edema with mental status changes (21/116, 18 %). Median Na^+ treatment trigger was 133 mEq/L (IQR 129–139) with no difference between diagnoses. Incidence and treatment of hyponatremia was more common in SAH and TBI [SAH (49/106, 46 %), TBI (39/97, 40 %), ICH (27/102, 26 %), tumor (22/95, 23 %); $p = 0.001$]. The most common initial treatment was hypertonic saline (85/137, 62 %), followed by oral sodium chloride tablets (42/137, 31 %) and fluid restriction (15/137, 11 %). Among treated patients, 60 % had a response at 24 h. Treated patients had lower admission GCS (12 vs. 14,

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$p = 0.02$) and higher APACHE II scores (12 vs. 10, $p = 0.001$). There was no statistically significant difference in outcome when comparing treated and untreated patients. *Conclusion* Sodium-altering therapy is commonly employed among neurologically injured patients. Hypertonic saline infusions were used first line in more than half of treated patients with the majority having a positive response at 24 h. Further studies are needed to evaluate the impact of various treatments on patient outcomes.

Keywords Hyponatremia · Neurocritical care · Intensive care unit · Subarachnoid hemorrhage · Intracerebral hemorrhage · Traumatic brain injury · Intracranial tumor

Introduction

Hyponatremia is an important and common electrolyte disorder in neurocritical patients. The incidence of hyponatremia varies vastly between types of neurologic injury. There is also a lack of consensus on the definition of hyponatremia, although it is commonly defined as serum sodium less than 135 mEq/L. Sodium disturbances are particularly common in patients with central nervous system (CNS) disease because of the major role the CNS plays in the regulation of sodium and water homeostasis. Common neurological disorders with high rates of clinical hyponatremia include subarachnoid hemorrhage (SAH), intraparenchymal hemorrhage (IPH), cerebral tumors, and traumatic brain injury (TBI) [1–9].

Declining serum sodium concentrations are a significant cause of morbidity and mortality in the brain injured patient and often may be difficult to diagnosis in the neurologically injured patients in the intensive care unit. If left untreated, serious neurologic complications and adverse outcomes, including death, can occur. Clinical symptoms vary with the degree of hyponatremia as well as the rate of decline [10, 11]. Clinical signs of falling serum sodium levels range from mild headache, confusion, lethargy, vomiting, mental status changes, to bradycardia, respiratory depression, seizures, coma, or death, and are most pronounced with rapid changes in serum sodium levels [12]. Importantly, hyponatremia is one of the major causes of refractory elevations in intracranial pressure in patients with TBI. Hasan and colleagues studied the relationship between hyponatremia and outcomes in SAH and found cerebral infarction occurred more frequently in the group with hyponatremia (61 %) when compared to those who remained normonatremic (21 %) ($p = 0.001$) [1]. Given the potential impact on neurological function, sodium concentrations are generally monitored closely in the neurologically injured patient.

The approach to sodium management in patients with acute neurologic injury may require different strategies than in the general critically ill population. For example, fluid restriction may not be advisable in patients with SAH where euvolemia is recommended to maintain adequate cerebral perfusion pressure [1]. Additionally, neurocritically ill patients may be uniquely susceptible to complications related to hyponatremia. Practice variations in the threshold for treatment and the most common treatments employed in this population have not been previously described. Additionally, effectiveness of individual treatment modalities has not been evaluated for divergence in either efficacy or outcomes. This study was conducted to characterize hyponatremia and describe current practice patterns in the prevention and treatment of hyponatremia in critically ill patients with acute neurological injury.

Methods

This retrospective, multicenter, observational cohort study identified patients admitted to an intensive care unit for more than 48 h with an ICD-9 code for aneurysmal SAH, TBI, IPH, or intracranial tumor between January 1, 2011 and July 31, 2012. Each site identified patients with each targeted diagnosis (SAH, TBI, IPH, and tumor) in reverse chronological order. Centers that did not have sufficient population of a particular diagnosis were identified a priori and the sample was distributed evenly throughout the institutions. Data collected included demographics, severity of diagnosis, APACHE II, Glasgow Coma Score (GCS), serum sodium (Na^+) concentrations, fluid rate and tonicity, sodium-altering therapies administered and the indication (hyponatremia, cerebral edema, worsening neurologic exam, other/unknown), time to treatment from admission, time to treatment from nadir Na^+, ICU and hospital length of stay, and discharge information including disposition and modified Rankin Score (mRS). Data were collected for the first 21 days or until ICU discharge, whichever occurred first. Study data were collected and managed using REDCap electronic data capture tools hosted at Virginia Commonwealth University. REDCap (Research Electronic Data Capture) is a secure, Web-based application designed to support data capture for research studies, providing: (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources [13]. IRB approval was obtained at each institution.

Hyponatremia was defined as a serum sodium <135 mEq/L. The severity of hyponatremia was further

defined as mild 131–134 mEq/L, moderate 125–130 mEq/L, and severe ≤124 mEq/L. The serum sodium level at the time treatment was initiated was labeled the "trigger sodium." Sodium response was defined as an increase by ≥4 mEq/L at 24 h after sodium-altering therapy initiation, similar to other sodium-altering trials. Good outcome was defined as mRs 0–3 and poor outcome 4–6.

All statistical analyses were conducted with SPSS (version 21, IBM Corporation, Armonk, NY). Categorical variables (e.g., age and incidence of sodium concentrations < 135 mEq/L) were evaluated with either Chi-square or Fisher's exact test. Continuous data were determined to have a normal distribution if the Shapiro–Wilk test had a significance value >0.05. Normal continuous data were evaluated with ANOVA. Non-normally distributed data were evaluated with Kruskal–Wallis test. Continuous measures were summarized as mean and standard deviation or median and interquartile rage as appropriate.

Results

A sample of 400 neurocritical patients from 17 institutions across the USA was collected. Over half (54 %) of the patients experienced hyponatremia. A full description of patient demographics is included in Table 1. The severity of hyponatremia varied, but the majority (71 %, $n = 152$) of the population was categorized as mild. Although the severity of hyponatremia was not different among diagnoses, hyponatremia was more common among SAH and TBI patients when compared to tumor and IPH groups [SAH 64 %, TBI 57 %, tumor 49 %, IPH 44 %; $p = 0.02$)] (Fig. 1). SAH and TBI patients had lower median Na+ values during their hospital stay compared to tumor and IPH patients [134 mEq/L vs. 136 mEq/L; $p = 0.01$)] (Table 2). Patients that experienced hyponatremia compared to those that were never hyponatremic had lower admission GCS 12 (10–14) versus 14 (13–14); ($p = 0.01$) and similar APACHE II scores 10 (9–12) versus 10 (10–11) ($p = 0.69$) respectively upon admission.

Sodium-altering therapy was initiated in 34 % (135/400) of all patients and was more likely to be utilized in patients with more severe hyponatremia (39 % mild [$n = 152$] versus 70 % moderate [$n = 57$] versus 100 % severe [$n = 6$]). The majority of the patients receiving treatment exhibited hyponatremia (sodium concentration < 135 mEq/L) at the onset of treatment (77 %, 105/137). Twenty-three percent of patients without hyponatremia received sodium-altering therapy. SAH and TBI patients were treated more commonly with sodium-altering therapy when compared to tumor and IPH patients [SAH 46 %, TBI 40 %, IPH 26 %, tumor; $p = 0.001$] (Fig. 1). The median trigger sodium that prompted sodium-altering therapy was 133 (IQR 129, 139) mEq/L and was similar among all diagnoses (Table 2). Patients who received sodium-altering therapy had worse neurologic deficits and severity of illness on admission when compared to those who did not as evidenced by their significantly lower GCS

Table 1 Demographics

Characteristic	TBI (n = 97)		Tumor (n = 95)		SAH (n = 106)		IPH (n = 102)		Overall (n = 400)	
	Na < 135 mEq/L	Na ≥ 135 mEq/L	Na < 135 mEq/L	Na ≥ 135 mEq/L	Na < 135 mEq/L	Na ≥ 135 mEq/L	Na < 135 mEq/L	Na ≥ 135 mEq/L	Hyponatremia treatment	No hyponatremia treatment
Hyponatremia treatment	46 % [45]	54 % [52]	38 % [36]	62 % [59]	51 % [55]	48 % [51]	35 % [36]	65 % [66]	34.2 % [137]	65.8 % [263]
Male gender	87 % [39]	60 % [31]	86 % [31]	42 % [25]	49 % [27]	25 % [13]	78 % [28]	41 % [27]	53 % [139]	60 % [82]
Ethnicity, %										
Caucasian	75 %	64 %	70 %	73 %	59 %	66 %	56 %	56 %	62 %	69 %
Black	18 %	24 %	6 %	6 %	24 %	31 %	31 %	28 %	23 %	17 %
Other	7 %	10 %	19 %	19 %	7 %	9 %	9 %	13 %	15 %	14 %
Age	54 [40–70]	53 [33–62]	58 [49–67]	62 [51–71]	55 [48–63]	59 [33–66]	61 [56–69]	59 [52–70]	58 [48–69]	58 [50–66]
GCS	9 [4–14]*	13 [7–15]*	14 [13–15]	15 [13–15]	14 [8–15]	14 [7–15]	11 [8–14]	14 [7–15]	14 [9–15]	12* [6–15]
APACHE II score	13 [8–19]*	11 [7–15]*	8 [6–13]	8 [5–12]	9 [6–15]	11 [5–17]	12 [9–17]	11 [7–15]	10 [6–14]	12* [7–18]

All data are % [n] or median [IQR]

* p value <0.05

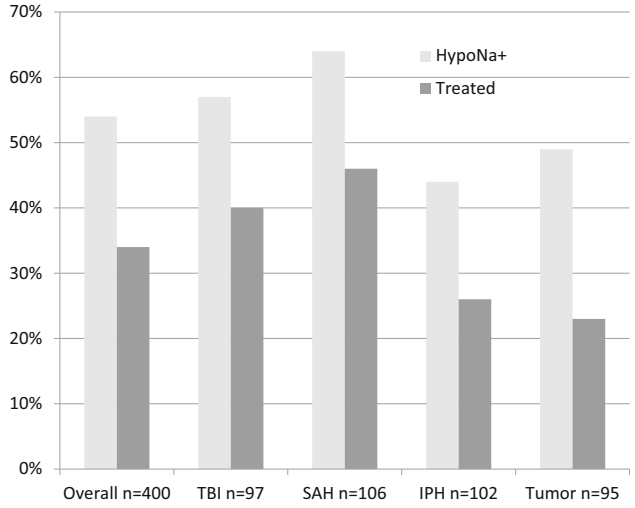

Fig. 1 Incidence of hyponatremia and treatment

and higher APACHE II scores (Table 1). Median time to treatment was significantly earlier in IPH patients at 19 h (IQR 17, 23) compared to TBI [26 h (IQR 23, 30)], tumor [36 h (IQR 35, 39)], and SAH [86 h (IQR 84, 91)] ($p < 0.006$) (Fig. 2). The most common indications for treatment ($n = 116$) were declining serum Na^+ (59 %) and cerebral edema with mental status changes (18 %).

Hypertonic saline was the most common initial treatment for hyponatremia ($n = 137$) at 62 % followed by oral sodium chloride tablets (13 %), fluid restriction (11 %), fludrocortisone (7 %), conivaptan (2 %), and demeclocycline (1 %) (Table 3). A minority of patients (13 %) received two treatment modalities as initial therapy, most commonly the combination of intravenous hypertonic saline and oral/enteral sodium chloride tablets. Sodium chloride tablet therapy was the most common second line agent added, with the exception of SAH patients, in which fludrocortisone was the most common second agent added. Otherwise, no predictable pattern of a sequence of agents used was detectable. Figure 3 depicts the use of various hyponatremia treatments by diagnosis.

Most treated patients ($n = 124$) had a follow-up serum Na^+ 24 h after sodium-altering therapy was initiated. Over half (60 %) of treated patients responded to sodium-altering therapies chosen with a median sodium rise of a 4.5 (IQR 2, 8) mEq/L. The response rate ranged from 51 to 70 % and was not significantly different between diagnoses. When evaluating each initial treatment employed, intravenous hypertonic saline and conivaptan demonstrated the most robust response. The median sodium change at 24 h for intravenous hypertonic saline was 6 (IQR 3, 10) and 7 (IQR 2, 10) mEq/L for conivaptan. Fluid restriction, oral sodium chloride tablets, and demeclocycline led to moderate sodium responses, 5 (IQR 5, 7), 3.5 (IQR 1, 6), and 3 (IQR 2, 3) respectively (Table 4).

When adjusted for APACHE II score and age, patients with hyponatremia had significantly longer ICU LOS [8 (IQR 4–13) vs. 4 (IQR 3–7) ($p < 0.0001$)] and hospital LOS [13 (IQR 8–21) vs. 7 (IQR 5–12), $p < 0.0001$)] (Table 5). Good outcome was achieved statistically more often in patients with normonatremia and mild hyponatremia with mRs 0–3 resulting 54 % and 53 % respectively when compared to only 45 % good outcome in patients with moderate hyponatremia ($p = 0.03$).

Discussion

Limited data exist to guide clinicians on the best agent to use for hyponatremia and the predicted response. This study describes the most common treatment threshold and therapeutic interventions for patients with neurologic critical illness and hyponatremia. Overall, more than half of the patients studied experienced hyponatremia (54 %). Of these, the majority (71 %) experienced mild hyponatremia (131–134 Eq/L). The median sodium value triggering treatment was 133 mEq/L across various diagnoses. Interestingly, 23 % of patients treated never had a serum sodium <135 mEq/L suggesting that a higher treatment threshold was used in some patients. This higher threshold may be employed in this population as experienced clinician's understand the acute neurologic consequences of hyponatremia and may treat empirically to prevent these effects from confounding the exam. Treatment of hyponatremia occurred within the first 1–2 days for most patients, although patients with SAH exhibited a more prolonged time to treatment initiation that correlated with a later sodium nadir.

Table 2 Lowest and trigger sodium in relation to admit and treatment times

	TBI	SAH	ICH	Tumor	Overall	*p* value
Median lowest Na^+ (mEq/L)	134 (132–137)	134 (132–137)	136 (133–139)	136 (133–138)	135 (132–138)	**0.01**
Trigger Na^+ (mEq/L)	133 [131–139]	135 [132–137]	132 [130–138]	133 [129–136]	133 [129–139]	0.2017
Time to trigger from admission (h)	22 [3–85]	81 [17–178]	14.5 [2–6]	33 [21–55]	38 [5–102]	**0.0059**
Time to treatment from admission (h)	26 (23–30)	86 (84–91)	19 (17–23)	36 (35–39)	43 (40–46)	**<0.001**

Bold values are statistically significant at $p < 0.05$

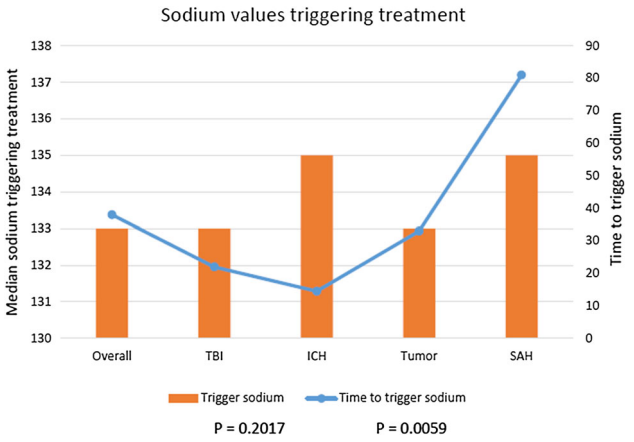

Fig. 2 Median sodium at initiation of hyponatremia treatment

Hyponatremia is a common, impactful complication in acute neurologic illness [1, 2, 12]. The neurocritical care patient may develop hyponatremia due to SIADH, cerebral salt wasting syndrome, adrenal insufficiency, and/or iatrogenic causes [14]. The present study did not examine the etiology of hyponatremia or differentiate the treatment by diagnosis. The incidence of hyponatremia (54 %) observed is comparable to the 40–60 % incidence reported previously in the literature [3, 7, 12].

Various treatment options were used, although hypertonic saline infusion (62 %) and oral sodium chloride tablets (13 %) were the more commonly initiated agents. Many patients required more than one treatment modality. Osmotic demyelinating syndrome is a dreaded complication of overcorrection or too rapid correction of the serum sodium in patients with chronic hyponatremia, and can often times occur when using large doses of hypertonic saline or more than one treatment strategy. The majority of the patients in our study had acute hyponatremia, which is defined as hyponatremia for <48 h. Administration of hypertonic saline infusion typically resulted in a rise in serum sodium of approximately 6 mEq/L at 24 h after initiation. This is within the recommended maximum rate of correction that is often suggested (10–12 mEq/L/24 h) and would often improve serum sodium concentrations in our population from mild hyponatremia to near normonatremia within 24 h [15]. The other commonly used option, oral sodium supplementation, had a less robust impact on serum sodium (3.5 mEq/L increase). Conivaptan (7 mEq/L increase) and fluid restriction (5 mEq/L increase) increased the serum sodium, but were rarely used so definitive conclusions cannot be drawn. Limited use of these treatment strategies is likely due to the specific fluid requirements of neurocritical care patients, particularly those with TBI and SAH, where cerebral perfusion pressure and euvolemia are priorities in treatment.

The time to sodium nadir differed slightly among the groups, most notably in patients with SAH. Typically, the nadir sodium was observed within 9–34 h of admission in patients with IPH, TBI, and tumor. However, the nadir sodium for SAH was over 80 h. The typical time to entry into the cerebral vasospasm window for patients with SAH mirrors the time to nadir sodium, supporting the hypothesis that some of the pathophysiology of SAH may be a factor in developing hyponatremia, or vice versa.

A longer ICU and hospital length of stay in patients with hyponatremia was observed, but there was no difference in mortality when compared to patients without hyponatremia. This is similar to previously published literature,

Table 3 Sodium-altering therapy employed as first or second choice, or given at any point in therapy

	Initial %	Secondary %	Anytime %
TBI (n = 39), %			
Hypertonic saline	64	5	69
Salt tablets/ flushes	33	8	41
Fluid restriction	10	5	15
Fludrocortisone	0	3	3
Conivaptan	0	0	0
Demeclocycline	3	0	3
Tumor (n = 22), %			
Hypertonic saline	41	5	45
Salt tablets/ flushes	41	9	50
Fluid restriction	18	0	18
Fludrocortisone	5	0	5
Conivaptan	5	0	5
Demeclocycline	0	0	0
SAH (n = 49), %			
Hypertonic saline	63	6	69
Salt tablets/ flushes	35	12	47
Fluid restriction	4	0	4
Fludrocortisone	14	12	27
Conivaptan	2	0	2
Demeclocycline	0	0	0
ICH (n = 27), %			
Hypertonic saline	74	0	74
Salt tablets/ flushes	11	7	19
Fluid restriction	19	4	22
Fludrocortisone	4	0	4
Conivaptan	4	0	4
Demeclocycline	0	0	0
Overall (n = 137), %			
Hypertonic saline	62	4	66
Salt tablets/ flushes	31	9	40
Fluid restriction	11	2	13
Fludrocortisone	7	5	12
Conivaptan	2	0	2
Demeclocycline	1	0	1

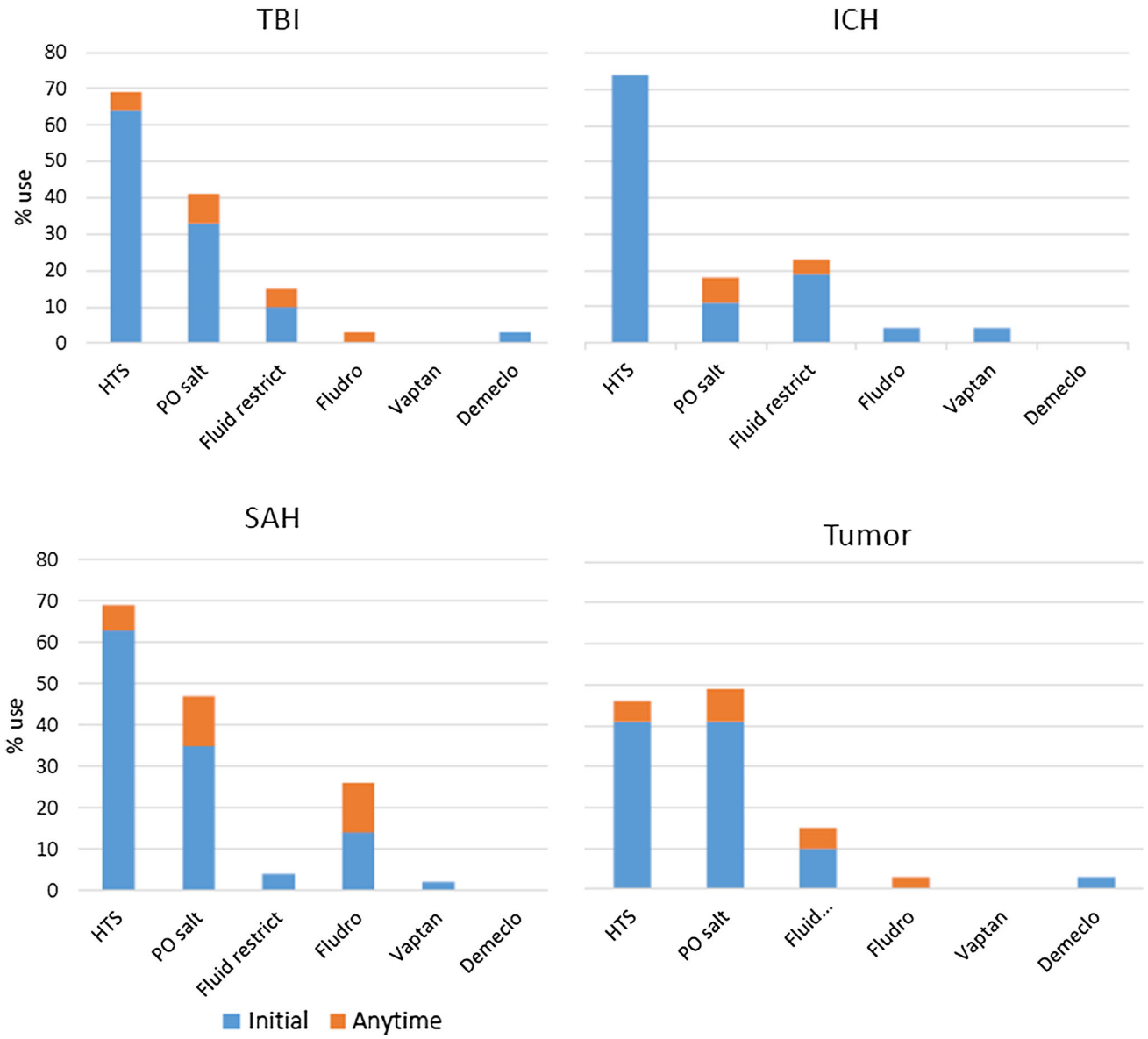

Fig. 3 Hyponatremia treatment by admission diagnosis

Table 4 Sodium response with treatment

Initial Therapy	*N*	Median Na^+ change (IQR)
Hypertonic saline	79	6 (3–10)
Salt tablets/flushes	36	3.5 (1–6)
Fluid restriction	15	5 (2–7)
Fludrocortisone	7	1 (−1 to 3)
Conivaptan	3	7 (2–10)
Demeclocycline	1	3 (3–3)

which suggests that critically ill patients with hyponatremia have an increased ICU and hospital LOS when to compared to normonatremic patients. In contrast, the mortality rate in our study was not associated with hyponatremia despite other published reports which indicate that hyponatremia is an independent risk factor for increased mortality [16].

This study has several limitations. First, it is a retrospective study with no control of various factors associated with care across multiple institutions. Thus, centers may have had a very different approach to treating patients which may have affected length of stay and outcomes. Second, we did not evaluate nutrition products or co-infusion of intravenous medications, such as antimicrobials which may contain sodium or be diluted in sodium containing fluids, or isotonic maintenance fluids. Normal saline is generally the fluid of choice for maintenance and may be sufficient for prevention or treatment of

Table 5 Clinical outcomes

	$Na^+ > 135$ $N = 185$	Na^+ 131–135 $N = 152$	Na^+ 125–130 $N = 57$	$Na^+ < 124$ $N = 6$	p value
% Alive at Discharge	56 % (145/185)	92 % (130/142)	80 % (40/50)	100 % (6/6)	0.11
ICU LOS (days) [IQR]	4 (3–7)	8 (4–13)	8.5 (5–14)	8 (6–11)	**<0.0001**
Hospital LOS (days) [IQR]	7 (5–12)	13 (8–21)	14 (10–20)	11.5 (9–17)	**<0.0001**
Minimum median Na^+ mEq/L [IQR]	138 (137–140)	133 (132–129)	129 (127–130)	122 (119–123)	**<0.0001**
Discharge Disp					
Home	51 %	43 %	44 %	67 %	
SNF	15 %	32 %	38 %	33 %	
Other	34 %	26 %	18 %	0	

Bold values are statistically significant at $p < 0.05$

hyponatremia in some patients. Third, the wide spectrum of diagnoses which were included creates variability in evaluating outcomes. For example, length of stay often is quite different for a routine postoperative pituitary tumor resection patient and a patient with aneurysmal SAH. Similarly, characterization of "good" outcomes is difficult with mRS across these various diagnoses because the definition of "good" after a severe TBI or high-grade SAH usually differs from those patients who have a lobar IPH or pituitary tumor resection. Finally, evaluation of subgroups (such as specific treatments like conivaptan) is difficult because in practice, as in our study, these treatments are not commonly used or used in combination with other treatments. Therefore, this study was under-powered to evaluate the impact of under-represented therapies.

Conclusion

Hyponatremia is common in patients with acute neurological injury and is most common among SAH and TBI patients. Hyponatremia generally occurs in the first 1–2 days after injury except in SAH where hyponatremia is detected around hospital day 3–4. Sodium-altering therapy is commonly employed among neurologically injured patients to prevent or treat hyponatremia. Hypertonic saline infusions are used as first line therapy in more than half of treated patients with the majority having a positive sodium response at 24 h. Hyponatremia is associated with an increased ICU and hospital length of stay. Further studies are needed to evaluate the impact of various treatments on patient outcomes and to optimize agent selection and dosing.

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