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Greater fluctuations in serum sodium levels are associated with increased mortality in children with externalized ventriculostomy drains in a pediatric intensive care unit

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Abstract

Objective—Dysnatremia is common in critically ill children due to disruption of hormonal homeostasis. Children with brain injury are at risk for SIADH, cerebral salt wasting and sodium losses due to externalized ventricular drain (EVD) placement. We hypothesized that among pediatric intensive care unit (PICU) patients managed with an EVD, hyponatremia is common, hyponatremia is associated with seizures and in-hospital mortality, and greater sodium fluctuations are associated with in-hospital mortality.

Design—Retrospective observational study

Setting—Tertiary care PICU

Patients—All pediatric patients treated in the PICU with an EVD from January 2005 to December 2009. Patients were identified by searching the physician order entry database for EVD orders. Hyponatremia was defined as the minimum sodium during patients' EVD time and was categorized as mild (131-134 meq/L) or moderate-severe (≤130 meq/L). Magnitude of sodium fluctuation was defined as the difference between a patient's highest and lowest sodium during the time in which an EVD was in use (up to 14 days). Seizure was defined as a clinically evident convulsion during EVD presence. *A priori* confounders were age, history of epilepsy, and EVD indication. Multivariable regression was performed to test the association between sodium derangements and outcomes.

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Interventions—None.

Measurements and Main Results—Three hundred eighty patients were eligible. One hundred nine (29%) had mild hyponatremia, and 30 (8%) moderate-severe hyponatremia. Twenty eight (7%) patients had a seizure while hospitalized. Eighteen patients died (5%) prior to discharge. Survivors had a median daily sodium fluctuation of 1 [0, 5] vs non-survivors 9 [6, 11], ($p< 0.001$) and a median sodium fluctuation of 5 meq/L [interquartile range 2, 8] vs non-survivors 15 meq/L [9, 24] ($p<0.001$) during EVD management. After controlling for *a priori* covariates and potential confounders, hyponatremia was not associated with an increased odds of seizures or in-hospital mortality. However, greater fluctuations in daily sodium (OR 1.38, 95% CI (1.06, 1.8)) and greater fluctuations in sodium during EVD management were associated with increased odds of in-hospital mortality (OR 1.59, 95% CI (1.2, 2.11)).

Conclusion—Hyponatremia was common in PICU patients treated with EVDs but not associated with seizures or in-hospital mortality. Greater sodium fluctuations during EVD management were independently associated with increased odds of in-hospital mortality.

Keywords

hyponatremia; externalized ventricular drain; children; seizures; dysnatremia; pediatrics; mortality

Introduction

Dysnatremia is common in critically-ill pediatric patients due to disruption of hormonal homeostasis (1). Poor outcomes in pediatric patients with extreme sodium derangements developing in the inpatient setting have been reported (2). Hyponatremia is a particularly well-known complication in children with central nervous system disease following neurosurgical procedures due to syndrome of inappropriate antidiuretic hormone (SIADH), cerebral salt wasting, adrenal insufficiency, and iatrogenic causes (diuretics and hypotonic fluids) (3-5). Hyponatremia has been associated with seizures, cerebral edema, encephalopathy and higher morbidity (6, 7). Due to the risk for these and other complications, neurosurgical patients represent an increasing percentage of patients managed in pediatric intensive care units (PICU) (8, 9).

Many of these patients also have externalized ventriculostomy drains (EVD) to manage intracranial hypertension and hydrocephalus associated with traumatic brain injury (TBI), intracranial hemorrhage (ICH), intracranial infections and brain tumors. While patients with EVDs are monitored closely for the associated risks of dislodgement, malfunction, hemorrhagic complications and infections, reported pediatric data is sparse regarding the associations of EVDs with hyponatremia and the important clinical effects of hyponatremia, such as seizures and worse outcomes (10-13). In adult ICU patients, both hyponatremia and large sodium fluctuations are associated with increased hospital mortality (14). However, it is currently unknown whether these electrolyte derangements are associated with mortality in children who are managed with EVDs.

The aims of this study were to identify factors associated with development of hyponatremia and large sodium fluctuations in pediatric patients with EVDs and to evaluate whether these

sodium derangements were associated with seizures and in-hospital mortality. We hypothesized that hyponatremia would be common in patients managed with an EVD, and would be associated with increased prevalence of seizures and increased in-hospital mortality. Furthermore, we hypothesized that patients who had large fluctuations in sodium during the time in which they had an EVD would have increased odds of in-hospital mortality.

Materials and Methods

We conducted a retrospective observational study in children with EVDs admitted to the PICU at The Children's Hospital of Philadelphia between January 1, 2005 and December 31, 2009. This dataset was previously published evaluating the association of EVDs and infection (15). This study was approved by the hospital Institutional Review Board and the requirement for obtaining informed consent was waived.

Patients were identified by searching the physician order entry database for EVD orders. Inclusion criteria included admission to the PICU and the presence of an EVD. The medical records of eligible patients were examined. Study data were collected and managed using Research Electronic Data Capture (REDCap) hosted at The Children's Hospital of Philadelphia. REDCap is a secure, web-based application designed to support data capture for research studies (16).

Variables collected included baseline demographics (age, gender, race, and weight), EVD indication, history of epilepsy, admission electrolytes, history of diuretic use on admission, clinical seizures during hospitalization, presence of intracranial pressure monitoring, days EVD was present, and survival to hospital discharge. During the study period, there was no standard protocol for EVD management, and it was left to the discretion of the attending neurosurgeon. Daily values were recorded for up to the first 14 days of EVD presence including ventriculostomy output, highest and lowest serum sodium, total daily fluid intake and output, daily volumes of intravenous (IV) 3% saline, 0.9% saline, 0.45% saline, 0.22% saline, total parenteral nutrition (TPN), and administration of enteral sodium chloride supplements. Based on these values, each patient had a daily fluid salt concentration administered calculated.

Based on the lowest serum sodium measured with the EVD in place, hyponatremia was defined as: mild (131-134 meq/L), moderate (125-130 meq/L) and severe (<125 meq/L). (17) Due to small numbers in the severe hyponatremia group, moderate and severe hyponatremia were grouped together for the analysis. Hypernatremia was defined as the patient's maximum sodium > 145 meq/L. Maximum daily sodium fluctuation was defined as the largest change in sodium in a 24 hour period (highest - lowest sodium (meq/L)) during the first 14 days of the patient's management with an EVD. Maximum sodium fluctuation during EVD management was defined as the difference between the highest and lowest sodium for a patient during EVD management. Seizure was defined as a clinical convulsion during EVD presence. EEG monitoring for subclinical seizures was not routinely performed during the study period.

Summary statistics are reported as median and interquartile ranges [IQR: 25th percentile, 75th percentile] for continuous data and counts and proportions for categorical data. The association of variables and mortality was performed using Wilcoxon rank sum or Kruskal Wallis for continuous data and chi-squared or Fishers exact test for categorical data. Logistic regression was used to test the association between hyponatremia groups and hospital mortality or PICU seizures and the magnitude of sodium fluctuation and hospital mortality. *A priori* confounders were EVD indication and history of epilepsy when assessing the association of sodium groups with seizures. Covariates that had a p-value < 0.2 on univariate analysis were sequentially introduced into the model and assessed for possible confounding. Variables introduced into the model that did not change the coefficient of the exposure variable by at least 10% were removed as the likelihood of confounding was low. For analysis of the exposures that were ordinal variable, the likelihood ratio test was performed after addition of each variable if the p-value was <0.05 then the variable remained in the model. If these variables did not affect the association between the exposure and outcome, they were removed from the final model. All statistics were performed using Stata 10 (College Station, Tx).

Results

Three hundred eighty patients were eligible for evaluation. One hundred thirty nine (37%) patients were hyponatremic during EVD presence (Na <135 meq/L): 109 (29%) had mild hyponatremia (Na 131-134 meq/L), and 30 (8%) had moderate or severe hyponatremia (≤130 meq/L)). Two hundred forty one (63%) did not have hyponatremia. Five (1.3%) patients were receiving diuretics on admission. Hyponatremic patients were younger (p= 0.015) and more often received TPN (p<0.001), intravenous three percent saline and oral sodium supplementation (p< 0.001) (Table 1a). Patients with hyponatremia were more likely to have meningitis, traumatic brain injury or spontaneous intracranial hemorrhage (p=0.038). Patients with severe or moderate hyponatremia had EVD in place longer (p<0.001) and had their lowest sodium level later in their EVD course (p=0.027). There was no difference in maximal daily cerebrospinal fluid loss between hyponatremia groups (p=0.38). Only twenty five (7%) patients were hyponatremic (Na< 135 meq/L) on PICU admission.

The median maximum daily sodium fluctuation during EVD management (n=380) was 5 [2.5, 9] meq/L. (Table 1b) Twenty percent of patients were hypernatremic (Na >145 meq/L) during their management with an EVD. Patients with traumatic brain injury or more severe hyponatremia had a greater magnitude of sodium fluctuation during EVD management (Table 1a and 1b). Patients who received intravenous quarter normal saline, half normal saline, three percent saline or TPN (standard sodium content 3-4meq/kg/day, not normal saline) or had a clinical seizure also had greater magnitudes of sodium fluctuations (Table 1b). The percentage of patients receiving each type of sodium containing fluid on each day of EVD management is presented in Table 2. There was no difference in the concentration of sodium containing fluids administered on any day compared by hyponatremia groups. However, patients who died were less likely to receive isotonic fluids on days 3, 5, 11 and 14. Quarter normal and half normal saline were infrequently administered.

Eighteen patients who received three percent saline during EVD management had hyponatremia (Na<135) on the day of three percent administration. Three of these patients received hypotonic saline or TPN in the 72 hours prior to initiation of three percent saline administration.

Twenty eight patients (7%) had a seizure. Seizures were more frequent in patients with hyponatremia (Na <135 meq/L) (11% vs 5%, p=0.05) (Table 3); however, severity of hyponatremia was not associated with seizures (p=0.058). Furthermore, patients with a sodium > 145 were more likely to have a seizure (p=0.044). Patients with clinical seizures were younger (p=0.025), more likely to have pre-existing epilepsy (p=0.002) and to have received TPN (p =0.013).

Nineteen patients (5%) died. There was no difference in survival by severity of hyponatremia (p=0.11), however, non-survivors had a significantly greater maximum daily sodium fluctuation (9 meq/L [6, 11] vs 1 meq/L [0, 5], p<0.001) and a significantly greater maximum sodium fluctuation: 15 meq/L [9, 24] vs 5 meq/L [2, 8] (p<0.001) during EVD management. Non-survivors were more likely to have seizures (21% vs 7%, p= 0.04), and were more likely to receive quarter normal saline, half normal saline, three percent saline, or TPN.

After controlling for *a priori* covariates and potential confounders, severity of hyponatremia subgroup was not associated with seizures or in-hospital mortality (Table 4a). However, the maximum daily sodium fluctuation and the magnitude of sodium fluctuation during the first 14 days of EVD management were associated with increased in-hospital mortality (Table 4b).

We performed a sensitivity analysis specifically evaluating the 164 patients who underwent ICP monitoring during EVD management. The association between maximal daily sodium fluctuation and mortality persisted (OR 1.55, 95% CI [1.12, 2.15]), after adjusting for ICP > 20 and EVD indication. ICP> 20 and EVD indication (tumor, TBI, ICH, and VPS) were not associated with mortality in this model. However, patients who had an EVD placed for meningitis had a higher odds of death (OR 8.28, 95%CI [1.16, 58.8], p= 0.035).

Discussion

In this large cohort of children treated with EVDs, greater sodium fluctuations were associated with increased odds of hospital mortality, even after controlling for hypertonic and hypotonic saline administration, initial hyponatremia and EVD indication. EVD associated hyponatremia occurred in 37% of children, but was not associated with seizures or in-hospital mortality. Risk factors for hyponatremia included receiving TPN, having longer duration of EVD management and younger age.

In our cohort, greater fluctuations in sodium over time were associated with increased odds of death, however, admission sodium and severity of hyponatremia during hospitalization were not associated with mortality. These data are important for three reasons. First, understanding mortality associated risk factors and the implications of management decisions allow clinicians to be thoughtful in the frequency of monitoring sodium levels, the

choice of type of fluid administered (hypotonic vs. isotonic), and the degree to which patients' sodium levels are permitted to fluctuate. Secondly, by identifying sodium fluctuations as an independent risk factor for hospital mortality, further exploration of physiologic causes and pathophysiologic impact may help clinicians delineate ways to identify at risk patients earlier with the hopes of decreasing mortality. Thirdly, hyponatremia did not increase the risk for seizures or mortality, suggesting that the EVD may have been protective perhaps by decreasing the risk of cerebral edema.

In our study, the magnitude of patients' sodium fluctuation during EVD management was significantly associated with in-hospital mortality. The median sodium fluctuation of survivors was 5 meq/L; however, patients who died prior to discharge had a median sodium fluctuation of 15 meq/L, significantly higher than survivors. These differences persisted despite controlling for the severity of a patient's hyponatremia, underlying neurologic diagnosis and administration of hypertonic and hypotonic intravenous fluids. Patients treated with EVDs represent a specific pediatric ICU population who have underlying neurologic injury or potential disruption of cerebral and hormonal homeostasis.

To evaluate the impact of more rapid sodium changes we evaluated the association of maximum daily sodium change for each patient and found an association with mortality. The greater change in sodium over a 24 hour period may impose more risk to the patient because of cerebral fluid shift that occur rapidly. In response to a hypertonic extracellular space, brain cells have the ability to generate idiogenic osmoles to maintain osmotic balance with the extracellular space without increasing intracellular ion concentrations to a level that may impact enzymatic pathways. Rapid shifts in extracellular sodium concentrations can lead to intracellular fluid shift, cellular edema and potentially worse outcomes. While more rapid and large sodium shifts may be due to underlying conditions, we included EVD indication in our analysis to account for underlying brain injury.

Several studies have found an independent association of hypernatremia with increased mortality after pediatric traumatic brain injury. After controlling for exogenous administration of mannitol and hypertonic saline, the association between hypernatremia and mortality persisted (18, 19). These studies did not specifically look at the change in sodium over time. It is unclear whether hypernatremia or large sodium fluctuations are influencing mortality.

Sakr et al examined the impact of dysnatremia in a very large adult surgical population (10,923 patients) and similar to our results, found that the median sodium fluctuation during the first week of hospitalization was 5 meq/L (14). Furthermore, they also found that a greater sodium fluctuation was associated with increased odds of in-hospital mortality. Our study extends these observations to a pediatric population, all of whom had an underlying condition requiring an EVD. The association between sodium fluctuations and in hospital mortality may be due to underlying severity of illness, severity of hormonal dysregulation, or adverse neurologic effects associated with correction of hyponatremia or hypernatremia.

More than one third of children in our study had documented hyponatremia, however, only 7 % of patients had a sodium < 135 meq/L on admission. The majority of these patients had

mild hyponatremia, and only one percent (4 patients) had a documented serum sodium less than 125 meq/L. Hyponatremia has been well described in children following brain tumor resection, cranial vault remodeling and endoscopic third ventriculostomy with prevalence ranging from (8-30%) (3, 4, 20, 21). A case series of three patients reported EVD associated severe dehydration (22). In a series of children who suffered traumatic brain injury, severe hyponatremia < 125 meq/dL was associated with increased mortality (18). Williams et al. evaluated 2,343 patients who underwent brain tumor resection and found hyponatremia occurred in 8.7% of patients (3). The authors noted that hyponatremia was associated with presence of an EVD. The prevalence of hyponatremia was substantially lower in their cohort than in our population and is likely in part due to the authors using an administrative database and ICD-9 codes for hyponatremia and SIADH rather than laboratory values *per se*. The variability in the prevalence of hyponatremia is likely associated with the underlying condition, fluids administered, frequency of serum sampling, presence of cerebral salt wasting or SIADH and losses from an EVD. The prevalence of hyponatremia in our cohort was higher than in a large study of adult ICU patients (14); however, the populations were inherently distinct with all of our patients having a neurologic indication for EVD placement and the adult population representing patients > 18 years of age of whom more than 70% had cardiothoracic or gastrointestinal surgery, and only 16% had neurosurgery.

Interestingly, when we compared patients who lived and died, the concentration of (mEq/L) sodium in intravenous fluids administered to these groups significantly differed at several points in time (Table 2). While the median concentration was similar between groups, patients who died received a wider range of sodium concentrations (84- 310 mEq/L/day). This observation is interesting because it has been well documented that children who receive hypotonic maintenance fluids are more likely to develop hyponatremia and severe hyponatremia (23). Hospitalized children are at higher risk for elevations in arginine vasopressin, especially when administered hyponatremic fluids (24). Our calculation of total daily administered sodium concentration was reflective of all intravenous fluids administered. It is possible that patients who died received a wider range of sodium concentrations because of required therapies, such as hypertonic saline or total parenteral nutrition, or that the total number of patients who died was so small that these wide ranges were more apparent because of the sample size. Regardless, the wide body of literature supporting the risks associated with intravenous hypotonic fluids should caution against their use in this at risk population.

After controlling for ventriculostomy indication, age and pre-existing epilepsy, hyponatremia was not associated with seizures or hospital mortality. Several small pediatric studies have described the association of hyponatremia and seizures in patients who have neurologic illness and surgery (4, 21). The lack of association with seizures may be due to frequent serum sodium evaluations, prompt treatment of hyponatremia in the PICU or the presence of an EVD drain that may have prevented a rapid rise in intracranial pressure due to CSF drainage.

In our population, admission serum sodium levels were significantly lower in patients who had moderate hyponatremia during their EVD management; however, admission sodium was not associated with in-hospital mortality. Previous studies have evaluated admission

hyponatremia as a risk factor for in-hospital mortality. In a large retrospective evaluation of 13 adult ICUs, mild hyponatremia on ICU admission was not independently associated with 30-day mortality (OR 1.08 (0.95-1.22)), but moderate and severe hyponatremia were [moderate: OR 1.18 (1.002, 1.4); severe (OR1.27 (1.01, 1.6)] (25). An even larger study of 151,486 patients in 77 adult medical and surgical ICUs showed that any hyponatremia on admission was independently associated with increased mortality (14, 26). It is not clear whether the worse outcomes were due to the effects of more severe hyponatremia or that more severe hyponatremia was associated with greater severity of the underlying illness. Nevertheless, these populations are distinct from our cohort in age, underlying medical condition and presence of EVD which may explain the differences in our findings.

Our study had several limitations. This data was collected retrospectively and therefore the documented sodium levels were determined by variable routine clinical care and not at set time intervals. We also did not have data regarding the hemodynamic status of patients and ICP measurements were only available on a subset of patients. Magnitude of sodium fluctuations were evaluated as absolute numbers without directionality. While this cohort is large for a pediatric center, our overall sample size was small for patients with more severe hyponatremia, and therefore we may have been underpowered to show a difference between patients with and without seizures, especially in the moderate and severe hyponatremia groups. Systematic continuous EEG monitoring was not performed during this time and therefore only clinical convulsions were documented and subclinical seizures may have been missed. Lastly, because these data were collected retrospectively one cannot conclude causality between larger maximum daily sodium changes and mortality. Further prospective evaluation would need to be performed to determine if this association persists when accounting for other potential confounders, such as the underlying diagnosis, the severity of illness and hemodynamic perturbations.

Conclusion

Hyponatremia is common in children treated with EVDs, but is not associated with increased odds of seizures or in-hospital mortality. Larger magnitude of sodium fluctuation is independently associated with increased in-hospital mortality. Further characterization of the etiologies and pathophysiologic effects of sodium fluctuations on the risk of mortality is warranted.

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Table 1

a. Patient demographics and interventions received by hyponatremia subgroups classified by patient's lowest sodium during the first 14 days managed with an externalized ventricular drain (EVD).

		Moderate and Severe Hyponatremia	Mild Hyponatremia	No Hyponatremia	
	Total	**Na <130 meq/L**	**Na 131-134 meq/L**	**Na >=135meq/L**	**p-value**
	n =380	**n =30 (8)**	**n =109 (29)**	**n =241 (63)**	
Demographics					
Age (years)	6.5 [2.1, 13.9]	3.5 [1.3, 8.7]	5 [1.9, 11.9]	7.8 [2.3, 14.3]	0.015
Sex					0.49
Male	169 (44)	16 (53)	45 (41)	108 (45)	
Female	211 (56)	14 (47)	64 (59)	133 (55)	
PRISM score at 24 hours	319	4 [0,9]	3 [0,5]	0 [0,5]	0.01
Ventriculostomy Indication					0.038
Tumor	122 (32)	7 (23)	39 (36)	76 (32)	
TBI	17 (5)	3 (18)	1 (1)	13 (5)	
Spontaneous ICH	23 (6)	1 (4)	9 (8)	13 (5)	
Ventricular shunt Externalization/other	209 (54)	16 (53)	58 (53)	135 (56)	
Meningitis	9 (2)	3 (10)	2 (2)	4 (2)	
Preexisting Epilepsy	73 (19)	6 (20)	21 (19)	46 (19)	0.99
Admission Sodium	138 [137, 141]	136.5 [132,139]	138 [136,140]	139 [138, 141]	<0.001
Maximum Daily CSF Output (ml)	279 [168, 374]	314 [215, 406]	256 [177, 368]	282 [142, 346]	0.38
Maximum Sodium Level	141 [139, 144]	142 [138, 150]	140 [138, 143]	141 [139, 144]	0.03
Magnitude of Maximum Daily Sodium Fluctuation (meq/L)	2 [0,6]	8[5, 11]	4 [0,8]	0 [0,4]	<0.001
Magnitude Sodium Fluctuation	5 [2.5, 9]	16 [11, 24]	7 [4,11]	3 [1,6]	<0.001
Hospital day of lowest Na	2 [1, 4.5]	3 [2, 7]	2 [1,5]	2 [1,4]	0.027
Interventions					
Normal Saline	377 (99)	30 (8)	109 (29)	238 (63)	0.65
Three percent Saline	56 (15)	11 (37)	21(19)	24 (10)	<0.001
Quarter NormalSaline	4 (1)	1 (3)	1 (1)	2 (1)	0.35
Half NormalSaline	18 (5)	4 (13)	3 (3)	11 (5)	0.069

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		Moderate and Severe Hyponatremia	Mild Hyponatremia	No Hyponatremia	
	Total	**Na <130 meq/L**	**Na 131-134 meq/L**	**Na >=135meq/L**	**p-value**
	n =380	**n =30 (8)**	**n =109 (29)**	**n =241 (63)**	
Total Parenteral Nutrition	33 (9)	12 (40)	9 (8)	12 (5)	<0.001
Oral Sodium Supplementation	27 (7)	13 (43)	12 (11)	2 (1)	<0.001
Days with ventriculostomy	6 [4,9]	11 [6, 14]	7 [4, 11]	6 [3,8]	<0.001

b. The magnitude of patients' maximum daily sodium fluctuation (difference between highest and lowest sodium each day) and the magnitude of patients' sodium fluctuation (difference between highest and lowest sodium) during the first 14 days managed with an externalized ventricular drain (EVD).

N =380	**Magnitude of Maximum Daily Sodium Fluctuation (meq/L) Median [IQR]**		**Magnitude of sodium fluctuation (meq/L) Median [IQR]**	
		p-value		**p-value**
Sex		0.49		0.17
Male	0 [2,6]		6 [3,10]	
Female	0 [2,6]		5 [2,9]	
Ventriculostomy Indication		<0.001		<0.001
Tumor	3 [1,7]			
TBI	10 [8,11]		19 [10, 26]	
Spontaneous ICH	7 [4,8]		9 [7, 19]	
Ventricular Shunt Externalization /other	0 [0,2]		4 [2,7]	
Meningitis	4 [0,7]		9 [6,11]	
Preexisting Epilepsy		0.03		0.65
Yes	0 [0, 5]		5 [2,11]	
No	2 [0, 6]		5 [3,9]	
ICP>20 (n=154)		0.002		<0.001
Yes	4 [0,8]		10 [6, 19]	
No	3 [0,7]		6[3,11]	
Interventions				
Normal Saline		0.74		0.42
Yes	2 [0,6]		5 [3, 9]	
No	0 [0, 11]		0 [0, 29]	

Three Percent Saline		<0.001		<0.001
Yes	8 [6, 11]		17 [9.5, 24]	
No	1 [0,4]		5 [2,7]	
Quarter Normal Saline		0.012		0.007
Yes	8 [6.5, 11.5]		15.5 [14. 20.5]	
No	2 [0,6]		5 [2, 9]	
Half Normal Saline		0.11		0.018
Yes	6.5 [0,14]		12.5 [3, 24]	
No	2 [0,6]		5 [2, 9]	
Total Parenteral Nutrition		<0.001		<0.001
Yes	7 [5,9]		15 [9, 23]	
No	1 [0,5]		5 [2, 8]	
Oral sodium supplementation		<0.001		<0.001
Yes	5 [2,9]		12 [7, 15]	
No	1 [0,5]		5 [2, 8]	
ICP > 20 (n=164)		<0.001		<0.001
Yes	7 [3,10]		10 [6, 19]	
No	4 [0,8]		6 [3, 11]	

CSF: cerebral spinal fluid, ICH: Intracranial hemorrhage, ICP: Intracranial pressure, IQR: interquartile range, ml: milliters, Na: sodium, meq/L: milliequivalents per Liter, TBI: traumatic brain injury, median [IQR]; n(%)

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Table 2

The percentage of patients who received each type of sodium containing fluid by day. The median [IQR] sodium concentrations (mEq/dL) received by day are presented by survival groups.

DAY of EVD	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N	380	372	349	300	243	209	173	151	115	100	83	70	59	48
Percent of patients Receiving Each Sodium Containing Fluid By day of Management														
Three percent saline	35 (9)	34 (9)	30 (8)	29 (10)	24 (10)	12 (6)	11 (6)	10 (7)	7 (6)	6 (6)	7 (8)	6 (9)	3 (5)	2 (4)
Quarter Normal Saline	1 (0.3)	2 (0.5)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.4)	0 (0)	0 (0)
Half Normal Saline	10 (2.6)	5 (1.3)	2 (0.6)	4 (1.3)	4 (1.6)	8 (3.8)	5 (2.9)	3 (2)	1 (0.9)	2 (2)	1 (1.2)	0 (0)	0 (0)	0 (0)
Normal Saline	366 (96)	331 (89)	295 (85)	238 (79)	195 (80)	164 (79)	135 (78)	116 (77)	86 (75)	71 (71)	61 (74)	47 (67)	41 (70)	45 (94)
TPN	9 (2.4)	10 (2.7)	19 (5)	21 (7)	23 (10)	30 (14)	18 (10)	12 (8)	11 (10)	11 (11)	8 (10)	8 (11)	6 (10)	4 (8)
oral sodium	3 (0.8)	7 (1.9)	9 (2.6)	11 (3.7)	9 (3.7)	7 (3.3)	9 (5.2)	8 (5.3)	8 (7)	9 (9)	9 (11)	7 (10)	9 (15)	7 (15)
Alive (N)	352	319	279	232	193	163	135	112	80	67	58	47	39	29
Alive	154 [154,154]	154 [154,154]	154 [154,154]	154 [154,154]	154 [154,154]	154 [154,154]	154 [154,154]	154 [154,154]	154 [154,154]	154 [154,154]	154 [154,154]	154 [154,154]	154 [154,154]	154 [154,154]
Dead (N)	19	19	18	15	14	13	10	10	10	9	7	7	6	4
dead	154 [154,208]	154 [129, 182]	154 [154,204]	154 [122,234]	154 [108, 216]	154 [94,224]	154 [87, 236]	154 [87, 236]	154 [89, 217]	154 [100, 187]	171 [154, 304]	154 [77, 310]	128 [77, 295]	115 [77, 154]
p-value	0.14	0.47	0.047	0.1	0.016	0.95	0.69	0.54	0.59	0.78	0.01	0.47	0.43	0.009

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Table 3

Seizure and mortality outcomes by sodium groupings, largest daily sodium fluctuation and largest sodium fluctuation during EVD management

	No Seizure	Seizure	p-value	survivors	non-survivors	p-value
	n= 352	**n =28**		**n=361**	**n=19**	
Sodium group			0.058			0.11
>= 135 meq/L	228 (65)	13 (46)		231 (64)	10 (53)	
131-134 meq/L	99 (28)	10 (36)		104 (29)	5 (26)	
<130 meq/L	25 (7)	5 (18)		26 (7)	4 (21)	
Sodium Fluctuation	5 [2,9]	7.5 [4.5, 13.5]	0.007	5 [2,8]	15 [9,24]	<0.001
Maximum Daily Sodium Fluctuation	2 [0,6]	4 [0,8]	0.077	1 [0,5]	9 [6,11]	<0.001
Hypernatremia (sodium > 145 meq/L)	65 (18)	10 (36)	0.044	63 (17)	12 (63)	<0.001
Maximum ICU Na	141 [139, 144]	143 [139, 148]	0.061	140 [139, 143]	148 [144, 160	<0.001
Age (years)	6.7 [2.2, 14]	2.4 [0.9, 10]	0.025	2 [0.7, 14]	6 [2.2,12.4]	0.63
Sex			0.314			0.79
Male	154 (44)	15 (54)		160 (44)	89(47)	
Female	198 (56)	13 (46)		201 (56)	10 (53)	
Ventriculostomy Indication			0.008			0.06
Tumor	115 (33)	7 (25)		117 (32)	5 (26)	
TBI	16 (5)	1 (4)		17 (5)	0 (0)	
Spontaneous ICH	20 (6)	3 (11)		20 (6)	3 (16)	
Externalization of VPS/other	196 (57)	13 (46)		200 (55)	9(47)	
Meningitis	5 (1)	4 (14)		7 (2)	2 (11)	
Preexisting Epilepsy	61 (17)	12 (43)	0.002	67 (19)	6 (32)	0.16
Admission Sodium	138 [137, 141]	138.5 [136, 140.5]	0.69	138 [137,141]	139 [136,142]	0.59
Maximum Daily CSF Output	282 [161, 373]	261 [193, 375]	0.99	284 [165, 375]	226 [170, 367]	0.37
ICP > 20	50 (33)	5 (38)	0.69	52 (34)	3 (30)	0.81
Days with ventriculostomy	6 [4,10]	6.5 [4, 12.5]	0.27	6 [4,10]	9 [4,15]	0.09
Seizure in hospital				24 (7)	4 (21)	0.04
Interventions						
Normal Saline	349 (99)	28 (100)	1.00	358 (99)	19 (100)	1.00

	No Seizure	Seizure	p-value	survivors	non-survivors	p-value
	n= 352	**n =28**		**n=361**	**n=19**	
Three Percent Hypertonic Saline	49 (14)	7 (25)	0.111	46 (13)	10 (53)	<0.001
Quarter Normal Saline	3 (1)	1 (4)	0.27	2 (1)	2 (11)	0.013
Half Normal Saline	16 (5)	2 (7)	0.63	15 (4)	3 (16)	0.054
Total Parenteral Nutrition	27 (8)	6 (21)	0.013	25 (7)	8 (42)	<0.001
Oral sodium Supplementation	24 (7)	3 (11)	0.44	26 (7)	1 (6)	1.00

CSF: cerebrospinal fluid, ICH: intracranial hemorrhage, ICP: intracranial pressure, ICU: intensive care unit, meq/L: milliequivalents

Table 4

a. Adjusted Odds Ratio for mortality after controlling for reason for ventriculostomy, three percent saline, and TPN administration. Adjusted odds ratio for seizures by lowest sodium groups after controlling for reason for ventriculostomy and preexisting epilepsy.

	Mortality			**Seizures**		
	OR	**95% Confidence Interval**	**p-value**	**OR**	**95% Confidence Interval**	**p-value**
Sodium > =135 meq/L	REF	REF	REF	REF	REF	REF
131-134 meq/L	0.55	0.16, 1.9	0.35	1.7	0.69, 4.3	0.25
<130 meq/L	0.52	0.08, 3.2	0.48	2.6	075, 9.4	0.13

b. Adjusted odds of mortality by for every increase in 3 of maximum daily change in sodium after controlling for three percent administration and total parental nutrition and ventriculostomy indication (TPN. meq/L: milliequivalents per liter) and change in sodium during EVD management after controlling for ventriculostomy indication, lowest sodium group, three percent and total parental nutrition (TPN).

	In-hospital mortality		
	OR	95% Confidence Interval	p-value
Maximum daily Change in Sodium (by 3 meq/L)	1.38	1.06, 1.8	0.016
Change in Sodium (by 3 meq/L)	1.59	1.2, 2.11	0.001