Complications Associated With Prolonged Hypertonic Saline Therapy in Children With Elevated Intracranial Pressure

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Objectives: Safe upper limits for therapeutic hypernatremia in the treatment of intracranial hypertension have not been well established. We investigated complications associated with hypernatremia in children who were treated with prolonged infusions of hypertonic saline.

Design: Retrospective chart analysis.

Setting: PICU in university-affiliated children's hospital.

Patients: All children from 2004 to 2009 requiring intracranial pressure monitoring (external ventricular drain or fiberoptic intraparenchymal monitor) for at least 4 days who were treated with hypertonic saline infusion for elevated intracranial pressure and did not meet exclusion criteria.

Intervention: Continuous hypertonic saline infusion on a sliding scale was used to achieve target sodium levels that would keep intracranial pressure less than 20 mm Hg once the conventional therapies failed.

Measurements and Main Results: Eighty-eight children met inclusion criteria. Etiologies of elevated intracranial pressure included trauma ($n = 48$), ischemic or hemorrhagic stroke ($n = 20$), infection ($n = 8$), acute disseminated encephalomyelitis ($n = 5$), neoplasm ($n = 2$), and others ($n = 5$). The mean peak serum sodium was 171.3 mEq/L (range, 150–202). The mean Glasgow Outcome Score was 2.8 (± 1.1) at time of discharge from the hospital. Overall mortality was 15.9%. Children with sustained (> 72 hr) serum sodium levels above 170 mEq/L had a significantly higher occurrence of thrombocytopenia ($p < 0.001$), renal failure ($p < 0.001$), neutropenia ($p = 0.006$), and acute respiratory distress syndrome ($p = 0.029$) after controlling for variables of age, gender, Pediatric Risk of Mortality score, duration of barbiturate-induced coma, duration of intracranial pressure monitoring, vasopressor requirements, and underlying pathology. Children with sustained serum sodium levels greater than 165 mEq/L had a significantly higher prevalence of anemia ($p < 0.001$).

Conclusions: Children treated by continuous hypertonic saline infusion for intracranial hypertension whose serum sodium levels exceeded certain thresholds experienced significantly more events of acute renal failure, thrombocytopenia, neutropenia, anemia, and acute respiratory distress syndrome than those whose sodium level was maintained below these thresholds. (*Pediatr Crit Care Med* 2013; 14: 610–620)

Key Words: acute kidney injury; acute respiratory distress syndrome; anemia; hypertonic saline solution; intracranial hypertension; neutropenia; thrombocytopenia

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Hypertonic saline (HS) therapy has evolved as an alternative to mannitol for treatment of elevated intracranial pressure (ICP) (1–12). HS may prove more effective in decreasing cerebral edema, compared with mannitol because of its higher osmotic reflection coefficient across the blood-brain barrier. HS offers the benefit of facilitating an increase in intravascular volume while reducing ICP without inducing or exacerbating hypotension through volume depletion (13, 14).

Large boluses or prolonged infusions of HS can elevate serum sodium levels causing a medically induced hypernatremia. Few investigations have evaluated the possible adverse effects of medically induced hypernatremia (7, 15, 16). Though moderate levels of hypernatremia (< 160 mEq/L) are thought to be relatively safe in the hospitalized patient, no safe upper limit has been clearly established.

We performed a retrospective review of all neurosurgical patients in a tertiary care PICU with an ICP monitoring device who were treated with HS for elevated ICP for at least 4 days. In the course of treatment, medically induced severe hypernatremia developed in many of these patients (serum sodium levels > 160 mEq/L). We evaluated for the occurrence of possible complications that may be associated with prolonged periods of medically induced supraphysiologic serum sodium levels and described our findings.

MATERIALS AND METHODS

Patient Selection

We performed a retrospective review of all children admitted to the 24-bed PICU at Rady Children's Hospital of San Diego from September 2004 to August 2009 who had an intracranial monitor (external ventricular drain or intraparenchymal fiberoptic device) in place for at least 4 days and were treated with continuous HS infusion for elevated ICP. A 4-day period was chosen to include the patient population with more difficult to control intracranial hypertension who were most likely to have been treated with prolonged HS administration and also because complications occurring earlier were unlikely to be associated with the therapy given in the ICU (15). Exclusion criteria included patients with thrombocytopenia (platelets < 100,000), coagulopathy (International Normalized Ratio [INR] > 1.4), or renal failure (creatinine more than double baseline value) at presentation, prior to treatment for intracranial hypertension. Demographic and clinical information including age, gender, duration of ICP monitoring device, lowest hemoglobin, duration of thiopental infusion for barbiturate-induced coma, and the requirement of vasopressor medications during ICP management were recorded for each patient. Pediatric Risk of Mortality (PRISM) score, Glasgow Coma Scale (GCS) at admission, Injury Severity Score (ISS) for trauma patients, and Glasgow Outcome Score (GOS) at discharge were also recorded.

Approval of the Rady Children's Hospital's Institutional Review Board was obtained for this retrospective collection of data. Rady Children's Hospital of San Diego is a freestanding tertiary academic pediatric hospital with a medical-surgical PICU containing 30 beds. The PICU is a closed unit managed by a PICU team with 24-hour in-hospital critical care attending coverage.

Procedures

In general, whether secondary to traumatic brain injury or due to other etiologies, all patients with intracranial hypertension were treated according to the guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents (17). Those who had an indication for intracranial surgery were treated surgically. Decompressive craniectomy was performed at the discretion of the attending neurosurgeon. Medical interventions in the PICU included elevation of head greater than 30°, sedation, paralysis and analgesia, controlled moderate hyperventilation ($Paco_2$, 30–35 mm Hg), mild hypothermia (34–35°C) with cooling blankets, ventricular drainage when possible, and barbiturate coma. Vasopressor and inotropic agents were used as needed to maintain the cerebral perfusion pressure above 50–65 mm Hg depending on age. No corticosteroid agents were used for the treatment of traumatic head injury but were sometimes used for other etiologies of cerebral edema. Mannitol was not routinely used due to a preference for HS in this institution.

Once conventional therapies as outlined above failed to adequately control ICPs from rising above a threshold of 20 mm Hg, a continuous HS infusion on a sliding scale was used to achieve target sodium levels that would keep ICP less than 20 mm Hg, as has been described previously by Peterson et al (9). Although not strictly protocolized, generally patients were given a bolus of 3% HS of 5 mL/kg and then placed on a continuous infusion between 1 and 3 mL/kg/hr to achieve a serum sodium goal. The initial target serum sodium level was 150–155 mEq/L. If ICP was not controlled at this serum Na level, as evident by ICP elevations greater than 20 mm Hg for more than 15 minutes duration, the goal serum sodium level was raised 5–10 mEq/L and the infusion of 3% HTS was increased by 1 mL/kg/hr in a stepwise fashion to meet this goal. Serum sodium levels were checked every 2–4 hours to assess the patient's response to the HTS infusion. In patients with the most severely refractory ICP elevations, serum sodium was sometime targeted to levels as high as 190 mEq/L.

All daily values for serum sodium, blood urea nitrogen, creatinine, body temperature, hematocrit, hemoglobin, platelet level, WBC count with differential, INR, prothrombin time, and partial thromboplastin time for each individual patient were reviewed and recorded. Sustained peak sodium levels were defined as the highest serum sodium levels maintained for a minimum of 3 days. This differs from peak sodium levels that may have only been present for a single measurement. Charts were reviewed for the occurrence of dialysis, blood product transfusions, infection, deep vein thrombosis, and acute respiratory distress syndrome (ARDS). Complications were recorded as defined below.

Renal Failure

The occurrence of acute kidney injury described in terms of risk, injury, and failure was determined by the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End stage kidney disease) criteria based on changes in serum creatinine from baseline levels (18).

Infection

Infection was defined by the presence of a positive culture of cerebrospinal fluid, blood, urine, respiratory culture, or skin, or if clinical signs (radiologic readings, lab values, etc.) led to treatment with more than one broad-spectrum antibiotic for at least 1 day.

Venous Thrombosis

The presence of deep venous thrombosis or pulmonary embolus was confirmed by Doppler ultrasound or spiral CT when suspected.

Hematologic Changes

Traumatic brain injury and acute intracerebral hemorrhages are well known to be associated with coagulopathy, including disseminated intravascular coagulation (DIC). When recording patients' hematologic changes, we excluded any abnormalities that were present within 48 hours of admission that could be attributed to acute DIC. Transfusions and low hematocrits associated with acute blood loss on presentation or from surgical procedures were not included in our analysis. All other blood product transfusions were recorded, including whole blood, packed RBCs, platelets, fresh frozen plasma (FFP), and cryoprecipitate. Because laboratory definitions of anemia in the clinical and critical care setting are not firmly established (19), we chose to categorize these complications according to the need for intervention as determined by the PICU team. Exact hemoglobin thresholds for transfusion varied by patient age, underlying pathology, daily trending, as well as by treating care teams. For this reason, anemia was defined as the need for RBC transfusion due to low hematocrit as determined by the acting PICU team. Neutropenia was defined as persistent absolute neutrophil count below 1,000 at which point granulocyte-colony stimulating factor (filgrastim) was initiated. Thrombocytopenia was defined as platelet level less than 100,000, a commonly accepted threshold for platelet transfusion in neurosurgical patients (20).

Acute Respiratory Distress Syndrome

ARDS was diagnosed based on acute onset of diffuse patchy infiltrates on plain film radiography associated with Pa_{O_2}/F_{IO_2} ratio less than 200 mm Hg, and no clinical evidence of left atrial hypertension (21) as determined by the daily progress notes recorded by the acting PICU team during the hospitalization.

Statistical Analysis

All statistical calculations and analysis were performed using R programming (version 2.14.1) (22) with the Survival and ROCR packages (23, 24). Cutoff points of sustained peak serum sodium levels by 5–10 point intervals (< 160, 160–164, 165–169, 170–174, 175–179, 180–189, ≥ 190 mEq/L) were chosen for graphical comparison of outcomes as an explorative analysis. Youden Index, the point that maximizes sensitivity and specificity, was calculated along each receiver operator characteristic (ROC) curve to determine optimal threshold serum sodium levels for each complication. Subsequently, the mean of the threshold levels calculated from the ROC curves (170 mEq/L) was used to divide patients into two groups in order to compare categorical outcomes of complications using Fisher exact test with two-tailed *p*-values. Demographic and clinical characteristics between the two groups were compared using the Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables. The effects of increasing sodium levels on percent change of creatinine were analyzed using Spearman's correlation. Univariate and multivariate logistic regression was performed for each complication as a dichotomous outcome variable using the following prediction variables: peak sustained serum sodium level dichotomized at greater than or equal to 170 mEq/L, duration of thiopental infusion for barbiturate-induced coma (days), duration of ICP monitoring (days), PRISM scores, whether or not vasopressors were required during ICP therapy, age, gender, and pathology (traumatic vs nontraumatic). The ISS was included as an additional variable on a subset analysis of patients with traumatic head injuries. All variables were included within the multivariate model and were chosen based on their potential clinical relevancy rather than their association to serum sodium levels. Results were considered statistically significant at an α of 5% ($p = 0.05$).

RESULTS

A total of 90 patients met the above inclusion criteria, from which two were excluded due to severe hematologic abnormalities and renal failure at presentation attributable to the underlying diagnosis of hemolytic-uremic syndrome. Eighty-eight children (51 males and 37 females), ages 3 weeks to 19 years (mean age, 6.8 ± 5.5 yr old) remained for analysis (**Table 1**). Etiologies of elevated ICP included trauma ($n = 48$), ischemic or hemorrhagic stroke ($n = 20$), infection ($n = 8$), acute disseminated encephalomyelitis ($n = 5$), neoplasm ($n = 2$), and others ($n = 5$). Patients whose sustained sodium levels exceeded 170 mEq/L during hospitalization were more likely to have presented with lower GCS scores (mean, 6 vs 7.3; $p < 0.001$), higher PRISM scores (mean, 10.6 vs 7.2; $p = 0.026$), and were treated for longer periods of time for elevated ICP (19 vs 10.9 days of ICP monitoring, < 0.001; and 9.7 vs 4.1 days of thiopental infusion for barbiturate-induced coma, $p < 0.001$). There were no significant differences in gender distribution, age, prevalence of vasopressor support, or underlying pathology (traumatic vs nontraumatic) between the two groups.

The overall mean GCS at presentation was 7.3 (± 3.4) though intense ICP management did not begin unless GCS deteriorated below 9. Peak sodium levels from all patients averaged 171.3 ± 13.2 mEq/L (range, 150–202 mEq/L). Five patients underwent decompressive craniectomy for medically refractory intracranial hypertension. There were 14 deaths among the patient charts reviewed. Seven of the deaths were due to cerebral herniation, three were from cardiac failure, and four were after withdrawal of life support. Six of the patients suffered from severe multiple organ failure at the time of death. Only two of 30 patients (6.7%) who had sustained serum sodium levels greater than or equal to 170 mEq/L had good or moderate outcomes by GOS. Patients who required sustained elevations of serum sodium above 170 mEq/L for control of refractory intracranial hypertension were more likely to be in a vegetative state or dead at discharge ($p < 0.001$) (**Table 2**).

Cutoff values for peak sustained serum sodium threshold levels by complication were assessed by plotting ROC curves (**Fig. 1**). The mean threshold level for developing complications was 170 mEq/L though some events such as the need for RBC transfusion were seen to occur at lower thresholds (166 mEq/L; area under the curve, 0.870; $p < 0.001$). Univariate and multivariate logistic regression modeling showed that exceeding a sustained serum sodium threshold of greater than or

TABLE 1. Summary of Patient Characteristics

Characteristics	Sustained Peak Serum Sodium Level (mEq/L)		*p*[a]
	Na < 170	Na ≥ 170	
Total patients, *n*	58	30	
Males (*n*, %)	31 (53%)	20 (67%)	0.262
Females (*n*, %)	27 (47%)	10 (33%)	
Age (mean, ±SD)	6.6 yr ± 5.3	7.3 yr ± 5.9	0.561
Range (3 wk to 19 yr)			
Glasgow Coma Scale (mean, ±SD)	7.3 ± 3.3	6 ± 2.6	0.049
Range (3–15)			
ICP monitor duration (mean, ±SD)	10.9 d ± 4.7	19 d ± 12.1	< 0.001
Range (5–62)			
ICP monitor type			
Intraparenchymal monitor	31	13	
External ventricular drain	23	10	
Both	4	7	
Pediatric Risk of Mortality score (mean, ±SD)	7.2 ± 5.5	10.6 ± 7.2	0.026
Range (0–28)			
Days of thiopental infusion (mean, ±SD)	4.1 ± 3.9	9.7 ± 9.5	< 0.001
Range (0–45)			
Vasopressors given (> 24 hr)	52 (90%)	29 (97%)	0.415
Yes or no			
Lowest Hgb during ICP therapy	8.7 ± 1.2	8.0 ± 1.3	< 0.001
Range (6.1–12)			
Discharge Glasgow Outcome Score (mean, ±SD)	3.1 ± 1.0	2.3 ± 1.0	< 0.001
Range (1–5)			
Mechanism			0.824[b]
Traumatic brain injury	21	11	
Nonaccidental trauma	10	6	
Subarachnoid hemorrhage (arteriovenous malformation or aneurysm rupture)	9	3	
Infection (meningitis/encephalitits)	7	1	
Acute disseminated encephalomyelitis	2	3	
Spontaneous intracerebral hemorrhage (neoplastic or unknown etiology)	2	2	
Ischemia (stroke, anoxia)	3	1	
Metabolic encephalopathy	1	2	
Tumor/carcinomatosis	2	0	
Straight sinus thrombosis	1	0	
Vanishing white matter disease	0	1	

ICP = intracranial pressure.

[a]*p* values were calculated by Wilcoxon rank sum test for quantitative variables and by Fisher exact test for categorical variables.

[b]Calculated comparing prevalence of traumatic versus nontraumatic mechanisms by Fisher exact test.

TABLE 2. Summary of the Associated Complications of Children Treated With Continuous Hypertonic Saline

Complication	Sustained Peak Serum Sodium Level (mEq/L)		
	< 170 (*n* = 58)	≥ 170 (*n* = 30)	*p*
Neutropenia, *n* (%)	3 (5.2)	11 (36.7)	**< 0.001**
Thrombocytopenia, *n* (%)	6 (10.3)	27 (90)	**< 0.001**
RBC Transfusion, *n* (%)	20 (34.5)	28 (93.3)	**< 0.001**
Fresh frozen plasma transfusion, *n* (%)	13 (22.4)	20 (66.7)	**< 0.001**
Renal failure, *n* (%)	2 (3.4)	16 (53.3)	**< 0.001**
Dialysis, *n* (%)	1 (1.7)	6 (20)	**0.006**
Acute respiratory distress syndrome, *n* (%)	1 (1.7)	10 (33.3)	**< 0.001**
Glasgow Outcome Score < 3, *n* (%)	10 (17.2)	14 (46.7)	**0.005**

Univariate statistical analysis of complication rate by peak sustained serum sodium level at threshold levels of 170 mEq/L by Fisher exact test. Statistically significant *p* values are given in bold font ($p < 0.01$).

equal to 170 mEq/L was the variable most associated with each complication occurrence. The only exception was the need for FFP transfusion (multivariate, $p = 0.094$) where the number of days in thiopental coma was more significantly associated with the complication than serum sodium levels (multivariate, $p = 0.006$) (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/A65). Odds ratios calculated by multivariate analysis for the development of each complication when sustained serum sodium levels exceeded 170 mEq/L are presented in **Table 3**. GOSs were not associated with sustained serum sodium levels on multivariate analysis.

A subset analysis of the patients with traumatic mechanisms of brain injury ($n = 48$) was performed separately in order to include the additional variable of ISS (**Table 4**). The results continued to show a significant association with the development of thrombocytopenia, and the need for transfusion of RBCs with serum Na levels sustained greater than or equal to 170 mEq/L. The development of neutropenia, renal failure, ARDS, and the need for FFP transfusion lost statistical significance on multivariate analysis, though the trends for each complication persisted.

Acute Renal Failure

Serum sodium elevations significantly correlated with increases in serum creatinine ($\rho = 0.608$; $p < 0.001$) (**Fig. 2**). Renal failure developed in 16 patients (53.3%) whose sodium levels were sustained greater than or equal to 170 mEq/L compared with only two patients (3.4%) whose sodium was kept below 170 mEq/L ($p < 0.001$, Fisher exact test) (**Fig. 3**). All surviving patients had resolution of renal dysfunction at the time of discharge and none required long-term dialysis or diuretic therapy after serum sodium levels were corrected.

Thrombocytopenia

Increasing serum sodium levels were significantly associated with coagulopathic changes as defined by the requirement of platelet and FFP transfusions (Fisher exact test, $p < 0.001$) (Table 2). The prevalence of thrombocytopenia was 90% in patients who sustained peak sodium levels greater than or equal to 170 mEq/L compared to a 10.3% prevalence of thrombocytopenia in patients whose sodium was kept below 170 mEq/L ($p < 0.001$) (**Fig. 4**).

Neutropenia

Neutropenia developed in 14 children (15.9%) who received prolonged HS and required the initiation of granulocyte-colony stimulating therapy with filgrastim (**Fig. 5**). The prevalence of neutropenia was 36.7% in patients whose sodium rose greater than or equal to 170 mEq/L, and only 5.2% in patients whose sodium was kept below 170 mEq/L ($p < 0.001$).

Anemia

Thirty-seven patients (80.4%) with sustained sodium levels greater than or equal to 165 mEq/L required packed RBC transfusions for anemia not attributable to acute or known sources of blood loss compared to only 11 patients (26.2%) whose sodium levels were kept below 165 mEq/L ($p < 0.001$) (Fig. 5).

Acute Respiratory Distress Syndrome

ARDS developed in 10 of 30 patients (33.3%) whose sustained sodium levels were greater than or equal to 170 mEq/L, whereas ARDS developed in only one of 58 patients (1.7%) whose sustained peak sodium levels were below 170 mEq/L ($p < 0.001$) (**Fig. 6**).

Others

We did not observe any instances of central pontine myelinolysis (CPM) by chart review despite several instances where serum sodium levels increase more than 20 mEq/L in a 24-hour period. Fifty-nine of the 88 children had MR imaging verifying the absence of CPM. There were no instances of rebound ICP observed with resolution of HS therapy. Eighty-seven of the 88 patients reviewed required more than 1 day of multiple broad-spectrum antibiotics during their treatment for elevated ICP.

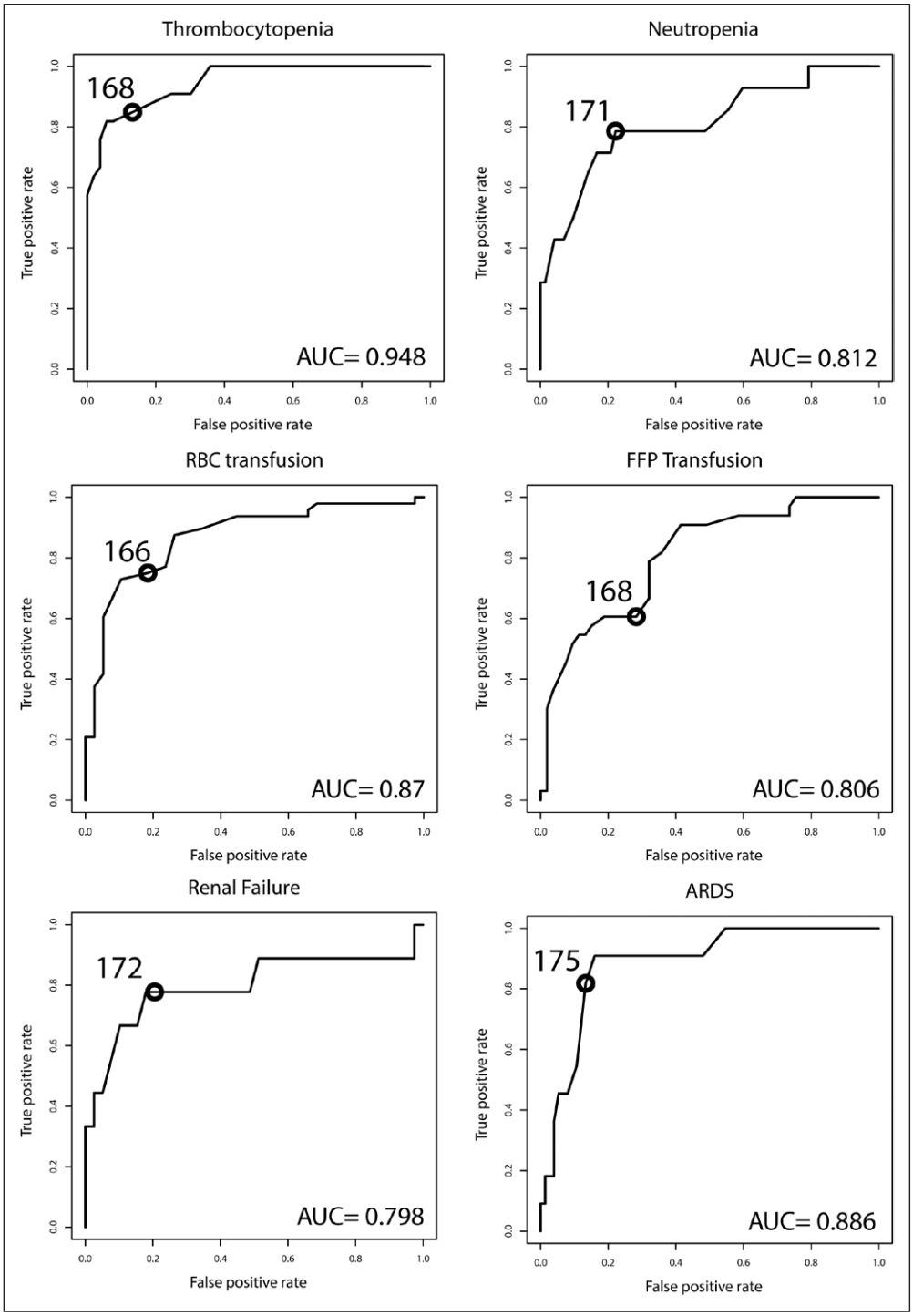

Figure 1. Receiver operating characteristic curves for each complication observed. Optimal threshold level as determined by Youden Index is labeled for each curve. AUC = area under the curve, FFP = fresh frozen plasma, ARDS = acute respiratory distress syndrome.

There was only one incident of deep venous thrombosis in our series, consistent with the previously reported low prevalence of deep venous thrombosis in the pediatric population.

DISCUSSION

A safe serum sodium threshold level during the administration of HS for treatment of intracranial hypertension has not been objectively identified. This undefined safe threshold may lead to either aggressive HS protocols targeting high serum sodium concentrations or withholding of HS when it could be efficacious in the treatment of intracranial hypertension. We performed a retrospective analysis of patients admitted to a single institution's PICU over a 5-year period who were treated with prolonged continuous infusions of HS for intracranial hypertension from a variety of etiologies. The results of our analysis show an increased prevalence of complications that may be associated with sustained peak serum sodium levels rising above certain threshold levels during HS therapy for intracranial hypertension which include renal failure, coagulopathies, immune dysfunction, ARDS, and an increased need for blood transfusions.

Previous reports observe that medically induced hypernatremia from HS administration for the purpose of treating intracranial hypertension is well tolerated with few attributable negative side effects (2, 7–9, 11, 13, 15, 25, 26). However, in most published studies, the serum sodium levels are targeted to stay below a hypernatremia threshold value of 155–160 mEq/L. Nonetheless, even in reports describing medically induced hypernatremia to peak levels exceeding the 160 mEq/L threshold (11, 15) and in some cases exceeding 180 mEq/L (8, 9), few or no related adverse effects have been reported.

Renal

Our findings that elevated sodium levels are associated with an increasing prevalence of renal failure differ from several previous reports that ascribe no renal failure attributable to extreme levels of induced hypernatremia during the management of ICP (8, 9, 15). One reason for this difference may be due to our use of the RIFLE score, which defines a standardized classification for acute renal failure, thus providing

TABLE 3. Association of Complications with Sustained Serum Sodium ≥ 170 mEq/L

	Univariate			Multivariate		
Complication	Odds Ratios	95% CI	*p*	Odds Ratios	95% CI	*p*
Thrombocytopenia	75	19.8–392.8	< 0.001	67.6	13.1–572.5	< 0.001
Neutropenia	10.2	2.8–48.9	< 0.001	9.9	2.1–59.8	0.006
RBC transfusion	25.2	6.6–166.5	< 0.001	12.7	2.6–105	0.004
Fresh frozen plasma transfusion	6.6	2.6–18.3	< 0.001	2.9	0.8–10.6	0.094
Renal failure	30.8	7.6–210.5	< 0.001	35.1	6.8–300.3	< 0.001
Acute respiratory distress syndrome	27.5	4.8–521.2	0.002	12.9	1.7–268.8	0.029

Odds ratios of developing each complication when sustained serum sodium level exceeds 170 mEq/L determined by univariate and multivariate logistic regression modeling, including variables of Pediatric Risk of Mortality score, days of thiopental infusion, days of intracranial pressure monitoring, administration of vasopressors, age, gender, and etiology (traumatic vs non-traumatic).

TABLE 4. Subset Analysis of Patients With Traumatic Head Injury (*n* = 48)

	Univariate			Multivariate		
Complication	Odds Ratios	95% CI	*p*	Odds Ratios	95% CI	*p*
Thrombocytopenia	31.5	7.0–194	< 0.001	71.6	6.8–1,807	0.002
Neutropenia	26.7	4.1–530.5	0.003	195	0.8–64,053,150	0.146
RBC transfusion	33.6	5.7–650.7	0.001	22.8	1.7–935.4	0.041
Fresh frozen plasma transfusion	9.5	2.5–41.6	0.001	3.9	0.6–27.1	0.156
Renal failure	10.2	2.1–76.3	0.009	17.5	1.0–540.7	0.064
Acute respiratory distress syndrome	12.5	1.8–253.2	0.028	7.7	0.3–354.4	0.239

Odds ratios of developing each complication when sustained serum sodium level exceeds 170 mEq/L determined by univariate and multivariate logistic regression modeling, including variables of Pediatric Risk of Mortality score, total Injury Severity Score, days of thiopental infusion, days of intracranial pressure monitoring, administration of vasopressors, age, and gender.

a more sensitive diagnostic criterion for renal failure than has been used in prior reports (18, 27, 28). Association of medically induced hypernatremia with kidney injury is consistent with published experiences in burn centers where HS administration correlated with oliguria and renal failure (29). The cause of increased acute kidney injury and failure observed in association with rising serum sodium levels is unknown, though animal studies have shown deleterious effects on renal function from rapid increases in sodium levels resulting in a reduction of renal blood flow, glomerular filtration rate, and an inhibition of renin secretion suggesting a causative role (30).

Coagulopathy

Coagulopathies were indirectly measured by the requirements of FFP and platelet transfusions. There was a significant increase in the development of thrombocytopenia in patients whose serum sodium levels rose above 170 mEq/L. FFP transfusions were also given more often to patients who exceeded this threshold. The exact mechanism of thrombocytopenia in patients whose sodium levels exceeded 170 mEq/L is unknown. We observed a gradual decrease in platelet level with rising serum sodium levels followed by a rebound thrombocytosis as the serum sodium corrected, similar to the pattern observed in consumptive coagulopathies, characterized by peripheral aggregation and destruction of platelets (31) (Fig. 4). The timing and pattern of platelet reductions is not consistent with acute DIC, as is seen at presentation in severe head injuries; however, an indolent, chronic form of DIC seen in severe trauma and sepsis cannot be ruled out as a potential etiology (32, 33).

Hanke et al (34) studied HS hydroxyethyl starch (HHES) effects on whole blood coagulation and platelet function in vitro. Their results demonstrated significant impairment of whole blood coagulation and platelet function in a dose-dependent manner and at concentrations that would be routinely used in clinical resuscitation. Hanke et al determined that the HS component of HHES to be the factor responsible for the observed platelet dysfunction. Scanning electron microscopy of platelets exposed to HS showed platelet dehydration and

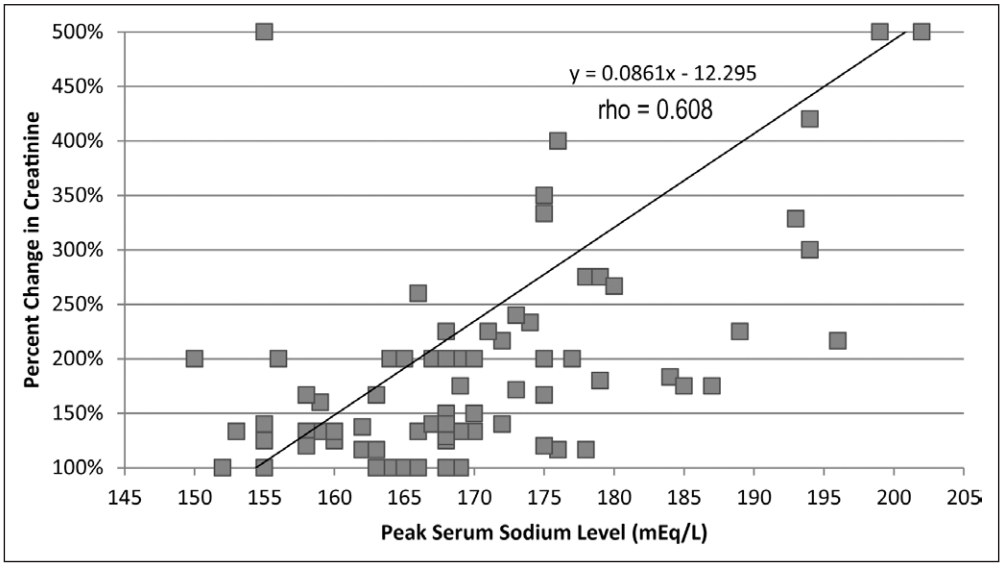

Figure 2. The correlation of peak serum sodium on creatinine in children treated with continuous hypertonic saline.

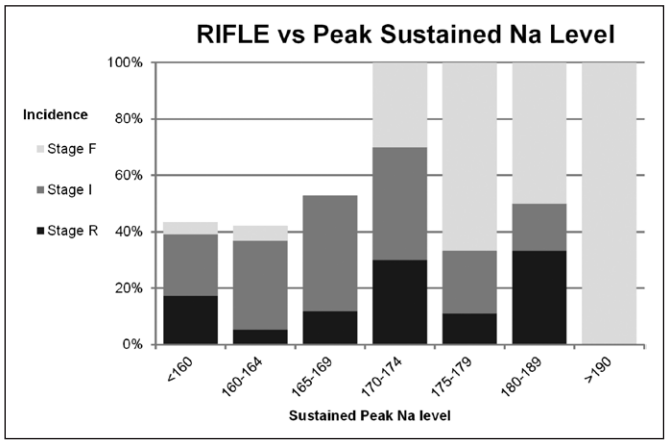

Figure 3. The correlation of sustained peak serum sodium with renal failure determined by RIFLE (Risk, Injury, Failure, Loss of kidney function, End stage renal disease) criteria.

activation causing accumulation of thrombocytes into large platelet aggregates (34).

Anemia

Our data showed that all but one patient (n = 29) whose sodium levels were sustained above 170 mEq/L required transfusion of RBCs due to anemia not associated with acute blood loss from surgery, trauma, or known source of hemorrhage. We are unable to discern through our retrospective analysis whether the cause of the anemia is from chronic disease through prolonged hospitalization, from iatrogenic blood loss through frequent sampling of blood, hematopoietic suppression, or from some peripherally destructive process related to the hypernatremia.

Immune System

We were unable to detect an effect of sodium levels on the prevalence of infection. The high rate of antibiotic usage, used to define infection in this study, likely reflects a low threshold for initiating antibiotic therapy rather than a true prevalence of infection. Other therapeutic interventions affecting our patients, including pressor support in the face of barbiturate-induced coma and sedation-associated hypotension, the use of mechanical ventilation, and strict temperature control with cooling blankets to induce mild-to-moderate hypothermia, combine to make definitive diagnoses of infections or sepsis unreliable.

HS has been credited with immunomodulatory effects, including a reduced prevalence of sepsis after trauma (35, 36). In our series of patients, there were significantly more episodes of severe neutropenia associated with HS use in patients whose sodium levels rose above 170 mEq/L. This profound level of neutropenia puts patients at high risk for infection and other complications related to an immunocompromised status.

Acute Respiratory Distress Syndrome

Timing of HS administration has been shown to be a critical determinant in its effects on inflammatory response (37, 38). Early resuscitation with HS has been shown to suppress neutrophil activation and degranulation, limiting the cytotoxic potential for organ tissue damage (26, 38). Conversely, delayed HS therapy increases neutrophil accumulation in tissues, augments neutrophil degranulation, and aggravates tissue injury (37). Consistent with these findings, our patient population of children receiving prolonged HS infusions past the early resuscitative period showed an increased prevalence of ARDS once sustained serum sodium levels exceeded 170 mEq/L.

Limitations

There are several inherent limitations to our study. First, given the retrospective nature of our report, our results can only demonstrate associations between hypernatremia and the complications examined. Causality cannot be proven. Second, we studied a heterogenous group of patients with varying causes of intracranial hypertension not limited to trauma. We saw no major differences in the development of complications on subgroup analysis comparing traumatic to nontraumatic etiologies of intracranial hypertension, nevertheless, not all etiologies of elevated ICP can be expected to respond identically to a single therapeutic modality. Third, our institution rapidly escalates therapy for refractory intracranial hypertension regardless of etiology. In the setting of prolonged intracranial hypertension studied here, multiple therapies are present simultaneously with potential for confounding

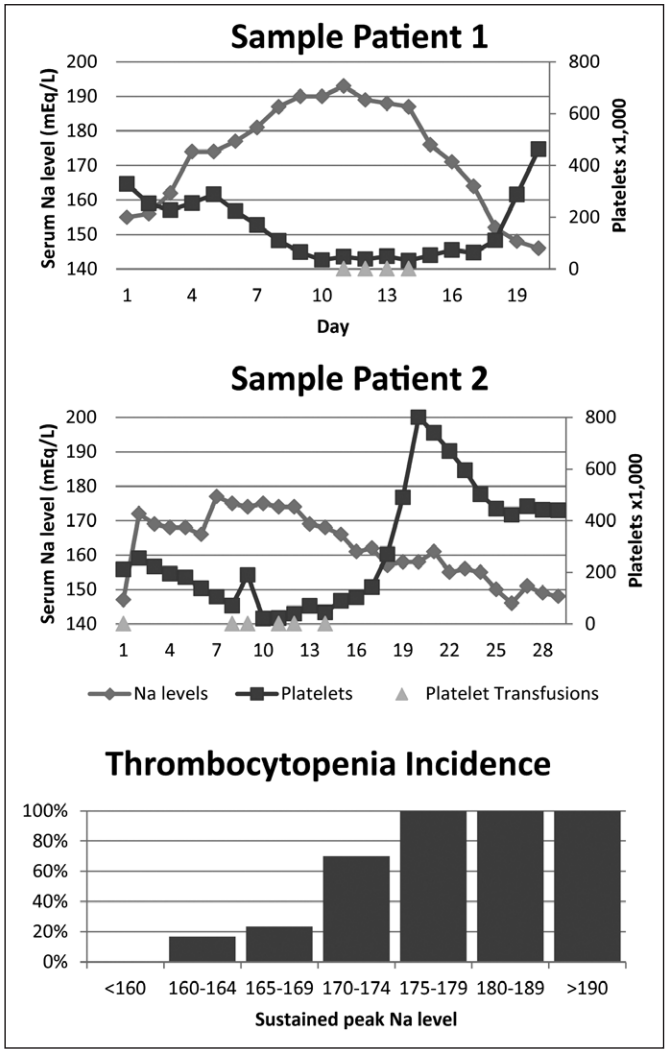

Figure 4. The effects of continuous hypertonic saline on the prevalence of thrombocytopenia. The daily trends of platelet level plotted against serum sodium level of two patients illustrate the steady fall in serum platelet levels with extreme hypernatremia followed by a rebound thrombocytosis upon correction of serum sodium levels.

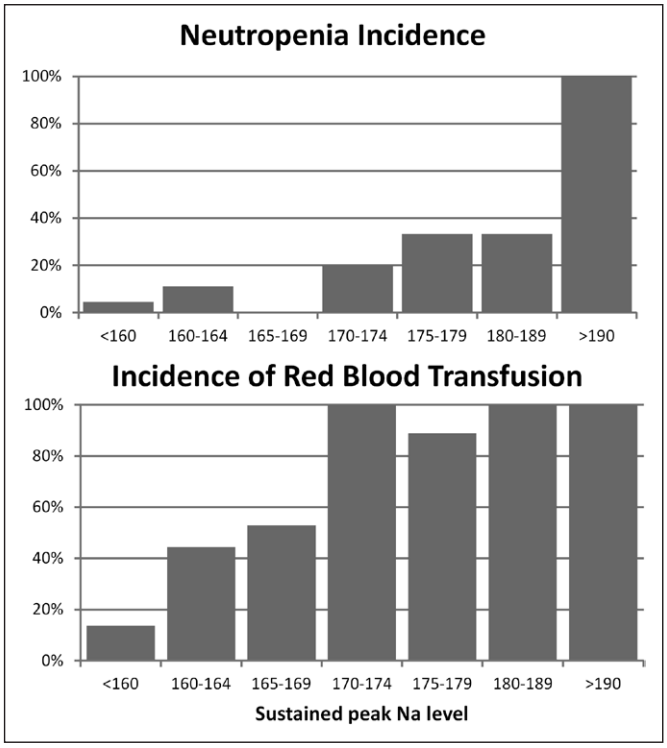

Figure 5. The prevalence of RBC transfusion and neutropenia in children treated with continuous hypertonic saline.

effects. There have been reports associating barbiturate therapy use with hypotension, impaired myocardial contractility (39), endocrinologic disturbances (40), renal failure (41), and immunosuppression with frequent nosocomial infections (42). It is also possible that the need to induce extreme levels of hypernatremia for ICP control merely reflected the underlying severity of illness of the individual children being treated. Although regression models controlling for severity of illness, barbiturate administration, and vasopressor use still demonstrated an independent association between increased serum sodium levels and the described complications, we cannot rule out potential confounders from other treatments applied simultaneously.

Whether or not prolonged HS therapy led to altered outcomes through better ICP control despite associated complications is not addressed in this study because this question could only be accurately answered through a randomized controlled clinical trial. The deleterious effects of intracranial hypertension with poor cerebral perfusion pressure and resultant cerebral ischemia are well documented. In the setting of refractory intracranial hypertension, clinicians may be forced to choose between escalating hypertonic therapies with the associated complications herein described, escalating other medical therapies (hyperventilation, pentobarbital coma) with known complications, surgery (with associated morbidity and mortality), or not escalating care in the face of a deteriorating patient with resultant poor outcome. Though aggressive HS administration may have contributed to the complications described in this article, the majority of these complications could be managed medically and were reversible with discontinuation of HS therapy upon resolution of intracranial hypertension. Future prospective studies are warranted to define the appropriate role of HS and to determine a safe threshold for medically induced hypernatremia in the management of intracranial hypertension.

CONCLUSIONS

This retrospective review of a single institution's experience using HS in the PICU for treatment of intracranial hypertension suggests that there may be increased rates of complications when serum sodium levels exceed certain thresholds. The rates of renal failure, need for dialysis, thrombocytopenia, neutropenia, and ARDS increased significantly when serum sodium levels were sustained greater than or equal to 170 mEq/L and the prevalence of RBC transfusions increased in patients whose levels were sustained above 165 mEq/L. The physiologic consequences of extreme hypernatremia on multiple organ systems are not well understood. These findings suggest the exercise

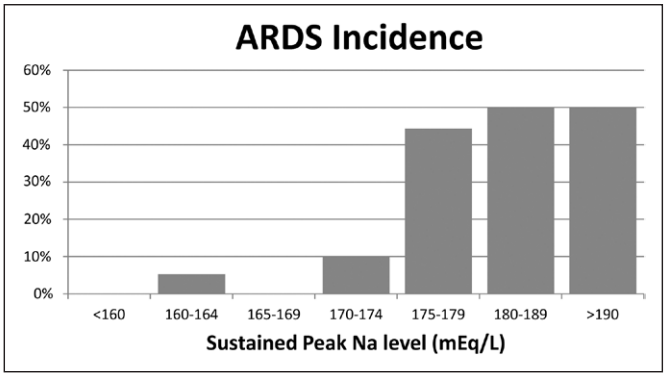

Figure 6. The prevalence of acute respiratory distress syndrome (ARDS) in children treated with continuous hypertonic saline.

of caution when serum sodium levels are elevated above 165 mEq/L in the treatment of elevated ICP with HS. Prospective randomized clinical trials are needed to determine the safety and efficacy of prolonged HS therapy in children.

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