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Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury

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Abstract

Objectives: To evaluate the effect of prolonged infusion of 3% hypertonic saline (514 mEq/L) and sustained hypernatremia on refractory intracranial hypertension in pediatric traumatic brain injury patients.

Design: A prospective study.

Setting: A 24-bed Pediatric Intensive Care Unit (Level III) at Children's Hospital.

Patients: We present ten children with increased intracranial pressure (ICP) resistant to conventional therapy (head elevation at 30°, normothermia, sedation, paralysis and analgesia, osmolar therapy with mannitol, loop diuretic, external vertricular drainage in five patients), controlled hyperventilation (PCO_2, 28-35 mm Hg), and barbiturate coma. We continuously monitored ICP, cerebral perfusion pressure (CPP), mean arterial pressure, central venous pressure, serum sodium concentrations, serum osmolarity, and serum creatinine.

Interventions: A continuous infusion of 3% saline on a sliding scale was used to achieve a target serum sodium level that would maintain ICP <20 mm Hg once the conventional therapy and barbiturate coma as outlined above failed to control intracranial hypertension.

Measurements and Main Results: The mean duration of treatment with 3% saline was 7.6 days (range, 4-18 days). The mean highest serum sodium was 170.7 mEq/L (range, 157-187 mEq/L). The mean highest serum osmolarity was 364.8 mosm/L (range, 330-431 mosm/L). The mean highest serum creatinine was 1.31 mg/dL (range, 0.4-5.0 mg/dL). There was a steady increase in serum sodium versus time zero that reached statistical significance at 24, 48, and 72 hrs ($p < .01$). There was a statistically significant decrease in ICP spike frequency at 6, 12, 24, 48, and 72 hrs ($p < .01$). There was a statistically significant increase in CPP versus time zero at 6, 12, 24, 48, and 72 hrs ($p < .01$). There was a statistically significant increase in serum osmolarity versus time zero at 12 hrs ($p < .05$) and at 24, 48, and 72

hrs ($p < .01$). Two patients developed acute renal failure and required continuous veno-venous hemodialysis; these were concurrent with an episode of sepsis and multisystem organ dysfunction. Both recovered full renal function with no electrolyte abnormalities at the time of discharge.

Conclusion: An increase in serum sodium concentration significantly decreases ICP and increases CPP. Hypertonic saline is an effective agent to increase serum sodium concentrations. Sustained hypernatremia and hyperosmolarity are safely tolerated in pediatric patients with traumatic brain injury. Controlled trials are needed before recommendation of widespread use.

Head injury is the most devastating component of childhood trauma and the leading cause of death in the injured child. Despite major advances in our understanding of the pathophysiology and treatment of traumatic brain injury, management issues in these patients continue to present a major challenge, and morbidity and mortality remain high. As primary brain injury cannot be reversed, postinjury management must focus on prevention and reversal of the secondary insults to improve outcome.

Control of intracranial pressure (ICP) is of paramount importance in-patients with traumatic brain injury, and multiple therapies are used to achieve ICP control. Nonsurgical therapy includes the use of osmotic and loop diuretics, hypothermia, sedation and paralysis, controlled hyperventilation, and barbiturate coma. Surgical therapies include ventriculostomy with therapeutic drainage, evacuation of mass lesion, and decompressive craniotomy.

Osmolar therapy is one of the main treatments for control of elevated intracranial pressure and cerebral edema after head injury. Although mannitol is the mainstay of osmolar therapy, hypertonic saline is being used more frequently to control intracranial hypertension in both adult and pediatric intensive care units (1-9). Several animal studies have demonstrated the beneficial effects of hypertonic saline on cerebral blood flow, ICP, and brain water content (10-13).

Hypertonic saline exerts its effect primarily through establishment of an osmotic gradient between the intravascular space and cerebral tissue. Water diffuses passively from the cerebral intracellular and interstitial space into capillaries, thereby reducing cerebral water content and ICP. In addition, hypertonic saline is an effective plasma volume expander, providing hemodynamic support in multiple trauma patients, and may have beneficial effects on cerebrovascular regulation. We report our experience with hypertonic saline infusion to control intracranial hypertension refractory to conventional therapeutic modalities.

MATERIALS AND METHODS

This study was performed at the Pediatric Intensive Care Unit of San Diego Children's Hospital. Approval was obtained from the Institutional Review Board of San Diego Children's Hospital, and parental consent was obtained for all subjects before enrollment. Data for this descriptive study were collected prospectively. Ten children aged 4 months to 12 yrs were enrolled. All patients sustained a severe head injury as defined by a Glasgow Coma Scale score of <=8. Subjects were entered into the protocol after failing conventional therapy that included head elevation,

paralysis and sedation with mechanical ventilation, osmolar therapy with mannitol (serum osmolarity, 315-320 mosm/L), diuretic therapy with loop diuretics, controlled hyperventilation (PCO_2, 28-35 mm Hg), external ventricular drainage (five patients), and thiopental sodium coma. In five patients, the neurosurgical consultant felt that placement of an intraventricular catheter for external ventricular drainage would not be successful, as the ventricles were small. Failure of conventional therapy and barbiturate coma was defined as ICP values of >20 mm Hg for >5 mins.

The study protocol included a continuous infusion of 3% saline (514mEq/L) on a sliding scale to achieve a target serum sodium level. Sodium values were obtained every 6 hrs and the infusion rate of 3% saline was adjusted accordingly. The target serum sodium value was increased as needed to maintain ICP at <20 mm Hg. The maximal rate of increase in serum sodium was defined as 15 mEq/L/day. The maximum rate of decrease in serum sodium was defined as 10mEq/L/day. This protocol was continued until ICP persisted at <20 mm Hg. No maximum serum sodium level or duration of therapy was defined.

The initial values for serum sodium and ICP were recorded for each patient before beginning hypertonic saline therapy. The following information was collected during the trial period for each patient: age and gender; admission Glasgow Coma Scale score; hourly ICP and cerebral perfusion pressure (CPP) measurements; hourly mean arterial pressure (MAP) and central venous pressure (CVP) measurements; frequency of ICP spikes >20 mm Hg (number/6-hr shift); serum sodium, osmolarity and $PaCO_2$ values obtained every 6 hrs; daily mannitol dose (20% or 25%) and thiopental sodium dose and level; daily serum creatinine, blood urea nitrogen, and creatinine clearance (if patient developed renal failure); and 3% saline dose. ICP, CVP, and MAP measurements were converted to 6-hr averages for the purposes of data analysis. The amount of ventriculostomy drainage was also recorded for the five patients who had ventriculostomy placement.

Euvolemia was maintained as guided by measurements of CVP or pulmonary artery occlusion pressure. Chest radiographs were obtained daily. Neurologic outcome was assessed at discharge and at 6 months after discharge by using the Glasgow Outcome Scale (GOS), scored as follows: 1, death; 2, vegetative state; 3, severe disability; 4, moderate disability; 5, mild or no disability (14). Brain computed tomographic (CT) scans of all patients were interpreted by a blinded pediatric neurosurgeon and were classified into one of five intracranial diagnosis groups (15) as follows: 1, diffuse injury with no visible intracranial pathology on CT scan; 2, diffuse injury, cisterns present with shift 0-5 mm and/or lesion densities present; 3, diffuse injury with swelling; cisterns absent or compressed, shift 0-5 mm; 4, diffuse injury with shift >5 mm; 5, evacuated mass lesion.

Statistical Methods. Data from all ten patients were combined, with comparisons made between the start of the trial (time zero) and 6, 12, 24, 48, and 72 hrs into the trial for each of the following: serum sodium (mEq/L), ICP (mm Hg), frequency of ICP spikes >20 mm Hg (number/6-hr shift), CPP (mm Hg), osmolarity (mosm/L), PCO_2 (mm Hg), mannitol dose (g/kg/6-hr shift), and infusion rate of thiopental sodium (mg/kg/hr). Analysis of variance was performed using Dunnett's test for repeated measures to control for the possibility of type I error with multiple comparisons. In addition, comparisons between time zero and 48 hrs were made for CVP and MAP using a Dunnett's test for repeated measures.

We next investigated the relationship between serum sodium and ICP; however, because of individual differences in trial length and in maximum values for ICP and serum sodium, statistical analysis was performed on each patient separately. In addition, ICP and sodium levels were noted to fluctuate between consecutive measurements, even with the use of 6-hr averages for each. Therefore, smooth continuous estimates of ICP and serum sodium over time were made using polynomial regression analysis. The relationship between sodium and ICP was then modeled using polynomial regression with serum sodium level as the independent variable and ICP level as the dependent variable. This allowed us to evaluate the prevailing trend rather than the point-to-point variability, placing more emphasis on the larger changes and less on the smaller ones. Statistical significance was defined for a p of <.05.

RESULTS

Between August 1, 1996 and March 31, 1998, there were 1,921 patients admitted to the trauma service at San Diego Children's Hospital. Of these, 965 patients were admitted with injuries to the head and neck. Of these, 215 were placed in the Pediatric Intensive Care Unit, and 48 required ICP monitoring. A total of 10 patients had uncontrolled intracranial hypertension with ICP values remaining >20 mm Hg despite conventional therapy and use of barbiturates as described above. These 10 were entered into the trial.

Descriptive data for the ten patients are displayed in Table 1. The mean age of the study population was 5.7 yrs (range, 4 months to 13 yrs). There were two females and eight males. Three patients were passengers involved in unrelated automobile accidents, two were struck by automobiles, two patients sustained head injury from fall, and three patients were subjected to nonaccidental trauma. The mean injury severity score was 30 (range, 18-45). The median CT intracranial diagnosis classification score was 2.5 (range, 2-4). The mean enrollment time was 3.2 days after admission (range, 1-6 days), and the mean duration of treatment with 3% saline was 8 days (range, 4-18 days). The median Glasgow Coma Scale score on presentation was 4 (range, 3-7), and the median 6-month GOS score was 4 (range, 1-5). Only one of the patients died of uncontrolled intracranial hypertension. Of the nine remaining patients, seven had a GOS score of 4 or 5. Initial, 48-hr, and maximum values for serum chemistries and hemodynamic variables for all ten patients are displayed in Table 2.

Patient	A	B	C	D	E	F	G	H	I	J
Age	15 m	12 yrs	15 m	3 yrs	3 yrs	11 yrs	6 yrs	4 m	6 yrs	13 yrs
Gender	F	F	M	M	M	M	M	M	M	M
Mechanism of injury	NAT	Bike	NAT	Fall	MVA	MVA	MVA	NAT	PVA	PVA
Initial GCS	7	7	5	3	4	5	4	4	4	4
ISS	27	21	18	26	27	43	27	29	45	38
ICD classification	2	3	2	2	3	3	4	2	4	3
Hospital day enrolled in the study	4	6	1	5	4	2	1	3	3	4
Days of treatment with 3% saline	8	6	4	7	7	8	7	4	18	7
GOS (6 months)	5	5	1	4	4	4	4	3	5	3

M, months; NAT, nonaccidental trauma; MVA, motor vehicle accident; PVA, pedestrian versus automobile accident; ISS, injury severity score.

Table 1. Descriptive data for each patient including demographics, mechanism of injury, intracranial diagnosis (ICD) classification based on computed tomographic scan, injury severity score, admission Glasgow Coma Scale score (GCS), and 6-month Glasgow Outcome Scale score (GOS)

Patient	A	B	C	D	E	F	G	H	I	J
ICP (mm Hg) at the time of enrollment	24	28	26	22	30	33	27	26	24	23
Initial MAP (mm Hg) (average at the time of enrollment) (range)	60 (52–66)	70 (58–78)	64 (54–70)	62 (49–68)	68 (54–76)	69 (60–74)	70 (55–80)	60 (48–70)	62 (45–72)	70 (52–75)
MAP (mm Hg) (average for 48 hours into study) (range)	68 (60–75)	75 (63–84)	67 (50–76)	65 (55–78)	70 (58–83)	78 (65–88)	72 (57–85)	60 (52–72)	68 (56–79)	78 (64–87)
Initial CVP (mm Hg) (average at the time of enrollment)	7 (5–10)	8 (5–11)	8 (6–10)	8 (5–12)	9 (5–11)	7 (4–9)	8 (6–10)	6 (5–9)	8 (6–12)	8 (5–12)
CVP (mm Hg) (average for 48 hrs into study) (range)	8 (6–12)	9 (7–12)	9 (6–14)	10 (7–16)	9 (7–12)	9 (5–12)	8 (6–12)	8 (7–11)	10 (7–15)	9 (7–14)
Initial sodium (mEq/L) at the time of enrollment	148	150	146	148	148	144	147	146	140	148
Maximum sodium (mEq/L)	166	186	187	176	157	181	168	158	171	157
Initial osmolarity (mosm/L) at the time of enrollment	315	315	320	322	318	315	325	320	316	318
Maximum osmolarity (mosm/L)	360	431	405	360	330	388	356	332	348	338
Maximum creatinine (mEq/L)	0.5	3.1	0.8	0.6	0.5	5.0	0.6	0.4	0.8	0.8

ICP, intracranial pressure; MAP, mean arterial pressure; CVP, central venous pressure.

Table 2. Initial, 48-hr, and maximum values for serum chemistries and hemodynamic variables for all ten patients

Before the initiation of hypertonic saline therapy, the mean ICP was 26.3 mm Hg (range, 22-33 mm Hg), the mean serum sodium was 146.7 mEq/L (range, 140-150 mEq/L), and the mean osmolarity was 318 mosm/L (range, 315-325 mosm/L). The mean MAP at the time of enrollment was 65 mm Hg (range, 60-72 mm Hg) and the mean CPP at the time of enrollment was 39.7 mm Hg (range, 36-47 mm Hg). The mean for highest serum sodium value achieved was 170.7 mEq/L (range, 157-187 mEq/L), the mean highest serum osmolarity was 364.8 mosm/L (range, 330-431 mosm/L), and the mean peak serum creatinine was 1.31 mg/dL (range, 0.4-5.0 mg/dL). The mean MAP before enrollment (65 mm Hg; range, 60-70 mm Hg) was significantly less ($p < .01$) than the mean MAP 48 hrs into the trial (71 mm Hg; range, 60-78 mm Hg). The mean CVP before enrollment (7.7 mm Hg; range, 6-9 mm Hg) was significantly less ($p < .01$) than the mean CVP 48 hrs into the trial (8.9 mm Hg; range, 8-10 mm Hg).

Figure 1 depicts the trends for serum sodium vs. ICP, frequency of ICP spikes, CPP, and serum osmolarity during the first 72 hrs. There was a steady increase in serum sodium vs. time zero that reached statistical significance at 24, 48, and 72 hrs ($p < .01$). There was a statistically significant decrease in ICP vs. time zero at 6, 12, 24, 48, and 72 hrs ($p < .01$). There was a statistically significant decrease in ICP spike frequency at 6, 12, 24, 48, and 72 hrs ($p < .01$). There was a statistically significant increase in CPP vs. time zero at 6, 12, 24, 48, and 72 hrs ($p < .01$). There was a statistically significant increase in serum osmolarity vs. time zero at 12 hrs ($p < .05$) and at 24, 48, and 72 hrs ($p < .01$).

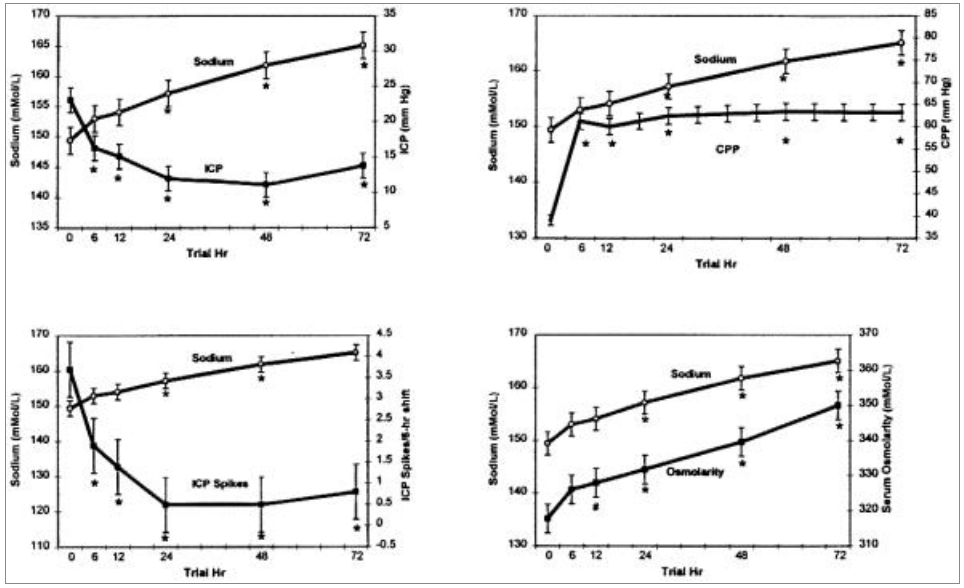

Figure 1. Combined data for all ten patients demonstrating values for serum sodium vs. intracranial pressure (*ICP*) (*upper left*), ICP spikes (*lower left*), cerebral perfusion pressure (*CPP*) (*upper right*), and serum osmolarity (*lower right*) during the first 72 hrs after initiating hypertonic saline therapy. #$p < .05$; *$p < .01$.

Figure 2 demonstrates values for serum sodium vs. PCO_2, 6-hr cumulative dose of mannitol, and infusion rate of thiopental sodium during the first 72 hrs. There was a statistically significant rise in PCO_2 vs. time zero at 6 hrs ($p < .05$) and at 48 and 72 hrs ($p < .01$). There was a statistically significant decrease in the amount of mannitol given vs. time zero at 24 hrs ($p < .05$) and at 48 and 72 hrs ($p < .01$). There was a statistically significant decrease in the infusion rate of thiopental sodium vs. time zero at 48 and 72 hrs ($p < .01$).

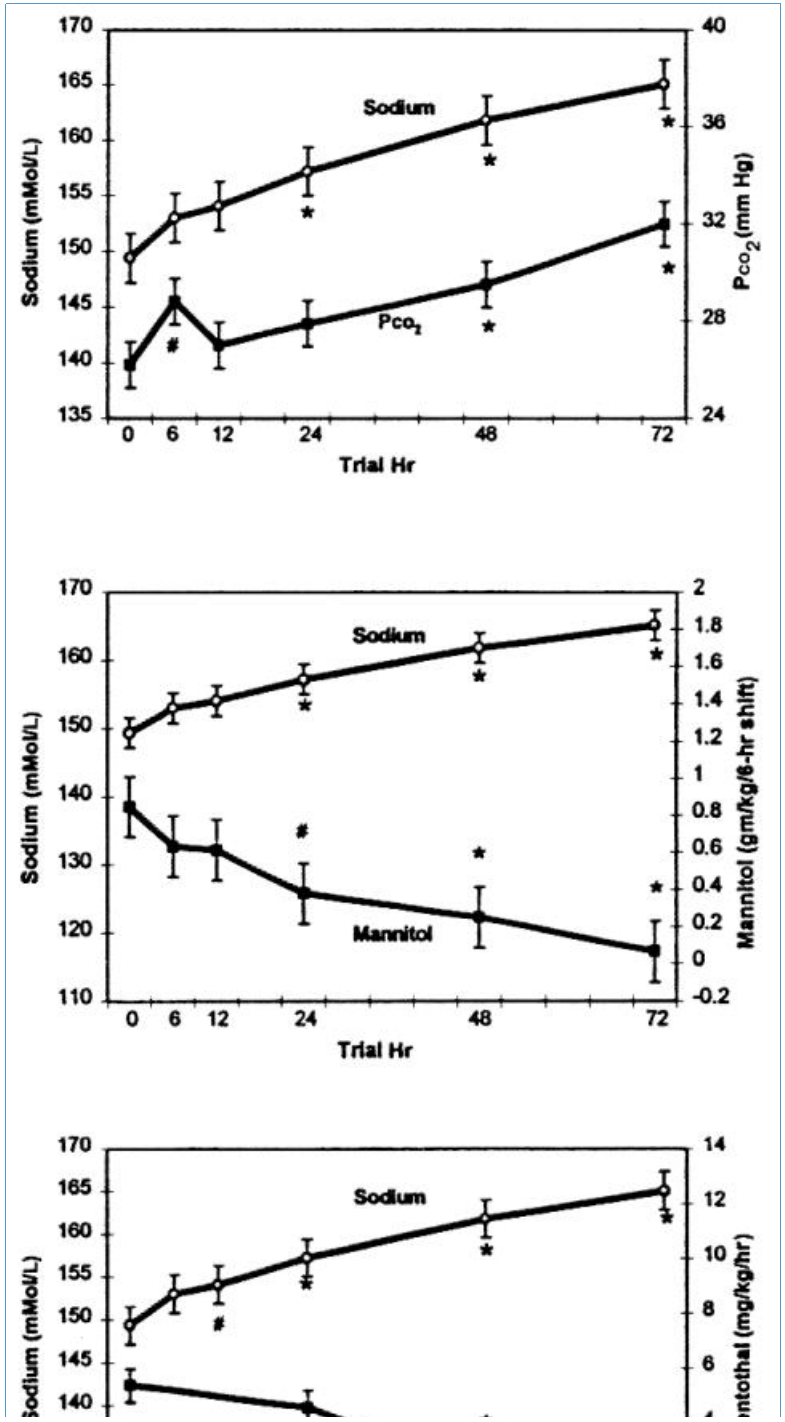
Sodium
Pco2
Sodium (mMol/L)
Pco2 (mm Hg)
Trial Hr
Sodium
Mannitol
Sodium (mMol/L)
Mannitol (gm/kg/6-hr shift)
Trial Hr
Sodium
Sodium (mMol/L)
ntothal (mg/kg/hr)

Figure 2. Combined data for all ten patients demonstrating values for serum sodium vs. PCO_2 (*top*), mannitol dose (*middle*), and thiopental sodium dose (*bottom*) for the first 72 hrs after initiating hypertonic saline therapy. #$p < .05$; *$p < .01$.

With regard to the individual data, a best-fit curve was created for serum sodium and ICP for each of the ten patients, with a statistically significant fit achieved in all but one curve. For this patient, a significant estimate of ICP over time could not be found because of the trial length of >2 wks; however, a statistically significant ($p < .05$) correlation was observed using the original values of serum sodium and ICP without the use of the best-fit curves. For exploratory purposes, the visually best fitting lower-order curve was used in the subsequent modeling of the relationship between ICP and sodium for this patient. There was a statistically significant ($p < .05$) correlation between the extrapolated values at 6-hr intervals in all cases.

A sample graph (Patient A) is shown in Figure 3. Our defined treatment goal was to limit the amount of time the ICP remained elevated, and a new target serum sodium was determined for any ICP elevation >20 mm Hg for >5 mins. Because of our use of 6-hr averages for ICP measurements, these intermittent rises in ICP are not necessarily reflected in an increase in the ICP value on the graph. This gives the false impression that serum sodium values were elevated unnecessarily when the individual graph is examined.

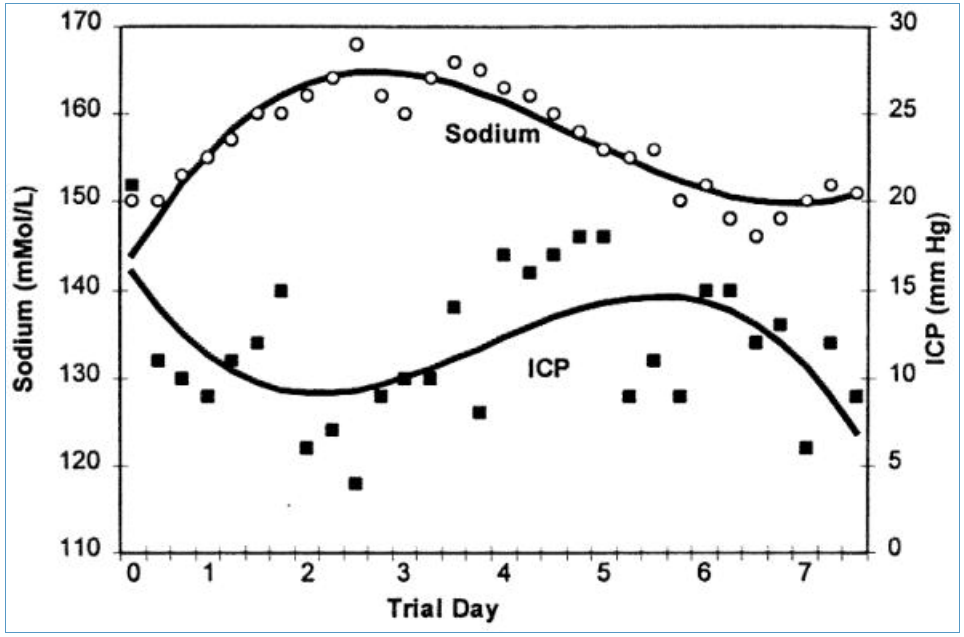

Figure 3. Sample individual graph demonstrating curves for serum sodium and intracranial pressure (*ICP*) over time, which were then used for polynomial regression analysis. Note the inverse relation-ship between serum sodium and ICP, which was statistically significant in all patients ($p < .05$).

Two patients developed acute renal failure and required dialysis with continuous veno-venous hemodialysis. However, the development of acute renal failure occurred well past the peak serum sodium values and in both cases was concurrent with an episode of sepsis and multiple system organ dysfunction. Bronchial brush cultures grew

Pseudomonas aeruginosa in one patient and methicillin-resistant *Staphylococcus aureus* in the other. Their renal function improved as multiple system organ dysfunction resolved, and both recovered full renal function without electrolyte abnormalities before discharge.

Care was withdrawn in one patient after discussion with the family regarding the futility of continued treatment. This patient had suffered severe brain injury from nonaccidental trauma and had presented to the emergency department almost 48 hrs after his initial injury.

DISCUSSION

We present our experience with the use of sustained and often profound hypernatremia to control intracranial hypertension after traumatic brain injury in a total of ten patients. A continuous infusion of 3% saline was used to decrease ICP to <20 mm Hg. All of our patients failed aggressive therapy for elevated ICP as outlined by the Brain Trauma Foundation using mannitol, hyperventilation, head elevation, ventricular drainage (five patients), and sodium thiopental coma (16).

We found that a statistically significant relationship exists between serum sodium and ICP and that hypertonic saline effectively controlled intracranial hypertension resistant to conventional therapy including sodium thiopental coma. There did not appear to be any short- or long-term complications with the use of hypertonic saline in these patients.

Data from previous studies suggests that neurologic outcome in head-injured patients is inversely related to the amount of time that ICP remains >20 mm Hg (17, 18). Unfortunately, standard therapies to achieve ICP control have significant adverse effects. Mannitol has been shown to produce improvement in intracranial hypertension; however, the effects are temporary, with rebound intracranial hypertension, intravascular volume depletion and renal insufficiency as common adverse effects (19-21). Hyperventilation is also an effective means to control the rise in ICP associated with traumatic brain injury; however, this comes at the expense of decreased cerebral perfusion and worsened outcomes in some trials (22, 23). Head elevation and ventricular drainage are temporizing measures at best and do not address cerebral edema at a cellular level. Sedative-hypnotic agents such as thiopental sodium decrease cerebral metabolism and are associated with improved survival; however, cardiovascular depression and immune suppression are common at higher doses (24-26).

Hypertonic saline solutions (1.8%-7.5% NaCl) used to treat laboratory models of head injury are associated with a significantly lower ICP and significantly lower cerebral water content than treatment with either hypotonic or isotonic fluids (10-13). Several recent studies in humans support the efficacy of hypertonic saline and induced hypernatremia for controlling intracranial hypertension (1-9). Suarez et al. (8) found that boluses of 23.4% saline produced a temporary drop in ICP without compromising hemodynamics in eight patients with intracranial hypertension from a variety of causes with serum sodium ranging from 149 ± 1 to 153 ± 6 mEq/L. Qureshi et al. (7) used 3% saline to induce mild hypernatremia and found temporary control of ICP could be achieved and edema on CT scan could be reduced. Khanna et al. (3) retrospectively reviewed data from head-injured children who received hypertonic saline for ICP control and found no adverse effects on either neurologic outcome or renal function, even with serum osmolarity values of >320 mosm/L. Simma et al. (9) compared the effects of lactated Ringer's solution

and hypertonic saline in children with severe head injuries during the first 3 days of hospitalization. They concluded that increases in serum sodium (130-172 mEq/L) were associated with lower ICP and higher CPP values. In addition, several trials have demonstrated improved survival of head-injured patients with concurrent hypotension when treated with a prehospital bolus of hypertonic saline (27, 28).

Hypertonic saline works by increasing serum sodium and serum osmolarity, creating an osmotic gradient to pull water from the intracellular and interstitial compartments of the brain, and reducing cerebral edema and ICP. Although mannitol works similarly, sodium chloride has a more favorable reflection coefficient (1.0) than mannitol (0.9) (5); that is, the blood-brain barrier is more able to exclude sodium chloride, making it an ideal agent in this regard. In addition, hypertonic saline has been demonstrated to enhance cardiac output and increase cerebral perfusion (29). This occurs not only by expansion of intravascular volume, but also via reduction of vascular resistance through decreased edema in the vascular endothelium of injured tissues (30). Hypertonic saline may also normalize resting membrane potentials and cell volumes by restoring normal intracellular electrolyte balances to injured cells. This suggests that hypertonic saline may preferentially benefit injured areas of the brain (31).

Osmolar therapy is limited by ability of brain cells to reestablish euvolemia despite alterations in serum osmolarity. This explains the limited duration of efficacy and rebound rise in ICP demonstrated in previous studies with both mannitol and hypertonic saline (7, 8, 21). Rebound cerebral swelling occurs when serum osmolarity falls rapidly and the residual hyperosmolar intracellular environment leads to an intracellular fluid shift. Our protocol was designed to prevent rapid reductions in serum sodium and osmolarity with a gradual return to normal serum sodium values once ICP control was achieved. As such, we did not observe significant ICP elevations when hypertonic saline therapy was gradually discontinued.

We believe that our study is unique for several reasons. The degree and duration of hypernatremia are beyond those that have been reported previously for treatment of intracranial hypertension. This was largely a result of our unique treatment strategy in which target serum sodium values were continually adjusted to achieve ICP control without defining a maximum serum sodium level or duration of treatment. We also observed excellent clinical outcomes in these patients. Nine patients survived with an average GOS of 4. The one exception died of uncontrolled intracranial hypertension, an outcome that was predicted based on the extent, severity, and delay of his initial presentation. This patient sustained severe intracranial injury secondary to shaken baby syndrome and did not come to medical attention for almost 48 hrs. This delay in treatment may have resulted in irreversible secondary brain insults.

We also believe that these outcomes may address the concerns regarding the adverse effects of prolonged and severe hypernatremia. It is possible that hypernatremia did contribute to renal insufficiency, however the influence of hypernatremia on renal function was negligible, and despite supraphysiologic values for both serum sodium and osmolarity, no patient developed chronic renal failure. The most compelling rationale for this observation is that intravascular dehydration did not occur in this group of patients. Thought to be part of the pathophysiology of mannitol-induced renal insufficiency, intravascular dehydration was much easier to avoid with hypertonic saline because the desired osmotic level required to control raised ICP could be achieved without excessive diuresis.

Theoretical concerns associated with the administration of all hypertonic substances include the development of central pontine myelinolysis, rapid shrinking of the brain associated with mechanical shearing or tearing of the

bridging vessels resulting in subarachnoid hemorrhage, coagulopathies, and rebound intracranial hypertension. Central pontine myelinolysis is a syndrome characterized pathologically by demyelination of deep white matter in both pontine and extrapontile tissues and clinically by the onset of lethargy and quadriparesis (32, 33). Central pontine myelinolysis has been reported with rapid correction of chronic hyponatremic to serum sodium levels of >132 mEq/L. In this study, no cases of central pontine myelinolysis were detected despite repeated evaluations via CT scan (all 10 patients) and magnetic resonance imaging (five patients). Shrinkage of the brain with resultant subarachnoid hemorrhage after rapid infusion of hypertonic saline was initially reported by Finberg (34). In that study, normal kittens were injected with 35 mL/100 g weight of 9% NaCl solution, increasing their serum sodium concentrations from 149 mEq/L to 206 mEq/L within 1 hr after injection. Our patients received hypertonic saline by infusion and experienced only gradual changes in serum sodium tailored to reducing raised ICP. The risk of subarachnoid hemorrhage was probably minimized because serum sodium increased slowly and only enough to reduce intracranial pressure to 10-20 mm Hg. We did not observe any unexplained subarachnoid hemorrhage on subsequent brain CT scan in these patients.

One of our goals was to determine whether there is a statistical relationship between ICP and serum sodium. However, the absence of controls and the variability between subjects with regard to both duration and degree of hypernatremia required a novel approach to data analysis. Polynomial regression models were used to first create best-fit curves for ICP and serum sodium over time, and extrapolated values from these curves were used for final analysis. We believe this statistical model firmly establishes that a relationship exists between serum sodium and ICP and that this relationship can be manipulated to control intracranial hypertension in head-injured patients. In examining the sample graph, it is important to recall that the ongoing fluctuations in ICP were smoothed by the use of 6-hr shift averages and through the model described above. Although it appears that immediate ICP control was achieved after institution of hypertonic saline and that the extreme hypernatremia achieved in may have been unnecessary, the continued rise in serum sodium was in response to intermittent rises in ICP. These transient rises in ICP are not necessarily reflected by either the 6-hr shift averages or in the polynomial curves, largely because of the efficacy of hypertonic saline in arresting these ICP spikes before they affected the 6-hr shift averages.

These results must be viewed in the light of the study limitations. Patients were not randomized to receive either placebo or hypertonic saline. Furthermore, aggressive standard therapy is generally sufficient to control ICP in most patients, leading to relatively few patients who qualified for the trial. We did utilize a standard approach in these patients as outlined by the Brain Trauma Foundation guidelines before enrollment in this trial allowing us to isolate the effect of sodium modulation on ICP without the simultaneous initiation of these other therapies as has been the case in previous trials. However, the absence of a control group limits the strength of our conclusions. We did observe a statistically significant decrease in the need for hyperventilation, mannitol, and thiopental sodium during the trial period, supporting the efficacy of hypertonic saline. This also avoids the potential adverse effects of each of these on cerebral perfusion and hemodynamic stability, perhaps equally significant with regards to eventual outcome.

CONCLUSIONS

We believe that we have presented evidence to support the efficacy of induced hypernatremia in controlling intracranial hypertension after traumatic brain injury. These conclusions are based on an original statistical model that establishes a relationship between serum sodium and ICP, as well as a decreased need for alternative and potentially harmful therapies. In addition, the neurologic outcome of these patients was better than would be

predicted given their initial presentation. Furthermore, these results were achieved without significant side effects. The limitations of hypertonic saline suggested in previous trials, specifically the limited duration of efficacy and the rebound effect observed on its withdrawal, have been overcome by gradual elevations and reductions in serum sodium through the duration of the critical injury period. Although we cannot support widespread institution of hypernatremia for ICP control based on this small descriptive trial, we believe that this is a promising new approach that warrants a prospective, controlled trial to examine its appropriateness as first-line therapy for the treatment of traumatic brain injury.

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Key Words: hypertonic saline; sodium; osmolarity; creatinine; intracranial pressure; cerebral perfusion pressure; Glasgow Coma Scale score; Glasgow Outcome Scale score; computed tomography; head injury

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IMAGE GALLERY

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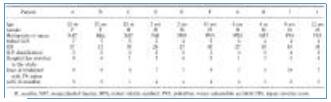

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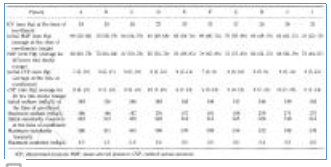

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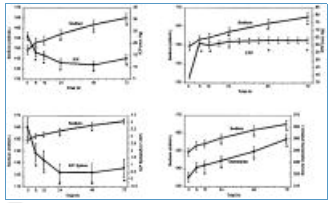

Figure 1

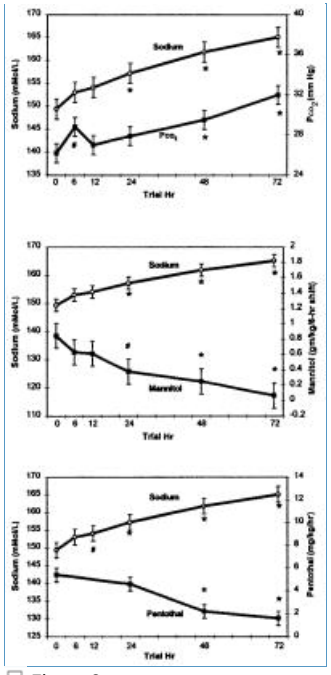

Figure 2

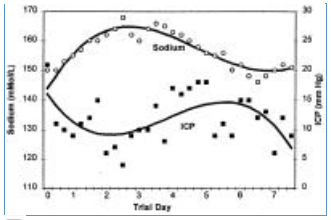

Figure 3

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