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Hypertonic Saline Lowers Raised Intracranial Pressure in Children After Head Trauma

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Summary: Eighteen pediatric patients who sustained traumatic brain injury were enrolled in a double-blind, crossover study comparing the effects of 3% saline and 0.9% saline infusions on raised intracranial pressure (ICP). After resuscitation, each patient received a bolus of each saline concentration, and ICP was monitored for 2 h. Initial mean ICP before 0.9% saline infusions equaled 19.3 mm Hg and averaged 20.0 mm Hg during the subsequent 2-h trials ($p = 0.32$). Baseline mean ICP before 3% saline administration equaled 19.9 mm Hg and averaged 15.8 mm Hg for 2 h postinfusion ($p = 0.003$). Central venous pressure did not change significantly in either group, nor did measurements of renal function. Serum sodium concentrations increased in all 18 trials of 3% saline. Maximal concentrations of serum sodium occurred 30 min after bolus administration of 3% saline. Three percent saline significantly reduces raised ICP after traumatic brain injury when compared with normal saline. Intravascular dehydration, as measured by central venous pressure, did not occur during the study period. **Key Words:** Hypertonic saline—Intracranial pressure—Head trauma.

Patients with major trauma who sustain head injuries are much more likely to die as compared with trauma patients without brain injury (1). Approximately 30% of trauma fatalities in children are the result of brain injuries and are associated with raised intracranial pressure (ICP) (2,3).

There are limitations to the current modalities used to combat elevated intracranial pressure after head trauma. Hyperventilation initially lowers intracranial pressure by lessening posttraumatic hyperemic cerebral blood flow but does not alleviate cerebral edema. Used injudiciously, hyperventilation may critically reduce cerebral blood flow and impair cerebral oxygen delivery (4). It is unclear to what extent and benefit chronic hyperventilation influences cerebral blood flow and cerebral edema (5). Diuretics, such as mannitol and furosemide, draw water from undamaged brain parenchyma. Vigorous administration of osmotic or loop diuretics can lead to intravascular dehydration and hypotension followed by prerenal failure (6) and reduced cerebral blood flow (7). Excessive administration of barbiturates to lower raised ICP may precipitate hypotension in the face of diminished cerebral autoregulation and also result in reduced cerebral blood flow.

Hypertonic solutions reduce ICP and augment intravascular volume and cardiovascular performance (8–13). Resuscitation of animals subjected to both brain injury and hemorrhagic shock with hypertonic saline solution results in the resolution of shock, reduction of ICP, and alleviation of cerebral

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edema (14,15). Hypertonic saline in various concentrations has been used to resuscitate trauma victims from shock because of its ability to restore vascular pressure rapidly with less volume administration than normotonic saline solutions (16–18). Worthley et al. administered 29.9% saline to two adult head trauma patients suffering from intracranial hypertension and prerenal failure due to prolonged mannitol and furosemide administration. Intravenous administration of hypertonic saline to those patients reduced ICP and improved renal function in both patients (6).

Hypertonic saline lessens intracranial pressure in experimental animals by reducing cerebral water content. Intracranial pressure is reduced by the dehydration of normal brain tissue (20). Water is drawn from the brain into the vascular compartment, decreasing ICP by an osmotic gradient produced within the cerebral circulation. An intact blood–brain barrier and an osmotic gradient between the intravascular space and the cerebral interstitial space are required for hypertonic solutions to work.

Increasing osmolarity is an accepted method for combating raised intracranial pressure in humans. Acute increases in serum sodium are well tolerated and occur physiologically. To date there are no published controlled trials studying the effect of hypertonic saline on raised intracranial pressure in adults or children. In this study we measured the acute effects of intravenous hypertonic saline administration on raised intracranial pressure in children after head trauma.

PATIENTS AND METHODS

This study was approved by the hospital institutional review board, and informed consent was granted by a legal guardian before admission into the study. From April 1987 to December 1988, 18 head trauma patients admitted through the pediatric trauma service at San Diego Children's Hospital were studied.

All patients required resuscitation from traumatic head injury before entering the study. Resuscitation universally required endotracheal intubation and hyperventilation. In admission, all patients had a subdural intracranial pressure monitor put in place via a ⅛-inch craniotomy drilled into either the left or right frontal skull. Arterial catheters were also placed in all 18 patients, and 16 of 18 patients were given a central venous pressure catheter.

Sixteen patients received a short-acting barbiturate, thiopental, 6–24 h before admission into the study. Thiopental was given during initial resuscitation to assist intubation, central line placement, and computerized tomography. Eight patients were administered an additional bolus of thiopental between 1.5 and 6 h before study admission, in order to facilitate reintubation, central line replacement, or repeat computerized tomography. Thiopental dosages ranged between 1 and 5 mg/kg.

After appropriate volume resuscitation, dopamine or epinephrine infusions were used to titrate blood pressure in the majority of patients. All patients were placed on dopamine at doses ranging from 2 to 10 mcg/kg/min. Hypotension despite adequate volume resuscitation and dopamine administration prompted initiation of epinephrine infusions for three patients at dosages ranging from 0.05 to 0.15 mcg/kg/min. After resuscitation, entry criteria required a rising intracranial pressure >15 mm Hg or a falling cerebral perfusion pressure (CPP) <50 mm Hg for 5 min despite hyperventilation and concomitant mannitol administration.

A saline bolus was administered to each patient the first two times entrance criteria were met. Saline boluses consisted of 3% saline (calculated osmolarity 1,025 mOsmol/L) and 0.9% saline (calculated osmolarity 308 mOsmol/L). Each patient received one bolus of each saline concentration administered in a blinded, randomized fashion. After the saline bolus, ICP was continuously measured over 2 h. Nine patients were randomized to receive a 3% saline trial initially, followed by a 0.9% trial, and the other nine patients received the two trials in the reverse order. Infusion rates were kept equivalent. Fifteen of 18 patients received 10 ml/kg of both saline concentrations. Because of baseline arterial hypertension at the beginning of the trial and an elevated central venous pressure (CVP), three patients were given between 6.5 and 8.5 ml/kg of each saline concentration.

Each trial lasted 120 min unless intervention was required. All methods that affect ICP were held constant. A trial was terminated prematurely and the patient was further hyperventilated and given mannitol or thiopental if the ICP rose above 23 mm Hg or CPP declined below 45 mm Hg for a 5-min

period during the trial. ICP, MAP, CPP, systolic and diastolic blood pressure, CVP, and heart rate were continuously monitored throughout each trial by a Marquette monitor with 24-h continuous trending capabilities (series 7010; Marquette Electronics Inc., Milwaukee, WI, U.S.A.). Graphic paper plots of ICP, MAP, CPP, CVP, and heart rate were reproduced at the end of each trial.

DATA AND STATISTICAL ANALYSIS

ICP was analyzed by determination of the area under the curve (AUC) of the ICP plots beginning at the start of the infusion and ending when the trial was either completed or terminated. The ICP graphic data were converted to digital data by plotting each point along the graph in 5-min intervals and entering the value into a computerized data base (R:Base System V; Microrim Inc., Redmond WA, U.S.A.). The digital information reproduced the patient's physiologic graphic record and allowed determination of the AUC for ICP over time by Simpson's rule (21,22). The ICP AUC for each trial was divided by the length of the trial to determine the average ICP per trial.

Paired *t* tests were used to assess differences in physiologic and laboratory parameters before and after infusion of either saline concentration. Paired *t* tests were also used to compare the AUC with respect to ICP between the 0.9% and 3% saline groups as well as the difference in ICP at time zero and the average ICP during each 2-h trial period. A nonpaired *t* test was used to evaluate the differences in ICP during the nonintervention trials.

Laboratory examinations consisted of arterial blood gas (model 278; Ciba-Corning, Medifield, MA, U.S.A.), serum osmolality (model 3MO; Advanced Micro-osmometer, Needham Heights, MA, U.S.A.), and serum electrolytes (Kodak Ektachem 700; Kodak, Rochester, NY, U.S.A.). Tests were taken before the start of each trial, at 30 min, and at 120 min.

RESULTS

Eighteen patients entered the study an average of 22 (SD = 10) h after head injury. Mean trauma and injury severity scores equaled 9.6 and 28.3, respectively (Table 1). The average Glasgow Coma Score (GCS) equaled 5.8 (SD = 2). Fifteen patients had a GCS of ≤8, and three patients scored 10 upon ar-

TABLE 1. *Admission data on pediatric head trauma patients*

Injury	Age	Pupils	GCS	TS	ISS	PS	CT reading
Bicyclist vs. mv	13.5	E & R	3	7	26	0.5136	S, I
Pedestrian vs. mv	7	BF & D	3	4	66	0.0115	S, L to R shift
Pedestrian vs. mv	3	UF & D	3	6	35	0.2445	I, C, NDfx
Pole through brain	7.5	BF & D	3	3	29	0.0734	No CT
Pedestrian vs. mv	4.5	BF & D	3	12	18	0.9621	S
Bicycle accident	8	E & R	10	9	16	0.8616	Normal
Fall	13.5	E & R	7	13	26	0.9593	S, C
Pedestrian vs. mv	8	E & R	6	11	30	0.8616	Normal
Mva	6.5	E & R	7	9	14	0.8783	Basilar fracture
Mva	6	E & R	4	9	27	0.7341	I
Skateboard	12	E & R	10	12	17	0.9647	E, I, temporal fracture
Pedestrian vs. mv	7.5	E & R	6	13	26	0.9593	Normal
Pedestrian vs. mv	14	E & R	4	7	35	0.3519	I
Mva	5.5	BF & D	6	11	29	0.8703	S, C, Dfx
Mva	10.5	E & R	8	8	38	0.4220	I, NDfx
Bicyclist vs. mv	7	E & R	7	13	26	0.9592	I, L to R shift, NDfx
Mva	0.6	E & R	10	14	18	0.9862	S, I
Mva	14.5	E & R	5	12	34	0.8860	E, Dfx

GCS, Glasgow Coma Score; TS, trauma score [scores for physiologic parameters of respiratory rate and effort, systolic BP, capillary refill, and Glasgow Coma Scale (23); best score = 16]; ISS, injury severity score [injuries scored in each of six body regions (24); worst score = 75]; PS, probability of survival [computed by TRISS methodology (25)]; CT, computerized tomography of the head; mv, motor vehicle; mva, motor vehicle accident; E & R, equal and reactive; BF & D, bilaterally fixed and dilated; UF & D, unilaterally fixed and dilated; S, subdural hematoma; E, epidural hematoma; I, intraventricular hemorrhage; Dfx, depressed skull fracture; NDfx, nondepressed skull fracture; C, cerebral contusion; L to R, left to right.

rival, but deteriorated. Intracranial hemorrhages were present in 13 patients. Five patients died in the hospital.

As described in Table 2, there were no significant differences in baseline ICP or osmolality between the 0.9% and 3% saline groups before infusion. There was a statistical difference in baseline serum sodium concentrations and $PaCO_2$ between the two groups.

A comparison of the initial ICP at baseline and the average ICP during each 2-h trial is depicted in Fig. 1. There was no significant difference between initial ICP and the average ICP over the trial period during the 18 trials of 0.9% saline. The initial ICP was 19.3 mm Hg, and the average ICP was 20.0 mm Hg ($p = 0.32$). However, there was a significant difference between the initial ICP and average ICP during the 3% saline trials. The initial ICP equaled 19.9 mm Hg, while the average ICP equaled 15.8 mm Hg ($p = 0.003$).

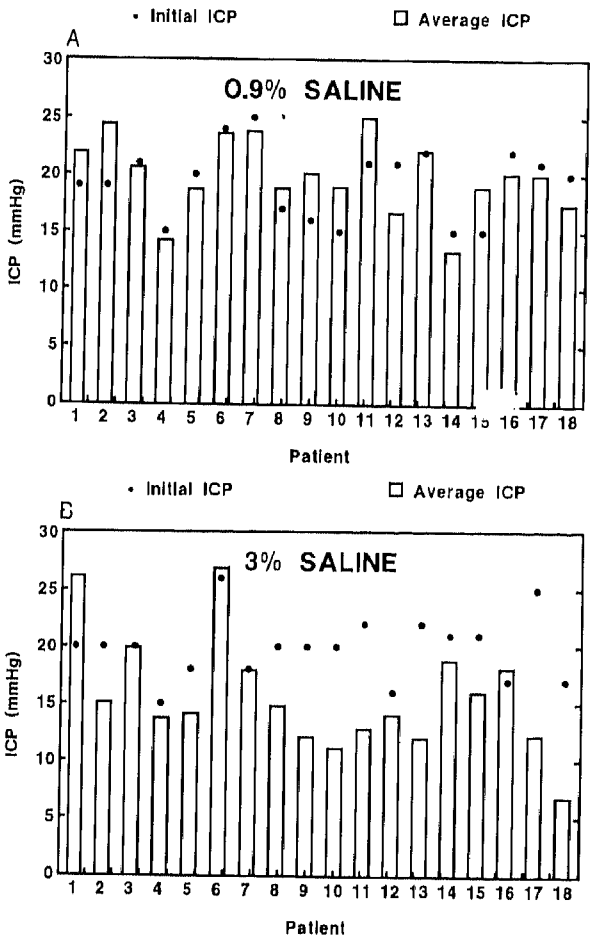

FIG. 1. Eighteen pediatric patients suffering from raised intracranial pressure treated with 0.9% and 3% saline infusions. Points represent intracranial pressure before saline infusion. Bars represent average intracranial pressure over a 2-h period after infusion.

The cumulative AUC for ICP during the 18 trials of 0.9% saline was 24,251 mm Hg/min over a combined period of 1,287 min. The cumulative AUC for ICP during the 3% saline trials came to 24,192 mm Hg/min over a combined period of 1,676 min. All 36 trials totaled 2,963 min, representing 593 ICP determinations.

Elevation in ICP occurred during 10 trials of the 0.9% saline between 15 and 102 min after the start of infusion, triggering cessation of the trial and intervention to reduce the ICP. Similar increases in ICP after infusion of 3% saline in six trials prompted intervention between 5 and 100 min. As a result, eight trials of 0.9% saline and 12 trials of 3% saline were completed without intervention. Analysis of ICP during these trials revealed an average ICP of 18.7 mm Hg and 14.0 mm Hg for the 0.9% and the 3% saline concentrations, respectively ($p = 0.029$).

Serum sodium concentrations increased in all 18 trials of 3% saline an average of 7 mEq/L. Maximal concentrations of serum sodium occurred at 30 min in 14 of 18 of the 3% saline trials. After infusion of 0.9% saline, the serum sodium concentration at 30 min increased in seven trials an average of 3 mEq/L, declined in 10 trials, and remained the same in one. There were no significant changes in mean carbon dioxide tensions measured at the beginning or end of the trial in either group (Table 2). Serum creatinine and BUN measurements taken before and 24 h after infusion were equivalent and normal for patient age.

Central venous pressure was measured in 15 patients. The initial CVP measurements before administration of either saline concentration were equivalent and averaged 5.2 mm Hg in the 0.9% saline group versus 4.7 mm Hg in the 3% saline group ($p = 0.65$). Central venous pressures did not change significantly in either group. Mean CVP at the termination of the trial measured 5.3 mm Hg for the 0.9% saline group and 5.6 mm Hg in the 3% saline group ($p = 0.67$). There was no evidence of morbidity or mortality attributed to saline infusion in any patient. No patient manifested protracted or rebound increases in intracranial pressure after study completion.

TABLE 2. *Mean physiologic parameters measured before and 30 and 120 min after intravenous administration of 0.9% and 3% saline to pediatric head trauma patients*

Minutes	0.9% Saline	(SD)	3% Saline	(SD)	p[a]
Baseline					
$[Na^+]$ mEq/L	147.8	(4.8)	144.7	(5.6)	0.003
$PaCO_2$ torr	27.6	(6.5)	26.1	(6.9)	0.02
[osmol] mOsmol	302.2	(11.2)	300.8	(13.4)	0.02
CPP mm Hg	59.2	(9.0)	59.3	(7.2)	0.98
30					
$[Na^+]$ mEq/L	147.3	(5.7)	151.8	(4.8)	0.0001
$PaCO_2$ torr	27.0	(6.6)	27.0	(6.1)	0.96
[osmol] mOsmol	303	(12.8)	312	(12.9)	0.001
CPP mm Hg	61.2	(7.7)	68.7	(9.2)	0.01
120					
$[Na^+]$ mEq/L	146.1	(5.3)	150.2	(4.2)	0.002
$PaCO_2$ torr	25.9	(6.7)	25.5	(6.5)	0.79
[osmol] mOsmol	302	(13.8)	306	(13.2)	0.15
CPP mm Hg	62.7	(8.5)	62.7	(9.1)	0.97

[a] Probability derived by two-tailed paired *t* test.

DISCUSSION

This study shows a significant reduction of ICP in a group of pediatric head trauma patients who received hypertonic saline. These patients were studied hours after traumatic brain injury during a period of active brain swelling. Brain injury, age, sex, and saline dose were controlled by the study design. Baseline ICP, serum osmolality, and central venous pressure were equivalent between the two groups before administration of either saline concentration. Mean serum sodium concentration at baseline was slightly higher in the 0.9% saline trials. This finding is the result of the study design. Patients first randomized to the 3% saline trial had slightly higher serum sodiums when they began the second infusion of 0.9% saline. The initial $PaCO_2$ determinations between the two groups differed by an average of 1.2 torr, which was statistically significant, although it probably was not clinically important.

In order to facilitate sedation, intubation, and central venous access, 16 patients received a bolus of thiopental during resuscitation. Eight were given an additional bolus of thiopental ≥90 min before admission into the study. The influence of thiopental on the ICP in these patients during the study period was probably minimal for three reasons: the dosages employed were small (1–5 mg/kg); the drug is short-acting and was administered ≥90 min before the study; and by study design all trials should have been influenced equally.

Analysis of ICP by the AUC provided an accurate reflection of ICP despite fluctuations that are otherwise difficult to analyze. Data from this study indicate that there was a 21% reduction in mean ICP during the 18 trials of hypertonic saline, as compared with a 4% increase in ICP after normal saline infusion. Comparison of serum sodium concentrations at baseline revealed a lower average serum sodium before infusion of 3% saline than in the 0.9% saline group (Table 2). However, 30 min after 3% saline administration, mean serum sodium concentration increased significantly only in the 3% saline group and was associated with a reduction of ICP. There was no change in serum sodium concentration or ICP in the 0.9% saline group.

Hypertonic saline infusion reduced ICP throughout the entire trial period in 12 patients. Administration of hypertonic saline in six patients was followed by elevation of ICP requiring intervention during the trial. These six patients fell into two groups. Three patients required intervention within the first 30 min of the trial, and three patients required intervention near the end of the trial, at 70 min or later. CPP in these six patients remained at baseline or increased despite increased ICP. The early elevation of ICP after infusion of hypertonic saline in three patients was associated with increased arterial pressure. Systemic hypertension in combination with compromised cerebral autoregulation and cerebral hyperemia may have led to an expansion of cerebral vascular volume in an already

tight intracranial compartment before adequate compensatory neuronal dehydration could be accomplished.

The ICP curves of the three late-intervention patients show initial reduction of ICP followed by a gradual return back to and above baseline as the effect of the hypertonic saline infusion diminished. Serum sodium measurements in these three patients correlated with ICP measurements; maximal serum sodium concentrations were seen at 30 min in all three patients, with a return to near or below baseline at the termination of the trial. Infusion of normal saline precipitated elevation of ICP in 10 trials of normal saline. Six trials required intervention in the first 30 min, lending credence to the concept that elevations in ICP occur when expansion of the cerebral vasculature is not compensated for by the intracellular removal of water from the brain.

Rebound intracranial hypertension was not detected in this group of patients, but this issue was not specifically addressed by the study. Rebound intracranial hypertension occurs when an elevated concentration of serum sodium equilibrates across a disrupted blood–brain barrier, producing delayed elevation in ICP after an initial period of ICP reduction. Whether or not rebound intracranial hypertension occurs in pediatric head trauma patients cannot be determined from these data, although there were no unexpected or intractable increases of ICP in patients who received 3% saline during the remainder of their hospitalization.

Cerebral perfusion pressure is commonly calculated by determination of mean arterial pressure less intracranial pressure. Factors influencing ICP were rigorously controlled during this study. Mean arterial pressure was not controlled by study design, but it was not manipulated by alteration of pressors or CVP during the study. Increases in MAP and, hence, CPP represent the influence of the saline boluses even though all patients were receiving dopamine infusions and three patients were given epinephrine infusions as well. Elevations of CPP may be helpful after traumatic brain injury. Providing that concomitant increases in cerebral vascular resistance do not occur, increased CPP will result in increased cerebral blood flow. The combination of increased cerebral blood flow and reduced ICP may result in improved delivery of oxygen and nutrients to the brain after brain injury.

Central venous pressure did not change over the 2 h after 3% saline infusion. Although hypertonic saline administration may reduce cardiac compliance, producing an inaccurate reflection of intravascular volume, this effect is probably not significant. It is well established that small volumes of hypertonic saline restore intravascular volume and increase blood pressure and cardiac output after a variety of shock states in humans and animals (11–13,15–19). Additionally, unlike mannitol, hypertonic saline administration does not result in profound diuresis and therefore would not be expected to cause intravascular dehydration. It is most likely that hypertonic saline administered to brain-injured patients will result in expansion of intravascular volume.

The influence on renal function of elevations of serum sodium to 160 mEq/L and osmolarity to 330 mOsmol/L produced by infusions of hypertonic solutions has been investigated and has been shown to be without significant complications in humans (12,16–18,26). Worthley and colleagues infused a small volume of a concentrated saline solution (29.9% NaCl) into two patients suffering from elevated ICP and prerenal failure, inducing a prolonged reduction in ICP and improved renal function in both cases (6). We estimate that those two patients received ~1.5 and 3.5 mEq Na^+/kg. In our study group, the majority of patients received ~5 mEq Na^+/kg as hypertonic saline. In addition to improvements of ICP, there was no change in the renal function as determined by BUN and creatinine measurements 24 h after the administration of hypertonic saline.

This study shows that acute hypernatremia is associated with decreased ICP in pediatric patients over a short time period. It should be realized that cerebral edema may persist for many days, and concern exists regarding the potential for adverse consequences on the blood–brain barrier, cerebral blood flow, and global neurological function from the use of hypertonic saline to produce prolonged elevations of serum sodium. Extreme and rapid elevation of serum sodium in animals without brain injury is harmful. Subdural and intracerebral hemorrhages are associated with severe increases in serum sodium concentrations and hypovolemia in kittens (27). However, the controlled administration of hypertonic saline to produce moderate increases in serum sodium concentration within an edematous brain has not been shown to be harmful. The short-

term use of hypertonic saline to combat cerebral edema appears to be well tolerated, but chronic administration of hypertonic saline to prolong hypernatremia in an effort to reduce raised intracranial pressure for a period of days to weeks requires further evaluation.

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