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Hypertonic Saline Resuscitation of Patients with Head Injury: A Prospective, Randomized Clinical Trial

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Abstract

Background: Experimental and clinical work has suggested that hypertonic saline (HTS) would be better than lactated Ringer's solution (LRS) for the resuscitation of patients with head injuries. No clinical study has examined the effect of HTS infusion on intracranial pressure (ICP) and outcome in patients with head injuries. We hypothesized that HTS infusion would result in a lower ICP and fewer medical interventions to lower ICP compared with LRS.

Methods/Design: Prospective, randomized clinical trial at two teaching hospitals.

Results: Thirty-four patients were enrolled and were similar in age and Injury Severity Score. HTS patients had a lower admission Glasgow Coma Scale score (HTS: 4.7 +/- 0.7; LRS: 6.7 +/- 0.7; $p = 0.057$), a higher initial ICP (HTS: 16 +/- 2; LRS: 11 +/- 2; $p = 0.06$), and a higher initial mean maximum ICP (HTS: 31 +/- 3; LRS: 18 +/- 2; $p < 0.01$). Treatment effectively lowered ICP in both groups, and there was no significant difference between the groups in ICP at any time after entry. HTS patients required significantly more interventions (HTS: 31 +/- 4; LRS: 11 +/- 3; $p < 0.01$). During the study, the change in maximum ICP was positive in the LRS group but negative in the HTS group (LRS: +2 +/- 3; HTS: -9 +/- 4; $p < 0.05$).

Conclusion: As a group, HTS patients had more severe head injuries. HTS and LRS used with other therapies effectively controlled the ICP. The widely held conviction that sodium administration will lead to a sustained increase in ICP is not supported by this work.

Head injury remains the leading cause of traumatic death. [1] Of those patients who die of head injury, 66 to 90% have pathologic evidence of secondary brain injury, defined as either diffuse edema, herniation, or necrosis. [1,2] Secondary injury occurs after the primary impact injury and is attributable to a decrease in cerebral oxygen delivery as a result of hypoxia, systemic hypotension, or relative hypoperfusion produced by intracranial hypertension. [3-5] Patients with moderate or severe head injuries who are in shock require rapid elevation of blood pressure to improve cerebral oxygen delivery, [6,7] but fluid therapy must not be excessive because it has been proposed that fluid and salt administration can lead to brain swelling and edema formation with a consequent increase in the intracranial pressure. [8,9]

Recent laboratory [10,11] and clinical studies [12,13] have suggested that hypertonic fluids might be preferable for treatment of patients with brain injury and shock. Despite the apparent improved cerebral physiology and apparent clinical efficacy, no clinical study has evaluated a completely hypertonic resuscitative regimen for patients who sustain moderate or severe brain injury.

We hypothesized that hypertonic solutions used for acute resuscitation and for maintenance intravenous fluid therapy after moderate and severe head injury would increase the intracranial compliance more than hypotonic solutions used for the same purposes, resulting in a smaller increase in intracranial pressure (ICP) after infusion and fewer interventions to control ICP. To validate this hypothesis, we under-took a prospective, randomized clinical trial with the following specific aims: (1) to compare hypertonic saline (HTS) with lactated Ringer's solution (LRS) for the treatment of hypovolemia attributable to hemorrhage or operative fluid loss in patients with moderate and severe head injury to determine their relative effects on ICP during the resuscitative, operative, and initial intensive care phases of treatment; (2) to compare hypertonic sodium chloride (0.9%, NS) with hypotonic sodium chloride (0.45%, 1/2NS) for maintenance fluid therapy in patients with moderate and severe head injury to determine their relative effects on ICP during the intensive care phase of treatment; and (3) to compare the outcome of patients who received hypertonic fluid for the initial and intensive care phases of treatment with the outcome of those who received isotonic or hypotonic fluid.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the University of Vermont. As originally planned, the study was to be performed entirely at the Medical Center Hospital at the University of Vermont. At the end of the first year, patient accrual (anticipated to be 30-50 patients after 12 months) was significantly less than anticipated. To improve patient accrual, we enlisted the Trauma Service at the Maine Medical Center after approval by the Maine Medical Center's Institutional Review Board. Patients meeting the entry criteria (Table 1) were primarily stratified into two groups: head injury only (International Classification of Diseases, Ninth Revision codes 850-854 and 800-804), with no injuries other than those to the integument (superficial abrasions, lacerations, or contusions); and head injury with associated injuries (injuries to the thorax, abdomen, spine, face, neck, or extremities).

Age ≥18 years
Blunt mechanism of injury
Injury within 12 hours of admission (patients who received operative therapy or definitive resuscitation at a referring hospital were excluded)
Admission GCS score ≤13, requiring monitoring of ICP or operative therapy and postoperative monitoring of ICP
Positive CT scan of the brain
mass lesion: epidural, subdural, intracerebral, intracerebellar
subarachnoid hemorrhage with swelling or parenchymal insult (mass lesion or contusion)
contusion
swelling: diffuse or hemispheric producing midline shift ≥2 mm
diffuse axonal injury
depressed skull fracture

Table 1. Patient entry criteria

After initial stratification according to injury, patients were then randomized, using a random-number table, to two groups: hypertonic and hypotonic. Hypertonic patients received 1.6% HTS (Table 2) for any hemodynamic instability (systolic blood pressure (SBP) 90 mm Hg and to restore the urine output to >0.5 mL/kg. Maintenance fluid for the hypertonic group during these phases was NS (Table 2) given at a rate of 15 mL/kg/day. During any operative therapy (requiring regional or general anesthesia) in the initial or ICU phases of care, patients received HTS for intraoperative fluid replacement provided that the serum sodium (S_{Na}) was Osm) was Na or the S_{Osm} exceeded those limits, patients were given NS for hemodynamic instability or intraoperative fluid loss.

Fluid	Na (%)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Ca (mEq/L)	Lactate (mEq/L)	Osmolarity (mOsm/L)
LRS	0.7	130	4	109	3	28	274
½NS	0.45	77	0	77	0	0	154
HTS	1.6	250	4	180	3	77	514
NS	0.9	154	0	154	0	0	308

Table 2. Composition of the experimental fluids

Hypotonic patients received LRS for any hemodynamic instability during their initial resuscitation, operative therapy, or during the first 5 days of ICU care. Fluid was given to return the SBP and to restore urine output using the same parameters used for the HTS group. Maintenance fluid for the hypotonic group during these phases was 1/2NS given at a rate of 15 mL/kg/day. During any operative therapy (requiring regional or general anesthesia), patients in the hypotonic group received LRS for hemodynamic instability or to replace operative fluid losses. Medications (i.e., antibiotics, phenytoin, etc.) were diluted using the maintenance fluid unless the medication and the fluid were not compatible.

After randomization and stratification, four study groups were initially defined: head injury only, hypertonic (group H1); head injury only, hypotonic (group O2); multiple injuries, hypertonic (group H3); and multiple injuries, hypotonic (group O4). As the study progressed, however, the patient accrual rate was much less than anticipated, and groups H1 and H3 were combined into a single hypertonic saline group (HTS) and groups O2 and O4 were combined into a single isotonic or hypotonic group (LRS). Patients were entered at the time of admission to the ER or, in the case of deterioration as an inpatient, at the time they manifested a Glasgow Coma Scale (GCS) score

Management of patients with moderate to severe head injury was standardized at both institutions. In summary, patients were admitted under the joint care of the Neurosurgery Service and the Trauma Service. All patients had an emergency computed tomographic (CT) scan of the head. Those with a GCS score or=to 20 mm Hg) was treated by hyperventilation, mannitol infusion, head elevation, and ventricular drainage. Barbiturate coma [14] was instituted only if all other modalities failed to control the ICP and the patient's S_{Osm} had exceeded 330 mOsm/L. After initial evaluation and diagnostic studies, the patient was admitted to either the operating room (for operative therapy) or the ICU. Cardiovascular monitors included an arterial cannula and a central venous pressure catheter. The need for more intensive cardiovascular monitoring (pulmonary artery catheter) was determined jointly by the attending neurosurgeon and the attending trauma surgeon. CT scanning was repeated at daily intervals for 3 days or more frequently if there was either neurologic deterioration or a marked and persistent increase in the ICP. All CT scans were later interpreted by a single, blinded neuroradiologist and scored by one of the authors (S.L.W., who was also blinded to the treatment group) using the scale developed by Marshall and colleagues. [15] The relative significance of an increase in ICP and the decision to scan at intervals less than those described by protocol were made by the attending neurosurgeon. Blood transfusion (as packed red blood cells) was given for a hemoglobin of 250 mL/h, or diarrhea), was advanced to a full-strength mixture within 12 hours. Steroids were not given. Patients were extubated, using a standard respiratory weaning protocol, when their ICP was stable at <20 mm Hg with a $PaCO_2$ of 40 mm Hg and mental status was adequate to control secretions. Patients were discharged from the ICU when they were neurologically stable and no longer had a need for either ventilatory support or invasive monitoring of ICP or blood pressure. Patients were transferred to a specialized neurosurgery floor or stepdown unit where they received specialized nursing care.

Data (Table 3) were entered during the acute inpatient stay by a nurse coordinator directly into a data base (Foxpro 2.5, Microsoft, Redmond, Wash) using a notebook personal computer. Formal neurologic evaluation was done at 6 weeks, 6 months, and 1 year and included assessment of Glasgow Outcome Score. [18]

Age
Gender
Mechanism of injury (E code)
Prehospital fluids (volume and type)
Prehospital urine output
Time from injury to arrival at study center ER
Admission Glasgow Coma Scale score[16]
Injury Severity Score[17]
Number and type of ICP interventions
Hyperventilation
Mannitol infusion
Ventricular drainage
Barbiturate coma
Sedation
Diuretics
Average 8-hour ICP
Maximum ICP during each 8-hour shift
MAP, central venous pressure at same intervals as ICP
Cerebral perfusion pressure (CPP = mean arterial pressure − ICP) at same intervals as ICP
Average daily net fluid balance (all input − all output)
Admission and daily S_{Na} and S_{Osm}
Findings on initial head CT scan (Initial head CT score)[15]
Blood urea nitrogen and serum creatinine on admission and daily while in the ICU

Table 3. Data collected

Data were validated by one of the investigators before transfer to a statistical analysis program (Minitab Inc., State College, Pa). Variables between groups were compared using unpaired Student's t test. Variables within groups measured at different times were compared using a paired Student's t test. Significance was attributed to a $p < 0.05$. Data are expressed as mean +/- SEM.

RESULTS

Between October 1, 1991, and September 30, 1994, a total of 861 patients with head injury (International Classification of Diseases, Ninth Revision codes 800-804 and 850-854) were treated at the two institutions. Of these, 108 were eligible for the study. Twenty-two were missed (permission not initially obtained, failure to notify study coordinator, etc.), 28 had no available next of kin to give consent, and 14 next of kin refused participation, leaving 41 patients as the study sample. Seven patients died during the first 48 hours of treatment and were eliminated from the analysis. Of the remaining patients, there were 18 in the HTS group and 16 in the LRS group. The groups were similar in age, gender ratio, mechanism of injury, the need for transfusion, the need for operation, and the anatomic severity of injury as determined by the Injury Severity Score (Table 4). The admission GCS score was lower in the HTS group, and the difference approached statistical significance ($p = 0.057$; Table 4). The grade of head injury by CT scan was higher (more severe) in the HTS group, but the difference was not significantly different.

	HTS	LRS
Age (years)	33 ± 15	31 ± 11
Gender		
Male	17	10
Female	1	6
Mechanism		
Motor vehicle crash	12	15
Fall	2	1
Pedestrian struck	2	0
Other	2	0
Transfusion	8	9
Operation		
Noncranial	5	8
Cranial	5	3
Mean arterial pressure <90	3	3
ISS	30 ± 2	32 ± 2
GCS score	4.7 ± 0.7[a]	6.7 ± 0.7
CT grade of head injury	2.7 ± 0.28	2.5 ± 0.24

[a] $p = 0.057$.

Table 4. Group demographics and injury severity

Before placement of the ICP monitor, the groups received a similar amount of fluid (Table 5). Daily fluid administration and fluid balance during the 5 days of the study were similar between the groups (Figure 1). The fluid balance after 5 days was significantly lower in the HTS group.

Fluid Type	HTS Group	LRS Group
HTS	1,210 ± 400 (0–6,500)	0
LRS	980 ± 230 (0–3,700)	1,970 ± 410 (0–6,000)
Blood	140 ± 110 (0–2,000)	140 ± 140 (0–2,500)
NS	120 ± 100 (0–1,900)	140 ± 110 (0–2,000)

Table 5. Mean volume (mL) and type of fluid infused before ICP monitoring (range)

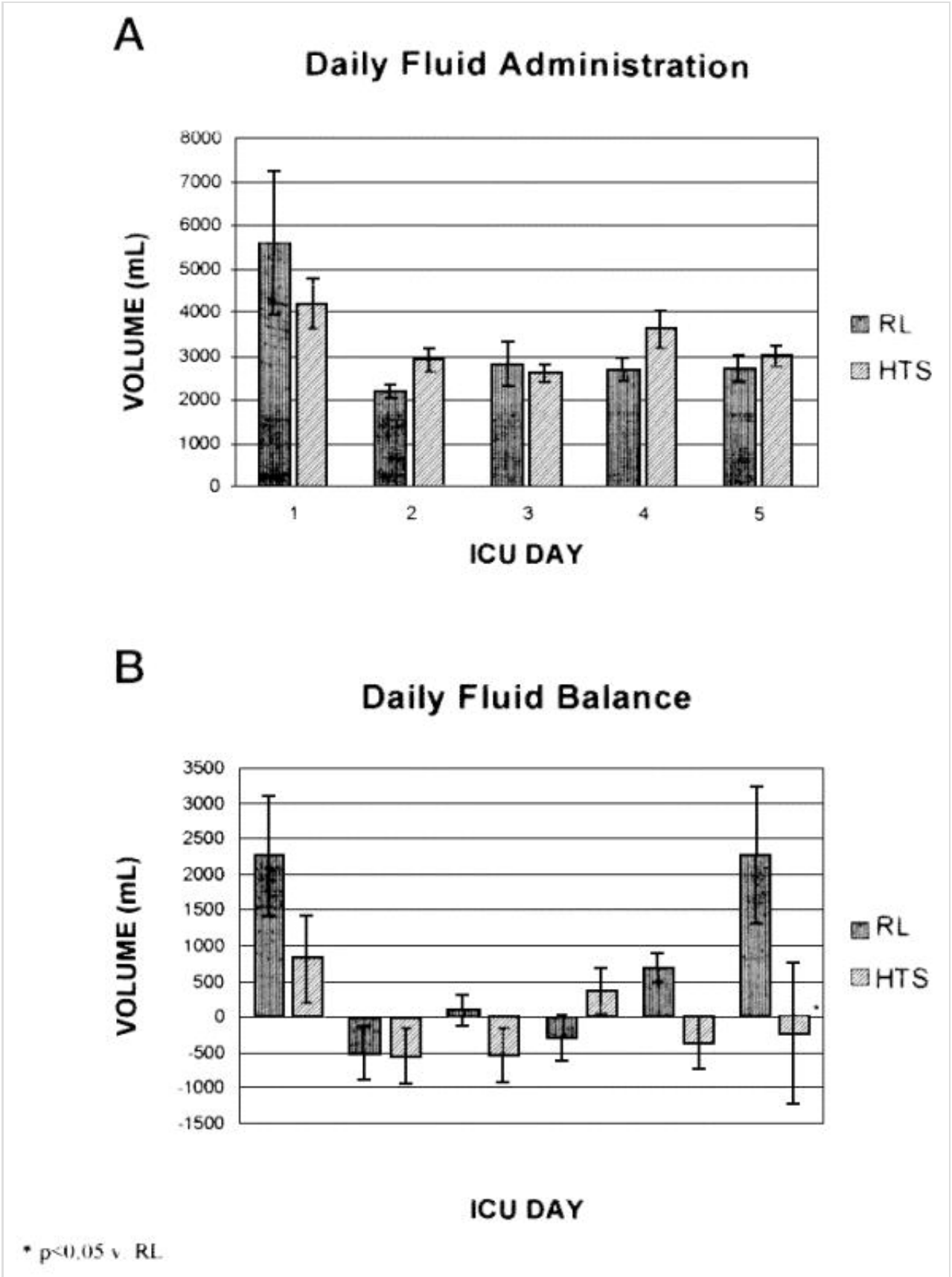
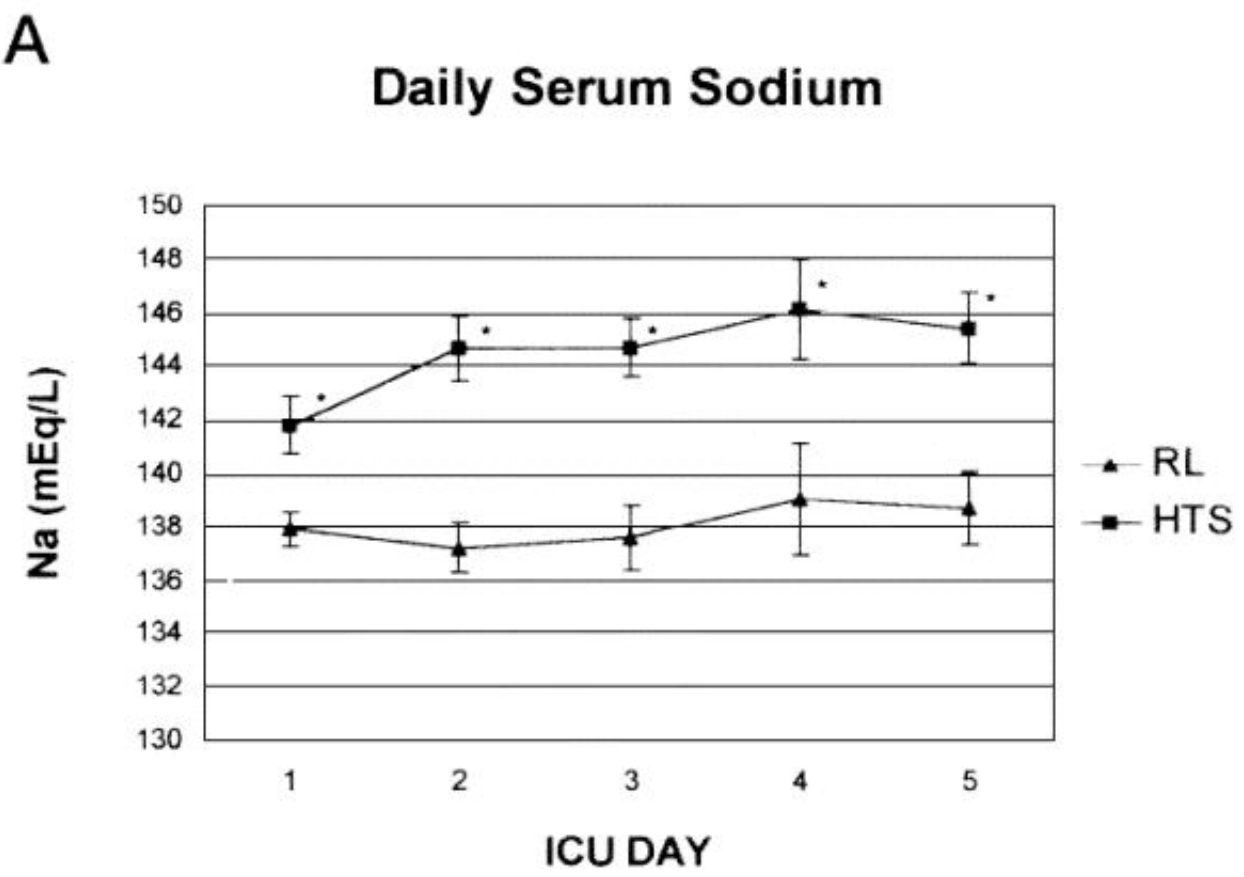


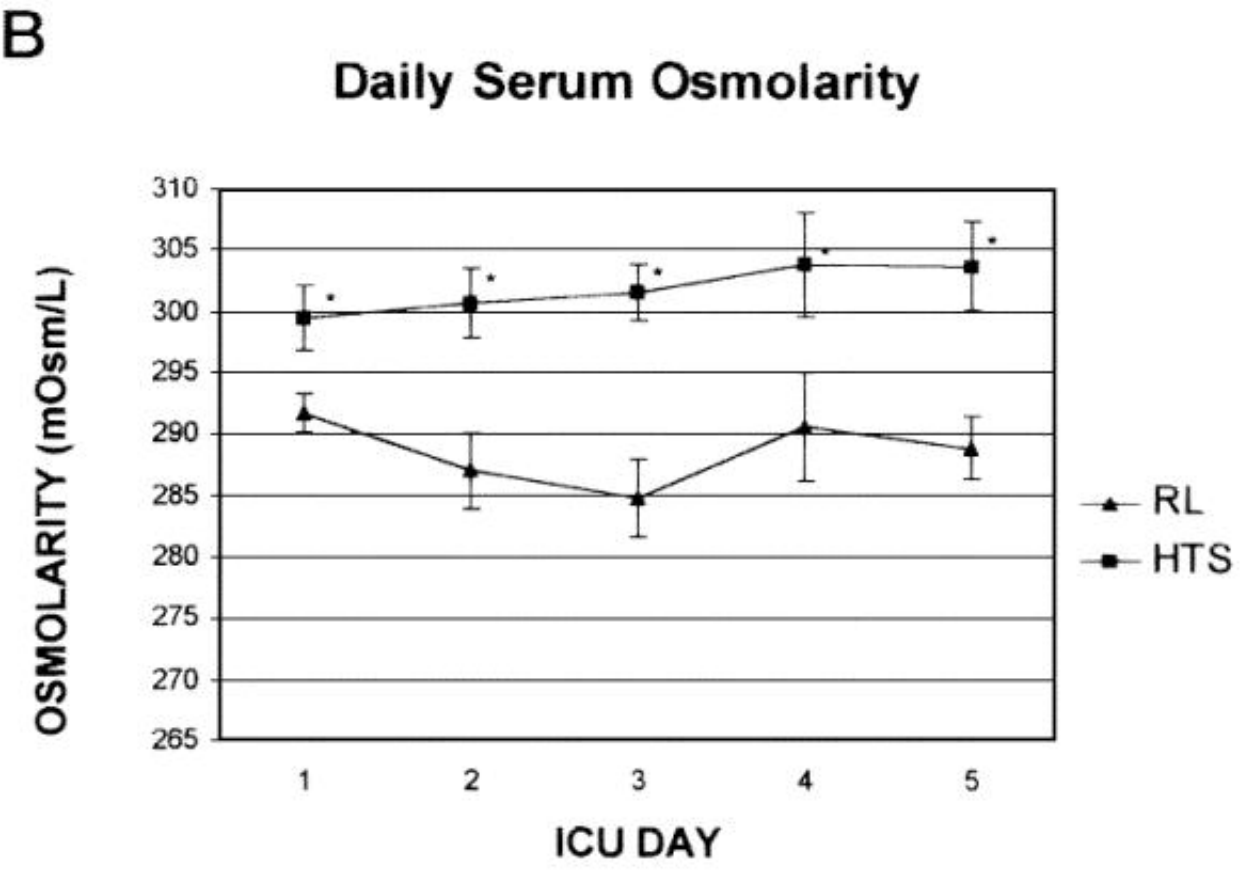
Figure 1. (A) Daily fluid administration. There was no significant difference between the groups in the amount of fluid received at any time during the study. (B) Daily fluid balance. There was no significant difference between the groups on any day of the study, but the cumulative fluid balance was significantly greater in the LRS group ($p < 0.05$). RL, lactated Ringer's solution.

The S_{Na} and the S_{Osm} were significantly greater in the HTS group throughout the study period (Figure 2). Despite the elevations in serum sodium and osmolarity in the HTS group, there were no instances of renal failure and no neurologic complications that could be related to either hypernatremia or hyperosmolarity. One patient in the HTS group had a S_{Na} of 157 mEq/L and a S_{Osm} of 357 mOsm/L without sequelae.

A


Daily Serum Sodium
Na (mEq/L)
150
148
146
144
142
140
138
136
134
132
130
1
2
3
4
5
ICU DAY
RL
HTS

B


Daily Serum Osmolarity
OSMOLARITY (mOsm/L)
310
305
300
295
290
285
280
275
270
265
1
2
3
4
5
ICU DAY
RL
HTS

* $p<0.05$ v. RL

Figure 2. (A) Serum sodium in the groups during the study. Serum sodium was significantly higher in the HTS group at all time periods. (B) Serum osmolarity in the groups during the study period. Serum osmolarity was significantly greater in the HTS group at all time periods. RL, lactated Ringer's solution.

There were no significant differences in either mean ICP or mean cerebral perfusion pressure (CPP) between the groups for the duration of the study period (Figure 3). The mean ICP and mean maximum ICP were significantly higher in the HTS group at study entry, but these decreased by the second day and subsequently were not significantly different from those in the LRS group (Figure 3 and Figure 4). The trend in the mean maximum ICP with therapy was negative in the HTS group (-9.1 +/- 3.6 mm Hg) and positive in the LRS group (2.5 +/- 3.3, $p < 0.05$).

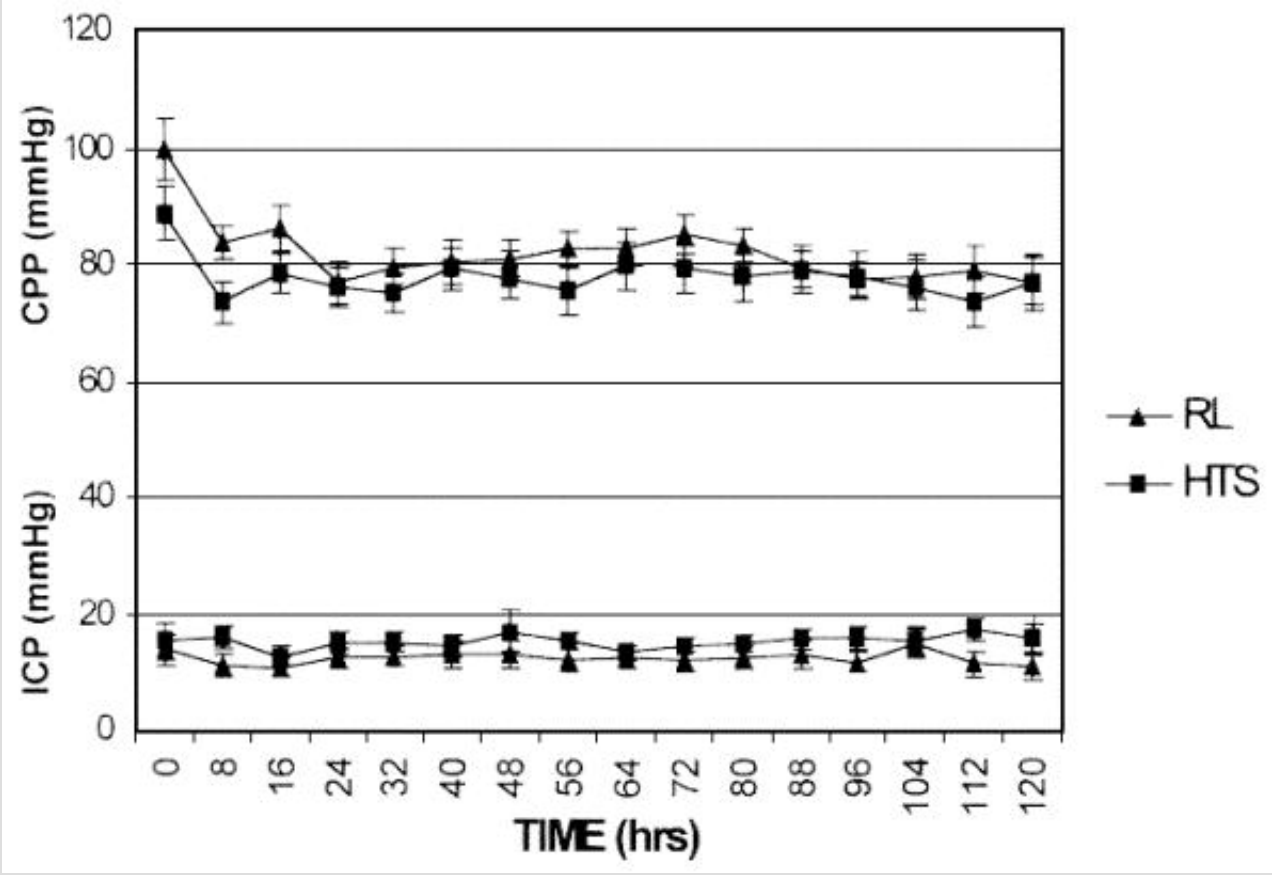


Figure 3. Mean ICP and CPP during the study. There was no significant difference between the groups in either mean ICP or mean CPP at any time during the study. RL, lactated Ringer's solution.

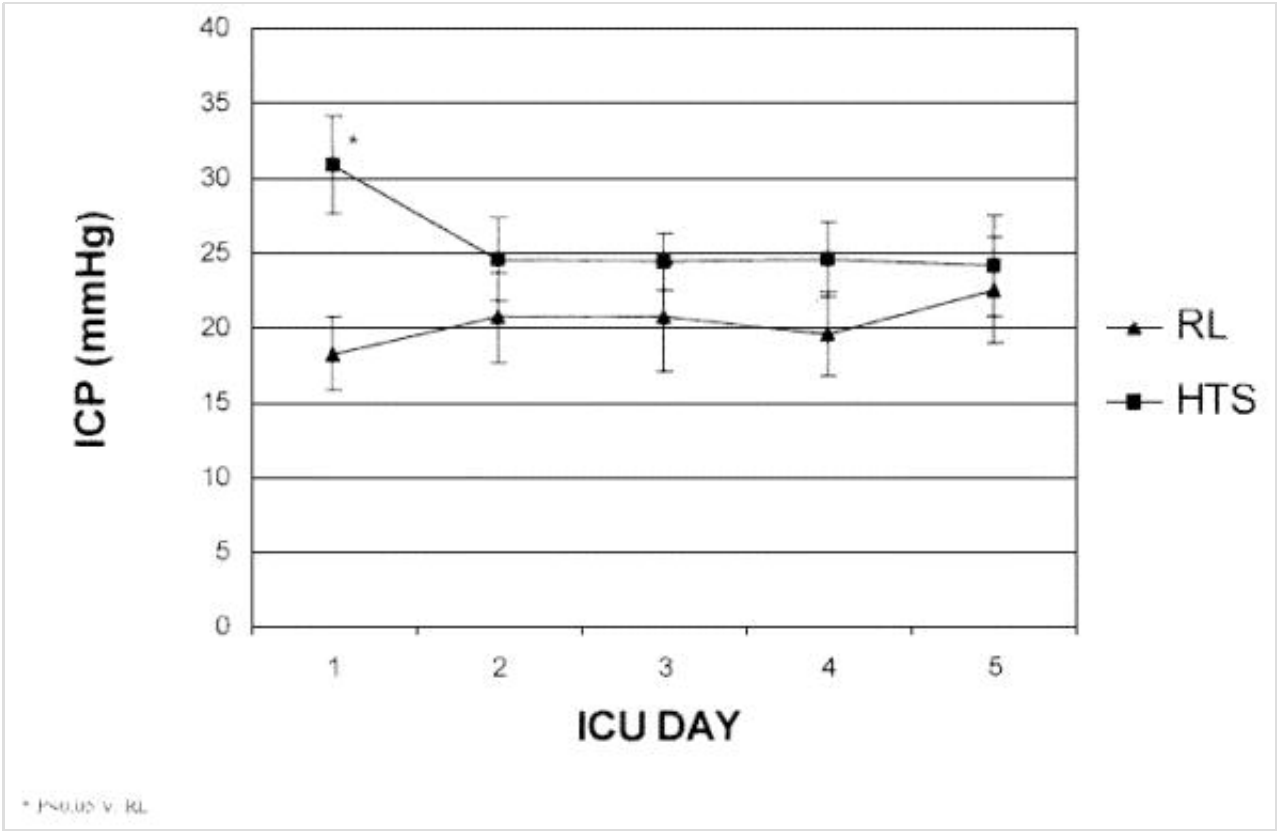


Figure 4. Mean maximum ICP during the study. The mean maximum ICP was significantly higher in the HTS group at study entry. After day 1, there was no significant difference between the groups. RL, lactated Ringer's solution.

The average total number of interventions to control elevations in the ICP during the entire study was significantly greater in the HTS group (31 +/- 4) than in the LRS group (11 +/- 3, $p < 0.01$). The average number of interventions per patient per day of monitoring was significantly greater in the HTS group on the first and last days of the study (Figure 5).

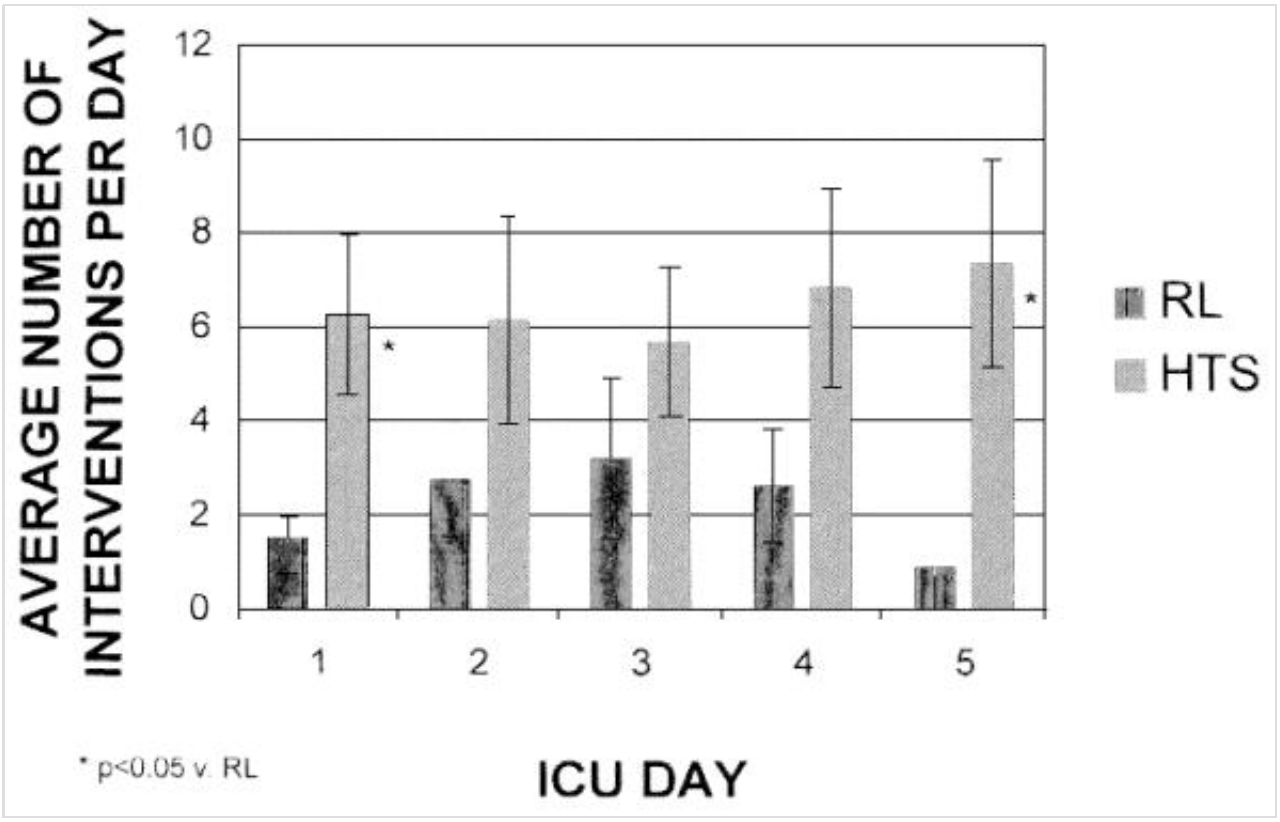


Figure 5. Daily interventions for ICP control. The daily average number of interventions to control ICP was significantly greater in the HTS group on day 1 and day 5. RL, lactated Ringer's solution.

Because of the apparent disparity in the severity of injury between the two groups based on admission GCS scores, initial mean maximum ICP, and CT scores, we examined the intervention data between groups using a subset of similar severity, stratifying the group by admission GCS scores. Because all of the HTS patients had GCS scores Figure 6), we compared interventions between subsets of the groups with GCS scores

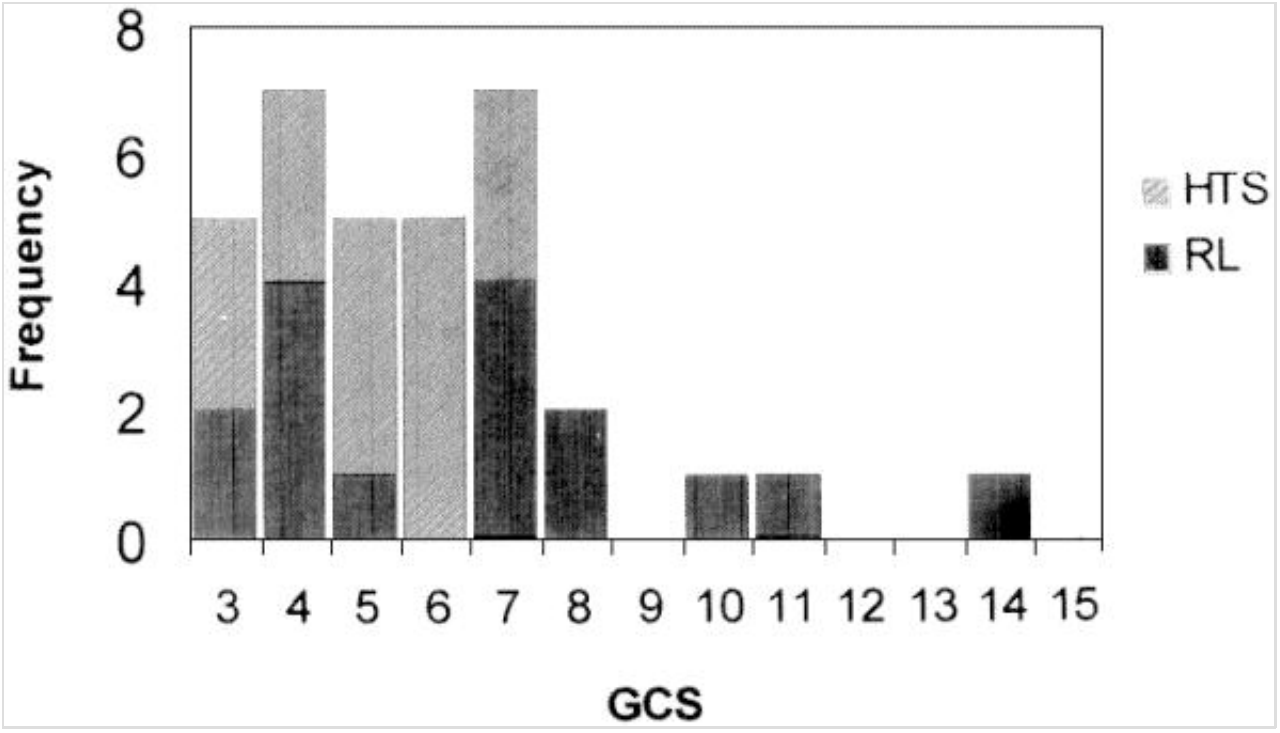


Figure 6. Histogram depicting the relative frequency of admission GCS scores in the two groups. As can be seen, all of the HTS patients had a GCS score

DISCUSSION

Secondary brain injury occurs after the primary impact injury and is attributable to a decrease in cerebral oxygen delivery as a result of either hypoxia, systemic hypotension, or relative hypoperfusion produced by intracranial hypertension. [3-5] Despite advanced prehospital and early hospital care available in trauma systems, 35% of patients with severe head injury are hypotensive or hypoxic during the early phases of care. [4] Of the two secondary insults, hypotension appears to have the greatest impact on outcome. [4,5]

These clinical studies emphasize the vulnerability of the injured brain to even brief periods of hypoperfusion. Rapid treatment of hypovolemia is extremely important in patients with severe brain trauma to prevent secondary injury. In fact, such recommendations have recently been published in the Guidelines for the Management of Severe Head Injury. [7]

Secondary insults can also occur as a result of increased ICP. Vasogenic edema and brain swelling, which accompany cerebral injury, [19] increase the ICP. The increase in ICP, if not accompanied by an increase in mean arterial pressure, decreases CPP and cerebral blood flow, resulting in decreased cerebral oxygen delivery. Increased ICP > 20 mm Hg is associated with a poor outcome. [20,21] For this reason, preventing an increase in or controlling ICP has become the major intent of medical treatment of patients with head injury. [22,23] Specific treatment methods aimed at reducing ICP include hyperventilation (to decrease cerebral blood volume), sedation (to prevent agitation, reduce muscular activity, and attempt to reduce the cerebral metabolic rate for oxygen), osmotic diuresis (to extract water from cells down an osmolar gradient and reduce cerebral tissue volume in areas with an intact blood brain barrier), and ventricular drainage (to reduce the volume of cerebrospinal fluid).

Fluid and salt restriction has also been advocated to control ICP to reduce vasogenic edema formation in areas of blood-brain barrier disruption [8,9]. Because vasogenic edema formation is driven by the capillary hydrostatic pressure acting at the site of injury, [24] it is logical to minimize the hydrostatic gradient between the capillary and cerebral tissue whenever possible. Fluid restriction or active diuresis can lower the capillary hydrostatic pressure and, theoretically, reduce edema formation.

It is often not possible to restrict fluid to patients sustaining head injury in association with other injuries, especially if they are hypotensive or require operative therapy. Asanguineous fluid and blood are necessary, often in volumes that exceed the amount of blood lost. [25,26] In fact, restricting fluids in hypovolemic patients could lead to hypotension and decreased perfusion to vulnerable areas of injured brain. [7]

The physician treating a hypotensive patient with a severe head injury must rapidly restore perfusion, avoid excessive elevations in capillary hydrostatic pressure, and control ICP to prevent secondary injury. Management of hypotension in the patient with head injuries has conventionally been achieved by the infusion of a balanced salt solution. Lactated Ringer's solution, a slightly hypotonic solution, has been recommended for the replacement of volume deficits until blood is available. [27] After stabilization of volume deficits, active diuresis together with restriction of fluid and salt are advocated in patients with elevated ICP. [28] Hypotonic fluid has been recommended to provide maintenance fluid and solute requirements, to keep intravenous lines open, and to administer medications. [8,28] Such therapy is directed at restricting salt administration to prevent retention of water. [8] There have been no studies, however, that have documented that salt restriction either decreases vasogenic edema formation or reduces ICP. [29] On the contrary, Bakay and co-workers [30] showed that administration of a slightly hypertonic salt solution (0.9%) lowered the cerebrospinal fluid pressure by 30 to 50% in patients in chronic coma, whereas a hypotonic salt solution (1/2NS) produced no change. The administration of fluid without ionizing solute (dextrose in water) resulted in a 14 to 100% increase in cerebrospinal fluid pressure. In a retrospective analysis of patients with multiple injuries who also sustained a severe head injury, Schmoker and colleagues demonstrated that the amount of salt and water administered during the first 72 hours of treatment was significantly correlated with net fluid balance (i.e., the more salt and water given, the greater the positive fluid balance) but that there was no relationship between the amount of fluid and salt administered to the mean ICP, the maximum ICP, or the change in GCS score. [31]

Hypertonic salt solution offers several advantages for the treatment of hypovolemic patients with head injuries. It restores blood pressure and cardiac output with significantly less volume and at lower capillary hydrostatic pressure than does lactated Ringer's solution. [32-34] Hypertonic fluids achieve this by having a positive inotropic effect [35,36] and by extracting water from the intracellular space to restore intravascular losses. [37,38]

Despite the potential advantages of hypertonic solution, there are sparse clinical data on its use in head injury. Holcroft and co-workers, [12] in a prospective, randomized, doubleblind trial, compared 7.5% hypertonic saline in 6% dextran 70 (HSD) to LRS as a prehospital bolus injection (250 mL) administered to injured patients with and without head injury. Both groups received LRS for definitive resuscitation after reaching the hospital. Overall survival was better in the HSD group. Although there were only 10 patients in each group, 4 in the HSD group and 7 in the LRS group had head injuries. They have now expanded their experience to 166 patients. [13] Although overall survival was similar in both groups in this expanded study, survival after severe head injury was significantly greater in patients treated with HSD (32%) than in patients treated with LRS (16%, $p < 0.05$).

It seemed to us that the effects of the prehospital hypertonic resuscitation were abrogated by the administration of the LRS for continued asanguineous resuscitation and for the replacement of operative fluid losses. If the potential benefit of improved intracranial compliance were to be realized, hypertonic fluids should be used throughout the acute phases of treatment. We reasoned that the administration of hypotonic fluid would lower S_{Osm} and result in fluid movement into cells, thereby reducing intracranial compliance and increasing ICP as the area of the injury continued to swell. We further reasoned that such treatment would logically result in more interventions to control the ICP. On the other hand, we believed that the continued use of hypertonic fluid would maintain an osmolar gradient favoring fluid movement from cells and would increase intracranial compliance, accommodate brain swelling with smaller increments in ICP, and result in fewer interventions to control the ICP.

The patients enrolled in this prospective study were similar in age, gender mix, and severity of associated injuries. Unfortunately, randomization of this small group of patients resulted in a greater number of patients with severe injuries being allocated to the HTS group (Figure 6).

The HTS group had a negative fluid balance at the completion of the 5 days of study, whereas the LRS group had a positive fluid balance. This difference was attributable to higher urine volumes in the HTS group as a result of the natriuresis observed with HTS infusion [39,40] and the more frequent use of mannitol and diuretics in this group.

The patients in the HTS group had a significantly higher S_{Na} and a significantly higher S_{Osm} than the patients in the LRS group. This was anticipated and reflects the desired treatment effect. It is important to point out that none of the patients manifested any neurologic signs or symptoms of osmotic demyelination syndrome [41] during treatment or during follow-up and that none developed renal failure or any decrement in renal function.

There was no difference between the groups in the mean ICP or in the mean CPP at any time during the study (Figure 3). Both groups were managed effectively with current therapies to control ICP, and the tonicity of the resuscitative and maintenance fluids had little effect on either the mean ICP or the mean CPP.

The mean maximum ICP was significantly higher in the HTS group during the first day of study. Treatment, which included HTS, effectively lowered this variable, which we believe is an indication of improved intracranial compliance. It is also important to examine the trends in the mean maximum ICP during the study (Figure 4). In the HTS group, there was a change of -9.1 +/- 3.6 mm Hg over the course of the study. In the LRS group, the change was +2.5 +/- 3.3 mm Hg ($p < 0.05$). In the aggregate, these data suggest that hypotonic fluids reduce intracranial compliance and that hypertonic fluids increase it.

The number of interventions used to control the ICP in the HTS group was significantly greater than in the LRS group. Although we attribute this to the greater severity of head injury in the HTS group, the possibility that HTS administration could have increased the ICP must be entertained. Given that HTS is known to reduce pial arteriolar tone, [42] it is possible that HTS reduced cerebrovascular resistance and increased cerebral blood volume to a greater degree than it reduced brain tissue volume through osmotic extraction of water. This seems unlikely given the experimental work, [10,11,43] clinical studies, [12,13] and case reports [44,45] that show either reduced ICP, improved outcome, or both. Hypertonic solutions are also known to reversibly open the blood-brain barrier, [46] which could conceivably have caused cerebral edema and increased the ICP. This is not likely because the osmolarity of HTS is 514 mOsm/L, well below the threshold of 1,600 mOsm/L that has been shown to open the blood-brain barrier. [46] The suggestion that hypertonic infusion could result in rapid, severe shrinkage of the brain and a mechanical shearing or tearing of bridging vessels, resulting in subarachnoid hemorrhage, is not likely. Subarachnoid hemorrhagic encephalopathy associated with hypernatremia has been observed only in severely dehydrated infants whose S_{Na} exceeded 175 mEq/L. [47]

There are a number of flaws in this study. Primary among them is the disparate randomization of patients with severe head injury. A second flaw is the small sample size. When we initially planned the study, we had hoped for greater patient accrual. Of patients previously treated at the two institutions who could potentially qualify for the study, 30% had a maximum ICP >or=to 20 mm Hg. We considered a 20% reduction in the incidence of a maximum ICP > 30 mm Hg to be significant. To detect that difference between the groups with an alpha of 0.05 and a beta of 0.8 would have required the enrollment of 320 patients. We were able to enroll only 12% of that number. The low enrollment also forced us to combine disparate groups of patients for analysis; we grouped patients with isolated head injuries with patients with head and torso injuries. The causes for the low enrollment were many, but primary among them was the reduction in severe head injuries that were treated at the two institutions during the study period. The third major flaw in the study was the multicenter format. When accrual of patients lagged during the first year of the study, we expanded to a second institution. Although there was generalized agreement on the major aspects of care, there were variations in management that could have affected the results. For example, it became clear as the study progressed that the threshold for the use of sedatives and muscle relaxants was variable among the participating neurosurgeons: some used them frequently, some occasionally, and some not at all. Such medications could affect the ICP and, therefore, the number of interventions. Finally, we had no control over the type of fluid administered in the prehospital arena. Several hypertonic patients received a moderate amount of LRS before arrival at the hospital.

In summary, this investigation failed to validate our hypothesis that HTS would lower ICP and result in fewer medical treatments to lower the ICP. Given the small number of patients and the disparity in head injury severity observed in the treatment groups, no conclusions regarding the efficacy of HTS or LRS should be drawn. The data suggest that HTS can be used safely with other treatment modalities in patients with brain injuries provided that the S_{Na} and the S_{Osm} are monitored during large volume infusions. The data also suggest that solute-free water may decrease intracranial compliance. A larger, single-center trial is needed to fully evaluate the role, if any, of hypertonic fluids in the resuscitation and treatment of patients with head injuries.

We believe that such a trial is indicated because of the promising experimental work demonstrating improved intracranial compliance and increased cerebral blood flow after head injury and shock. Furthermore, our clinical data and those of others [12,13] have demonstrated that hypertonic solutions are safe and produce no adverse effects on renal, cerebral, or pulmonary function in severely injured patients.

DISCUSSION

Dr. Charles E. Wiles, III (Baltimore, Maryland): At our center, the surest way to make a clinical problem disappear is to design a study about it.

For most of the past half century, surgeons have practiced as if 1-liter containers of lactated Ringer's solution fit all instances of resuscitation from trauma. With the dawn of the new millennium, trauma surgeons will be able to pick and choose from a boutique full of resuscitation fluids ranging from salt solutions in various strengths through salt/starch combinations and recycled hemoglobin to engineered artificial blood and soon to resurrection infusions designed to produce something close to suspended animation.

The authors have presented a clear, concise paper discussing their findings from a well-designed prospective randomized clinical trial examining a significant problem in trauma care. The clinical study was based on their previous experimental work on the topic. Its methodology is sound. The conclusions are ambiguous.

The research question addressed concerned the appropriate resuscitation fluid for patients with head injury. In its ultimate form, the study compared hypertonic saline (HTS) with lactated Ringer's solution. The authors hypothesized that an hypertonic solution used for resuscitation and maintenance fluid therapy after moderate and severe head injury would increase intracranial compliance resulting in a smaller increase in intracranial pressure and fewer interventions to lower intracranial pressure. They neither confirmed nor refuted their hypothesis. The data presented suggest that hypertonic solutions are not significantly superior and may be more difficult to use.

In their discussion of the results presented, the authors point out that a sample size of n = 320 would have been needed for statistical analysis. Thirty-four patients were enrolled despite the eventual recruitment of patients from a second trauma center. They mention the vexations of a multiple center study. A further criticism of their findings is that only six patients, three in each arm, met their definition of shock.

Head injury remains the most frustrating area in the care of the trauma patient. The results of this paper do not demonstrate any pressing argument to abandon current crystalloid resuscitation fluids. The opportunity to pursue the discussion in a larger single center trial remains open. Do the authors think that the results of this study are encouraging enough to continue this present effort or would they recommend addressing another facet of the head injury problem? Finally, are there other interesting properties of hypertonic solutions that might recommend their use in trauma care?

Dr. Shuji Shimazaki (Tokyo, Japan): I enjoyed your paper very much. I basically agree with you and I have published a paper of the efficacy of HTS for patients with head trauma. Let me ask two simple questions. The first question is about sodium concentration. In your study you used a solution with 1.8% sodium, which should have about 300 milliequivalent of sodium in 1 liter of the solution. Have you tried a solution with a higher sodium concentration for patients with head trauma? The second question is about HTS effects on cerebral perfusion pressure. Rather than intracranial pressure, cerebral perfusion pressure may be more important to evaluate therapeutic modality in a patient with head injury. Could you tell us about change of cerebral perfusion pressure in your patients. Thank you.

Dr. Charles E. Lucas (Detroit, Michigan): Nice presentation. What was the effect of your treatment regimen on renal function? More specifically, did the hypernatremia and hyperosmolality lead to altered GFRs on day 2 and day 4?

Dr. James W. Davis (Tampa, Florida): I'd like to congratulate the group for their continued effort in researching HTS in head injury.

Two questions. Again, like Dr. Shimazaki said, why not more concentrated sodium solution, for example, 3%? And then why not use the HTS solution continuously rather than going down to normal saline. Thank you.

Dr. Janice A. Mendelson (San Antonio, Texas): Did you study the effects on immediate and subsequent pulmonary function in this study? Thank you.

Dr. Errington Thompson (Shreveport, Louisiana): I enjoyed this study very much, and I was wondering what were the end points of resuscitation?

And second of all, what were the rates of multiple organ dysfunction? Thank you.

Dr. Steven R. Shackford (closing): That was Paul Bourguignon who presented the paper, a resident at the University of Vermont, and I neglected to tell the moderators. I apologize.

First, Dr. Wiles, I thank you very much for your very kind comments and your analysis. Your question-which you were kind enough to give me before the meeting, and I'm appreciative of that-do we think "that the results of this study are encouraging enough to continue this present effort or would they recommend addressing another facet of head injury?"

I believe that we should continue to do this. When we set about to study this problem, which was funded by the National Institutes of Health for 3 years, I was a little bit naive in two aspects. I thought that at that time we would be able to accrue enough patients. It soon became apparent that the vagaries of prospective randomized clinical trials are such that it is extremely difficult. First, getting consent on comatose patients requires that you have to get it from next-of-kin, and running them down is difficult at 2:00 in the morning.

Secondly, I was naive because brain injury is really a family of injuries, and it represents injuries that are hemorrhagic and nonhemorrhagic. Also, there are nonhemorrhagic lesions that become hemorrhagic. The brain's response, the reactivity of the cerebral circulation in a hemorrhagic injury is quite a bit different than it is in a nonhemorrhagic injury. So to drop them all into one bucket is an error.

We are now just scratching the surface on understanding both the anatomic and physiologic differences between brain injuries, and I think it is important that if we can characterize these in a better way, the study of hypertonic resuscitation or any type of resuscitation will be advanced.

Dr. Shimazaki and Dr. Davis, thank you very much for your questions. Why not higher concentrations? What about a 5% or a 10% solution? As you probably are aware, as you get up around 10%, the possibility of opening up the blood-brain barrier occurs. As you get to higher tonicity of infusate, you will run the potential possibility of shrinking the endothelium so much that you will in fact open the blood-brain barrier. This has been shown by intracarotid injections with very high percentage solutions up to around 10%. So that is why we haven't gone that high. Certainly, a 3% solution is acceptable. You will, however, have to monitor the serum sodium and sodium osmolality very carefully.

Dr. Shimazaki asked about the cerebral perfusion pressure. I agree with you. As we showed there was an initial decrease in the cerebral perfusion pressure in both groups. Our neurosurgeon on the study, Dr. Wald, felt that we probably could have been a little more aggressive in our resuscitation. Cerebral perfusion pressure is important, and it is a parameter that should be followed.

In designing future studies, I think that instead of using interventions in the aggregate that one should use an intervention score, because not all interventions have the same weight.

Dr. Lucas, you asked about the effect of hypertonic saline on renal function. We monitored the serum creatinine and BUN twice daily in all of these patients, and using serum creatinine as a surrogate for glomerular filtration rate, there were no detrimental effects. The serum creatinine did not rise in any of the patients. BUN rose slightly in the hypertonic group, but that was probably due to dehydrational effects.

Dr. Mendelson, pulmonary function was followed by arterial blood gasses done every 8 hours, and there was no deterioration in pulmonary function in either of the two groups. Nor was there no difference between the groups.

And finally, Dr. Thompson, what were the end points of resuscitation? We resuscitated patients in the emergency room to a mean arterial pressure of greater than 90, and to keep the urine output at greater than half a ml per kilogram.

I thank all of the discussants for their interesting questions, and the Association for the opportunity to present this data. Thank you.

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IMAGE GALLERY

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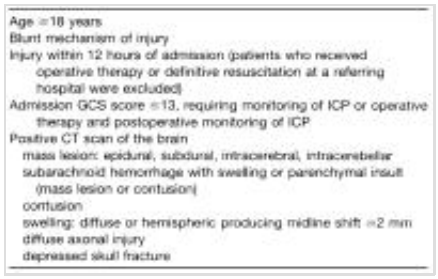
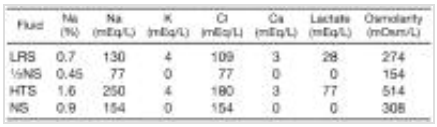

Age ≥18 years
Blunt mechanism of injury
Injury within 12 hours of admission (patients who received operative therapy or definitive resuscitation at a referring hospital were excluded)
Admission GCS score ≤13, requiring monitoring of ICP or operative therapy and postoperative monitoring of ICP
Positive CT scan of the brain
mass lesion: epidural, subdural, intracerebral, intracerebellar
subarachnoid hemorrhage with swelling or parenchymal insult (mass lesion or contusion)
contusion
swelling; diffuse or hemispheric producing midline shift ≥2 mm
diffuse axonal injury
depressed skull fracture

Table 1



Fluid	Na (%)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Ca (mEq/L)	Lactate (mEq/L)	Osmolarity (mOsm/L)
LRS	0.7	130	4	109	3	28	274
½NS	0.45	77	0	77	0	0	154
HTS	1.6	250	4	180	3	77	514
NS	0.9	154	0	154	0	0	308

Table 2

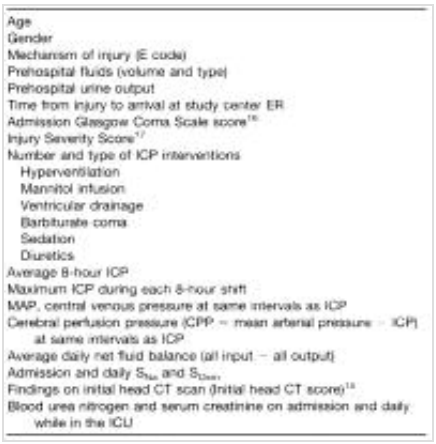
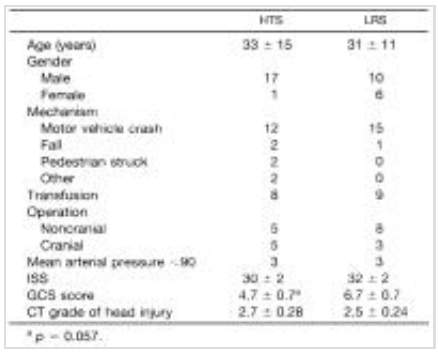

Age
Gender
Mechanism of injury (E code)
Prehospital fluids (volume and type)
Prehospital urine output
Time from injury to arrival at study center ER
Admission Glasgow Coma Scale score[16]
Injury Severity Score[17]
Number and type of ICP interventions
Hyperventilation
Mannitol infusion
Ventricular drainage
Barbiturate coma
Sedation
Diuretics
Average 8-hour ICP
Maximum ICP during each 8-hour shift
MAP, central venous pressure at same intervals as ICP
Cerebral perfusion pressure (CPP = mean arterial pressure − ICP) at same intervals as ICP
Average daily net fluid balance (all input − all output)
Admission and daily S_{Na} and S_{Osm}
Findings on initial head CT scan (initial head CT score)[18]
Blood urea nitrogen and serum creatinine on admission and daily while in the ICU

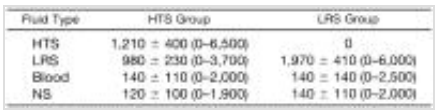
Table 3



	HTS	LRS
Age (years)	33 ± 15	31 ± 11
Gender		
Male	17	10
Female	1	6
Mechanism		
Motor vehicle crash	12	15
Fall	2	1
Pedestrian struck	2	0
Other	2	0
Transfusion	8	9
Operation		
Noncranial	5	8
Cranial	5	3
Mean arterial pressure <90	3	3
ISS	30 ± 2	32 ± 2
GCS score	4.7 ± 0.7*	6.7 ± 0.7
CT grade of head injury	2.7 ± 0.28	2.5 ± 0.24

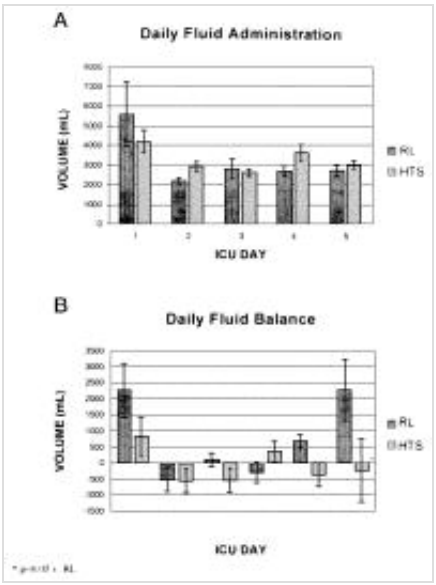
*$p = 0.057$.

Table 4



Fluid Type	HTS Group	LRS Group
HTS	1,210 ± 400 (0–6,500)	0
LRS	980 ± 230 (0–3,700)	1,970 ± 410 (0–6,000)
Blood	140 ± 110 (0–2,000)	140 ± 140 (0–2,500)
NS	120 ± 100 (0–1,900)	140 ± 110 (0–2,000)

Table 5



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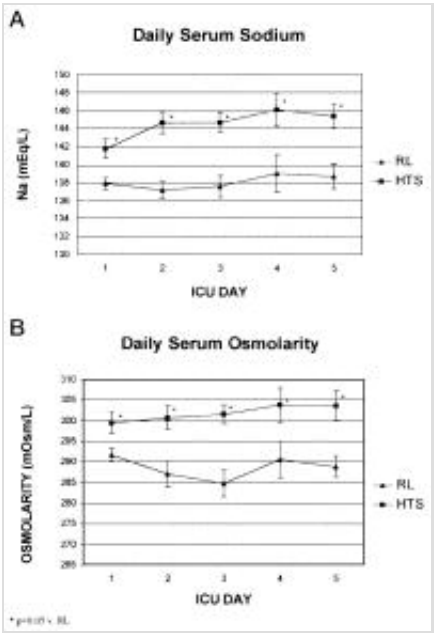

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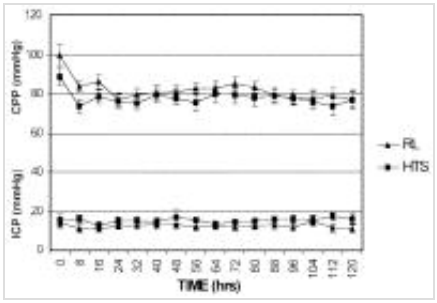

Figure 3

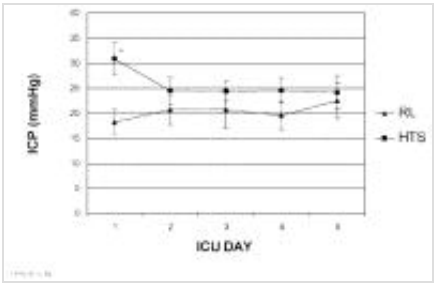

Figure 4

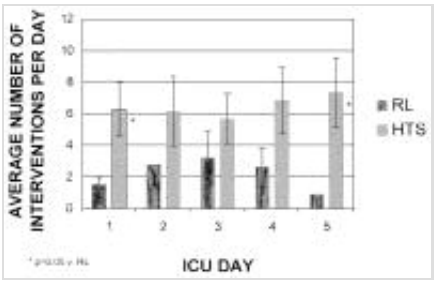

Figure 5

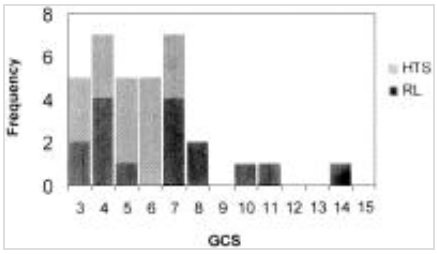

Figure 6

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