The Effect of Hypertonic Sodium Chloride on Intracranial Pressure in Patients With Acute Liver Failure

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Acute liver failure (ALF) is a rare condition characterized by the development of encephalopathy in the absence of chronic liver disease. Cerebral edema occurs in up to 80% of patients with Grade IV encephalopathy. In the current prospective randomized controlled clinical trial, we examined the effect of induced hypernatremia on the incidence of intracranial hypertension (IH) in patients with ALF. Thirty patients with ALF and Grade III or IV encephalopathy were randomized. Patients in Group 1 (n = 15) received the normal standard of care. Patients in Group 2 (n = 15) received standard care and hypertonic saline (30%) via infusion to maintain serum sodium levels of 145–155 mmol/L. Intracranial pressure (ICP) was monitored in all patients with a subdural catheter (Camino Systems, San Diego, CA) for up to 72 hours after inclusion. Serum sodium levels became significantly different from the levels observed in the control group at 6 hours (P < .01). Over the first 24 hours, norepinephrine dose increased relative to baseline in the control group (P < .001; 13 patients) but not in the treatment group. ICP decreased significantly relative to baseline over the first 24 hours in the treatment group (P = .003; 13 patients) but not in the control group. The incidence of IH, defined as a sustained increase in ICP to a level of 25 mm Hg or greater, was significantly higher in the control group (P = .04). In conclusion, induction and maintenance of hypernatremia can reduce the incidence and severity of IH in patients presenting with ALF. (HEPATOLOGY 2004;39:464–470.)

Acute liver failure (ALF) is defined as the acute cessation of normal liver function in a patient without a history or clinical signs of chronic liver disease. The defining state is the onset of hepatic encephalopathy. The classification of ALF into hyperacute, acute, and subacute categories based on the time from the onset of jaundice to the development of encephalopathy aids in predicting outcome. Patients with rapidly progressive liver failure have a greater risk of developing cerebral edema and intracranial hypertension (IH).

Although IH in ALF is not completely understood, there are thought to be two main pathologic processes that contribute to this condition. These processes are brain swelling caused by water influx down an osmotic gradient into astrocytes (cytotoxic edema) and cerebrovascular vasodilation, which results in increased cerebral blood volume.

Under normal conditions, ammonia, which is produced mainly in the gut, kidney, and pancreas, is metabolized in the liver to both urea and glutamine. When the liver fails, there is an increase in circulating ammonia levels. Increased metabolism occurs at alternative sites, such as skeletal muscle and the brain, during liver failure. Within the brain, ammonia is detoxified in astrocytes. Here, glutamine is produced when ammonia combines with the excitatory neurotransmitter glutamate via the enzyme glutamine synthetase. The ammonium load associated with liver failure fuels this reaction, and the glutamine produced increases the osmotic potential within astrocytes. In fact, inhibition of glutamine synthetase ameliorates brain edema and improves survival results in animal models of ALF. The rapidity of onset of ALF reduces the time available for cellular adaptation. In contrast, in chronic liver disease, astrocytes have time to adapt to the increase in circulating ammonia levels.
The glutamine hypothesis suggests that water diffuses across the blood-brain barrier and into astrocytes, resulting in cerebral edema and IH. Thus, it can be expected that agents that increase extracellular osmolality, such as mannitol, will reduce IH and that in contrast, a decrease in extracellular fluid osmolality will be associated with an increase in brain swelling.

In the current prospective randomized controlled clinical trial, we investigated the effects of systemic hypernatremia via hypertonic saline infusion on the incidence of IH in patients with ALF and Grade III or IV encephalopathy. We hypothesized that systemic hypernatremia may reduce the incidence of cerebral edema and IH.

**Patients and Methods**

After approval was granted by the local hospital ethics committee, 30 patients with ALF and Grade III or IV encephalopathy were entered into the current trial. Due to the nature of the disease, consent requirements were eschewed and informed assent was obtained from next of kin. The sample size was based on previously reported data. A difference of 10 mm Hg in mean intracranial pressure (ICP) between groups was anticipated, based on previous anecdotal experience using hypertonic saline to treat patients with ALF. This expectation, together with an α value of 0.05 and a β value of 0.2, yielded a target sample size of 29 patients.

On entry into the trial, patients were randomized into 2 groups using sealed envelopes. Group 1 (n = 15) received standard care. Group 2 (n = 15) received standard care plus a 30% hypertonic saline infusion via a syringe driver. The infusion rate was titrated between 5 and 20 mL per hour to maintain serum sodium levels at 145–155 mmol/L.

The primary endpoint of the study was onset of IH, which was defined as a sustained rise (lasting 10 minutes or longer) in ICP to 25 mm Hg or greater. Data were recorded for up to 72 hours after inclusion.

Management of both groups was standardized. Ventilation was provided using a volume-controlled mode, with minute volume adjusted to achieve a pCO₂ of 4.5–5.5 kilopascals (34–42 mm Hg). All patients were nursed with 15–20 degrees of head elevation to facilitate venous drainage and sedated with fentanyl and midazolam. ICP was measured with a subdural ICP probe (Integra Neuro-Sciences, Plainsboro, NJ) inserted into the nondominant frontoparietal region. Before insertion of the probe, fresh-frozen plasma and platelets were administered. A reverse jugular venous catheter was inserted into the right or left internal jugular vein. Irrespective of cause, all patients received N-acetylcysteine (150 mg/kg per day) via continuous intravenous infusion. Hemodynamic monitoring included arterial access via a radial artery for arterial blood gas measurement and central venous access. Further hemodynamic monitoring was determined by clinical need. If mean arterial blood pressure decreased below 70 mm Hg, the patient was adequately volume-loaded and noradrenaline administration was initiated and titrated to maintain a mean blood pressure of 75–80 mm Hg. All patients were fed enterally and given prophylactic antibiotics. Hemoglobin levels were maintained at 8–10 g/dL with packed red cells. Endotracheal suction and patient turning were minimized to reduce the risk of bringing about cerebral edema.

Group 1, the control group, consisted of 12 patients with acetaminophen hepatotoxicity, 1 patient with non-A, non-B hepatitis (seronegative hepatitis), 1 patient with acute hepatitis B, and 1 patient following acute hepatotoxicity in response to antiretroviral therapy. Group 2, the treatment group, consisted of 12 patients following acetaminophen hepatotoxicity, 1 patient with acute hepatitis B, 1 patient with hepatotoxicity due to use of the recreational drug ‘ecstasy’ (3,4-methylenedioxymethamphetamine), and 1 patient following hepatotoxicity due to a traditional Chinese medication.

Censoring occurred after death, liver transplantation, or resolution of illness. Physiologic data were collected at six hourly intervals. Patients with ICP ≥ 25 mm Hg received an escalating treatment regimen. Sedation was increased and followed by mannitol, 0.5 g/kg, over 10 minutes in conjunction with the removal of 500 mL of ultrafiltrate via hemofiltration if the patient was in anuric renal failure. Surface cooling was performed for patients with ICP that was resistant to initial measures. Two patients in the control group had resistant IH and received 20 mL bolus injections of 30% hypertonic saline. Both of these patients died with intractable IH.

Statistical analysis was performed using SPSS Version 10 (SPSS Inc., Chicago, IL) and Unistat 4.5 (London, United Kingdom). Study data are presented as mean values with standard errors. Within-group analysis consisted of nonparametric ANOVA (Quade two-way ANOVA). Between-group data were compared using the Mann-Whitney U test. Kaplan–Meier analysis with Breslow’s test for significance was used to compare the incidence of clinically significant IH between groups. Spearman’s test was used to evaluate correlations. A P value of less than .05 was considered significant.

**Results**

The average time from admission to the hospital until entry into the trial was 36.5 hours, with a range of 3–73 hours. Sixteen of the 30 patients in the trial had encephalopathy on arrival at the intensive care unit; for these
patients, the exact timing of the onset of encephalopathy was unclear. For the remaining 14 patients, the average time from the onset of encephalopathy to entry into the trial was 31 hours, with a range of 5–55 hours.

Seven patients in the control group and 9 patients in the treatment group had sodium levels of less than 135 mmol/L on admission into the intensive care unit. One patient in the control group had a serum sodium level of less than 130 mmol/L, compared with 6 patients in the treatment group. On admission to the trial, no patient in either group had a serum sodium level of less than 130 mmol/L; 1 patient in each group, however, had a serum sodium level of less than 135 mmol/L. The relation between serum sodium level at admission and the first available ICP measurement was investigated in all patients (Fig. 1); a weak but significant inverse correlation was observed ($r^2 = 0.06; P = .02$).

Over the study period, there was no difference between the two groups in terms of the volume of fluids administered or the amount of blood transfused. Eight patients in the control group required mannitol, compared with five in the treatment group; this difference was not significant. The number of interventions also did not differ significantly between the two groups. Fourteen of 15 patients in the control group and 13 of 15 patients in the treatment group underwent continuous venovenous hemofiltration, with a blood flow rate of 200 mL per minute and a median ultrafiltrate rate of 4 L per hour in both groups. For all patients, the indication for continuous venovenous hemofiltration was oliguric or anuric renal failure.

Serum sodium levels increased in both groups between admission to the intensive care unit and entry into the trial. These increases resulted from the use of hemofiltration for the majority of patients in both groups. In the treatment group, serum sodium concentration increased significantly from its initial levels and, at 6 hours, became significantly different from the levels observed in the control group ($P < .01$) (Fig. 2). During the first 24 hours, the treatment group received an average of 6.5 mL of 30% saline per hour. Each 10 mL ampoule of 30% saline contains 50 mmol of sodium chloride; thus, the average sodium load during the first 24 hours was approximately 780 mmol. The mean peak serum sodium concentration for patients in the treatment group was 153 ± 0.8 mmol/L.

Mean arterial pressure did not differ between the two groups, because of the management protocol. Vasopressor use was compared over time within each group and between groups. Norepinephrine dose increased significantly compared with baseline over the first 24 hours in the control group ($P < .001; 13$ patients). This increase continued to be observed at 36 hours ($P < .001; 11$ patients) but was no longer apparent at 48 hours (9 pa-

**Table 1. Clinical Data on Admission by Treatment Group**

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Hypertonic Saline Group</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>36</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>4.7 ± 0.6</td>
<td>7.9 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Jugular venous O₂ sats (%)</td>
<td>68.4 ± 7.3</td>
<td>71.7 ± 3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>135.3 ± 1.1</td>
<td>131.7 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>ICP on insertion (mm Hg)</td>
<td>16.9 ± 3.5</td>
<td>17.2 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>5.51 ± 0.9</td>
<td>4.67 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Base deficit (mmol/L)</td>
<td>−6.55 ± 2.3</td>
<td>−5.26 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>147 ± 62</td>
<td>110 ± 24</td>
<td>NS</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>99 ± 10</td>
<td>116 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>6828 ± 1273</td>
<td>6798 ± 1263</td>
<td>NS</td>
</tr>
<tr>
<td>γ-GT</td>
<td>76 ± 13</td>
<td>123 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>256 ± 37</td>
<td>250 ± 34</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NOTE:** All numeric values are means ± standard errors. 
Abbreviations: INR, international normalised ratio; NS, not significant; sats, saturation; γ-GT, γ-glutamyl-transferase.

**Fig. 1.** Relation between serum sodium concentration at admission and initial ICP measurement ($r^2 = 0.06; P = .02$).

**Fig. 2.** Serum sodium concentration (mean values with standard errors) in the control (○) and treatment (●) groups. Asterisks indicate that $P < .01$ (Mann-Whitney U test).
In the treatment group, there was a nonsignificant increase in norepinephrine dose from baseline over the first 24 hours. The difference between groups was not significant (Fig. 3).

ICP data from the study were analyzed within each group, over time, and between groups. Over the first 24 hours, there was a significant reduction in ICP relative to admission values in the treatment group ($P = .003; 13$ patients). ICP remained significantly decreased at 48 hours ($P = .001; 11$ patients). In the control group, ICP increased over these time periods, but not significantly ($13$ patients at 24 hours; $8$ patients at 48 hours) (Fig. 4). The difference in ICP between groups became significant at 42 hours ($P = .04$).

The primary outcome, incidence of IH, also was compared between groups. Seven patients in the control group had $ICP \geq 25$ mm Hg, compared with $3$ patients in the treatment group ($P = \text{not significant}; \text{Fisher’s exact test}$). Using survival analysis to account for case censoring (due to death, transplantation, or recovery) (Fig. 5), the cumulative risk of having $ICP \geq 25$ mm Hg during the 72-hour trial was found to be significantly greater in the control group ($P = .04$). No difference in terms of cerebral perfusion pressure or jugular venous saturation data was found between the two groups.

Seven patients in the control group reached the primary endpoint of the trial, an ICP of $25$ mm Hg. Eight patients did not reach the primary endpoint; $5$ of these $8$ were censored ($2$ due to early death and $3$ due to transplantation). Overall, there were $7$ transplantations and $6$ early deaths in the control group at 72 hours. Three of the six deaths resulted from IH, and the remaining three resulted from unsupportable hypotension.

Three patients in the treatment group reached the primary endpoint of the trial, and $12$ patients did not. Of the $12$ patients who did not reach the primary endpoint, $7$ were censored ($3$ due to early death, $1$ due to transplantation, and $3$ due to early removal of ICP bolts because of improved medical condition). ICP bolts were removed at the discretion of the attending medical team; one patient’s ICP monitor was removed at $66$ hours, another patient’s monitor was removed at $48$ hours, and the third patient’s monitor was removed at $60$ hours. Overall, there were $5$ transplantations and $5$ early deaths at 72 hours. Two of the five deaths resulted from IH, and the remaining three resulted from unsupportable hypotension.

After termination of the trial, seven patients in the control group and eight patients in the treatment group died while in intensive care. Late deaths were due to sepsis.

**Discussion**

Slightly more than half of all patients in the current study had hyponatremia on admission to the intensive
of poor outcome for patients with ALF. We found a
ponatremia previously has been reported to be a predictor
mmol/L or less, and 32% had serum sodium levels of 130
phen toxicity who presented to the liver unit at our insti-
In a consecutive group of 240 patients with acetamino-
related use of hemofiltration. The high ultrafiltration rate
was chosen as the treatment target because of the antici-
uter these conditions, the total dose is heavily dependent
as the treatment target because of the anticipated use of hemofiltration. The high ultrafiltration rate (median, 4 L per hour) demanded a rapid feedback mecha-
serum sodium concentration, rather than serum osmolality,
serum sodium concentration, measured by near-patient blood gas analysis, was determined to be the
most appropriate target. The total volume of hypertonic saline infused varied among patients in the treatment
group, but the total quantity in mmol of sodium admin-
istered was not used as an indicator of osmolar load, be-
cause of the daily plasma water (and sodium chloride) exchange of as much as 96 L during hemofiltration. Un-
der these conditions, the total dose is heavily dependent
upon the ultrafiltration rate. In the setting of ALF with
high-grade encephalopathy, renal failure is quite com-
mon, and the majority of patients in the current study
were managed with renal replacement therapy. In fact, the
results of this study may only apply to patients with ALF
and renal failure.

The sodium loads associated with the treatment group
were very high. A 24-hour infusion of 30% saline at 10
mL per hour results in a sodium load of 1200 mmol.
Without hemofiltration to buffer the sodium load, rapid
changes in serum sodium concentration can occur; thus,
30% saline infusions should be used with caution, espe-
cially in patients with abnormal renal function.

In the treatment group, we found that induction of
moderate hypernatremia reduced ICP from its baseline
level. ICP decreased significantly during the first 6 hours
of the study. In contrast, there was a nonsignificant
increase in ICP in the control group. We defined IH as a
sustained increase in ICP to 25 mm Hg or greater for 10
minutes or more; this criterion was the treatment trigger
in use at our institution at the time of the study and was
based on previously published work. When compar-
ing the two groups directly, the difference in number of
patients reaching the primary endpoint (7 in the control
group vs. 3 in the treatment group) was not significant.
This lack of significance may stem from the relatively
small sample size. After controlling for withdrawal from
the study, however, the difference in incidence of IH was
significant.

There are several possible mechanisms by which hyper-
tonc saline and the induction of hypernatremia may pre-
vent IH in patients with ALF. One such mechanism is the
osmotic effect. The blood-brain barrier prevents the bulk
flow of water and solute from the circulation into the
brain and occurs as a result of tight junctions between
endothelial cells in brain capillaries. Water crosses the
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genic cerebral edema. Generally, a reduction in cerebral blood flow coupled with a reduction in cerebral metabolic rate early in the course of high-grade hepatic encephalopathy in ALF is followed by gradual cerebral vasodilatation and an increase in cerebral blood volume in severe cases. Variation in regional cerebral blood flow, however, has been reported in patients with ALF; this finding suggests that some areas of the brain may be more prone to ischemia. Increased cerebral lactate efflux shortly after episodes of IH in patients with severe ALF also has been reported. Whether hypertonic saline has any effect on cerebral blood flow and metabolism in patients with ALF currently is unknown and requires further investigation.

Other effects of hypertonic saline also may be important in controlling IH. Hypertonic saline solutions can restore normal resting potential in membranes and thereby potentially stabilize cerebral endothelial cell membranes, helping to inhibit the occurrence of vasogenic cerebral edema. The stability of resting membrane potential is important in the inhibition of seizure activity, which is not well characterized in patients with ALF. Hypertonic saline has been used successfully in the management of patients with status epilepticus induced by hyponatremia.

The systemic inflammatory response syndrome has been implicated in the development of both hepatic encephalopathy and IH in ALF. A correlation between serial cytokine levels and the severity of hepatic encephalopathy in patients with ALF also has been found. Recent investigation in animals has demonstrated that the addition of lipopolysaccharide to a toxic liver trauma exacerbates liver injury and IH. These findings suggest that some product of systemic inflammation either precipitates or (more probably) intensifies brain swelling in patients with ALF.

Hypertonic saline has profound effects on immune function. Hypertonicity inhibits neutrophil activation by preventing adhesion and degranulation and has been shown to reduce neutrophil accumulation in the lungs in a hemorrhagic shock model. Hypertonic saline also inhibits the production of proinflammatory cytokines (such as tumor necrosis factor) while enhancing the expression of anti-inflammatory cytokines (such as interleukin 10). This effect on systemic inflammation may help reduce the severity of IH. Published findings on this topic are conflicting, however, and it may be that systemic inflammatory response syndrome and cerebral edema are coincident phenomena.

The improvement in systemic hemodynamics was an unexpected finding and is difficult to interpret given our study design. Mean arterial pressure was managed above protocol limits with intravenous fluid and vasopressor and thus did not differ between groups. The norepinephrine dose required to maintain acceptable arterial pressure increased significantly in the control group over the first 6 hours and remained elevated for the following 24 hours. Hypertonic saline is known to have significant effects on the cardiovascular system. These effects include an increase in blood pressure mediated by the activation of the sympathetic nervous system, an increase in vasopressin release, and an increase in extracellular fluid volume. Peripheral infusion of hypertonic saline increases blood pressure and reduces heart rate via a baroreceptor-mediated reflex. In a rat model, some of the effects of hypertonic saline appear to operate centrally. The use of hypertonic saline may induce a degree of hemodynamic stability in patients with ALF, although this possibility requires further investigation.

The induction of hypernatremia has been investigated in the setting of head injury. Hypernatremia induced with 3% saline in patients with resistant IH results in a significant reduction in ICP and an increase in cerebral perfusion pressure. Simma et al. performed a randomized controlled clinical trial investigating fluid therapy in pediatric head trauma. They compared hypertonic saline with lactated Ringer’s maintenance fluid and concluded that hypertonic saline was superior in the management of severe head injury. These investigators also found that increased serum sodium concentration was significantly correlated with decreased ICP and increased cerebral perfusion pressure. In addition, they observed that fewer interventions, fewer complications, and a shorter time in intensive care were associated with hypertonic saline use.

From the results of the current study, we conclude that inducing moderate hypernatremia with 30% hypertonic saline can decrease ICP relative to baseline and reduce the incidence of clinically significant IH in patients with ALF. Larger trials are required to determine whether this simple intervention reduces the incidence of cerebral death or improves intensive care or hospital survival results.

References
