The role of hypertonic saline in neurotrauma

H. White*, D. Cook†, B. Venkatesh‡

*QE II Hospital, Department of Anesthesiology; †University of Queensland, Princess Alexandra Hospital, Department of Intensive Care, Brisbane, Australia

Summary
Animal and human studies suggest that hypertonic saline is a potential therapeutic agent to assist with the medical treatment of patients with traumatic brain injury. It may have a place as osmotherapy to decrease brain size, predominately of uninjured brain and has several potential advantages over mannitol. Hypertonic saline has clinically desirable physiological effects on cerebral blood flow, intracranial pressure and inflammatory responses in models of neurotrauma. Animal studies support its use, but definitive human trials using mortality end-points in brain trauma are lacking. Hypertonic saline may be considered a therapeutic adjunct to the medical management of traumatic brain injury, awaiting definitive evidence to support routine use.

Keywords: SALINE SOLUTION HYPERTONIC; INTRACRANIAL PRESSURE; INTRACRANIAL HYPERTENSION; MANNITOL.

Introduction – the role of osmotherapy in TBI
Cerebral oedema and subsequent intracranial hypertension are important causes of morbidity and mortality after traumatic brain injury (TBI). Intracranial hypertension following TBI results from cerebral oedema, disruption of the blood/brain barrier (BBB) and disordered autoregulation. Over the past 30 yr, osmotherapy has emerged as the cornerstone of management of intracranial hypertension following TBI.

Traditionally, the salutary effects of osmotherapy on intracranial pressure (ICP) were thought to result from brain shrinkage following the shift of water out of the brain substance. This has been confirmed in animal studies where osmotherapy following brain injury has led to shrinkage of normal but not injured brain tissue [1,2]. Interestingly, low ICP persists for some time after the serum concentration of the osmotic agent has fallen below the level considered as osmotically active.

A number of osmotic agents have been investigated in TBI for the management of raised ICP following TBI. These include urea, glycerol, sorbitol, mannitol and, more recently, hypertonic saline (HTS). Urea, glycerol and sorbitol are associated with significant side-effects. Mannitol has been proven to be efficacious and safe and is recommended by both the Brain Trauma Foundation and the European Brain Injury Consortium as the osmotic agent of choice [3,4]. Side-effects with mannitol include renal dysfunction, hypotension in the volume-depleted patients and rebound intracranial hypertension on cessation. HTS has emerged as a suitable alternative to mannitol.

Pharmacology of HTS
HTS solutions are available in a range of formulations; examples are listed in the table below (Table 1).

Pharmacology and mechanisms of action
The proposed beneficial effects of HTS in TBI are thought to arise from several mechanisms – the
dehydrating the normal brain tissue. HTS increases the volume of concussed tissue while pressure (MAP) and cerebral perfusion pressure (CPP) increased circulating blood volume, mean arterial

<table>
<thead>
<tr>
<th>Sodium concentration (mmol L⁻¹)</th>
<th>Osmolality* (mOsm kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% saline</td>
<td>154</td>
</tr>
<tr>
<td>Lactated Ringer’s solution</td>
<td>130</td>
</tr>
<tr>
<td>20% mannitol</td>
<td>–</td>
</tr>
<tr>
<td>1.7% saline</td>
<td>291</td>
</tr>
<tr>
<td>3% saline</td>
<td>513</td>
</tr>
<tr>
<td>7.5% saline</td>
<td>1283</td>
</tr>
<tr>
<td>10% saline</td>
<td>1712</td>
</tr>
<tr>
<td>23.4% saline</td>
<td>4004</td>
</tr>
<tr>
<td>29.2% saline</td>
<td>5000</td>
</tr>
</tbody>
</table>

*The osmolality of a solution is the number osmoles of solute per kg solvent. Osmolality can be measured by determining a change in the solutions colligative properties or calculated as the sum of the concentration of the solutes present in the solution. Reproduced from White and colleagues [44].

creation of an osmotic gradient between the intravascular and intracellular/interstitial compartments, leading to the shrinkage of brain tissue (where BBB is intact) and therefore to a reduction in ICP [5,6], increased circulating blood volume, mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) [7], restoration of the neuronal membrane potential, and modulation of the inflammatory response [8–10]. HTS increases the volume of concussed tissue while dehydrating the normal brain tissue.

HTS – a critical review of the evidence

Weed and McKibben [11] reported the first use of HTS therapy following TBI in 1919. Worthley and colleagues [12] reported prolonged reduction in ICP following its use in two patients with refractory intracranial hypertension. While there is widespread acceptance that HTS therapy improves ICP control, there is general recognition of the need for more human studies before definitive recommendations can be made. Published data on HTS are limited by small sample sizes, lack of a control population in some and many of them are case reports or small prospective studies. A recent study by Cooper and colleagues [13], where HTS was administered prehospital to patients with TBI, failed to demonstrate an improved outcome compared to placebo. It is important therefore that clinicians should use HTS with a certain amount of circumspection.

Animal studies

TBI has been extensively studied in animals. Several different models are used to replicate the complex pathophysiology of the injured brain including the mechanical percussion (produces contusions and subdural haemorrhages), cryogenic injury (focal injury with disruption of BBB) and balloon infusulation models (ischaemic injury) [14]. Areas of research include the influence of HTS on cerebral water content, ICP, CPP, MAP, cerebral blood flow (CBF) and cerebral oxygenation, studies on haemorrhagic and resuscitation, effects on microcirculation and metabolism, and comparisons with a variety of resuscitation solutions [1,2,15–20]. Animal experiments suggest that small-volume resuscitation with HTS solution may be beneficial in elevating CPP and CBF and decreasing ICP while maintaining haemodynamic stability following haemorrhagic shock associated with TBI. Studies by Shackford [15] also suggest that the use of HTS is associated with a reduction in the cerebral water content in the uninjured brain and an improvement in intracranial compliance. In rodent models of head injury, the use of HTS was associated with improved microcirculation and a reduction in endothelial cell adhesion, suggestive of an attenuation of the inflammatory cell response. As noted, HTS appeared to be better with respect to these parameters when compared with other solutions such as Hetastarch, Ringer’s lactate and Normal saline.

The efficacy of HTS with respect to ICP reduction has been compared with that of mannitol. At equiosmolar doses, HTS achieved a greater degree of reduction in ICP for a longer duration when compared to mannitol.

Human studies

There are published data supporting the use of HTS for resuscitation and ICP management (Table 2; 34–44). There are also data to suggest that HTS may be useful in the management of refractory intracranial hypertension. There are also preliminary data in children that suggest that outcomes may improve when HTS is used for osmotherapy. HTS has also demonstrated efficacy at reducing intracranial pressure in non-traumatic causes of cerebral oedema including subarachnoid haemorrhage (SAH), acute liver failure and stroke [21–23].

Results between studies are difficult to compare owing to differences in study design, differences in the concentration of HTS used and differing modes of administration of HTS (single dose vs. multiple doses vs. continuous infusions).

**HTS for refractory ICP in adult patients**

One of the fundamental challenges with comparing studies on refractory ICP is the definition of
<table>
<thead>
<tr>
<th>References</th>
<th>Patient population</th>
<th>Study design</th>
<th>Patients</th>
<th>Hypertonic fluid</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worthley and colleagues [12]</td>
<td>TBI with ICP resistant to conventional therapy</td>
<td>Case series</td>
<td>2</td>
<td>29.2% HTS (bolus)</td>
<td>Immediate decrease in ICP</td>
</tr>
<tr>
<td>Einhaus and colleagues [34]</td>
<td>TBI with ICP resistant to conventional therapy</td>
<td>Case report</td>
<td>1</td>
<td>7.5% HTS (bolus)</td>
<td>Immediate decrease in ICP by over 50%</td>
</tr>
<tr>
<td>Hartl and colleagues [35]</td>
<td>TBI with ICP resistant to conventional therapy observational</td>
<td>Prospective</td>
<td>6</td>
<td>7.5% HTS/HHES (250 mL)</td>
<td>Significant decrease in ICP and increase in CPP at 30 min</td>
</tr>
<tr>
<td>Schatzmann and colleagues [36]</td>
<td>TBI with ICP resistant to conventional therapy observational</td>
<td>Prospective</td>
<td>6</td>
<td>10% HTS (100-mL bolus)</td>
<td>42 episodes of raised ICP treated, mean ICP decreased in 43% (18 mmHg), effect lasted for a mean of 93 min</td>
</tr>
<tr>
<td>Horn and colleagues [37]</td>
<td>TBI and SAH and ICP resistant to conventional therapy</td>
<td>Prospective observational</td>
<td>10</td>
<td>7.5% HTS (2-mLkg⁻¹ bolus)</td>
<td>HTS effective in reducing ICP</td>
</tr>
<tr>
<td>Qureshi and colleagues [38]</td>
<td>Intracranial pathology and cerebral oedema</td>
<td>Retrospective</td>
<td>27</td>
<td>3% HTS to increase serum sodium</td>
<td>ICP controlled in TBI group; however, rebounded after 3–4 days</td>
</tr>
<tr>
<td>Shackford and colleagues [39]</td>
<td>HTS vs. LRS for fluid resuscitation TBI</td>
<td>Prospective randomized</td>
<td>34</td>
<td>1.6% HTS vs. LRS for SBP &lt; 90 mmHg</td>
<td>No difference in ICP. Groups poorly matched</td>
</tr>
<tr>
<td>Suarez and colleagues [40]</td>
<td>Increased ICP from TBI and other pathology</td>
<td>Retrospective</td>
<td>8</td>
<td>23.4% HTS (30 mL)</td>
<td>Significant decrease in ICP during first 3 h</td>
</tr>
<tr>
<td>Qureshi and colleagues [24]</td>
<td>Severe TBI</td>
<td>Retrospective case–control</td>
<td>36 cases, 46 controls</td>
<td>2% or 3% HTS (infusion) vs. 0.9% NaCl</td>
<td>No difference in outcome</td>
</tr>
<tr>
<td>Khanna and colleagues [27]</td>
<td>Severe head-injured children with ICP resistant to conventional therapy</td>
<td>Prospective observational</td>
<td>10</td>
<td>3% HTS to increase serum sodium</td>
<td>Decrease in ICP spike with hypernatremia. Peak Na 187 mmol L⁻¹ with 2 cases of renal failure</td>
</tr>
<tr>
<td>Peterson and colleagues [41]</td>
<td>Severely head-injured children</td>
<td>Retrospective</td>
<td>68</td>
<td>3% HTS until ICP &lt; 20 mmHg</td>
<td>Reduced ICP upon initiation of HTS therapy, no adverse effects. Observed only 3 deaths from uncontrolled ICP</td>
</tr>
<tr>
<td>Munar and colleagues [42]</td>
<td>TBI with raised ICP</td>
<td>Prospective observational</td>
<td>14</td>
<td>7.2% HTS (1.5 mL kg⁻¹)</td>
<td>Decrease in ICP associated with raised osmolality</td>
</tr>
<tr>
<td>Vailet and colleagues [43]</td>
<td>TBI with ICP refractory to conventional therapy</td>
<td>Prospective randomized</td>
<td>20</td>
<td>7.5% HTS vs. 20% mannitol 2 mL kg⁻¹</td>
<td>HTS more effective than mannitol for lowering ICP</td>
</tr>
<tr>
<td>Cooper and colleagues [13]</td>
<td>Prehospital resuscitation of patients with TBI</td>
<td>Prospective randomized</td>
<td>114 cases, 115 controls</td>
<td>7.5% HTS vs. Ringer’s lactate (250 mL)</td>
<td>No difference in mortality or neurological outcome</td>
</tr>
</tbody>
</table>

TBI: traumatic brain injury; ICP: intracranial pressure; HTS: hypertonic saline; SAH: subarachnoid haemorrhage; CPP: cerebral perfusion pressure.

Reproduced from White and colleagues [44].
refractory intracranial hypertension. Nevertheless, both anecdotal reports and small clinical trials have demonstrated a benefit in ICP reduction with the use of HTS for refractory intracranial hypertension. There was a correlation between reductions in ICP and elevations in serum osmolality but not with serum sodium (Na) concentration.

Does HTS improve survival in the ICU adult population with TBI?

It is important to note that convincing data of improved survival in both adults and children when HTS is used for the management of elevated ICP in isolated TBI are absent [24–27]. Support for the early administration of HTS solutions in brain injury came from post hoc analysis of patients with multi-trauma. Some of the original data came from Vasser and colleagues [28]. In a cohort of patients with multi-trauma undergoing helicopter transport, it was a prospective, double blind, randomized comparison of 250 mL of 7.5% HTS/dextran, compared to Ringer’s lactate solution. While significant differences in survival between the groups were not demonstrable, in a subsequent study the same group [29] compared different hypertonic solutions. Overall survival in the four treatment groups was not statistically different. Survival to hospital discharge in patients with Glasgow Coma Scale scores of 8 or less was associated with HTS treatment (34% survival in the HTS group vs. 12% lactated Ringer’s group).

Wade and colleagues [30] undertook a cohort analysis of individual patient data from previous prospective randomized double-blind trials. Study patients came from a variety of sources including emergency department, ambulance and helicopter and included both blunt and penetrating trauma. Treatment with HTS solutions led to an improved survival to discharge (odds ratios of 2.12 (P = 0.048)). Despite the apparent benefit of HTS, confounding cannot be excluded as the data come from a diverse group of patients and centres and the studies were not primarily designed to examine head-injury patients.

The most recent large-scale study investigating the use of HTS for the pre-hospital management of TBI comes from Cooper and colleagues [13]. They compared a 250 mL bolus of 7.5% HTS with lactated Ringers in 229 head-injured and hypotensive patients. Despite a small but statistically significant difference in Na concentration on admission (148 vs. 143 mmol L\(^{-1}\), P < 0.001), outcome measures were similar between the two groups (ICP-10 vs. 15 mm Hg, P = 0.08, CPP 73 vs. 69 mmHg, respectively). All survival data, including during admission, at 6 months and on discharge from hospital, were equal in both groups. They concluded that the routine use of HTS in pre-hospital treatment of TBI has no advantage over resuscitation with Ringer’s lactate.

One of the difficulties with studies on HTS in TBI is that most resuscitation studies are based on the assumption that a single dose of HTS will reduce mortality. Furthermore, the influence of associated injuries on mortality needs to be accounted for. Many patients die before admission to ICU. It is often not clear whether they die from injuries related to multi-trauma or TBI. Some investigators use albumin solutions as part of their resuscitation regimen. Subgroup analysis from the SAFE study demonstrated a possible link between the use of albumin and poor outcome following TBI [31]. Therefore, despite the negative findings of the Cooper study, it remains unclear as to whether HTS should be initiated in the resuscitation phase of multi-trauma, TBI patients.

Complications

The potential adverse effects of HTS include renal failure, osmotic demyelination syndrome (ODS), a rebound rise in ICP and various systemic complications including coagulopathies, volume overload and electrolyte abnormalities.

Renal failure

The use of mannitol has been traditionally associated with renal dysfunction when serum osmolality exceeded 30 mOsm kg\(^{-1}\). The link between the use of HTS and the development of renal failure remains tenuous. A single study has shown an association between HTS use and renal failure in burns patients associated with an increased mortality in the HTS cohort [32]. Data in TBI are scant. In a study of head-injured children (who received HTS), Khanna and colleagues [27] reported the development of ARF following HTS, although a large number of those patients had multi-organ failure. Thus the relative contribution of hypernatremia to renal failure is unclear.

Osmotic demyelination syndrome

This syndrome originally described in 1959 as a disease affecting alcoholics and the malnourished [33] was subsequently shown to be associated with rapid changes in serum Na in patients with chronic hyponatremia. No human studies of TBI have specifically examined the incidence of ODS following HTS administration.
Rebound increases in ICP
Rebound increases in ICP following mannitol use have been reported. While theoretical concerns exist about a similar process with the use of HTS, convincing data do not exist.

Systemic side-effects
Other systemic side-effects include the development of hypernatraemia, hyperchloraemia and non-anion gap acidosis. Fluid overload, hypokalaemia second-
ary to exaggerated diuresis and the need for a central venous cannula to administer HTS are other concerns.

References


43. Viallet R, Albanese J, Thomachot L et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. *Crit Care Med* 2003; 31: 1683–1687.