Effective treatment of refractory intracranial hypertension after traumatic brain injury with repeated boluses of 14.6% hypertonic saline

Clinical article

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Object. Normal intracranial pressure (ICP) and cerebral perfusion pressure (CPP) have been identified as favorable prognostic factors in the outcome of patients with traumatic brain injuries (TBIs). Osmotic diuretics and hypertonic saline (HTS) are commonly used to treat elevated ICP in patients with TBI; however, sustained effects of repeated high-concentration HTS boluses for severely refractory ICP elevation have not been studied. The authors’ goal in this study was to determine whether repeated 14.6% HTS boluses were efficacious in treating severely refractory intracranial hypertension in patients with TBI.

Methods. In a prospective cohort study in a neurocritical care unit, adult TBI patients with sustained ICP > 30 mm Hg for more than 30 minutes after exhaustive medical and/or surgical therapy received repeated 15-minute boluses of 14.6% HTS over 12 hours through central venous access.

Results. Response to treatment was evaluated in 11 patients. Within 5 minutes of bolus administration, mean ICP decreased from 40 to 33 mm Hg (30% reduction, p < 0.05). Intracranial pressure–lowering effects were sustained for 12 hours (41% reduction, p < 0.05) with multiple boluses (mean number of boluses 7 ± 5.5). The mean CPP increased 22% and 32% from baseline at 15 and 30 minutes, respectively (p < 0.05). The mean serum sodium level (SNa) at baseline was 155 ± 7.1 mEq/L, and after multiple boluses of 14.6% HTS, SNa at 12 hours was 154 ± 7.1 mEq/L. The mean heart rate, systolic blood pressure, blood urea nitrogen, and creatinine demonstrated no significant change throughout the study.

Conclusions. The subset of TBI patients with intracranial hypertension that is completely refractory to all other medical therapies can be treated effectively and safely with repeated boluses of 14.6% HTS rather than a one-time dose.

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Key Words • hypertonic saline solution • traumatic brain injury • intracranial pressure • refractory • intracranial hypertension • neurocritical care

E very year in the US, approximately 1.4 million people experience TBIs, resulting in more than 235,000 hospitalizations and 50,000 deaths.24,34 Patients who experience severe TBI have a high risk of subsequent injury not only from systemic trauma, but also from secondary ischemic brain injury due to elevated ICP and inappropriately low CPP. Neurosurgeons are often challenged to maintain normal ICP in the setting of TBI. Establishing critical care strategies to combat intracranial hypertension is a cornerstone of saving patients with critically severe TBI. The treatment course for many of these patients involves close neurological observation and ICP monitoring. The neurosurgical community has recently begun to accept aggressive medical strategies in nonsurgical TBI patients to manage elevated ICP. In the largest multicenter evaluation of survival predictors for TBI, Farahvar et al.11 recently reported a 64% lower risk of death in TBI patients who responded to ICP-lowering therapies. These authors reported that patients who maintained fewer hours of elevated ICP (> 25 mm Hg; p < 0.0001) and those without arterial hypotension on the 1st day of TBI (p = 0.001) have a significantly reduced rate of death 2 weeks after TBI. The study involved more than 1400 patients at 22 centers; 380 of whom were treated for ICP elevation > 25 mm Hg. Therefore, TBI patients with intracranial hypertension require aggressive ICP-lowering therapies that do not cause systemic hypotension early in the course of their hospitalization to provide the best possible chance for recovery.

In a subset of TBI patients, however, elevated ICP will become refractory to standard therapy. Patients in whom
Treating refractory intracranial pressure after TBI

standard medical and surgical therapies do not adequately lower ICP to allow for physiologically adequate CPP are at an extremely high risk for irreversible damage from brain ischemia, hemorrhage, and herniation syndromes, which could all lead to death. Although previous studies document the treatment of refractory elevation in ICP, the standards used to define refractoriness are quite low.19,21,29,41,43,48 Truly refractory intracranial hypertension is a stage of TBI progression in which treatments may become futile and patients usually succumb to their injuries. The use of hypertonic fluids and mannitol has allowed control of elevated ICP, but only recently has the use of highly concentrated (14.6% or 23.4%) HTS become a mainstay among neurosurgeons involved in the care of patients with TBI.2,14,15,19,27,28,30,36,41

Since the first reported successes with HTS therapy, its benefits have been touted in the literature.8,42 Hypertonic saline infusions at concentrations from 1.6% to 23.4% have shown powerful ICP-lowering effects,3 and recent data have suggested that HTS has intravascular volume replenishment properties as well as benefits at the cellular level.1,17,22 Although several studies have described the benefits of HTS in controlling elevated ICP and establishing normal CPP, relatively few studies have examined its use for the management of refractory ICP elevation.23,41,48 A literature search revealed that no investigators have monitored ICP, CPP, and other vital signs beyond 6 hours to determine whether the effects of HTS are sustained in the treatment of refractory intracranial hypertension.19,33,41 Moreover, we found studies on nonrepeated boluses of HTS but none utilizing the highest concentrations of HTS (14.6% or 23.4%) for the treatment of severely refractory elevated ICP.2,6,9,10,12–17,19,21,29,35–38,40,41,43,47 Furthermore, no studies have examined the efficacy of 14.6% HTS in the treatment of ICP.

In the current prospective cohort study, we evaluated the efficacy and safety of repeated boluses of 14.6% HTS as a treatment for patients with otherwise refractory intracranial hypertension in the setting of TBI. The effects of repeated boluses of 14.6% HTS were monitored for a period of 12 hours. We hypothesized that there would be a clinically significant reduction in ICP with each bolus of 14.6% HTS and that these effects would be prolonged over 12 hours if repeated boluses were administered.

Methods

Pilot Study

A concentration of 14.6% HTS was selected for this study as a compromise between the well-known 3% HTS and the highest concentration of 23.4% HTS. Provisionally, after proving that 14.6% HTS could be safely used to treat refractory ICP elevation, we would plan for a randomized controlled study of various administration methods of 23.4% HTS for use in elevated global ICP. After obtaining approval from the Pharmacy and Therapeutics Committee to use this concentration at our institution, we developed a protocol for 40-ml boluses of 14.6% HTS (Hospira, Inc.) as an alternative to mannitol in patients with TBI whose ICP remained completely refractory to conventional thera-
pies (see inclusion criteria). We obtained approval from the institutional review board to evaluate the use of 14.6% HTS in these patients with waiver of consent. During a pilot study (20 individual boluses) to assess preliminary safety and efficacy, the boluses contained 50 ml of 14.6% HTS. After efficacy and safety were demonstrated, 40-ml boluses were used because this was the amount within 1 vial of 14.6% HTS. After evaluation of the pilot study data demonstrated no significant difference between using boluses of 40 and 50 ml, all data were included in this cohort study.

Patient Population

Patients in the study were treated in the neurocritical care unit at our large academic teaching hospital and Level 1 trauma center. Eligible patients were older than 17 years of age, had experienced TBI, and subsequently demonstrated severely refractory intracranial hypertension. Intracranial pressure elevation was considered severely refractory if it was sustained at > 30 mm Hg for more than 30 minutes without response to the following ICP-lowering treatments: patient repositioning, relative hypocarbia (arterial blood 33 mm Hg < PaCO2 < 38 mm Hg) with an alkalotic pH, 3% saline boluses and continuous infusion, sedation (fentanyl, midazolam, or propofol) and paralytic agents (vecuronium or cisatracurium), normothermia (< 37.5°C), external ventricular drainage (if appropriate), and surgical intervention (if appropriate). Patients were excluded if they did not have a continuously recording ICP monitor, experienced renal failure (serum creatinine > 2.0 mg/dl or urine output < 30 ml/hour), had treatment with mannitol within the previous 24 hours, or had a SNa > 175 mEq/L or serum osmolality > 360 mOsm/kg. All patients were treated with standard medical therapy as dictated by the critical care team in this cohort study. At our institution, all patients are treated with best evidence as outlined in the Traumatic Brain Injury Guidelines.6 Therefore, profound hypotension, hypocapnia, and hypothermia were avoided.

Experimental Protocol

During the period between March 2009 and March 2011, patients with severely refractory ICP despite medical and surgical treatment for TBI were enrolled. The neurointensivist or the nurse with physician supervision administered individual boluses of 14.6% HTS over 15 minutes through central venous access. Each bolus administration of 14.6% HTS (not each patient) was considered an individual exposure for the purposes of this study. Repeated boluses were administered after 60 minutes only if the patient once again met the inclusion criteria for having refractory ICP. At infusion, the ICP, CPP, HR, and SBP were recorded. Serum sodium levels and serum osmolality were recorded per regular intensive care unit protocol, which was usually every 4–6 hours. Subsequent recordings of ICP, CPP, HR, and SBP occurred as follows: every 5 minutes for 30 minutes, every 15 minutes for 1 hour, and every hour for 12 hours. Evaluation of ICP and CPP changes restarted at Time 0 with each new infusion of 14.6% HTS. If ICP elevations continued past 12 hours, then 14.6% HTS boluses were administered again.

The primary outcome of this study was the efficacy

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of repeated 14.6% HTS boluses in lowering ICP in the setting of severely refractory intracranial hypertension. To determine this outcome, the preadministration ICP (Time 0) was compared with the 12-hour time point after bolus initiation. Secondary outcomes included evaluation of changes in CPP, HR, and SBP from Time 0 to each subsequent time point starting 5 minutes after initiation of the bolus. Treatment effect was measured as a statistically significant reduction in ICP at each recorded time point compared with the baseline ICP at the time of initiation of the bolus. Safety assessments included monitoring of hemodynamic status (HR and SBP), electrolyte status (SNa, potassium and chloride levels, and osmolality), renal function (blood urea nitrogen and creatinine levels), pCO₂, and pH levels (from blood gas readings).

Statistical Analysis

Prior to initiation of the prospective cohort study, a power analysis was performed. We predicted a 20% decrease in ICP from baseline (Time 0) at 12 hours. For a power of 0.8 (beta error of 20%), a total of 9 individuals would have been required. Inclusion of at least 56 doses raised the estimated power to 0.99. Normalization tests that screen the mean values of outcome variables across the time points were used prior to statistical analysis. Analysis of variance and post hoc Scheffé tests were performed on the primary outcome of ICP change from pre-HTS bolus levels. Values at all time points (starting 5 minutes after initiation of bolus) were compared with baseline values and with values at the 12-hour time point. Statistical analyses of secondary and safety outcomes, including CPP, HR, SBP, SNa, and serum osmolality, are also reported. Data reported as the means ± standard deviations were drawn from normal distributions. A Scheffé post hoc analysis was performed with the Bonferroni correction, and statistical significance was set at p < 0.05.

Results

During the 2-year accrual, 11 patients and 56 boluses were included in this study (Table 1). Two patients had craniectomies, 10 had external ventricular drains, and 1 had no surgical intervention besides placement of an ICP monitor. All surgical procedures were performed according to the attending neurosurgeon’s clinical decision making. The 14.6% HTS boluses were administered according to the inclusion/exclusion criteria regardless of surgical procedures. Only 2 patients (Cases 10 and 11) had surgical interventions after the initiation of the 14.6% HTS boluses. One of these patients survived, requiring decompression from a traumatic subdural hematoma, followed by replacement of a bone flap and ventriculoperitoneal shunt placement. The other patient did not survive because the family elected to withdraw care. Although 14.6% HTS boluses were delivered over 15 minutes, mean ICP measurements decreased from 40 ± 12 mm Hg at baseline to 33 ± 10 mm Hg within 5 minutes of bolus initiation (p < 0.05; Fig. 1). By 10 minutes, there was a reduction in mean ICP to 28 ± 9 mm Hg (p < 0.05) even though the bolus was not yet completed. Reduction of ICP compared with baseline continued through the first 60 minutes of recording (p < 0.05).

For patients in whom full 12-hour measurements were available, all had received multiple boluses of 14.6% HTS to maintain adequate ICP reduction (Fig. 2). Within the 12-hour timeframe, repeated administration of 14.6% HTS boluses was allowed if patients once again met the inclusion criteria. For these patients, a statistically significant reduction in ICP from baseline was maintained if repeated boluses were administered. The mean ICP was lowered by 41%, from 40 ± 12 mm Hg at baseline to 23 ± 9 mm Hg at 12 hours (p < 0.05).

There was no restriction on the number of additional boluses given as long as patients continued to meet the inclusion criteria. In the majority of boluses, prolonged ICP reduction effects were generated from repeated administration of additional boluses, with the overall duration of treatments being greater than 12 hours for multiple patients. By 4 hours after the first dose of 14.6% HTS, 10 doses of 14.6% HTS were repeated; by 8 hours after the first dose, 32 doses were repeated; and by 12 hours after the first dose, 42 doses were repeated. Thirteen single boluses of 14.6% HTS led to sustained ICP < 30 mm Hg for more than 12 hours. Of the total repeated boluses, 24 resulted in an ICP < 30 mm Hg for 12 or more hours and 3 resulted in ICP < 30 mm Hg for more than 72 hours. A mean of 7 ± 5.5 boluses were given per patient.

Cerebral perfusion pressure measurements showed similar trends and significance, with elevation in the mean CPP seen immediately from 60 ± 12 mm Hg at baseline to 63 ± 16 mm Hg at 5 minutes (p < 0.05; Fig. 1 lower). Within 20 minutes of bolus initiation, mean CPP had risen to 77 ± 13 mm Hg (p < 0.05). After the 5-minute time point, mean CPP did not drop below 70 mm Hg throughout the 12-hour recording period. After multiple boluses of 14.6% HTS by 12 hours, mean CPP was 70 ± 10 mm Hg (18% increase compared with baseline). Although various vasopressor agents were used to maintain appropriate CPP goals under our standard clinical CPP management protocol (goal CPP: 50–70 mm Hg), once 14.6% HTS boluses were administered and ICP was reduced, vasoactive agents used for the maintenance of mean arterial pressure and CPP were reduced (data not shown).

The mean HR and SBP did not change significantly during HTS infusions or for the 12-hour recording period thereafter (Fig. 3). Measurements of SNa and osmolality showed an appropriate increase of 2–3 mEq/L after initiation of each 14.6% HTS bolus; however, even after multiple boluses of 14.6% HTS, the mean SNa at all time points up to 12 hours did not change significantly (p > 0.05). The mean SNa at the initiation of 14.6% HTS boluses was 155 ± 7.1 mEq/L, and mean SNa at 12 hours after initiation of dosing was 154 ± 7.1 mEq/L (Fig. 4). The maximum SNa at the initiation of treatment with 14.6% HTS was 173 mEq/L in a single patient, but it counterintuitively decreased to 172 mEq/L at 10 hours. Serum osmolality showed similar trends, without a clinically or statistically significant rise in mean osmolality throughout the 12-hour recording period (p > 0.05): the mean serum osmolality at Time 0 (327 ± 11.5 mOsm/kg) and 12 hours after repeated boluses (327 ± 7.5 mOsm/kg) were not significantly different. The maximum serum osmolality initially after bolus in any patient was 358 mOsm/kg at 3 hours after administration of 14.6% HTS.
### TABLE 1: Demographic and clinical data from all patients included in the study

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Presentation &amp; Intracranial Diagnosis</th>
<th>Admission GCS Score</th>
<th>Minimum GCS Score</th>
<th>Discharge GCS Score</th>
<th>Alive at Hospital Discharge?</th>
<th>Total Boluses†</th>
<th>GOS Score at 6 Mos</th>
<th>GOS Score at 1 Year‡</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>25</td>
<td>bar fight, pushed down stairs; TBI; bilat occipital fractures; rt temporal fracture; subdural hematoma</td>
<td>13</td>
<td>3</td>
<td>15</td>
<td>Y</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>52</td>
<td>seizure &amp; fall; SAH; IPH; subdural hematoma</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>N</td>
<td>19</td>
<td>—</td>
<td>—</td>
<td>cardiopulmonary arrest due to TBI; w/drew care</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>20</td>
<td>skateboarding accident; rt IPH; lt subdural vs epidural</td>
<td>13</td>
<td>3</td>
<td>3</td>
<td>N</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>cardiopulmonary arrest due to severe brain injury &amp; pulmonary embolism; w/drew care</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>26</td>
<td>MVA w/ rollover; TBI; it basal ganglia IPH; rt SAH</td>
<td>6</td>
<td>3</td>
<td>11</td>
<td>Y</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>56</td>
<td>skateboarding accident; epidural hematoma; lt parietooccipital fracture; IPH</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>N</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>cardiopulmonary arrest due to TBI; w/drew care§</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>23</td>
<td>high-speed motorcycle crash; TBI; lt temporal bone fracture; subdural hematoma; SAH</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>N</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>cardiopulmonary arrest due to TBI; w/drew care</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>20</td>
<td>dirt bike accident; TBI w/ diffuse axonal injury</td>
<td>3</td>
<td>3</td>
<td>11</td>
<td>Y</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>20</td>
<td>jumped out of moving vehicle traveling approximately 40 mph; SAH; bilat parietal fracture; subdural hemorrhage; basilar skull fractures; multiple abrasions &amp; lacerations to head; atlantooccipital disassociation</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>N</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>cardiac death (donor)</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>68</td>
<td>fell backwards down 2 steps, hitting back of head; multiple traumatic cerebral contusions; SAH</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>N</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>cardiopulmonary arrest due to TBI; w/drew care</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>22</td>
<td>unrestrained passenger in motor vehicle rollover, ejected; TBI w/ diffuse cerebral edema; multiple intraparenchymal contusions; subdural hematoma</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>N</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>cardiopulmonary arrest due to TBI; w/drew care; surgery after 14.6% HTS initiation; decompressive hemicraniectomy &amp; Trach/Peg after 14.6% HTS administration</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>39</td>
<td>fell 12 ft from a balcony; cerebellar hemorrhage; TBI; subdural hematoma</td>
<td>12</td>
<td>3</td>
<td>8</td>
<td>Y</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

* GCS = Glasgow Coma Scale; IPH = intraparenchymal hemorrhage; MVA = motor vehicle accident; N = no; SAH = subarachnoid hemorrhage; Trach/Peg = tracheostomy and percutaneous endoscopic gastrostomy; VPS = ventriculoperitoneal shunt; Y = yes.
† Of the 77 total boluses given, 56 met the inclusion criteria for the study.
‡ Glasgow Outcome Scale scores were only available for Cases 1, 4, 7, and 11.
§ Died because of extensive traumatic injury shortly after first dose of HTS.
ANOVA, compared with Time 0). No re-
lasted through 60 minutes (†p < 0.05, ANOVA, compared with Time
CPP from baseline was noted within 5 minutes of bolus infusion, which
peated boluses were given within 60 minutes of previous bolus.
compared with Time 0).
ANOVA, compared with Time 0; *p < 0.05, ANOVA and Scheffé test,
minutes of bolus initiation, which lasted through 60 minutes (†p < 0.05,
administration of repeated boluses of highly concentrated HTS
in a population of patients with completely refractory ICP
elevation has yet to be documented in the literature. Our
study suggests that this method of controlling severely re-
fractory ICP is not only safe, but also highly effective.
In the late 1980s, interest in HTS was generated based
on a few favorable case reports. Since then, multiple hu-
man and animal studies have supported the beneficial ef-
effects of HTS therapy. In an animal study, da Silva et al.10
used a rabbit model to induce a potentially lethal increase
in ICP by inflating an intracranial balloon, then compared
equimolar doses of 10% HTS and 20% mannitol as acute
treatment. Animals in the study survived, on average, 53
minutes with an ICP of 50 mm Hg without treatment.
Animals treated with HTS showed statistically significant
lowering of ICP and elevation of CPP as well as a survival
benefit. Qureshi and colleagues31,32 have published several
studies on the use of a single bolus of 23.4% HTS to re-
verse unilateral hematoma-induced transtentorial hernia-
ion in a dog model. They also demonstrated impressive
increases in regional cerebral blood flow within both the
ipsilateral and contralateral cortex as well as the thalamus,
compared with significant decreases in regional cerebral
blood flow before treatment.32 One important aspect of the
study by Qureshi et al. is that a bolus of highly concentrat-
ed HTS was able to reverse a potentially life-threatening
condition, namely, transtentorial herniation. These ani-
mal models share similarities with our population of pa-
tients with severely refractory intracranial hypertension,
in which clinical signs indicated that all patients enrolled
would have died of uncontrollable ICP.
Hypertonic saline boluses of 23.4% have also been shown
to reverse transtentorial herniation in a retrospec-
tive human study by Koenig et al.23 Human studies on
HTS treatment vary with respect to the concentration
of saline used (1.6%–23.4%) and the volume of infusion
(30–250 ml), but in 2009, Strandvik40 evaluated 26 clini-
cal trials that utilized HTS for the treatment of elevated
ICP in brain injury and found the most common treat-
ment concentration studied was 7.5% saline in 2-ml/kg
bolus doses. Of these 26 studies, 15 specifically examined
bolus periods for each bolus of 14.6% HTS administered. Se-
rum values of potassium, chloride, and bicarbonate were
also assessed for clinically significant changes before and
after bolus administration (Table 2). No statistically or
clinically significant differences were noted in the serum
blood urea nitrogen, creatinine, potassium, chloride, or bi-
carbonate levels throughout this study. No patients were
prevented from receiving 14.6% HTS boluses because of
S_{Na} or serum osmolality levels.
Outcomes were measured using the GOS at 6 and 12
months postdischarge (Table 1). The GOS score for each
of the 4 patients who survived was between 3 and 5 at 6
months and again at 12 months. Two of the 4 patients im-
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unchanged in 2 patients (GOS Score 3 to 3 and 5 to 5). The
GOS score did not worsen in any of these patients after
discharge from the hospital.

**Discussion**

The major finding of this study is that repeated bolus-
es of highly concentrated (14.6%) HTS can treat severely
refractory intracranial hypertension, even in the setting of
malignant ICPs of 40–50 mm Hg and high pre-dose S_{Na}
and osmolarities. Although the use of single-dose, highly
concentrated osmotic agents has been described for other-
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istration of repeated boluses of highly concentrated HTS
in a population of patients with completely refractory ICP
was noted within 5 minutes of bolus infusion, which lasted through 60 minutes (†p < 0.05, ANOVA, compared with Time 0). Lower: Statistically significant increase in CPP from baseline was noted within 5 minutes of bolus infusion, which lasted through 60 minutes (‡p < 0.05, ANOVA and Scheffé test, compared with Time 0).

![Graphs showing immediate response of ICP and CPP to administration of a bolus of 14.6% HTS](image-url)

**Fig. 1.** Graphs showing immediate response of ICP and CPP to administration of a bolus of 14.6% HTS (means ± standard deviations, 56 doses). Fifteen-minute bolus infusion started at Time 0. Upper: Statistically significant decrease in ICP from baseline was noted within 5 minutes of bolus initiation, which lasted through 60 minutes (‡p < 0.05, ANOVA, compared with Time 0; *p < 0.05, ANOVA and Scheffé test, compared with Time 0). Lower: Statistically significant increase in CPP from baseline was noted within 5 minutes of bolus infusion, which lasted through 60 minutes (‡p < 0.05, ANOVA, compared with Time 0; *p < 0.05, ANOVA and Scheffé test, compared with Time 0). No repeated boluses were given within 60 minutes of previous bolus.

Serum values of blood urea nitrogen and creatinine were recorded as a marker of renal function. These values were not only used for inclusion criteria as stated above, but were also monitored throughout the pre- and postbolus periods for each bolus of 14.6% HTS administered. Serum values of potassium, chloride, and bicarbonate were also assessed for clinically significant changes before and after bolus administration (Table 2). No statistically or clinically significant differences were noted in the serum blood urea nitrogen, creatinine, potassium, chloride, or bicarbonate levels throughout this study. No patients were prevented from receiving 14.6% HTS boluses because of $S_{Na}$ or serum osmolality levels.

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ment concentration studied was 7.5% saline in 2-ml/kg
bolus doses. Of these 26 studies, 15 specifically examined
HTS in patients with TBI. Five were case-control stud-
ies14,17,21,28,36 that showed that HTS boluses could signifi-
cantly reduce ICP in patients with elevated ICP refractory
to mannitol therapy. Conversely, Shackford et al.37 report-
ed that HTS is not more effective than lactated Ringer so-
lution in lowering ICP in a group of 34 adults with TBI;
however, it is important to note that the HTS group had
more severe head injuries as a potential confounding vari-

![Graph showing immediate response of ICP and CPP to administration of a bolus of 14.6% HTS](image-url)
Fig. 2. Graphs showing sustained response of ICP and CPP to repeated boluses of 14.6% HTS (means ± standard deviations). **Upper:** Although a slight rebound was noted after the 60-minute time point, repeated boluses of 14.6% HTS provided sustained ICP-lowering effects for the duration of the 12-hour experimental period (*p < 0.05, comparing each time point with Time 0). **Lower:** Similar results were seen in CPP improvement with repeated boluses of 14.6% HTS (*p < 0.05, comparing each time point with Time 0). Despite a slight rebound lowering of CPP after 60 minutes, sustained CPP averaged between 70 and 75 mm Hg for the 12-hour experimental period.

Fig. 3. Graph demonstrating hemodynamic status during repeated boluses of 14.6% HTS represented by HR (**upper**) and SBP (**lower**) over a 12-hour experimental period (means ± standard deviations). No statistically or clinically significant variation in SBP or HR was noted during repeated boluses.
able, and thus making these conclusions weak. Despite this and other clinical and experimental studies that have reported mixed data regarding the efficacy of HTS in the treatment of elevated ICP, other scientifically rigorous studies have shown beneficial effects with few side effects or detrimental consequences. Fisher et al.\(^\text{12}\) and Simma et al.\(^\text{38}\) showed that HTS is more effective than normal saline or lactated Ringer solution in lowering ICP in children. Harutjunyan and colleagues\(^\text{15}\) also showed an increase in CPP, which was used as a surrogate marker for brain perfusion. Francony et al.\(^\text{13}\) revealed the efficacy of HTS in significantly lowering ICP and increasing CPP but did not demonstrate superiority to equimolar doses of mannitol.

In the most recent and largest meta-analysis of published data evaluating the efficacy of HTS in treating elevated ICP, Mortazavi and colleagues\(^\text{27}\) reviewed 36 articles on the subject. Although inconsistent protocols and limited data made conclusive recommendations difficult, these authors importantly concluded that the literature supports HTS, either bolus or infusion, as superior to mannitol in lowering elevated ICP.

Mannitol administered with the hope of reducing ICP is considered the mainstay of potentially life-saving measures for clinically refractory intracranial hypertension by many, if not all, neurointensivists and neurosurgeons. Based on past empirical experience and numerous published studies, the beneficial effects of mannitol have often been short lived and potentially caused refractory elevation in ICP worse than originally encountered.\(^\text{2,7,10,13–15, 17,18,20,22,26,27,31,39,43,45,46,49}\) Potentially lethal rebound intracranial hypertension as well as systemic hypotension has been reported with mannitol administration. Concomitant dangerous decreases in CPP, which can lead to brain tissue ischemia, stroke, and even death, argue against the use of mannitol alone in the setting of elevated ICP.

**TABLE 2: Serum laboratory recordings measured before and after administration of each bolus of 14.6% HTS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prebolus</th>
<th>Postbolus</th>
<th>% Change*</th>
</tr>
</thead>
<tbody>
<tr>
<td>renal function (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>blood urea nitrogen</td>
<td>9.3</td>
<td>9.6</td>
<td>3.23</td>
</tr>
<tr>
<td>creatinine</td>
<td>0.65</td>
<td>0.63</td>
<td>−3.54</td>
</tr>
<tr>
<td>other electrolytes (mm/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K⁺</td>
<td>3.49</td>
<td>3.48</td>
<td>−0.29</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>121.8</td>
<td>129.2</td>
<td>6.08</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>20.5</td>
<td>20.1</td>
<td>−1.95</td>
</tr>
</tbody>
</table>

* None of the changes were statistically significant.
Ours is the only reported study that combines the use of repeated boluses of highly concentrated HTS for the treatment of severely refractory intracranial hypertension in patients who have TBI with monitoring of the ICP-lowering effects for a period of 12 hours. Twelve hours of highly meticulous vital sign, ICP, and CPP recordings is the longest that we could find in the literature. Nevertheless, the study has some limitations. It is a nonrandomized nonblinded study, and two different volumes of 14.6% boluses were included in the final analysis, although no significant differences were realized between boluses in the pilot portion of the study. Despite the large number of individual boluses to analyze, the number of patients in the study might be considered small (11 patients and 56 boluses); however, given the statistical power that was achieved in this very specific patient population—namely, TBI patients in whom all traditional methods to lower ICP had been exhausted—this number could be considered adequate. In the future, more detailed outcome studies on this patient population along with randomization of treatment methods, including different methods of HTS bolus administration, would be helpful in determining the superiority of various treatments.

Conclusions

We have demonstrated for the first time that patients with severely refractory intracranial hypertension from TBI can be treated effectively and safely with repeated boluses of 14.6% HTS and that ICP-lowering effects after repeated boluses are maintained for extended periods of time (12–72 hours). Furthermore, ICP-lowering effects can be achieved with HTS even in the face of substantially elevated S na+ and osmolality levels. A concentration of 23.4% HTS is the most commonly used highly concentrated HTS at this time, but studies of 23.4% HTS is the most commonly used highly concentrated HTS at this time, 27, 31, 32, 44 but studies of 23.4% HTS is the most commonly used highly concentrated HTS at this time, and CPP recordings is the longest that we could find in the literature. Nevertheless, the study has some limitations. It is a nonrandomized nonblinded study, and two different volumes of 14.6% boluseswere included in the final analysis, although no significant differences were realized between boluses in the pilot portion of the study. Despite the large number of individual boluses to analyze, the number of patients in the study might be considered small (11 patients and 56 boluses); however, given the statistical power that was achieved in this very specific patient population—namely, TBI patients in whom all traditional methods to lower ICP had been exhausted—this number could be considered adequate. In the future, more detailed outcome studies on this patient population along with randomization of treatment methods, including different methods of HTS bolus administration, would be helpful in determining the superiority of various treatments.

Critical revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hoesch. Statistical analysis: Eskandari, Filtz.

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