Int Surg 2016;**101**:361–366
DOI: 10.9738/INTSURG-D-16-00131.1

Traumatic Brain Injury: Bolus Versus Continuous Infusion of 3% Hypertonic Saline

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Hypertonic saline (HTS) is used as an adjunct in the conservative management of increased intracranial pressure; however, the ideal concentration or route of delivery is unknown. Our objective was to assess whether there is a difference in route of delivery, bolus versus infusion, of 2% versus 3% HTS in patients with traumatic brain injury. The study comprises a retrospective analysis of all patients who sustained traumatic brain injury resulting in increased intracranial pressure that required HTS from January 2012 to December 2014. We examined time to therapeutic serum sodium concentration greater or equal to 150 mEq; incidence of ventriculostomy placement and neurosurgical intervention for refractory intracanial hypertension; and disability burden among the different infusates and route of delivery. A total of 169 patients received either 2% or 3% HTS, given as a bolus or continuous infusion. Patients had an average age of 61.4 years; 100 patients (59.2%) were male and 69 (40.8%) were female; 62 patients were taking either an antiplatelet or anticoagulant agent. Infusion of 3% saline was associated with the shortest interval to reaching a therapeutic level at 1.61 days ($P = 0.024$). There was no statistically significant difference between placement of a ventriculostomy among the bolus and infusion groups of 3% normal saline (NS) ($P = 0.475$). However, neurosurgical intervention was less prevalent in those receiving 3% infusion ($P = 0.013$). Infusion of 3% HTS was associated with a more rapid increase in serum sodium to therapeutic levels. Neurosurgical intervention for refractory hypertension was less prevalent in the 3% NS infusion group.

Key words: Intracranial hypertension – Hypertonic saline – Traumatic brain injury

During the golden hour following the initial trauma, key steps in the management of traumatic brain injury (TBI) can avoid secondary insult that follows from increased intracranial pressure (ICP). In the United States, among all age groups, TBI is the leading cause of trauma-related

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deaths, accounting for more than 60% of trauma-related deaths.[1] Mortality correlates with intracranial hypertension ranging from 18.4% for patients with pressures less than 20 mmHg to 55.6% for those with pressures greater than 40 mmHg. Those who survive the trauma burden often sustain various degrees of disability. Each year approximately $60 billion is spent for ongoing care of more than 80,000 persons who have varying degrees of TBI.[2] Goals of treatment are targeted at decreasing cerebral swelling, avoiding herniation and ischemia. Intensive care unit admissions for these patients focus on early recognition of changes in Glasgow Coma Scale (GCS), ICP and hemodynamics. Pharmacologic agents, such as hypertonic saline (HTS) and mannitol, are employed to manage intracranial hypertension along with the help of neurosurgical interventions. HTS is used in many different concentrations, ranging from 2% to 23.4% administered as bolus or infusion.[3]

There are no prospective randomized controlled trials exploring the use of HTS in the setting of TBI. The Brain Trauma Foundation cannot provide strong recommendations for the use of HTS over mannitol in the setting of elevated intracranial hypertension, despite its frequent use. Pediatric societies, as a level II recommendation, endorse the use of HTS.[2,4] To our knowledge, there are no studies that have specifically assessed the therapeutic value of bolus versus infusion routes of delivery for HTS. We performed a retrospective review of all patients who received 2% and 3% saline for elevated ICP. The route and concentration administered were examined to see which combination reached therapeutic range of serum sodium (150–159 mEq) in the shortest amount of time. Secondary outcomes that were assessed included change in GCS, neurosurgical intervention, and disposition after hospitalization.

Methods

NYU Lutheran functions as a Level I trauma center and a designated stroke center. A retrospective analysis was performed examining all patients who received HTS, 2% or 3%, from January 2012 through December 2014. Institutional Review Board approval was obtained for a retrospective chart analysis for prospectively collected data. A total of 169 patients were identified who had sustained an injury that resulted in elevation of ICP. To increase the power of this analysis, a decision was made to include all patients who sustained a TBI regardless of mechanism of injury. Patients were admitted under medical or surgical service pending their etiology. There is no definitive protocol established at our institution for the use of HTS. Use of 2% or 3% saline was under the discretion of the neurosurgeon and neurologist in coordination with the medical/surgical intensivist. Generally, boluses were administered at 4- to 6-hour intervals versus continuous infusion of HTS infusate from initiation to termination of therapy. All patients were managed according to the recommended guidelines for patients with TBI. Intensive care unit admission with continuous hemodynamic monitoring, hourly neuro checks, ventilatory support when indicated, and management of medical conditions or trauma burden was performed. Neurosurgery was consulted in all cases of intracranial hemorrhage regardless of etiology. Blood products were transfused in setting of previous antiplatelet/anticoagulant agent use as well as hypotension secondary to hemorrhagic shock. Serial computed tomography scans were performed on admission and at 4- to 6-hour intervals to monitor progression of intracranial hemorrhage. A serum sodium concentration between 150 and 159 mEq was defined as therapeutic, and administration of HTS was held when sodium was greater than 160 mEq or serum osmolality was greater than 320. This was based on common practice at our institution because no literature consistently supports a particular range of serum sodium. Statistical analysis of the resulting data set was performed with SPSS statistical software. Time to return of laboratory serum sodium concentration >150 mEq from admission to hospital was assessed for patients who received 2% and 3% HTS. Regression analysis was used to examine the relationship between route (bolus versus infusion) and concentration of HTS (2% versus 3% HTS), and degree of neurosurgical intervention. Neurosurgical intervention was targeted at treating refractory intracranial hypertension with placement of a ventriculostomy or decompressive surgery when indicated. Analysis of variance was used to compare both posthospitalization disposition location and GCS trend to infusate.

Results

A total of 169 patients received either 2% or 3% HTS, given as a bolus or continuous infusion; average age was 61.4 years; and 100 patients (59.2%) were male and 69 (40%) were female. Table 1 demonstrates the comorbidities that existed in our patient population:

Table 1 Patient demographics

Epidemiology	No. (%)
Male	100 (59.2)
Female	69 (40.8)
Average age, y, ±SD	61.4 ± 20.6
HTN	103 (60.9)
DM	40 (23.7)
CHF	56 (33.1)
CAD/Afib	56 (33.1)
CKD/ESRD	8 (4.7)
HLD	46 (27.2)
Antiplatelet/anticoagulant	62 (36.7)
Systolic blood pressure <90 on admission	6 (3.6)
Transfused blood products on admission	15 (8.9)

Afib, atrial fibrillation; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HLD, hyperlipidemia; HTN, hypertension.

60.9% of the patients suffered from hypertension. Antiplatelet and anticoagulant use, including clopidogrel, full-dose aspirin, warfarin, and rivaroxaban, were analyzed; 62 of the patients took one of the two agents for their comorbid conditions. On presentation, 6 of 169 patients presented hypotensive with systolic blood pressures below 90 mmHg; however, only 15 patients required blood product transfusion for purposes of hemorrhagic shock and antiplatelet/anticoagulant use. The etiologies for elevated intracranial hypertension are represented in Table 2.

On admission, the mean GCS for the patients who received 2% HTS was 12 and 10.77 for bolus and infusion, respectively. The mean GCS for patients receiving 3% HTS was 8.28 and 9.6 for bolus and infusion, respectively (Table 3). Examining the effect of HTS on GCS change on hospital day 1, it was noted that the administration of HTS as a bolus versus infusion in both the 2% (–0.33 versus –0.49) and 3% (–0.225 versus –0.36) HTS groups was

Table 2 Distribution of injury profile associated with elevated ICPs

Mechanism	No. (%), n = 169
MVA	8 (4.7)
Assault	10 (5.9)
Hemorrhagic stroke	54 (32)
Fall	25 (14.8)
Coiling	4 (2.4)
Ischemic stroke	34 (20.1)
Metabolic	7 (4.1)
Pedestrian struck	12 (7.1)
Ischemic stroke converted to hemorrhagic stroke	10 (5.9)
Other	5 (3)

MVA, motor vehicle accident.

Table 3 Mean Glasgow Coma Scale (GCS) on admission for the corresponding infusates reviewed

Infusate	GCS on admission, mean	No. (n = 168)
Bolus 2%	12 ± 4.38	6
Infusion 2%	10.77 ± 4.22	66
Bolus 3%	8.28 ± 4.36	43
Infusion 3%	9.6 ± 4.8	53

associated with a smaller drop in mean GCS ($P = 0.984$). This difference was also seen on hospital days 3 and 7, but it was not statistically significant as well.

Time to serum sodium concentration greater than 150 mEq from admission was assessed to determine both the infusate and route that reached the therapeutic level in the shortest amount of time. Infusion of 3% saline was associated with the shortest interval to reaching a therapeutic level at 1.61 days ($P = 0.024$), as seen in Fig. 1.

The disability burden is reflected through the location of discharge: death, home, or rehab/skilled nursing facility (Fig. 2). As depicted there were no statistically significant differences between the 2% and 3% normal saline (NS) groups, for both infusion and bolus administrations.

The effect on reducing neurosurgical intervention, including ventriculostomy placement, is depicted in Fig. 3. It was decided that only patients who received 3% HTS were examined, because they had the lowest GCS scores on admission. There was no statistically significant difference between placement of a ventriculostomy among the bolus and infusion groups ($P = 0.475$). However, neurosurgical

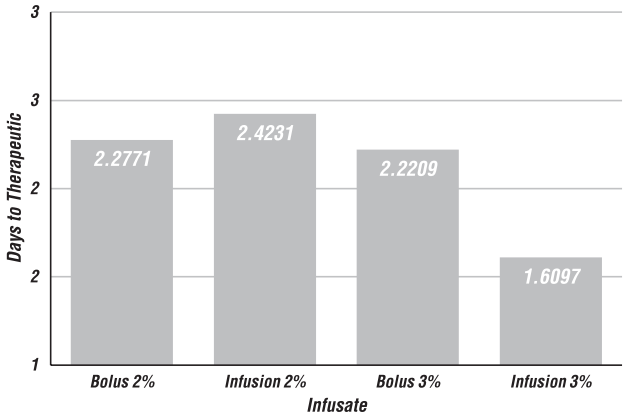

Fig. 1 Infusion of 3% NS reached serum Na^+ in 1.61 days from time of admission ($P = 0.024$).

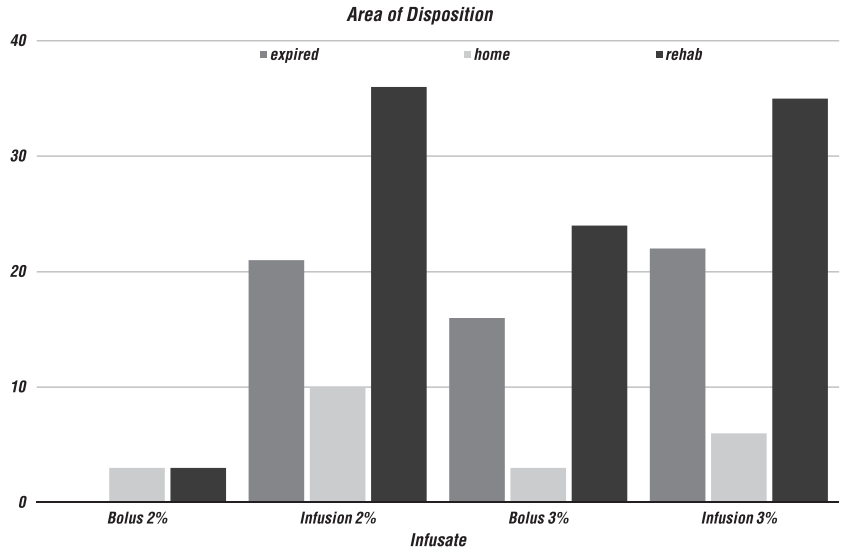

Fig. 2 Location of discharge (home, rehabilitation/skilled nursing facility, expiration) versus infusate and route of IV versus bolus. No statistically significant differences were seen ($P = 0.08$).

intervention was less prevalent in those receiving 3% infusion ($P = 0.013$). Performing a logistic regression analysis accounting for use of antiplatelet and anticoagulant agents, there was a persistent association between the degree of neurosurgical intervention and use of 3% NS as a bolus, with an odds ratio of 3.794 ($P = 0.005$).

Discussion

Etiologies for intracranial hypertension include, but are not limited to, TBI, ischemic stroke, neoplasm, infection, liver dysfunction, and aneurysmal rupture. Approximately 1.4 million people every year sustain a TBI, resulting in 235,000 hospitalizations and 50,000 deaths.[5] Mortality rate is directly proportional to episodes of hypotension and hypoxia in the setting of TBI, reaching 75%. The use of osmotic agents is a key component of nonsurgical management of TBI. The effectiveness depends on blood-brain barrier integrity, reflection coefficient of osmotic agent, and osmotic gradient created.[6] The use of HTS as osmotic therapy to target elevated intracranial hypertension has an effect on both ICP and cerebral perfusion pressure. The effect of lowering ICP is believed to result from its capacity to lower brain water. Additionally, HTS induces a change in blood viscosity that is hypothesized to affect cerebral blood flow, increasing cerebral perfusion pressure in areas that are hypoperfused at baseline.[7] Hyponatremia can result in the setting of TBI secondary to cerebral salt-wasting syndrome or inappropriate antidiuretic hormone secretion. This leads to brain ischemia resulting from swelling of perivascular astrocytes and an increase in the brain-contusion volume and ICP.[8]

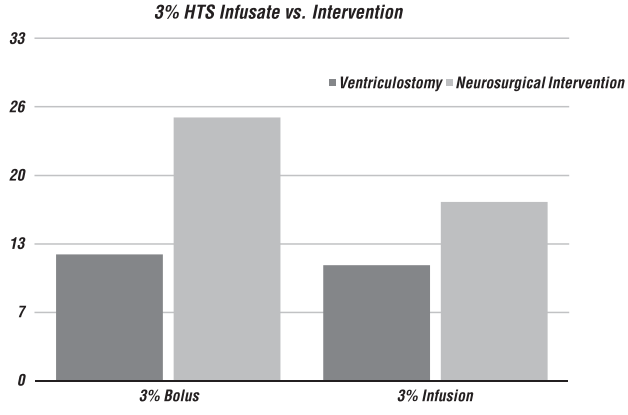

Fig. 3 No difference seen in ventriculostomy placement between 3% bolus versus infusion. Neurosurgical intervention more likely in 3% bolus group ($P = 0.013$). Performing a logistic regression analysis accounting for use of antiplatelet and anticoagulant agents, there was still a higher degree of neurosurgical intervention, with an odds ratio of 3.794 ($P = 0.005$).

There are studies that show a reduction in ICP, and improvement in cerebral perfusion pressure (CPP), from repeated boluses of HTS (1.6%–23.4%).[5,6] Similarly, continuous infusion of HTS in TBI patients has been shown to increase natremia and osmolarity, decrease intracranial hypertension, and improve CPP.[8–15] Administration of HTS as either a continuous infusion or bolus has been proven to be efficacious in the setting of intracranial hypertension; however, the most optimal route and concentration is unknown due to lack of random-

ized controlled trials. We performed a retrospective analysis on prospectively collected data at our institution, which serves as both a designated stroke center and trauma center. We examined all patients from January 2012 through December 2014 who received either 2% or 3% HTS. It was determined that 3% saline administered as a continuous infusion reached therapeutic levels in the shortest period of time from admission, at 1.61 days. There was no bolus given prior to starting the infusion.

Neurosurgical intervention can assist in the management of refractory hypertension. In our patient population of 169 patients, 42 (43.8%) underwent decompressive surgery. Patients who received 3% NS had a lower GCS on admission, 8.28 versus 9.6 for bolus and infusion, respectively. Bolus of 3% NS saline was associated with an increased rate of neurosurgical intervention compared with infusion ($P = 0.013$). There was a logistic regression analysis performed taking into account the use of antiplatelet and anticoagulant agents. Despite their presence there was a higher rate of neurosurgical intervention seen in the bolus group, with an odds ratio of 3.794 ($P = 0.005$). There was no statistically significant difference in the placement of a ventriculostomy in the two groups, as seen in Fig. 3.

TBI can result in significant impairment, leading to long-term placement in a rehabilitation or skilled nursing facility. Figure 2 depicts the location to which the patients were discharged, as well as the number of people that died. There was no statistically significant difference among the bolus and infusion groups of 3% NS. To note, the bolus group did have a lower mortality of 16 patients versus 22 in the infusion group; however, this was not statistically significant.

Conclusion

The Brain Trauma Foundation currently cannot advise for or against the use of HTS in the setting of elevated ICP in the adult population. There currently are no randomized controlled trials to date, and data are lacking on ideal concentration and route of delivery of HTS. In our retrospective review we found a shorter time to therapeutic sodium levels, indicating faster time to treatment in the infusion of 3% NS. Additionally, need for neurosurgical intervention to control refractory intracranial hypertension was less in the infusion group. There were no statistically significant differences in mortality and location to which they were discharged. There are a number of limitations in this study: 1) no uniform patient population, because all patients regardless of etiology were grouped together to increase the power of this study; 2) being a retrospective analysis, we used time from admission to reported lab values as time to therapeutic levels; 3) there is no established protocol for administration of hypertonic saline at our institution, thus confounding variables, such as use of other agents to increase diuresis, were not accounted for; and 4) the sodium level that was used as therapeutic was selected based on common practice at our institution and available literature.

We conclude that there is a difference in outcomes regarding the route of delivery of HTS in the treatment of TBI patients. Further studies need to be performed, with a larger sample size, to examine the ideal route of administration of HTS as well as the most efficacious and safest concentration to use.

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