Comparison of Weight-Based Dosing versus Fixed Dosing of 23.4% Hypertonic Saline for Intracranial Pressure Reduction in Patients with Severe Traumatic Brain Injury

Kirsten Busey, Jason Ferreira, Petra Aldridge, Marie Crandall, Donald Johnson
Departments of Pharmacy and Surgery, University of Florida Health Jacksonville, Center for Health Equity and Quality Research, University of Florida Health Jacksonville, Jacksonville, Florida, USA

Abstract

Context: Hypertonic saline (HTS) is a pharmacologic therapy used in patients with severe traumatic brain injuries to decrease intracranial pressure (ICP) associated with cerebral edema. Aims: The purpose of this study was to compare ICP reduction between fixed doses of 23.4% HTS and weight-based doses. Setting and Design: This was a retrospective study that included adult patients at a level 1 trauma center who had nonpenetrating traumatic brain injury, an ICP monitor, and received at least one dose of 23.4% HTS. Subjects and Methods: Doses were classified as either high weight-based (>0.6 ml/kg), low weight-based (<0.6 ml/kg), or standard fixed dose (30 ml). Only doses given within 5 days post-injury were evaluated. Percent reduction in ICP was compared pre- and post-dose between dosing groups, and each dose was evaluated as a separate episode. Statistical Analysis: The primary and secondary endpoints for the study were analyzed using mixed-model, repeated-measures analysis of covariance. Results: A total of 97 doses of HTS were evaluated. The primary endpoint of ICP reduction showed a 42.5% decrease in ICP after the administration of a high weight-based dose, a 36.7% reduction after a low weight-based dose, and a 31.5% reduction after a fixed dose. There was no significant relationship between dose group and percent change in ICP ($P = 0.25$). A sub-analysis of doses received within 48 h postinjury found a significant relationship between both dose group and percent change in ICP, and initial ICP and percent change in ICP ($P = 0.04$, and $<0.0001$ respectively). Conclusions: Our data did not show a significant difference between fixed- and weight-based doses of 23.4% HTS for ICP reduction.

Keywords: Hypertonic saline, intracranial pressure, traumatic brain injury

INTRODUCTION

Traumatic brain injuries are a leading cause of morbidity and mortality in the United States, with the Center for Disease Control estimating 57,000 deaths for the nearly 1.7 million traumatic brain injuries that occur annually.[1] Traumatic brain injury (TBI) can have a multitude of effects on an individual, including the changes in behavior, judgment, speech, and function, which can require ongoing care and rehabilitation. In 2000, the combined direct and indirect costs of TBI treatment and recovery in the United States were approximated to be $76.5 billion.[2] The primary insult to the brain sustained after severe TBI can result in elevated intracranial pressure (ICP), leading to ischemia and consequent secondary injury. In an attempt to decrease the extent of secondary injury and improve neurological outcomes, therapy with hyperosmolar agents is frequently employed to relieve cerebral edema and restore blood flow to hypoxic areas.[3]

Currently, the guidelines for the management of severe TBI published in 2017 list mannitol (0.25–1 g/kg) as a Level II recommendation for the reduction of elevated ICP.[4] The Brain Trauma Foundation Guidelines are unable to recommend the use of hypertonic saline (HTS) for ICP reduction due to the...
lack of strong clinical evidence to support its efficacy and establish usage protocols. Despite the lack of randomized clinical trials, osmotic therapy with HTS has been associated with an effective ICP reduction in multiple smaller studies[1,4,5] HTS has also shown utility in patients who developed elevated ICP resistant to mannitol.[1,2] The dosing of HTS has been highly variable in studies evaluating its use in head injury patients.[7-11] In 1988, the first documented use of HTS included the case reports of one-time HTS doses to treat two head injury patients who had developed elevated ICP refractory to mannitol therapy.[12] The calculated doses were based on the need to establish an osmolar gradient of 10–30 mOsm between the serum and intracranial vault to mobilize and extract intracranial free water. More recent studies have used 30 ml of 23.4% HTS as their treatment dose, as it contains an equiosmolar load to 0.5–1 g/kg of mannitol.[10,13,14] Until recently, practice at our institution was to administer the fixed doses of 30 ml of 23.4% HTS to TBI patients with elevated ICP >20 mmHg. Over the past several years, practice has shifted from fixed dosing to a weight-based dosing of 23.4% HTS using a dose of approximately 0.6 ml/kg (2.4 mEq/kg). The rationale for the use of weight-based dosing of 23.4% HTS is based on pediatric dosing strategies which take into account the total body water of the patient. Pediatric doses of HTS for the purpose of ICP treatment are generally given using 3–5 ml/kg of 3% HTS solution (1.5–2.6 mEq/kg), which is equivalent to the sodium load provided by our institution’s weight-based dosing strategy.[15] The objective of this study was to validate the practice of utilizing weight-based dosing of HTS in TBI patients with elevated ICP and its efficacy in lowering elevated pressures compared to a fixed dose of 30 ml.

Subjects and Methods

Study design and population
The protocol for this study was reviewed and approved by the institutional review board. Patients were selected for this retrospective observational study through the hospital’s electronic medical record (EMR) system and trauma registry. A Business Operations report was run via the EMR for patients who were administered 23.4% HTS during their hospital admission from February 2012-February 2014. Patients were included if they were >18 years of age, had a traumatic, nonpenetrating brain injury with a baseline GCS <8, had placement of an ICP monitor, and were administered at least one dose of 23.4% HTS. Patients were excluded if they were administered mannitol for >24 h postinjury.

Endpoints
The primary endpoint of this study was to determine the ICP reduction immediately following weight-based dosing of 23.4% HTS in comparison to a fixed dose approach in the management of severe TBI. All doses administered within 5 days postinjury were recorded and categorized into one of three groups depending on the volume of HTS administered. A volume of >0.6 ml/kg (>2.4 mEq/kg) was considered to be a high weight-based dose; a volume of <0.6 ml/kg (<2.4 mEq/kg) was considered to be a low weight-based dose; and any dose of 30 ml (120 mEq) was considered to be a standard fixed dose. Each dose was evaluated separately for clinical effect due to patients receiving both fixed- and weight-based doses of HTS. The secondary endpoints included the change in cerebral perfusion pressure (CPP) and adverse effects. A post hoc analysis of doses administered within 48 h postinjury was also performed.

Data collection
Doses of 23.4% HTS administered within the first 5 days postinjury were recorded to assess the lowering of ICP during the acute phase of TBI. Doses administered outside of this time frame were not assessed to reduce the possibility of the effect of HTS being diluted by pathological processes not related to the inciting injury. ICP and CPP were recorded both before and after administration of a HTS dose. The lowest ICP achieved following a dose of HTS, but before the subsequent dose, was recorded for the purpose of determining the maximum decrease in ICP regardless of the time from dose administration. The highest CPP was recorded in the same manner.

Demographic and physiologic data related to the treatment of TBI were collected for each patient. Laboratory data were gathered following each dose of HTS. Nursing and progress notes were reviewed to screen for adverse events and other indicators of patient’s clinical status. Adverse events were evaluated for the duration of HTS therapy or 5 days, depending on which the time period was longer. Adverse events included pneumonia (ICD-9 Code 486), pulmonary edema (PaO2/FiO2 ratio of <300 on a peak-end expiratory pressure >10 cmH2O, bilateral infiltrates with no indication of infection or volume overload), cardiovascular collapse defined as the utilization of a vasoactive agent not for the purpose of maintaining CPP, central pontine myelinolysis (ICD-9 Code 341.8), hyperchloremia (serum chloride >110 mmol/L), acute renal failure (50% increase in serum creatinine from baseline or serum creatinine >1.5 mg/dl), and coagulopathy (INR >1.5).

Statistical analysis
Continuous variables were summarized by the mean ± standard deviation; categorical variables were summarized using frequencies and percentages. The primary and secondary endpoints for the study were analyzed using mixed-model, repeated measures analysis of covariance (ANCOVA). Each consecutive dose was assigned an episode number (i.e., 1, 2, 3 …) to account for potential changes over time. Means for individual levels of dose group, episode, and the interaction of these, are estimated using least-square means (LS means), which are model-based predictions of the marginal means, often called “adjusted means”. The model that best fits the data were selected using the corrected Akaike Information Criterion. The estimated change in ICP and CPP was calculated from the percent change LS means and estimated LS means of the initial values. The estimates for the initial values of ICP and CPP were computed using ANCOVA.
models. All analysis was done in SAS® Version 9.4 for Windows (Cary, NC, USA).

RESULTS

A total of 19 patients were identified with severe TBI requiring ICP monitoring who received at least one dose of 23.4% HTS for ICP reduction. Information on 97 doses of HTS was collected from the 19 patients. Baseline demographics showed a male predominance and an average age of 39.3 years [Table 1]. The most common mode of injury was motor vehicle accident, followed by pedestrian versus motor vehicle accidents. The mean injury severity score and revised trauma score were 24 ± 5.7 and 4.8 ± 1.5, respectively. The mean probability of survival as calculated by the trauma registry was 0.66 ± 0.27.

Patients in the study received a range of 1–18 doses of HTS per patient (median 4). Forty-seven percent of patients received more than one type of HTS dosing during their admission. A total of 41 high weight-based doses were given, with a median of 2.89 mEq/kg/dose (range: 2.57,3.33); 22 low weight-based doses with a median of 2.08 mEq/kg/dose (range: 1.8,2.28); and 34 standard fixed-doses with a median of 1.4 mEq/kg/dose (range: 0.9,1.91). In the ANCOVA model, there was no significant relationship between dose group (high weight-based, low weight-based, or fixed) and percent change in ICP when controlling for episode and initial ICP. However, there was a significant relationship between episode and percent change in ICP, and initial ICP and percent change in ICP (P = 0.04, and <0.0001, respectively) when controlling for episode. However, there was no significant relationship between episode and percent change in ICP (P = 0.73). An estimated LS mean confirmed the significant relationship between dose group and percent change in ICP; however, there was no significant relationship found between dose group and percent change in CPP [Table 2].

A sub-analysis of doses received within the first 48 h was also conducted. In this model, there was a significant relationship between dose group and percent change in ICP, and initial ICP and percent change in ICP (P = 0.04, and <0.0001, respectively) when controlling for episode. However, there was no significant relationship between episode and percent change in ICP (P = 0.73). An estimated LS mean confirmed the significant relationship between dose group and percent change in ICP; however, there was no significant relationship found between dose group and percent change in CPP [Table 2].

Pairwise comparisons were used to further explore the relationship between dose group and percent change in ICP. There was a significant difference in percent change in ICP between the high weight-based dose group and the fixed-dose group (P = 0.02). There was no significant difference in percent change in ICP between the high weight-based dose group and the low weight-based dose group or the low weight-based dose group and the fixed-dose group (P = 0.06 and 0.70, respectively).

Hyperchloremia was the most common adverse effect associated with the use of HTS; other observed adverse effects were less prevalent [Table 3].

DISCUSSION

Hyperosmolar agents are a cornerstone of TBI treatment for the reduction of ICP. Mannitol has been used since the 1960s for ICP reduction; however, the overall evidence for the use of mannitol for ICP reduction is unconvincing. HTS emerged as a salvage therapy used in patients who continued to have an elevated ICP despite mannitol administration and continues to be used in both the pediatric and adult populations for ICP reduction following TBI.[18,14,15] In our study, there was no difference found in the primary endpoint of percent ICP reduction between dosing groups; however, the larger percentage reductions in ICP in the high weight-based dosing group may be clinically, if not statistically, significant and could be attributed to the higher osmolar load of this dosing strategy. The significant relationship found between change in ICP and episode, and change in ICP and initial ICP suggests that administration of weight-based doses of HTS early on in a TBI patient’s treatment course may have more of an effect on ICP reduction than doses given farther out postinjury. This is further supported by the sub-analysis of all doses given within 48 h postinjury. In contrast to the all-time point’s analysis, in the 48-hour analysis, there was a significant relationship seen between dosing groups and percent reduction in ICP even when episode and initial ICP were controlled for.

Table 1: Baseline characteristics (n=19)*

| Characteristic                        | n (%)     |
|--------------------------------------|-----------|
| Male (%)                             | 16 (84%)  |
| Age (years)                          | 39.3 ± 16.1 |
| Cause of TBI (%)                     |           |
| Fall                                 | 3 (16)    |
| Motor vehicle accident               | 8 (42)    |
| Other                                | 8 (42)    |
| Cranioectomy (%)                     | 6 (32)    |
| Admitting Glasgow coma scale score   | 5 ± 2     |
| ISS                                  | 24 ± 5.7  |
| RTS                                  | 4.8 ± 1.5 |
| Probability of survival              | 0.66 ± 0.27 |

*All continuous variables reported as mean±SD. SD: Standard deviation, ISS: Injury severity score, RTS: Revised Trauma Score, TBI: Traumatic brain injury
Our results did not show any significant relationship between dosing group and percentage increase in CPP in either the all-time point’s analysis or the 48 h sub-analysis. CPP is frequently used as a surrogate marker of brain tissue oxygenation (PbtO₂) in TBI patients. An increase in PbtO₂ and the prevention of further cerebral ischemia is the goal of hyperosmolar therapy, and the reason why small differences in acute ICP measurement could have a large impact on the long-term prognosis of a TBI patient. In theory, the net effect of a higher osmolar load would be a more pronounced increase in MAP and decrease in ICP, and thus a more substantial increase in CPP; however, this was not shown by our data.

There is very limited evidence relating ICP reduction to improved patient morbidity and mortality after TBI, and our study design did not allow for an analysis of patient outcomes. A study by Rockswold et al. evaluating ICP reduction after 30 ml doses of 23.4% HTS identified a mean increase in PbtO₂ of 3.1 mmHg (P < 0.01) that accompanied ICP reduction, suggesting that ICP reduction may be a surrogate marker of increased cerebral oxygenation.[13] In addition, compliance with the Brain Trauma Foundation guidelines in the treatment of TBI patients has been shown to significantly decrease 2-week mortality, indicating adherence to recommendations regarding ICP and CPP management may improve survival.[4]

The use of 23.4% HTS for ICP reduction in TBI patients is becoming a more common practice in trauma centers,[9] however, to the knowledge of the authors, there is no literature directly comparing alternate volume or osmolar dosing strategies for 23.4% HTS. This study is the first to evaluate the efficacy bolus doses of 23.4% HTS >120 mEq per dose. The limitations of this study included the retrospective design and small sample size. The practice of 23.4% HTS dosing was not standardized, and doses were determined by physicians based on patient presentation and laboratory parameters. As a result, many patients in the study received both fixed and weight-based doses. The adverse events observed were consistent with those seen in other studies using HTS in TBI and were difficult to attribute solely to HTS administration as many of the adverse events recorded are also commonly associated with massive trauma. The relatively low rate of adverse effects observed in this study suggests that higher doses may be safe and effective in the care of these patients, although appropriate laboratory monitoring should be performed given the potential risks of hyperosmolar therapy.[16]

**Conclusion**

In contrast to doses used in currently published literature, doses in our study ranged from 120 to 360 mEq, substantially higher than most studies using doses of 120 mEq or less. This study had significant limitations and was not adequately designed to evaluate the differences in patients who received varying dosing strategies; however, the finding that high weight-based dosing of 23.4% HTS had the most pronounced effect on ICP within the first 48 h of injury highlights an important area for additional research. Prospective randomized trials are needed to examine the effects of using weight-based boluses of 23.4% HTS for ICP management in adult TBI patients.

**Acknowledgments**

The authors would like to thank Dale Kraemer, PhD for his help with statistical design and analysis, and Julia Paul of the Trauma Registry for obtaining patient records.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Faul M, Xu L, Wald MM, Coronado VG. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002–2006. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
2. Coronado VG, McGuire LC, Faul MF, Sugerman DE, Pearson WS. Traumatic brain injury epidemiology and public health issues. In: Zasler ND, Katz DI, Zafonte RD, editors. Brain injury medicine: principles and practice. 2nd ed. New York, NY: Demos Medical Publishing; 2012; 84–100.
3. Carney N, Totten AM, O’Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery 2017;80:6-15.
4. Gerber LM, Chiu YL, Carney N, Härtl R, Ghaifar J. Marked reduction in mortality in patients with severe traumatic brain injury. J Neurosurg 2013;119:1583-90.
5. Hays AN, Lazaridis C, Neyens R, Nicholas J, Gay S, Chalela JA. Osmotherapy: Use among neurointensivists. Neurocrit Care 2011;14:222-8.
6. Lazaridis C, Neyens R, Bodle J, DeSantis SM. High-osmolarity saline in

---

**Table 2: Estimated least-square means of percent change in intracranial pressure and cerebral perfusion pressure posthypertonic saline in first 48 h (n=50 doses for intracranial pressure and 48 for cerebral perfusion pressure)*

|                | High weight-based | Low weight-based | Standard | P   |
|----------------|-------------------|------------------|----------|-----|
| ICP change (%) | 54.9 (44.3, 65.5) | 39.4 (24.7, 54.1) | 36.6 (24.1, 49.1) | 0.04 |
| CPP change (%) | 23.5 (11.6, 35.9) | 18.5 (1.9, 34.7) | 20.3 (4.2, 34.9) | 0.80 |

*Data represented as LS means and 95% CI. CPP: Cerebral perfusion pressure, CI: Confidence intervals, ICP: Intracranial pressure, LS: Least-square

**Table 3: Adverse effects per patient (n=19)**

| Adverse effect                  | n (%) |
|---------------------------------|-------|
| Acute renal failure             | 1 (5) |
| Central pontine myelinolysis    | 0 (0) |
| Cardiovascular collapse         | 2 (11)|
| Hyperchloremia                  | 19 (100)|
| Pneumonia                       | 6 (32)|
| Coagulopathy                    | 4 (21)|
| Pulmonary edema                 | 2 (11)|
neurocritical care: Systematic review and meta-analysis. Crit Care Med 2013;41:1353-60.
7. Lewandowski-Belfer JJ, Patel AV, Darracott RM, Jackson DA, Nordeen JD, Freeman WD. Safety and efficacy of repeated doses of 14.6 or 23.4% hypertonic saline for refractory intracranial hypertension. Neurocrit Care 2014;20:436-42.
8. Kerwin AJ, Schinco MA, Tepas JJ 3rd, Renfro WH, Vitarbo EA, Muehlberger M. The use of 23.4% hypertonic saline for the management of elevated intracranial pressure in patients with severe traumatic brain injury: A pilot study. J Trauma 2009;67:277-82.
9. Sakellaridis N, Pavlou E, Karatzas S, Chroni D, Vlachos K, Chatzopoulos K, et al. Comparison of mannitol and hypertonic saline in the treatment of severe brain injuries. J Neurosurg 2011;114:545-8.
10. Suarez JI, Qureshi AI, Bhardwaj A, Williams MA, Schnitzer MS, Mirski M, et al. Treatment of refractory intracranial hypertension with 23.4% saline. Crit Care Med 1998;26:1118-22.
11. Vialet R, Albanèse J, Thomachot L, Antonini F, Bourgouin A, Alliez B, 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;31:1683-7.
12. Worthley LI, Cooper DJ, Jones N. Treatment of resistant intracranial hypertension with hypertonic saline. Report of two cases. J Neurosurg 1988;68:478-81.
13. Rockswold GL, Solid CA, Paredes-Andrade E, Rockswold SB, Jancik JT, Quickel RR. Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure, and brain tissue oxygen. Neurosurgery 2009;65:1035-41.
14. Ware ML, Nemani VM, Meeker M, Lee C, Morabito DJ, Manley GT. Effects of 23.4% sodium chloride solution in reducing intracranial pressure in patients with traumatic brain injury: A preliminary study. Neurosurgery 2005;57:727-36.
15. Brenkert TE, Estrada CM, McMorrow SP, Abramo TJ. Intravenous hypertonic saline use in the pediatric emergency department. Pediatr Emerg Care 2013;29:71-3.
16. Webster DL, Fei L, Falcone RA, Kaplan JM. Higher-volume hypertonic saline and increased thrombotic risk in pediatric traumatic brain injury. J Crit Care 2015;30:1267-71.