Journal of Clinical Neuroscience 39 (2017) 147–150

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Case study

Method of Hypertonic Saline Administration: Effects on Osmolality in Traumatic Brain Injury Patients

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ARTICLE INFO

Article history:
Received 4 November 2016
Accepted 22 January 2017

Keywords:
Traumatic brain injury
Hypertonic saline
Osmolality
Intracranial pressure

ABSTRACT

Hypertonic saline (HTS) is an effective therapy for reducing intracranial pressure (ICP). The ideal method of administration is unknown. The purpose of this study was to evaluate the method of HTS infusion and time to goal osmolality. A retrospective cohort analysis was conducted in severe TBI patients with ICP monitoring in place who received 2 doses of HTS. Patients were divided into bolus versus continuous infusion HTS cohorts. The primary outcome was median time to goal osmolality. Secondary outcomes included percentage of patients reaching goal osmolality, percent time at goal osmolality, mean cerebral perfusion pressure (CPP) and ICP, ICU length of stay, and mortality. Safety outcomes included rates of hyperchloremia, hypernatremia, and acute kidney injury (AKI). 162 patients were included with similar baseline characteristics. Time to goal osmolality was similar between cohorts (bolus 9.78 h vs. continuous 11.4 h, $p = 0.817$). A significant difference in the percentage of patients reaching goal osmolality favoring the continuous group was found (93.9% vs 73.3%, $p = 0.003$). The continuous group was maintained at goal osmolality for a higher percentage of osmolality values after reaching goal (80% vs. 50%, $p = 0.032$). No difference was seen in CPP, ICP, length of stay and mortality. Rates of hypernatremia were similar, but significant higher rates of hyperchloremia (0.77 vs 1.58 events per HTS days, $p < 0.001$) and AKI (0% vs 12.9%, $p = 0.025$) were observed in the continuous cohort. Although no difference in time to goal osmolality was observed, continuous HTS was associated with a higher percentage of patients achieving goal osmolality.

1. Introduction

The ideal hyperosmolar agent for elevated intracranial pressure (ICP) (>20 mmHg) and method of administration remains debated in patients with traumatic brain injury (TBI). Hyperosmolar treatment is typically instituted to optimize the cerebral blood flow and to improve tissue oxygenation of the injured brain after non-pharmacologic treatments and sedation have been optimized [1–3]. This therapy reduces ICP by creating an osmotic gradient across an intact blood brain barrier to draw water from the interstitial space to the vascular space. It also decreases blood viscosity and cerebral blood volume [3,4]. In patients with persistently elevated ICP readings, hyperosmolar therapy is often repeated until a goal blood osmolality is reached [5–8].

Mannitol and hypertonic saline (HTS) have been studied extensively as hyperosmolar agents in TBI, but recent meta-analyses have favored hypertonic saline. These studies have indicated a greater reduction of ICP with HTS than mannitol, as well as potential reduction in the rate of rebound intracranial hypertension and acute kidney injury [9–11]. Proposed mechanisms for these advantages include the reduced likelihood of HTS crossing the blood brain barrier, its ability to improve the mean arterial pressure by increasing circulating volume, modulation of neuroinflammatory pathways, and improvement in blood rheology within the cerebral vasculature [12]. Despite recommendations from the Brain Trauma Foundation for mannitol, HTS is increasingly used as the first-line hyperosmolar agent in severe TBI [13]. It can be administered as either an intravenous bolus, continuous infusion, or a combination of both. The safety and efficacy of both bolus and continuous infusion HTS have been demonstrated in previous studies [14,15]. However, the efficacy of the two different methods of administration has not been directly compared. The purpose of this study was

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http://dx.doi.org/10.1016/j.jocn.2017.01.025
0967-5868/

to evaluate the effects of HTS continuous infusion on the time to goal osmolality. We hypothesize that patients receiving bolus only HTS will reach goal osmolality more rapidly than patients receiving continuous infusion HTS.

2. Methods

This IRB-approved retrospective cohort analysis was conducted at an academic Level 1 trauma center. Trauma patients included in this study were admitted to a 14-bed trauma ICU and managed by a multidisciplinary team led by trauma surgeons.

2.1. Hyperosmolar therapy

Hyperosmolar therapy at our institution is directed by center specific guidelines and by the attending trauma surgeon and neurosurgery service. It is initiated when an elevated ICP is suspected or documented by an ICP monitor or external ventricular drain (EVD). The standard preparation of HTS utilized at our institution is 3% sodium chloride. In 2011, our institution transitioned HTS therapy from bolus only to mostly combination therapy with a continuous infusion. However, both approaches continue to be used based on team preference. For patients who receive bolus only therapy, HTS boluses of 250–500 mL are typically given until both goal ICP (<20 mmHg) and blood osmolality (≥310 mOsm/kg) are reached. Patients who receive HTS therapy as a continuous infusion will start at a rate of 30–50 mL/h with repeatable bolus doses as needed to achieve a goal ICP. The infusion is titrated to maintain a sodium of 150–160 mEq/L and an osmolality value >310 mOsm/kg. ICP is monitored continuously by an EVD or ICP monitor and laboratory values are obtained every six hours. Mannitol is often reserved for HTS refractory ICPs or extreme elevations in ICP if maximum serum sodium or osmolality has not been achieved.

2.2. Study design

Patients eligible for inclusion were identified by the Trauma Registry of the American College of Surgeons (TRACS) from January 2008 to May 2014. Patients with a diagnosis of severe TBI (Glasgow Coma Scale score <9) who received an ICP monitor or EVD as well as two or more doses of 3% sodium chloride were included in the study. Patients were excluded if they underwent a craniotomy as ICP was surgically managed in these patients. HTS cohorts were divided into those patients who received bolus HTS only and those who received continuous infusion HTS with "as needed" bolus HTS therapy. Rescue mannitol administration was permitted in both groups.

The primary outcome of this study was time to goal osmolality. Goal osmolality was defined as a serum osmolality value of ⩾310 mOsm/kg. Time zero was the first documented HTS dose on the medication administration record or the first documented HTS flow rate in the nursing flowsheet. Secondary outcomes included percentage of patients reaching goal osmolality, percent of osmolality values at goal while on HTS, mean CPP and ICP, ICU length of stay, and ICU mortality. Safety outcomes included the incidence of AKI, hypernatremia (Na >160 mEq/L), and hyperchloremia (Cl >120 mEq/L). Acute kidney injury was defined as an increase in serum creatinine of 1.5 times baseline serum creatinine value, according to the RIFLE criteria [16]. The incidence and indication for hemodialysis and continuous renal replacement therapy (CRRT) in the ICU was collected as well as requirements for long-term dialysis at discharge. The incidence of electrolyte abnormalities was normalized to total patient days on HTS per cohort since more patients received continuous infusion instead of bolus only HTS.

Demographic data, including age, gender, admission Glasgow Coma Scale score (GCS), Injury Severity score (ISS), and head/neck Abbreviated Injury Scale score (AIS) were collected through TRACS. Medication administration record, laboratory values and vital signs were extracted from the electronic medical record. From this data, time to goal osmolality and ICP were calculated, along with percentage of osmolality values at goal range while on HTS.

2.3. Statistical analysis

Statistical analysis was performed using SPSS Statistics Version 22. Due to the retrospective nature of the study, a power calculation was not performed. Medians were utilized to analyze non-normally distributed data and means were used to analyze normally distributed data. Non-parametric categorical data was analyzed with the Fisher's Exact Test. The Mann–Whitney U test was used for non-parametric continuous data.

3. Results

Two hundred sixteen patients were identified for inclusion. Reasons for exclusion included less than 2 doses of HTS ($n = 36$), ICP monitoring not available during HTS administration ($n = 14$), craniotomy ($n = 2$), and administration of HTS outside of the trauma ICU ($n = 2$). Thus, a total of 162 patients were included with 132 in the continuous infusion HTS arm and 30 in the bolus only HTS arm.

Patient demographics were relatively similar between the two groups. Baseline characteristics are summarized in Table 1. The majority of patients included were young males without comorbidities who were admitted after blunt trauma. More HTS was administered in the continuous infusion cohort compared to the bolus only cohort (1250 mL vs. 2735 mL, $p < 0.001$). Mannitol administration was greater in the continuous infusion cohort, but this did not reach statistical significance (127.5 g vs. 87.5 g, $p = 0.181$).

For the primary outcome, no difference was observed in time to goal osmolality. Patients receiving continuous infusion HTS

Table 1
Baseline characteristics.

Characteristic	Continuous infusion HTS ($n = 132$)	Bolus only HTS ($n = 30$)
Age, median (IQR)	29.4 (22.4–46.2)	29.1 (19.3–51.6)
Male sex, No. (%)	101 (76.5%)	20 (66.7%)
Admission GCS, median (IQR)	3 (3–3)	3 (3–3)
Admission ISS, median (IQR)	37 (29–45)	33.5 (26–42.8)
Admission AIS Head/Neck, median (IQR)	5 (4–5)	5 (4–5)
Opening pressure, median (IQR)	15 (9–23)	15 (8.3–21.5)
Blunt trauma, No. (%)	126 (95.4%)	29 (96.7%)
Total HTS administered (mL), median (IQR)	2735 (1790–4395)	1250 (750–1937.5)
Total mannitol administered (g), median (IQR)	127.5 (50–250)	87.5 (6.25–193.75)