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Clinical Study

Hypertonic saline infusion in traumatic brain injury increases the incidence of pulmonary infection

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ABSTRACT

We aimed to investigate the incidence of electrolyte abnormalities, acute kidney injury (AKI), deep venous thrombosis (DVT) and infections in patients with traumatic brain injury (TBI) treated with hypertonic saline (HTS) as osmolar therapy. We retrospectively studied 205 TBI patients, 96 with HTS and 109 without, admitted to the surgical/trauma intensive care unit between 2006 and 2012. Hemodynamics, electrolytes, length of stay (LOS), acute physiological assessment and chronic health evaluation II (APACHE II), injury severity scores (ISS) and mortality were tabulated. Infection, mechanical ventilation, DVT and AKI incidence were reviewed. HTS was associated with increased LOS and all infections ($p = 0.0001$). After correction for the Glasgow coma scale (GCS) and ventilator need, pulmonary infections ($p = 0.001$) and LOS remained higher with HTS ($p = 0.0048$). HTS did not result in increased blood pressure, DVT, AKI or neurological benefits. HTS significantly increased the odds for all infections, most specifically pulmonary infections, in patients with GCS < 8. Due to these findings, HTS in TBI should be administered with caution regardless of acuity.

1. Introduction

Hypertonic saline (HTS) administration has become common practice in the treatment of brain injury in the critically ill. It is administered either as a bolus to treat acute elevations of intracranial pressure (ICP) or infused as osmolar therapy in an attempt to prevent central nervous system (CNS) edema. Bolus HTS, in high concentrations, has proven to be as effective as mannitol in treating elevated ICP [1,2].

At 3% concentration, HTS infusion maintains relatively high serum sodium (Na) levels in patients with CNS pathology [3,4]. The understanding is that higher osmolarity should minimize CNS edema and prevent rises in ICP [5].

Though commonly used, evidence that HTS improves CNS edema is lacking. The perceived safety of HTS has likely facilitated its popularity, even though small studies have identified complications including deep venous thrombosis (DVT), acute kidney injury (AKI), increased infections and serum potassium (K) abnormalities [1,6,7]. In retrospective studies with few traumatic brain injury (TBI) patients, there were no clear negative outcomes with HTS [3,7]. Only one study suggested neurological benefits [8].

HTS infusion is commonly used at our center to treat TBI. We were concerned that the Na load may have adverse physiological effects on mean arterial pressure (MAP) or electrolytes. Having reviewed data from our TBI patients and finding increased infections [6], we further concentrated our investigation on HTS infectious risks.

2. Methods

The Elmhurst Hospital trauma center in New York City admits a large volume of TBI patients to the surgical/trauma intensive care unit (STICU). We retrospectively identified 225 charts of TBI patients admitted to the STICU over 48 hours between January 2006 and December 2012. HTS administration was according to the neurosurgeon's decision and based on clinical, radiological and laboratory studies.

Exclusion criteria included death within 24 hours, less than 12 hour HTS infusion and pediatric patients. HTS (3%) was infused

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at 30 mL/hour, titrated to Na between 145 and 155 milliequivalents (mEq)/L. Ventriculostomy was determined by the neurosurgical team based on Glasgow coma score (GCS) $\leqslant$ 8, clinical exam, presence of hydrocephalus and/or intraventricular hemorrhage. Patients received standard STICU support including DVT prophylaxis, ventilator bundle, gastrointestinal prophylaxis, and were treated in accordance with TBI guidelines [9–11].

Data collected at 0 (start of HTS), 24 and 48 hours included MAP, Na and K levels, GCS and Rotterdam scores (RTDM). Since the average starting time of HTS infusion was 24 hours after STICU admission, time 0 for the no HTS (nHTS) group was similarly defined. RTDM evaluates four CT scan findings to generate a numerical score consistent with the motor score of the GCS: basal cistern compression, midline shift, epidural mass lesion, intraventricular or subarachnoid hemorrhage [10]. Higher RTDM scores indicate greater injury. CT scans prior to, and on average 4 days after, HTS commencement were reviewed by a neuroradiologist who calculated the RTDM.

Injury severity scores (ISS) were obtained from the trauma registry. Length of stay (LOS) represents STICU days while mortality refers to in-hospital death. Positive blood, urine, endotracheal aspirate and/or cerebrospinal fluid cultures within 2 to 10 days after HTS were considered infections. Cultures beyond 10 days were excluded (not considered to be HTS related). Positive endotracheal cultures were considered pulmonary infections (PI) if two of three were present: white blood cell count >11 $\times$ 10^3/μL, temperature >100.5 F, or consistent chest radiograph findings. Ventilator days are defined as days between initial intubation and extubation.

DVT was defined as positive Doppler studies of extremities within 2 weeks of infusion. AKI was defined as persistent rises in serum creatinine of >0.3 mg/dL, unresponsive to fluid within 48 hours, and risk or greater by risk, injury, failure, loss in end-stage kidney disease (RIFLE standards). Acute physiological assessment and chronic health evaluation II (APACHE II) scores were calculated from admission data.

All parameters were presented as potential independent factors that lead to infections using forward regression analysis. Bivariate and multivariate regression analyses were utilized where appropriate using Stata version 12.1 (StataCorp, College Station, TX, USA). All results are presented as the mean ± standard error of the mean. This project was approved by the Mount Sinai Medical School Institutional Review Board in cooperation with the New York City Health and Hospitals Corporation.

3. Results

3.1. Total population

Patients excluded from the study included two pediatric, 14 with HTS for <12 hours, and four who had HTS restarted. Charts were reviewed from 205 patients. The average age of the group was 53.1 ± 1.5 years (range: 17–98; Table 1). Mechanisms of injury were falls (55.28%), motor vehicle accidents (21.61%), assaults (11.56%), and other (11.56%). Average ISS and APACHE II scores were 18.8 and 11.9, respectively. Follow-up head CT scans for 76% of patients were conducted on average 4 days after admission. Intraventricular devices were used in 30% of patients. Four patients had DVT, all of whom had nHTS.

3.1.1. HTS versus nHTS

Of the total patient population, 46.8% received HTS, none received bolus HTS. Mean Na was 137 mEq/L at HTS start. Of the patients receiving HTS, 73% had an initial Na >135 mEq/L, suggesting HTS was not for hyponatremia. Despite similar ISS and APACHE II scores, the HTS group had significantly lower GCS at commencement. Admission alcohol levels, RTDM scores and K were similar in both groups (Table 1).

3.1.2. Outcomes

Na rapidly and significantly increased within 24 hours of HTS (p = 0.0001), increasing by 8.0 mEq/L in 48 hours (137.0 ± 0.6 to 145.0 ± 0.9; Fig. 1a), a rise of 0.16 mEq/L/hour. In 13% of patients, Na rose to >150 mEq/L by 24 hours. K decreased in both groups at 48 hours (Fig. 1a). There were no significant changes in MAP after 48 hours (Table 1), DVT incidence, or AKI in the HTS group. Vasopressors were required in 23% of HTS *versus* 9.2% of nHTS patients (p = 0.0108).

3.1.3. Infectious outcomes

Of the HTS patients compared to nHTS, 47.9 *versus* 21.1% developed infections, and 35.4 *versus* 8.25% had PI, respectively (Table 2). Odds of infection, primarily pulmonary, were higher with HTS (Table 3). When subtracting PI, there were no differences in infections between the groups. HTS demonstrated an association with PI (p < 0.0005; Table 2) and appears to be a factor leading to PI, particularly with GCS $\leqslant$ 8 (Table 4). Patients whose Na exceeded 150 mEq/L in 48 hours (n = 33) had a higher PI incidence compared to those below that level (61 *versus* 24%, respectively; p = 0.0001). The odds of an infection with HTS were 4.2 times higher compared to nHTS. The odds of PI were 5.68 times greater compared to nHTS (Table 3). LOS and ventilator days were significantly longer with HTS (Table 2; Fig. 2).

3.1.4. Neurological outcomes

In both groups, RTDM improved from entry (HTS p = 0.0004; nHTS p = 0.0001; Table 1 and 2). GCS improved in the nHTS group by 15% (p = 0.0032) but not in the HTS group (Table 1 and 2). In patients with a Na rise of >150 mEq/L in 48 hours (n = 33) GCS did not change.

Table 1
Traumatic brain injury patient characteristics at admission, treated with or without hypertonic saline infusion (HTS or nHTS, respectively)

Covariates	All (n = 205)	nHTS (n = 109)	HTS (n = 96)	p value
Age, years	53.12 ± 1.51	59.93±1.98	45.39 ± 2.07	0.0005*
Sex, male, n (%)	157 (76.59)	75 (68.80)	82 (85.4)	0.005*,Ŧ
ISS	18.84 ± 0.90	18.33 ± 1.06	19.45 ± 1.5	0.548
APACHE II	11.89 ± 0.447	11.73 ± 0.66	12.07 ± 0.58	0.7042
Ventilator need at admission, n (%)	132 (64.39)	59 (54.12)	73 (76)	0.001*,Ŧ
GCS	8.75 ± 0.313	9.74 ± 0.44	7.63 ± 0.41	0.0007*
RTDM Initial	2.63 ± 0.10	2.51 ± 0.14	2.76 ± 0.14	0.239
MAP (mmHg)	89.44 ± 1.16	90 ± 1.4	88.81 ± 1.85	0.612

All data is expressed as the mean ± standard error of the mean, unless otherwise specified.
APACHE II = acute physiological assessment and chronic health evaluation II, GCS = Glasgow coma scale, HTS = hypertonic saline, ISS = injury severity score, MAP = mean arterial pressure, nHTS = no hypertonic saline, RTDM = Rotterdam score.
* p < 0.05.
Ŧ Chi-squared.