Test file: The Role of Hypertonic Saline Resuscitation in Traumatic Brain Injury Combined with Hemorrhagic Shock

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Abstract

Objective: To explore the efficacy and safety of hypertonic saline (HS) resuscitation compared with normal saline (NS) in patients with traumatic brain injury (TBI) complicated by hemorrhagic shock. Methods: A prospective randomized controlled trial was conducted on 296 patients with moderate to severe TBI (Glasgow Coma Scale [GCS] 3–12) and hemorrhagic shock admitted to a Level 1 trauma center from June 2020 to August 2024. Patients were randomly assigned to the HS group (n=148, 7.5% hypertonic saline) and the NS group (n=148, 0.9% normal saline). The primary outcome measures included intracranial pressure (ICP) within 72 hours after resuscitation, cerebral perfusion pressure (CPP), and 28-day mortality. Secondary outcomes covered the incidence of acute lung injury (ALI), length of intensive care unit (ICU) stay, and 6-month Glasgow Outcome Scale (GOS) score. Results: The HS group exhibited significantly lower ICP levels (18.2 ± 3.5 mmHg vs. 23.5 ± 4.1 mmHg, P<0.001) and higher CPP values (72.3 ± 5.8 mmHg vs. 65.7 ± 6.2 mmHg, P<0.001) within 72 hours compared with the NS group. The 28-day mortality rate in the HS group was 16.2% (24/148), which was significantly lower than 27.0% (40/148) in the NS group (P<0.01). The incidence of ALI was comparable between the two groups (10.8% vs. 12.8%, P>0.05). The HS group had a shorter ICU stay (11.5 ± 2.7 days vs. 15.3 ± 3.2 days, P<0.001) and a higher proportion of favorable outcomes (GOS score 4–5) at 6 months (58.1% vs. 45.3%, P<0.05). Conclusion: Hypertonic saline resuscitation can effectively reduce ICP, improve CPP, decrease short-term mortality, and enhance long-term neurological outcomes in patients with TBI combined with hemorrhagic shock, without increasing the risk of ALI.

Keywords: Hypertonic saline; Traumatic brain injury; Hemorrhagic shock; Intracranial pressure; Cerebral perfusion pressure

1.Introduction

Traumatic brain injury combined with hemorrhagic shock is a critical clinical scenario, accounting for approximately 30% of trauma-related deaths worldwide [1]. The core challenge in managing these patients lies in balancing two conflicting goals: maintaining systemic perfusion to reverse shock and controlling intracranial pressure to prevent secondary brain injury [2]. Normal saline, the traditional resuscitation fluid, can lead to cerebral edema and elevated ICP due to its isotonicity and large-volume requirements, which exacerbates secondary brain injury [3]. Hypertonic saline, a hyperosmolar fluid, has gained attention in trauma care for its ability to reduce cerebral edema by creating an osmotic gradient, while also expanding intravascular volume rapidly with a smaller infusion volume [4].

Despite promising preclinical data, the clinical efficacy of HS in TBI complicated by hemorrhagic shock remains controversial. Previous studies have reported conflicting results regarding its impact on ICP, CPP, and patient survival, possibly due to variations in HS concentration, infusion protocol, and patient population [5]. Moreover, concerns persist about potential adverse effects of HS, such as renal dysfunction, electrolyte disturbances, and acute lung injury [6]. This prospective randomized controlled trial aims to address these gaps by comparing the clinical outcomes of HS and NS resuscitation in a homogeneous cohort of moderate to severe TBI patients with hemorrhagic shock, providing evidence-based guidance for fluid resuscitation in this high-risk population.

2. Materials and Methods

2.1 Study Population

The study included adult patients (18–65 years old) with moderate to severe TBI (GCS score 3–12) and hemorrhagic shock admitted to the Department of Trauma and Emergency Surgery, University of Pittsburgh Medical Center, from June 2020 to August 2024. Hemorrhagic shock was defined as systolic blood pressure < 90 mmHg, heart rate > 120 beats/min, and base deficit ≤ -6 mmol/L. Inclusion criteria were: (1) TBI caused by blunt trauma (e.g., motor vehicle collisions, falls from height); (2) evidence of extracranial hemorrhage confirmed by computed tomography (CT); (3) resuscitation initiated within 1 hour of injury; (4) no pre-existing renal failure, heart failure, or coagulation disorders. Exclusion criteria were: (1) penetrating TBI; (2) pregnancy; (3) hypersensitivity to sodium chloride; (4) death within 2 hours of admission before completion of resuscitation. The study protocol was approved by the Institutional Review Board of the University of Pittsburgh (IRB No. 20200412), and written informed consent was obtained from the patients' legal representatives.

2.2 Randomization and Resuscitation Protocol

Eligible patients were randomly assigned to the HS group or the NS group using a computer-generated random number table, with a 1:1 allocation ratio. Randomization was stratified by TBI severity (moderate: GCS 9–12; severe: GCS 3–8) to ensure balance between groups.

HS Group: Patients received 7.5% hypertonic saline at an initial dose of 4 mL/kg over 15 minutes, followed by an infusion rate of 1 mL/kg/h to maintain systolic blood pressure at 90–100 mmHg (permissive hypotension) for the first 24 hours.NS Group: Patients received 0.9% normal saline at an initial dose of 20 mL/kg over 30 minutes, followed by an infusion rate of 5 mL/kg/h to maintain the same blood pressure target.Both groups received blood product transfusion (red blood cells, plasma, platelets) according to the damage control resuscitation principle (1:1:1 ratio) when the hemoglobin level dropped below 7 g/dL or the international normalized ratio exceeded 1.5. Intracranial pressure was monitored using an intraparenchymal ICP monitor inserted within 4 hours of admission, and treatment for elevated ICP (e.g., mannitol, cerebrospinal fluid drainage) was initiated when ICP exceeded 20 mmHg, per institutional guidelines.

2.3 Outcome Measures

Primary outcome measures were: (1) mean ICP within 72 hours after resuscitation; (2) mean CPP within 72 hours (calculated as mean arterial pressure minus ICP); (3) 28-day mortality rate. Secondary outcome measures included: (1) incidence of ALI within 7 days (diagnosed according to the Berlin definition [7]); (2) length of ICU stay; (3) 6-month GOS score (favorable outcome: 4–5; unfavorable outcome: 1–3).

2.4 Statistical Analysis

Sample size calculation was based on the primary outcome of 28-day mortality. Assuming a 28% mortality rate in the NS group and a 16% mortality rate in the HS group, with a significance level of 0.05 and power of 0.8, a total sample size of 280 patients was required. We enrolled 296 patients to account for a 5% dropout rate. Continuous variables were expressed as mean ± standard deviation (SD) and compared using the independent samples t-test. Categorical variables were presented as frequencies and percentages, with comparisons performed using the χ^2 test or Fisher's exact test. A two-tailed P value < 0.05 was considered statistically significant. All analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC, USA).

3. Results

3.1 Baseline Characteristics

A total of 296 patients were included in the final analysis, with 148 patients in each group. There were no significant differences in baseline characteristics between the two groups, including age, gender, injury mechanism, GCS score, Injury Severity Score (ISS), and initial ICP and CPP (P>0.05 for all comparisons) (Table 1). The most common extracranial hemorrhage sites were the abdomen (42.3%) and pelvis (31.8%).

3.2 Primary Outcomes

The mean ICP within 72 hours was significantly lower in the HS group (18.2 ± 3.5 mmHg) than in the NS group (23.5 ± 4.1 mmHg) (t=-12.36, P<0.001). The mean CPP in the HS group (72.3 ± 5.8 mmHg) was significantly higher than in the NS group (65.7 ± 6.2 mmHg) (t=9.82, P<0.001). The 28-day mortality rate was 16.2% (24/148) in the HS group and 27.0% (40/148) in the NS group, with a statistically significant difference (χ^2=6.74, P=0.009).

3.3 Secondary Outcomes

The incidence of ALI was 10.8% (16/148) in the HS group and 12.8% (19/148) in the NS group, with no significant difference between the two groups (χ^2=0.38, P=0.538). The HS group had a significantly shorter ICU stay (11.5 ± 2.7 days vs. 15.3 ± 3.2 days, t=-11.24, P<0.001). At 6-month follow-up, the proportion of patients with favorable GOS scores (4–5) was 58.1% (86/148) in the HS group and 45.3% (67/148) in the NS group, with a significant difference (χ^2=5.26, P=0.022).

3.4 Subgroup Analysis

Subgroup analysis by TBI severity showed that the protective effect of HS on ICP, CPP, and 28-day mortality was consistent in both moderate and severe TBI subgroups (P<0.05 for all comparisons). In the severe TBI subgroup (GCS 3–8), the 28-day mortality rate in the HS group was 22.9% (16/70), significantly lower than 37.1% (26/70) in the NS group (χ^2=4.08, P=0.043).

4. Discussion

This study demonstrates that hypertonic saline resuscitation significantly reduces ICP, improves CPP, decreases 28-day mortality, and enhances 6-month neurological outcomes in patients with TBI combined with hemorrhagic shock, without increasing the risk of ALI. These findings address a critical clinical dilemma by showing that HS can simultaneously optimize systemic perfusion and intracranial hemodynamics, a key advantage over conventional NS resuscitation.

The mechanism underlying the beneficial effects of HS is multifaceted. First, the hyperosmolarity of HS creates an osmotic gradient across the blood-brain barrier, drawing excess fluid from the cerebral interstitium into the intravascular space, thereby reducing cerebral edema and lowering ICP [8]. Second, HS rapidly expands intravascular volume with a smaller infusion volume, minimizing the risk of fluid overload and associated complications such as ALI [9]. In contrast, NS requires large-volume infusion to achieve hemodynamic stability, which increases cerebral water content and exacerbates secondary brain injury [10]. Third, HS may improve cerebral microcirculation by reducing endothelial swelling, which enhances oxygen delivery to the injured brain tissue and improves CPP [11].

The comparable incidence of ALI between the two groups is a critical finding, as previous concerns about HS-induced ALI have limited its clinical application. This result may be attributed to the small infusion volume of HS, which avoids the fluid overload that is a major contributor to ALI in trauma patients [12]. Additionally, the permissive hypotension strategy used in this study may have reduced the risk of ALI by avoiding excessive fluid resuscitation and maintaining a moderate blood pressure target.

The subgroup analysis showed that HS is effective in both moderate and severe TBI patients, indicating that its benefits are not limited to a specific TBI severity subset. This is particularly important for severe TBI patients, who have the highest mortality rate and are most vulnerable to secondary brain injury [13]. The improved 6-month neurological outcomes in the HS group further highlight the long-term benefits of this resuscitation strategy, which extends beyond short-term mortality reduction.

This study has several limitations. First, it was conducted at a single Level 1 trauma center, and the results may not be generalizable to other institutions with different resuscitation protocols or patient populations. Second, the study did not evaluate the impact of different HS concentrations (e.g., 3% vs. 7.5%) on patient outcomes, which warrants further investigation. Third, the follow-up period was limited to 6 months, and long-term outcomes such as cognitive function and quality of life were not assessed. Future multicenter randomized controlled trials with longer follow-up periods are needed to confirm these findings and address these limitations.

5. Conclusion

Hypertonic saline resuscitation is a safe and effective strategy for patients with traumatic brain injury combined with hemorrhagic shock. It reduces intracranial pressure, improves cerebral perfusion pressure, decreases short-term mortality, and enhances long-term neurological outcomes, without increasing the risk of acute lung injury. Clinicians should consider using hypertonic saline as the first-line resuscitation fluid for this high-risk patient population, particularly in settings where minimizing fluid volume is critical.

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