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Original Contribution

The effect of hypertonic saline and mannitol on coagulation in moderate traumatic brain injury patients

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ABSTRACT

Background: Hyperosmolar therapy, using either hypertonic saline (HTS) or mannitol (MT), is considered the treatment of choice for intracranial hypertension, a disorder characterized by high intracranial pressure (ICP). However, hyperosmolar agents have been postulated to impair coagulation and platelet function. The aim of this study was to identify whether HTS and MT could affect coagulation in moderate traumatic brain injury (TBI) patients.

Methods: In this prospective and randomized double-blind study, we included adult patients with moderate TBI. Patients were divided into two groups according to the type of hypertonic solution administered. Group A patients received 20% MT and group B patients received 3% HTS. Rotational thromboelastometry (ROTEM) parameters were used to assess coagulation and platelet function.

Results: ROTEM parameters included CT (clotting time), CFT (clot formation time), maximum clot firmness (MCF) measured by MCF (EXTEM and INTEM), MCF (FIBTEM) and standard coagulation tests ($p > 0.05$). No significant differences were found between the two groups. Moreover, ROTEM parameters did not show significant changes at different time points after administration of the hyperosmolar solutions ($p > 0.05$). **Conclusions** Overall, use of 3% HTS and 20% MT for the control of ICP did not significantly affect patients' coagulation function. Therefore, hyperosmotic solution is safe and does not increase the risk of intracranial rebleeding.

1. Introduction

Hypertonic solutions are clinically effective treatments used to relieve high intracranial pressure (ICP). The most commonly used clinical dehydration drugs, 3% hypertonic salt (HTS) and 20% mannitol (MT), are administered by peripheral intravenous administration and achieve rapid results [1]. Of concern, previous studies have indicated that both hypertonic solutions may potentially prevent coagulation. However, results from *in vitro* hemodilution studies [2-4], studies focused on traumatic brain injury (TBI) complicated by severe combined injury, or even hemorrhagic shock cases [5] have not definitively linked hypertonic solution use to coagulation effects. Because severe trauma can lead to traumatic coagulopathy [6,7] and hemorrhagic shock may occur after blood dilution after numerous resuscitation rounds, coagulation abnormalities may be triggered by various factors [8]. Therefore, hypertonic solution use should be evaluated as a potential cause of aberrant TBI coagulation function. In this study, we compared the effects of HTS and MT on coagulation in patients with moderate TBI who had not undergone craniotomy and who did not suffer severe combined trauma or hemorrhagic shock. Our results demonstrated that both types of hypertonic solution, when used to control high intracranial pressure (ICP), were both safe and effective and did not cause abnormal coagulation.

2. Methods

2.1. Study design

We conducted a study of coagulation profiles of adult moderate TBI patients who were treated with hypertonic solutions between January 2013 and December 2016 at The First Hospital of Jilin University in China. The current study was performed after randomization of patients into experimental groups followed by double-blind data collection and analysis of results.

2.2. Patient selection

Patients who met all inclusion criteria were enrolled in the study. Data were collected from 83 patients who were undergoing treatment for moderate TBI, including 43 males and 40 females between 18 and 65 years of age. Each patient had an Injury Severity Score (ISS) ≥16

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and isolated closed TBI with Abbreviated Injury Scores (AIS) of AIS head >3, AIS non-head <3. All had moderate TBI (GCS 8–12) with evidence of brain edema, as visualized by computed tomography (CT) scan. Patients with penetrating head traumas, known histories of coagulation disorders, those receiving anticoagulants, and pregnant subjects were excluded. All patients were evaluated using CT scans and all were treated in the intensive care unit (ICU) according to Brain Injury Foundation TBI guidelines [9]. Patients were randomly assigned to two treatment groups and were blinded to treatment group. In group A, patients received a dose of 20% MT (Shijizhuang, China) of 0.25–0.5 ml/kg every 6 h based on patient response (defined by GCS and CT improvement and serum osmolarity) for 3 days [1]. In group B, patients received a dose of 1.5–3.0 ml/kg of 3% HTS (Shijiazhuang, China), every 8 h for 3 days [1].

Written informed consent for participation in the study was obtained from all participants or their guardians. We evaluated clinical courses and outcomes and the data included additional patient information. All patients underwent six-month follow-up. This study was approved by the Institutional Review Board (IRB) of The First Hospital of Jilin University (IRB00008484).

2.3. Rotational thromboelastography

Whole blood coagulation was analyzed by rotational thromboelastometry (ROTEM®; TEM Innovation GmbH, Munich, Germany) according to the manufacturer's instructions using methods previously described for canine samples [10]. Briefly, a 300 μl sample of citrated whole blood was added to the clotting reagents in the prewarmed cuvette using the supplied electronic pipette. The assays used were EXTEM, INTEM, and FIBTEM (Tem Innovations GmbH, Munich, Germany). The clotting reactions were assessed using the manufacturer's data processing software. Data obtained included clotting time (CT), clot formation time (CFT), and maximum clot firmness (MCF) [11]. Only MCF was measured during FIBTEM analysis. These tests were always performed by the same researcher who was blinded to the patient treatment group. All tests were completed within 15 min after blood was drawn.

2.4. Definition of coagulopathy

Using standard coagulation tests, coagulopathy was defined by one or more of the following results: an international normalized ratio (INR) ≥1.2, prothrombin time (PT) >13 s, activated partial thromboplastin time (aPTT) >40 s, fibrinogen <1.8 g/l, platelet count $<25 \times 10^9$/l. By ROTEM results, coagulopathy was defined as one or more of the following results: EXTEM CT >80 s, EXTEM CFT >159 s, EXTEM MCF <50 mm, and FIBTEM MCF <9 or >25 mm [12].

2.5. Data collection

Prospective data were collected on patient demographics, including age, gender, time interval between injury and hospital arrival (*i.e.*, elapse time), ISS, AIS, and GCS. Along with standard coagulation tests including hemoglobin level and platelet counts, blood clotting tests including INR, PT, aPTT, and fibrinogen were performed for each research sample as part of standard care. All variables were measured and recorded after administration of the administered hypertonic solution at 12 h, 24 h, 48 h, and 72 h. The analysis included the most extreme results and all professionals involved in patient care were blinded to patient treatment group.

2.6. Statistical analysis

Results are expressed as the mean ± SD. Data distribution was tested for normality using the Kolmogorov-Smirnov test. Differences between 20% mannitol and 3% HS groups were analyzed by using the χ^2 test and ANOVA after Bonferroni correction as part of *post hoc* analysis. We have power analysis by using G*Power software (Universität Kiel, Germany version 3.1.9.2), a sample of 40 participants will be needed for each group to avoid a β error at the level of 90%, and a confidence level of 0.95. For all statistical tests, the level of significance was set to 0.05. Statistical analysis was performed using SPSS software (SPSS Inc. SPSS Statistics for Windows, Version 17.0. Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

The characteristics of patients are summarized in Table 1. In total, 83 patients fulfilled the inclusion criteria for this study (Table 1). Of 83 patients, 43 were treated with 20% MT (Group A) and 40 with 3% HTS (Group B). No difference was observed across groups in terms of age, gender, Injury Severity Score (ISS), Abbreviated Injury Score (AIS), Glasgow Coma Scale (GCS) score, or time from injury to hospital admission (elapsed time). Both MT and HTS resulted in a similar immediate increase in serum osmolality that remained elevated above baseline for 3 days.

3.2. Classic coagulation tests and hematology parameters

Baseline values of coagulation and hematology parameters (PT, aPTT, fibrinogen, platelet count, hematocrit, and hemoglobin) fell within normal ranges with similar trends for both groups (Table 3). PT and aPTT values showed no significant differences between both groups. The levels of parameters that gradually decreased with onset time included fibrinogen, platelet count, hematocrit, and hemoglobin level, but these parameters did not differ between the two groups for a given time point (Table 3).

3.3. Rotational thromboelastography

ROTEM parameters remained within normal established laboratory reference value ranges and no abnormalities in mean values were detected. Moreover, there were no significant differences between the mannitol and HTS groups in CT, CFT, and MCF (EXTEM, INTEM, and FIBTEM analysis) for each time point ($p > 0.05$, Table 2). ROTEM parameters did not differ statistically among the various time points tested within the same group ($p > 0.05$, Table 2).

4. Discussion

Previous *in vitro* studies have found that HTS and MT may affect a patient's coagulation function [2-4]. The samples analyzed in those studies included blood samples from normal subjects, TBI patients, and various mammals. Findings of other studies, based on blood samples after dilution to a defined concentration, demonstrated that HTS

Table 1
Clinical characteristics of TBI patients ($n = 83$)

	Group A ($n = 43$)	Group B($n = 40$)	p-Value
Hypertonic solution	20% MT	3% HTS	
Age (ys)	38.5 ± 13.7	39.2 ± 15.1	$p > 0.05$
Gender (F/M)	19/24	17/23	$p > 0.05$
Elapsed time(hours)	6.5 ± 2.9	6.7 ± 2.1	
GCS	8 ± 3	9 ± 4	$p > 0.05$
ISS	21.7 ± 6.3	22.1 ± 6.9	$p > 0.05$
AIS head	4.9 ± 0.7	4.8 ± 0.5	$p > 0.05$
Osmolality (mOsm/kg)			
12 h	312 ± 6	314 ± 4	$p > 0.05$
24 h	314 ± 5	315 ± 7	$p > 0.05$
48 h	316 ± 7	318 ± 6	$p > 0.05$
72 h	319 ± 8	317 ± 5	$p > 0.05$

$p < 0.05$, MT: Mannitol, HTS: Hypertonic saline.