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Reliability of calcium-binding protein S100B measurement toward optimization of hyperosmolal therapy in traumatic brain injury

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Abstract. – BACKGROUND: Osmotherapy is a cornerstone for the management of severe Traumatic Brain Injury (TBI). Hypertonic saline (HTS) has advantages as being preferred osmotic agent, but there is inadequte knowledge regarding dose and its saftey in comparison to mannitol. S100B, as a specific neuroinflammatory biomarker in TBI might be a reliable therapeutic index following osmotic therapy.

AIM: To compare both administration ways of HTS 5% (bolus and infusion) with mannitol upon S100B as a therapeutic tool for monitoring treatment in TBI patients.

METHOD: Adult patients wih modrate to severe TBI were recruited and have randomly received one of the three protocols: 125 cc of HTS 5% every 6 hrs (N: 11) as bolus; 500 cc of HTS 5% (N: 12) as infusion for 24 hrs; or 1 g/kg mannitol of 20% (N: 10) as a bolus, repeated with a dose of 0.25-0.5 g/kg every 6 hrs based on patient's response for 3 days. Serum S100B, blood pressure, serum sodium and osmolality and Glascow coma score (GCS) were measured at baseline and daily for 3 days.

RESULTS: Initial serum S100B level in TBI patients was higher than control group ($p < 0.0001$). Levels of measured S100B have decreased for all treatment groups, but reduction wasn't significantly after hyperosmolal therapy. GCS level increased significantly in infusion group ($p = 0.002$) and there were negative and significant correlation between serum S100B level and GCS level in some days. Mean arterial pressure increased significantly in HTS groups (bolus: $p = 0.002$, infusion < 0.0001).

CONCLUSIONS: S100B is closely related to the pathophysiological mechanism in TBI and may be useful as a therapeutic tool for treatment monitoring in TBI patients HTS is a safe and effective osmotic agent in TBI setting.

Key Words:
Traumatic brain injury, Hypertonic saline 5%, Mannitol, S100B, Osmotherapy, Intracranial hypertension.

Introduction

Traumatic Brain Injury (TBI) remains a major reason of morbidity and mortality around the world both developed and underdeveloped countries[1]. TBI leading to 20-50% lethal outcome and 30-55% severe neurological disability. Vehicle-related accidents and falling are the two main causes of head trauma in the world[1,2].

Pathophysiology of TBI including primary injury due to mechanical damage to brain tissue at the first minute of injury following by secondary

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injuries results in an inflammatory cascade that increases the production of oxygen derived free radicals, intracellular free calcium, glutamate and interleukins[3,4]. Cerebral edema and elevated intracranial pressure (ICP) are the consequence of secondary brain damage. Reduction of ICP improves the cerebral perfusion pressure (CPP) and decreases the mechanical damage caused by compartmental shifts and local compression of brain tissue[5]. Osmotherapy remains the cornerstone of medical therapy for the brain edema[5,6]. Osmotic agents reduce the volume of intracranial contents coupled with other routine measures[7].

Mannitol is the recommended first line agent for reduction of ICP, but the side effects such as dehydration, hypotension, renal failure and rebound increase in ICP limit its use, leading to introduction of new osmotic agents such as hypertonic saline (HTS)[6,8]. Besides reduction in water content in brain tissue and ICP, HTS improve mean arterial pressure (MAP) and subsequently CPP and oxygen delivery. HTS has some other systematic effects including transient volume expansion, natriuresis, hemodilution, reduction of blood viscosity, immunomodulation and improved pulmonary gas exchange[9-11].

Different randomized clinical trials[12-19] and recent meta analysis[20] suggest HTS as an more efficient and favourable agent in comparison to mannitol for the reduction of ICP after head trauma but still there is inadequate knowledge regarding safety, optimum duration and dose of HTS in TBI patients. So we decided to compare HTS 5% both way of administration (bolus and continuous infusion) with mannitol in TBI patients.

Current method for evaluation of the treatment efficacy such as neuroimaging study, neurological examination and ICP monitoring are not precise enough[21,22]. Emerging data suggest that biomarkers of brain injury have potential utility as diagnostic and prognostic factor in TBI[21,23-25]. S100B is a calcium binding protein that has both neuroprotective and neurotrophic effects and released from cerebral and extracerebral tissues. It seems that S100B serum levels correlated with brain injury positively and negatively with outcome[21]. Some studies suggested S100B as a biomarker for determining severity of brain injury and also monitoring of therapeutic intervention[26].

In this study we are going to compare both administration methods of HTS delivering (bolus and continuous infusion) versus mannitol and evaluate the role of S100B as a therapeutic tool for monitoring treatment.

Patients and Methods

This study was an open label randomized clinical trial (clinical registration ID: 201011055107N1) conducted at three Intensive Care Units (ICU) in Iran (between October 2009 and May 2011).The study have received ethical approval from the Ethic Committee of Tehran University of Medical Sciences and Health Services (TUMS). Written informed consent was obtained from each patient's relatives.

Patients

All the patients recruited in this investigation had severe brain injury (Glasgow Coma Scale (GCS) ≤ 12) and have been admitted within 24 hours from Emergency Department to surgical or general ICU.

Patients were included if they were aged between 18 to 65 years, GCS ≤ 12 and evidence of brain edema on head Computed Tomography (CT) scan (e.g. sulci effacement, hypodensity surrounding discrete brain lesions in structures associated with consciousness, abnormal diffuse white matter lucency, lateral shift of midline structure).

Patients with penetrating head trauma, serum sodium > 160 meq/L or < 130 meq/L, serum osmolarity > 350 mOsmol/kg, acute renal failure (an abrupt (within 48 hours) absolute increase in the serum creatinine concentration of ≥ 0.3 mg/dL from baseline, a percentage increase in the serum creatinine concentration of ≥ 50 percent, or oliguria of less than 0.5 mL/kg per hour for more than six hours) during the study, hepatic failure (ALT, AST > 5 upper limit normal or cirrhosis) before or during the study, shock (mean arterial pressure: MAP ≤ 60 mmHg), heart failure [Ejection Fraction (EF) < 40%] and pulmonary edema [central venous pressure (CVP) > 15 mmHg)], Body Mass Index (BMI) > 25 kg/m^2, psychiatric and neurologic disorders history, and pregnant women were excluded from the study.

All patients were managed in the ICU based on the Brain Trauma Foundation TBI guidelines[27]. They were intubated and received mechanically ventilation with a head elevation of 30^o. Volume resuscitation was achieved with 0.9% normal saline for a target CVP of 8-12 mmHg. After adequate fluid resuscitation, MAP was kept above 90 mmHg. Sedation and analgesia were provided for all patients, using continuous infusion of midazolam and morphine to maintain good analgesic control and sedation. Insulin treatment was administered to maintain glucose at < 200 mg/dl.

Measurements

For each patient a set of variables included demographic (age, gender), admitting neurological diagnosis, initial GCS and Acute Physiology And Chronic Health Evaluation (APACHE) II[28] score and Sequential Organ Failure Assessment (SOFA)[29] score were collected on standardized form.

The following parameters were assessed at baseline and daily for 3 days. Temperature, creatinine, blood urea nitrogen (BUN), glucose, hematocrit, haemoglobin, platelet, WBC ount, MAP, CVP, heart rate (HR), Pupillary reaction (normal, unilaterally or bilaterally abnormal), blood osmolarity, electrolytes, arterial blood gas (ABG), and pH. Serum sodium was checked every 6 hours and the treatment was stopped if sodium reached above 155 meq/l. Serum osmolarity was measured by osmomat 030 (Gonotec, Berlin, Germany).

SOFA score and GCS were assessed daily for 3 days.

Length of ICU and hospital stay, mortality and 60 days survival were recorded for all patients for outcome evaluation.

Intervention

If the patient met our inclusion criteria, he was entered in the study. Six block randomization was applied for each treatment group.

In Group A, mannitol 20% (Samen, Iran), 1 g/kg was administered over 20 minutes via central venous catheter and repeated with a dose of 0.25-0.5 g/kg every 6 hours based on patient response (defined by GCS and CT improvement) for 3 days.

Second group (B), received 125 mL HTS 5% (Samen, Iran), over an hr via central venous catheter every 6 hours for 3 days. In the third group (C) 500 mL HTS 5% was continuously infused over 24 hrs for 3 days.

A group of healthy volunteers (N=30) without any psychiatric and neurologic disorders history and BMI < 25 kg/m^2 were assessed for establishment of normal serum levels of S100B.

Biomarker Measurement

Venous blood samples were collected in 5 ml non-additive tube from central venous catheter at baseline and following 3 days of treatment on a certain time daily. Each sample was kept for 20 minutes at room temperature to clot and then centrifuged (3500 rpm) for 15 minutes. The serum was separated and stored at –80°C for further analysis. Serum S100B was analyzed using commercially available ELISA kit (Bio Vendor, Research and Diagnostic Products, Modrice, Czech Republic) according to the manufacturer instruction.

Statistical Analysis

All data were assessed for normality by one sample Kolmogorov-Smirnov test. Qualitative variables were recorded by frequency and percent and quantitative variables by Mean ± SD (Standard Deviation). Qualitative variables were compared by Fisher's exact test. ANOVA and Kruskal-Wallis test were used, for comparing quantitative variables in three groups, when was appropriate and Mann-Whitney U test was made for comparing quantitative variables in two groups. Repeated measurement analysis was conducted for serial comparisons of biomarker concentration and quantitative variables and comparisons between groups in different times of treatment. Pairwise comparison was applied by Scheffe. The correlation between quantitative variables was made by Spearman test. For survival analysis, Kaplan-Meier method was applied and for comparison between groups in survival, Log-Rank test was selected. All statistical analysis were conducted using SPSS version 11.5 and 13 (SPSS Inc., Chicago, IL, USA) and p value of less than 0.05 was considered significant.

Results

39 consecutive patients with moderate and severe TBI were assessed, 6 of them were ineligible, and one in mannitol group died after 3 doses. One in bolus and one infusion of HTS 5% were misdiagnosed and 2 patients in bolus and one infusion of HTS 5% were received 2 doses of mannitol instead of HTS. From 33 remaining patients, 10 of them received mannitol (group A), 11 patients received HTS as a bolus (group B) and 12 patients as a continuous infusion of HTS (group C). Baseline demographic and clinical characteristics are shown in Table I. There was no significant difference between patient groups except gender. Evaluation of 60 days survival between patients have demonstrated that there was no significant difference in 60 days survival of patients in different groups ($p = 0.1$) (Table II, Figure 1).

The mean serum concentration of S100B was 0.01±0.004 µg/l for control group. As compared to the healthy control group, TBI patients had significantly higher initial serum levels of S100B

Table I. Baseline demographic and clinical characteristics of TBI patients

	Mannitol	Bolus of HTS	Infusion of HTS	p value
Age (year)	34.2 ± 9	33.6 ± 13.05	40.58 ± 16	0.1[a]
Gender, n (% M)	6 (60%)	11 (100%)	11 (92%)	0.002[b,*]
Mechanism of injury, n (%)				0.6[a]
Car accident	4 (40%)	5 (45.5%)	5 (41.7%)	
Motor accident	5 (50%)	4 (36.4%)	3 (25%)	
Falling	1 (10%)	1 (9.1%)	4 (33.3%)	
Electricity insult	0 (0%)	1 (9.1%)	0 (0%)	
Initial GCS	6.5 ± 3.3	8.1 ± 2.1	6.4 ± 1.5	0.1[a]
Initial SOFA	6.7 ± 2.2	6.5 ± 1.5	6.5 ± 2.4	0.9[a]
Initial APACHE II	14.6 ± 5.4	12.18 ± 5.9	17.08 ± 4.6	0.1[a]
Initial S100B (µg/l)	0.05 ± 0.03	0.04 ± 0.03	0.37 ± 1.1	0.1 c,
Initial Serum Na^+ (mEq/l)	138 ± 3.06	141.55 ± 7.6	146.33 ± 7.9	0.02[a,*]
Initial Serum Osmolality (mOsml/kg)	310 ± 18.73	307.82 ± 16.8	288.42 ± 25.48	0.03[a,*]
Initial MAP (mmHg)	85 ± 7.2	85.45 ± 14.5	84.16 ± 5.4	0.9
LoICU stay (day)	16.9 ± 9	14.2 ± 12	11.17 ± 7.7	0.5[a]
LoH stay (day)	20.7 ± 21.25	18.18 ± 12.4	18.09 ± 1.84	0.9[a]
Morbidity				
Sepsis, n (%)	3 (30%)	0 (0%)	2 (17%)	
MOF, n (%)	3 (30%)	0 (0%)	1 (8%)	
Seizure, n (%)	1 (10%)	0 (0%)	0 (0%)	

a: One way ANOVA; b: Fisher' exact test; c: Kruskal-wallis test; *$p < 0.05$ considered significant. TBI: traumatic brain injury; HTS: hypertonic saline; GCS: Glasgow Coma Scale; APACHE II: Acute Physiologic and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; LoICU: Length of Intensive Care Unit; LOH: Length of Hospital; MOF: Multi Organ Failure; Na^+: Sodium; MAP: Mean Arterial Pressure.

at ICU admission ($p < 0.0001$) (Table I). Following intervention, the levels of S100B decreased in all groups but this reduction was not significant ($p = 0.3$), and there was no differences between groups (p=0.4) (Table III, Figure 2).

GCS level increased significantly during study period ($p = 0.047$). The evaluation of each group showed that this elevation was significant only for infusion part ($p = 0.002$). Our intervention reduced SOFA score significantly ($p = 0.018$), and the evaluation of each group showed that this reduction was significant only in bolus group ($p = 0.002$) (Table IV).

We have evaluated the correlation between serum S100B and GCS level and SOFA score in different times during the study. There was a negative correlation between serum S100B level and GCS on first and third study day (r = –0.401, $p = 0.021$ and r = –0.469, $p = 0.006$ respectively) (Table V).

Mean serum sodium concentration was significantly higher in infusion of HTS group as compared to mannitol at baseline ($p = 0.005$). Serial values of serum sodium concentration weren't significant for all the treatment groups during the study ($p = 0.7$) and hypernatremia state (serum sodium > 155 meq/L) wasn't detected.

Following the intervention serum osmolarity had increased in all treatment groups ($p = 0.001$). The assessment of each group determined that serum osmolarity significantly increased in HTS window. Nevertheless, during intervention the serum osmolarity has remained in normal range (305-324 mOsm/kg) (Table VI).

Table II. 60 days survival of patients in three groups.

Group	Survival	Mean of survival	Std. error	95% confidence interval	p value
Mannitol	21%	28.9	8.5	12.06-45.7	0.1
Bolus of HTS	82%	40.2	4.9	30.5-49.9	
Infusion of HTS	65.5%	46.8	9.2	28.7-64.8	
Overall	48%	41.9	5.9	30.4-53.5	

Kaplan-Meier method for survival analysis and log-rank test for comparison between groups.

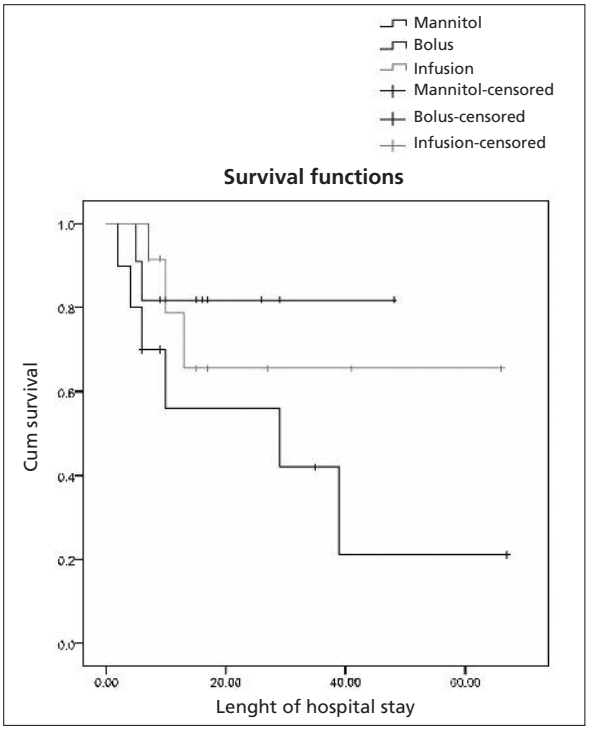

Figure 1. 60 days survival in three treatment groups.

Table VI is showing MAP changes during the study. Following the intervention, MAP was significantly increased in bolus of HTS (p= 0.002) and infusion of HTS groups ($p < 0.0001$).

Discussion

The results of this investigation are indicating that S100B levels have decreased during intervention with both osmotic agents (Mannitol and HTS) and GCS increased significantly along with S100B reduction. To our knowledge, this was the first study which was compared both administration means of HTS delivering (bolus and continuous infusion) versus mannitol and evaluated the role of S100B as a therapeutic tool for monitoring treatment.

S100B is the best-known biomarker for determining severity of brain damage and has been shown to predict prognosis after acute TBI[30,31]. As we can't monitor ICP in our centers, S100B was selected for evaluation of therapeutic response to osmotic agents. Limited studies examined S100B as a biomarker in TBI management.

S100B is an astrocyte-glial derived calcium binding protein involved in multiple intracellular and extracellular processes. Within cells, S100B affects protein phosphorylation and enzyme activation, also via interaction with cytoplasmic cytoskeleton proteins such as GFAP and CAPz, regulates cell morphology[32,33]. The extracellular functions are concentration-dependent. S100B has neuroprotective and neurotropoic actions at nonamolar concentration. Activation of NF-kB and anti-apoptotic proteins are suggested mechanisms that promote neuronal survival[34,35]. At micromolar concentration; S100B has apoptotic function and causes neuronal damage. Activation of signaling pathways such as ERK, NF-kB and production of nitric oxide and peroxinitrite through overexpression of nitric oxide synthase result in apoptosis[36,37]. Some studies indicated that S100B is a component of neuroinflammatory responses which likely contribute to the pathogenesis of secondary injuries[21].

Baker et al[26] in a randomized controlled trial compared serum concentration of S100B and other biomarkers in adult patients with severe TBI (GCS ≤ 8) after resuscitation with 7.5% HTS/6% dextran 70 (HSD) versus 0.9% normal saline (NS). Compared to NS group, S100B were twofold lower in HSD-treated patients. Elevated levels of S100B in patient's group were along with worse outcome. They concluded that prehospital resuscitation with HSD is associated with the reduction of serum S100B which are correlated with better outcome after severe TBI. In our study, the use of HTS was associated with a higher impact on the measured concentration of S100B and GCS level in comparison with manni-

Table III. Serum S100B concentrations at baseline and during the study in treatment groups.

p value (between groups)	Infusion of HTS	Bolus of HTS	Mannitol	S100B (µg/l)
0.4	0.37 ± 1.1	0.042 ± 0.035	0.058 ± 0.03	Baseline
	0.28 ± 0.8	0.04 ± 0.02	0.041 ± 0.009	The 1th day
	0.035 ± 0.01	0.04 ± 0.024	0.034 ± 0.006	The 2th day
	0.03 ± 0.00	0.03 ± 0.0	0.03 ± 0.01	The 3th day
	0.3	0.2	0.06	*p* value

*$p < 0.05$ considered significant. Repeated measurement analysis.

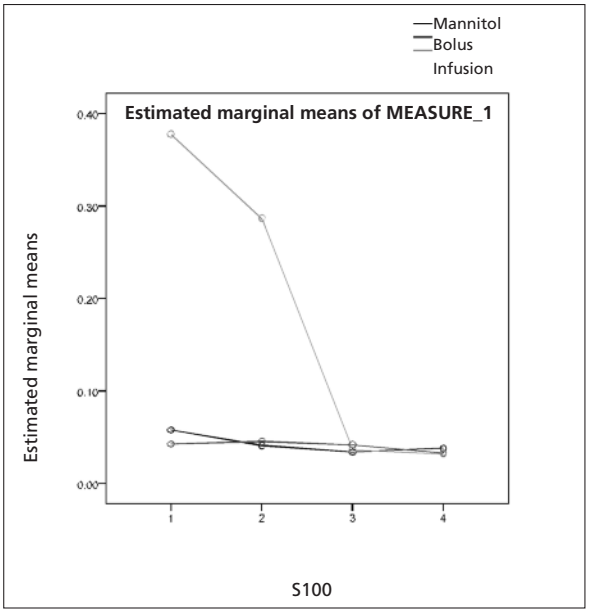

Figure 2. Initial serum levels of S100B at baseline and following the intervention in treatment groups.

tol and implicated that HTS could have some neuroprotective effects unrelated to relief of elevated ICP which reduce secondary brain damage and improve neuronal and glial cell survival.

HTS reduces leukocyte activation/adhesion, down regulates proinflammatory cytokines production, upregulates anti-inflammatory cytokines in TBI patients (5,11,38) and reduction of S100B levels could be suggestive for the anti-inflammatory role of HTS.

In our study, infusion of HTS group had the highest mean baseline S100B but more patients died in mannitol group (60 days survival was 21%), also rate of complication such as sepsis and multiorgan failure were higher with mannitol group. It seems that HTS mechanism in the management of TBI is very complex and interaction between osmotic, vasoregulatory, antiinflammatory and neurochemical modulation affecting whole process of TBI management.

Several studies have evaluated the therapeutic benefits of mannitol vs HTS. The recent meta-analysis by Kamel et al[20] have found that HTS is more effective than mannitol for treatment of elevated ICP, but it seems that both agents weren't directly affecting patient's survival. In our study more patients have died in mannitol group. To investigate the true impact of these agents on survival calls for larger sample size researches.

Most of the studies which have administered HTS as a bolus, had an ICP reduction lasting for > 120 min[13,16-18,39] and for more persistent reduction of ICP, repeated bolus of HTS shall be necessary. Nevertheless, in comparison to mannitol HTS has a longer duration of effect. Based on our result HTS as continuous infusion had more favorable outcome, greater decline in S100B, higher elevation in GCS level and better steady MAP. Qureshi et al[14] have showed that continuous infusion of HTS transiently improved ICP, but it sometimes followed by rebound intracranial hypertension. Other studies showed no improvement in neurologic outcome after continuous infusion of HTS therapy. Also there were not any significant relation between continuous infusion of HTS and adverse effects[14,15,40]. Therefore, role of continuous infusion of HTS in management of TBI patients remained somewhat unclear.

Bolus administration of HTS resulted in acute increase in serum sodium concentrations (a 250 ml bolus of 7.5% HTS elevate serum sodium to

Table IV. Neurologic and organ function severity data at baseline and during the study in treatment groups.

p value (between groups)	Infusion of HTS	Bolus of HTS	Mannitol	GCS
0.1	6.4 ± 1.5	8.1 ± 2.1	6.5 ± 3.3	Baseline
	6.7 ± 1.5	7.9 ± 2.02	5.9 ± 3.3	The 1th day
	7 ± 1.8	8.3 ± 2.1	7 ± 2.7	The 2th day
	7.6 ± 1.9	9 ± 2.3	6.6 ± 3.5	The 3th day
	0.002*	0.2	0.7	*p* value
SOFA				
0.9	6.5 ± 2.4	6.5 ± 1.5	6.7 ± 2.2	Baseline
	6.7 ± 2.4	7 ± 1.9	6.4 ± 2.2	The 1th day
	6.2 ± 2.4	5.7 ± 2	6.7 ± 2.5	The 2th day
	6.2 ± 2.09	5.3 ± 1.5	6 ± 1.8	The 3th day
	0.5	0.002*	0.4	*p* value

GCS: Glasgow Coma Scale, SOFA: Sequential Organ Failure Assessment. *$p < 0.05$ considered significant repeated measurement analysis.

Table V. Correlation between serum S100B level with GCS and SOFA every day during the treatment in all patients.

S100B third day	S100B second day	S100B first day	S100B baseline	
			r = -0.401 *p* = 0.021*	GCS baseline
		r = -0.146 *p* = 0.417		GCS first day
	r = -0.262 *p* = 0.141			GCS second day
r = -0.469 *p* = 0.006*				GCS third day
			r = 0.211 *p* = 0.239	SOFA baseline
		r = -0.059 *p* = 0.743		SOFA first day
	r = 0.101 *p* = 0.576			SOFA second day
r = 0.139 *p* = 0.439				SOFA third day

*$p < 0.05$ considered significant spearman analysis.

160 meq/l) which were associated with rapid reduction of ICP and increased in CPP[41]. However, continuous infusion of HTS have increased serum sodium gradually and maintained it for a large period of time[42,43]. In Peterson et al[44] study, continuous infusion of HTS 3% resulted in favorable control of ICP without any hypernatremic adverse state. Even an administration of HTS 23.4% have caused a greater reduction in ICP in severe TBI without any adverse effect as compared with mannitol[12]. Similarly, in our study, patients in both HTS groups did not experienced any side effect of hypernatremic state.

Fluid strategy is a major challenge in patients with TBI for both preserving cerebral blood flow and oxygen delivery[45]. Following our intervention, MAP was significantly improved in HTS groups. HTS increases MAP by increasing intravascular volume and cardiac output. Based on Francony et al[46] and Oddo et al[47] studies, MAP didn't change

Table VI. Physiological variables before and after intervention in treatment groups.

MAP (mmHg)	Mannitol	Bolus of HTS	Infusion of HTS	*p* value (between groups)
Baseline	85 ± 7.2	85.45 ± 14.5	84.16 ± 5.4	0.01[d,*]
The 1th day	85 ± 6.7	93.6 ± 10.06	94.08 ± 7.6	
The 2th day	85 ± 7.1	97.4 ± 8.6	94.83 ± 4.8	
The 3th day	86 ± 7.05	99.4 ± 8.9	95.8 ± 4.4	
p value	0.7	0.002*	< 0.0001*	
Sodium (mEq/l)				
Baseline	138 ± 3.06	141.55 ± 7.6	146.33 ± 7.9	0.1
The 1th day	140.02 ± 5.4	141.9 ± 7.9	143.5 ± 4.5	
The 2th day	142.5 ± 5.4	141.9 ± 6.2	142.4 ± 3.8	
The 3th day	140.4 ± 3.5	139.9 ± 4.9	143.6 ± 5.2	
p value	0.09	0.5	0.2	
Osmolality (mOsm/kg)				
Baseline	310 ± 18.73	307.82 ± 16.8	288.42 ± 25.48	0.01[e,*]
The 1th day	326.7 ± 29.02	317.18 ± 21.52	294.25 ± 18.93	
The 2th day	331.2 ± 41.93	324.36 ± 20.03	301.67 ± 17.07	
The 3th day	328.4 ± 40.94	319 ± 14.34	305.33 ± 19.15	
p value	0.1	0.01*	0.01*	

MAP: Mean Arterial Pressure; d: The significant difference between mannitol and bolus of HTS group ($p = 0.01$); e: The significant difference between mannitol and infusion of group ($p = 0.01$); *$p < 0.05$ considered significant repeated measurement analysis, pairwise comparison by scheffe.

significantly during mannitol and HTS treatment groups. However, HTS improved CPP more efficiently while decreasing ICP more efficiently than mannitol group[18,19,48]. Also repeated administration of mannitol resulted in diuresis, hypovolemia and rebound increase in ICP[49]. Therefore, HTS could be considered as a better choice for fluid therapy in other similar settings.

Our data suggest that osmotherapy with HTS and mannitol is associated with the reduction in S100B levels and consequently improving of GCS and SOFA. S100B is closely related to the pathophysiological mechanism in TBI and may be useful as a therapeutic tool for treatment monitoring in TBI patients. More studies are necessaries with larger sample size. HTS is not only safe and effective as an osmotic agent but also has a cytoprotective effect, as has been verified by S100B serum level reduction.

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