

Equimolar doses of hypertonic agents (saline or mannitol) in the treatment of intracranial hypertension after severe traumatic brain injury

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Abstract

Background: Mannitol and hypertonic saline (HTS) are effective in reducing intracranial pressure (ICP) after severe traumatic brain injury (TBI). However, their efficacy on the ICP has not been evaluated rigorously.

Objective: To evaluate the efficacy of repeated bolus dosing of HTS and mannitol in similar osmotic burdens to treat intracranial hypertension (ICH) in patients with severe TBI.

Methods: The authors used an alternating treatment protocol to evaluate the efficacy of HTS with that of mannitol given for ICH episodes in patients treated for severe TBI at their hospital during 2017 to 2019. Doses of similar osmotic burdens (20% mannitol, 2 ml/kg, or 10% HTS, 0.63 ml/kg, administered as a bolus via a central venous catheter, infused over 15 minutes) were given alternately to the individual patient with severe TBI during ICH episodes. The choice of osmotic agents for the treatment of the initial ICH episode was determined on a randomized basis; osmotic agents were alternated for every subsequent ICH episode in each individual patient. Intracranial pressure (ICP), mean arterial pressure (MAP), and cerebral perfusion pressure (CPP) were continuously monitored between the beginning of each osmotherapy and the return of ICP to 20 mm Hg. The duration of the effect of ICP reduction (between the beginning of osmotherapy and the return of ICP to 20 mm Hg), the maximum reduction of ICP and its time was recorded after each dose. Serum sodium and plasma osmolality were measured before, 0.5 hours and 3 hours after each dose. Adverse effects such as central pontine myelinolysis (CPM), severe fluctuations of serum sodium and plasma osmolality were assessed to evaluate the safety of repeated dosing of HTS and mannitol.

Results: Eighty three patients with severe TBI were assessed, including 437 ICH episodes, receiving 236 doses of HTS and 221 doses of mannitol totally. There was no significant difference between equimolar HTS and mannitol boluses on the magnitude of ICP reduction, the duration of effect, and the time to lowest ICP achieved ($P > .05$). The proportion of efficacious boluses was higher for HTS than for mannitol, although which showed a slight difference ($P = 0.207$), as was the increase in serum sodium ($P = .038$). The serum osmolality increased immediately after osmotherapy with a significant difference ($P = .017$). No cases of CPM were detected.

Conclusion: Repeat bolus dosing of 10% HTS and 20% mannitol appears to be significantly and similarly effective for treating ICH in patients with severe TBI. The proportion of efficacious doses of HTS on ICP reduction may be slightly higher than mannitol.

Abbreviations: CPM = central pontine myelinolysis, CPP = cerebral perfusion pressure, CT = computed tomography, CTA = computed tomography angiography, CVP = central venous pressure, GCS = Glasgow Coma Scale, GOS = Glasgow Outcome Scale, HTS = hypertonic saline, ICH = intracranial hypertension, ICP = intracranial pressure, ICU = intensive care unit, MAP = mean arterial pressure, TBI = traumatic brain injury.

Keywords: efficacy, hypertonic saline, intracranial hypertension, mannitol, traumatic brain injury

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1. Introduction

Severe TBI is one of the leading causes of death in industrialized countries, and is a major cause of long-term disability. The vast majority of patients with severe TBI have ICH (ICP above 20 mm Hg), which is associated with the poor neurological outcomes of the patients. The literature reports that the mortality rate of patients with head injury with ICP below 20 mm Hg is 18.4%, while the mortality rate is as high as 55.6% in those patients with ICP above 40 mm Hg.^[1] Therefore, the Brain Trauma Foundation has recommended that treatment protocols for the management of ICH should be instituted immediately when ICP rises above 20 mm Hg.^[2,3]

Hyperosmolar therapy is the standard medical management strategy for ICH after supportive care which is most important for neuroprotection (sedation, analgesia, position, and so on). Currently, only 2 osmotic agents are utilized for this purpose: mannitol and HTS. Mannitol has been the primary hyperosmolar agent for nearly a century and remains a common treatment for ICH. Guidelines currently recommend mannitol as the mainstay in the treatment of ICH.^[2,3] Nevertheless, with the wide application of mannitol, its side effects have attracted the attention of more and more scholars. Its side effects such as ICP rebound, acute tubular necrosis, and acute kidney failure are not uncommon after repeated doses.^[4–6] Furthermore, the effect becomes less after multiple doses, especially greater than 3 to 4 doses/24 hours.^[7,8] Due to these concerns, it is urgent to find a new, safe and effective medication for reducing ICP. Over the past 30 years, HTS has become a progressively good alternative, and several recent studies have suggested its relative superiority.^[9,10] These findings have prompted calls for large-scale case-control trials of mannitol and HTS. The comparison of various concentrations of HTS and 20% mannitol in the treatment of ICH have been reported commonly, but a head-to-head comparison of 10% HTS and 20% mannitol in equimolar loads in the treatment of ICH has not been reported. In this study, from January 2017 to February 2019, we randomized intravenous infusions of 10% HTS and 20% mannitol in similar osmotic burdens to patients with severe TBI at ICP greater than 20 mm Hg for more than 5 minutes to evaluate the efficacy of HTS and mannitol to reduce ICP.

2. Methods

2.1. Patients selection

This study was reviewed and approved by the Medical Ethics Committee of the hospital. Informed consent was granted by a legal guardian before admission to the study. From January 2017 through February 2019, we recruited adults with severe TBI in the intensive care units (ICUs) of our hospital.

Our inclusion criteria were eligible patients at least 18 years old, with severe TBI (GCS \leq 8) at admission, and with an ICP intraparenchymal monitor. Our exclusion criteria were shock or brain death; combined with serious dysfunction of organs such as heart, lung, liver, and kidney; combined with severe electrolyte disturbances (especially serum sodium concentration $<$ 125 mmol/L) and blood gas dysfunction, which are difficult to correct in a short time.

We included ICH episodes of over 20 mm Hg for over 5 minutes. Our exclusion criteria were ICP increased during the observation period due to irritability, pain, endotracheal suctioning, and urinary retention.

2.2. Conventional treatment

In general, the patients were treated according to the Brain Trauma Foundation Guidelines.^[2,3] All patients were admitted to ICUs after completion of head CT scans and initial therapeutic measures, either from the emergency room or from the surgical theater (for those who required craniectomy for the evacuation of intracranial bleeding, decompressive craniectomy, or placement of a ventricular drain). An arterial line and a central venous catheter were also placed. ICP monitor was (CaminoICP monitoring system, Integra Neurocare, USA) initiated with the catheter placed inside the brain parenchyma as soon as they were admitted to ICUs or during intracranial procedures. All patients were sedated with continuous infusion of analgesics (morphine or fentanyl) in combination with hypnotics (midazolam or propofol) to facilitate mechanical ventilation as usual. The head-end of the patients bed was elevated by 30°.

2.3. Experimental design

The aim of the therapy was to maintain the ICP below 20 mm Hg and CPP above 60 mm Hg. If ICP increased above 20 mm Hg, adequacy of sedation, ventilation, and head position would be the first-line intervention. If the ICP still remained high (above 20 mm Hg for above 5 minutes) in spite of first-line intervention, patients would receive osmotic agents. We gave one of the 2 osmotic agents on a random basis. Thereafter the choice of osmotic agents was alternated for each successive ICH event (mannitol \rightarrow HTS \rightarrow mannitol \rightarrow HTS . . . or HTS \rightarrow mannitol \rightarrow HTS \rightarrow Mannitol \rightarrow HTS...). The use of osmotic agents was continued as long as the ICP was increased above 20 mm Hg or until serum osmolality was up to 320 mOsm/L. In this study, based on theoretical calculation, 20% mannitol (administered at a dosage of 2 ml/kg) has a similar osmotic burdens to 10% HTS (administered at a dosage of 0.63 ml/kg). Mannitol and HTS were infused as a bolus via a central venous catheter over 15 minutes. If the ICP continued to be pathologically elevated after an osmotic agent, another osmotic agent, hyperventilation, barbiturate coma would be used in sequence. Then mild hypothermia and decompressive craniectomy could be performed after repeated head CT.

2.4. Efficacy and safety monitoring

We continuously measured ICP from the point at which the osmotic agents started to use until the ICP rebounded to 20 mm Hg. The time of Lowest ICP (the time that ICP dropped to the lowest after the end of the each infusion), the reduction of ICP (maximum reduction of ICP after the end of the each infusion), and the duration of the action (time to next ICH episode after the end of the each infusion) were recorded. Serum sodium and osmolality by arterial blood gas were measured before, 0.5 hours and 3 hours after the end of each infusion.

Heart rate and oxygen saturation were monitored continuously. The aim of mechanical ventilation was to maintain a SpO₂ of $>$ 95%, a PaO₂ $>$ 60 mm Hg, and partial pressure of carbon dioxide of about 35 mm Hg. Blood pressure was monitored every 15 minutes and hypotension (systolic blood pressure $<$ 90 mm Hg) avoided. Central venous pressure (CVP) was measured before, 0.5 hours and 3 hours after administration. MAP and CPP were documented at quarter-hourly intervals. Renal function tests were done once a day. Daily fluid intake-output balance was noted.

Finally, we studied the GCS and Glasgow Outcome Scale (GOS) scores of the patients, and their extended IMPACT score (a prognostic tool of 6-month outcome post moderate and severe TBI).^[11]

2.5. Statistical analysis

SPSS software was utilized to analyze the data. Continuous variables with normal distribution were compared with Student *t* test. Continuous variables with abnormal distribution were compared with the use of the Mann–Whitney test. Categorical variables were compared with the use of the χ^2 test. Different models of repeated-measures ANOVA were used for evaluation of the main effect of mannitol and HTS over various physiological and clinical parameters. Tukey–Kramer multiple comparison procedure was used for posthoc analysis of possible differences when appropriate. A *P* value of <.05 was considered significant.

3. Results

3.1. Patient characteristics

We identified 134 patients that met the inclusion criteria (Fig. 1). Fifty one patients were excluded for the following reasons: in shock (n=2), brain death (n=3), severe renal insufficiency only using HTS (n=2), without ICP monitoring (n=16), ICP data without complete documentation (n=6), ICP remained under 20 mm Hg (n=22). A total of 83 patients were included in the study, and these patients had a total of 437 hypertensive events,

received 458 boluses of osmotic agents (including 21 boluses did not work in the reduction of ICP). Fifteen patients underwent surgery for treatment of acute subdural hematoma, 3 patients of epidural hematoma, 12 patients of traumatic intracerebral hematoma and contusions, and 6 patients of decompressive craniectomy. In 53 cases, no surgery was performed (Table 1).

3.2. Effect of mannitol and hypertonic saline on intracranial pressure and cerebral perfusion pressure

Comparative analysis of results showed that HTS and mannitol were significantly and similarly effective in decreasing ICP and improving CPP. Specifically, the magnitude of ICP reduction, the duration of this effect, and the time of lowest ICP achieved with the 2 osmotic agents did not show any significant difference (Tables 2 and 3).

3.3. Effect of mannitol and hypertonic saline on mean arterial pressure and central venous pressure

MAP and CVP varied slightly after osmotherapy, but there was no significant difference between the 2 groups (*P* > .05) (Table 2).

3.4. Effect of mannitol and hypertonic saline on serum sodium

With each dose of HTS administration, the average serum sodium increased from 141.8 mmol/L at pre-dose to 146.7 mmol/L at 0.5 hours after administration, and 143.5 mmol/L at 3 hours after each dose, the change was found to be statistical signification (*P*

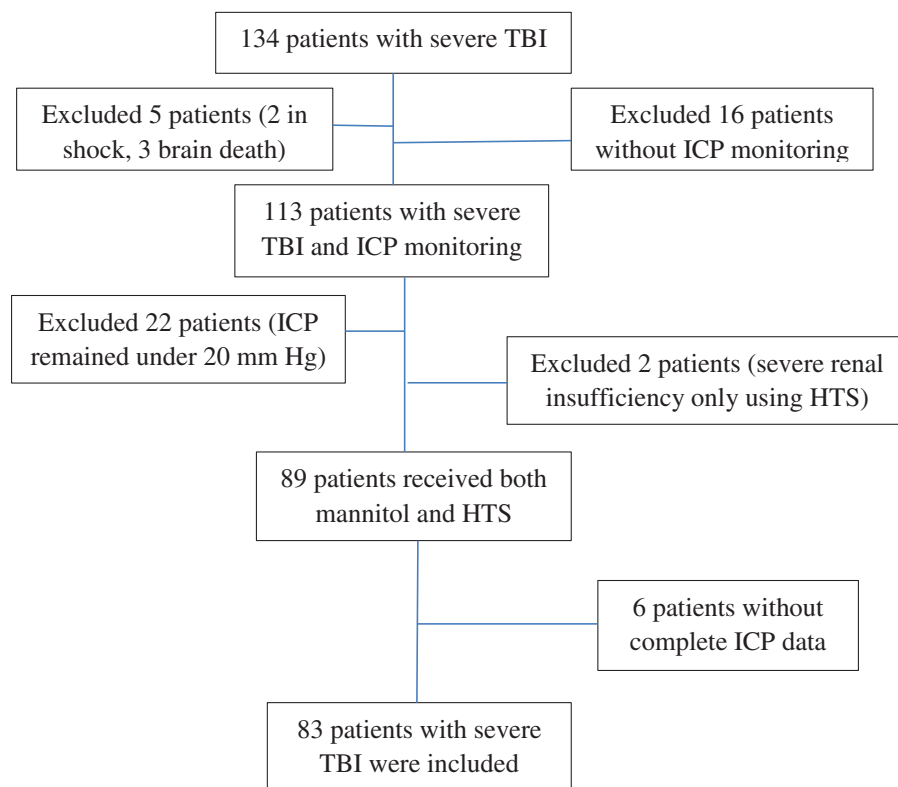


Figure 1. A flow chart of inclusion and exclusion of patients. GCS = Glasgow Coma Scale, HTS = hypertonic saline, ICP = intracranial pressure, TBI = traumatic brain injury.

Table 1
Patients and injury characteristics.

	n=83
Age, years	35 ± 19
Female:male	32:51
Mechanism of injury (n)	
Motor vehicle/motorcycle crash	62
Pedestrian struck	5
Fall	8
Assault	2
Other	6
Severity of injury	
GCS (post resuscitation, preintubation)	5 (3–7)
Extended IMPACT predicted 6 month % mortality	25 (13–38)
Surgery, (n)	
Subdural hematoma evacuation	15
Epidural hematoma evacuation	3
Intracerebral hematoma evacuation	12
Decompressive craniectomy	6

Data are expressed as mean ± standard deviation or median (interquartile range) unless otherwise indicated.

GCS = Glasgow Coma Scale, ICP = intracranial pressure, IMPACT = International Mission for Prognosis and Analysis of Clinical Trials in Traumatic brain injury.

< .05). No correlation was observed between the number of doses administered and increases in serum sodium. After treatment with 20% mannitol, the serum sodium decreased marginally ($P > .05$) (Table 2).

3.5. Variation in serum osmolality

After administration of 20% mannitol and 10% HTS, the serum osmolality increased immediately and then decreased 0.5 hours after osmotherapy with significant difference ($P < .05$), and reduced to the preliminary level 3 hours after osmotherapy ($P > .05$). There was no statistical difference between the HTS group and the mannitol group ($P > .05$) (Table 2).

3.6. Additional interventions

Two patients developed hyperosmolarity and electrolyte disturbances after repeated doses of hyperosmolar agents administration, necessitating temporary withdrawal of the study for

Table 2
Effect of hypertonic agents on physiological variables.

Parameter	Hypertonic saline (n=236)			Mannitol (n=221)			P value	
	before	After 30 min	After 180 min	before	After 30 min	After 180 min	P _t	P _{t+g}
ICP (mm Hg)	23.6 ± 3.3	12.9 ± 4.3*	15.9 ± 4.1 ^{†‡}	23.3 ± 2.9	13.5 ± 4.2*	16.7 ± 3.9 ^{†‡}	.001	ns
CPP (mm Hg)	70.3 ± 6.9	82.2 ± 7.8*	78.6 ± 7.6 ^{†‡}	71.1 ± 7.4	80.1 ± 7.6*	77.4 ± 6.9 ^{†‡}	.002	ns
MAP (mm Hg)	93.7 ± 7.3	94.8 ± 8.6	93.9 ± 8.3	94.3 ± 7.9	94.4 ± 8.5	94.2 ± 7.1	ns	ns
CVP (cmH ₂ O)	8.4 ± 2.1	8.5 ± 2.7	8.6 ± 2.9	8.5 ± 2.2	8.7 ± 2.8	8.4 ± 2.5	ns	ns
Na ⁺ (mmol/L)	141.8 ± 4.7	146.7 ± 5.1*	143.5 ± 4.5 ^{†‡}	142.3 ± 3.3	141.8 ± 4.7	141.5 ± 4.0	.038	.029
Osmolality (mOsm/L)	306.4 ± 12.3	325.6 ± 12.8*	311.6 ± 13.1 ^{†‡}	307.5 ± 11.7	323.6 ± 13.4*	310.5 ± 12.5 ^{†‡}	.017	ns

For each parameter, the averaged values of each population over the clinical course before, and 30 and 180 minutes after, completion of hyperosmolar infusion were compared. Comparisons were made using a repeated-measures model of ANOVA with analysis of infusion effect (p_i) and the combined effect of infusion and treatment group (p_{t+g}).

Post-hoc analysis (Tukey-Kramer) -

* between baseline and 30 minutes.

† between baseline and 180 minutes.

‡ between 30 minutes and 180 minutes.

CPP = cerebral perfusion pressure, CVP = central venous pressure, ICP = intracranial pressure, MAP = mean arterial pressure, Na⁺ = Serum sodium.

Table 3
Response to individual boluses of hyperosmolar agents on intracranial pressure.

	HTS (n=236)	Mannitol (n=221)	P value
Reduction of ICP (mm Hg)	9.8 ± 3.1	8.9 ± 2.6	.143
Time of Lowest ICP (min)	21.6 ± 6.1	29.7 ± 9.1	.294
Duration of the effect (h)	5.1 ± 2.7	4.4 ± 2.3	.121
Efficacy of individual doses			
Effective doses (n)	228	209	0.207
Ineffective doses (n)	8	13	χ ² = 1.59

Data are expressed as mean ± standard deviation unless otherwise indicated.

HTS = hypertonic saline, ICP = intracranial pressure.

about 10 hours with discontinuous hyperventilation and additional sedation boluses, and then they were back after osmolality and electrolyte were normal. The ICP in 4 patients did not decrease effectively after repeated doses of mannitol, and then they were dropped out of the experiment, but HTS was effective in the reduction of ICP. One patient suffered serious kidney dysfunction after repeated doses and then quit the program, as HTS was the only osmotic agent in the reduction of ICP. The ICP in 6 patients still continued to be pathologically elevated after an osmotic agent, although another osmotic agent, additional sedation boluses, hyperventilation, and barbiturate coma had been used in sequence. After repeated head CT scans, decompressive craniectomy and then mild hypothermia was performed. Finally, the patients received 236 boluses of HTS (including 8 boluses did not work in reducing ICP), and 221 boluses of mannitol (including 13 boluses did not work in reducing ICP). The percentage of the efficacy of HTS on ICP reduction appeared to be higher than mannitol, although which showed a slight difference (Table 3).

3.7. Central pontine myelinolysis

No case of CPM was confirmed in the 83 patients in this study. During hospitalization, all patients in this study received head noncontrast CT scans (range: 3–12) for the main neuroimaging modality to monitor brain lesion, edema, and structural changes, with no patient having changes consistent with CPM. Twenty five patients in the study had MRI scans while hospitalized, with no patient having changes consistent with CPM.

3.8. Neurological outcome

Neurological outcome at 3 months were measured with the GOS; 7 patients were dead, 9 were in vegetative state, 7 were bad, 34 were moderate in, and 36 were good. One death was ascribed to pulmonary embolism.

4. Discussion

We analyzed 83 consecutive patients who received osmotherapy with both HTS (236 boluses) and mannitol (221 boluses) for refractory ICH after severe TBI. We observed that:

1. HTS and mannitol were significantly and similarly effective in decreasing ICP and improving CPP;
2. The percentages of the efficacy of HTS on ICP reduction appeared to be slightly higher than mannitol.

Hyperosmolar therapy is a corner stone of the treatment of TBI patients with ICH. Mannitol has been shown to be effective for reducing ICP in TBI since the 1960 (Class II evidence) and is indicated for the treatment of ICH when signs and symptoms suggest herniation or other complications of ICH. Adults neurotrauma guidelines currently recommend mannitol for TBI patients with ICH.^[2,3] HTS, used in various concentrations alone or in combination with colloids, has been found to be useful in the management of ICH.^[12,13] The use of HTS has been increasing in recent years, primarily because of fear of acute kidney failure from repeated doses of mannitol and rebound of ICP when mannitol is withdrawn. At present, for want of conclusive evidence, it is being used as a second line hyperosmolar agent. However, a dispute exists regarding the utilization of the most ordinary osmotic agents: mannitol and HTS. Despite its long history of use in the reduction of ICH, no Class I evidence supports the use of HTS or mannitol as an agent to reduce ICP or improve neurologic outcome, and no large controlled trials comparing mannitol and HTS in these clinical studies have been performed.^[12,13] Nevertheless, it is worth discussing the relative merits of these 2 osmotic agents to determine which agent should be selected in diverse clinical situations.

Conflicting results have been reported in earlier studies that compared mannitol with HTS in TBI.^[14–21] This variation appears to be related to differences in the concentrations and doses of HTS, use of colloids in combination with HTS.^[16–19] The concentration and volume of HTS used varied significantly, ranging from 1.5% to 23.5% in concentration and 1 to 30 ml/kg in volume.^[13,22,23] There is no clinical trial to assess which concentration of HTS is the most effective in reducing ICP.^[13,23] Head-to-head comparisons of HTS and mannitol in equimolar loads for the treatment of ICH in TBI patients are very few.^[16,19] These studies examined the effects of the two agents on individual ICH episodes rather than patients, as done in this study. Sakellaridis et al reported that equimolar HTS and mannitol (mannitol 20%, 2 ml/kg, or saline 15%, 0.42 ml/kg) were significantly and similarly effective with respect to magnitude and duration of decrease in ICP.^[16] While Battison et al reported that when given in an equimolar, rapid, intravenous infusion, HTS reduced ICP more effectively than mannitol.^[19]

In the present study, we evaluated the efficacy of 10% HTS and 20% mannitol in similar osmotic burdens to treat ICH in patients with severe TBI. Doses of osmotic agents (20% mannitol, 2 ml/kg, or 10% saline, 0.63 ml/kg, which are similar osmotic load) were given alternately to the individual patient with severe TBI. We used episodes of ICH rather than patients as our units of

statistical analysis, which avoids grouping errors. Therefore, this experiment can objectively evaluate the effect of mannitol and HTS in treating episodes of ICH. As we utilized 2 osmotic agents alternately in the same patients, we could not compare the incidence of complications, survival rate, disability rate, and mortality.

The results showed that both 10% HTS and 20% mannitol decreased ICP and improved CPP effectively after infusion of them at a similar osmotic dose in the treatment of severe TBI patients with ICH ($P < .05$). HTS showed a more profound, more rapid and longer lasting effect on ICP than mannitol, although there were no significant differences in the reduction of between HTS and mannitol ($P > .05$). These are consistent with the results reported in lots of literature.^[22–24]

Whereas for patients with intractable ICH who are ineffective with mannitol, the clinical standard treatment is intractable to decrease ICP. In 4 patients of this study, who had severe diffuse brain contusions, mannitol worked very well in lowering ICP at the beginning of the osmotherapy. However, the reduction of ICP and duration of the effect decreased gradually after several doses of mannitol. Each of them received a total of 13 to 21 doses of mannitol before the effect of reducing ICP disappeared. These patients dropped out of the experiment as the ICP continued to be pathologically elevated after mannitol administration, hyperventilation, blood pressure elevation, and barbiturate coma had been used with little success, but HTS was effective in lowering ICP in these 4 patients.

In the study, in terms of ICP control, the magnitude of ICP reduction, the duration of this effect was moderately higher in the HTS group (9.8 ± 3.1 mm Hg, 5.1 ± 2.7 hours, respectively) in comparison with the mannitol group (8.9 ± 2.6 mm Hg, 4.4 ± 2.3 hours, respectively), although the difference was not statistically significant. When comparison of ICP responses to hyperosmolar infusions was based on analysis of the efficacy of individual doses, the percentages of the efficacy of HTS on ICP decrease appeared to be higher than mannitol, although which showed a slight difference ($P = 0.207$) (Table 3). Scholars also found that HTS can still effectively reduce ICP when mannitol has failed in small clinical trials.^[25,26] Nevertheless, such cases are rarely reported and are warranted to further investigate these findings. Anyway, as for patients with intractable ICH who are ineffectual with mannitol, HTS may be another choice. Presumably, the concentration of accumulated mannitol is related to the cumulative dose and duration of mannitol therapy which reverses the osmotic gradient and leads to less effectiveness in the magnitude of ICP reduction and the duration of this effect.^[7,8,27,28]

In the experiment, the plasma osmolality in 1 patient rose to 358 mOsm/L half an hour after mannitol infusion and decreased to 335 mOsm/L 3 hours after mannitol administration. Meanwhile, the creatinine of the patient increased to $156 \mu\text{mol/L}$, which was $57 \mu\text{mol/L}$ at admission. Then the patient quit the programs as HTS was the only osmotic agent used for the subsequent treatment of ICH, and the creatinine decreased to normal after mannitol discontinuation. It is wary not to exceed a plasma osmolality of 320 mOsm/L when mannitol infusion because acute kidney failure may precipitate.^[29–31]

In the study, only 1 patient developed hypernatremia (serum sodium concentration 163 mmol/L) half an hour after HTS administration and decreased to 147 mmol/L 3 hours after HTS infusion. Generally, serum sodium should be kept below 160 mmol/L.^[32] However, in clinical situations of intractable ICH, sodium concentrations as high as 180 mmol/L have been

tolerated without complications, and patients have made full recoveries from extreme levels of hyponatremia in spite of the fear of more complications.^[24]

In the experimental study, no patient had changes consistent with CPM. Our result is in conformity with those reported in the current literature.^[33,34] CPM is a feasible complication if a rapid rise in serum sodium occurs.^[35] Despite the fact that CPM has never been reported after the use of HTS, it may be best to avert using it in patients with chronic hyponatremia.

In our study, we found that 20% mannitol and 10% HTS are significantly and similarly effective in decreasing ICP. Nevertheless, the use of ICH episodes instead of patients does not permit us to reach conclusions about complications rate, because every individual patient received both 10% HTS and 20% mannitol alternately. For patients with ICH, we use HTS and mannitol alternately, not the single osmotic agent, which maybe the answer that there are few complications in the study. These results would depend on a multicenter randomized controlled clinical trials, which should be performed in the future to validate the results of the current study.

5. Conclusions

In conclusion, within the limitation of the present study, these data suggest that repeat bolus dosing of 10% HTS and 20% mannitol are significantly and similarly effective in decreasing ICP and augmenting CPP, but the effect observed in this study suggests that the proportion of efficacious doses of HTS on ICP reduction appeared to be slightly higher than mannitol. Large randomized trials are needed to further investigate these findings.

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