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Original Article

Effects of hypertonic saline - hydroxyethyl starch and mannitol on serum osmolality, dural tension and hemodynamics in patients undergoing elective neurosurgical procedures

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Abstract: Objective: To investigate effect of equal volumes (250 ml) of 7.2% hypertonic saline - 6% hydroxyethyl starch (HS-HES) and 20% mannitol (M) on dural tension, serum osmolality and hemodynamics in patients during elective neurosurgical procedures. Material and methods: Forty ASA I-II patients scheduled for elective neurosurgical supratentorial procedures were randomly assigned to two groups. About 30 min before skull opening, patients received either HS-HES or M at infusion rate 750 ml/h. Dural tension score was used to evaluate the dural tension by neurosurgeons. Serum osmolality was tested at following time points: before, 125 ml infused, 250 ml infused, 30 min and 60 min after infusion. Hemodynamic variables were measured by FloTrac. Results: Patients who received HS-HES had a significant decrease in dural tension scores ($P < 0.05$) and obtained more satisfactory brain relaxation for neurosurgeon (95% vs. 75%). In HS-HES group, the peak of serum osmolality occurred earlier and hyperosmolality lasted for longer time. Transient decrease in mean arterial pressure was observed in M group at 10 min after the start infusion ($P < 0.01$). Heart rate significantly decreased after HS-HES infusion, whereas no significant changes were observed in M group. In HS-HES group, stroke volume variation significantly decreased from 9.7 ± 3.5 at the initiation of infusion to 6.7 ± 2.4 at 30 min after the infusion and remained decreased more than 60 min while it decreased from 6.8 ± 3.1 to 5.3 ± 1.5 in M group. Moreover, urine output in HS-HES group from initiation to 60 min after the infusion was significantly less than those in M group.Conclusion: HS-HES might be an alternative to mannitol in treatment of intracranial hypertension.

Keywords: Hypertonic saline, hydroxyethyl starch, mannitol, dural tension, neurosurgery anesthesia

Introduction

Therapeutic efforts to decrease the brain size and to avoid injuring the dura mater and brain tissue during intracranial procedures include cerebral vasoconstriction by means of anesthetic intravenous agents and/or hypocapnia, volume reduction of cerebrospinal fluid (CSF), and brain dehydration with osmotic agents [1]. The effect of hyperosmolar solutions on brain tissue was first introduced by Weed and McKibben nearly 90 years ago [2]. Gradually, mannitol becomes the most widely used agent for treating intracranial hypertension but can result in systemic hypotension [3]. Currently, there is evidence that hypertonic saline solution may produce similar effects based on various experimental and clinical studies [4-7]. Small volume resuscitation with hypertonic saline showed obvious advantages including volume expansion and cerebral and systemic hemodynamics improvement especially in patients undergoing traumatic brain injury (TBI) [8-12]. Moreover, few clinical studies addressed the possible role of hypertonic saline for patients undergoing elective neurosurgical procedures.

This prospective randomized clinical study was designed to compare the efficacy and safety of intravenous administration of hypertonic saline 7.2% - hydroxyethyl starch 6% (HS-HES) and 20% mannitol (M) at equal volume (250 ml) for controlling intracranial pressure in patients undergoing elective neurosurgical procedures. Our pervious study had evaluated the blood

Table 1. Demographic data of patients treated with M (n = 20) or HS-HES (n = 20)

	Group M	Group HS-HES
Age (yrs)	37 ± 9	40 ± 13
Sex (M/F)	11/9	11/9
Height (cm)	166 ± 8	169 ± 8
Weight (kg)	65 ± 11	68 ± 13
Brain lesion		
Glioma	20	18
Meningioma	0	2

Data were presented as the mean ± SD. M: mannitol, HS-HES: 7.2% hypertonic saline - 6% hydroxyethyl starch solution.

coagulation and electrolytes changes after HS-HES infusion [13]. This study focuses on the effects of both solutions on dural tension, hemodynamics and serum osmolality.

Material and methods

Study population

After informed consent was obtained, consecutive ASA I-II patients scheduled for supratentorial elective procedures (resection of glioma, meningiomas or other brain tumors) were enrolled in this prospective randomized study, which was approved by the ethics committee of Beijing Sanbo Brain Hospital, Capital Medical University. The patients were randomized to receive either 7.2% hypertonic saline - 6% hydroxyethyl starch (HperHAES®, Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany) or 20% mannitol [Baxter®, Baxter Healthcare (Shanghai) Co., LTD, China]. The exclusion criteria included age < 18 years or > 65 years, clinical signs of significantly increased ICP such as severe headache, blurred vision and/or papilledema, history of cardiac, pulmonary and renal dysfunction, electrolyte disturbances, preoperative coagulation disorders. The protocol has been registered at Chictr.org (ChiCTR-TRC-12002357).

Anesthetic management

Patients were premedicated with midazolam (0.05 mg/kg, iv) and penehyclidine hydrochloride injection (1 mg, im) at 15 min before anesthesia. Radial arterial catheters were inserted under lidocaine local anesthesia and connected with FloTrac sensor (Edward Lifescience, USA) to monitor hemodynamic variables. General anesthesia was induced with fentanyl 3 μg/kg, propofol 2 mg/kg and vecuronium bromide (0.1 mg/kg). After endotracheal intubation, ventilation was controlled by intermittent positive pressure ventilation to maintain the end-tidal CO_2 pressure at 30-35 mmHg. Anesthesia was maintained with sevoflurane (1-1.3 minimum alveolar concentration, MAC) combined with intravenous bolus of fentanyl and vecuronium intermittently.

Intraoperative fluid management

About 30 min before the skull opening, patients were assigned by random number to receive 250 ml of hypertonic saline 7.2% - hydroxyethl starch 6% solution (Group HS-HES, 750 ml/h) or 20% mannitol (Group M, 750 ml/h). Maintenance fluid consisting of Ringer's solution was supplied at the rate 5-10 ml/kg/h during the study period, to maintain stable hemodynamics and the mean of arterial pressure (MAP) ≥ 65 mmHg. Packed red blood cells (PRBC) were transfused if necessary.

Measurements

Clinical measurements included age, sex, height, weight, brain lesion and urine output. Dural tension score was estimated by the same team of neurosurgeons immediately after the skull opening who was blinded to the groups. The reliability and validity of dural tension scores were tested in our previous study [13]. Grade I, Normal dural tension, it was easy for the neurosurgeon to open the dura mater. Grade II, Increased dural tension, the dura mater could be opened without additional procedures to lower the ICP. Grade III, Pronouncedly increased dural tension, it was necessary to apply additional procedures of lowering the ICP such as hyperventilation in order to open the dura mater. We considered Grade I and II as the satisfactory level of brain relaxation for neurosurgeons. Serum osmolality was measured by freezing point depression. Serum osmolality was tested at the following time points: before (baseline), 125 ml infused, 250 ml infused, 30 min and 60 min after infusion. Hemodynamic measurements included mean arterial pressure (MAP), heart rate (HR), cardiac index (CI) and stroke volume variation (SVV) which were monitored continuously by the monitor (GE-Ohmeda S/5 and FloTrac, USA). These

Table 2. Clinical parameters of patients treated with M (n = 20) or HS-HES (n = 20)

	Group M	Group HS-HES
Operation duration (min)	231 ± 58	207 ± 35
Total fluid input (ml)	3808 ± 606	3353 ± 750*
Ringer's solution (ml)	3558 ± 606	3103 ± 750*
Autologous blood transfusion (ml)	10 ± 45	10 ± 45
PRBC (ml)	0	0
Total urine output (ml)	1686 ± 918	869 ± 470**
urine output-1 (ml)	489 ± 306	156 ± 202**
urine output-2 (ml)	804 ± 478	286 ± 283**
Blood loss	364 ± 174	310 ± 126
Fluid balance	1768±950	2184±842
Dural tension scores (Grade I/II/III)	4/11/5	12/7/1*

Compared with group M, *$P < 0.05$, **$P < 0.01$. Data were presented as the mean ± SD. Urine output-1: urine output from the start of infusion to 30 min after the end of infusion. Urine output-2: urine output from the start of infusion to 60 min after the end of infusion. PRBC: packed red blood cells.

Table 3. Changes of serum osmolality in two groups

Time	Group M	Group HS-HES
Before infusion	295.1 ± 5.8	293.3 ± 6.1
125 ml infused	307.0 ± 7.8††	317.7 ± 4.8††,**
250 ml infused	308.6 ± 5.5††	316.1 ± 5.4††,**
30 min after infusion	302.5 ± 5.4††	308.2 ± 4.8††,**
60 min after infusion	300.3 ± 4.6††	304.7 ± 3.6††,**

Compared with group M, **$P < 0.01$. Compared with values before infusion, ††$P < 0.01$. Data were presented as the mean ± SD.

parameters were documented at the 5 time points.

Statistical analysis

Statistical analysis was performed with SPSS 17.0 software. All data were presented as the mean ± SD. Categorical data were compared by χ^2 test or Fisher's exact test (types of brain tumors and dural tension scores). Differences within groups were evaluated using paired student t test and clinical variables differences between two groups were evaluated using unpaired student t test (age, height, weight, operation duration, fluid input, urine output, blood loss and fluid balance). For variables with multiple measurements (hemodynamic variables), a repeated measures analysis of variance was used to evaluated the effects of time and group assignment, while two-way analysis of variance was used to compare the difference within the groups. P value of < 0.05 was considered statistically significant.

Results

A total of 40 patients were included in the study, 20 in each group. Demographic data are summarized in **Table 1**. There were no significant differences between two groups with respect to sex, age, height, weight and brain lesion.

Dural tension in HS-HES group decreased significantly compared with M infusion ($P < 0.05$, **Table 2**) and neurosurgeons were satisfactory with brain relaxation in 19 of 20 HS-HES treated and in 15 of 20 mannitol treated patients. Diuresis was different between the two groups. Urine output from the start of infusion to 30 min after the infusion was 156 ± 202 ml in HS-HES group and 489 ± 306 ml in M group. And urine output in HS-HES group from the start of infusion to 60 min after the infusion was significantly less than that in M group (286 ± 283 ml vs. 804 ± 478 ml, $P < 0.01$).

In both groups, serum osmolality displayed a trend of rising from baseline level and then decreased after the administration. The maximal serum osmolality appeared at 10 min after the start of HS-HES administration, whereas occurred later in M group, at 20 min after the start of mannitol administration. And the peak was significantly higher in HS-HES group (317 ± 4.8 vs 308 ± 5.5 mosm/kg, $P < 0.01$). Serum osmolality in HS-HES treated patients returned to control level at 60 min after the end of infusion (304.7 ± 3.6 mosm/kg), and 95% confidence interval (CI) was 303.0-306.3 mosm/kg, whereas it returned earlier in M group, at 30min after the end of mannitol infusion (302.5 ± 5.4, 95% CI, 299.9-305.0 mosm/kg). It is obviously observed that hyperosmolality of HS-HES lasted longer time compared with mannitol and showed a higher increase in serum osmolality with HS-HES administration (**Table 3**).

In term of hemodynamics, transient decrease of MAP was observed in M group at 10 min after the start of infusion ($P < 0.01$), while there was a slightly increase in HS-HES, but no statistical significance. In the HS-HES group, heart

Table 4. Changes of HR, MAP, CI and SVV in two groups

Time	HR (bpm)		MAP (mmHg)		CI (L/min per m^2)		SVV (%)	
	M (n = 20)	HS-HES (n = 20)	M (n = 20)	HS-HES (n = 20)	M (n = 16)	HS-HES (n = 20)	M (n = 16)	HS-HES (n = 20)
Before infusion	71.2 ± 17.2	71.9 ± 8.8	78.4 ± 9.3	70.6 ± 6.8	3.03 ± 0.81	3.32 ± 1.00	6.8 ± 3.1	9.7 ± 3.5
125 ml infused	72.8 ± 17.5	72.7 ±11.8	74.2 ± 9.2††	72.7 ± 7.0	3.24 ± 1.00	3.51 ± 1.00	5.3 ± 1.5†	9.0 ± 3.6
250 ml infused	72.4 ± 15.3	65.2 ± 9.8†	76.8 ± 8.2	71.6 ± 5.5	3.23 ± 0.64	3.28 ± 0.95	5.4 ± 2.2	7.1 ± 3.0†
30 min after	70.3 ± 13.0	61.6 ± 8.8††	77.9 ± 6.1	71.3 ± 6.6	3.13 ± 0.64	3.28 ± 0.95	5.4 ± 1.9	6.7 ± 2.4††
60 min after	72.0 ± 13.0	64.2 ± 9.9††	78.0 ± 8.0	73.0 ± 7.2	2.98 ± 0.67	3.07 ± 0.77	6.4 ± 2.3	7.1 ± 2.6†

Compared with values before infusion, †$P < 0.05$, ††$P < 0.01$. Data were presented as the mean ± SD.

rate significantly decreased from 71.9 ± 8.8 bpm at initiation of infusion to 61.6 ± 8.8 bpm 30 min after terminating infusion, whereas it showed no clinically relevant changes in M group. Cardiac index was slightly increased during the administration of both solutions, but the difference was not statistically significant. In HS-HES group, SVV significantly decreased from 9.7 ± 3.5 at initiation of infusion to 7.1 ± 3.0 at the end of infusion and remained significantly decreased to 6.7 ± 2.4 at 30 min after infusion. In M group, SVV decreased from 6.8 ± 3.1 at initiation of infusion to 5.3 ± 1.5 during infusion, but remained unchanged later (**Table 4**).

Discussion

In the present study, we compared the effects of HS-HES and M in terms of dural tension, urine output, hemodynamic and serum osmolality in patients undergoing the elective neurosurgical procedures. The main findings were as follows: (1) 250 ml HS-HES could remarkably reduce the dural tension scores and provide more satisfactory brain relaxation than mannitol for operation. (2) Compared with M-treated patients, the peak of serum osmolality occurred earlier and hyperosmolality lasted longer time in HS-HES group. (3) Patients in HS-HES group displayed an upward trend of MAP and a decrease of SVV after the administration, whereas patients suffered from transient decrease in MAP after mannitol infusion. These presented that HS-HES could augment intravascular volume and improve hemodynamic states. (4) Though all hyperosmolar agents cause diuresis, the diuretic effect of HS-HES was weaker in comparison with mannitol. It might result from the stimulation of natriuretic peptide (ANP) release and not a direct osmotic diuresis, which might assist in avoiding hypovolemia and hypotension. (5) In our previous and present study, patients with HS-HES infusion did not show any other relative hyperosmolality complication except for hypernatremia and hyperchloraemia. Plasma sodium decreased into the normal range for 1 h and plasma chlorine normalized within 24 h. These findings provided the substantial evidence that the HS-HES solution was effective and safe to decrease dural tension and improve cardiovascular performance with small volume administration during the neurosurgery.

In our study, we used dural tension scores as an alternative parameter for indirectly reflecting ICP. We found HS-HES could remarkably reduce the dural tension scores and provide more satisfactory brain relaxation for neurosurgeons. In the clinical practice, the ICP is not routinely measured during elective neurosurgical procedure. Dural tension scores have shown strongly positive correlation between the degree of cerebral edema and ICP [14, 15]. In clinical, neurosurgeons evaluated tension of dura mater based on their experiences before opening the dura mater. If the tension of dura mater was high enough, brain tissue might protrude through the craniotomy site, which increased the risk of cerebral ischemia with possible worsening outcome. In the present study, we deduce the improvement in the dural tension scores in the HS-HES group may arise from the effect of HS, which showed osmotic changes from HS-HES infusion were significantly higher than mannitol. Infusion of HS creates an osmotic force that draws the fluid back into the interstitial and intravascular area from the intracellular area due to the impermeability of the blood-brain barrier (BBB) to sodium [6, 9]. In addition, HS also decrease the formation and/or increase the resistance to reabsorption of the CSF [16-18]. In an animal model, Toung et al. [19] examined the effect of HS on cerebral edema secondary to tumor effects. They

found HS was more effective than mannitol in reducing both ipsilateral and contralateral hemispheric water content as measured by wet-to-dry weight radios [19]. In clinical studies, HS has also been shown to reduce ICP in different intracranial diseases, particular in head trauma with increased ICP [7, 20, 21]. Additionally, researches have demonstrated that HS remains effective in intracranial hypertension refractory to treatment with mannitol [22, 23]. Moreover, our data showed that the peak osmolality with HS-HES administration occurred earlier than mannitol administration (10 min vs. 20 min after the start of infusion). And serum osmolality in HS-HES treated patients returned to normal range later than M-treated patients (60 min vs. 30 min after the end of infusion). These findings both revealed that osmotic effect of HS-HES would last longer time. It might arise from HS-HES combination with colloids (hydroxyethyl starch). Previous studies that compared changes in ICP with the use of HS or mannitol in TBI patients found that both significantly reduced ICP and that HS had a longer duration of action than mannitol [24-26].

Our hemodynamic data indicated that patients suffered from transient hypotension during the infusion of mannitol, while patients with HS-HES administration displayed a upward trend of MAP. In HS-HES group, SVV significantly decreased from 9.7 ± 3.5 at initiation of infusion to 6.7 ± 2.4 at 30 min after terminating infusion and remained significantly decreasing more than 60 min after the end of infusion. We deduced that these changes arised from expanding intravascular volume of adiministration of HS-HES and improving cardiovascular performance. Multiple mechanisms could explain this volume-expanding property, including compartment redistribution with fluid shift to the vascular bed, positive effects in cardiac output [27, 28], and immunologic effects [29, 30]. Relative studies also indicated that an infusion of 7.5% hypertonic saline dextran could increase the intravascular volume by as much as four times the infused volume within minutes of infusion, and after osmotic equilibrium, about 4 h of a bolus dose, the net effect is to increase the plasma volume by 750 ml for every liter administered [31]. Besides, HS-HES was able to exert these plasma expanding effects with administration of small volumes (250 ml). Our previous study demonstrated that 250 ml HS-HES could reduce the volume of intraoperative fluid [9] and other results indicated that HS could decrease postoperative fluid input. A near zero fluid balance was observed in patients with hypertonic saline-dextran (HSD) infusion during the first 48 hours after cardiac surgery [32] and HSD patients ran a slightly negative fluid balance over the first 72 h following cardiopulmonary bypass [33], while control patients ran a large positive fluid balance. Those data showed that effect of HS-HES on the perioperative fluid treatment might not be neglected. Though all hyperosmolar agents could cause diuresis, we found the diuretic effect of hypertonic saline solutions differed from that of mannitol by monitoring urine output from the start of infusion to 30 and 60 min after the end of infusion. We analyzed that it might result from the stimulation of atrial natriuretic peptide (ANP) release and not in a direct osmotic diuresis, which might assist in avoiding hypovolemia and hypotension [34].

Additionally, other important issues deserved attention with HS including changes of blood coagulation function, electrolyte and serum osmolality after HS-HES infusion. These blood variables were measured in our previous study [13] including plasma electrolyte concentration (sodium, potassium, chloride, calcium), hemoglobin concentration (Hb), platelet (Plt), hematocrit (Hct), and coagulation parameters [prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen (Fbg)]. And previous results showed no or slight impairment on blood coagulation function and no significant increase of blood loss. Electrolyte abnormalities such as hypernatremia and hyperchloraemia occurred immediately after HS-HES infusion, then plasma sodium returned normal level about 1 h after terminating infusion and plasma chloride decreased to normal range within 24 h after HS-HES infusion. The plasma potassium level took on biphasic changes with increasing at the beginning and then decreasing later, but did not exceed normal range. At present guidelines recommend maintaining serum osmolality < 320 mosm/kg when using mannitol and suggest that the maximal serum osmolality is 360 mosm/kg when using hypertonic saline solutions [34-36]. In our study, the maximum of serum osmolality was 318 mosm/kg in M group and 330 mosm/kg in HS-HES group, within the recommended range. And there were no potential side effects

such as cardiac failure, phlebitis, central pontine myelinolysis found in the whole study period. So we considered it was relatively safe to administer 250 ml bolus dose of 7.2% hypertonic saline - 6% hydroxyethyl starch within 20 min.

In conclusion, 7.2% hypertonic saline - 6% hydroxyethyl starch infused before skull opening is an attractive choice in reducing dural tension during neurosurgical procedures. HS-HES could provide more satisfactory brain relaxation for neurosurgeon and this effect may last longer time than mannitol. HS-HES received a more stable hemodynamic state with its volume-expanding property and weaker-diuresis, which avoided transient hypotension of mannitol infusion. Our results indicate HS-HES may represent a new avenue for osmotherapy the during the neurosurgical procedures.

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Disclosure of conflict of interest

None.

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