

## Original Article

# Comparison of equiosmolar concentrations of hypertonic saline and mannitol for intraoperative lax brain in patients undergoing craniotomy

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## Abstract

**Background:** Osmotherapy is the frequently used for the treatment of intracranial pressure. The purpose of the study was to compare the effect of equiosmolar solution of 3% hypertonic saline and 20% mannitol on brain relaxation in supratentorial tumor surgery.

**Methods:** After institutional review board approval and written informed consent, 50 patients aged >18, Glasgow Coma Scale (GCS) >13 with ASA physical status 1, 2, and 3 scheduled to undergo craniotomy for supratentorial tumors were enrolled in this prospective, randomized study. Patients received 5 ml/kg of either 3% hypertonic saline ( $n = 25$ ) or 20% mannitol ( $n = 25$ ). Hemodynamic variables (heart rate [HR], SBP, DBP, MBP, and central venous pressure [CVP]), serum electrolytes, serum osmolality, urine output, and fluid balance were measured. The surgeon assessed the brain condition on four point scale (1 = perfectly relaxed, 2 = satisfactorily relaxed, 3 = firm brain, and 4 = bulging brain), who was blinded to study drug.

**Results:** Brain relaxation was comparable in two groups and there was no significant difference ( $P = 0.633$ ). The number of brain conditions classified as perfectly relaxed, satisfactorily relaxed, firm brain, and bulging brain in the HS group was 8, 13, 3, and 1, respectively, whereas it was 5, 17, 3, and 0, respectively, in the M group. There was no significant difference in hemodynamic variables between the two groups except CVP at 30 min ( $P = 0.48$ ). Compared with mannitol, hypertonic saline caused increase in the serum osmolality at 120 min ( $P = 0.008$ ) and in serum sodium at 120 min ( $P = 0.001$ ). Urine output was higher with mannitol than hypertonic saline ( $P = 0.001$ ).

**Conclusion:** 3% hypertonic saline and 20% mannitol are equally effective for brain relaxation in elective supratentorial tumor surgery and compared with mannitol, hypertonic saline was associated with less diuretic effect.

**Key Words:** Brain relaxation, hypertonic saline, mannitol

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## INTRODUCTION

One of the main goals of anesthesia during any neurosurgical procedure is to provide a relaxed or 'slack' brain that will allow retraction of the brain and thereby reduce brain retractor ischemia. Various adjuncts are used to relax the brain. Although practices vary, they are all directed at the components of the intracranial vault, namely the brain tissue volume, cerebrospinal fluid (CSF) volume and blood volume. Osmotherapy is frequently used to reduce brain tissue volume and intracranial pressure (ICP) during neurosurgical operation. Mannitol (20%) and hypertonic saline (HS) are most commonly used hyperosmolar solutions in the treatment of elevated ICP.<sup>[14,23]</sup>

Mannitol is recommended as a first-choice hyperosmotic agent for the treatment of increased ICP.<sup>[23]</sup> The hyperosmolarity of mannitol reduces ICP by withdrawing water from the brain parenchyma to the intravascular tissue with intact blood-brain barrier (BBB). It reduces blood viscosity and transiently increases cerebral blood flow leading to reflex cerebral vasoconstriction. In addition mannitol facilitates decrease in ICP by decreasing CSF volume by virtue of decreasing the rate of formation of CSF. The use of mannitol is frequently associated with serious adverse effects, such as intravascular volume depletion, hyponatremia, rebound ICP elevation, and renal failure.<sup>[20]</sup>

Initially, HS solutions were used in small volumes for resuscitation of hypovolemic trauma patients. Now HS solutions are increasingly used as an alternative to mannitol for reduction of ICP.<sup>[21]</sup> Brain trauma foundation guidelines recommend HS, when mannitol fails to reduce ICP.<sup>[15]</sup>

HS is used in various concentrations and with varying osmolar loads. HS reduces ICP by dehydration of brain tissue by creation of the osmotic gradient, decreasing blood viscosity leading to cerebral vasoconstriction and increasing plasma tonicity, which favors rapid absorption of CSF. Compared with mannitol, HS have additional beneficial effects like enhancement of cardiac output, mean arterial pressure, and reduction of extravascular lung volume, leading to improved gas exchange and improved partial pressure of oxygen in the blood.<sup>[1,3,7,11,13]</sup>

Clinical trials that compared the effects of HS and mannitol on ICP have suggested that HS is at least as effective, if not better, than mannitol in the treatment of increased ICP.<sup>[2,5,6,14,15,18]</sup> Few studies have shown that HS is better than mannitol for brain relaxation<sup>[4, 7,9,10,23,24,25]</sup> and others have revealed that they are equally effective.<sup>[19]</sup> Moreover, these studies differ in the amount and osmolarity of mannitol or HS used, thus making it difficult to interpret the results. Hence this study was designed to compare the equiosmolar concentrations of mannitol (20%) and

HS (3%) for brain relaxation in patients undergoing elective craniotomies for supratentorial tumors.

## MATERIALS AND METHODS

After obtaining institutional ethical committee approval on patients posted for elective supratentorial craniotomies, written informed consent was obtained from the patients or relatives of the patients. Fifty patients were enrolled in this prospective, randomized study and they were divided into two groups of 25 each assigned to receive 5 ml/kg of either 20% mannitol or 3% HS. The surgeon was blinded to the agents under study. Patients with age group 18–65 years, with Glasgow coma scale (GCS) >13, and ASA physical status 1–3 were included in the study. Patients with the presence of raised ICP, electrolyte imbalance, with severe cardiac, respiratory, or renal disease were excluded from the study. Patients who are already on mannitol or HS treatment were also excluded from the study.

### Procedure

All patients satisfying the inclusion criteria were recruited to the study, after approval by ethics committee and written informed consent from the patients or their relatives. Patients were randomly allocated into two groups – mannitol (M group) and HS (HS group) by a computer-generated randomization chart. In the operation room, peripheral intravenous line was secured and 0.9% normal saline was given for fluid management. The standard monitors including electrocardiogram (ECG), noninvasive blood pressure (NIBP), and pulse oximeter were attached and baseline heart rate (HR), NIBP, and SPO2 readings were recorded. After preoxygenation with 100% O<sub>2</sub> for 3 min, general anesthesia was induced with 2 mcg/kg fentanyl hydrochloride and 2 mg/kg propofol. Muscle relaxation was achieved using 0.1 mg/kg vecuronium bromide. Postinduction radial artery was cannulated and central venous catheter was placed depending on the need of surgery. Intraoperative anesthesia was maintained using oxygen-nitrous oxide mixture (40:60) with 0.7–1 minimal alveolar concentration (MAC) of isoflurane. Opioids for analgesia and vecuronium bromide for muscle relaxation were repeated as needed. PaCO<sub>2</sub> was maintained between 30 and 34 mmHg. HR and invasive arterial blood pressure were kept within  $\pm$  20% of the baseline values. Normal saline (0.9%) was used as maintenance fluid at 2 ml/kg/h with additional replacement for urine output, third space loss, and blood loss. At the time of scalp incision patients received 5 ml/kg of either 20% mannitol (1 g/kg, osmolarity = 1098 mOsm/l; M group) or 3% HS (osmolarity = 1024 mOsm/l; HS group) over a period of 15 min through central line for intraoperative brain relaxation.

Brain relaxation was assessed by the operating neurosurgeon, who was blinded to the study drug upon opening the dura on four point scale:

- Perfectly relaxed – 1
- Satisfactorily relaxed – 2
- Firm brain – 3
- Bulging brain – 4.

If the surgeon was not satisfied with the degree of brain relaxation on dural opening, an additional bolus dose of 3 ml/kg of same study drug was administered and hyperventilation to a PaCO<sub>2</sub> of 25 – 30 mmHg was initiated to provide relaxation for surgical access.

### Parameters studied

- Hemodynamic variables, including (HR), nonNIBP/IBP, central venous pressure (CVP) were recorded before infusion (T0) and after administration of study drugs at 15 min (T15), 30 min (T30), 60 min (T60), 90 min (T90), and 120 min (T120) and at the end of the surgery
- Serum electrolytes at T0, T60, T120 min
- Serum osmolality at T0 and T120 min
- Urine output at T60, T120, T180, T240, and T300 and T360 min.

Details of fluid input, blood loss, blood transfused and duration of anesthesia were noted. At the end of surgery patients were either extubated or shifted to neurosurgical intensive care unit for elective mechanical ventilation.

### Statistical analysis

For power analysis calculation, we considered a difference of 1 point in brain relaxation score between the groups to be clinically significant. A power analysis based on 95% confidence interval with 90% power, the sample size of 25 in each group was sufficient. The total sample size required was 50 for 90% statistical power and 5% level of significance assuming 1 point difference of brain relaxation between two groups.

Statistical analysis was carried out using SPSS 19.0. Results on continuous measurements are presented as Mean ± SD and median was used for non-Gaussian distribution. Categorical measurements were presented in number and percentages. Student *t*-test (two tailed, independent) was used to find the significance of study parameters on a continuous scale between two groups on metric parameters. Differences between the mannitol and HS groups were analyzed using Chi-square/Fisher exact test (demographic variables), Mann–Whitney U test (brain relaxation scores). To compare the effects of drugs between the groups over time, one-way repeated ANOVA was used (hemodynamic variables). All statistical analysis was carried out at 5% level of significance.  $P < 0.05$  was considered significant.

## RESULTS

Fifty neurosurgical patients admitted at our institution between October 2010 and march 2013 were enrolled in the study after satisfying the inclusion and exclusion criteria, and were randomized into group HS and group M to receive either 3% HS ( $n = 25$ ) or 20% mannitol ( $n = 25$ ).

There was no significant difference between the groups in age, sex, weight, severity of illness, and brain pathology [Table 1] and the baseline hemodynamic and laboratory parameters were comparable in two groups [Table 2].

## INTRAOPERATIVE DATA

### Hemodynamic parameters

There was no significant difference in the HR and mean blood pressure in two groups [Figures 1 and 2].

CVP was recorded in 19 patients in HS group and 18 patients in the mannitol group. There was a significant

**Table 1: Patients demographic data**

	Group HS (n=25)	Group M (n=25)	p value
Age (mean±SD), years	41.6±12.9	38.8±11.9	0.42
Sex (M/F), n	12/13	9/16	0.39
Weight (mean±SD), kg	60.8±11.8	60.2±7.9	0.94
ASA physical status			
1/2/3	0/11/14	0/12/13	
Type of tumor			
Glioma	10	11	
Meningioma	12	9	
Craniopharyngioma	1	3	
Choroid plexus papilloma	1	0	
Astrocytoma	0	1	
Glioblastoma	1	1	
Total	25	25	

NS: Not significant, M/F: Male/Female, SD: Standard deviation, ASA: American Society of Anesthesiologists, HS: Hypertonic Saline

**Table 2: Baseline hemodynamic and laboratory parameters in two groups**

Baseline parameters	Group HS (mean±SD)	Group M (mean±SD)	p value
HR, (bpm)	83±11	87±15	0.26
BP (SBP/DBP/MBP), (mmHg)	121/73/89	115/73/87	>0.05
CVP, (mmHg)	6.6±2.8	4.8±3.2	0.09
Serum Na, (mEq/l)	137.9±4.0	137.3±5.6	0.65
Serum k, (mEq/l)	4.1±0.5	4.2±0.6	0.49
Serum osmolality, (mmol/l)	289.7±8.8	291.2±10.0	0.57
Art Na, (mEq/l)	136.7±4.1	135.5±4.8	0.34
Art K, (mEq/l)	3.6±0.5	3.9±0.6	0.10

NS: Not significant, HR: Heart rate, BP: Blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CVP: Central venous pressure, SD: Standard deviation, HS: Hypertonic Saline

difference in CVP between two groups after 30 min of study drug infusion [Figure 3].

### Brain relaxation

The number of conditions classified as perfectly relaxed, satisfactorily relaxed, firm brain, and bulging brain in the HS group was 8, 13, 3, and 1, respectively, whereas it was 5, 17, 3, and 0, respectively, in the M group. Brain relaxation was comparable in two groups and there was no significant difference ( $P = 0.633$ ) [Table 3]. However, two patients in the HS group required the administration of additional study drug for brain relaxation ( $P = 0.49$ ).

### Serum osmolality and electrolytes

Compared with mannitol, HS caused increase in the serum osmolality at 120 min ( $P = 0.008$ ) and in serum sodium at 120 min ( $P = 0.001$ ) but there was no significant difference in serum potassium at 0 and 120 min in two groups. Compared with group M, there was significant increase in the arterial sodium at 60 and 120 min in the HS group but arterial potassium were comparable in two groups [Table 4].

### Urine output

There was a significant increase in the urine output in the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> hour after the infusion in group M, when compared with the group HS. There was a significant increase in the total urine output in the mannitol group, when compared with HS group [Figure 4].

### Others

There was no significant difference in the fluid input, blood loss [Table 5]. The duration of surgery were comparable in both the groups (Group M  $456 \pm 126$  min vs. Group HS  $459 \pm 151$  min,  $P > 0.05$ ).

### DISCUSSION

Our study compared the effects of equiosmolar boluses of 3% HS (group HS) and 20% mannitol (group M) on brain relaxation in patients with supratentorial tumor who were posted for elective craniotomies. Fifty patients (25 in each group) were randomly allocated to receive either mannitol or HS. We also compared the hemodynamic effect of these drugs in these patients.

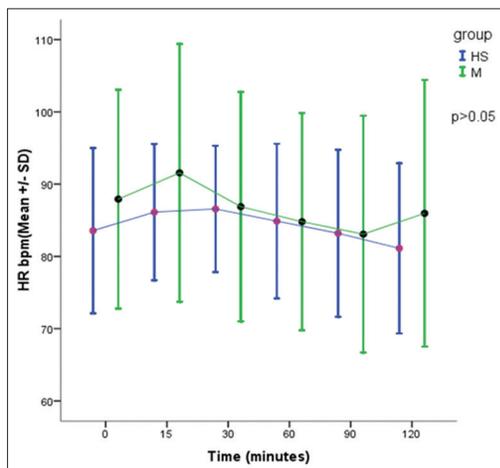


Figure 1: Comparison of heart rate in two groups,  $P > 0.05$  – Not significant

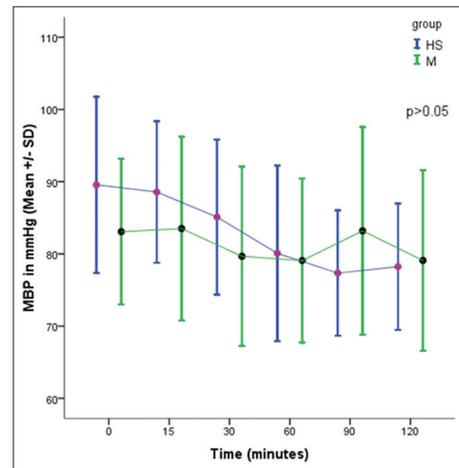


Figure 2: Comparison of mean blood pressure in two groups,  $P > 0.05$  – Not significant

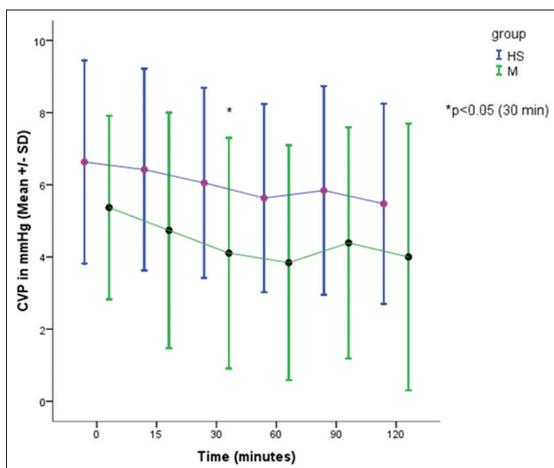


Figure 3: Comparison of CVP in two groups,  $*P < 0.05$  – significant

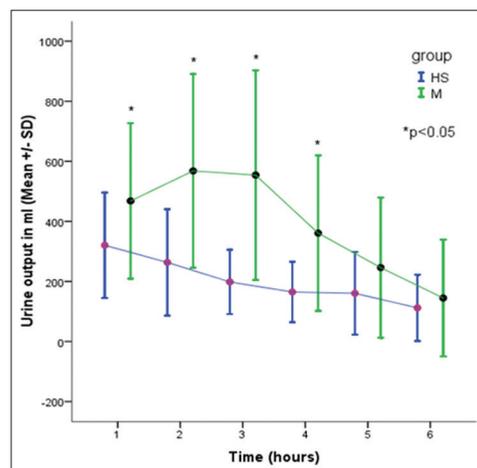


Figure 4: Comparison of urine output in two groups

**Table 3: Comparison of brain relaxation score in two groups**

BR score	Group HS		Group M		P value
	No	%	No	%	
1	8	32.0	5	20.0	
2	13	52.0	17	68.0	
3	3	12.0	3	12.0	
4	1	4.0	0	0.0	
Total	25	100.0	25	100.0	
Median grade (range)	2 (1-4)		2 (1-3)		0.633

BR: Brain relaxation, HS: Hypertonic saline

**Table 4: Comparison of intraoperative laboratory parameters in two groups**

Parameters	Group HS (n=25)	Group M (n=25)	p value
Serum osmolality			
SO (baseline)	289.7±8.8	291.2±10.0	0.57
SO at 120 min	301.2±10.6	293.0±10.3	<0.05
Serum sodium			
Na (baseline)	137.9±4.0	137.3±5.6	0.65
Na at 120 min	143.7±5.4	138.9±4.4	0.001
Serum potassium			
K (baseline)	4.1±0.5	4.2±0.6	0.49
K at 120 min	3.9±0.7	3.9±0.8	0.89
Arterial sodium			
Art Na (baseline)	136.7±4.1	135.5±4.8	0.34
Art Na at 60 min	143.9±7.3	134.6±4.4	0.001
Art Na at 120 min	142.0±6.2	136.3±4.6	0.001
Arterial potassium			
Art K (baseline)	3.6±0.5	3.9±0.6	0.10
Art K at 60 min	3.7±0.7	3.9±0.7	0.42
Art K 120	3.7±0.6	3.7±0.6	0.89

Values expressed as mean±SD, P&lt;0.05 statistically significant. HS: Hypertonic saline

**Table 5: Comparison of intraoperative fluids and blood loss in two groups**

Fluids (in ml) (mean±SD)	Group HS (n=25)	Group M (n=25)	p value
Crystalloids	4012±1244	4620±2105	0.22
Colloids	340±494	448±409	0.18
Total fluid intake	4296±1347	5172±2361	0.114
Blood transfused	326±512	208±298	0.16
Blood loss	860±592	796±599	1.0
Blood loss, liter	No of patients		
<1 l	17	18	1.0
1-2 l	6	6	
>2 l	2	1	

HS: Hypertonic saline, SD: Standard deviation

At the end of infusion both HS and mannitol has created an osmolar gradient across the intact BBB, causing an increase in serum osmolality due to the impermeability of the BBB to both HS and mannitol, this leads to

water absorption from the brain tissue parenchyma to intravascular tissue causing decreased water content and ICP, which has been shown in several animal<sup>[16,22]</sup> and human<sup>[12]</sup> studies in patients with traumatic brain injury and brain tumors, treated with either HS or mannitol. In our study, both mannitol and HS provided acceptable brain relaxation. HS provided perfect and satisfactory brain relaxation in 8 patients (32%) and 13 patients (52%), respectively, whereas mannitol in 5 patients (20%) and 17 patients (68%), respectively, ( $P > 0.05$ ). The physical effects of HS and mannitol on the brain relaxation have been investigated previously by several researchers. In a similar study by Rozet *et al.*,<sup>[14]</sup> comparing equiosmolar solutions of HS and mannitol on intraoperative brain relaxation found no difference in the brain relaxation score in two groups. Gemma *et al.*,<sup>[6]</sup> and Di vivo *et al.*,<sup>[4]</sup> reported satisfactory brain relaxation in equal volumes of nonequiosmolar solutions of 7.5% HS and 20% mannitol. Wu *et al.*,<sup>[23]</sup> reported that HS provided better brain condition as compared with mannitol at equiosmolar doses (0.02). They have classified the brain relaxation on 3 point scale of 1 - soft, 2 - adequate, and 3 - tight as compared with our study, where we have used 4 point scale, which is more objective way of classifying brain relaxation.

All the patients in both the groups remained hemodynamically stable, with no significant changes in HR, systolic, diastolic, and mean blood pressure. This could be due to better anesthesia and fluid management to avoid fluctuations in blood pressure. We monitored CVP in 19 patients in HS group and 18 patients in the mannitol group. In the mannitol group, there was a gradual reduction in CVP with time as compared with HS group. At 30 min there was a significant reduction in CVP with mannitol as compared with HS ( $P < 0.05$ ), coinciding with the onset of peak action of mannitol.

Being an osmotic diuretic, infusion of mannitol leads to significant diuresis. In our study, hourly urine output for the first 4 h was more in the mannitol group as compared with HS ( $P < 0.05$ ), whereas during 5<sup>th</sup> and 6<sup>th</sup> hour of the surgery there was no difference in urine output between the groups, indicating fading action of mannitol. The total urine output was significantly more in the mannitol group as compared with HS group. These results are in concordance with earlier studies.<sup>[5,14,19,23]</sup>

We measured both serum and arterial sodium values. HS lead to increase in arterial sodium levels at 60 and 120 min as compared with mannitol ( $P < 0.05$ ). At the end of 2 h, serum sodium was higher in HS group as compared with mannitol group.<sup>[4,5,8,14,17,23]</sup> The serum and arterial potassium were comparable at all time intervals. Rozet *et al.*,<sup>[14]</sup> found HS caused increased sodium levels but also a transient hypokalemia. Mannitol leads to a gradual increase in potassium levels. In our study we have measured the arterial and serum sodium

at less frequent intervals as compared with Rozet *et al.*,<sup>[14]</sup> which might be responsible for missing arterial and serum potassium level changes.

## CONCLUSIONS

Administration of equiosmolar concentrations of mannitol and HS provided acceptable brain relaxation. Mannitol, being an osmotic diuretic, resulted in a significant increase in urine output. HS resulted in a significant increase in serum sodium and osmolality compared with mannitol, without diuretic effect. HS can be routinely used in place of mannitol to achieve brain relaxation in elective supratentorial craniotomies.

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