Original Article

Effects of two different doses of 3% hypertonic saline with mannitol during decompressive craniectomy following traumatic brain injury: A prospective, controlled study

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Abstract

Background and Aims: The current study was designed to compare the effects of two different doses of 3% hypertonic saline with mannitol on intraoperative events during decompressive craniectomy in traumatic brain injury (TBI). Primary outcome measures included assessment of intraoperative brain relaxation, hemodynamic variables, and serum electrolytes. Effect on the postoperative outcome, in terms of the Glasgow coma scale (GCS), length of stay in the ICU, and mortality were the secondary outcome measures.

Material and Methods: Ninety patients with TBI undergoing craniotomy were enrolled. Patients were assigned to receive 300 mL (328 mOsm) of mannitol (n = 26, M) only or 300 mL of mannitol with 150 mL (482 mOsm) of 3% HS (n = 35, HS_1) or with 300 mL (636 mOsm) of 3% HS (n = 29, HS_2). Brain relaxation was assessed and if required, a rescue dose of mannitol (150 mL) was given. GCS was assessed preoperatively, 24 h postoperatively, and at the time of discharge from the ICU and total duration of stay was noted.

Results: Acceptable brain relaxation was observed in 89.66% (n = 26, HS_2) and 80% (n = 28, HS_1) patients as compared to 46.1% (n = 12, M) patients ($P < 0.001$) with significantly less number of patients requiring rescue doses of mannitol in groups $HS_1$and HS_2(n = 7 and 3, respectively) as compared to group M (n = 14) ($P < 0.05$). There was a significant improvement in GCS at 24 h and at the time of discharge from the ICU in patients with a severe head injury in group HS_2 ($P = 0.029$). In patients with moderate head injury there was a significant improvement in GCS at the time of discharge among all the three groups ($P < 0.05$).

Conclusion: Increasing osmotic load by addition of 3% HS to mannitol provides better intraoperative brain relaxation than mannitol alone during decompressive craniectomy. An addition of 300mL 3% HS was found to be more effective in improving GCS in patients with severe TBI.

Keywords: Brain relaxation, hypertonic saline, mannitol, traumatic brain injury

Introduction

During neurosurgical procedures, providing brain relaxation which allows retraction of the brain with a reduction of consequent retractor ischemia is one of the important anesthetic goals. Osmo therapy with hyperosmotic agents such as mannitol and hypertonic saline (HS) administered before opening the duramater, is widely used to produce cerebral relaxation and facilitate intracranial surgery. Mannitol is considered the hyperosmotic agent of choice and exerts its ICP lowering effects by both an immediate and delayed effect. The

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immediate effect results in a decrease in the rate of formation of cerebral spinal fluid (CSF) due to plasma volume expansion, reduction in blood viscosity, increase in cerebral blood flow, and cerebral vasoconstriction. The delayed effect reduces ICP due to its osmotic effect.[1-4]Hypertonic saline has been considered an attractive alternative to mannitol for satisfactory brain relaxation and a decrease in ICP.[5]Compared with mannitol, HS is considered to have a more strong and long-lasting effect.[6,7]It can be used in various concentrations with varying osmolar loads and has additional benefits such as enhancement of cardiac output thus maintaining mean arterial pressure, decrease in extravascular pulmonary fluid improving ventilation, and partial pressure of arterial gases, arteriolar dilatation which increases cerebral microvascular flow.[8-11]

The current study was designed to compare the effects of two different doses of 3% hypertonic saline with mannitol on intraoperative events during decompressive craniectomy in traumatic brain injury (TBI). Primary outcome measures included assessment of intraoperative brain relaxation, hemodynamic variables, and serum electrolytes between the groups. Effect on the postoperative outcome, in terms of the Glasgow coma scale (GCS) along with the length of stay in the ICU and mortality, were the secondary outcome measures.

Material and Methods

After approval of the institutional ethics committee, this study was conducted from March 2016 to December 2017 at a tertiary care center. Written informed consent was taken from a legally authorized representative of patients before involvement in this study. Ninety patients, aged 18–65 years, with traumatic brain injury undergoing craniectomy were enrolled into a prospective, randomized, controlled study. Patients with electrolyte imbalance with severe cardiac, respiratory, or renal diseases, traumatic brain injury with extradural hematoma, large intracranial hemorrhage causing massive brain bulge, and any other injury-causing hemodynamic instability were excluded from the study.

The total sample size was calculated by a power analysis for 90% statistical power and a 5% level of significance assuming a 1 point difference of brain relaxation between the three major groups. Based on a 95% confidence interval with 90% power, the sample size was calculated as a minimum of 25 patients in each group. Patients were randomly allocated into three groups each assigned to receive 300 mL (328 mOsm) of mannitol (n = 26, M) only or 300 mL of mannitol with 150 mL (482 mOsm) of 3% HS (n = 35, HS_1) or with 300 mL (636 mOsm) of 3% HS (n = 29, HS_2) and randomization was achieved by computer-generated random number table. Since different volumes of study drugs were used, the anesthesiologist could not be blinded, hence only the operating neurosurgeon was blinded to the study groups.

All the patients were preoperatively assessed for vitals, GCS, arterial blood gases including electrolytes and CT scans. In the operation room, standard monitoring including electrocardiogram (ECG), non-invasive blood pressure (NIBP), and pulse oximeter were attached and baseline heart rate (HR), NIBP, and SpO_2 were recorded. Patients were pre loaded with 500 mL of balanced salt solution and after pre oxygenation, general anesthesia was induced with 2 mcg/kg fentanyl and 2 mg/kg propofol along with 0.9 mg/kg rocuronium for muscle relaxation. Following endotracheal intubation (if not already intubated), anesthesia was maintained using an oxygen-air mixture (50:50) with 50–100 mcg/kg/min propofol infusion and fentanyl and vecuronium for intraoperative analgesia and muscle relaxation. Mechanical ventilation was adjusted to maintain $EtCO_2$ at 30 ± 2mmHg. The balanced salt solution was used as a maintenance fluid at 3 mL/kg/h with an additional replacement for urine output and blood loss. The patient received the study drugs as per the group over 30 min at the time of skin incision for intraoperative brain relaxation. Both mannitol and hypertonic saline were given simultaneously through a triple lumen central line placed in the internal jugular or subclavian vein.

Intraoperatively, hemodynamic variables including HR, blood pressure (BP), and mean arterial pressure (MAP) were recorded before induction (T_0), then regularly at intervals of 15 min for 1st hour (T_{15}, T_{30}, T_{60}) then every ½ hourly (T_{90}, T_{120}) and at the end of the surgery. Serum electrolytes (Na^+ and K^+) were recorded preoperatively (T_0), after the infusion of study drug (T_{inf}), immediately (T_c) and 24 h (T_{24}) after the completion of surgery. Details of fluid input, urine output, blood loss, and blood transfusions were also noted.

Brain relaxation was assessed by both neuro surgeons and anesthesiologists at the time of dural incision.[1] Neurosurgeon assessed brain relaxation on a four-point scale:

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

Anesthesiologist assessed brain relaxation on a three-point scale:

- Brain fully relaxed (below both outer and inner table) - 1
- Brain partially relaxed (lying between outer and inner table) - 2
- Brain bulging out of cranial cavity - 3.

If the respective gradings were assessed as 3, 4 (neurosurgeon) and 3 (anesthesiologist), an additional 150 mL dose of mannitol was given with hyperventilation to decrease $EtCO_2$ to 25 mmHg or surgical intervention was done. At the end of the surgery, patients were either extubated or shifted to the neurosurgical intensive care unit for elective mechanical ventilation. All the patients were assessed for GCS at 24 h postoperatively and at the time of discharge from the ICU. The total duration of stay in ICU was also noted.

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.[1,2] Data were entered in MS Excel software and analyzed using SPSS software version 21.0, IBM Inc. Frequency and proportion data (demographic/categorical) were analyzed using Chi-square/Fisher exact test. Continuous data were analyzed using ANOVA (>2 groups) and student *t*-test (unpaired). For non-normal distribution, non-parametric tests such as the Kruskal-Wallis test (>2 groups) and Mann–Whitney U test was used. Results on continuous measurements are presented as Mean ± SD. $P < 0.05$ was considered significant.

Results

Ninety patients with TBI were enrolled in the study and randomized into three groups as described previously. There was no significant difference in mean age, sex, and duration of surgery among the three groups [Table 1].

Out of 90 patients, 30 patients were received intubated. There was no statistically significant difference in distribution of intubated and non- intubated patients among the three groups. On assessing and grading the brain relaxation in different groups, Grade 1 and 2 relaxation was found to be acceptable to the neurosurgeon. Hence, on combining the two grades, 89.66% ($n = 26$, HS_2) and 80% ($n = 28$, HS_1) patients had acceptable brain relaxation as compared to 46.1% ($n = 12$, M) patients ($P < 0.001$). However, 69% ($n = 20$) patients in HS_2 had grade 1 relaxation while only 14.3% ($n = 5$) patients in HS_1 had grade 1 relaxation [Table 2]. Similarly, as per anesthesiologist grading 93.1% ($n = 27$, HS_2) and 88.57% ($n = 31$, HS1) patients had acceptable brain relaxation as compared to 69.23% ($n = 18$, M) patients ($P < 0.001$).

The number of patients requiring rescue doses of mannitol was significantly less in groups HS_1 and HS_2 ($n = 7$ and 3, respectively) as compared to group M ($n = 14$) ($P < 0.05$).

There was a rise in serum sodium levels in both the groups HS_1 and HS_2 after the infusion of study drug though this increase in serum sodium levels was statistically nonsignificant ($P > 0.05$). This rise was transient which returned near baseline values on completion of surgery in both the groups. In group M, there was a

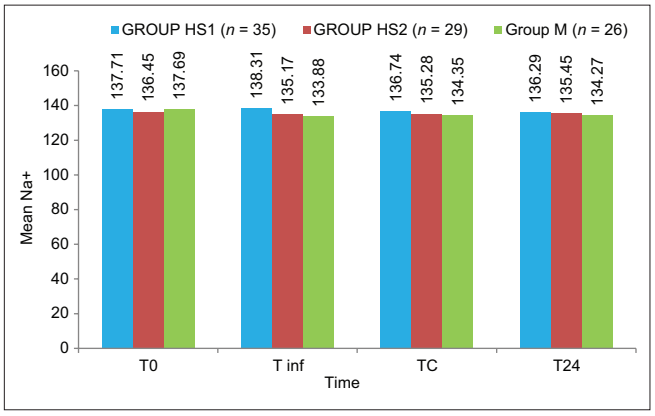

Figure 1: Graphical representation of mean Na^+ levels in different groups during surgery

Table 1: Comparison of demographic data, GCS, and duration of surgery

Variable	Parameter	Group HS_1 (n=35)	Group HS_2 (n=29)	Group M (n=26)	P
Age Group	<35	17 (48.57%)	10 (34.48%)	11 (42.31%)	0.25 (NS)
	35-49	15 (42.86%)	15 (51.72%)	11 (42.31%)	0.45 (NS)
	>49-65	3 (8.57%)	4 (13.79%)	4 (15.38%)	0.47 (NS)
	Mean±SD	35.94±8.07	37.83±11.32	36.62±9.62	0.62 (NS)
Sex	Female	9 (25.71%)	4 (13.79%)	6 (23.08%)	P=0.48 (NS)
	Male	26 (74.29%)	25 (86.21%)	20 (76.92%)	
GCS	≤8	12	11	11	0.67 (NS)
	9-12	21	15	13	0.46 (NS)
	13-15	2	3	2	0.49 (NS)
Duration of Surgery (h)	1-2	4	3	2	0.77 (NS)
	>2-3	27	25	22	0.33 (NS)
	>3	4	1	2	0.23 (NS)
	Mean±SD	2.20±0.47	2.10±0.38	2.17±0.41	0.63 (NS)

Table 2: Grading of brain relaxation in different groups as per neurosurgeon

Grade as per Neurosurgeon	Group HS_1 (n=35)	Group HS_2 (n=29)	Group M (n=26)	ANOVA P	HS_1/HS_2 P	HS_1/M P	HS_2/M P
1	5 (14.3%)	20 (69%)	3 (11.5%)	<0.001* (HS)	<0.001* (HS)	>0.05 (NS)	<0.001* (HS)
2	23 (65.7%)	6 (20.7%)	9 (34.6%)	<0.001* (HS)	<0.001* (HS)	<0.01* (HS)	>0.05 (NS)
3	3 (8.6%)	1 (3.4%)	6 (23.1%)	0.16 (NS)	>0.05 (NS)	>0.05 (NS)	<0.05* (S)
4	4 (11.4%)	2 (6.9%)	8 (30.8%)	0.14 (NS)	>0.05 (NS)	>0.05 (NS)	<0.05* (S)
(1+2)*	28 (80%)	26 (89.66%)	12 (46.1%)	<0.05 (S)	>0.05 (NS)	<0.01 (HS)	<0.01 (HS)

**Acceptable grades*

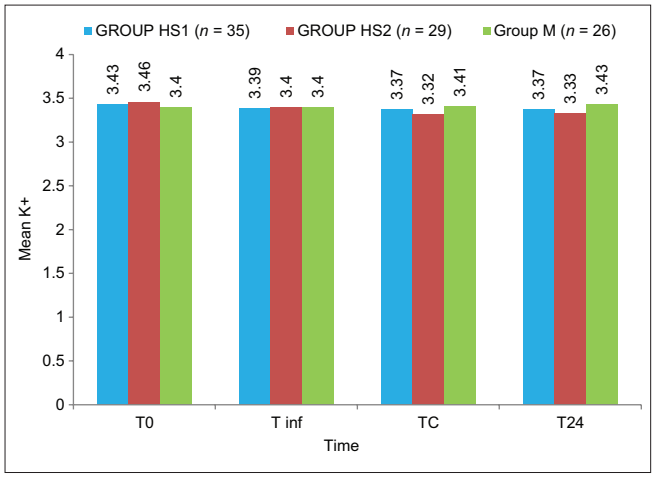

Figure2: Graphical representation of mean K^+ levels in different groups during surgery

significant decrease in sodium levels immediately after the infusion of study drugs which persisted up to 24 h postoperatively [Figure 1].

Serum potassium levels decreased after the infusion of study drug in HS_1 and HS_2, though this decrease was statistically nonsignificant ($P > 0.05$).However, there was a rise in serum potassium levels in group M at 24 h postoperatively but this rise was also statistically nonsignificant ($P > 0.05$) [Figure 2].

On grouping patients according to baseline GCS, in patients with severe head injury (GCS = 3–8), there was a statistically significant improvement in GCS at 24 h and at the time of discharge in group HS_2 ($P = 0.029$) while there was no significant improvement in group HS_1 and group M. In patients with moderate head injury (GCS = 9–12), there was a significant improvement in GCS at the time of discharge in all the three groups ($P < 0.05$), though changes at 24 h and at the time of discharge were highly significant in group HS_2 ($P = 0.00$). In patients with mild head injury (GCS = 13–15), there was no statistically significant improvement in GCS in all the three groups ($P > 0.05$) [Table 3].

The mean length of stay in the ICU in groups HS_1, HS_2, and M were 8.62, 6.83, 6.92 days, respectively ($P > 0.05$).

In our study, mortality occurred in four patients (group HS_2) in the postoperative period during their ICU stay. The cause of death was fulminant meningitis ($n = 2$, death occurring on days 4 and 5) and ventilator-associated pneumonia (VAP, $n = 2$, death occurring on days 7 and 8). Two of these patients had a severe head injury with preoperative GCS of 4 and 5 while the other 2 had a moderate head injury with preoperative GCS of 9 and 11.

Discussion

In recent years, the use of HS has increased as an osmotic agent for hyperosmolar therapy.[12] Similar to mannitol, its principal mechanism of action is the creation of an osmolar gradient across the blood-brain barrier (BBB) leading to cerebral parenchymal fluid shift thus reducing cerebral edema and ICP. Compared to mannitol, the reflection coefficient of HS, which denotes its impermeability to BBB, is higher so the incidence of rebound rise in ICP after its withdrawal is less.[2,13]

Mishra *et al.*[12]and Wu *etal.*[3] compared the effect of 3% HS and 20% mannitol in patients undergoing supratentorial brain tumor surgery. They found that brain relaxation in the HS group was better than the mannitol group. Sharma *et al.*[14]had also compared equiosmolar and euvolemic solutions 20%mannitol versus 3% HS for intraoperative brain relaxation during aneurysm surgery but found no significant difference in brain relaxation between both the groups as was also concluded by Rozet *et al.*[2] On the contrary, Chatterjee *et al.*[15]had compared euvolemic but non-equiosmolar solutions (2 mL/kg 7.5% HS vs 2 mL/kg 20% mannitol) in patients with a severe head injury and found that HS with higher osmotic load was more effective than mannitol for the treatment of refractory intracranial hypertension. Schwarz *et al.*[16]had evaluated the effect ofthe addition of 10% HS to mannitol (non-equiosmolar) in stroke patients with raised ICP and found that the addition of HS decreases the ICP and increases the cerebral perfusion pressure. In view of these studies,[2,3,14,15,17,18] we had combined HS in different volumes with mannitol to assess its effect on intraoperative brain relaxation. On comparing different volumes of HS, there was no significant difference in intraoperative brain relaxation when combining grade 1 and grade 2 relaxation (HS_2[89.66%]

Table 3: Distribution of patients according to GCS in different groups

GCS Score	Groups	Preop GCS Mean±SD	After 24 h GCS Mean±SD	At time of Discharge GCS Mean±SD	ANOVA, *P*
3-8	GROUP HS1 (*n*=12)	6.416±1.676	6.454±1.507	6.714±1.380	*P*=0.915 (NS)
	GROUP HS2 (*n*=9)[#]	5.272±1.272	6.235±1.521	7.142±1.214	*P*=0.029 *(S)
	Group M (*n*=11)	6.727±1.190	6.75±1.288	6.571±1.511	*P*=0.954 (NS)
ANOVA, *P*		*P*=0.051 (NS)	*P*=0.646 (NS)	*P*=0.725 (NS)	
9-12	GROUP HS1 (*n*=21)	10.285±0.845	9.809±0.928	10.478±0.897	*P*=0.046 *(S)
	GROUP HS2 (*n*=13)[#]	9.933±0.457	10.6±1.074	10.23±1.091	*P*=0.000 *(HS)
	Group M (*n*=13)	10.153±1.068	9.916±0.792	10.933±1.099	*P*=0.030 *(S)
ANOVA, *P*		*P*=0.452 (NS)	*P*=0.097 (NS)	*P*=0.179 (NS)	
13-15	GROUP HS1 (*n*=2)	13.5±0.707	13.666±0.577	13.6±0.547	*P*=0.953 (NS)
	GROUP HS2 (*n*=3)	13.333±0.577	13.5±0.707	13.2±0.447	*P*=0.795 (NS)
	Group M (*n*=2)	14.5±0.707	14±1.414	13.75±0.957	*P*=0.743 (NS)
ANOVA, *P*		*P*=0.236 (NS)	*P*=0.846 (NS)	*P*=0.446 (NS)	

[#]*Four patients who died during ICU were excluded*

v/s HS_1[80%]) though its efficacy was significantly superior to mannitol alone. In the present study, non-equiosmolar solutions were used in the three groups, thus generating different osmotic gradients (HS_1 = 482 mOsm, HS_2 = 636 mOsm, M = 328 mOsm). The direct effect of higher volumes generating more osmotic gradients resulting in superior brain relaxation can be observed in HS groups as compared to the group M. Higher osmotic load in group HS_2 had significantly more patients with grade 1 relaxation as compared to patients in group HS_1 ($P > 0.001$).

In our study, several patients requiring rescue doses of mannitol were much less in the non-equiosmolar groups (HS_1 and HS_2) as compared to group M which can again be attributed to better relaxation in HS groups. Other authors[2,14] have found no difference in brain relaxation due to equiosmolar concentrations of osmotic agents thus the requirement of rescue dose of mannitol was same in these studies.

Sharma *et al.*[14] showed a significant increase in serum sodium at 1 h following administration of hypertonic saline which normalized within 24 h while no change was observed in the mannitol group. They documented a significant rise in potassium levels in the mannitol group at 24 h. Similarly Rozet *et al.*[2] found that HS caused an increase in serum sodium, which was sustained for 6 h, and acute, but transient, hypokalemia. In contrast, mannitol caused acute hyponatremia, but a step wise increase of potassium over time. In our study too, a rise in serum sodium level in HS groups with high osmolar load was consistent with previous studies.[2,14]It is postulated that hypokalemia after HS administration develops to maintain electrical neutrality after induced hyperchloremic acidosis associated with the infusion. Several studies have reported hyperkalemia with mannitol administration but the precise mechanism is hypothetical attributing it to a cellular potassium efflux with water in hyperosmolar conditions.[2,19]

TBI can result in permanent neurological deficits leading to increased hospital stay and morbidity.[20] Chang *et al.*[21]had compared the effect of equiosmolar doses of 3% HS and 20% mannitol after decompressive craniectomy and found no significant difference in mean ICU and hospital stay, ICP burden (h of raised ICP/day), GCS score at discharge, and mortality. On the contrary, Mangat *etal.*[6]found decreased ICU stay and ICP burden with similar 2 weeks mortality in patients treated with HS as compared to equios molar mannitol. In our study, we found a similar length of stay in all three groups. There was a significant improvement in GCS of severe head injury patients at 24 h and discharge from ICU in group HS_2 which could be attributed to the higher osmolar load (636 mOsm).

Limitations

Failure to assess chloride levels, serum osmolality, and postoperative renal functions are some of the limitations of this study. Further research in a larger group of patients along with ICP monitoring is recommended. This can give us a more comprehensive analysis of the superiority of different volumes of HS (150 mL vs 300 mL) by increasing the osmotic load; in terms of intraoperative brain relaxation and improvement of GCS.

Conclusion

From the data obtained, it is concluded that increasing osmotic load by the addition of 3% HS to mannitol provided better intraoperative brain relaxation than mannitol alone during decompressive craniectomy. This increased osmotic load is not associated with significant aberrations in serum sodium and potassium levels. In patients with severe TBI (baseline GCS from 3–8), the addition of 300 mL3% HS was found to be more effective in improving GCS at discharge from the ICU.

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Conflicts of interest
There are no conflicts of interest.

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