A Comparative Study of Bolus Dose of Hypertonic Saline, Mannitol, and Mannitol Plus Glycerol Combination in Patients with Severe Traumatic Brain Injury

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BACKGROUND: This prospective randomized controlled study compared the efficacy of an equiosmolar and isovolumetric dose of 3% hypertonic saline, 20% mannitol, and 10% mannitol plus 10% glycerol combination in reducing the raised intracranial pressure (ICP) in patients with severe traumatic brain injury (TBI).

METHODS: A total of 120 patients of severe TBI with increased ICP were randomized to receive an equiosmolar and isovolumetric dose of 3% hypertonic saline, 20% mannitol, and 10% mannitol plus 10% glycerol combination at a defined infusion rate, which was stopped when ICP was ≤15 mm Hg.

RESULTS: A total of 120 patients with severe TBI (aged ≥18 years, Glasgow Coma Scale ≤8, and had sustained elevated ICP of ≥20 mm Hg for more than 5 minutes) were randomized during the study. All data were presented as mean (minimum-maximum). A one-way analysis of variance test was used to analyze the effect across the treatment group, and Tukey's method was used for multiple comparisons. A paired *t*-test was employed to analyze the effect of the medication within each group. All 3 drugs decreased ICP below 15 mm Hg ($P \leq 0.0001$). The maximum change in ICP occurred after a bolus dose of 3% hypertonic saline followed by 10% mannitol plus 10% glycerol combination and then 20% mannitol (60% vs. 57% vs. 55%, respectively). Mean arterial pressure and cerebral perfusion pressure were increased after the bolus dose of study medications. Maximum changes occurred after infusion of 3% hypertonic saline followed by 10% mannitol plus 10% glycerol combination and 20% mannitol ($P \leq 0.0349$ and ≤0.0013, respectively). There was no statistically significant change in the hematocrit value noted after the bolus dose of any of the study medications. Serum sodium and osmolarity were raised significantly after the bolus dose of study medications. Maximum changes in serum sodium and osmolarity occurred after the bolus dose of 3% hypertonic saline. The mean dose required to reduce ICP below 15 mm Hg for 3% hypertonic saline: 1.4 mL/kg, for 10% mannitol plus 10% glycerine: 1.7 mL/kg, and for 20% mannitol: 2.0 mL/kg. The mean time required to reduce ICP below 15 mm Hg for 3% hypertonic saline: 16 minutes, for 10% mannitol plus 10% glycerine: 19 minutes, and for 20% mannitol: 23 minutes. The maximum change in the Glasgow Coma Scale occurred after the bolus dose of 3% hypertonic saline, followed by 10% mannitol plus 10% glycerol combination and then 20% mannitol.

CONCLUSIONS: All 3 osmotic compounds exhibit comparable effectiveness in reducing ICP when a similar osmotic load is administrated, but 3% hypertonic saline appeared to be more effective followed by 10% mannitol plus 10% glycerol combination and 20% mannitol. A dose of 1.4 mL/kg can be recommended as an initial bolus dose for 3% hypertonic saline. Hypertonic saline can be recommended to treat patients with pretreatment hypovolemia, hyponatremia, or renal failure. There is no clear benefit compared with 20% mannitol in regard to neurologic outcome, even though there is a minor positive trend for 3% hypertonic saline and 10% mannitol plus 10% glycerol combination.

Key words
- Hypertonic saline
- Mannitol
- Mannitol plus glycerol combination
- Raised intracranial pressure
- Severe traumatic brain injury

Abbreviations and Acronyms
CPP: Cerebral perfusion pressure
GCS: Glasgow Coma Scale
HR: Heart rate
HTS: Hypertonic saline
IC-HTN: Intracranial hypertension
ICP: Intracranial pressure
MAP: Mean arterial pressure
TBI: Traumatic brain injury

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INTRODUCTION

Intracranial hypertension (IC-HTN) is a medical emergency requiring prompt attention and intervention to prevent devastating neurologic outcomes.[1] Over the past few years, the use of previously recommended therapies such as barbiturates or hyperventilation has been increasingly questioned because they are known to reduce the cerebral perfusion pressure (CPP) through negative effects on the systemic blood pressure or excessive cerebral vasoconstriction.[2,3] From that perspective, treatment with hypertonic fluids is still an attractive means of decreasing the intracranial pressure (ICP) without having a negative effect on the CPP. There are many reports supporting potential of substances such as glycerol and mannitol in decreasing edema formation in brain.[4]

Various clinical and experimental studies have demonstrated that single doses of mannitol can substantially reduce increased ICP.[5] However, the long-term beneficial effects of mannitol are still controversial, and there are few reports of aggravated brain edema after repeated mannitol treatment.[1,5]

Glycerol (glycerine) is another attractive agent that has been found to exert beneficial effects in controlling ICP in edema and other pathologic conditions. Apart from their hypertonic nature, they also act as a free radical scavenger, antioxidant, and activator of plasma prostaglandin resulting in vasodilation. Furthermore, 10% glycerol may improve ischemic brain energy metabolism as evident from the available literature.[6]

The combination of mannitol and glycerol comprises 2 sugars with better osmotic diuretic properties. Either glycerol or mannitol can be administered individually; however, the addition of glycerol to mannitol avoids rebound edema, which is likely to be observed with the intravenous administration of only mannitol.[7] This provides a strong rationale for combining glycerol and mannitol in the management of cerebral edema and raised ICP. This combination strategy is able to enhance the diffusion of water from cerebrospinal fluid back into plasma by elevating the osmolality of the plasma.[8]

Mannitol has been used for several decades to reduce raised ICP, and there is accumulating evidence from pilot studies suggesting beneficial effects of hypertonic saline (HTS) for similar purposes.[4,9]

An ideal therapeutic agent for ICP reduction should reduce ICP while maintaining cerebral perfusion (pressure). Although mannitol can cause dehydration over time, HTS helps to maintain normovolemia and cerebral perfusion. Prophylactic therapy is not recommended with mannitol, although it may be beneficial with HTS.[5,9]

The current evidence suggests that mannitol is effective in reducing ICP in the management of traumatic IC-HTN and carries mortality benefit compared with barbiturates. Current evidence regarding the use of HTS in severe TBI is limited to smaller studies, which illustrate a benefit in ICP reduction and perhaps mortality.[9]

Till date no study has been performed to compare the effect of 10% mannitol plus 10% glycerol combination and 3% HTS and 20% mannitol with a similar osmotic load in patients with severe TBI.

This study aims to compare the efficacy of the above-mentioned 3 drugs in patients with traumatic brain injury (TBI) with raised ICP.

MATERIALS AND METHODS

This was a prospective randomized controlled study conducted for 2 years (2015–2017) in the Department of Neurosurgery, Sri Aurobindo Institute of Medical Science and P. G. Institute, Indore (Madhya Pradesh). Institutional ethical committee clearance was taken before start of the study and an informed written consent was taken from all patients' relatives.

All the patients recruited in this study had isolated severe TBI due to road traffic accident. After assessing the Glasgow Coma Scale (GCS), computed tomography of the head was performed to rule out the need for immediate surgery. Patients were included if they were aged $\geq$18 years, GCS $\leq$8, and had sustained elevated ICP of >20 mm Hg for more than 5 minutes.

Patients were excluded if they had any of the following criteria:

- An imminent cranial or extracranial surgery
- Previous decompressive craniectomy
- Leakage or drainage of cerebrospinal fluid
- Polytrauma
- Oliguria, renal failure
- Hemoglobin <8 g/L
- Serum osmolality of >320 mOsm/L
- The use of mannitol or HTS in the previous 6 hours.

Methodology

Total 120 patients were included in this study. All the patients were divided into 3 groups (40 in each group) using the sealed envelope method of physical randomization.

Group 1 received 20% mannitol.

Group 2 received 10% mannitol plus 10% glycerol combination.

Group 3 received 3% HTS.

Analgesia was provided to all the patients and if required sedation also provided in irritable patients (dexmedetomidine). Vasoactive support (norepinephrine) was administered in hypotensive patients. Insulin treatment was administered to maintain glycemia at <140 mg/dL. For each patient, a set of variables was collected that included demographic characteristics data, initial GCS, and timing of studied treatment. The ICP was continuously monitored by using an intracranial bolt (**Figure 1**). Other monitoring included mean arterial pressure (MAP), serum osmolality, blood levels of sodium, and hemoglobin. When ICP exceeded 20 mm Hg and lasted for more than 5 minutes, isovolume and equimolar bolus dose of hyperosmolar solutes such as 20% mannitol or 3% HTS or 10% mannitol plus 10% glycerol combination was infused via the central venous line at a defined infusion rate, that is, 6 mL/minute or 120 drops/minute (osmolarity of mannitol, mannitol plus glycerol combination, and 3% HTS are almost the same, ie, 1100 mOsm/L, 1049 mOsmo/L, and 1027 mOsm/L, respectively). The infusion was stopped when ICP was reduced to <15 mm Hg, which was our treatment goal.

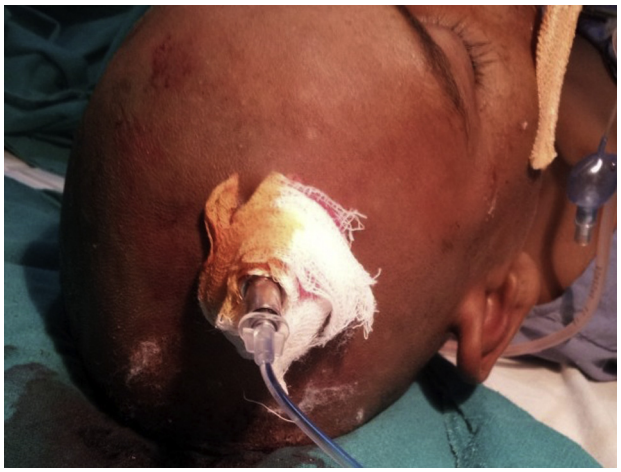

Figure 1. Intracranial pressure measurement via subdural bolt.

Data Acquisition and Statistical Analysis

Heart rate (HR), MAP, ICP, and calculated CPP were continuously measured. ICP was measured by the intracranial bolt. Analysis of these parameters was performed at the following time points:

- Initiation of infusion
- After termination of infusion (ICP <15 mm Hg achieved)
- 10 minutes after terminating infusion
- 30 minutes after terminating infusion
- 60 minutes after terminating infusion.

Serum sodium level, hematocrit, and serum osmolality were measured before and after the therapy. Individual outcomes were assessed by change in GCS before and after the study.

All demographic data and result were presented as mean (minimum-maximum). The clinical values in all 3 groups were normally distributed. A one-way analysis of variance test was used to analyze the effect across the treatment group, and Tukey's method was used for multiple comparisons. A paired *t*-test was employed to analyze the effect of the medication within each group. $P < 0.05$ was regarded as statistically significant.

RESULTS

In this study, a total of 120 patients were recruited; minimum age was 18 years and maximum age was 75 years. The mean age of patients was 38.42 ± 15.50 years.

HR and Blood Pressure

The average baseline HR was 73 (56–90) beats per minute (bpm) in the 20% mannitol group, 68 (52–90) bpm in the 3% HTS group, and 74 (50–94) bpm in 10% mannitol plus 10% glycerol combination group. Although no clinically significant changes occurred in HR after the bolus dose of any of the 3 drugs, there was a statistically significant change noted across the treatment when 3 groups were compared with each other during each time point.

The initial MAP was 76 (68–84) mm Hg in the 20% mannitol group, 75 (60–86) mm Hg in the 3% HTS group, and 78 (64–88) mm Hg in the 10% mannitol plus 10% glycerol combination group. The maximal change in MAP occurred in the 20% mannitol group after 10 minutes. The maximal changes in MAP occurred in the 10% mannitol plus 10% glycerol combination group after 10 and 30 minutes. The MAP was 81 (68–90) mm Hg and 83 (68–96) mm Hg, and 83 (64–98) mm Hg, respectively. In patients receiving 3% HTS, the maximum change in MAP occurred after 60 minutes (87 [58–102] mm Hg). Statistical analysis for MAP shows that a statistically significant change occurred in all the 3 groups when they were compared with each other during each time point ($P < 0.05$) (Table 1).

Table 2 shows that there was no statistical significance noted when 3% HTS was compared with 20% mannitol and when 20% mannitol was compared with 10% mannitol plus 10% glycerol combination across any time points. Statistical significance was seen when 3% HTS was compared with 10% mannitol plus 10% glycerol combination at termination of infusion and at 30 and 60 minutes of observation period.

Table 3 shows that before administration of the study medication, the mean ICP was 27 (22–31) mm Hg in the 20% mannitol group, 26 (21–31) mm Hg in the 10% mannitol plus 10% glycerol group, and 25 (21–33) mm Hg in the 3% HTS group.

After infusion with 20% mannitol, the ICP decreased to 14 (12–14) mm Hg, 13 (12–14) mm Hg in the 10% mannitol plus 10% glycerol group, whereas after infusion with 3% HTS, ICP decreased to 14 (11–14) mm Hg.

This effect was achieved within 23 (10–70) minutes by 20% mannitol, 19 (7–50) minutes by the 10% mannitol plus 10% glycerol group, and 16 (6–39) minutes by the 3% HTS group. After achieving our treatment goal, that is, reduction of ICP below 15 mm Hg, the patient was observed for 1 hour.

Statistical analysis showed that a statistically significant change occurred during each time point after the bolus dose of individual drugs. The maximum change in ICP occurred after the bolus dose of 3% HTS.

Table 3 shows that CPP increased significantly after the bolus dose of all study medications, but the maximum change occurred in CPP after the bolus dose of 3% HTS.

Table 4 shows that the maximum decrease in ICP was produced by 3% HTS (60%), followed by the 10% mannitol plus 10% glycerol combination group (57%) and then 20% mannitol (55%).

When the 3 groups were compared, 3% HTS required the lowest dose, that is, 1.4 mL/kg, followed by the 10% mannitol plus 10% glycerol combination group, that is, 1.7 mL/kg, and then the 20% mannitol group, that is, 2 mL/kg.

The time required to reduce ICP below 15 mm Hg was the lowest in the 3% HTS group, that is, 16 minutes, followed by the 10% mannitol plus 10% glycerol combination group (19 minutes) and then 20% mannitol (23 minutes) (Table 5).

Table 6 shows that a statistically significant change did not occur in hematocrit values after the bolus dose of any of the above-mentioned 3 drugs ($P > 0.05$). In our study, serum sodium level increased significantly after infusion of the 3 drugs ($P < 0.0001$), but the maximum change occurred after the bolus

Table 1. Changes in Heart Rate and Blood Pressure

	Starting Fusion Mean (Minimum-Maximum)	Termination of Infusion Mean (Minimum-Maximum)	After 10 Minutes Mean (Minimum-Maximum)	After 30 Minutes Mean (Minimum-Maximum)	After 60 Minutes Mean (Minimum-Maximum)
HR (beats/minute)					
3% hypertonic saline	68 (52–90)	70 (52–88)	68 (52–90)	70 (52–86)	68 (52–86)
20% mannitol	73 (56–90)	71 (52–88)	72 (52–88)	72 (52–90)	74 (52–90)
10% mannitol plus 10% glycerol	74 (50–94)	73 (52–94)	74 (54–98)	76 (52–94)	75 (56–96)
P value across the treatment group	0.0536	0.0113	0.0093	0.0075	0.0020
MAP (mm Hg)					
3% hypertonic saline	75 (60–86)	83 (64–94)	84 (62–96)	86 (60–98)	87 (58–102)
20% mannitol	76 (68–84)	79 (70–88)	81 (68–90)	80 (66–94)	80 (62–98)
10% mannitol plus 10% glycerol	78 (64–88)	82 (68–94)	83 (68–96)	83 (64–98)	82 (62–98)
P value across the treatment group	0.0317	0.0349	0.049	0.0051	0.0020

One-way analysis of variance was used to analyze the effect across the treatment group.
HR, heart rate; MAP, mean arterial pressure.

dose of 3% HTS. Serum osmolarity was increased significantly after infusion of all 3 drugs ($P < 0.0001$); the maximum change occurred after the bolus dose of 3% HTS.

Outcome

Table 7 shows that after the end of the observation period, there was improvement in GCS in all 3 groups, but the maximum change in GCS was noted in the 3% HTS group.

DISCUSSION

Elevation of ICP by more than 20 mm Hg plays a major role in the worsening of neurologic status through the impairment of brain perfusion. Several clinical studies have demonstrated that the outcome is improved by adequate pharmacologic or neurosurgical treatment.[10,11]

According to established treatment guidelines, an ICP >20 mm Hg and a CPP <60 mm Hg are considered critical. Early

Table 2. Comparison Between the Groups

	HR			MAP		
	P Value			*P* Value		
	A-B	A-C	B-C	A-B	A-C	B-C
Starting fusion	0.1724	0.0548	0.8577	0.2938	0.0241	0.4841
Termination of infusion	0.3303	0.0079	0.2432	0.0296	0.6675	0.2027
After 10 minutes	0.1895	0.0066	0.3711	0.0383	0.5304	0.3442
After 30 minutes	0.1042	0.0059	0.5261	0.0034	0.1762	0.2858
After 60 minutes	0.0641	0.0014	0.3991	0.0017	0.0391	0.5458

Tukey's method has been used for multiple comparisons.
$P < 0.05$ = significant, $P > 0.05$ = nonsignificant.
A, 3% hypertonic saline; B, 20% mannitol; C, 10% mannitol plus 10% glycerol combination; HR, heart rate; MAP, mean arterial pressure.

Table 3. Changes in ICP and CPP

	Starting Fusion Mean (Minimum-Maximum)	Termination of Infusion Mean (Minimum-Maximum)	After 10 Minutes Mean (Minimum-Maximum)	After 30 Minutes Mean (Minimum-Maximum)	After 60 Minutes Mean (Minimum-Maximum)
ICP (mm Hg)					
3% hypertonic saline	25 (21—33)	14 (11—14)	11 (6—18)	10 (5—23)	10 (5—27)
20% mannitol	27 (22—31)	14 (12—14)	13 (8—19)	12 (6—29)	12 (6—33)
10% mannitol plus 10% glycerol	26 (21—31)	13 (12—14)	12 (7—19)	11 (6—26)	11 (6—30)
P value (across treatment)	0.6015	<0.0001	0.0246	0.1690	0.3555
CPP (mm Hg)					
3% hypertonic saline	49 (31—62)	72 (50—87)	74 (46—89)	76 (41—92)	78 (34—97)
20% mannitol	52 (40—66)	67 (56—78)	68 (49—81)	68 (37—86)	68 (29—91)
10% mannitol plus 10% glycerol	52 (36—66)	69 (54—80)	71 (49—87)	71 (40—89)	70 (32—91)
P value (across treatment)	0.1033	0.0013	0.0239	0.0118	0.016

One-way analysis of variance was used to analyze the effect across the treatment group.
CPP, cerebral perfusion pressure; ICP, intracranial pressure.

recognition of such critical episodes by multimodal neuromonitoring and selection of an effective and safe drug for treatment are essential for neuroprotection.[12,13]

Osmotherapy has been used since the early 20th century to treat increased ICP. The physiological basis and concept of osmotherapy was first published in 1919. Intravenous infusion of mannitol is considered to be the "gold standard" for the treatment of increased ICP. Experimentally, intravenous application of HTS increases global cerebral perfusion and causes right shift in the oxygen dissociation curve, which results in improvement of oxygen delivery. At the same time, an increase of cerebral compliance and a decrease in ICP occur by the decrease of the brain edema.[14]

It has become a generally accepted treatment goal to keep the CPP above 70 mm Hg, because episodes of CPP <60 mm Hg or ICP >20 mm Hg are associated with a worse outcome.[15] These goals were incorporated into the current treatment protocol.

Infusion of mannitol is supported by the "Guidelines for the Management of Severe Traumatic Brain Injury"[15] even though there is no class I evidence in patients with TBI supporting this intervention. Today, HTS is used alternatively with mannitol as a treatment for persistent IC-HTN, but there are relatively few prospective randomized studies on hyperosmolar solutions. Trials that exist show only level II evidence supporting the use of continuous infusion of 3% HTS for the treatment of elevated ICP in pediatric TBI.[15,16]

Several experimental and clinical studies have investigated the effects of HTS and mannitol in patients with raised ICP in TBI.[15,16] There are few studies on 10% mannitol plus 10% glycerol combination in the treatment of raised ICP, but there is no study comparing these 3 drugs against each other in patients with severe TBI.

In this study, we compared the efficacy of an equiosmolar and isovolumetric bolus dose of 3% HTS, 20% mannitol, and 10%

Table 4. Changes in ICP

Groups	Maximum ICP (mm Hg), Mean (Minimum-Maximum)	Minimum ICP (mm Hg), Mean (Minimum-Maximum)	Maximum Change in ICP in Percentage (%)
3% hypertonic saline group	25 (21—33)	10 (5—23)	60
20% mannitol group	27 (22—31)	12 (6—29)	55
10% mannitol plus 10% glycerol combination group	26 (21—31)	11 (6—26)	57

ICP, intracranial pressure.

Table 5. Dose and Time Required to Reduce ICP Below 15 mm Hg

	Dose (mL/Application)	Dose (mL/kg)	Time (Minutes)
3% hypertonic saline	94 (38—234)	1.4 (0.5—3.3)	16 (6—39)
20% mannitol	137 (40—422)	2.0 (0.5—6.3)	23 (10—70)
10% mannitol plus 10% glycerol combination	118 (44—302)	1.7 (1.6—4.0)	19 (7—50)

ICP, intracranial pressure.

mannitol plus 10% glycerol combination in reducing the raised ICP in patients with severe TBI.

In the present study, all changes in brain and systemic variables could be attributed to the administration of each treatment because several potential confounding factors were excluded from the study (eg, the use of mannitol, mannitol plus glycerol or HTS in the previous 6 hours, imminent cranial or extracranial surgery, previous decompressive craniectomy, leakage or drainage of cerebrospinal fluid, oliguria, renal failure, serum osmolality of >320 mOsm/kg).

In our study, all the 3 drugs reduced the ICP after administration of the bolus dose. The magnitude of ICP reduction was in line with other studies.[17-26] We found that the duration of ICP reduction after the bolus dose was prolonged and there was no evidence of return to baseline values during the 60 minutes of observation period in survived patients in all 3 groups. In the 3% HTS group, we found that there was an equal reduction in ICP at all time points during the 60-minute observation period. Francony et al[21] also made a similar observation in their study.

In this study, there was no evidence of a rebound ICP rise during the observation period. In the Battison et al study,[19] ICP returned to the pretreatment level after a median time of 90 minutes. In the Battison et al study, mannitol was administrated as a 5-minute bolus dose. When mannitol was administered at a slower rate (20—30 minutes), no ICP rebound was observed within 2 hours after infusion. This indicates that the rate of infusion could be involved in the duration of the effect of mannitol: the faster the infusion, the more likely would be the termination of effect through a rapid renal elimination or a penetration of mannitol into brain tissue.[27]

When the 3 groups were compared with each other, we found that 3% HTS treatment reduced ICP more effectively than 20% mannitol or 10% mannitol plus 10% glycerol combination (60% vs. 55% vs. 57%, respectively). These findings were in line with other studies where the mean maximum ICP reduction ranged from 38% to 93%.[17-26] In our study, all 3 drugs elevated the MAP and CPP after the bolus dose, and statistically significant differences were observed at each measurement point. HTS was more potent among these 3 drugs.

In this study, we assessed the early effects of 20% mannitol, 10% mannitol plus 10% glycerol combination, and 3% HTS. It appeared that hyperosmolar solutions decrease an elevated ICP, and, therefore, they are beneficial in emergency situations in an acutely deteriorating patient before initiation of surgery. For that indication, HTS appeared to act more rapidly and effectively.

In our series, systemic effects after 20% mannitol, 10% mannitol plus 10% glycerol combination, and 3% HTS bolus dose were in accordance with the literature.[17-27] There was no change in hematocrit values after administration of any of the above-mentioned drugs. Serum sodium and osmolarity was raised after administration of all 3 drugs, but 3% HTS raised serum sodium and osmolarity significantly compared with the other 2 drugs.

An excessive increase in sodium level and osmolarity results in volume overload with heart failure and lung edema, or may induce hyperchloremic metabolic acidosis and coagulation disorders.[28,29] Therefore, the use of hypertonic solutions in patients with a compromised cardiac function should be done under close cardiac monitoring.

We assessed the outcome by change in the GCS at the end of the observation period, that is, 60 minutes after termination of

Table 6. Clinical Biochemistry

	Hematocrit (%)			Serum Sodium (mEq/L)			Serum Osmolarity (mOsm/kg)		
	Before Mean (Minimum-Maximum)	After Mean (Minimum-Maximum)	*P* Value	Before Mean (Minimum-Maximum)	After Mean (Minimum-Maximum)	*P* Value	Before Mean (Minimum-Maximum)	After Mean (Minimum-Maximum)	*P* Value
3% hypertonic saline	34 (24—46)	34 (27—47)	0.903	134 (123—141)	143 (134—152)	<0.0001	288 (265—301)	306 (287—323)	<0.0001
20% mannitol	34 (23—46)	34 (23—46)	0.892	134 (122—143)	137 (125—145)	<0.0001	288 (263—305)	294 (269—309)	<0.0001
10% mannitol plus 10% glycerol combination	34 (26—47)	34 (27—47)	0.850	135 (126—145)	140 (129—151)	<0.0001	290 (271—309)	300 (277—321)	<0.0001

$P < 0.05$ = significant, $P > 0.05$ = nonsignificant.

Table 7. Change in GCS

	Initial GCS (Mean)	GCS at the End of the Observation Period (Mean)	*P* Value
3% hypertonic saline	6 (3—8)	8 (3—12)	<0.0001
20% mannitol	5 (3—7)	6 (3—10)	<0.0001
10% mannitol plus 10% glycerol combination	5 (3—6)	7 (3—11)	<0.0001

$P < 0.05$ = significant, $P > 0.05$ = nonsignificant.
GCS, Glasgow Coma Scale.

infusion, and we found that there was improvement in GCS in all 3 drugs. The 3% HTS and 10% mannitol plus 10% glycerol combination group had maximum improvement.

The majority of the studies showed a more favorable short-term ICP outcome for HTS, irrespective of the concentration or administration mode (bolus or continuous drip). Worse outcome after HTS was not seen in any bolus study.[17-26]

In our study, 1.40 mL/kg HTS was needed to reduce ICP below 15 mm Hg (our treatment goal) and this effect occurred in 16 minutes. Mannitol (2.00 mL/kg) and mannitol plus glycerol (1.75 mL/kg) were needed to achieve the same effect, and the time required was 23 minutes and 19 minutes, respectively. Thus, HTS was superior among these 3 drugs. There is no recommended bolus dose suggested for 3% HTS in TBI. However, we found that 1.40 mL/kg can be recommended as an effective bolus dose to reduce increased ICP. Harutjunyan et al[18] also recommended 1.4 mL/kg dose for HTS in the treatment of raised ICP in severe TBI. Various studies have used HTS in varying concentration of 3% to 23.4%; doses ranged from 30 to 300 mL by volume and 1.5 to 10 mL/kg by weight, 2 mL/kg being the most common.[30-32]

Our study results were in line with other studies. Vialet et al[17] showed that HTS is more effective than mannitol in patients with TBI, but in that study, the osmolar difference between solution was present. Patients with HTS arm received a higher osmotic load than those with mannitol arm. This may limit the validity of the study.

Battison et al,[19] Ichai et al,[22] and Cottenceau et al[26] studies concluded that when the same osmotic load is administered, HTS is more effective than mannitol in patients with severe TBI, but Francony et al[21] and Sakellaridis et al[25] studies concluded that mannitol and HTS are equally effective in the treatment of raised ICP in patients with severe TBI.

Till date no study has been performed to compare the effect of 10% mannitol plus 10% glycerol combination and 3% HTS and 20% mannitol with a similar osmotic load in patients with severe TBI.

Since the last decade, HTS had received increasing attention as a good substitute for mannitol because of its excellent tonic properties and lack of hypovolumic hypotensive tendency that mannitol causes. Mannitol may precipitate acute renal failure, whereas HTS is renoprotective.

Our study concluded that 3% HTS is the most effective drug among the 3 drugs followed by 10% mannitol plus 10% glycerol combination and then 20% mannitol for the treatment of raised ICP in patients with severe TBI.

There are some limitations to this study. We aimed at investigating the immediate effects of an osmotic compound in a single bolus dose; hence, we did not analyze the late effects of osmotic agents, effects of repeated infusion or maintenance dose, and any side effects of the drugs. We measured the ICP by a subdural bolt; any complications associated with its placement, and advantages or disadvantages of the ICP measuring technique were not analyzed because it was beyond the scope of this study. We analyzed the patient outcome by the change in GCS at the end of the observation period that was 60 minutes. A detailed analysis of the outcome was not done as it was beyond the scope of this study.

CONCLUSIONS

The results of this randomized controlled trial provide insights that may help to improve the choice between 3% HTS, 10% mannitol plus 10% glycerol combination, and 20% mannitol when osmotherapy is indicated in patients with severe TBI.

All 3 osmotic compounds exhibit comparable effectiveness in reducing ICP when a similar osmotic load is administrated, but 3% HTS appeared to be more effective followed by 10% mannitol plus 10% glycerol combination and 20% mannitol.

A dose of 1.4 mL/kg can be recommended as an initial bolus dose for 3% HTS. HTS can be recommended to treat patients with pretreatment hypovolemia, hyponatremia, or renal failure.

There is no clear benefit compared with 20% mannitol in regard to neurologic outcome, even though there is a minor positive trend for 3% HTS and 10% mannitol plus 10% glycerol combination.

Further randomized control studies will be needed to analyze the late effects, effects of repeated infusion/maintenance dose or any side effects, and long-term neurologic outcome.

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