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Comparative Study of Efficacy of Mannitol and Hypertonic Saline in Clinically Assessed Raised Intracranial Pressure in Acute Stroke

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Abstract

Background: Mannitol has been used for decades for treating raised Intracranial Pressure (ICP). Recent studies reported that Hypertonic Saline (HTS) formulations are better than mannitol with a favorable safety profile. The present study's purpose was to compare the efficacy of 20% mannitol versus 3% HTS in clinically raised ICP in patients of acute stroke managed conservatively.

Materials and Method: This Randomize Controlled Trail (RCT) was conducted at the Department of Neurology, Chittagong Medical College Hospital, Chattogram from July 2021 to June 2022. Sixty-eight confirmed ischemic or hemorrhagic stroke patients with clinical signs of increased ICP and GCS 8 or below were randomly allocated to either mannitol or 3% HTS in the Chittagong Medical College Hospital, Department of Neurology. After Hyperosmolar Therapy (HT), blood pressure, Mean Arterial Pressure (MAP), heart rate, pupillary reaction, respiratory rate, and GCS were monitored for 6-48 hours. Patients' outcomes were assessed two weeks after treatment by the Glasgow Outcome Scale (GOS) and the Modified Rankin scale (mRS) score one month later.

Results: Both groups were comparable at baseline regarding demographic and clinical characteristics. SBP, DBP, and MAP reduced significantly in two groups 6 to 48 hours from baseline. The median (Interquartile range) percentage reduction of the MAP from baseline was 6.3 (-3.9 to 19.2) % in the HTS group and 10 (-4.7 to 14.9) % in the Mannitol group (p=0.544). The mean GCS improved significantly from baseline values in both groups in 6, 12, 24, 36 and 48 hours. The thirty-day mortality rate was 11.8% and 38.2%, respectively, in the HTS and mannitol groups (p=0.021). In multivariate regression analysis, the patients in the mannitol group were 7.9 times (OR: 7.85, 95% CI:1.45-42.52, p=0.017) more likely to expire within 30 days than the patients in the HTS group.

Conclusion: HTS could be used safely as an alternative therapy to mannitol in managing raised ICP after acute stroke.

Key words: Hypertonic saline; Intracranial pressure; Mannitol; Osmotherapy; Outcome; Stroke.

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Introduction

Large hemispheric strokes have the potential to produce a mass effect on the brainstem, which may be related to the volume of the core lesion or space-occupying vasogenic and cytotoxic edema. In either scenario, Hyperosmolar Therapy (HT) is the standard first-line medical therapy to reduce the intracranial volume to minimize midline shift.[1] Recent guidelines state that the use of HT for clinical deterioration is reasonable but do not comment on or against its prophylactic use.[2]

The optimal osmotic agent for HT should not cross the intact blood-brain barrier, be non-toxic, and remain in the intravascular compartment to provide a favorable osmotic gradient.[3] Although this optimal agent does not exist, mannitol and HTS are the two most widely used osmotic agents in clinical practice because they possess more favorable characteristics. These agents share similar effects in reducing brain volume and ICP by a biphasic mechanism. HTS has several theoretical advantages over mannitol, such as less permeability across an intact blood-brain barrier and lack of a diuretic effect. These theoretical advantages suggest hypertonic saline is less likely to cause dehydration and hypotension than mannitol.[4]

Although few studies suggested that infusion of HTS decreases increased ICP after stroke effectively, it does not increase Cerebral Perfusion Pressure (CPP) as much as mannitol.[5,6] However, HTS infusion decreases elevated ICP and increases CPP in stroke patients with failed mannitol, and the effect persists for four hours.[6] Recently, 3% HTS was associated with a more significant reduction of ICP than 20% mannitol in different pediatric populations. Mannitol has several side effects, 3% HTS would be a safe and effective alternative.[7,8] According to a literature

review, HTS appears to achieve a more significant reduction in ICP than mannitol, with better clinical outcomes in children with raised ICP.[9] In Traumatic Brain Injury (TBI) HTS had significantly lower treatment failure, lower ICP and higher CPP 30–60 minutes after infusion termination compared to mannitol. The evidence suggests that HTS is not inferior to mannitol at reducing increased ICP in aneurysmal subarachnoid hemorrhage.[10-12]

There was little research about HT in patients with ischaemic stroke, and there is no uniform approach to its use. The benefit of HTS relative to long-term neurological outcomes compared to mannitol was unclear. In the study site, mannitol was the preferred one for managing raised ICP, probably due to the need for more local evidence regarding the safety and efficacy of HTS. Therefore, to better understand the relative effectiveness and safety of mannitol and HTS, this study compared their efficacy and safety in treating clinically suspected elevated ICP associated with acute stroke.

Materials and methods

This Randomize Controlled Trail (RCT) was conducted at the Department of Neurology, Chittagong Medical College Hospital, Chattogram, Bangladesh, from July 2021 to June 2022. Ethical Review Committee of Chittagong Medical College approved the study protocol. As the patients were not at the stage of providing consent, written informed consent was obtained from the caregivers of the patients.

Patients with large ischemic stroke with brain edema with tissue shifts compressing the midline structures or hemorrhagic stroke with brain edema and some of the supporting evidence (Raised blood pressure, Bradycardia, Pupils-unequal, Increased respiratory rate, GCS ≤8) were included in this study. Patients on hemodialysis or peritoneal dialysis for end-stage renal disease and those suffering from acute kidney injury, subarachnoid hemorrhage, brain tumor, congestive cardiac failure, metabolic encephalopathy (Hepatic encephalopathy, hypoglycemia or hyperglycemia, dyselectrolytemia) large hemorrhagic stroke with ventricular extension with obstructive hydrocephalus which may need neurosurgical intervention were excluded.

At study entry, data on demography, clinical features, and baseline laboratory parameters were collected [Age, sex, history of cardiovascular risk factors, hypertension, type 2 diabetes, atrial fibrillation, smoking, alcohol consumption, family history of cardiovascular disease), history of concomitant CVD (Coronary heart disease, previous ischemic stroke, heart failure)]. All enrolled patients were randomized 1:1 to receive either 20% mannitol [20% solution (0.5-1gm/kg), 250ml iv stat and then 125 ml iv 8 hourly for 48 hours (Total 200gm in 48 hours, osmolarity 1100 mosm/litre)] or 3% HTS [250 ml iv bolus, initiate at 1 to 2 ml/kg/hour (Administration rate range: 75 to150 ml/hour) and then continue at 0.5ml/kg/hr which may take up to three to four hours].

The patient in the Mannitol group was monitored by clinical signs of raised ICP from starting the initial bolus dose up to the completion of one hour and then extending for up to 6 hours and then at 12h, 24h, 36h & 48hr. Patient in the 3% HTS group was monitored by clinical signs of raised ICP from starting one fixed bolus dose up to the completion of three to four hours and then extended for up to 6 hours and then at 12h, 24h, 36h, and 48 h. Blood pressure, respiratory rate, heart rate, pupillary reflexes, and GCS were monitored at admission (Baseline) and 6h, 12h, 24h, 36h, 48hr (after HT).

ICP was assessed indirectly by measuring MAP.[7] MAP indirectly represents ICP [CPP=mean arterial pressure –intracranial pressure, i.e., MAP=CPP+ICP (in a particular range of CPP)] formula applied: MAP α ICP. Adverse effects of drugs were identified by evaluating symptoms and signs. The outcome was assessed two weeks after HT by the GOS and after one month by the mRS score.

Depending on the distribution, quantitative data were expressed as mean ± Standard Deviation (SD) or median and interquartile (25%–75%) range. Categorical variables were presented as frequency (Percentages) or proportions. Student t-test or Mann–Whitney U-test was used for normally distributed and skewed quantitative data, respectively. For within-group comparison, paired sample t-test and Wilcoxon test were used for normally distributed and skewed quantitative data, respectively. Pearson's Chi-square test (Fisher's

exact test when the expected value was less than 5 in one cell) tested the association between two qualitative variables. Independent factors associated with 30-day mortality were determined by multivariate regression analysis. $p < 0.05$ was considered statistically significant.

Results

Overall, the mean age was around 60 years in the study, and there was male predominance. However, both groups were comparable at baseline regarding their demographic and clinical characteristics (Table I).

Table I Baseline demographic and clinical characteristics of the patients

Variables	HTS group (n=34)	Mannitol group (n=34)	p-value
Age, years	60.4±13.6	60.0±12.7	0.898†
Male sex	18 (52.9)	24 (70.6)	0.134*
Hypertension	28 (82.4)	27 (79.4)	0.758*
Smoking	19 (55.9)	21 (61.8)	0.622*
Ischemic heart disease	13 (38.2)	11 (32.4)	0.61*2
Diabetes mellitus	10 (29.4)	10 (29.4)	1.0*
Dyslipidaemia	9 (26.5)	8 (23.5)	0.779*
Side of stroke			
Right	16 (47.1)	14 (41.2)	0.625*
Left	18 (52.9)	20 (58.8)	
Type of stroke			
Ischemic	24 (70.6)	22 (64.7)	0.604*
Hemorrhagic	10 (29.4)	12 (35.3)	
SBP, mm Hg	150.7±28.6	151.2±21.4	0.210†
DBP, mmHg	90.0±12.8	91.8±12.4	0.721†
MAP, mmHg	110.2±16.1	111.6±14.2	0.721†
Heart rate, /min	82.6±11.5	83.1±11.5	0.850†
Respiratory rate, /min	18.8±2.2	20.2±4.1	0.079†
GCS	7.7±0.9	7.9±0.7	0.375†

Data were expressed as frequency (Percentage) if not mentioned otherwise, HTS: Hypertonic Saline, †Independent sample t-test, *Chi-square test. ‡Fisher's exact test, *Chi-square test.

Mean SBP reduced significantly in 6, 12, 24, 36, and 48 hours from the baseline values in both groups (Table II).

Table II Comparison between both groups as regards mean systolic blood pressure in mm of Hg

Time	HTS group (n=34)	Mannitol group (n=34)	p-value between groups†	p-value relative to baseline#	p-value relative to baseline¥
6 hours	141.2±23.6	138.8±21.6	0.670	0.003	<0.001
12 hours	137.2±23.9	141.8±22.5	0.421	0.004	0.012
24 hours	134.8±19.5	139.6±21.3	0.343	0.001	0.002
36 hours	132.5±22.8	138.24±21.8	0.293	<0.001	0.001
48 hours	134.3±20.1	134.6±19.3	0.951	0.001	<0.001

Data were expressed as mean±SD, †By Independent sample t-test, #In the HTS group by paired t-test, ¥In the Mannitol group by paired t-test.

Mean DBP reduced significantly in 6, 12, 24, 36 and 48 hours from the baseline values in both groups (Table III).

Table III Comparison between both groups as regards mean diastolic blood pressure in mm of Hg

Time	HTS group (n=34)	Mannitol group (n=34)	p-value between groups†	p-value relative to baseline#	p-value relative to baseline¥
6 hours	84.4±13.9	85.6±11.9	1.0	0.008	0.004
12 hours	83.7±11.2	86.8±13.8	0.329	0.009	0.008
24 hours	82.4±11.8	85.2±11.8	0.301	<0.001	<0.001
36 hours	83.0±11.9	83.2±10.8	0.560	0.004	<0.001
48 hours	84.4±12.1	83.7±12.7	0.970	0.042	<0.001

Data were expressed as mean±SD, †By Independent sample t-test, #In the HTS group by paired t-test, ¥In Mannitol group by paired t-test.

Regarding MAP, a significant reduction was observed in both groups from the baseline values y in 6, 12, 24, 36, and 48 hours (Table IV). The median (Interquartile range) percentage reduction of the MAP from baseline was 6.3 (-3.9 to 19.2) % in the HTS group and 10 (-4.7 to 14.9) % in the Mannitol group. However, the difference was not significant statistically (p=0.054, Mann-Whitney U test).

Table IV Comparison between both groups as regards mean Mean arterial pressure in mm of Hg

Time	HTS group (n=34)	Mannitol group (n=34)	p-value between groups†	p-value relative to baseline#	p-value relative to baseline¥
6 hours	103.3±16.3	103.3±13.9	1.0	0.001	<0.001
12 hours	101.5±14.2	105.1±15.8	0.329	0.002	0.003
24 hours	99.8±12.9	103.3±14.2	0.301	<0.001	<0.001
36 hours	99.6±14.7	101.6±13.6	0.560	<0.001	<0.001
48 hours	101.0±13.8	100.6±13.9	0.907	0.003	<0.001

Data were expressed as mean±SD, †By Independent sample t-test, #In the HTS group by paired t-test, ¥In the Mannitol group by paired t-test.

When comparing the two groups together, there were no statistical differences between the mean values from baseline to 48 hours regarding mean heart rate and mean respiratory rate. Within groups, follow-up heart and respiratory rates were similar to baseline values. There were no significant differences in the abnormal pupillary

response between the two groups. The mean GCS improved significantly from baseline values in both groups in 6, 12, 24, 36 and 48 hours. However, the mean GCS values were similar between the two groups at all time points.

Regarding mean electrolyte values, only mean Na levels increased significantly from baseline in 6 hours in the HTS group, but the Mannitol group observed the opposite trend. However, the mean Na levels in 12, 24, 36 and 48 hours significantly decreased from both groups' baseline values. There were no significant changes in serum K, Cl and HCO3 levels between or within groups from baseline to 48 hours.

Regarding serum creatinine, blood urea, and RBS levels, only the median creatinine values at 48 hours differ significantly between the HIT and Mannitol groups. The most frequent adverse effect observed in the study was drowsiness, followed by lethargy, vomiting, and acute kidney injury. Though these events occurred more frequently in the Mannitol group than in the HTS group, none of the differences reached statistical significance.

Two weeks after enrollment, most of the patients in both groups (70% and 92%, respectively, in the HTS and Mannitol groups) found severe disability. Both the groups were similar in terms of their 2-week GOS score. At 30 days after enrollment, most of the patients in both groups were moderately severe to severely disabled. Both the groups were similar in terms of their 30-day mRS score. The thirty-day mortality rate in the HTS group was 11.8%, and in the Mannitol group, it was 38.2%, and the difference was significant statistically (p=0.021) (Figure 1).

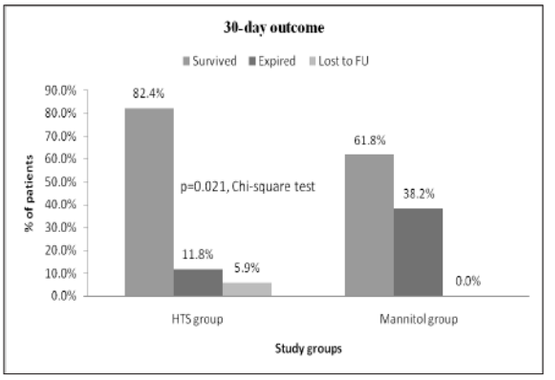

Figure 1 30-day outcome in the two study groups

After adjusting for other variables, the patients in the mannitol group were 7.9 times (OR:7.857, 95% CI:1.452-42.524, p=0.017) more likely to expire within 30-days from enrollment than the patients in the HTS group (Table V).

Table V Multivariate binary logistic regression analysis to determine the independent association between intervention and 30-days mortality

Variables	B	OR	95% CI for OR		p-value
			Lower	Upper	
Mannitol vs. HTS	2.061	7.857	1.452	42.524	0.017
Age, years	0.019	1.019	0.953	1.090	0.573
Male vs. female	0.881	2.414	0.307	18.964	0.402
Smoking	0.205	1.228	0.155	9.721	0.846
Hypertension	0.538	1.713	0.131	22.460	0.682
Diabetes mellitus	-0.398	.672	0.105	4.277	0.673
Ischemic heart disease	0.139	1.149	0.208	6.337	0.873
Interval, days	-0.181	.835	0.256	2.725	0.765
Ischemic vs. hemorrhagic	-2.315	.099	0.007	1.357	0.083
SBP, mmHg	0.007	1.007	0.959	1.058	0.776
DBP, mmHg	0.032	1.033	0.945	1.129	0.476
GCS	0.437	1.549	0.594	4.036	0.371
Serum Na, mEq/L	-0.131	.877	0.653	1.177	0.381
Serum Na	-0.533	.587	0.124	2.774	0.501
Serum Na	-0.209	.812	0.604	1.090	0.166
Creatinine, mg/dl	0.967	2.630	0.115	60.350	0.545
Blood Urea, mg/dl	0.022	1.023	0.971	1.076	0.395

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, Interval from onset to admission' OR: Odds Ratio, CI: Confidence Interval.

Discussion

Few studies evaluated the use of HT in the treatment of post-cerebral infarction patients with brain edema. As a result, there needed to be more information on the standard protocol for its use in managing raised ICP following acute stroke. In this regard, the present study findings have important clinical implications. The study demonstrated that the percentage reduction of MAP (Indirect measurement of ICP) was similar in both groups. Still, the cumulative survival was significantly higher in the HTS group than in the Mannitol group from baseline to 30, and treatment with mannitol was independently associated with 30-day mortality.

Overall, the mean age was around 60 years in both groups, with male predominance. The most frequent risk factor was hypertension, smoking, ischemic heart disease, diabetes mellitus and dyslipidemia. Left-sided strokes and ischemic

strokes were more frequent in both groups. The study participants' characteristics were similar to other studies conducted in and around Bangladesh.[13-15]

Both SBP, DBP and MAO reduced significantly in 6, 12, 24, 36, and 48 hours compared to baseline values in both groups without any statistical difference between the two groups. The median (IQR) percentage reduction of the MAP from baseline was lower in the HTS group than the mannitol group (6.3% versus 10%), but the difference was not significant statistically. In addition, the mean GCS improved significantly from baseline values in 6, 12, 24, 36, and 48 hours in both groups. In 1998, Schwarz et al.[5] compared the effect of 100 ml, 75 ml of HTS, 60 g/l of hydroxyethyl starch HES and 200 ml of 20% mannitol in equiosmolar doses in 9 patients with 30 episodes of intracranial hypertension. They conclude that single doses of 100 ml HTS-HES or 40g of mannitol effectively reduce elevated ICP in patients with brain edema and show no adverse effects on MAP or CPP. However, HTS appears to have a faster onset and is more effective at lowering elevated ICP. Zidan and his colleague found that HTS was more effective in improving GCS in patients with MCA infarction with cerebral edema.[16]

Regarding mean electrolytes values, only mean Na levels increased significantly from baseline in 6 hours in the HTS group, but the opposite trend was observed in the Mannitol group. However, the mean Na levels in 12, 24, 36, and 48 hours significantly decreased from both groups' baseline values. Serum K, Cl, and HCO3 levels were similar in two groups and within groups at baseline to 48 hours. Zidan and his colleague observed a significant statistical difference in calculated osmolarity between the two groups over the 48 hours of therapy, as osmolarity was higher in patients receiving HTS than in those receiving mannitol.[16]

The most frequent adverse effect observed in the study was drowsiness, followed by lethargy, vomiting, and acute kidney injury. Though these events occurred more frequently in the Mannitol group than in the HTS group, the differences were not statistically significant in the present study, which indicated a similar safety margin for both drugs. Mannitol can be nephrotoxic due to dose-dependent vasoconstriction of the renal artery and osmotic diuresis-induced intravascular volume depletion. The evidence on AKI due to HTS is limited in the neurocritical care unit.[17] However, there is an association between prolonged hypernatremia (> 160 mEq/L) and oliguric AKI in burn patients resuscitated with HTS.[18] In the current study, the five patients who developed AKI were in the mannitol group.

Two weeks after enrollment, most of the patients in both groups (70% and 92%, in the HTS and Mannitol group, respectively) were found to have a severe disability. Both the groups were similar in terms of their 2-week GOS score. At 30 days after enrollment, most of the patients in both groups were moderately severe to severely disabled. Both the groups were similar in terms of their 30-day mRS score. The thirty-day mortality rate was significantly higher in the mannitol group than in the HTS group. After adjusting for other variables, the patients in the mannitol group were 7.9 times more likely to expire within 30 days from enrollment than the patients in the Mannitol group. Although Cerebral Blood Flow (CBF) was not measured in the present study, the effects of HTS on cerebral hemodynamics might have contributed to this favorable outcome. Current study results agreed with other studies.[8,19] In contrast, a recent meta-analysis failed to detect any difference in mortality reduction and improvement in coma score between HTS and mannitol in adult patients with TBI, which might be due to the heterogenicity and small sample size of the individual study.[20]

Limitations

The inability to use ICP monitoring invasively for a more accurate result was the main limitation of the present study. Moreover, cerebral hemodynamics and metabolism were not investigated in the study. The fixed and intermittent dosing strategy of 20% mannitol and a different osmolar load of 3%-HTS and 20%-mannitol were used in the study.

Conclusion

In conclusion, the study demonstrated that in acute stroke patients with raised ICP, 3%-HTS and 20%-mannitol had a similar effect on hemodynamic parameters in the first 48 hours of infusion. Both the drugs had identical safety margins and functional outcomes till 30 days. However, 3%-HTS was superior to 20%-mannitol in terms of 30-day survibility.

Recommendations

Three percent of HTS could be used safely as an alternative therapy to mannitol in the management of raised ICP after acute stroke. However, considering the limitations of the present study, further multicentric trial with direct measurement of ICP is necessary for an evidence-based recommendation of 3%-HTS in place of 20%-mannitol.

Contributions of authors

RMM: Conception, data collection, analysis, manuscript drafting & final approval.

DKDV: Data collection, analysis, drafting & final approval.

MH: Supervision and manuscript drafting, design, interpretation of data, critical revision & final approval.

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Disclosure

All the authors declared no conflict of interest.

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