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Comparative study between Mannitol versus Hypertonic saline continuous infusion versus Hypertonic saline boluses in treatment of edema of traumatic brain injury

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ABSTRACT

Background: Severe brain edema that is not successfully treated can lead to progressive intracranial hypertension, cerebral ischemia, brain herniation, and progression to death. Many studies have shown that hypertonic saline may be effective in treatment of all kinds of cerebral edema and intracranial hypertension caused by various causes, including traumatic brain injury.
Methods: The current study was carried out on 90 adult patients aged ≥ 16 years admitted to Alexandria Main University Hospital with brain edema due to traumatic brain injury with GCS ≤ 12. patients were divided into 3 groups: Group I (30 patients): for patients who received mannitol 20%.Group II (30 patients): for patients who received hypertonic saline 3% continuous infusion. Group III (30 patients): for patients who received hypertonic saline 3% boluses.The efficacy of treatment was assessed radiologically by serial CT brain and clinically by GCS of patients.
Results: After two days of treatment, CT brain findings revealed that mannitol was effective in 70% of patients in group I, HTS infusion was effective in 76.7% of patients in group II and HTS boluses was effective in 83.3% of patients in group III without statistical significant difference between them. GCS improved significantly in all groups after 48 hours of treatment. The main side effect of mannitol treatment was hypovolemia. The main side effects of HTS were Hypernatremia, hyperchloremia and hyperchloremic metabolic acidosis. Patients who received HTS spent fewer days in ICU than patients who received mannitol; also, there was a tendency for a higher survival rate in HTS groups in comparison to mannitol group but with no statistical significance.
Conclusions: HTS is a promising treatment of brain edema due to TBI. There are side effects recorded in patients treated with mannitol and HTS. No significant difference as regarding survival rate and length of ICU stay between mannitol and HTS treatment

Key words – Mannitol, Hypertonic saline continuous infusion, hypertonic saline boluses, brain edema.

INTRODUCTION

Trauma is the commonest cause of death in young people worldwide. [(1)] Brain edema is included in many neurological diseases e.g. cerebral ischemia or hemorrhage, brain trauma and tumor of the brain or abscess. [(2)] Cerebral edema can be classified as either cytotoxic and vasogenic. Cytotoxic edema is the swelling of cells secondary to injury, typically ischemic or toxic. Vasogenic edema is extracellular edema occurred secondary to capillary disruption, leading to breakdown of blood brain barrier (BBB). Vasogenic edema is associated more with traumatic brain injury, tumor and abscesses, although recent data suggest that cytotoxic edema predominates in traumatic brain injury. [(3)]

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Traumatic brain edema (TBE) following TBI is defined as increased liquid content in brain.

Dehydration therapy is the major method to treat the TBE.[4-6] Mannitol is the osmotically active agent most commonly employed in clinical practice; [7] however, mannitol has many clinically adverse effects, such as renal failure and hypovolemia. [8] In recent years, many studies have shown that HTS may be effective in treatment of all kinds of cerebral edema and ICH caused by several causes, including TBI. [9] HTS is present in many different concentrations, commonly as a 2% or 3% bolus or continuous infusion or in boluses of 5%, 7.5%, or 23.4 %. [10] Several randomized clinical trials have suggested that sodium-based hypertonic solutions may be better than mannitol in reducing ICP, [11, 12] but the impact of these studies on clinical practice has been limited, partly because of the different specific formulations used and partly because of the small size of these studies. [13]

AIM OF THE WORK:

The aim of this study was to compare the efficacy and safety of mannitol, HTS continuous infusion and HTS boluses in treatment of edema of TBI.

PATIENTS AND MATERIAL

This study was conducted on 90 adult patients admitted to the units of the Critical Care Medicine department of Alexandria Main University Hospital, Egypt.

Informed consent was taken from patients. In case of incompetent patients the informed consent will be taken from the next of kin.

Inclusion criteria:

- Patients aged ≥ 16 years.
- Patients with brain edema due to traumatic brain injury i.e. Glasgow coma scale (GCS) ≤ 12.

Exclusion criteria:

- Patients aged < 16 years old.
- Patients with mild traumatic brain injury i.e. GCS ≥ 13.
- Patients with subarachnoid hemorrhage.
- Patients with fracture skull base.
- Patients who need surgical intervention.
- Patients on hemodialysis with end-stage renal disease.
- Patients with hypernatremia i.e. sodium level ≥ 150mEq/L.
- Physical exam compatible with brain death.
- Serum osmolality ≥ 320mOsm/kg.

Subjects and methods:

Using envelope method of randomization patients was randomized into 3 groups :[14]

Group I (30 patients): for patients who received mannitol 20%.

Group II (30 patients): for patients who received HTS 3% continuous infusion.

Group III (30 patients): for patients who received HTS 3% boluses.

Management:

Patients were classified into 3 groups using conventional method of randomization by envelope technique.

Group I: for patients who received mannitol 20% for 48 hours provided that blood pressure ≥ 110/70 and central venous pressure (CVP) ≥ 5cmH_2O.

Loading dose: 0.5 g/kg over 30 minutes.

Maintenance dose: 0.5 g/kg per dose every 6hours over 30 minutes.

Group II: for patients who received hypertonic saline 3% continuous infusion for 48 hours.

Dose: 1ml/kg/hour through central venous catheter.

Group III: for patients who will receive hypertonic saline 3% boluses for 48 hours.

Dose: 3ml/kg per dose every 6 hours (over 30 minutes) through central venous catheter.

The efficacy of mannitol and HTS treatment was assessed radiologically by serial CT brain (on admission, after 24 and 48 hours) and clinically by GCS of the patients every 12 hours. Routine investigations i.e. complete blood count (CBC), blood urea nitrogen (BUN), serum creatinine (s.cr), SGOT, SGPT, arterial blood gases (ABG), random blood sugar (RBS), serum electrolytes (Na, K and CL), Prothrombin Time (PT), Partial Thromboplastin Time (PTT), INR, D-dimer, total bilirubin level, serum albumin level were measured on admission. Follow up investigations were done i.e. BUN, S Cr, ABG, RBS, serum electrolytes (Na, K and CL) and calculated serum osmolality after 24 and 48 hours of admission.

RESULTS

The current study was carried out on 90 adult patients admitted to Alexandria Main University Hospital with brain edema due to TBI with GCS ≤ 12 meeting the inclusion and exclusion criteria.

The age of the studied patients ranged from 18 to 70 years with a mean of 36.77 ± 14.23 years old in group I, 34.87 ± 12.07 years old in group II and 35.73 ± 12.04 years old in group III. Of those, 34 were females and 56 were males.

Road traffic accident (RTA) was responsible for TBI in 66 of the patients, falling from height in 17 patients and blunt trauma in 7 patients .No significant differences between the 3 groups were observed in age, sex and mechanism of trauma. All patients had CT brain on admission; sylvian fissures, ventricular effacement, basal cistern and optic nerve diameter sheath were reported to diagnose brain edema. There were no significant differences between the groups as regard those parameters.

After 48 hours of treatment with mannitol and HTS (infusion and boluses); we found that mannitol failed to reduce brain edema in 30% of patients in group I; whereas HTS infusion and boluses failed to reduce it in

23.3% and 16.7% of patients in group II and III respectively and there was no statistical significant difference between them (Table-1).

Table-1. Comparison between the three studied groups according to brain edema

Brain edema	Mannitol (n = 30)		HTS Infusion (n = 30)		HTS Boluses (n = 30)		χ^2	p
	No.	%	No.	%	No.	%		
After 48 hours								
Effective	21	70	23	76.7	25	83.3	1.491	0.475
Failed	9	30	7	23.3	5	16.7		

χ^2: Chi square test

After 2 days of treatment, sylvian fissures, ventricular effacement and basal cistern changed significantly in all groups (Table-2,3,4).

The mean values optic nerve diameter sheath decreased significantly in the three groups after 48 hours of treatment (Table-5). GCS improved significantly in all groups after 48 hours of treatment.

The main side effect of mannitol treatment was hypovolemia i.e. 23.3% of the patients had hypotension.

The main side effects of HTS (infusion and boluses) treatment after 48 hours of treatment were Hypernatremia (mean values; 160.0 ± 5.05 mEq/L in infusion group and 150.0 ± 4.11 mEq/L in boluses group), hyperchloremia (mean values; 120.63 ± 5.02 mEq/L in infusion group and 110.73 ± 3.56 mEq/L in boluses group) and hyperchloremic metabolic acidosis (30% of patients treated with HTS infusion and 4% of patients treated with HTS boluses).

Patients who received HTS spent fewer days in ICU than patients who received mannitol i.e. 9.37 ± 5.96 days in mannitol group, 8.67 ± 4.42 days in HTS infusion group and 8.80 ± 4.44 days in HTS boluses group; also, there was a tendency for a higher survival rate in HTS groups in comparison to mannitol group i.e. 56.7% of patients survived in mannitol group, 63.3% in HTS infusion group and 70% of patients in HTS boluses group; but with no statistical significant difference.

DISCUSSION

Osmotic agents are important components of all treatment protocols, especially mannitol as it is a well-established treatment for increased ICP following brain injury. Surveys of the critical care management of head injured patients show that 83% of the centers in the United States and 100% of the centers in the United Kingdom used mannitol to control ICP. [15-17]

HTS is an interesting alternative to mannitol, because there is experimental and clinical evidence that it can reduce ICP and improve CPP. [18,19] Experimental studies in animals suffering from a combination of hemorrhagic shock and head trauma demonstrated a significant reduction of ICP, an improvement of CPP and/or a reduction of brain edema. [18, 20, 21]

Table-2. Comparison between the three studied groups according to Basal cistern

Basal cistern	Mannitol (n = 30)		HTS Infusion (n = 30)		HTS Boluses (n = 30)		χ^2	p
	No.	%	No.	%	No.	%		
On admission								
Open	5	16.7	3	10.0	4	13.3	1.831	^{MC}p= 0.802
Absent	11	36.7	8	26.7	10	33.3		
Compressed	14	46.7	19	63.3	16	53.3		
After 24 hours								
Open	10	33.3	10	33.3	13	43.3	2.174	0.704
Absent	7	23.3	4	13.3	4	13.3		
Compressed	13	43.3	16	53.3	13	43.3		
p_1	0.221		0.077		0.052			
After 48 hours								
Open	14	46.7	18	60.0	19	63.3	2.668	0.615
Absent	6	20.0	5	16.7	6	20.0		
Compressed	10	33.3	7	23.3	5	16.7		
p_2	0.020*		<0.001*		<0.001*			

χ^2: Chi square test for comparing between the three groups
MC: Monte Carlo for Chi square test for comparing between the three groups and each two groups
Significant between periods was done using Marginal Homogeneity Test
p_1: p value for comparing between on admission and after 24 hours

Table-3. Comparison between the three studied groups according to Sylvian fissure

Sylvian fissure	Mannitol (n = 30)		HTS Infusion (n = 30)		HTS Boluses (n = 30)		χ^2	P
	No.	%	No.	%	No.	%		
On admission								
Open	4	13.3	2	6.7	4	13.3	1.039	$^{MC}p=0.936$
Effaced	17	56.7	18	60.0	17	56.7		
Obliterated	9	30.0	10	33.3	9	30.0		
After 24 hours								
Open	10	33.3	8	26.7	13	43.3	2.608	0.625
Effaced	14	46.7	16	53.3	14	46.7		
Obliterated	6	20.0	6	20.0	3	10.0		
p_1	0.003*		0.002*		<0.001*			
After 48 hours								
Open	13	43.3	17	56.7	18	60.0	2.164	0.706
Effaced	11	36.7	9	30.0	7	23.3		
Obliterated	6	20.0	4	13.3	5	16.7		
p_2	0.005*		<0.001*		0.001*			

χ^2: Chi square test for comparing between the three groups
MC: Monte Carlo for Chi square test for comparing between the three groups and each two groups
Significant between periods was done using Marginal Homogeneity Test
p_1: p value for comparing between on admission and after 24 hours
p_2: p value for comparing between on admission and after 48 hours
*: Statistically significant at $p \leq 0.05$

Table-4. Comparison between the three studied groups according to Ventricular effacement

Ventricular effacement	Mannitol (n = 30)		HTS Infusion (n = 30)		HTS Boluses (n = 30)		χ^2	P
	No.	%	No.	%	No.	%		
On admission								
Open	6	20.0	10	33.3	8	26.7	1.458	0.834
Effaced	17	56.7	15	50.0	16	53.3		
Obliterated	7	23.3	5	16.7	6	20.0		
After 24 hours								
Open	14	46.7	15	50.0	13	43.3	1.282	$^{MC}p=0.893$
Effaced	11	36.7	12	40.0	14	46.7		
Obliterated	5	16.7	3	10.0	3	10.0		
p_1	0.004*		0.035*		0.005*			
After 48 hours								
Open	17	56.7	19	63.3	17	56.7	1.987	0.738
Effaced	6	20.0	7	23.3	9	30.0		
Obliterated	7	23.3	4	13.3	4	13.3		
p_2	0.012*		0.033*		0.012*			

χ^2: Chi square test for comparing between the three groups
MC: Monte Carlo for Chi square test for comparing between the three groups and each two groups
Significant between periods was done using Marginal Homogeneity Test
p_1: p value for comparing between on admission and after 24 hours
p_2: p value for comparing between on admission and after 48 hours
*: Statistically significant at $p \leq 0.05$

The aim of this study was to compare the efficacy and safety of mannitol and HTS (infusion and boluses) in treatment of edema due to TBI. Most of the patients conducted in the three groups were males; 63.3% in the group I, 53.3% in the group II and 70% in the group III. In most of the studies, TBI was more prevalent in males than females; this is because males are driving vehicles, more often going to work, participating more in risky outdoor activities than females. [22, 23]

RTA were the most common mechanism of trauma among the studied patients constituting 66.7% in group I, 80.0% in group II and 73.3% in group III. This could be attributed to poor compliance to traffic rules and prevalence of ill-prepared roads. Falling from height was the second cause of severe head injury in the studied patients. These results are consistent with most of the studies (Murray GD et al., Braakman R et al.) demonstrating that RTA are the most common cause of TBI worldwide. [22, 23] In our study, the efficacy of mannitol and HTS treatment was assessed radiologically by serial CT brain (on admission, after 24 and 48 hours) and clinically by GCS of the patients.

We commented on basal cistern, ventricular effacement, sylvian fissures and ONDS in CT brain of patients on admission, after 24 and 48 hours of treatment to diagnose brain edema and to assess the efficacy of mannitol and HTS. According to our results, we found that 70% of the patients treated with mannitol (group I) showed significant improvement of those parameters in CT brain after 48 hours of treatment. Also, patients treated with HTS infusion (group II) and HTS boluses (group III) showed significant improvement in 76.7% and 83.3% of the patients respectively.

Regarding to clinical state of patients, GCS was assessed on admission and every 12 hours after initiation of treatment for two days. Our results illustrated that the mean values of the GCS of the patients in the three groups showed significant improvement during these follow up periods; as it was with mannitol (group I) 7.67 ± 2.47 on admission and it improved to 8.43 ± 3.05, 8.57 ± 3.30, 8.67 ± 3.63 and 9.07 ± 4.14 respectively. As regarding HTS infusion (group II) the mean values were 6.47 ± 2.19, 7.70 ± 2.71, 8.0 ± 2.86, 8.50 ± 3.33 and 8.77 ± 3.51; while with HTS boluses (group III) they were 7.13 ± 2.34, 8.17 ± 2.65, 8.43 ± 2.76, 8.87 ± 3.33 and 9.03 ± 3.49 respectively.

According to previously mentioned data, mannitol and HTS (infusion and boluses) were significantly effective in treatment of brain edema due to TBI and HTS (infusion and boluses) treatment was more effective than mannitol but without statistical significance. Hypertonic saline and mannitol share similar mechanisms in reducing raised ICP. Both of them work by establishing an osmotic gradient across the blood brain barrier, leading to fluid shift from the intercellular space into the microcirculation. [24] Battison et al. [25] performed a prospective randomized controlled trial (RCT) over nine patients with ICP and found that hypertonic saline was more effective than mannitol. Ichai et al. [26] compared mannitol and HTS in treatment of 34 patients with severe TBI and GCS ≤ 8 and revealeed that HTS treatment reduced ICP more effectively than mannitol.

Kamel et al. [27] in 2011 carried out a meta-analysis of all randomized studies that comparing mannitol and HTS for the treatment of increased ICP. The conclusion was that HTS is more effective than mannitol. In 2012 a meta-analysis was done by Mortazavi et al. [28] a study was performed to collect most of papers pertaining to HTS use in reduction of ICP.A greater part of data suggested that HTS was more effective than mannitol in reducing elevated ICP.

However, not all the studies reported positive effects of HTS on reduction of ICP. Francony et al. [13] and Larive et al. [29] did not find HTS to be superior to mannitol in controlling elevated ICP or clinical outcomes. In our study, there was a significant increase of calculated osmolality of patients treated with HTS (infusion and boluses) but not mannitol and this goes with results of Harutjunyan et al (2005) [12] and Battison et al (2005) [25]

In our study we reported the safety of mannitol and HTS treatment, the main side effect of mannitol

Table-5. Comparison between the three studied groups according to optic nerve diameter

Optic nerve diameter	Mannitol (n = 30)	HTS Infusion (n = 30)	HTS Boluses (n = 30)	F	P
On admission					
Min. – Max.	4.80 –5.90	5.0 – 5.90	4.80 – 5.90	0.560	0.573
Mean ±SD	5.48 ± 0.30	5.50 ± 0.26	5.43 ± 0.28		
Median	5.55	5.60	5.40		
After 24 hours					
Min. – Max.	3.80 – 5.90	4.10 – 5.90	4.10 – 5.90	1.899	0.156
Mean ±SD	4.77 ± 0.52	5.0 ± 0.49	4.98 ± 0.51		
Median	4.80	4.80	4.90		
p_1	<0.001*	<0.001*	<0.001*		
After 48 hours					
Min. – Max.	3.70 – 5.90	4.10 – 5.90	3.90 – 5.80	0.288	0.750
Mean ±SD	4.63 ± 0.61	4.75 ± 0.58	4.68 ± 0.59		
Median	4.60	4.50	4.50		
p_2	<0.001*	<0.001*	<0.001*		

F: F test (ANOVA)
Significant between periods was done using Post Hoc Test (LSD) for (ANOVA) with repeated measures
p_1: p value for comparing between on admission and after 24 hours
p_2: p value for comparing between on admission and after 48 hours
*: Statistically significant at p ≤ 0.05

treatment was hypovolemina; it was evaluated by measuring of CVP and MAP on admission and every 24 hours after treatment. We found that there was a significant decrease of CVP measurements (23.3% of patients had hypovolemia) in patients treated with mannitol. In contrast, the mean values of CVP measurements increased significantly in HTS groups. We found also that mannitol treatment significantly decreased MAP; this is due to its diuretic effect, however there was no significant change in HTS groups. Our results go with the results of Harutjunyan et al. [12] found that MAP decreased with mannitol and no change of it after HTS after one hour of administration. Munar et al. [30] found that HTS significantly reduced ICP without changes in MAP.

The main side effects of HTS infusion and boluses administration were hypernatremia, hyperchloremia and hyperchloremic metabolic acidosis especially with HTS infusion. Sodium level increased significantly after 48 hours of initiation of treatment to160.0 ± 5.05 mEq/L in group II (33% of patient's sodium level was ≥155 mEq/L) and 150.0 ± 4.11 mEq/L in group III (16.7% of patient's sodium level was ≥155 mEq/L). Chloride level also increased significantly to 120.63 ± 5.02 mEq/L and 110.73 ± 3.56 mEq/L in groups II and III respectively; also, 30.0% of patients treated with HTS infusion and 13.3% of patients treated with HTS boluses had hyperchloremic metabolic acidosis. This goes with the results of Antoine Roquilly et al. [31]

In two studies; Khanna et al. and Froelich et al [32,33], found that continuous infusion of HTS 3% in TBI patients without a prior dose adaptation decreased ICP but cause severe hypernatremia that reached up to 180 mmol/L, that may cause neurologic complications and kidney failure. According to our results, potassium level was not significantly changed, no pulmonary edema or acute kidney injury was detected, pontine myelinolysis was not clinically suspected and rebound edema was not occurred in the three groups. Our results are consistent with the results of Antoine Roquilly et al. [31]

In contrast to our study, Qureshi et al. [34] found that risks of fluid overload with continuous infusion of HTS 3% may result in poor outcomes. The current study also provided data on the length of ICU stay and survival rate; according to our results, patients who received HTS spent fewer days in ICU, (8.67 ± 4.42 days) and (8.80 ± 4.44 days) in groups II and III respectively, than patients who received mannitol (9.37 ± 5.96 days); Also, there was a tendency for a higher survival rate in the HTS groups (63.3%) in group II and (70%) in group III in comparison to mannitol group (56.7%) but with no statistical significant difference.

Our results are consistent with Halinder et al. [35]. In contrast to our study, Vialet et al. [11] did not find differences in mortality rate and outcomes over 90 days. Qureshi et al. [34] analyzed the effect of of HTS 2% or 3% continuous infusion in patients with TBI. He found a higher in hospital mortality rate in patients receiving HTS.

CONCLUSION

- HTS (infusion and boluses) is a promising treatment of brain edema caused by moderate and severs TBI.
- There are side effects recorded in patients treated with mannitol and HTS.
- No significant difference as regarding survival rate and length of ICU stay between mannitol and HTS treatment.

Conflict of Interests

Authors declare that there is no conflict of interests regarding the publication of this paper.

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