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Hypertonic saline versus mannitol in treatment of diffuse brain edema in patients with moderate and severe traumatic brain injury

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ABSTRACT

Background: Hyperosmolar therapy is the primary medical management strategy for brain edema and raised intracranial pressure.
Objective: The aim of the work was to compare between Hypertonic saline 3% and Mannitol 20% in the treatment of diffuse brain edema after traumatic brain injury.
Methods: A sample of 40 patients with diffuse brain edema after traumatic brain injury was included and divided into two groups; Group A: 20 patients were treated with hypertonic saline 3%, Group B: 20 patients were treated with mannitol 20%.
Results: hypertonic saline 3% was significantly better than mannitol 20% in treatment of brain edema according to CT brain criteria; mannitol 20% significantly increases serum creatinine levels more than hypertonic saline 3%. Moreover, both improves Glasgow Coma Scale (GSC) but significantly more with hypertonic saline 3%
Conclusion: hypertonic saline 3% improves GCS better than mannitol 20% in treating diffuse brain edema after traumatic brain injury with less adverse effects.

Key words: Hypertonic saline, Mannitol, Brain edema, Traumatic brain injury.

INTRODUCTION

Traumatic Brain Injury (TBI) is a major cause of death and disability, leading to great personal suffering to victim and relatives, as well as huge direct and indirect costs to society. [1] According to the World Health Organization (WHO), TBI will be the major cause of death and disability by the year 2020. [2]

Cerebral edema is defined as an increase in brain water leading to an increase in total brain mass. [3] Brain edema is recognized as one of the major causes of mortality, as well as poor neurologic outcome, because severe brain edema that is not successfully treated can lead to progressive intracranial hypertension, cerebral ischemia, brain herniation, and eventual progression to death. [4]

A number of mediators have been identified that play a role in edema formation after TBI. [5] The identification of the water-channel proteins, aquaporins (AQPs), as a key player in the development and resolution of cerebral edema has highlighted their potential as a therapeutic target to prevent brain swelling. [6]

Hyperosmolar therapy is the primary medical management strategy for brain edema and raised intracranial pressure. [7]

The role of osmotic therapy with either mannitol or hypertonic saline is based on the principle that these agents will help to remove water from brain tissue across an intact blood brain barrier. [8]

Mannitol is a sugar alcohol that is not significantly metabolized and is excreted unchanged in the urine after intravenous (IV) infusion. [9] Mannitol's primary effect is to increase the osmotic gradient across the blood brain barrier (BBB), if it remains intact, and it promotes osmosis of water from the brain parenchyma,

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thereby decreasing brain water content and increasing intravascular volume acutely. [10]

Hypertonic saline (HTS) has similar osmotic effects as mannitol but is a less potent diuretic, so the initial advantage in certain clinical situations is that hypertonic saline expands the intravascular volume, increases blood pressure, increases cardiac output, and, theoretically, increases cerebral blood flow. [11]

In this study we compared between Hypertonic saline 3% and Mannitol 20% in treatment of diffuse brain edema in patients with moderate to severe traumatic brain injury.

MATERIAL AND METHODS

Informed consent was received from patient family or next of kin after approval from ethics committee of Alexandria Faculty of Medicine. This study was designed as a clinical prospective cohort study that was performed in Critical Care Medicine Department, faculty of medicine, Alexandria University. All adult patients with brain edema diagnosed by computed tomography (CT) scan as effacement of the cerebral sulci, loss of the gray-white differentiation, unilateral cerebral edema or midline shift [12] after moderate and severe traumatic brain injury defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force,[13] were included in the study. All patients were submitted to a stabilization phase to verify the inclusion criteria and to confirm the diagnostic criteria of brain edema by CT scan of the brain. Eligible patients were divided randomly into two groups (Table-1): Group A: 20 patients were treated with mannitol 20% intravenous through central venous catheter by loading dose 1gm/kg followed by 0.25gm/kg every 6 hours for 48 hours as maintenance dose. Group B: 20 patients were treated with hypertonic saline 3% intravenous through central venous catheter by loading dose 5ml/kg followed by 2ml/kg every 6 hours for 48 hours as maintenance dose.[14]

Pregnant females, patients with heart failure, patients with Renal impairment [creatinine clearance less than 30ml/min], post cardiac arrest patients, patients with serum sodium Na+ below 135meq/l or above 150meq/l on admission, serum osmolarity more than 320mosm/l on admission and hemodynamically unstable patients [systolic BP < 90 mmHg, equal to shock class III–IV][15] were excluded from the study.

All patients included in the study were subjected to the following parameters: demographic data, habits, past history of heart failure or renal failure, Glasgow Coma Scale (GCS) every 6 hours for 48 hours, CT scan of the brain at the start of hyperosmolar therapy and after 48 hours, routine laboratory investigations including: daily complete blood count [CBC], serum sodium [Na], blood urea nitrogen [BUN], serum creatinine every 12 hours and calculated creatinine clearance [ml/min] by cockroft-Gault equation, serum blood glucose level every 12 hours and calculated serum osmolarity every 12 hours by the equation = [Na x 2] + [glucose/18] + [blood urea nitrogen [BUN]/2.3]. [16]

Table 1: Patient demographic data

	Mannitol		*Hyperton ic*		*Test of sig*	*p*
	No	%	No	%		
Sex						
Male	13	65	15	75	□□= 0.476	0.490
Female	7	35	5	25		
Age						
Min.–Max.	21.0 – 54.0		21.0 – 56.0		t= 0.383	0.704
Mean±SD.	33.20 ± 9.73		34.35 ± 9.25			

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 21.0. (IBM Corp, Armonk, NY) for Windows. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level using: Chi-square test for categorical variables, to compare between different groups, Student t-test for normally quantitative variables, to compare between two studied groups, Paired t-test for normally quantitative variables, to compare between two periods.

RESULTS

Both hypertonic saline 3% and mannitol improves GCS significantly but GCS improved significantly with hypertonic saline more than mannitol after 24 hours (P=0.015) and 48 hours (P=0.027) respectively (table-2).

Table 2: showed effect of hyperosmolar therapy on GCS

GCS	*Base*	*After 24 hours*	*After 48 hours*
Mannitol (n = 20)			
Min. – Max.	6.0 – 9.0	4.0 – 11.0	3.0 – 13.0
Median	7.50	9.50	10.0
p_1		0.012*	0.010*
Hypertonic saline (n = 20)			
Min. – Max.	6.0 – 9.0	3.0 – 14.0	3.0 – 14.0
Median	7.0	11.0	11.50
p_1		<0.001*	<0.001*
p_2	0.137	0.015*	0.027*

Creatinine clearance by Cockroft-Gault equation was found to be affected significantly after 24 hours and 48 hours of administration of mannitol (P=0.042 and

P=0.037) respectively while there wasn't any significance between hypertonic saline and creatinine clearance as shown in table 3 and fig.1.

Table-3: showed a comparison between the two studied groups according to creatinine clearance.

Creatinine clearance (ml/min) (Cockcroft-Gault equation)	*Base*	*After 12 hours*	*After 24 hours*	*After 36 hours*	*After 48 hours*
Mannitol (n = 20)					
Min. – Max.	90.0 – 110.0	69.0 – 109.0	70.0 – 110.0	50.0 – 104.0	50.0 – 104.0
Mean ± SD.	97.05 ±6.10	96.55 ±9.68	94.35 ±13.04	85.40 ±17.67	84.15 ±18.77
p_1		1.000	1.000	0.042*	0.037*
Hypertonic saline (n = 20)					
Min. – Max.	90.0 – 110.0	90.0 – 105.0	90.0 – 105.0	88.0 – 103.0	88.0 – 103.0
Mean ± SD.	97.30 ± 6.11	97.80 ± 3.76	96.70 ± 4.64	93.95 ± 4.52	93.65 ± 4.13
p_1		1.000	1.000	0.079	0.119
p_2	0.898	0.595	0.455	0.048*	0.038*

Figure-1: Comparison between the two groups according to creatinine clearance.

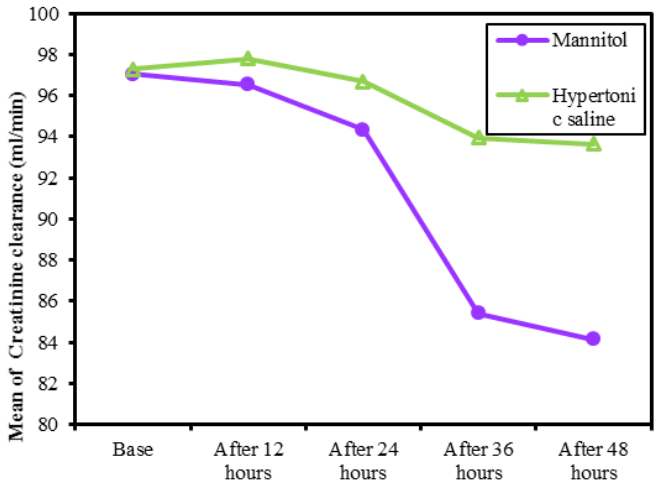

Table-4 showed a significant response with hypertonic saline over mannitol as regard CT brain criteria (P=0.028).

Serum sodium (Na) was affected significantly with hypertonic saline more than mannitol (P=0.037), (P=0.018) and (P=0.024) respectively.

Serum osmolarity was affected significantly with hypertonic saline over mannitol (P=0.026), (P=0.022) and (P=0.001) respectively.

Table-4. Comparison between the two groups according to different parameters.

	Mannitol	Hypertonic saline	p
CT brain (After)			
Responding	12 (60.0%)	18 (90.0%)	0.028*
Non Responding	8 (40.0%)	2 (10.0%)	
Na^+			
Base	137.1 ± 3.7	137.6 ± 3.2	0.618
After 12 hrs	138.5 ± 3.7	140.9 ± 4.2	0.066
After 24 hrs	139.7 ± 3.5	142.8 ± 5.3	0.037*
After 36 hrs	141.7 ± 4.4	145.9 ± 6.3	0.018*
After 48 hrs	143.2 ± 3.8	146.5 ± 5.1	0.024*
Osmolarity			
Base	287.5 ± 7.1	288.5 ± 7.4	0.666
After 12 hrs	290.9 ± 8.0	296.3 ± 9.6	0.061
After 24 hrs	293.1 ± 7.6	300.6 ± 12.1	0.026*
After 36 hrs	297.5 ± 8.7	306.1 ± 13.4	0.022*
After 48 hrs	298.7 ± 7.5	308.9 ± 10.9	0.001*

DISCUSSION

Hyperosmolar therapy is the primary medical management strategy for brain edema and raised intracranial pressure. (7)

The role of osmotic therapy with either mannitol or hypertonic saline is based on the principle that these agents will help to remove water from brain tissue across an intact blood brain barrier. (8)

In the present study the two groups were matched in age and sex; age ranged between 21-56 years with a mean age of 32.5 year; this is consistent with worldwide studies concerning TBI that quote mean ages between 28 and 44 years. (17) Abbassy et al.(18) reported a mean age of 31.6 years in an epidemiological study of 970 TBI patients admitted to Alexandria Main University Hospital.

Serum osmolarity increased significantly in both groups after 12 hours and also was higher significantly in hypertonic saline group than mannitol group in our study after 24 hours of administration of the two drugs which was similar to the findings of Manninen PH et al(19) as they were studying the effect of mannitol on serum and urinnary electrolytes and osmolarity in neurosurgical patients and Malik Z et al, (20) in their study where they were comparing the effect of hyperosmolar therapy on reduction of brain bulk during resection of brain tumor.

In our study serum creatinine and creatinine clearance was found to be affected significantly in mannitol group after 24 hours of administration of Mannitol which may be due to its potent diuretic effect, we found serum creatinine start to rise significantly after 24 hours, while in hypertonic saline group there was no statistical difference, similar findings were reported by Fink ME et al. (4)

In the current work GCS improved significantly in mannitol group after 24 hours and the same with hypertonic saline group but improvement with hypertonic saline was significantly better than mannitol, this finding was supported by Diringer MN et al. [21] in their review.

CONCLUSION

Hypertonic saline 3% was better than mannitol 20% as regard improvement of CT brain criteria of brain edema, improvement of GCS and effect on renal functions. Also we can conclude that hypertonic saline 3% may replace mannitol 20% in the treatment of brain edema after traumatic brain injury due to its better efficacy and less adverse effects.

Limitations of the study

Intracranial pressure monitoring was not available at time of our study and the small sample size was one of the limitations.

Conflict of Interests

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

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