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Optic Nerve Sheath Diameter: An Ultrasonographic Window for Comparing between Hypertonic Saline and Mannitol in Severe Traumatic Brain Injuries

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Abstract

Background: Clinically both mannitol and hypertonic saline (HTS) have been utilized successfully to manage elevated intracranial pressure (ICP), although which therapy is superior is yet unclear.

Aim of the work: To compare the efficacy of hypertonic saline 3% and mannitol 20% in the reduction of increased intracranial pressure in sever traumatic brain injuries by ultrasonographic measurement of optic nerve sheath diameter (ONSD).

Patient and methods: This prospective, double blind, randomized, observational, comparative study was performed on 30 patients who admitted to surgical intensive care unit in Aswan University Hospital with severe traumatized brain injury. All patients were examined by ultrasound to measure ONSD, we used a cut off value for ONSD as 5.5 mm to diagnose increase in ICP>20 mm Hg. Patients with signs of increased ICP were allocated into 2 groups; Group A: Patients received Mannitol 20% in a dose of 0.5gm/kg (2.5ml/kg) every 6 hours intravenously over a period of 20 minutes for 48 hours, Group B: Patients received hypertonic saline 3% in a dose of 3ml/kg every 6 hours (0.5ml/kg/hr) infusion intravenously for 48 hours.

Results: The ONSD values in HTS and mannitol groups were statistically significant decreased from admission values at 6 hours, 12 hours, 24 hours & 48 hours after treatment. The ultrasonographic ONSD values were significant lower in HTS group than mannitol group at 12 hours, 24 hours & 48 hours (P=0.012, 0.039, 0.001respectively). The percentage decrease of the ultrasonographic values of ONSD at 48 hour of treatment was higher in HTS group than mannitol group (P=0.001), while there was no statistically significant difference at 24 hours of treatment between the two study groups.

Conclusion: ONSD routine monitoring in ICU helped to early detect patients with raised intracranial pressure when invasive ICP monitoring is not available. Hypertonic saline causes decrease ICP more effectively than mannitol with less rebound elevation to ICP than mannitol and there was no significant effect of hyperosmolar therapy on hemodynamics.

Keywords: Traumatic Brain Injury (TBI); Mannitol; Hypertonic saline (HTS); Optic Nerve Sheath Diameter (ONSD)

Introduction

Traumatic brain injury (TBI) remains the leading cause of death and disability in young adults in the developed world. The pathophysiology of traumatic brain injury (TBI) can be splited into primary and secondary injury. A key composition in the management of severe TBI is the prevention of secondary brain injury accompanied with elevated intracranial pressure (ICP) [1]. Intracranial hypertension and cerebral hypo perfusion are common occurrences after severe TBI and are associated with poorer clinical outcome, which has led to considerable interest in its monitoring and manipulation in patients who have suffered TBI, whereas a response to ICP lowering treatment is associated with a decreased mortality rate [2]. Elevation of ICP to 20 mm Hg or greater can result in impaired brain perfusion, poor neurological outcome, and mortality. In one review, the incidence of death was 18.4% for patients with an ICP<20 mm Hg but rose to 55.6% for those with an ICP greater than 40 mm Hg [3].

There are various methods of controlling ICP; however, one of the main pharmacological interventions in severe TBI is hyperosmolar therapy. Mannitol and hypertonic saline (HTS) solutions are commonly used hyperosmolar agents for this purpose despite a lack of high-quality clinical trials. Both agents are believed to lower ICP predominantly by creating an osmolar gradient that leads to mobilization of fluid from the brain to the intravascular compartment [4]. The beneficial effects of both these agents has also been postulated around their neuroprotective effects at a cellular level, based on prevention of oxidative stress and secondary insults from inflammation and cytokine-mediated cellular pathways [5]. Ocular US can be used to evaluate intracranial pressure (ICP) by measuring the optic nerve sheath diameter (ONSD) even before development of papilloedema which takes several hours to develop. US can be used as point of care for rapid, bedside, non-invasive means of detecting

elevated ICP. Increased ICP is transmitted to the subarachnoid space surrounding the optic nerve causing optic nerve sheath expansion [6]. Bedside ultrasound measurement of optic nerve sheath diameter (ONSD) is emerging as a non-invasive technique to evaluate and predict raised intracranial pressure (ICP). It has been shown in previous literature that ONSD measurement has a good correlation with surrogate findings of raised ICP such as clinical and radiological findings suggestive of raised ICP [7-10].

Enlarged ONSD is highly correlated with direct measurement of ICP with high specificity and sensitivity of more than 90%. A recent study has documented the changes in ONSD measurement reliably and rapidly with changes in ICP so it can be used as a bedside monitoring for changes in ICP [8-9]. Aim of our study was to compare the efficacy of hypertonic saline 3% versus mannitol 20% to decrease intracranial pressure in traumatized brain injuries by using ultrasonographic measurement of optic nerve sheath diameter, secondary outcome ONSD routine monitoring in ICU helped to early detect patients with raised intracranial pressure when invasive ICP monitoring is not available; it also allowed to detect elevated ICP when ONSD is rapidly increased over time especially in those neurocritical patients, sedated and mechanically ventilated, who hardly develop signs of cerebral deterioration.

Patients and Methods

After approval of the ethical committee in Aswan University Hospital, this prospective, randomized, double blinded, observational study was performed on 30 patients who admitted to the Surgical Intensive Care Unit with sever traumatized brain injury [Glasgow Coma Scale(GCS≤ 9)] from May 2018 till November 2018. Patients were randomly allocated into two groups 15 in each (Mannitol groups and hypertonic saline groups) by a random sequence number generated by the computer kept in sealed envelopes. On admission, all patients characteristics data were obtained (age, sex, weight, and Glasgow Coma Scale [GCS]) then evaluated haemodynamically (heart rate, blood pressure), respiratory rate, and oxygen saturation and neurologically by Glasgow coma scale (GCS). All patients with GCS ≤ 9 were intubated and consequently head CT scans were performed to evaluate possible brain injury. The Patients were examined by ultrasound to measure ONSD, we used a cut off value for ONSD as 5.5 mm to diagnose increase in ICP> 20 mm Hg. The consent that has all the required information about the study was informed and signed by the relatives.

Inclusion criteria: Patients who having traumatized brain injury GCS ≤ 9, both genders, age: between 20 and 60 and cut off value for ONSD as 5.5 mm to diagnose increase in ICP> 20 mm Hg.

Exclusion criteria: Hypotension for mannitol group, Pregnancy, Renal failure, Coagulopathy, and cardiac dysfunction.

Patients with signs of increased ICP were allocated into 2 groups by a random sequence number generated by the computer and kept in sealed envelopes:-

Group A: Mannitol 20 % in a dose of 0.5 gm/kg (2.5ml/kg) intravenously over a period of 20 minutes every 6 hours for 48 hours.

Group B: hypertonic saline 3% in a dose of 3ml/kg every 6 hours (0.5 ml/kg/hr) infusion intravenously for 48 hours, Target Na+ 145-155 mEq/L.

All patients were evaluated by ultrasonographic measurement of ONSD at 0, 6, 12, 24 and 48 hours and the investigator who measured ONSD also blind as regard treatment by mannitol or hypertonic saline. Haemodynamic monitoring (Heart rate and mean arterial blood pressure) were obtained at 0, 6, 12, 24 and 48 hours whereas serum Na + and K+ were obtained at 0, 12, 24 and 48 hours.

Technique:

A 12MHz linear ultrasound probe were adjusted to give a suitable angle for displaying the entry of the optic nerve into the globe and the measurement performed at the depth of 3mm behind the ocular globe [11]. Right and left ONSD are measured in the transversal plane, with slight rotation of the probe to obtain the better optic nerve visualization. ONSD measured in 3 consecutive measurements in each eye then the mean ONSD obtained (Figure 1 and 2).

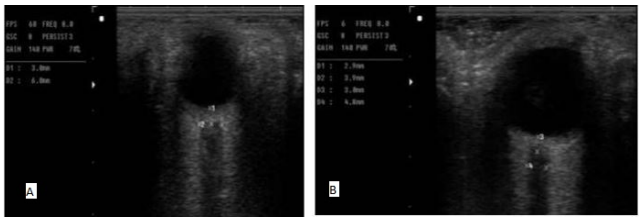

Figure 1: The scan images of ONSD measurement with B-scan ultrasound. (A): picture of ultrasonic measurement of ONSD in a patient with sever traumatized brain injury, optic nerve sheath diameter (ONSD) 6 mm. (B): picture of ultrasonic measurement of ONSD in the same patient after 48 hours treatment with mannitol 20%, optic nerve sheath diameter (ONSD) 4.8 mm.

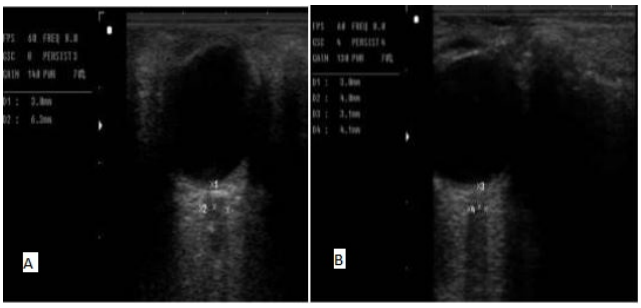

Figure 2: The scan images of ONSD measurement with B-scan ultrasound. (A): picture of ultrasonic measurement of ONSD in a patient with sever traumatized brain injury optic nerve sheath diameter (ONSD) 6.3 mm. (B): picture of ultrasonic measurement of ONSD in the same patient after 48hr treatment with HTS 3%, optic nerve sheath diameter (ONSD) 4.1 mm.

Statistical analysis:

The data was analyzed by package SPSS 22.0 (SPSS Inc. Chicago, IL, USA). Demographic and hemodynamic data will be analyzed by Student's t-test, for intra-group analysis, unpaired t-test was applied. P<0.05 was considered as statistically significant.

Results

There was no statistically significant difference between the two studied groups regarding the age, gender or GCS on admission as shown in [Table1].

Demographic variable		Mannitol group (n=15)	HTS group (n=15)	p-Value
Age	Mean ± SD	36.6 ± 12.7	39.1 ± 11.5	0.582
Gender	Male no (%)	12 (80%)	10 (66.7%)	0.409
	Female no (%)	3 (20%)	5 (33.3%)	
GCS	Mean ± SD	6.8 ± 1.9	6.3 ± 2.4	0.56
HTS: Hypertonic saline; GCS: Glasgow coma scale				

Table 1: Demographic Data of the studied groups.

The Ultrasonographic ONSD values in HTS and mannitol groups were statistically significant decreased from admission values at 6 hours, 12 hours, 24 hours & 48 hours after treatment and they were statistically significant lower in HTS group compared with mannitol group at 12 hours, 24 hours & 48 hours (P=0.012, 0.039, 0.001 respectively) (figure 3).

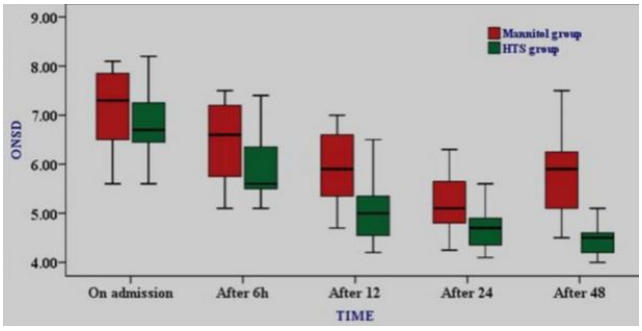

Figure 3: Boxplot chart for ONSD values in Mannitol and HTS groups (the bar represents the median value and the 25th to 75th percentile. ONSD in HTS group is significantly lower than that in those with Mannitol group at 12 hours, 24 hours and 48 hours (P < 0.012, 0.039, 0.001 respectively).

The percentage decrease of the ultrasonographic values of ONSD at 48 hours of treatment was higher in HTS group than mannitol group (P=0.001), while there was no statistically significant difference at 24 hours of treatment between the two study groups (table 2).

Percentage decrease of ONSD (Mean ± SD)	Mannitol group (n=15)	HTS group (n=15)	t	p-Value
24 hours	26.25 ± 7.6%	30.86 ± 8.8%	-1.538	0.135
48 hours	16.53 ± 13.9%	33.97 ± 8.9%	-4.065	0.001*
p-value	0.025#	0.135	-	-
ONSD: Optic nerve sheath diameter; HTS: Hypertonic saline; *significant between the studied groups; #significant in the same group				

Table 2: The mean percentage decrease of the ultrasonographic values of ONSD.

The mean Serum Na+ values in HTS group were statistically significant increased from admission values at 6 hours, 12 hours, 24 hours & 48 hours while in mannitol group they were statistically significant decreased from admission values at 12 hours, 24 hours & 48 hours. The mean Serum Na+ values in HTS group were statistically significant higher than mannitol group at 12 hours, 24 hours & 48 hours (P=0.001, all) (Figure 4).

Figure 4: Comparison between the two study groups regarding serum Na+ level.

The mean Serum k+ values were statistically significant decreased from admission values at 12 hours, 24 hours & 48 hours in both study groups and there were no statistically significant difference between the two study groups all over the study period (Figure 5).

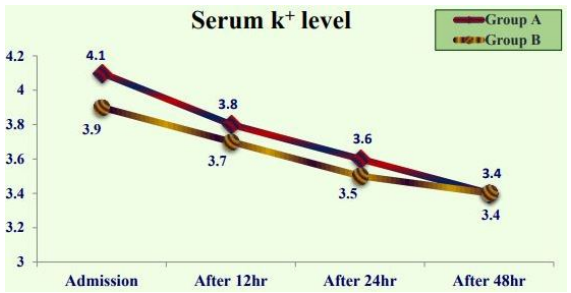

Figure 5: Comparison between the two study groups regarding serum K+ level.

There was no statistically significant difference in the mean HR and the MAP values between the two study groups all over the study period. But there was a significant negative correlation of ONSD values with HR values in mannitol group at 12 hours & 24 hours of treatment (P=0.027, 0.007 respectively) where the mean HR increased with the decreased ONSD values.

Discussion

Intracranial pressure (ICP) is a major predictor of neurological deterioration in patients with TBI and post-traumatic intracranial hypertension (ICH) is being associated with poor neurological outcome. Prompt identification of elevated intracranial pressure is life-saving and invasive monitoring is not always utilized appropriately. Normal ICP in healthy adults is usually regarded as 5-15mmHg [12] and in TBI an Intracranial pressure (ICP) of >20mmHg is widely accepted as intracranial hypertension (ICH) [13]. Measurement of ONSD is rapidly gaining popularity as it is quick, easily available and has a short learning curve. The optic nerve sheath is continuous with dura mater, and subarachnoid compartment of optic nerve communicates with that of brain so that any increase in ICP causes expansion of ONSD [14].

This study is the first double blinded randomized study to compare the efficacy of hypertonic saline 3% and mannitol 20% in the reduction of increased intracranial pressure in sever traumatic brain injuries with ultrasonographic measurement of Optic Nerve Sheath Diameter (ONSD). The study was performed on 30 patients admitted with severe traumatized brain injury. All patients were examined by ultrasound to monitor ONSD; we used a cut off value for ONSD as 5.5 mm to diagnose increase in ICP> 20 mm Hg. Patients with signs of increased ICP were randomly allocated into 2 groups; Group A: Patients received Mannitol 20% in a dose of 0.5 gm/kg (2.5ml/kg) every 6 hours intravenously over a period of 20 minutes for 48 hours, Group B: Patients received hypertonic saline 3% in a dose of 3ml/kg every 6 hours intravenously infusion for 48 hours (0.5ml/kg/hr).

Hypertonic solutions such as mannitol and hypertonic Saline (HTS) are recommended early in the management of intracranial hypertension (ICH) after severe TBI. Clinically both mannitol and hypertonic saline (HTS) have been utilized efficiently to manage elevated intracranial pressure (ICP), although which therapy is superior is yet unclear and there is also lacking evidence to support the application of any specific hyperosmolar drug for patients with severe traumatic brain injury. In addition, all studies published to date examined the effects of mannitol or HTS only on discrete episodes of intracranial hypertension, and the rapidity and duration of reduction of ICP spikes, and no data exist on the efficacy of either agent in reducing the cumulative ICP burden. Therefore, we undertook this study to compare the effects of mannitol and HTS on the cumulative and daily ICP burdens rather than on single episodes of ICH in patients with severe TBI using ultrasonographic measurement of optic nerve sheath diameter (ONSD).

The results of our study showed that both HTS 3% and Mannitol 20% significantly decrease ONSD from admission values and patients received HTS 3% had significant decrease in ONSD than other group received mannitol 20%. The percentage decrease of ultrasonographic values of ONSD at 48 hour of treatment was higher in HTS group than mannitol group, while there was no statistically significant difference at 24 hour of treatment between the two study groups.

Liu et al. (2017)[15] concluded that ultrasound measurement of ONSD may be a good surrogate of invasive ICP measuring and this non-invasive methodology could be an alternative approach to predict the ICP value of patients whose ICP measuring via lumbar puncture are in high risk. Similarly, Toscano et al. (2017)[16] demonstrated that ONSD is a powerful marker of intracranial hypertension, easy to be performed with a minimal training and routine ONSD daily monitoring could be of support in Intensive Care Units when invasive intracranial pressure monitoring is not available.

Jeon and colleagues [17] concluded that ONSD linear correlated with directly measured ICP in patients with brain lesions. The mean values of ONSD in patients with increased ICP was 5.80 ± 0.45 mm, which was significantly higher than that in those without increased ICP (5.30 ± 0.61 mm) (P<0.01) and the optimal cut-off point of ONSD for identifying increased ICP was 5.6 mm, yielding a sensitivity of 93.75% and a specificity of 86.67%. In addition, Amini and colleagues also used the sonographic measurement of the ONSD and located that the ONSD of greater than 5.5 mm was a good indicator of high ICP (>20 cm H2O) with sensitivity and specificity of 100% (95% CI, 100-100) (P<0.001)[9].

In agreement with our results, a meta-analysis of randomized clinical trials by Kamel and colleagues comparing mannitol and HTS in the treatment of raised ICP and supported that HTS is more effective than and may be superior to mannitol for the treatment of elevated ICP [18]. Many studies have compared mannitol with HTS and in concordance with our findings HTS seems to have a greater and longer lasting reduction of ICP than mannitol, and also has less failure rates [19]. These findings have been further verified by a meta-analysis by Mortazavi et al. [20] which showed that HTS may be more effective in reducing ICP than mannitol with odds ratio of 0.36 (0.19-068; p=0.002).

Additionally, A Cochrane review by Prabhakar and colleagues [21] compared HTS with mannitol for brain relaxation during craniotomy and found that brain relaxation was inadequate in 42 of 197 patients in HTS group vs 68 of 190 patients in mannitol group with risk ratio for brain bulge or tense brain in HTS group being 0.60 (0.44-0.83).

Mangat et al, 2015 [22] conducted a retrospective cohort study over 50 patients with severe TBI using HTS 3% and mannitol 20% in two different groups and parallel to our study they found Hypertonic saline provided lower daily and cumulative increased ICP and shorter period of ICU hospitalization than mannitol .

Similarly, a systematic review and meta-analysis by Li and colleagues [23] concluded that greater ICP-lowering effects are obtained from hypertonic saline. Cottenceau et al. [24] in 2011 conducted a prospective, randomized controlled trial (RCT) which included 47 patients with severe TBI and ICP> 15 mmHg. The patients were randomized and divided into two groups: the group taking 4 ml/kg dose of 20% mannitol (n=25) and the group taking 2 ml/kg of 7.5% hypertonic saline (n=22). The two fluids had the same osmolarity. The results of the study showed that both fluids were equally effective in lowering ICP, but stronger and longer duration of ICP reduction effect was shown in hypertonic saline group and there was no significant difference in neurological outcome between groups for 6 months using the Glasgow Outcome Score (GOS). Also, a study by Jagannatha AT and colleagues [25] compared equiosmolar concentration of mannitol with HTS and found physiological advantages of HTS over mannitol (significantly less increase in ICP, greater slope of fall in ICP after a bolus dose) but it did not translate into long term benefit in terms of ICP control or mortality.

In controversy to our results GU and colleagues [26], in a meta-analysis of randomized controlled trials reported that the pooled mean difference (MD) of maximal ICP reduction, comparing HS to mannitol, was -0.16 (95% CI: −0.59 to 0.27, p=0.473), indicating that there was no difference on the efficacy of ICP reduction between the two drugs.

Two other studies showed that there is no statistically significant difference in the ability to reduce intracranial pressure between HTS and mannitol. Systematic review in 2016 by Burgess et al. [27] found that there was no significant difference between mannitol and hypertonic saline in reducing mortality, ICP, and the neurological output in the patients with severe TBI. This review included seven well-publicized trials up to November 2015. This systematic review wrote that the data which were currently utilized were still limited due to the high heterogeneity of each study and Sakellarindis et al. in 2011[28]conducted a prospective study to compare the effectiveness of mannitol and hypertonic saline in dose with similar osmolarity. Twenty-nine patients with severe TBI and suffering continuous intracranial hypertension (> 20 mmHg for 5 minutes) were treated with either 20% mannitol (2 ml/kg) or 15% hypertonic saline (0.42 ml/kg). The study found that there was no significant difference both in decreasing ICP and duration of the action of the two fluids.

In our study, we evaluated serum Na+ and serum K+ levels on admission and after 12hr, 24 hours & 48 hours. Regarding serum Na+ level in mannitol group there was a statistically significant decrease in mean Serum Na+ level after 12 hours, 24 hours & 48 hours, while oppositely in group HTS 3% there was a statistically significant increase in mean Serum Na+ level after 12 hours, 24 hours & 48 hours.

Supporting our study findings a systemic review by Gu and colleagues (2018)[26]which performed on seven studies provided data on serum sodium within 6hr after hyperosmolar therapy. The results suggested that HTS 3% significantly increases the concentration of serum sodium when compared to mannitol 20% (WMD: 5.30, 95% CI: 4.37 to 6.22, p< 0.001).

In controversy to our findings, Jagannatha et al., (2016)[25] in his study reported that there was no statistically difference in serum Na+ levels for both mannitol 20% group and HTS 3%.

In our study we found that there was no statistically significant difference in the MAP & HR values at 6hr, 12hr, 24hr or 48hr comparing with admission values in each study group individually or between the two study groups all over the study period. Jagannatha et al., (2016)[25] supported our results that there is no statistically difference between mannitol 20% and HTS 3% in HR & MAP values.

Conclusion

Hypertonic saline causes decrease ICP more effectively than mannitol with less rebound elevation to ICP than mannitol and there was no significant effect of hyperosmolar therapy on hemodynamics. ONSD routine monitoring in ICU helped to early detect patients with raised intracranial pressure when invasive ICP monitoring is not available. ICP monitoring has contributed to neurocritical care advancements and improved patient outcome. It is important to identify early those patients who would benefit from ICP monitoring and apply interventions to treat raised ICP. The goal of treatment is to reduce long-term damage and prevent secondary insults to the injured brain tissues.

In the future the dosing and concentration of HTS that is the most beneficial is yet undetermined. Studies are required to find out the optimal dosing and concentration for HTS as well as efficacy of prolonged infusions in relation to outcome.

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