Maintaining Osmotic Therapy in Severe Traumatic Brain Injury Using Non-Invasive Ultrasound Tool

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ABSTRACT

Background: Trauma of the head is the leading cause of death. Monitoring of intracranial pressure (ICP) by non-invasive methods is practiced with the use of bedside ocular ultrasound. **Objective:** to assess the usage of the bedside ultrasound optic nerve sheath diameter (ONSD) as a guiding tool for elevated ICP to limit using mannitol to patients currently having elevated ICP. **Patients and methods:** This descriptive observational study included adult patients with acute blunt head trauma with loss of consciousness with severe traumatic brain injury who were intended to intensive care unit at Suez Canal University Hospital. Serum sodium, creatinine and osmolality prior to each mannitol dose was tested and recorded till stopping mannitol. GCS, FOUR score, and APACHE II score, and Mean arterial blood pressure (MAP) was assessed. **Results:** The mean baseline GCS was 5.05 ±1.432, FOUR score ranged from 1 to 12.There was no significant difference between the different serum sodium and creatinine levels follow-up. There was a statistically significant difference between the different potassium and osmolarity levels follow-up. A significant difference between ONSD after treatment follow-up of the studied sample at 5^{th} dose and 6^{th} dose. **Conclusion:** ONSD sonography is a useful and user-friendly, noninvasive tool to detect ICP elevation.Under dynamic conditions, this correlation remains valid even after osmotherapy with mannitol.

Keywords: Intracranial pressure; Ultrasound; Mannitol; Serum sodium; Osmolality

INTRODUCTION

In severe head injury, intracranial bleeding and idiopathic intracranial hypertension, several studies showed close association between optic nerve sheath diameter (ONSD) and raised intracranial pressure (ICP) **(1)**. Raised ICP can be detected with an increase in ONSD due to the presence of continuity of meninges and subarachnoid space around the optic nerve **(2)**.

Intravenous mannitol is the most widely used solute for the treatment of brain edema due to increased ICP Its effect in lowering ICP usually starts in few minutes after initiation of mannitol administration with a peak effect at 20-60 minutes **(3).** Previous studies have demonstrated the effect of mannitol in lowering ICP, but the underlying mechanisms remain a matter of debate **(4)**.

Possible theories include decreasing cerebral volume due to extracting water from the brain tissue, a fall in cerebral blood flow due to cerebral vasoconstriction from increasing blood pressure, and a decrease of serum viscosity **(5)**. Intra-parenchyma micro dialysis method demonstrated decrease of lactate/pyruvate ratio, which indicated an improvement of intracranial metabolism following mannitol treatment in patients with severe hemorrhagic stroke **(6)**.

There is lack of evidence to recommend repeated regular administration of mannitol over several days, beside that mannitol therapy is not completely beneficial as it has many side effects as repeated administration can result in high serum sodium and osmolarity that may lead to osmotic demyelination syndromes, also rebound increase in ICP can occur after initial reduction due to passage of mannitol into the brain, for that it has to be targeted therapy giving only on need guided by monitoring of ICP **(7)**.

Ultrasound (US) is a cost-effective treatment modality which does not require transportation of the patient. It is a helpful bedside noninvasive method in measuring ONSD. It can be repeated at regular intervals which help in close monitoring of ICP as well, also ONSD is suggested to be a quick monitor for changes in ICP which detect immediate changes in ICP in patients with TBI **(8)**.

Our rational was to prove that using ONSD measurement as a tool to guide osmotic therapy of increased ICP is beneficial, decreasing the high cost of other measuring tools, avoiding recurrent transportation of the critically ill patient for CT brain scanning and avoiding exposure to high dose of radiation. Thus, the current study targeted to evaluate the usage of the bedside ultrasound ONSD as a guiding tool for elevated ICP to limit using mannitol to patients currently having elevated ICP. Thus this study aimed to assess the usage of the bedside ultrasound ONSD as a guiding tool for elevated ICP to limit using mannitol to patients having elevated ICP.

PATIENTS AND METHODS

This descriptive observational study included adult patients with acute blunt head trauma with loss of consciousness with severe traumatic brain injury who were intended to intensive care unit at Suez Canal University Hospital.

Methods:

The techniques were explained to the patient's legal guardian (as the patients were unconscious) including benefits and complications. Training for the ICU physicians consisted of a one-hour hands-on workshop by an expert radiologist on ocular ultrasonography; during which they were observed to measure the optic nerve sheath in volunteer patients.

Information was gathered on the following topics: age, gender, body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP), mean arterial blood pressure (MABP) (calculated as $1/3 \times SBP + 2/3 \times DBP$), level of consciousness as determined by Glasgow Coma Scale (GCS) score at presentation, and clinical neurological examination. In addition, the Full Outline of Unresponsiveness (FOUR Score) is available **(9)**. The eye reaction, motor response, brainstem reflexes, and breathing pattern are the four equally weighted components that make up the FOUR score. This scale is easy to memorize because it comprises 4 components, each having a maximal value of 4. For a comprehensive and precise evaluation of the level of coma, brainstem reflexes are taken into account. Acute Physiology and Chronic Health Evaluation (APACHE II) is a generic measure of disease severity based on current physiologic measures, age, and prior health conditions. The score can aid in the evaluation of patients to evaluate the amount and severity of diagnostic and therapeutic intervention.

As a result, head CT scans were performed to assess any potential brain injury. The CT scans were read by skilled on-site radiologists. The initial brain CT revealed signs of increased ICP, such as sulci effacement, substantial edema, midline displacement, and ventricle collapse. Based on the findings of the head CT scan, osmotic treatment was determined to be necessary.

According to the local ICU recommendations for TBI management, the ICU physician is responsible for monitoring and management extremes of blood pressure and heart rate either high or low, volume status, fluid balance, and mechanical ventilation configuration.

The following clinical biochemical parameters were collected on: serum sodium, serum potassium, osmolarity, and serum creatinine.

Care was taken to keep the hemoglobin concentration above 9 gm/d and the arterial partial oxygen pressure above 80 mmHg by adjusting the mechanical ventilation settings through the fraction-inspired oxygen and the positive end-expiratory pressure (PEEP). Ventilation was judiciously controlled to reach the optimal points of oxygenation and ventilation obtained by arterial blood gases (ABG) parameters. If necessary, blood pressure was supported with vasopressor therapy. If the patient was diabetic Blood glucose was adjusted to values between 110-140 mg/dl by continuous application of human insulin. Patients' core temperature was measured through the axilla, with a target temperature of 36.5–37.5°C. If the temperature exceeded 37.5°C, external cooling blankets were used to cool the patient; otherwise, patients were covered either with an additional blanket or with an active heating blanket. Total fluid intake and urine output were noted.

After the baseline readings were recorded, ONSD was measured and patients with elevated ICP was given mannitol therapy **(Figure 1)**. 5g/kg of 20% mannitol infused over 30 minutes via a central venous access every 6 hours for 72 hours to be guided by ONSD.

The findings of brain CT were reported by the on-site radiologist, and they were correlated with bedside ONSD measurement by ocular sonography.

Serum sodium, creatinine and osmolality prior to each mannitol dose was tested and recorded till stopping mannitol. Time of mechanical ventilation, length of stay in ICU, length of stay in the hospital and mortality at 7 days were recorded.

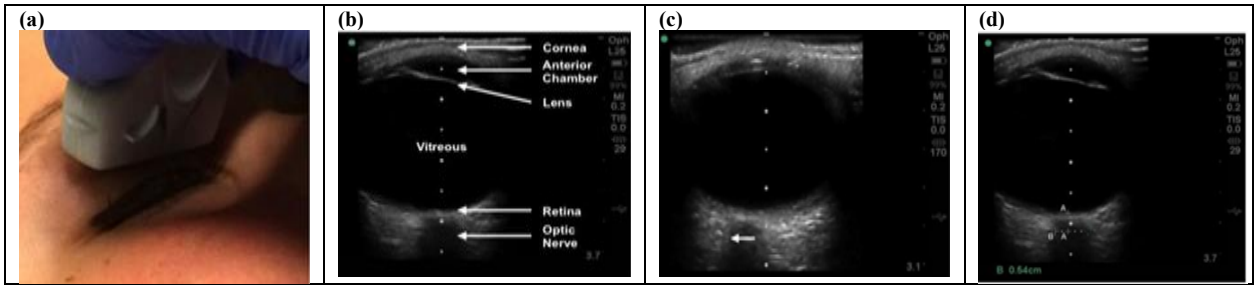

Figure (1): Ocular ultrasound showed **(a,b)** the transverse plane using a linear transducer to identify the optic nerve ; **(c)** The nerve sheath was included in ONSD measurements when visualized (arrow); **(d)** measurements were taken at a depth of 3 mm posterior to the globe.

Statistical analysis:

Data were entered to IBM SPSS) version 23. The quantitative data and qualitative variables were presented Chi-square test,Independent t-test, Mann-Whitney test, One Way ANOVA test and Kruskall-Wallis test, and Spearman correlation coefficients were used. The confidence interval was set to 95%. So, the p-value was considered as the following: P-value >0.05 represented non-significant (NS), P<0.05 represented significant (S), P < 0.01 represented highly significant (HS).

RESULTS

The present study showed the mean baseline GCS was (5.05 ± 1.432), ranged from 3 to 8, FOUR score from 1 to 12 and APACHE II score from 4 to 22 **(Table 1)**.

There was no statistically significant difference was found between the different serum sodium levels follow-up of the studied sample **(Table 2)**. There was a statistically significant difference was found between the different potassium levels follow-up of the studied sample **(Table 3)**.There was no statistically significant difference was found between the different creatinine levels follow-up of the studied sample **(Figure 2)**.

There was a statistically significant difference was found between the different Serum Osmolarity levels follow-up **(Figure 3)**. There was a statistically significant difference was found between the different MAP after treatment follow-up of the studied sample except the 11th dose **(Table 4)**.

There was a statistically significant difference was found between ONSD after treatment follow-up of the studied sample at 5th dose and 6th dose **(Figure 4)**.

Table (1): Baseline GCS, FOUR score, and APACHE II score

	Mean ± SD	Median	Range	IQR
Baseline GCS	5.05 ± 1.432	5.00	3.0, 8.0	4.00, 6.00
FOUR score	6.85±3.23	7.5	1,12	4.5, 9
APACHE II	14.95±4.5	15.5	4,22	12.5,18

Data is expressed as mean and standard deviation, median, range and interquartile range.

Table (2): Sodium levels follow-up of the studied sample.

	Mean & SD	Median	Range	IQR	P
1st mannitol dose	139.00 ± 3.449	139.00	132.0, 145.0	136.25, 141.75	-
2nd mannitol dose	138.40 ± 2.873	138.00	134.0, 143.0	136.00, 140.75	0.209
3rd mannitol dose	139.70 ± 2.774	139.50	136.0, 144.0	137.00, 142.75	0.337
4th mannitol dose	141.00 ± 3.055	141.00	134.0, 147.0	139.00, 143.00	0.023
5th mannitol dose	141.39 ± 3.913	141.50	131.0, 148.0	139.00, 144.00	0.016
6th mannitol dose	140.33 ± 5.984	141.00	128.0, 151.0	137.00, 142.00	0.234
7th mannitol dose	138.25 ± 6.956	138.50	126.0, 152.0	133.50, 143.00	0.968
8th mannitol dose	138.40 ± 6.586	139.50	128.0, 151.0	133.75, 142.00	0.838
9th mannitol dose	138.33 ± 8.109	139.00	127.0, 152.0	131.00, 144.00	0.881
10th mannitol dose	137.75 ± 8.631	138.00	126.0, 154.0	130.00, 141.00	0.815
11th mannitol dose	139.00 ± 8.000	140.00	126.0, 151.0	134.25, 142.75	0.959
12th mannitol dose	139.67 ± 7.202	140.00	128.0, 150.0	135.50, 144.00	0.874

Data is expressed as mean and standard deviation, median, range and interquartile range.
P is generated by comparing each value to the 1st dose value. P is significant when < 0.05.

Table (3): Potassium levels follow-up of the studied sample.

	Mean & SD	Median	Range	IQR	P
1st mannitol dose	4.20 ± 0.505	4.15	3.5, 5.1	3.73, 4.60	-
2nd mannitol dose	3.95 ± 0.662	4.00	2.8, 5.0	3.25, 4.50	**0.001**
3rd mannitol dose	3.85 ± 0.620	3.95	2.8, 4.8	3.33, 4.43	**< 0.001**
4th mannitol dose	3.77 ± 0.463	3.70	3.1, 4.6	3.40, 4.00	**< 0.001**
5th mannitol dose	3.48 ± 0.436	3.50	2.8, 4.3	3.10, 3.80	**< 0.001**
6th mannitol dose	3.41 ± 0.407	3.40	2.7, 4.0	3.20, 3.70	**< 0.001**
7th mannitol dose	3.49 ± 0.401	3.55	2.8, 4.2	3.13, 3.80	**< 0.001**

8th mannitol dose	3.37 ± 0.323	3.40	2.8, 4.0	3.18, 3.53	**0.001**
9th mannitol dose	3.31 ± 0.333	3.30	2.7, 3.7	3.10, 3.65	**< 0.001**
10th mannitol dose	3.30 ± 0.330	3.35	2.8, 3.8	3.03, 3.50	**0.003**
11th mannitol dose	3.37 ± 0.216	3.35	3.1, 3.7	3.18, 3.55	**0.004**
12th mannitol dose	3.38 ± 0.458	3.40	2.8, 4.0	2.95, 3.78	**0.012**

Data is expressed as mean and standard deviation, median, range and interquartile range.
P is generated by comparing each value to the 1st dose value. P is significant when < 0.05.

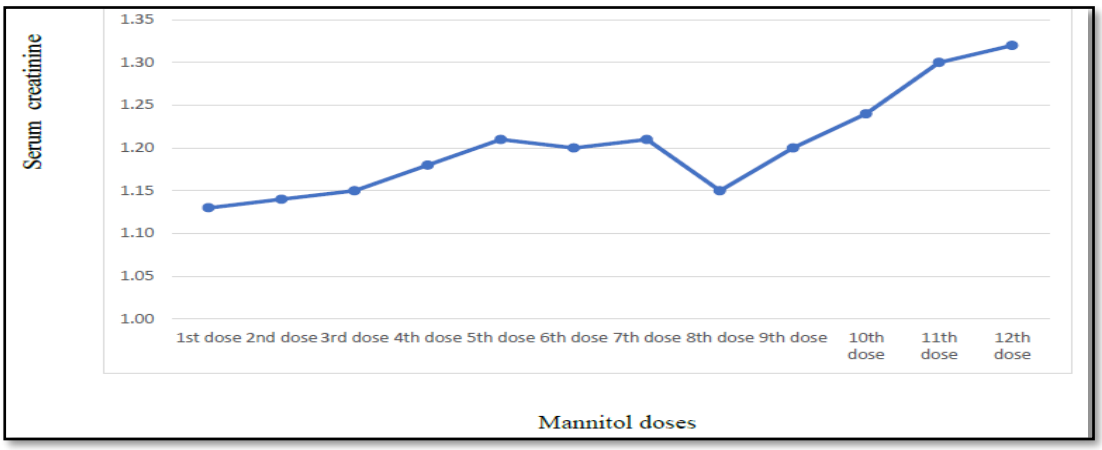

Figure (2): Distribution of Serum Creatinine levels follow-up among studied patients.

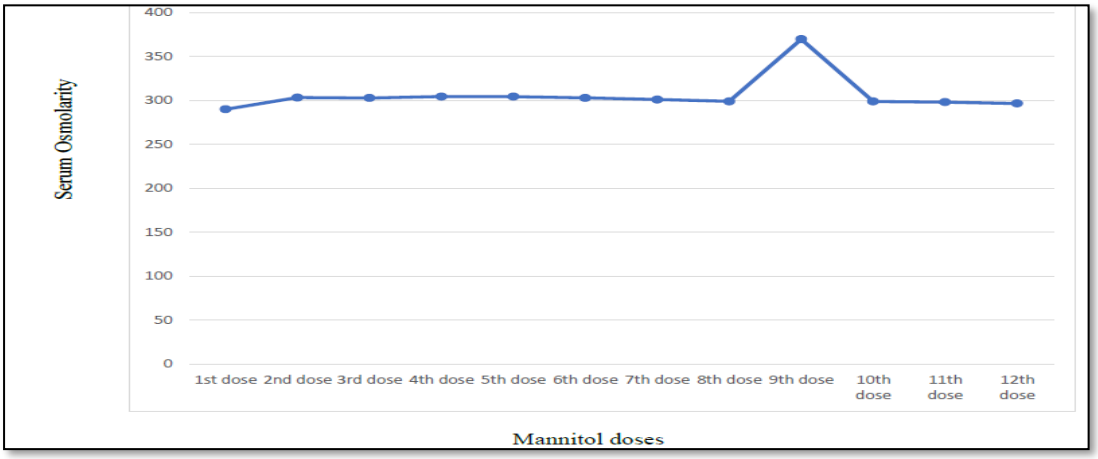

Figure (3): Distribution of Serum Osmolarity levels follow-up among studied patients.

Table (4): MAP after treatment follow-up of the studied patients.

	Mean & SD	Median	Range	IQR	P
1st mannitol dose	86.50 ± 12.215	83.50	70.0, 110.0	77.50, 94.75	-
2nd mannitol dose	83.90 ± 11.912	82.50	66.0, 106.0	73.50, 93.25	**< 0.001**
3rd mannitol dose	82.55 ± 10.971	82.50	69.0, 102.0	70.75, 92.25	**< 0.001**
4th mannitol dose	81.32 ± 10.583	80.00	67.0, 100.0	72.00, 93.00	**< 0.001**
5th mannitol dose	79.78 ± 11.022	78.00	64.0, 99.0	69.75, 88.75	**< 0.001**
6th mannitol dose	80.40 ± 10.986	79.00	64.0, 101.0	71.00, 92.00	**< 0.001**
7th mannitol dose	82.92 ± 11.188	81.00	66.0, 102.0	73.50, 93.00	**0.001**

8th mannitol dose	80.30 ± 11.576	74.00	69.0, 99.0	71.50, 91.75	**0.002**
9th mannitol dose	80.67 ± 10.677	78.00	68.0, 97.0	71.50, 90.50	**0.006**
10th mannitol dose	81.50 ± 9.943	82.00	67.0, 96.0	72.75, 90.50	**0.013**
11th mannitol dose	78.67 ± 8.548	77.00	70.0, 92.0	70.75, 86.75	0.072
12th mannitol dose	78.00 ± 8.989	73.50	70.0, 93.0	72.25, 87.00	**0.027**

Data is expressed as mean and standard deviation, median, range and interquartile range.
P is generated by comparing each value to the 1st dose value. P is significant when < 0.05.

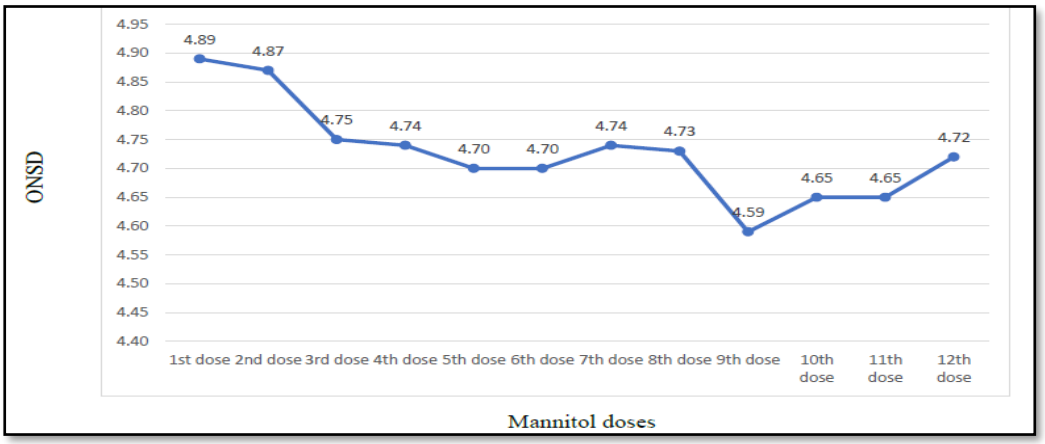

Figure (4): Distribution of ONSD after treatment follow-up among studied patients.

DISCUSSION:

Early detection, evaluation and treatment of elevated ICP improve the outcome of TBI. Invasive ICP monitoring is the gold standard method for ICP monitoring, but invasive techniques are associated with risk of complications such as hemorrhage and infection, also, it is not available in all places and requires high expertise **(10)**.

Some non-invasive methods for measuring ICP can be used as alternatives to invasive techniques, including transcranial Doppler, ONSD, CT, MRI, and fundoscopy **(11)**. These non-invasive techniques do not carry the risk of complications as with invasive methods. Recently, adult studies have reported that measuring ONSD with non-invasive imaging technologies such as CT, MRI and ultrasound can be used as an alternative method to evaluate increased ICP **(12)**.

Moreover, measuring ONSD via ultrasound is a repeatable and quick method, as the orbital window is easily available and uncomplicated in most patients (**13**).

Osmotherapy is a treatment intervention in the care of patients with severe head injury resulting in cerebral edema and intracranial hypertension. The effect of hyperosmolar solutions on brain tissue was first studied nearly 90 years ago. Since that time, mannitol has become the most widely used hyperosmolar solution to treat elevated intracranial pressure **(14)**.

So, this descriptive observational study was carried out to evaluate changes in ICP associated with acute severe TBI using the bedside ultrasound ONSD.

In the current study, statistically significant difference was found between the different potassium levels follow-up of the studied sample. While no statistically significant difference was found between the different sodium levels follow-up of the studied sample.

Similarly, in **Amin et al. (15)** revealed a highly statistically significant increase in serum potassium with minimal decrease in serum sodium but not statistically significant and this result

agree with **Czupryna et al. (16)** that show the effect of a single dose of mannitol on hydration status and electrolyte concentrations in patients with tick-borne encephalitis.

Also, our study results have revealed that ther was no statistically significant difference was found between the different creatinine levels follow-up of the studied sample.

Similarly, in **Amin et al. (15)** showed no statistically significant difference in urea and statistically significant decrease in serum creatinine, and agree with **Sari et al. (17)** monitored the effect of mannitol on serum creatinine and BUN and concluded that no significant change.

Also, **Amin et al. (15)** found there was no statistically significant difference in any of vital parameters such as BP, HR and temperature.

In our study, a statistically significant difference was found between the baseline ONSD and different after treatment follow-up.

The results of **Amin et al. (15)** study show that ONSD is highly significant in early detection on increasing ICP. There is a highly significant decrease in ONSD after osmotherapy with mannitol 20% that indicates successful treatment correlates with negative CT finding of increasing ICP in third day. **Launey et al. (18)** who performed a study to determine the rate of ONSD variation after Mannitol administration for increased ICP episodes. They included thirteen patients in their study comparing and correlating the changes in ONSD, pulsatility index and invasively monitored ICP. The ONSD significantly decreased after Mannitol infusion from 6.3 to 5.56mm (p=0.0007). **Jun et al. (19)** aimed at studying the effect of mannitol on ONSD as a surrogate for intracranial pressure during robot assisted laparoscopic prostatectomy with pneumo-peritoneum and the tredelenburg position. Mannitol (0.5 g/kg) was administered after pneumoperitoneum establishment and shifting to the Trendelenburg position.

In addition, **Amini et al. (20)** 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).

Rajajee et al. (21) who performed a prospective blinded observational study on 65 patients in the ICU. All patients in the study had either had an EVD or intra-parenchymal ICP monitor in situ. The authors used individual as well as mean ONSD values to account for possible fluctuation in the ICP during ONSD measurement. For the individual ONSD measurements the median was 0.53 cm for ICP > 20 mmHg and was 0.4 cm for ICP < 20 mmHg (p < 0.0001). An ONSD of 0.48 cm demonstrated a sensitivity of 96% and specificity of 94% for predicting ICP > 20 mmHg.

Jeon et al. (22) 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%. The difference from our study that we depend on noninvasive method to detect ICP not directly in spite of it being more accurate.

Another study performed in the Indian population by **Shirodkar et al. (8)** evaluated the efficacy of ONSD by ultrasonography as a non-invasive method for detecting raised intracranial pressure in intensive care unit to compare with CT/MRI findings of raised ICP and to prognosticate ONSD value with treatment. The results showed a sensitivity of detecting raised ICP by ONSD to be 84.6% and a specificity approaching around 99%.

Although this was a small patient sample and at 1 institution, other studies have reported similar findings in other mixed patient populations with other inclusion criteria.

Conclusion:

Patients with elevated ICP associated with acute severe TBI, monitoring by using ultrasound measured ONSD influence management of mannitol therapy. As ONSD sonography is a useful and user-friendly, noninvasive tool to detect ICP elevation.Under dynamic conditions, this correlation remains valid even after osmotherapy with mannitol.

ONSD used by dehydrating measures in cases of increased ICP and can be utilized as a tool for decision making and point-of-care utility.

Recommendations

The practical extension of the study results, if validated in larger studies, is that with small portable sonographic machines, the evaluation of the head injured patient for elevated intracranial pressure could possibly occur with triage and management implications. In the setting of disaster or simultaneous multiple trauma patients, a rapid bedside test would be helpful. The ability to rule out elevated intracranial pressure among several unconscious victims would help select the person most in need of rapid transport to an appropriate facility. Portable ultrasonography could be used during long transport times to better monitor acutely ill patients and institute treatment protocols for possible elevated intracranial pressure. Monitoring of hospitalized patients with elevated intracranial pressure would be assisted by such a test, as the movement of such patients requires tremendous expenditure of nursing and hospital resources.

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Author contribution: Authors contributed equally in the study.

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