Monitoring the Effect of Mannitol 20% Solution on Brain Midline Shift Using Transcranial Ultrasonography in Severe Traumatic Brain Injury

Prof. Dr. Mohamed Anwer Elshafey, Assist. Prof. Dr. Ghada Mohamed Samir, Dr. Riham Fathy Galal, and Ahmed Metwally Mahmoud ElAtrash

Anesthesia and Intensive Care, Faculty of Medicine – Ain Shams University, Cairo, Egypt
A_metwally2001@yahoo.com

Abstract: Brain midline shift (MLS) in traumatic brain injury is a life-threatening condition that requires urgent diagnosis and treatment. The early detection of a MLS in severe traumatic brain injury patients is thus very important because it allows starting an appropriate treatment plan. Head CT is considered to be the gold standard to diagnose MLS. Transcranial B-mode sonography (TCS) is a bedside neuroimaging technique which is safe, painless, and accurate. The aim of the present study is to monitor the effect of mannitol 20% solutions on brain mid line shift by using transcranial ultrasonography in severe traumatic brain injury. The current study is a prospective observational study conducted on 30 adult male and female admitted to the Critical Care Medicine Departments in Ain Shams University Hospital with the diagnosis of severe traumatic brain injury. In the current study, there was a positive correlation between APACHE II and ICU stay and mortality. We also found that brain edema, midline shift, Glasgow coma score and FOUR score were improved after the use of mannitol 20% solution. The most important finding in this study was that transcranial ultrasonography can detect and monitor MLS with only a small difference in comparison to CT brain so it provide a cheap accurate noninvasive and bedside tool for diagnosis and monitoring MLS.

[Mohamed Anwer Elshafey, Ghada Mohamed Samir, Riham Fathy Galal, and Ahmed Metwally Mahmoud ElAtrash. **Monitoring the Effect of Mannitol 20% Solution on Brain Midline Shift Using Transcranial Ultrasonography in Severe Traumatic Brain Injury.** *Nat Sci* 2019;17(5):78-88]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 9. doi:10.7537/marsnsj170519.09.

Keywords: Monitoring; Effect; Mannitol; Solution; Brain; Midline; Shift; Transcranial; Ultrasonography; Traumatic Brain Injury

1. Introduction

Anatomy of the nervous system

The nervous system is divided into central and peripheral nervous systems, the central nervous system is composed of brain and spinal cord, peripheral nervous system is composed of spinal and cranial nerves.

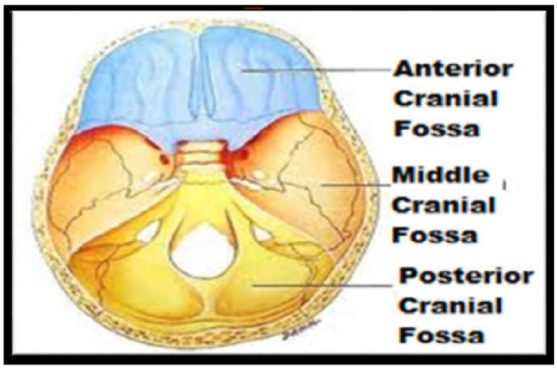


Fig (1): Skull base fosse (**Blumenfeld, 2002**)

A. The Skull: composed of:

(1) *Vault (clavarai):* thin at temporal region which cushioned by temporalis muscle.

(2) *Base:* irregular and contributes to injury as brain moves within the skull during acceleration and deceleration (**Drake et al., 2008).**

Floor of cranial cavity is divided in to 3 cranial fosses (Figure1):

- Anterior fossa: houses frontal lobe.
- Middle fossa: temporal lobes.
- Posterior fossa: brain stem and cerebellum **(Blumenfeld, 2002)**

B. Meninges: Consist of 3 layers (Figure2):

- *Dura:* tough fibrous membrane that adheres firmly to internal surface of skull, it's not attached to the underlying arachnoid forming subdural space so the veins that travel from surface of brain to superior sagittal sinus in midline (bridging veins) may tear forming subdural hematoma.

Meningeal arteries lie between the dura and internal surface of the skull (epidural space), laceration of these arteries by skull fractures lead to epidural hematoma. Most common injured vessels are middle meningeal artery which is located over temporal fossa.

- *Arachnoid:* thin transparent membrane beneath dura. Cerebrospinal fluid circulates in subarachnoid space, hemorrhage in this space

(subarachnoid hemorrhage) frequently caused by brain injury.

- *Pia:* firmly attached to surface of brain **(Drake et al., 2008)**

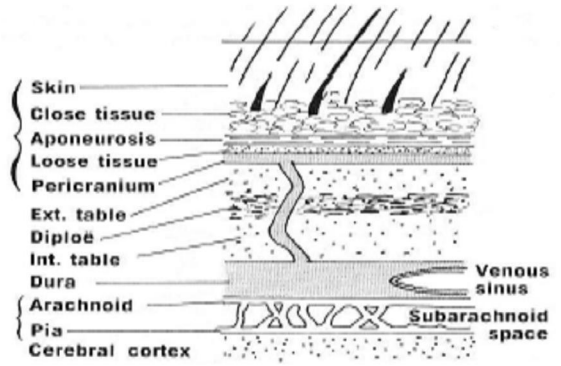
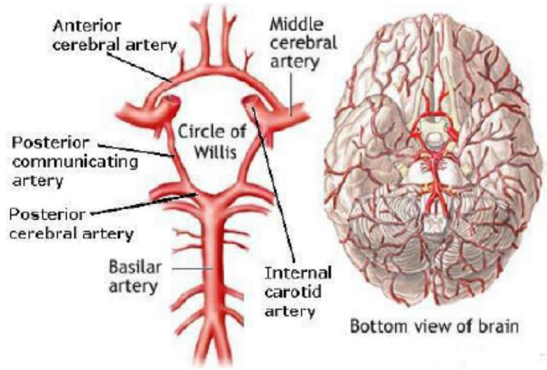


Fig (2): Meninges and scalp layers (**Drake et al., 2008)**

C. Brain: composed of 3 components**:**

- *Cerebrum:* is composed of right and left hemi-spheres that are separated by falx cerebri.
- *Cerebellum:* responsible for co-ordination and balance.
- *Brain stem:* composed of mid-brain, pons, and medulla. Mid-brain and upper Pons: contain reticular activating system which is of responsible for state of alertness. Vital cardio-respiratory centers reside in medulla (**Blumenfeld, 2002)**



-

Fig (3): Vascular supply of the brain (**Drake et al., 2008)**

D. Cerebrospinal fluid

- CSF is produced by choroid plexus (located in the roof of ventricles) at rate of 20 ml\hr. CSF travels from lateral ventricle (through foramen of Monro) → 3rd ventricle (through aqueduct of sylvius) → 4th ventricle (through foramen of Lushka and magindi) → sub-arachnoid space → superior sagittal sinus through arachnoid granulation (**Blumenfeld, 2002).**
- Bleeding in CSF can occlude arachnoid granulation, impair CSF reabsorption and result in increased intracranial pressure (post-traumatic communicating hydrocephalus).

E. Vascular supply of the brain

- The brain is supplied by the two internal carotid and the two vertebral arteries (Figure3). The four arteries lie within the subarachnoid space, and their branches anastomose on the inferior surface of the brain to form the circle of Willis (**Drake et al., 2008).**

The Venous drainage of the brain and coverings includes the veins of the brain itself, the dural venous sinuses, the dura's meningeal veins, and the diploic veins between the tables of the skull (**Drake, Vogl et al., 2008).**

F. Cerebral blood flow

- Cerebral blood flow is the blood supply to the brain in a given period of time. In an adult, cerebral blood flow is typically 750 ml/min or 15% of the cardiac output.
- This equates to an average perfusion of 50 to 54 ml of blood per 100 grams of brain tissue per minute **(Drake et al., 2008).**

Cerebral blood flow is tightly regulated to meet the brain's metabolic demands. Too much blood (hyperemia) can raise intracranial pressure (ICP), which can compress and damage delicate brain tissue. Too little blood flow (ischemia) results if blood flow to the brain is below 18 to 20 ml per 100 g per minute, and tissue death occurs if flow dips below 8 to 10 ml per 100 g per minute. Cerebral blood flow is determined by a number of factors, such as viscosity of blood, dilatation of blood vessels and the net pressure of the flow of blood into the brain, known as cerebral perfusion pressure (**Blumenfeld, 2002).**

Aim of the Work

The aim of the work was to monitor the effect of mannitol 20% solution on brain midline shift by using transcranial ultrasonography in severe traumatic brain injury.

2. Patients and Methods

Patients

The study was carried out on 30 patients of both sexes who were admitted to the Ain Shams University Hospitals at the Critical Care Medicine units who were indicated for brain CT scan. Approval of the medical ethics committee of Ain Shams faculty of Medicine, and an informed consent was taken from the next of kin before conducting the study.

Inclusion criteria:

Severe traumatic brain injured patients with MLS by CT brain from both sex with a Glasgow Coma Scale (GCS) score of 3 to 8 on admission.

Exclusion criteria:

1. Patients with brain midline shift due to other causes as brain tumours.

2. Patients on heamodialysis with end-stage renal disease.

3. Patients with hypernatremia i.e. sodium level ≥ 150mEq/L.

4. Physical examination consistent with brain death.

Methods

All patients included in the study subjected to the followings:

History taking and physical examination:

1. Informed consent was taken from the next of kin.

2. Complete history taking including: age, sex, past medical history and drug history.

3. Severity of illness assessed by acute physiology and chronic health evaluation (APACHE II) scores.

4. Neurological assessment: the patient's level of consciousness assessed by GCS and FOUR score.

All patients included in the study received the standard treatment for management of severe traumatic brain injury according to the guidelines.

The protocol of treatment was not changed during the study time.

Ultrasonography:

The ultrasound MLS was measured through the temporal acoustic bone window using a low frequency (2 to 4 MHz) probe using (EMP 2100-shenzhen Emperor Electronic Technology Co., Ltd. China) ultrasound device as soon as possible before the brain CT. The third ventricle was identified as a double hyperechogenic image over the midbrain; the distance between the external bone table and the Centre of the third ventricle was measured bilaterally, the difference between two measures divided by two is used to calculate MLS.

MLS was measured using transcranial sonography at day of admission and repeated after 48 hours after using mannitol 20% solution.

Hyperosmolar solution used was mannitol, 0.25 to 2 g/kg as a 20% solution IV over at least 30 min administered every 6 to 8 hrs for 48 hrs.

The results of ultrasonography were compared by the results of CT brain at day of admission and after 48 hours.

Computed Tomography:

CT brain was done on admission and after 48 hours of mannitol 20% solution administration to patients with brain edema and MLS after using ultrasonography.

The CT MLS was measured by two methods.

- The distance between the external bone table and the centre of the third ventricle at the orbito-meatal plane that allows visualization of the third ventricle (in the same plane as the sonographic measurement).
- The distance between the ideal mid line and the septum pellucidum, normally used by the neuroradiologist.

Laboratory investigations:

Routine laboratory investigations including: CBC, Na, K, random blood sugar, BUN and creatinine was done.

Sensitivity, specificity, positive and negative predictive values of the ultrasonographic assessment of the MLS changed in comparison to the CT brain finding calculated.

Statistical analysis of the data

Data were fed to the computer and analyzed using pass program, setting error at 5% and power 90%. Results from the previous study showed apposition correlation between TCS and CT (r=0.65). Based on this value, the needed sample was 30 cases.

Using IBM SPSS software package version 20.0 **(**Armonk, NY: IBM Corp**)** Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution 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.

3. Results

This study was conducted on 30 severe traumatic brain injury patients of both sexes admitted to The Critical Care Units in Ain Shams University Hospital, intubated & mechanically ventilated, fulfilled the inclusion and exclusion criteria. Approval of the medical ethics committee of Ain Shams faculty of Medicine, and an informed consent was taken from the next of kin before conducting the study.

Demographic characteristic data:

Table (1) The age of studied patients ranged from 30.0 – 60.0 year with a mean of 46.07 ± 9.16 year. There was 13 females (43.3%) and 17 patients (56.7%) were males.

Table (1): Distribution of the studied cases according to demographic data (n=30)

	No.	%
Sex		
Male	17	56.7
Female	13	43.3
Age (years)		
30 – 40	10	33.3
>40 – 50	10	33.3
>50 – 60	10	33.3
Min. – Max.	30.0 – 60.0	
Mean ± SD.	46.07 ± 9.16	
Median	46.50	

Distribution of study according to patient's medical history Table (2)

Table (2): Distribution of the studied cases according to patient's medical history (n = 30)

Patient's medical history	No.	%
None	7	23.3
DM	8	26.7
HTN	11	36.7
IHD	7	23.3
Hepatic	2	6.7

According to the study and patient's medical history about 7 patients were free medical history, 8 patients were diabetic, 11 patients were hypertensive, 7 patients were ischemic heart diseases (IHD) and 2 patients were hepatic.

3) Lab investigations

a) Hemoglobin: Table (3)

On admission, it ranged from 9.0 – 14.0(g/dl) with a mean of 10.50 ± 1.43(g/ dl).

b) White cell count: Table (6)

On admission, it ranged from 4.0 – 13.0 ($x10^9$/l) with a mean of 9.10 ± 2.35($x10^9$/l).

c) Platelet count: Table (3)

On admission, it ranged from 118.0 – 432.0 ($x10^9$/l) with a mean of 256.47 ± 82.35 ($x10^9$/l).

d) Random blood sugar: Table (3)

On admission, it ranged from 90.0 – 350.0 (mg/dl) with a mean of 193.83 ± 66.53 (mg/dl).

Table (3): Descriptive analysis of the studied cases according to CBC and RBS (n = 30)

	Min. – Max.	Mean ± SD.	Median
HB (g/dl)	9.0 – 14.0	10.50 ± 1.43	10.0
WBCs ($x10^9$/l)	4.0 – 13.0	9.10 ± 2.35	9.35
PLT ($x10^9$/l)	118.0 – 432.0	256.47± 82.35	234.50
RBS (mg/dl)	90.0 – 350.0	193.83 ± 66.53	184.50

e) Na+ level: Table (4)

On admission, it ranged from 130.0 – 145.0 (mEq/l) with a mean of 135.75 ± 4.76 (mEq/l). Patients with hypernatremia have been excluded.

f) k+ level: Table (4)

On admission, it ranged from 2.90 – 4.50 (mEq/l) with a mean of 3.87 ± 0.33 (mEq/l).

Table (4): Descriptive analysis of the studied cases according to electrolytes (n = 30)

	Min. – Max.	Mean ± SD.	Median
Na (mEq/l)	130.0 – 145.0	135.75 ± 4.76	134.50
K (mEq/l)	2.90 – 4.50	3.87 ± 0.33	3.90

g) Urea: Table (5)

On admission, it ranged from 13.0 – 43.0 (mg/dl) with a mean of 34.70 ± 8.66 (mg/dl).

h) Creatinine: Table (5)

On admission, it ranged from 0.40 – 1.30 (mg/dl) with a mean of 0.97 ± 0.28 (mg/dl). Patients on hemodialysis with end-stage renal failure have been excluded.

Table (5): Descriptive analysis of the studied cases according to renal function (n = 30)

	Min. – Max.	Mean ± SD.	Median
Urea (mg/dl)	13.0 – 43.0	34.70 ± 8.66	39.50
Creatinine (mg/dl)	0.40 – 1.30	0.97 ± 0.28	0.95

4) Descriptive analysis of the studied patients according to APACHE II: Table (6)

On admission, APACHE II ranged from 19.0 – 27.0 with a mean of 22.87 ± 2.40.

Table (6): Descriptive analysis of the studied cases according to APACHE2 (n = 30)

	Min. – Max.	Mean ± SD.	Median
APACHE2	19.0 – 27.0	22.87 ± 2.40	23.0

5) Descriptive analysis of the studied patients according to ICU stay: Table (7)

In the study patient's stay in ICU ranging from 4.0 – 28.0 days with a mean of 13.80 ± 6.57.

Table (7): Descriptive analysis of the studied cases according to ICU stay (n = 30)

	Min. – Max.	Mean ± SD.	Median
ICU stay	4.0 – 28.0	13.80 ± 6.57	12.50

6) Distribution of the studied patients according to survival: Table (8)

Regarding outcome, eight patients (26.7%) died; twenty two patients (73.3%) survived.

Table (8): Distribution of the studied cases according to survival (n = 30)

Survival	No.	%
Alive	22	73.3
Die	8	26.7

7) Comparison between the studied periods according to GCS and FOUR score (n = 30): Table (9)

According to GCS, it ranged from 3.0 – 8.0 with a mean of 5.30 ± 1.68 on admission and ranged from 3.0 – 8.0 with a mean of 5.73 ± 1.78 after 24 hrs and ranged from 4.0 – 9.0 with a mean of 6.33 ± 1.63 after 48 hrs of using mannitol 20% solution.

According to FOUR score, it ranged from 4.0 – 9.0 with a mean of 6.30 ± 1.68 on admission and ranged from 4.0 – 9.0 with a mean of 6.93 ± 1.66 after 24 hrs and ranged from 5.0 – 10.0 with a mean of 7.33 ± 1.63 after 48 hrs of using mannitol 20% solution.

Table (9): Comparison between the studied periods according to GCS and FOUR score (n = 30)

	At admission	After 24 hours	After 48 hours	Fr	P
GCS					
Min. – Max.	3.0 – 8.0	3.0 – 8.0	4.0 – 9.0		
Mean ± SD.	5.30 ± 1.68	5.73 ± 1.78	6.33 ± 1.63	44.921*	<0.001*
Median	5.0	5.50	6.0		
Sig. bet. Periods	p_1=0.017*, p_2<0.001*, p_3=0.001*				
4 score					
Min. – Max.	4.0 – 9.0	4.0 – 9.0	5.0 – 10.0		
Mean ± SD.	6.30 ± 1.68	6.93 ± 1.66	7.33 ± 1.63	44.614*	<0.001*
Median	6.0	7.0	7.0		
Sig. bet. Periods	p_1=0.001*, p_2<0.001*, p_3=0.024*				

Fr: **Friedman test**, Sig. bet. Periods were done using **Post Hoc Test (Dunn's)**

p: p value for comparing between the studied periods

p_1: p value for comparing between at admission and after 24 hours

p_2: p value for comparing between at admission and after 48 hours

p_3: p value for comparing between after 24 hours and after 48 hours

*: Statistically significant at $p \leq 0.05$

8) Distribution of the studied cases according to GCS and FOUR score (n=30) Table (10)

According to GCS, after 48 hrs about twenty seven patient (90%) improved, one patient (3.3%) was stable; two patients (6.7%) were deteriorated. **Table (10)**

According to FOUR score, after 48 hrs about twenty seven patient (90%) improved, one patient (3.3%) was stable; two patients (6.7%) were deteriorated. **Table (10)**

Table (10): Distribution of the studied cases according to GCS and FOUR score (n=30)

	No.	%
GCS		
Improved	27	90.0
Stable	1	3.3
Deteriorated	2	6.7
Min. – Max.	-2.0 – 0.0	
Mean ± SD.	-1.03 ± 0.32	
Median	-1.0	
4 score		
Improved	27	90.0
Stable	1	3.3
Deteriorated	2	6.7
Min. – Max.	-2.0 – 0.0	
Mean ± SD.	-1.03 ± 0.32	
Median	-1.0	

9) Comparison between MLS on admission and after 48 hrs of using mannitol 20% solution by using transcranial U/S: Table (11)

According to transcranial U/S, MLS ranged from 0.70 – 10.0(mm) with a mean of 4.52 ± 2.55(mm) on admission and ranged from 0.50 – 9.60(mm) with a mean of 4.33 ± 2.49(mm) after 48 hrs of using mannitol 20% solution.

10) Comparison between MLS on admission and after 48 hrs of using mannitol 20% solution by using CT1: Table (11)

According to CT1, MLS ranged from 1.0 – 12.0(mm) with a mean of 5.23± 2.98(mm) on admission and ranged from 0.80 – 11.50(mm) with a mean of 5.05 ± 2.94(mm) after 48 hrs of using mannitol 20% solution.

11) Comparison between MLS on admission and after 48 hrs of using mannitol 20% solution by using CT2: Table (11)

According to CT2, MLS ranged from 1.0 – 12.0(mm) with a mean of 5.39 ± 3.0(mm) on admission and ranged from 0.80 – 11.60(mm) with a mean of 5.20 ± 2.96(mm) after 48 hrs of using mannitol 20% solution.

Table (11): Comparison between the studied periods according to US, CT1 and CT 2 (n = 30)

	At admission	After 48 hours	Z	P
US				
Min. – Max.	0.70 – 10.0	0.50 – 9.60		
Mean ± SD.	4.52 ± 2.55	4.33 ± 2.49	0.783	0.434
Median	3.70	3.60		
CT 1				
Min. – Max.	1.0 – 12.0	0.80 – 11.50		
Mean ± SD.	5.23 ± 2.98	5.05 ± 2.94	0.659	0.510
Median	4.25	3.90		
CT 2				
Min. – Max.	1.0 – 12.0	0.80 – 11.60		
Mean ± SD.	5.39 ± 3.0	5.20 ± 2.96	0.690	0.490
Median	4.50	3.90		

Z: **Wilcoxon signed ranks test** p: p value for comparing between the studied periods

30% (9/30) of patients after admission were associated with midline shift (MLS) more than 5 mm in TCUS, while 36.67% (11/30) in the 2 methods of brain CT.

TCUS and the 2 methods of brain CT showed results after 48 hrs. 26.67% (8/30) of patients were associated with MLS more than 5 mm in TCUS and the 2 methods of CT.

12) Relation between survival and APACHE II: Table (12)

The relation between APACHE II score and survival rate was statistically significant, the greater the APACHE II score the higher the mortality rate.

Table (12): Relation between survival with APACHE II

	Survival		T	P
	Alive (n = 22)	Die (n = 8)		
APACHE2				
Min. – Max.	19.0 – 25.0	20.0 – 27.0		
Mean ± SD.	22.18 ± 2.08	24.75 ± 2.31	2.901*	0.007*
Median	22.0	26.0		

t: Student t-test
p: p value for comparing between the studied periods
*: Statistically significant at $p \leq 0.05$

13) Relation between survival with ICU stay: Table (13)

The relation between ICU stay and mortality rate was statistically significant, the higher the ICU stay the higher the mortality rate.

Table (13): Relation between survival with ICU stay

	Survival		U	P
	Alive (n = 22)	Die (n = 8)		
ICU stay				
Min. – Max.	5.0 – 28.0	4.0 – 16.0		
Mean ± SD.	15.36 ± 6.73	9.50 ± 3.78	41.0*	0.027*
Median	14.50	9.0		

U: Mann Whitney test
p: p value for comparing between the studied periods
*: Statistically significant at $p \leq 0.05$

14) Correlation between ICU stay with different parameters: Table (14)

Table (14): Correlation between ICU stay with different parameters

	ICU stay	
	r_s	P
APACHE II	0.714*	<0.001*
US 48 hr.	-0.358	0.052
CT1 48 hr.	-0.372*	0.043
CT2 48 hr.	-0.387*	0.035

r_s: Spearman coefficient
*: Statistically significant at $p \leq 0.05$

There was only a positive correlation between ICU stay and APACHE II**,** there was negative correlation between ICU stay and MLS detected in CT1 after 48hrs**,** there was negative correlation between ICU stay and MLS detected in CT2 after 48hrs.

15) Agreement for U/S on admission with CT1 on admission: Table (15)

The sensitivity and specificity of US to detect a significant MLS on admission (MLS >5mm) were analysed with the ROC curve. In method (1) the area under the ROC curve was 0.981 and with a cut-off of 3.8mm, the sensitivity and specificity were 100%, 84.21% respectively with positive predictive value 78.6% and negative predictive value 100%.

Table (15): Agreement (sensitivity, specificity) for U/S on admission with CT1 on admission

	AUC	P	95% C.I		Cut off	Sensitivity	Specificity	PPV	NPV
			LL	UL					
U/S on admission	0.981*	**<0.001***	0.943	1.00	**>3.8#**	100.0	84.21	78.6	100.0

AUC: Area Under a Curvep value: Probability value
CI: Confidence Intervals Cut off was done by using Youden index
NPV: Negative predictive value PPV: Positive predictive value *: Statistically significant at $p \leq 0.05$

16) Agreement for U/S after 48 hours with CT1 after 48 hours of using mannitol 20% solution: Table (16)

The sensitivity and specificity of US to detect a significant MLS after48 hours of admission after using mannitol 20% solution (MLS >5mm) were analysed with the ROC curve. In method (1) the area under the ROC curve was 0.998 and with a cut-off of 4mm, the sensitivity and specificity were 100%, 94.74% respectively with positive predictive value 91.7% and negative predictive value 100%.

Table (16): Agreement (sensitivity, specificity) for U/S after 48 hours with CT1 after 48 hours.

	AUC	P	95% C.I		Cut off	Sensitivity	Specificity	PPV	NPV
			LL	UL					
U/S after 48 hr.	0.998*	**<0.001***	0.988	1.00	**>4#**	100.0	94.74	91.7	100.0

AUC: Area Under a Curve p value: Probability value
CI: Confidence Intervals Cut off was done by using Youden index
NPV: Negative predictive value PPV: Positive predictive value
*: Statistically significant at $p \leq 0.05$

17) Agreement for U/S on admission with CT2 on admission: Table (17)

The sensitivity and specificity of US to detect a significant MLS on admission (MLS >5mm) were analysed with the ROC curve. In method (2) the area under the ROC curve was 0.981 and with a cut-off of 3.8mm, the sensitivity and specificity were 100%, 84.21% respectively with positive predictive value 78.6% and negative predictive value 100%.

Table (17): Agreement (sensitivity, specificity) for U/S on admission with CT2 on admission

	AUC	P	95% C.I		Cut off	Sensitivity	Specificity	PPV	NPV
			LL	UL					
U/S on admission	0.981	**<0.001***	0.943	1.00	**>3.8#**	100.0	84.21	78.6	100.0

AUC: Area Under a Curvep value: Probability value
CI: Confidence Intervals #Cut off was done by using Youden index
NPV: Negative predictive value PPV: Positive predictive value
*: Statistically significant at $p \leq 0.05$
#Cut off was done by using Youden index

18) Agreement for U/S after 48 hours with CT2 after 48 hours of using mannitol 20% solution: Table (18)

The sensitivity and specificity of US to detect a significant MLS after48 hours of admission after using mannitol 20% solution (MLS >5mm) were analysed with the ROC curve. In method (2) the area under the ROC curve was 0.986 and with a cut-off of 4mm, the sensitivity and specificity were 91.67%, 94.44% respectively with positive predictive value 91.7% and negative predictive value 94.4%.

Table (18): Agreement (sensitivity, specificity) for U/S after 48 hours with CT2 after 48 hours.

	AUC	P	95% C.I		Cut off	Sensitivity	Specificity	PPV	NPV
			LL	UL					
U/S after 48 hr.	0.986	**<0.001***	0.955	1.00	>4#	91.67	94.44	91.7	94.4

AUC: Area Under a Curvep value: Probability value
CI: Confidence Intervals #Cut off was done by using Youden index
NPV: Negative predictive value PPV: Positive predictive value
*: Statistically significant at $p \leq 0.05$

4. Discussion

In most cases, patients who present with severe TBI require high levels of sedation and/or muscle relaxation to adapt properly to MV and control ICP, and access to clinical data is very limited. A transfer to the radiology department represents a life-threatening risk to these patients in some cases.

Diagnosis of MLS is important both for preventing further secondary neurological injury by early neurosurgical intervention, but also neuro-prognostication. Any amount of MLS is considered abnormal, but poor neurological outcome can be associated with a clinically significant midline shift of as little as 0.5cm (**Lau and Arntfield, 2017).**

This study was conducted on 30 severe traumatic brain injury patients 13 of them were females and 17 of them were males admitted to The Critical Care Units in Ain Shams University Hospital, intubated & mechanically ventilated, fulfilled the inclusion and exclusion criteria with a mean of age of 46.07 years.

7 patients had no past medical history, 8 patients were diabetic, 11 patients were hypertensive, 7 patients were ischemic heart disease and 2 patients were hepatic.

30% (9/30) of patients were associated with midline shift (MLS) more than 5 mm in TCUS, while 36.67% (11/30) in the 2 methods of brain CT.

Then, after 48 hrs from the administration of hyperosmolar solution (mannitol 20%) 0.25 to 2 g/kg IV over 30 min every 6-8 hrs, TCUS and the 2 methods of brain CT showed similar results. 26.67% (8/30) of patients were associated with MLS more than 5 mm in TCUS and the 2 methods of CT.

As ultrasound technology has improved, the same transcranial acoustic windows used for the doppler assessment of the cerebral circulation may also be used to achieve two-dimensional (2D) images of the brain parenchyma. Though anatomic detail is inferior to CT imaging, resolution is sufficient to answer emergent bedside questions such as mass effect leading to MLS and predict adverse outcomes after stroke (**Lau and Arntfield, 2017)**

In this study, the mean of MLS measured at admission using TCUS (4.52 ± 2.55) mm was insignificantly lower than that was measured using CT in method 1 (CT1) (5.23 ± 2.98) and that was measured using CT in method 2 (CT2) (5.39 ± 3.0).

The mean of MLS measured after the administration of mannitol 20% solution using TCUS (4.33 ± 2.49) mm was insignificantly lower than that was measured using CT in method 1 (CT1) (5.05 ± 2.94) and that was measured using CT in method 2 (CT2) (5.20 ± 2.96).

Llompart Pou et al., study in 2004 compared MLS measurements using TCUS with those obtained with cranial CT in 41 patients with TBI. The mean value of MLS measured by cranial CT was 1.6 ±2.24 mm, and obtained with TCUS was 1.5 ±2.02 mm (**Llompart et al., 2004).**

Motuel J et al., in 2014 studied 52 neurosurgical ICU patients. A MLS measurement was possible using TCUS in all 52 patients. A MLS >0.5 was observed in 25% (13/52) of the patients. The mean of MLS was 0.32 ± 0.36 using TCUS and 0.47 ± 0.67 using CT. The Pearson's correlation coefficient (r^2) between them was 0.65 (p <0.001) (**Motuel et al., 2014).**

Oliveira et al., in 2017 in a recent cross-sectional retrospective observational study compared between brain CT and TCUS in evaluation of 3rd Ventricle Width, peri-mesencephalic cistern, and sylvian fissure in TBI Patients. TCUS was performed within 6 h before a brain CT scan in 15 patients. The mean MLS using CT was 3.6 ± 4.5 mm and using TCUS was 3.3 ± 4.17 mm (p <0.01) (**Oliveira et al., 2017).**

In this study, the mean differences between CT method 1, 2 and TCUS at admission and after administration of mannitol 20% fluids were without significant difference and intra class correlation between US, CT1 show coefficient index of 95% (0.964 – 0.992) and (p <0.001) with high agreement between US and CT1 method, also intra class correlation between US and CT2 show coefficient index of 95% (0.962 – 0.991) and (p <0.001) with high agreement between TCUS and CT2 method.

In Llompart Pou et al., study, the mean difference between the two methods was 0.12 ±1.08 mm, with a 95% CI of – 0.15 to 0.41 mm (p=0.36). The coefficient of linear correlation between the two methods studied was 0.88 (p<0.0001) (**Llompart et al., 2004).**

In a recent study by Cattalani et al., 32 patients affected by chronic subdural hematoma were enrolled between July 2016 and January 2017. MLS values obtained by TCUS and brain CT were compared using Bland-Altman plot and linear regression analysis. 64 MLS values obtained before and after surgery by TCUS were comparable to those obtained by CT (**Cattalani et al., 2017).**

In Oliveira et al., study, an excellent correlation was observed between the 2 methods concerning midline structural shifts (b: 0.978, $p < 0.01$). In Oliveira et al., study, the mean difference between the CT scan and TCUS was −0.308 (95% CI: 4.42–3.80, $p = 0.57$). The agreement between the methods for both measures was excellent and no systematic bias was observed (**Oliveira et al., 2017).**

In this study, TCUS after admission was found to be an excellent tool (AUC=0.981) at a cutoff value of 3.8mm to detect MLS when compared to CT in method 1 (95%CI: 0.943 – 1.00, p<0.001). It showed a sensitivity and specificity of 100% and 84.21% respectively. Positive predictive value was 78.6% and negative predictive value was 100%. Also, it was found to be an excellent tool (AUC=0.981) at a cutoff value of 3.8 mm to detect MLS when compared to CT in method 2 (95%CI: 0.943 – 1.00, p<0.001). It showed a sensitivity and specificity of 100% and 84.21% respectively. Positive predictive value was 78.6% and negative predictive value was 100%.

Also, TCUS after the administration of mannitol 20% was found to be an excellent tool (AUC=0.998) at a cutoff value of 4 mm to detect MLS when compared to CT in method 1 (95%CI: 0.988 – 1.000, p<0.001). It showed a sensitivity and specificity of 100% and 94.74% respectively. Positive predictive value was 91.7% and negative predictive value was 100%. Also, it was found to be an excellent tool (AUC=0.986) at a cutoff value of 4 mm to detect MLS when compared to CT in method 1 (95%CI: 0.955 – 1.000, p<0.001). It showed a sensitivity and specificity of 91.67% and 94.44% respectively. Positive predictive value was 91.7% and negative predictive value was 94.4%.

In Motuel J et al., study, the bias was 0.09 and the limits of agreements were 1.10 and -0.92. The sensitivity and the specificity of TCUS to detect a significant MLS (that is, MLS >0.5 in method 2 of the CT scan) were analyzed with the ROC curve. The AUC for ROC curve was 0.86 (95% CI: 0.74- 0.94%) and, with a cut-off of 0.35, the sensitivity was 84.2% (95% CI: 60.4-96.4%), the specificity 84.8% (95% CI: 68.1-94.8%) and the positive likelihood ratio 5.56. When the CT method 1 was used, the AUC for ROC curve was 0.85 (95% CI: 0.73-0.94%) and with a cut-off of 0.30, the sensitivity was 85.7% (95% CI: 57.2-97.8%) and the specificity 84.2% (95% CI: 68.7 to 93.9%) (**Motuel et al., 2014).**

Pablo Blanco et al., (2015) in a case report of a previously healthy 46-year-old male patient who was admitted to the ICU after evacuation of a right temporal lobe hematoma. The patient developed severe intracranial hypertension and TCUS detected at the bedside a significant leftward MLS and these findings were confirmed by cranial CT. The conclusion was that TCUS was a rapid tool to detect the ICH and its related complications (**Blanco et al., 2015).**

After literature review, there are few studies about the use of mannitol 20% in control of increased intracranial pressure after severe traumatic brain injury. No studies evaluated the use of TCUS in this area. Most of studies were focused on classification of patients according to the presence or absence of MLS using the same two methods of CT used in this study, without exact determination of size of MLS. A considerable number of published studies were found to discuss the effect of mannitol 20% on midline shift in spontaneous intracerebral hemorrhage and ischemic infarction of the brain, many other studies focused on mannitol effect on cerebral blood volume and intracranial pressure.

Misra et al., studied CT proven primary supratentorial ICH patients having MLS of 3 mm, were randomized into 20% mannitol (1.5 g/kg) and control groups. 12 patients each were in mannitol and control groups. On visual analysis of magnetic resonance imaging before infusion, the evidences of herniation were found in 11 patients, which included cingulate herniation in 6, uncal in 3, cingulate and uncal in 1, and combination of cingulate, uncal and tonsillar herniation in another patient. One patient each with uncal and cingulate herniation had infarction in posterior cerebral and anterior cerebral artery territory respectively. The mean horizontal shift was 6.4 ± 2.5 (range 3.8–10.6) mm. There was no difference in the initial values of horizontal shift (t ¼ 0.36, P ¼ 0.69) (**Misra et al., 2007).**

Regarding hyperosmolar fluid limitations in this study, the hyperosmolar fluid used "mannitol 20%" showed no complications in all enrolled patients. But, evidence showed that osmotic diuretics reduce brain volume by drawing free water out of the tissue and into the circulation, where it is excreted by the kidneys, thus dehydrating brain parenchyma. The use of any osmotic agent should be carefully evaluated in patients with renal insufficiency. Useful parameters to monitor in the setting of mannitol 20% therapy include serum sodium, serum osmolality, and renal function.

Regarding technique's limitations, there were no limitations in the use of TCUS in this study. But it is known that there are some limitations due to thicker cranial vaults causing higher bone attenuation. The literature states that 5–20% of patients will have difficult views leading to un-interpretable transcranial windows and images (**White, 2006).**

MLS measurement relies heavily on finding a proper trans-temporal window. There are no data correlating angle of insonation and accuracy of TCUS midline shift measurements. The American Institute of Ultrasound in Medicine (AIUM) guidelines state that the upward angle of insonation should be no greater than 10–15°, but that may not always be possible (**AIUM practice guideline, 2012).**

Regarding mortality, there was no any significant correlation between the measured MLS in patients at admission or after the administration of mannitol 20% solution and the mortality. This may be due to the small sample size enrolled.

Kiphuth IC. et al., in 2012 studied 68 patients with spontaneous intracranial hemorrhage. TCUS was used to measure MLS upon admission and then subsequently, using serial examinations in 24-hour intervals up to day 14. Kiphuth and his colleagues showed that a MLS of 12 mm or greater on TCUS at any time indicated mortality with a sensitivity of 69%, a specificity of 100% and positive and negative predictive values of 100 and 74%, respectively **(Kiphuth et al., 2012).**

To summarize, the results obtained in this study confirmed that TCUS is a reliable technique for monitoring the effect of mannitol 20% solution on

MLS in patients with severe TBI. But, this technique is not a substitute for brain CT to determine MLS at presentation. It is especially useful in monitoring these patients after the initial CT, because it is non-invasive and easily applicable in routine practice at the patient's bedside, avoiding the risks involved in transporting the patient to the radiology department, also good predictor of survival and mortality.

Conclusions

- This study suggests that transcranial ultrasonography is comparable to computed tomography (the corner stone tool in neuroimaging) in early diagnosis and follow up of midline shift in severe traumatic brain injury after using mannitol 20% solution.
- This study suggests that transcranial ultrasonography can be used to follow up conscious level of the patients with severe traumatic brain injury through Glasgow coma score and FOUR score as there was improvement in these scores after administration of mannitol 20% solution and decrease of MLS.

Recommendations

Transcranial ultrasonography can be used in early diagnosis and monitoring of midline shift in severe traumatic brain injury.

Transcranial ultrasonography may provide a non-invasive, rapid and accurate tool that we can rely on starting an appropriate treatment plan with a less risk of transportation hazards.

References

1. AIUM practice guideline for the performance of a transcranial Doppler ultrasound examination for adults and children. J Ultrasound Med 2012; 31(9):1489-500.
2. Blanco P, Do Pico JL and Matteoda M. Intracranial hematoma and midline shift detected by transcranial color-coded duplex sonography. Am J Emerg Med 2015; 33(11):1715.e5-7.
3. Blumenfeld H. Neuroanatomy through clinical cases, Sinauer Sunderland, MA. 2002.
4. Cattalani A, Grasso VM, Vitali M, et al. Transcranial color-coded duplex sonography for evaluation of midline-shift after chronic-subdural hematoma evacuation (TEMASE): A prospective study. Clin Neurol Neurosurg 2017; 162:101-7.
5. Drake R, et al. Gray's atlas of anatomy. Philadelphia: Churchill Livingstone, Elsevier. 2008. 30(8): 1672-5.
6. Kiphuth IC, Huttner HB, Breuer L, et al. Sonographic monitoring of midline shift predicts outcome after intracerebral hemorrhage. Cerebrovasc Dis 2012; 34(4):297-304.
7. Lau VI and Arntfield RT. Point-of-care transcranial Doppler by intensivists. Crit Ultrasound J 2017; 9(1):21.
8. Llompart JA, Abadal JM, Palmer M, et al. Monitoring midline shift by transcranial color-coded sonography.
9. in traumatic brain injury. A comparison with cranial computerized tomography. Intensive Care Med 2004;
10. Misra UK, Kalita J, Vajpayee A, et al. Effect of single mannitol bolus in intracerebral hemorrhage. Eur J Neurol 2007; 14(10):1118-23.
11. Motuel J, Biette I, Srairi M, et al. Assessment of brain midline shift using sonography in neurosurgical ICU patients. Crit Care 2014; 18(6):676.
12. Oliveira RA, De Oliveira LM, Paiva WS, et al. Comparison between Brain Computed Tomography Scan and Transcranial Sonography to Evaluate Third Ventricle Width, Peri-Mesencephalic Cistern, and Sylvian Fissure in Traumatic Brain-Injured Patients. Front Neurol 2017; 8:44.
13. White H and Venkatesh B. Applications of transcranial Doppler in the ICU: a review. Intensive Care Med 2006; 32(7):981-94.

3/10/2019