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Monitoring the effect of hyperosmolar solutions on brain midline shift using transcranial ultrasonography in severe traumatic brain injury

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Abstract

***Objective*: To assess the effect of hyperosmolar solutions on brain midline shift (MLS) using transcranial ultrasonography in patients with severe traumatic brain injury (TBI).**

***Design*: A prospective observational study.**

***Setting*: Critical Care Medicine Units at Kafr El-Dawar General Hospital, Beheira Health Directorate.**

***Patients and participants*: A total of 55 patients with severe TBI (Glasgow Coma Scale [GCS] score of 3-8) and evidence of MLS on brain computed tomography (CT) were enrolled. Patients with brain midline shift due to other causes, end-stage renal disease requiring hemodialysis, hypernatremia (serum Na≥150 mEq/l), clinical signs of brain death, or age below 18 years were excluded.**

***Interventions*: MLS was measured using transcranial sonography at admission and repeated 48 hours after administering hyperosmolar solutions. The results were compared with brain CT findings obtained at the same time points using two measurement methods.**

***Measurements and results*: The negative difference in MLS between ultrasound (U/S) and CT method I showed a mean positive predictive value (PPV) of 75% and a mean negative predictive value (NPV) of 90.32%. The sensitivity of CT in diagnosing MLS using method I was 85.71%, while the specificity was 82.35%. In comparison, the negative difference in MLS between U/S and CT method II demonstrated a mean PPV of 83.33% and a mean NPV of 77.42%. The sensitivity of CT in diagnosing MLS using method II was 74.07%, while the specificity was 85.71%.**

***Conclusions*: Ultrasonography provides comparable accuracy to CT in diagnosing midline shift in severe TBI patients. However, it offers advantages such as reduced radiation exposure and minimized patient transport burden, making it a safer and more accessible alternative in critical care settings.**

Keywords: Traumatic brain injury, brain sonography, midline shift, hyperosmolar solution.

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Introduction

Severe traumatic brain injury (TBI) accompanied by a midline shift (MLS) of the brain constitutes a critical, life-threatening condition necessitating urgent diagnostic evaluation and prompt medical intervention. (1)The diagnosis of severe TBI is contingent upon a Glasgow Coma Scale (GCS) score within the range of 3 to 8. (2)

TBI is broadly categorized into two distinct phases: primary and secondary injury. Primary injury encompasses the immediate structural damage to the brain parenchyma, including neuronal tissue and

blood vessels, occurring at the moment of impact. In contrast, secondary brain injury arises from a cascade of pathophysiological processes, including cerebral edema, intracranial hematomas, hydrocephalus, vasospasm, metabolic disturbances, infections, elevated intracranial pressure, and seizures. (3)

When the MLS exceeds 1 cm, the risk of mortality doubles. (4) An MLS greater than 0.5 cm, as detected on the initial brain CT scan, has been identified as a predictor of poor neurological outcomes. (1)

Extensive research has established that implementing evidence-based standardized protocols in the management of severe TBI is associated with enhanced clinical outcomes. These studies have reported that guideline-based management protocols were associated with better functional outcomes, reduced mortality rates, lower healthcare costs, and shorter hospital stays. (5)

The objective of this study was to investigate the effect of hyperosmolar therapy on brain MLS in severe TBI patients, utilizing transcranial ultrasonography for assessment.

Patients and methods

This prospective study included 55 patients admitted to the Critical Care Medicine Units at Kafr El-Dawar General Hospital, Beheira Health Directorate, with severe TBI and a GCS score of 3-8 at the time of admission, accompanied by radiological evidence of MLS on brain CT. The study was done after being approved by the Institutional Review Board, Faculty of Medicine, Cairo University (Approval no: CMDRF132701). Given the critical condition of the patients, written informed consent was obtained from their legal guardians or next of kin before study enrollment.

Patients were excluded if their MLS was due to other causes, such as brain tumors, or if they were on hemodialysis for end-stage renal disease, had hypernatremia (serum Na≥150 mEq/l), had a physical examination consistent with brain death, or were under 18 years of age.

The baseline characteristics of all patients, including sex, age, past medical history, vital signs, Acute Physiology and Chronic Health Evaluation (APACHE) II score, GCS, and Full Outline of UnResponsiveness (FOUR) score, were carefully recorded upon admission.

Radiological investigations

Ultrasonography

Using transcranial sonography (TCS), MLS was measured through the temporal acoustic bone window with a low-frequency (2-4 MHz) probe, integrated into an EMP 2100 ultrasound system (Shenzhen Emperor Electronic Technology Co., Ltd., China). Measurements were conducted at the earliest possible time following brain CT.

The third ventricle presented as a double hyperechogenic signal located above the midbrain. Bilateral measurements were taken from the external bone table to the midpoint of the third ventricle, with MLS calculated as half the difference between these two values.

On admission, MLS was measured using TCS and re-evaluated 48 hours post-treatment with hyperosmolar solutions. The findings were subsequently correlated with brain CT scans performed at baseline and 48-hour follow-up.

Computed tomography

Brain CT examinations were performed upon hospital admission and repeated after 48 hours of hyperosmolar therapy in patients with documented brain edema and MLS.

CT-based MLS assessment was performed using two established methods: 1) Measuring the distance from the external bone table to the center of the third ventricle at the orbito-meatal plane, mirroring the transcranial sonographic measurement reference; and 2) Measuring the deviation of the septum pellucidum from the theoretical midline, a standard neuroradiological technique.

Biochemical analysis

A panel of routine laboratory investigations was performed, encompassing complete blood count (CBC), serum electrolytes (sodium [Na] and potassium [K]), blood urea nitrogen (BUN), random blood glucose, and creatinine levels.

Statistical analysis

Statistical analyses were conducted using SPSS software, version 16 (SPSS Inc., Chicago, IL, USA). Categorical variables were summarized as frequencies and percentages, whereas continuous variables were reported as mean±standard deviation (SD) for normally distributed data or as median with interquartile range (IQR) and range for non-normally distributed data. Comparisons between categorical variables were performed using either the chi-square test (χ^2) or Fisher's exact test (FET), as appropriate. Cohen's kappa coefficient was employed to evaluate inter-rater agreement. The assumption of normality was assessed using the Shapiro-Wilk test, with a p-value >0.05 indicating a normal distribution. Parametric comparisons of normally distributed variables were carried out using

the Student's t-test, whereas non-parametric data were analyzed via the Mann-Whitney U test. For multiple group comparisons, the Kruskal-Wallis test was applied, followed by Bonferroni post hoc analysis when necessary. Correlations between variables were determined using Spearman's rank correlation coefficient. The predictive accuracy of ultrasonographic MLS changes in relation to CT brain findings was examined through receiver operating characteristic (ROC) curve analysis, with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) being calculated. A p-value <0.05 was considered indicative of statistical significance.

Results

Thirty-nine of the patients were male (39/55, 70.9%), while 16 were female (16/55, 29.1%), resulting in a male-to-female ratio of 2.4:1. Statistical analysis revealed a predominance of males, which is likely due to their higher exposure to trauma as a result of greater physical activity. The patients' ages ranged from 21 to 61 years, with a mean age of 41.22±10.86 years.

The APACHE score was assessed at admission and ranged from 5 to 15, with a mean score of 9.62±2.28. The GCS score at admission ranged from 3 to 8, with a mean score of 5.93±1.37. After 48 hours of hyperosmolar therapy, it ranged from 3 to 10, with a mean score of 6.89±1.61. Statistical analysis revealed a significant improvement in the GCS score following hyperosmolar therapy (p<0.001). The FOUR score at admission ranged from 1 to 10, with a mean score of 5.84±2.46. After 48 hours of hyperosmolar therapy, it ranged from 1 to 12, with a mean score of 7.35±2.61. Statistical analysis indicated an improvement in the FOUR score after 48 hours of hyperosmolar therapy.

Using ultrasonography (U/S), the MLS at admission ranged from 1.1 to 16 mm, with a mean shift of 6.55±3.64 mm. After 48 hours of hyperosmolar therapy, it ranged from 0.6 to 14.1 mm, with a mean shift of 5.62±3.35 mm. Statistical analysis revealed a significant reduction in MLS following hyperosmolar therapy (p<0.001) (**Table 1**).

Evaluation of MLS using CT method I (CT I) at admission showed a range of 1.0 to 15.9 mm, with a mean shift of 6.48±3.62 mm. After 48 hours of hyperosmolar therapy, MLS ranged from 0.6 to 14.1 mm, with a mean shift of 5.49±3.24 mm. Statistical analysis confirmed a significant reduction in MLS after hyperosmolar therapy (p<0.001). Similarly, MLS assessed using CT method II (CT II) at admission ranged from 1.0 to 15.9 mm, with a mean shift of 6.48±3.62 mm. After 48 hours of hyperosmolar therapy, it ranged from 0.6 to 14.1 mm, with a mean shift of 5.49±3.24 mm, again demonstrating a significant reduction (p<0.001) (**Table 1**).

The change in MLS measured by U/S ranged from -6.0 to 0.0 mm, with a mean change of -0.94±1.01 mm. Using CT I, the change in MLS ranged from -5.0 to 0.0 mm, with a mean change of -0.99±1.09 mm. With CT II, the change ranged from -5.0 to 0.0 mm, with a mean shift change of -1.04±1.11 mm. Statistical analysis revealed no significant differences between the change in MLS measured by U/S and CT I (p=0.796), between U/S and CT II (p=0.658), or between CT I and CT II (p=0.879) (**Table 2**).

When comparing the negative MLS difference between U/S and CT I, a negative difference of >1 mm occurred in both U/S and CT in 18 cases (32.73%). A negative difference of >1 mm in U/S but ≤1 mm in CT I occurred in 6 cases (10.91%). A negative difference of ≤1 mm in U/S but >1 mm in CT I occurred in 21 cases (38.18%). A negative difference of ≤1 mm in both U/S and CT I occurred in 28 cases (50.91%). The PPV of CT ranged from 58.7% to 86.36%, with a mean PPV of 75%. The NPV ranged from 76.39% to 96.42%, with a mean NPV of 90.32%. The sensitivity of CT in diagnosing MLS using method I was 85.71%, while the specificity was 82.35% (**Table 3**).

Similarly, when comparing the negative MLS difference between U/S and CT II, a negative difference of >1 mm occurred in both U/S and CT in 20 cases (36.36%). A negative difference of >1 mm in U/S but ≤1 mm in CT II occurred in 4 cases (7.27%). A negative difference of ≤1 mm in U/S but >1 mm in CT II occurred in 7 cases (12.73%). A negative difference of ≤1 mm in both U/S and CT II occurred in 28 cases (50.91%). The PPV of CT II ranged from 66.26% to 92.72%, with a mean PPV of 83.33%. The NPV ranged from 64.03% to 86.85%, with a mean NPV of 77.42%. The sensitivity of CT in diagnosing MLS using method II was 74.07%, while the specificity was 85.71% (**Table 4**).

Discussion

Our study suggested that brain MLS could be detected by ultrasound with reasonable accuracy in severe TBI patients in the intensive care unit (ICU). This approach may facilitate early diagnosis and treatment, thereby reducing the secondary risks associated with patient transfer to the radiology department for MLS assessment via CT, which, in some cases, could pose a life-threatening risk.

According to Gerriets et al. (6) , an MLS exceeding 0.4 cm, as measured via ultrasound within the initial 32-hour period, was linked to an almost certain mor-

tality outcome. A follow-up study by the same investigators, published in 2001, yielded comparable results, further substantiating this association.

In our study, MLS was detected using ultrasound with a mean shift of 6.55±3.64 mm, showing no statistically significant difference when compared to CT measurements, which had a mean shift of 6.48±3.62 mm.

In 2006, Tang et al. (7) investigated 51 patients with spontaneous supratentorial intracerebral hemorrhage (ICH) using both CT and transcranial color-coded sonography (TCCS) within the first 12 hours of presentation. The MLS measurements obtained via TCCS (mean±SD = 3.2±2.6 mm) demonstrated a strong correlation with those acquired through CT (3.0±2.4 mm), yielding a correlation coefficient of γ=0.91 ($p<0.01$). (8)

This finding aligned with our study, as the correlation between MLS measured by TCCS (mean±SD = 6.55±3.64 mm) and CT (6.48±3.62 mm) was also high.

In 2004, Llompart et al. (8) evaluated 41 patients with TBI (35 men and 6 women) using CT and TCCS. The correlation coefficient between MLS measured by CT and TCCS was 0.88, with a bias of 0.12 mm, a precision of 1.08 mm, and agreement limits ranging from +2.33 to -2.07 mm. No statistically notable variations were observed in MLS measurements based on age, sex, or type of lesion.

This finding was consistent with our study, which detected no meaningful statistical disparities in MLS measurements between the two techniques concerning age, sex, or type of lesion. However, our study included a larger number of patients.

In 2000, Bertram et al. (9) assessed 21 patients with space-occupying ischemic middle cerebral artery infarction and brain hemorrhage using TCCS within 2 hours before or after follow-up cranial CT scans. The mean absolute difference between MLS measurements by TCCS and cranial CT was 1.1 mm (SD=1.46 mm), with a linear correlation coefficient of R=0.94.

This study aligned with our findings; however, in Bertram et al.'s study, (9) MLS was measured once and compared with CT, whereas in our study, MLS was evaluated using both CT and ultrasound before and after mannitol administration.

In their study, Motuel et al. (10) assessed MLS among 52 neurosurgical ICU patients using both TCS and CT. The mean±SD MLS values recorded were 0.32±0.36 cm for TCS and 0.47±0.67 cm for CT. A Pearson correlation coefficient (r^2) of 0.65 ($p<0.001$) indicated a strong association between the two imaging modalities. The bias was estimated at 0.09 cm, with agreement limits extending from -0.92 cm to 1.10 cm. The ROC analysis showed that TCS had an area under the curve (AUC) of 0.86 (95% CI: 0.74-0.94) for detecting significant MLS. With a threshold of 0.35 cm, the sensitivity and specificity were 84.2% and 84.8%, respectively, and the positive likelihood ratio was 5.56.

This study correlated with our findings, but we further compared the negative difference in MLS between ultrasound and CT using two methods. The sensitivity of CT in diagnosing MLS using method I was 85.71%, with a specificity of 82.35%, whereas for method II, sensitivity was 74.07% and specificity was 85.71%.

Oliveira et al. (11) studied 15 consecutive patients (80% male, mean age 42±23 years, mean Glasgow Coma Scale score of 5). The mean discrepancy between MLS measurements obtained via brain CT scan and TCCS was 0.30±2.1 mm, with an intraclass correlation coefficient (ICC) of 0.93 ($p<0.01$). Additionally, a strong correlation was noted between both techniques in evaluating third ventricle width, as indicated by an ICC of 0.88 ($p<0.01$). Agreement analysis using Bland-Altman plots did not reveal any systematic bias. TCCS exhibited high accuracy in predicting non-compressed perimesencephalic cisterns (AUC: 0.83, 95% CI: 0.46-1.0) and reliably identified the Sylvian fissure on CT scans (AUC: 0.91, 95% CI: 0.73-1.0).

Cattalani et al. (12) examined 32 patients with chronic subdural hematoma. MLS measurements obtained pre- and post-operatively using transcranial ultrasound (TCUS) closely matched those from CT scans, as evidenced by Bland-Altman plots and linear regression analysis. A total of 64 paired MLS values from TCUS and CT were evaluated. The Bland-Altman analysis showed no systematic bias, while linear regression indicated a significant correlation between the two modalities before and after hematoma evacuation.

Their study utilized Bland-Altman diagrams, similar to ours, and reported a significant correlation between the two methods before and after intervention. However, the key difference between the two studies is that Cattalani et al. (12) measured MLS before and after hematoma evacuation, whereas our study assessed MLS before and after the administration of hypertonic solutions.

This investigation was limited by the relatively low number of enrolled patients and the deliberate exclusion of pediatric subjects.

Conclusions

Ultrasonography provides comparable diagnostic accuracy to CT scans in detecting midline shifts in severe TBI cases. However, ultrasonography offers

the advantages of reduced radiation exposure and minimized patient transport burden.

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Table 1. Comparison of MLS at admission and after 48 hours of hyperosmolar therapy using ultrasound and CT (two methods) in study patients (n=55)

Methods	Midline shift (mm)		p
	At admission	48 hours after hyperosmolar therapy	
U/S	1.10-16.00 6.55±3.64	0.60-14.10 5.62±3.35	<0.001*
CT I	1.00-15.90 6.48±3.62	0.60-14.10 5.49±3.24	<0.001*
CT II	1.00-15.90 6.48±3.62	0.60-14.10 5.49±3.24	<0.001*

Legend: MLS=midline shift; CT=computed tomography; U/S=ultrasound; CT I=CT method I; CT II=CT method II.
Data were presented as range and mean±standard deviation and were tested by paired t-test.
*Statistically significant at $p<0.05$.

Table 2. Comparison between different methods of diagnosis of MLS (U/S, CT I, and CT II) after 48 hours of using hyperosmolar therapy in cases of the study

Methods	Change in MLS (mm)	p1	p2	p3
U/S	-6.00-0.00 -0.94±1.01	0.879	0.796	
CT I	-5.00-0.00 -0.99±1.09			0.658
CT II	-5.00-0.00 -1.04±1.11		0.796	

Legend: MLS=midline shift; U/S=ultrasound; CT I=computed tomography method I; CT II= computed tomography method II; p1=p-value for the comparison between U/S and CT I; p2=p-value for the comparison between U/S and CT II; p3=p-value for the comparison between CT I and CT II.
Data were presented as range and mean±standard deviation.

Table 3. Agreement between MLS negative difference by U/S and CT I

MLS negative difference		By CT I		
		>1 mm	≤1 mm	Total
By U/S	>1 mm, n (%)	18 (32.73%)	6 (10.91%)	24 (43.64%)
	≤1 mm, n (%)	3 (5.45%)	28 (50.91%)	31 (56.36%)
	Total, n (%)	21 (38.18%)	34 (61.82%)	55 (100.0%)
p-value		<0.001*		
Sensitivity		85.71%		
Specificity		82.35%		
PPV, mean (range)		75.00% (58.70% to 86.36%)		
NPV, mean (range)		90.32% (76.39% to 96.42%)		

Legend: MLS=midline shift; U/S=ultrasound; CT I=computed tomography method I; PPV=positive predictive value; NPV=negative predictive value.
*Statistically significant at $p<0.05$.

Table 4. Agreement between MLS negative difference by U/S and CT II

MLS negative difference		By CT II		
		>1 mm	≤1 mm	Total
By U/S	>1 mm, n (%)	20 (36.36%)	4 (7.27%)	24 (43.64%)
	≤1 mm, n (%)	7 (12.73%)	24 (43.64%)	56.36 (56.36%)
	Total, n (%)	27 (49.09%)	28 (50.91%)	55 (100.00%)
p-value		<0.001*		
Sensitivity		74.07%		
Specificity		85.71%		
PPV, mean (range)		83.33% (66.26-92.72%)		
NPV, mean (range)		77.42% (64.03-86.85%)		

Legend: MLS=midline shift; U/S=ultrasound; CT II=computed tomography method II; PPV=positive predictive value; NPV=negative predictive value.
*Statistically significant at $p<0.05$.

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