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Relationship of the optic nerve sheath diameter and repeated invasive intracranial pressure measures in traumatic brain injury patients; a diagnostic accuracy study

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Abstract: **Objective:** The purpose of this study was to quantitatively evaluate if the use of the optic nerve sheath diameter (ONSD) can be a suitable noninvasive surrogate approach for repeated invasive intracranial pressure (ICP) measures.

Methods: The study used a sample of 22 adult patients with traumatic brain injury (TBI) from an in intensive care unit (ICU). ICP levels were measured using the gold standard and recorded in cmH20. ONSD was measured using ultrasonography with 5.6-5.7 MHz linear probe and recorded in millimeters. The data analysis was done using STATA software version 15.

Results: The results showed a strong positive correlation between ICP and ONSD (r = 0.743, p = 0.001). The accuracy of the sonographic ONSD declined over time, starting from a high of 90.9% at the baseline and declining to a low of merely 20.0% after 48 hours.

Conclusion: These findings indicate that the ONSD approach could be very useful alternative and noninvasive method for monitoring ICP.

Keywords: Intracranial Pressure; Optic Nerve; Point-of-Care Systems; Ultrasonography

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1. Introduction

Increased intracranial pressure (ICP) is a challenging and potentially fatal complication of traumatic brain injury (TBI) (1,2). Although, invasive intraventricular monitoring is still the gold standard for measuring ICP, due to the several complications associated with intraventricular catheter placement, including difficulty in catheter placement, bleeding, and infection, non-invasive methods for accurate ICP monitoring are sought (3-7). Measurement of optic nerve sheath diameter (ONSD) is among the non-invasive ICP measurement methods that have been introduced in this regard. The optic nerve, as part of the central nervous system, is covered by the leptomeninges, which extend to the anterior part behind the globe (8-10). As the ICP rises, cerebrospinal fluid (CSF) travels to small edges of the subarachnoid space, which is pressed between the sheath and the nerve, causing the dura to expand. These changes are more pronounced in the anterior part of the nerve behind the globe (11). Ultrasound has been shown to enable rapid detection of elevated intracerebral pressures through measuring the ONSD, in which ONSD more than 5 mm at 2 mm distance from retina indicates elevated ICP. Assessing the ONSD using ultrasound is a non-invasive, feasible, and reliable method for measuring ICP in patients with severe TBI (12-14). However, the amount of changes in the ONSD with changes in ICP has been less considered in previous studies, and even unsuitability for continuous measurements has been mentioned as its main drawback (15); but we believed that more evidence was needed to refute or confirm such assertion. Therefore, this study was to quantitatively evaluate if the use of the ONSD can be a suitable noninvasive surrogate approach for repeated invasive ICP measures in TBI patients admitted in the intensive care unit (ICU).

2. Methods

2.1. Study design and setting

This diagnostic accuracy study was conducted from April to September 2018 in the ICU of Sina Hospital, Tehran, Iran. This study was not associated with serious ethical challenges and conducting the current study caused no interference in the course of treatment of the patients. This study also did not impose additional costs on patients. In addition, this study was ethically evaluated and approved in the Tehran University of Medical Sciences (TUMS) ethics committee in research (IR.TUMS.MEDICINE.REC.1396.4137).

2.2. Study population

Based on the supervisor's opinion and considering the limitations of the study for invasive ICP monitoring, both in performing and in supplying equipment for invasive ICP monitoring in our hospital, 22 adult patients with TBI, of both sexes with Glasgow Coma Score (GCS) ≤ 8 were included. Patients with globe trauma were excluded.

2.3. ICP measurement

In the first 48 hours after trauma, ICP of the patients was measured using intraventricular catheter placement as the gold standard method. ICP measures were recorded in cmH_2O. Simultaneously, ONSD was measured by a trained person using an ultrasound device model SonoSite M-Turbo with 5-10 MHz linear probe. ONSDs were recorded in millimeter.

2.4. Data collection

A researcher-made checklist was used for collecting data. The checklist was completed by an ICU fellowship and contained: sheet number, admission number, demographic data including: age, sex and weight, admission date, death data, on arrival GCS, the Sequential Organ Failure Assessment (SOFA) score, the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system, and cerebrospinal fluid (CSF) analysis - if obtained. Other variables included ONSD, ICP, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and arterial blood gas (ABG), which were recorded on arrival to ICU and 8, 16, 24, 32, 40 and 48 hours after admission.

2.5. Statistical analysis

The quantitative data were reported as mean with standard deviation (SD) and qualitative data were described as frequency with percentage. Due to the different scales, the standardized Z-score was calculated to compare the score as well as the agreement between the ICP (cmH_2O) and sonographic ONSD (mm). The Bland-Altman plot was used to measure the agreement between the two approaches. To construct a Bland-Altman plot, the Z-score difference between the two approaches was plotted on the y-axis against the Z-score of ICP on the x-axis. Since the standardized Z-score was used to check the agreement, we used the 95% limits of agreement (LoA) overall and at different times during the follow-up. Also, the correlation of ICP and sonographic ONSD was evaluated using Pearson's correlation coefficient overall and at different times during the follow-up.

The ICP>18 cmH_2O that was measured via invasive ICP monitoring was considered as the gold standard cut-off point. The accuracy of sonographic ONSD compared with the gold standard was assessed using Receiver Operating Characteristic (ROC) curve analysis and sensitivity, specificity, negative and positive likelihood ratio (NLR and PLR), and negative and positive predictive value (NPV and PPV) with 95% confidence interval were calculated for different cut-off points. The best cut-off point of sonographic ONSD for diagnosis of elevated ICP was selected using the J-Youden statistics. These analyses were performed using STATA software version 15.

3. Results

In total, 22 cases with the mean age of 53.41 (SD=19.06) years were enrolled, 13 (59.1%) of whom were male. The mean ICP was 27.32 (SD=4.16) cmH_2O in baseline and decreased to 17.91 (SD=1.51) after 48 hours. Also, the mean sonographic ONSD was 5.22 (SD=0.29) mm in baseline and decreased to 4.42 (SD=0.28) after 48 hours (Table 1). The decrease in ICP and sonographic ONSD during the follow-up time was statistically significant (P<0.001).

The 95% limits of agreement (LoA), based-on the Bland-Altman method for standardized z-score, was -1.41 to 1.40 during the whole follow-up time. This analysis showed that the agreement between ICP and sonographic ONSD in higher values of ICP was more than that in lower values (Figure 1). Also, analysis based on follow-up time showed that the LoA in initial follow-up times (±0.96 in baseline) was lower than the final times (±2.7 in after 48h). So, the agreement between ICP and ONSD in the initial follow-up times was higher than the final times (Table 1).

The correlation between ICP and sonographic ONSD during the whole follow-up time was 0.743 (P<0.001). This correlation was significant and higher in initial follow-up times compared to the final times. So, the correlation was 0.879 and 0.695 in baseline and after 8 hours, respectively, and reached 0.240 and 0.026 after 40 and 48 hours, respectively (Figure 2).

The area under the ROC curve (AUC- ROC) of sonographic ONSD based on ICP>18, as the gold standard, was 0.798 (95%CI: 0.727 to 0.868) during the whole follow-up time. The AUC- ROC in the initial follow-up times (0.913 in after 8h) were higher than the final times (0.429 in after 48h).

The best cut-off point for sonographic ONSD was >4.89 mm with 66.29% sensitivity and 89.23% specificity (Table 2). The accuracy of sonographic ONSD in this cut-off point (>4.89 mm) in the initial follow-up times (90.9% in baseline and 81.8% after 8h) was higher than the final times (77.3% in after 48h). Also, the sensitivity of ONSD in the initial follow-up times (90.9% in baseline and 80.0% in after 8h) was higher than the final times (20.0% in after 48h) (Table 3).

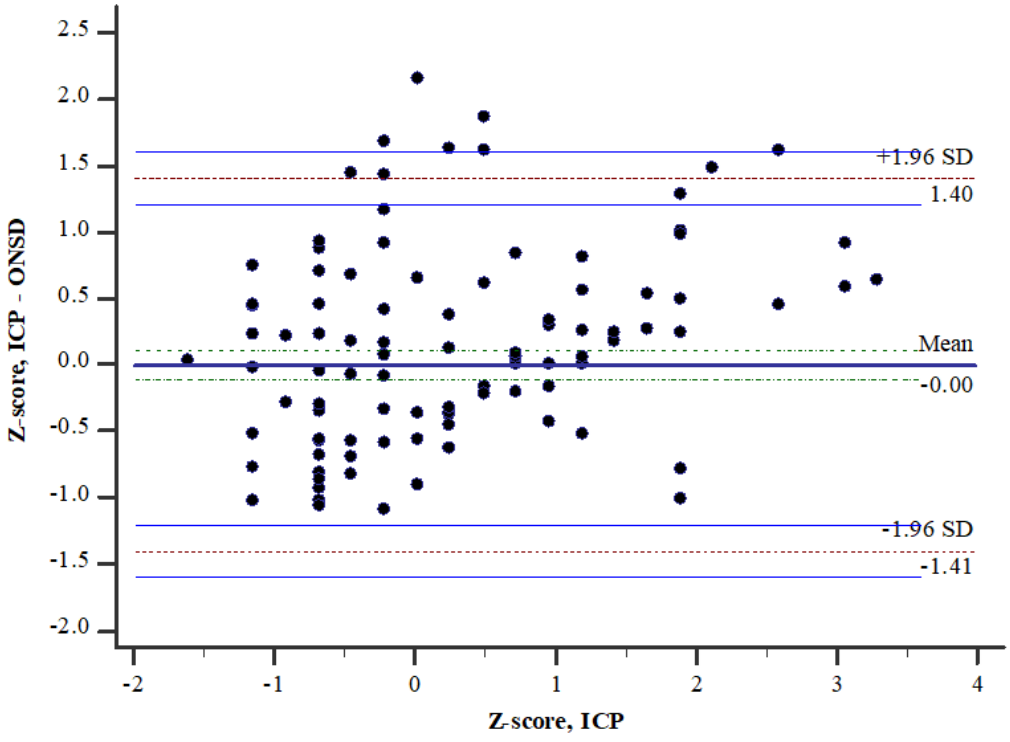

Figure 1 Bland-Altman plot with 95% limits of agreement for standardized Z-score values of intracranial pressure (ICP) and optic nerve sheath diameter (ONSD) in patients with severe traumatic brain injury throughout the follow-up time

Table 1 The distribution of intracranial pressure (ICP) and optic nerve sheath diameter (ONSD) and agreement between them in patients with severe traumatic brain injury

Follow-up time	ICP (cm H_2O)		ONSD (mm)		95% limits of agreement*
	Min-Max	Mean (SD)	Min-Max	Mean (SD)	
Baseline	20.0-35.0	27.32 (4.16)	4.64-5.80	5.22 (0.29)	-0.96 to 0.97
After 8h	18.0-29.0	23.73 (3.63)	4.50-5.90	5.03 (0.33)	-1.53 to 1.53
After 16h	18.0-30.0	20.91 (2.86)	4.10-5.03	4.79 (0.27)	-2.1 to 2.1
After 24h	16.0-27.0	19.45 (2.94)	4.0-5.22	4.70 (0.30)	-2.1 to 2.1
After 32h	16.0-25.0	19.05 (2.57)	3.90-5.10	4.59 (0.33)	-2.3 to 2.3
After 40h	14.0-20.0	18.00 (1.31)	4.0-4.85	4.48 (0.27)	-2.4 to 2.4
After 48h	16.0-22.0	17.91 (1.51)	4.0-4.90	4.42 (0.27)	-2.7 to 2.7

*Based on the Bland-Altman method for standardized z-score, h: Hours, SD: Standard deviation.

Table 2 The accuracy of sonographic optic nerve sheath diameter in diagnosis of elevated invasive intracranial pressure measures in patients with severe traumatic brain injury

Cut-off	Sensitivity	Specificity	PLR	NLR	PPV	NPV
			(95% CI)			
>4.6	77.53 (67.4 - 85.7)	61.54 (48.6 - 73.3)	2.02 (1.5 - 2.8)	0.37 (0.2 - 0.6)	73.4 (63.3 - 82.0)	66.7 (53.3 - 78.3)
>4.64	76.40 (66.2 - 84.8)	63.08 (50.2 - 74.7)	2.07 (1.5 - 2.9)	0.37 (0.2 - 0.6)	73.9 (63.7 - 82.5)	66.1 (53.0 - 77.7)
>4.7	71.91 (61.4 - 80.9)	67.69 (54.9 - 78.8)	2.23 (1.5 - 3.2)	0.41 (0.3 - 0.6)	75.3 (64.7 - 84.0)	63.8 (51.3 - 75.0)
>4.8	67.42 (56.7 - 77.0)	84.62 (73.5 - 92.4)	4.38 (2.4 - 7.9)	0.39 (0.3 - 0.5)	85.7 (75.3 - 92.9)	65.5 (54.3 - 75.5)
>4.85	66.29 (55.5 - 76.0)	87.69 (77.2 - 94.5)	5.39 (2.8 - 10.5)	0.38 (0.3 - 0.5)	88.1 (77.8 - 94.7)	65.5 (54.6 - 75.4)
>4.89*	66.29 (55.5 - 76.0)	89.23 (79.1 - 95.6)	6.16 (3.0 - 12.6)	0.38 (0.3 - 0.5)	89.4 (79.4 - 95.6)	65.9 (55.0 - 75.7)
>4.9	55.06 (44.1 - 65.6)	100.00 (94.5 - 100)	-	0.45 (0.4 - 0.6)	100.0 (92.7 - 100)	61.9 (51.9 - 71.2)

*Best cut-off point, CI: Confidence interval, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value.

4. Discussion

The results of the current study show a significant statistical correlation between the ONSD and ICP levels in TBI patients. The findings of this study illustrate a strong positive correlation between the ICP levels and ONSD from the baseline. This correlation declines over time as the follow-up

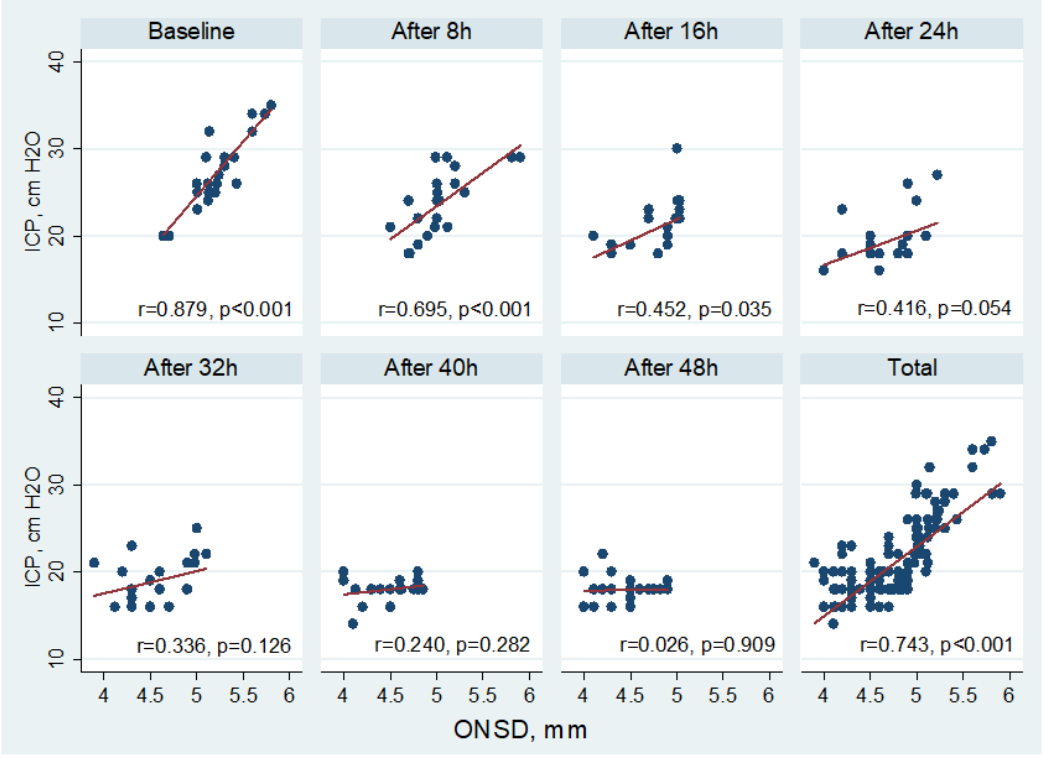

Figure 2 The correlation of intracranial pressure (ICP) and sonographic optic nerve sheath diameter (ONSD) in patients with severe traumatic brain injury based on follow-up time

Table 3 The accuracy indices of sonographic optic nerve sheath diameter (ONSD) (>4.89 mm) compared with intracranial pressure (ICP)>18 (as gold standard) in diagnosis of elevated invasive intracranial pressure measures in patients with severe traumatic brain injury

Time	ICP			AUC-ROC*	Accuracy	Sesitivity	Spesificity	PLR	NLR	PPV	NPV
	ONSD	N	P		(95% CI)						
Baseline	N	-	2	NA	90.9 (70.8, 98.9)	90.9 (70.8, 98.9)	-	-	-	100 (83.2, 100)	-
	P	-	20								
After 8h	N	2	4	0.913 (0.790, 1.0)	81.8 (59.7, 94.8)	80.0 (56.3, 94.3)	100 (15.8, 100)	-	0.20 (0.08, 0.5)	100(79.4, 100)	33.3 (4.3, 77.7)
	P	0	16								
After 16h	N	5	5	0.747 (0.543, 0.951)	77.3 (54.6, 92.2)	70.59 (44.0, 89.7)	100 (47.8, 100)	-	0.29 (0.1, 0.6)	100 (73.5, 100)	50.0 (18.7, 81.3)
	P	0	12								
After 24h	N	9	4	0.654 (0.395, 0.913)	63.6 (40.7, 82.8)	55.56 (21.2, 86.3)	69.23 (38.6, 90.9)	1.81 (0.7, 4.9)	0.64 (0.3, 1.5)	55.6 21.2, 86.3)	69.2 (38.6, 90.9)
	P	4	5								
After 32h	N	10	5	0.621 (0.360, 0.882)	68.2 (45.1, 86.1)	50.0 (18.7, 81.3)	83.33 (51.6, 97.9)	3.0 (0.7, 12.3)	0.60 (0.3, 1.2)	71.4 (29.0, 96.3)	66.7 (38.4, 88.2)
	P	2	5								
After 40h	N	16	6	0.510 (0.188, 0.832)	72.7 (49.8, 89.3)	0.0 (0.0, 45.9)	100 (79.4, 100)	-	1.0 (1.0, 1.0)	-	72.7 (49.8, 89.3)
	P	-	-								
After 48h	N	16	4	0.429(0. 112, 0.746)	77.3 (54.6, 92.2)	20.0 (0.5, 71.6)	94.12 (71.3, 99.9)	3.40 (0.3, 45.2)	0.85 (0.5, 1.3)	50.0 (1.3, 98.7)	80.0 (56.3, 94.3)
	P	1	1								

* AUC-ROC calculated based on numerical value of ONSD compared with ICP>18 (as gold standard). AUC-ROC: Area under the receiver operating characteristic curve, CI: Confidence interval, h: Hours, N:Negative, NA: Not applicable, NLR: Negative likelihood ratio, NPV: Negative predictive value, PLR: Positive likelihood ratio, P: Positive, PPV: Positive predictive value.

times progress from the baseline to 48 hours, with the correlation being the weakest at the 48th hour. The overall correlation, as seen in figure 1 in the results section, indicates an overall strong positive correlation between ICP and ONSD. The study findings further indicated that the accuracy of the ONSD in predicting ICP declines over time from the baseline, with the baseline's accuracy being 90.9% with a sensitivity of 66.29% and specificity of 89.23%, and declining over the testing period to reach a low of an accuracy of 20.0% at the 48th hour. Many conditions may come into play to lower the levels of ICP following a severe TBI, and current literature shows that measurements of ICP should decline as time passes from the occurrence of severe TBI (16).

Consequently, the findings of this study are consistent with current literature and more importantly, they show that ONSD measurement can be a reliable non-invasive approach for use as a surrogate method for the monitoring of ICP. In order to be considered a reliable alternative for the continuous monitoring of ICP, ONSD must produce results that are consistent with those of the invasive methods for monitoring ICP (17). Consistent with the findings of the current study, Kalantari et al. (2013) (18) provided substantial evidence that

ONSD measurement can be a useful approach for monitoring ICP in TBI patients non-invasively and continuously.
One critical area where continuous monitoring of ICP is required, and ONSD can be used is on the bedside, where the invasive gold standard methods of assessing ICP may not be feasible (19). Koziarz et al. (2019) (20) performed a systematic review on ultrasonographic ONSD for the diagnosis of ICP. Their results were consistent with the findings of the current study and indicated that ONSD measurement can be used for continuous measurement of ICP on the bedside; because, like the results of this study have shown, it has high sensitivity under normal circumstances and high specificity under circumstances of elevated intracranial pressure. Consequently, considering the sensitivity and specificity of ONSD, it can be used as effective method for continuous monitoring of elevated ICP on the bedside (20).

5. Limitations

The small sample size is the main limitation of this study. Multicentric studies with larger sample sizes are suggested for further investigations in future.

6. Conclusion

In conclusion, our findings indicate that ONSD measurement could be a very useful, non-invasive alternative for the conventional invasive gold standard technique, which provides comparable results for continuous monitoring of ICP in TBI patients particularly in early hours.

7. Declarations

7.1. Acknowledgment

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7.2. Authors' contribution

The conception and design of the work by SM, AA and AN; Data acquisition by SM, TZ, HA and KH; Analysis and interpretation of data by VP KB and KK; Drafting the work by SM, TZ, VP and KB; Revising it critically for important intellectual content by AA, AN, HA, KH and KK; All the authors approved the final version to be published; AND agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work.

7.3. Conflict of interest

The authors declared that there is no competing interest to declare.

7.4. Funding

The study was conducted without any funds.

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