EMAT

Original Article

Association of optic nerve sheath diameter in ocular ultrasound with prognosis in patients presenting with acute stroke symptoms

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ABSTRACT

Background: Measurement of optic nerve sheath diameter (ONSD) by means of ocular ultrasound (US), can diagnose elevated intracranial pressure (ICP). Stroke accompanied by elevated ICP might have a worse prognosis.
Objective: To determine the relationship of ONSD in ocular US with prognosis in acute stroke in the emergency department (ED).
Methods: Patients with acute presentations of stroke, presenting to the ED in 2017 (during six months), were enrolled in our study. US exam was performed on all of them and ONSD was determined in two longitudinal and transverse dimensions. Demographic data, rate of patients' admission in the ward or intensive care unit, one-month patients' outcome and type of stroke were recorded. The relationship of mean ONSD was evaluated with study variables.
Results: In this study, 60 patients were enrolled. The mean ± SD ONSD in the deceased cases was 4.40 ± 0.64 mm and in the survived patients was 3.83 ± 0.56 mm. Youden index calculated ONSD > 3.9 mm as the best cut-off point in mortality prognosis. It has a sensitivity of 83.3% and a specificity of 59.2%.
Conclusions: Increased ONSD had a direct relationship with mortality rate in acute stroke.

1. Introduction

Stroke is a major cause of long-term disability and also the fifth leading cause of death in the United States of America.[1] Literature says that, in-hospital mortality rate of ischemic stroke is 5–10% and in hemorrhagic type is 40–60%.[2,3] Elevated intracranial pressure (ICP), caused either by neurologic and non-neurologic conditions (such as head trauma or even idiopathic)[4,5,6] can be dangerous. Thus, prediction and monitoring of ICP are recommended in stroke and in cases suspicious of having intracranial hypertension.[7] Recent studies show that measurement of optic nerve sheath diameter (ONSD) (a membrane continuous with the dura mater) by ultrasound (US), is indirectly an indicator of ICP.[8]

There is no consensus regarding the normal range of ONSD in healthy populations. In a study in china in 2015, ONSD of 519 healthy patients was measured and the mean ONSD was determined to be 5.1 mm (95% CI 4.7 to 5.4).[9] In a systematic review in 2010, it was revealed that measuring ONSD by US had a sensitivity of 90% and specificity of 85% in detecting elevated ICP.[8]

Significant elevation in ICP may be correlated with higher mortality rate after large acute ischemic stroke[10](11). Any diagnostic method that leads to earlier detection of elevated ICP in this population of patients is quite valuable. US is fast, accessible and noninvasive and in emergency department (ED), physicians can easily perform it. By measuring ONSD physicains can estimate patient ICP indirectly.

There are few studies showing that ONSD was related with the infarction site, type and also mortality of patients in acute stroke.[12,13]

In addition, there are few studies evaluating the association between ONSD and stroke prognosis. By using an easily accessible bedside exam, we can predict prognosis in patients suffering stroke. In this

study we decided to determine this relationship.

2. Methods

This study was a prospective cohort study done on patients older than 18 years old, with acute (less than 48 h) presentations of stroke referring to the ED. Exclusion criteria were: unwillingness to participate in our study, discharge against medical advice, any previous history of having space occupying lesions, neurologic deficits due to previous cerebrovascular diseases.

This study was conducted in 2017 (during 6 months) in an ED of a tertiary referral center of Tehran University of Medical Sciences. The study was approved by the ethics committee of the university (ID:9411307021). Patients were interviewed and examined by emergency medicine (EM) chief resident (PGY3) on shift and all data were recorded. Acute stroke was initially diagnosed clinically (any acute presentations of neurologic deficit) and then confirmed by magnetic resonance imaging (MRI) (whether ischemic or hemorrhagic). The informed written consent was taken of all patients or their legal guardians and the whole process was explained to them. Our sampling method was convenience sampling. Seven chief EM residents passed one-month US training course under the supervision of EM attending (chief investigator) and they each performed 20 ocular US exams on healthy volunteers before the study.

After confirmation of their expertise in this field, EM chief residents performed ocular US exam (by Madison SonoAce X8 model) on all patients entered the study and ONSDs of both right and left eyes were measured in two conventional dimensions; transverse and vertical. Ocular ultrasound was performed within half hour of patients' admission time. Patients were examined in the supine position by a 10 MHz phased linear array probe with closed eyes. The structure of each eye was visualized and the optic nerve was aligned directly behind the probe. ONSD was measured perpendicular to the vertical axis of the scanning plane, 3 mm behind the papilla. The mean ONSD of both eyes was calculated. All measurements were done one more time by the chief investigator and he estimated the interrater reliability among residents to be 90%.

Patients were followed during the process of treatment and the results of MRI, type of stroke, patient's demographic data, patient's disposition, hospital length of stay, ward of admission, one-month mortality and morbidity rates and National Institute of Health Stroke Scoring Scale (NIHSS) were documented.

2.1. Primary and secondary outcomes

Our primary outcomes were to evaluate the relationship of 1-month stroke mortality with ONSD and also find the best cut-off point for predicting mortality. Our secondary outcomes were finding the relationship between mortality and patients' demographic data, NIHSS score, hospital length of stay and ward of admission (patients' disposition).

2.2. Power estimation, data collection and primary analysis

We evaluated 87 patients in our study with acute presentations of stroke during a 6-month interval. Categorical data are expressed as number and frequency. Continuous data are presented as mean ± SD. We checked normality assumption with Shapiro–Wilk test.

Chi-square test, or Fisher's exact test was used for categorical variables. Student t-test was used for normally distributed continuous data. Receiver operating characteristic (ROC) analysis was used to determine the accuracy of ONSD in mortality prediction and we used Youden index in order to calculate the best cut-off point. The sensitivity and specificity were calculated with their 95% confidence intervals (CIs). A value of $p < 0.05$ was accepted as statistically significant. Data were analyzed using SPSS v. 22 and Stata v.14.

Table 1
Baseline and clinical characteristics of patients.

Variable		
Age (years old)		69.67 ± 13.23
Gender (N (%))	Male	33 (55%)
	Female	27 (45%)
Weight (kg)		69.93 ± 8.91
Hospital length of stay (day)		4.73 ± 5.44
NIHSS score		9.17 ± 5.80
Optic nerve sheath diameter (mean ± SD of both eyes) (mm)		3.89 ± 0.59
Type of stroke on MRI (N (%))	Ischemic	52 (87%)
	Hemorrhagic	8 (13%)
Prognosis (N (%))	Deceased	6 (10%)
	Survived	54 (90%)

Post-hoc power calculation was performed. By considering a sample size of 60 patients and 6 expired cases, post-hoc power was calculated to be 60%.

3. Results

In this prospective study, 87 patients were evaluated. Twenty-seven cases had the exclusion criteria: eleven had brain mass and nine had previous neurologic disease (previous stroke). The diagnosis of acute stroke was not confirmed in seven cases by MRI. In the end, 60 patients were included in the final analysis in our study.

Patients' baseline and clinical characteristics are shown in Table 1.

The mean length of stay at hospital was 4.73 ± 5.44 days. Only one person in our study was admitted to the intensive care unit and all other patients were admitted either to ED or neurology ward. The mean NIHSS score of patients was 9.17 ± 5.80. 52 patients had ischemic stroke and 8 patients had hemorrhagic stroke. Nineteen out of 52 patients were treated by fibrinolytic. Six patients deceased during hospital admission time and 54 survived patients were finally discharged from the hospital and none of them deceased during one month after discharge. The mean ONSD was 3.89 ± 0.59 mm.

The association of mortality with other secondary outcomes is shown in Table 2. Patients in the deceased group were older than the survived ones and their NIHSS score was also significantly higher. The mean ONSD in the deceased group was significantly more than the survived group. Patients with hemorrhagic stroke had significantly more mortality than ischemic type.

The ROC curve diagram of mean ONSD is shown in Fig. 1.

Area under curve (AUC) was 0.75 (95% CI = 0.63 to 0.86). Best cut-off value of ONSD was > 3.9 mm based on Youden index. By considering ONSD > 3.9, the odds ratio of mortality was estimated to be 7.3. Data are shown in Table 3.

4. Discussion

Our study concluded that, ONSD measurement by US exam in acute

Table 2
Association factors of mortality in stroke.

Variable		Deceased	Survived	P-value
Gender (N (%))	Male	2 (33.3%)	31 (57.4%)	0.275
	Female	4 (66.7%)	23 (42.6%)	
Age (year old)		80.33 ± 13.03	68.48 ± 12.83	0.051
Weight (kg)		63.33 ± 6.05	70.67 ± 8.91	0.284
NIHSS score		17.17 ± 9.15	8.28 ± 4.65	0.008
Optic nerve sheath diameter (mean ± SD of both eyes) (mm)		4.40 ± 0.64	3.83 ± 0.56	0.036
Type pf stroke (N (%))	Ischemic	2 (33.3%)	50 (92.5%)	0.001
	Hemorrhagic	4 (66.7%)	4 (7.5%)	
Fibrinolytic receive (N (%))	Yes	0 (0%)	19 (32%)	0.998
	No	6 (10%)	35 (58%)	
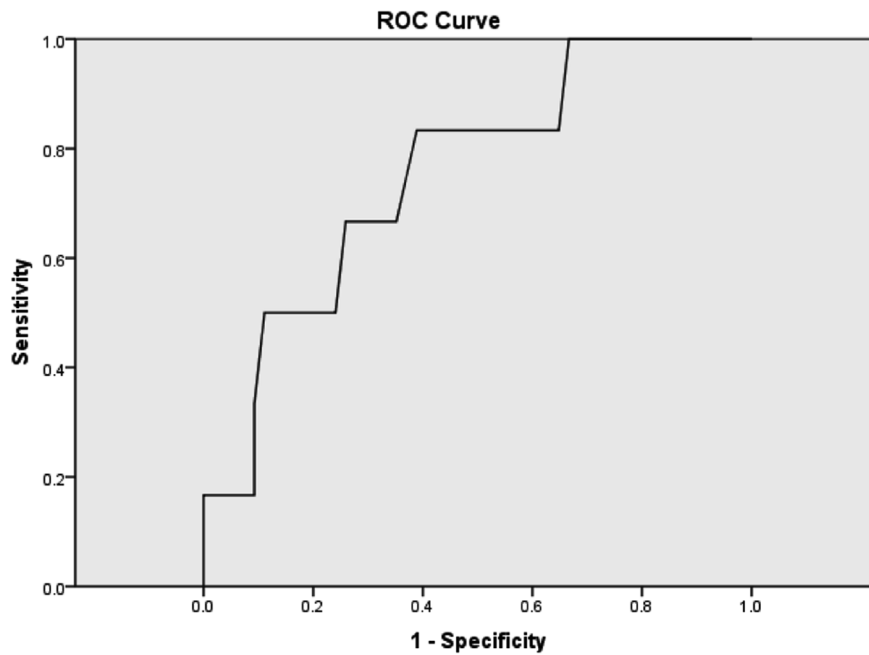
Fig. 1. ROC curve diagram of mean ONSD.

stroke might be helpful in the prediction of death. In this study, we found that increased mean ONSD was related to the increased mortality rate (p-value = 0.036). Most of our deceased patients had hemorrhagic stroke (p-value = 0.001). NIHSS score in the deceased group was significantly higher than the survived one (p-value = 0.008).

ONSD assessment has long been introduced as an alternative means of detecting raised ICP. ONSD is directly linked to elevated ICP.[8] US has a good validity in ONSD estimation.[14,15,16] Significant rise in ICP is reported in large acute cerebral infarcts.[10,11] Dramatic increase in ICP is mostly followed by death in broad ischemic stroke.[10]

There is no definite agreement on the normal range of ONSD in different populations.[9,17,18,19] Evidence shows that ocular US in the earliest phase of severe brain injury is quite useful.[20]

Gökcen et al., in 2017, compared ONSD in patients with cerebrovascular disease with a control group. They revealed that, ONSD was significantly higher in the case group especially when the anterior circulation was involved (p < 0.001).[12] They also reported that right ONSD had a significant predictive value in cerebrovascular diseases (AUC = 0.941, p < 0.001). Optimal cut-off value was 5.4 mm with 75% sensitivity and 91% specificity. Left ONSD had also a significant predictive value (AUC = 0.922, p < 0.001). Optimal cut-off value was 5.3 mm with 80% sensitivity and 84% specificity. We did not find such a significant cut-off value with good sensitivity and specificity.

Henda et al., in 2015, studied 86 patients with stroke and ocular US exam was performed on all of them on consecutive days. They determined a significant difference in ONSD between the deceased and survived groups. They reported that each 0.1 cm increase in ONSD

increased the mortality rate 4.2 and 6.2 times in ischemic and hemorrhagic stroke respectively.[13]

It seems that increase in ONSD is mostly seen in the acute phase of large and severe stroke. The present study comprehensively evaluated most variables involved in stroke prognosis. Further similar studies in this field are required to exactly find the correlation between mean ONSD and stroke prognosis.

4.1. Limitations of the study

The sample size in this study might be insufficient to detect the exact validity of ONSD measurement by US and stroke prognosis. This was a pilot study performed during a 6-month interval. Further studies with larger sample sizes should therefore be performed to identify most reliable results.

5. Conclusion

ONSD estimation can be a good noninvasive and fast exam in patients with massive stroke. Increased ONSD is directly related to the increased mortality rate in acute stroke.

Statements

There are no submissions or previous reports that might be regarded as redundant publication of the same or very similar work.

Table 3
Accuracy indicator in different cut-off point and best cut-off point for ONSD.

ONSD (mm)	Sensitivity (95%CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
> 3.55	83.3% (35.9 to 99.6)	35.1% (22.7 to 49.4)	12.5% (4.2 to 26.8)	95.0% (75.1 to 99.9)
> 3.9	83.3% (35.9 to 99.6)	59.2% (45.0 to 72.4)	18.5% (6.3 to 8.1)	97.0% (84.2 to 99.9)
> 3.95	66.6% (22.3 to 95.7)	64.8% (50.6 to 77.3)	17.4% (5.0 to 38.8)	94.6% (81.8 to 99.3)
> 4.15	66.6% (22.3 to 95.7)	74.0% (60.3 to 85.0)	22.2% (6.4 to 47.6)	95.2% (83.8 to 99.4)
> 4.25	50.0% (11.8 to 88.2)	75.9% (62.4 to 86.5)	18.8% (4.0 to 45.6)	93.2% (81.3 to 98.6)
> 4.4	50.0% (11.8 to 88.2)	88.8% (77.4 to 95.8)	33.3% (7.5 to 70.1)	94.1% (83.8 to 98.8)

There is no conflict of interest

The manuscript has been read and approved by all the authors. The requirements for authorship as stated in this document have been met, and each author believes that the manuscript represents honest work.

Contributors

All authors made an individual contribution to the writing of the article including: conception and design, acquisition of data or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval of the version published.

JS, MA, EV and FS conceived the study, designed the trial. JS and EV supervised the conduct of the trial and data collection. MA, FS, and JS undertook recruitment of participating centers and patients and managed the data, including quality control. EV and JS provided statistical advice on study design and analyzed the data; EV chaired the data oversight committee. EV drafted the manuscript, and all authors contributed substantially to its revision. EV takes responsibility for the paper as a whole.

Conflicts of interest

None declared.

Patient consent

Obtained.

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References

1. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke.* 2014;45(7):2160–2236.
2. Morgenstern LB, Hemphill JC, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage. *Stroke.* 2010;41(9):2108–2129.
3. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke. *Stroke.* 2013;44(3):870–947.
4. Marmarou A, Anderson RL, Ward JD, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. *J Neurosurg.* 1991;75(Supplement):S59–S66.
5. Stein DM, Hu PF, Brenner M, et al. Brief episodes of intracranial hypertension and cerebral hypoperfusion are associated with poor functional outcome after severe traumatic brain injury. *J Trauma.* 2011;71(2):364–374.
6. Vik A, Nag T, Fredriksli OA, et al. Relationship of "dose" of intracranial hypertension to outcome in severe traumatic brain injury. *J Neurosurg.* 2008;109(4):678–684.
7. Hawthorne C, Piper I. Monitoring of intracranial pressure in patients with traumatic brain injury. *Front Neurol.* 2014;5.
8. Frattalone AR, Stevens RD. Intracranial pressure and its surrogates. *Intensive Care Med.* 2011;37(7):1051–1053.
9. Chen H, Ding G-S, Zhao Y-C, Yu R-G, Zhou J-X. Ultrasound measurement of optic nerve diameter and optic nerve sheath diameter in healthy Chinese adults. *BMC Neurol.* 2015;15(1):106.
10. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. "Malignant" middle cerebral artery territory infarction: clinical course and prognostic signs. *Arch Neurol.* 1996;53(4):309–315.
11. Ropper AH, Shafran B. Brain edema after stroke. Clinical syndrome and intracranial pressure. *Arch Neurol.* 1984;41(1):26–29.
12. Gökcen E, Caltekin İ, Savrun A, Korkmaz H, Savrun Ş.T, Yıldırım G. Alterations in optic nerve sheath diameter according to cerebrovascular disease sub-groups. *Am J Emerg Med.* 2017;35(11):1607–1611.
13. Henda VS, Rastogi V, Weeks E, Patel RP. Use of optic nerve sheath diameter in emergency department to predict stroke outcome. *Stroke.* 2015;46:AWMP83.
14. Blaivas M, Theodoro D, Sierzenski PR. Elevated intracranial pressure detected by bedside emergency ultrasonography of the optic nerve sheath. *Acad Emerg Med.* 2003;10(4):376–381.
15. Shirodkar CG, Munta K, Rao SM, Mahesh MU. Correlation of measurement of optic nerve sheath diameter using ultrasound with magnetic resonance imaging. *Indian J Crit Care Med.* 2015;19(8):466–470.
16. Lochner P, Leone MA, Coppo L, et al. B-mode transorbital ultrasononography for the diagnosis of acute optic neuritis: a systematic review. *Clin Neurophysiol.* 2016;127(1):803–809.
17. Bäuerle J, Lochner P, Kaps M, Nedelmann M. Intra- and interobsever reliability of sonographic assessment of the optic nerve sheath diameter. *J Neuroimaging.* 2012;22(1):42–45.
18. Maude RR, Hossain MA, Hassan MU, et al. Transorbital sonographic evaluation of normal optic nerve sheath diameter in healthy volunteers in Bangladesh. *PLoS One.* 2013;8(12).
19. Goeres P, Zeiler FA, Unger B, Karakitsos D, Gillman LM. Ultrasound assessment of optic nerve sheath diameter in healthy volunteers. *J Crit Care.* 2016;31(1):168–171.
20. Geeraerts T, Launey Y, Martin L, et al. Ultrasonography of the optic nerve sheath may be useful for detecting raised intracranial pressure after severe brain injury. *Intensive Care Med.* 2007;33(10):1704–1711.