ORIGINAL RESEARCH

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The Role of Optic Nerve Sheath Diameter in Differential Diagnosis in Patients with Headache, A Prospective, Randomized Controlled Study

Ayşegül İşlek Yüksel[1], Fatih Selvi[2], Serkan Yüksel[3], Mustafa Avcı[2], Gülsüm Çalışkan Günay[4], Nalan Kozacı[5]

[1]Kahta State Hospital, Clinic of Emergency Medicine, Adıyaman, Türkiye
[2]University of Health Sciences Türkiye, Antalya Training and Research Hospital, Clinic of Emergency Medicine, Antalya, Türkiye
[3]Kahta State Hospital, Clinic of Radiology, Adıyaman, Türkiye
[4]Atatürk State Hospital, Clinic of Emergency Medicine, Antalya, Türkiye
[5]Alanya Alaaddin Keykubat University, Alanya Training and Research Hospital, Clinic of Emergency Medicine, Antalya, Türkiye

Abstract

Objective: This study aimed to evaluate the usability of the optic nerve sheath diameter (ONSD) in the differential diagnosis of headache.

Materials and Methods: This study included non-traumatic patients with headache. Patients were divided into three groups. Primary headache was assigned to group 1, secondary headache to group 2, and healthy volunteers to group 3. ONSD was measured by ultrasonography before computed cranial tomography imaging.

Results: A total of 50 patients in groups 1 and 2 and 50 healthy volunteers in group 3 were included. The mean ONSD of healthy volunteers was 4.2 mm, and the mean ONSD difference between eyes was 0.2 mm. The mean ONSD for the primary headache was 4.5 mm, and the mean ONSD difference for both eyes was 0.2 mm. The ONSD of the secondary headache was measured as 6.2 mm, and the ONSD difference between the eyes was 0.3 mm. The ONSD difference in both eyes and the ONSD of patients with secondary headache were higher than those in groups 1 and 3 ($p<0.001$). The ONSD cutoff value, which was positive on CT imaging, was 5.2 mm.

Conclusion: The ONSD and difference in ONSD can be used in the differential diagnosis of primary and secondary headache.

Keywords: Computed cranial tomography, emergency medicine, headache, optic nerve sheath diameter, ultrasonography

Introduction

Headache is a common complaint in the emergency department (ED) and accounts for approximately 2.5% of all ED visits. Headache can be classified as primary or secondary, depending on its underlying cause [1]. The international classification of headache disorders defines primary headaches as migraine, tension-type, cluster, or one of the other trigeminal autonomic cephalalgias. Primary headaches comprise about 95-98% of all headaches. Secondary headaches are caused by underlying diseases, such as trauma, cerebrovascular disorders, infection, intoxication, or malignancy [1-3]. The primary goal of the emergency physician is to distinguish life-threatening secondary headache from primary headache. Failure or delay in recognizing a life-threatening headache can result in morbidity and mortality. The second goal of the emergency physician is to alleviate the symptoms [4].

Emergency physicians may need to use neuroimaging to exclude life-threatening conditions in patients with headache

Address for Correspondence: Assoc. Prof. Mustafa Avcı, University of Health Sciences Türkiye, Antalya Training and Research Hospital, Clinic of Emergency Medicine, Antalya, Türkiye
E-mail: dravcimustafa@gmail.com **ORCID-ID:** orcid.org/0000-0002-5018-9070
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[1]. Cranial computed tomography (CCT) is the first imaging modality of choice for excluding secondary headache causes (intracranial events) in EDs. However, CCT imaging involves high-dose radiation. Therefore, it is important to correctly identify patients who will undergo CCT imaging [5,6].

The optic nerve is an anatomical structure of the central nervous system, and the optic nerve sheath is associated with the meninges and subarachnoid space. Therefore, events that increase the pressure in the central nervous system cause an increase in the optic nerve sheath diameter (ONSD). ONSD measurement with bedside ultrasonography (US) is a non-invasive, easy-to-apply, fast, and reproducible method [7-13]. Compared with CCT and Magnetic resonance imaging (MRI), US is easy to use and inexpensive, especially in emergency conditions. However, it should be noted that ONSD shows huge variation with age [11,14]. The aim of this study was to evaluate the usability of ONSD for the differential diagnosis of headache in patients admitted to the ED with headache. Thus, to detect intracranial events in the early period, perform ONSD measurement before CCT imaging, and contribute to the literature.

Materials and Methods

This prospective, single-blind, randomized controlled study was initiated after University of Health Sciences Türkiye, Antalya Training and Research Hospital Clinical Research Ethics Committee (approval number: 3/17 date: 31.01.2019). The study was conducted in the adult ED of University of Health Sciences Türkiye, Antalya Training and Research Hospital between February 4, 2019 - July 18, 2019. Patients were consecutively included in the study. Power analysis was performed using the G*Power program version 3.1.9.7 (2020) for windows 10 (Düsseldorf University, Germany) with reference to similar studies in the literature. Sample size was calculated as 44 with 95% power and 0.05 type 1 error rate. Patients admitted with a complaint of non-traumatic headache, who underwent CCT, who were older than 18 years, and who provided consent to participate in the study were included in the study. Patients with a history of trauma, who were younger than 18 years of age, who have pregnant, who had eye surgery, who have eye prosthesis, who did not have CCT scan, whose data is missing and who did not volunteer to participate in the study were excluded. All patients and volunteers provided informed consent before participation. Patients included in the study were divided into two groups: primary and secondary headache groups according to their final diagnosis. Final diagnoses were decided according to the CCT findings. Patients who did not present with pathology on CCT scans were enrolled in group 1 (primary headache), and those who had pathologies were enrolled in group 2 (secondary headache). Healthy volunteers were included in Group 3. Healthy volunteers were not visualized using CCT.

A standard data record form was created. Vital signs (blood pressure, pulse, fever and oxygen saturation values), visual analog scale (VAS), Glasgow coma score (GCS), ONSD measurements, CCT imaging interpretations, final diagnosis, and outcome patterns of the patients were recorded on the form. The ONSD of all patients and healthy volunteers was measured by a single emergency physician. The physician who measured ONSD was blind to the patient's clinical condition. ONSD was measured immediately before CCT imaging. All CCTs were interpreted by the on-call radiologist within 30 minutes after CCTs were performed.

ONSD Measurement Technique

ONSD measurements were performed by an emergency physician using a 7-13 MHz linear ultrasound probe (Mindray Portable Ultrasound Systems, M5, Germany) in the ED. The emergency physician who measured the ONSD of the patients was blind to patient history, physical examination, clinical findings, and laboratory results of the patient. Patients were examined in the supine position with a closed eyelid. Ultrasound gel was applied on the eyelid surface. First, both eyes were scanned in the vertical and horizontal planes through the eyelid, and then the optic disk of the eye was viewed and ONSD measurements were performed in the transverse and sagittal planes using hypoechoic lines 3 mm proximal to the optic disk, as references (Figure 1).

Statistical Analysis

For statistical analysis, Statistical Package for the Social Sciences (SPSS1) version 21 was used. First, a Kolmogorov-Smirnov analysis was performed to evaluate whether the distribution of values is normal or not. Parametric data were analyzed using Student's t-test and one-way analysis of variance tests. Non-parametric data were analyzed using Mann-Whitney and Kruskal-Wallis tests. Pearson's correlation analysis was performed for variables with normal distribution, and Spearman's correlation analysis was performed for variables not showing normal distribution. Categorical variables were expressed as numbers and percentages, and continuous variables were as mean and standard deviation (median and minimum - maximum, where necessary). X^2 test statistic was used to compare categorical variables. Receiver operating characteristic curves were used to assess the usefulness of measurements and to determine the sensitivity and specificity of the test. $P<0.05$ was considered statistically significant.

Study Outcomes

The primary outcome of the study was to evaluate the usability of ONSD for the differential diagnosis of headache in patients admitted to the ED with headache. The secondary outcome of the study was to evaluate the correlation of vital signs (blood pressure, pulse, fever and oxygen saturation values),

VAS, GCS, ONSD measurements, ONSD difference of both eyes, and CCT imaging interpretations in patients with primary and secondary headache.

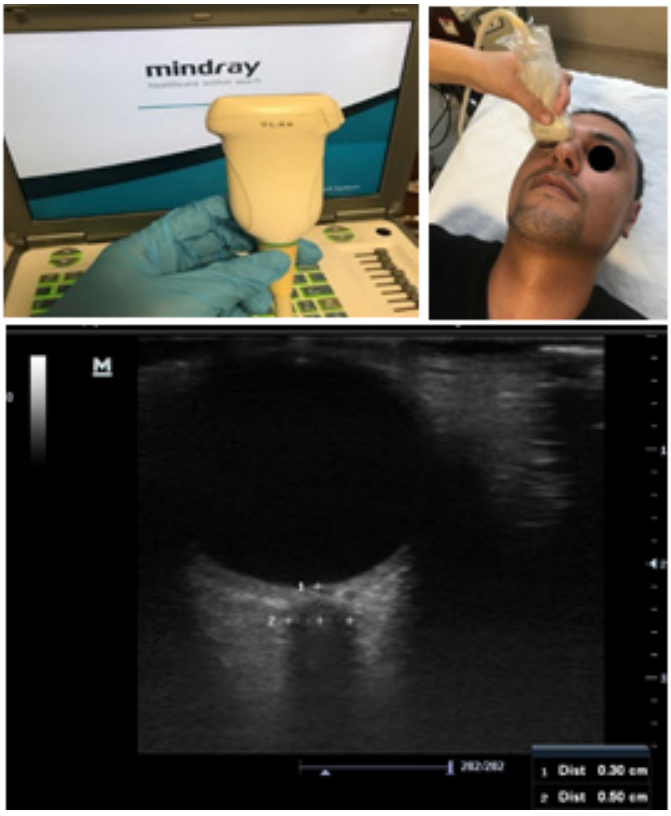

Figure 1. ONSD measurement technique. Measurement number 1: for the measurement, the optic nerve is traced 3 mm from the eyeball. Measurement number 2: the diameter is then measured in the transverse plane

ONSD: Optic nerve sheath diameter

Results

In this study, 50 patients from groups 1 and 2 each and 50 healthy volunteers from group 3 were included. There were no significant differences in age and sex between the groups. There were significant differences in systolic blood pressure (SBP), diastolic blood pressure (DBP), ONSD, and ONSD in both eyes between the groups. The difference in SBP, DBP, ONSD, and ONSD of both eyes in patients with secondary headache was very high ($p<0.001$) compared with the other patients. Patients with primary headache had higher SBP ($p=0.003$), DBP ($p<0.001$) and ONSD ($p<0.001$) than healthy volunteers (Table 1). There was no pathology in the CCT images of patients with primary headache. The CCT images of patients with secondary headaches showed subarachnoid hemorrhage (28%, n=14), intra-parenchymal hemorrhage (28%, n=14), subdural hemorrhage (16%, n=8), intracranial mass (16%, n=8), and acute ischemic stroke (12%, n=6). The ONSD cutoff value, which shows the pathology in the CCT images, was determined as 5.2 mm. At this value, the sensitivity was 98% and the specificity was 100% [area under the curve (AUC): 0.998; 95% confidence interval (CI): 0.992-1.000] (Figure 2). A difference was observed between the GCS scores of patients with primary and secondary headaches ($p<0.01$). On the other hand, there was no statistically significant difference between the VAS scores of the patients ($p=0.148$) (Table 2).

A negative correlation was found between GCS and ONSD in patients with headache. GCS was not correlated with VAS, SBP, or DBP. ONSD was not correlated with VAS, SBP, or DBP (Table 3). Midline shift (MLS) was detected in 9 (9%) patients on CCT images. The ONSD of patients with MLS was 6.3±0.6 mm, and the ONSD of patients without MLS was 5.2±1.0 mm ($p<0.001$).

Table 1. Comparison of the groups' vital signs and ONSD measurements

Findings		Mean ± SD lower bound	95% CI		p
			Upper bound		
SBP	Healthy	130±18	125	135	0.001
	Primary	143±24	136	149	
	Secondary	156±35	146	166	
DBP	Healthy	73±8	70	75	0.001
	Primary	86±13	82	89	
	Secondary	88±19	82	93	
ONSD	Healthy	4.2±0.2	4.2	4.3	0.001
	Primary	4.5±0.4	4.4	4.6	
	Secondary	6.2±0.5	6.0	6.3	
ONSD difference of both eyes	Healthy	0.2±0.1	0.1	0.2	0.001
	Primary	0.2±0.1	0.2	0.3	
	Secondary	0.3±0.2	0.3	0.4	

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ONSD: Optic nerve sheath diameter, CI: Confidence interval, SD: Standard daviation

Patients with secondary headache were hospitalized, 10 of them were admitted to the neurology and neurosurgery clinic, and 40 of them were admitted to the intensive care unit. Patients with primary headache were discharged after treatment in the ED. Eleven (22%) patients with secondary headache did not survive. The ONSD of the non-surviving patients was 6.9±0.2 mm, and the ONSD of the survivors was 5.1±0.9 mm ($p<0.001$). The cutoff value of ONSD for the detection of mortality was determined to be 6.5 mm. The sensitivity and specificity at this cutoff value were determined as 100% and 92% (AUC: 0.984; 95% CI: 0.963-1,000), respectively (Figure 3).

Discussion

In the initial evaluation in the ED, secondary headaches that can be potentially life-threatening should be differentiated from primary headaches. However, it is difficult to distinguish between primary and secondary headaches in emergencies. In such cases, extensive laboratory and imaging studies may be required [1,8]. CCT and MRI are frequently used for imaging intracranial events in the ED. Recently, ONSD has been found to increase in intracranial events such as ischemic stroke, hemorrhagic stroke, meningitis, encephalitis, brain edema, intracranial hypertension, and traumatic brain injury (subarachnoid, subdural and epidural hemorrhage) that

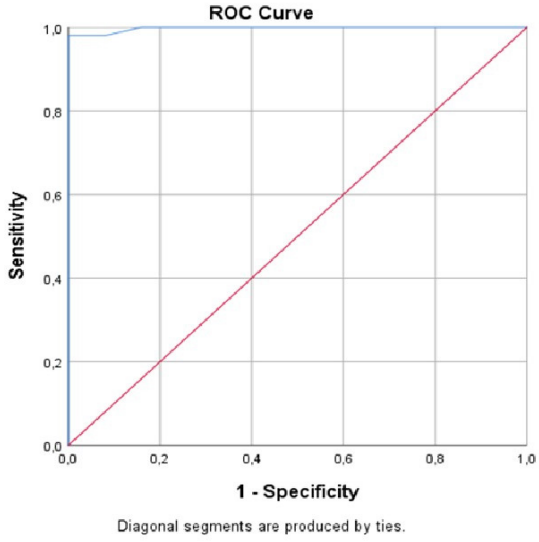

Figure 2. ROC analysis of ONSD as a predictor for patients with secondary headache

ROC: Receiver operating characteristic, ONSD: Optic nerve sheath diameter

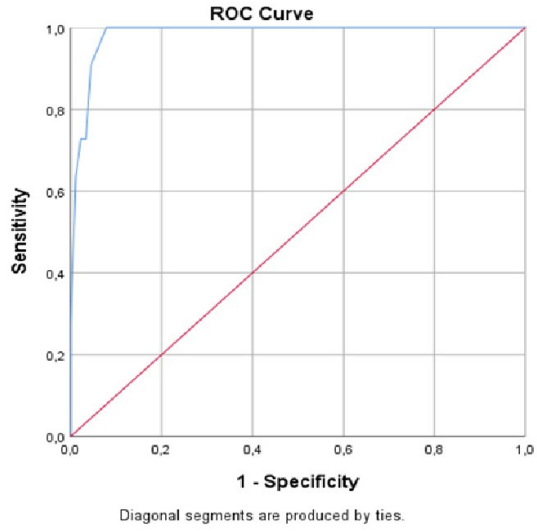

Figure 3. ROC analysis of ONSD as a mortality predictor in patients with headache

ROC: Receiver operating characteristic, ONSD: Optic nerve sheath diameter

Table 2. Comparison of GCS and VAS score of patients with primary and secondary headaches

Findings	Groups	Median	Minimum	Maximum	p
GCS	Primary	15	15	15	0.001
	Secondary	12	5	15	
VAS	Primary	10	6	10	0.148
	Secondary	10	4	10	

GCS: Glasgow coma scale, VAS: Visual analog scale

Table 3. Correlation between patients' GCS, ONSD, VAS, SBP, and DBP

	Findings		ONSD	VAS	SBP	DBP
Spearman's rho (n=100)	GCS	R	**-0.669**	0.056	-0.030	-0.047
		P	**0.001**	0.580	0.767	0.640
	ONSD	R	1.000	-0.094	0.251	0.131
		P	.	0.352	0.012	0.193

VAS: Visual analog scale, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, GCS: Glasgow coma scale, ONSD: Optic nerve sheath diameter, R: Correlation coefficient

cause increased intracranial pressure. In these studies, ONSD and intracranial pressure (ICP) were found to be correlated [7,10-12,15,16]. There are studies indicates that extra-cranial events such as COVID-19 and alcohol intoxication, increase ONSD [3,17]. Furthermore, ONSD has been found to decrease postdural puncture headache [18] and during migraine attacks [19]. In this study, we investigated the role of ONSD in the differential diagnosis of patients with headache. In CCT scans, subarachnoid hemorrhage, intra-parenchymal hemorrhage, subdural hemorrhage, intracranial mass, and acute ischemic stroke were detected in patients with secondary headache. There were no pathological signs in patients with primary headache. The ONSD values measured by bedside US were 4.2 mm in healthy volunteers, 4.5 mm in patients with primary headache, and 6.2 mm in patients with secondary headache. This result suggests that ONSD can be used to differentiate patients with secondary headache. In a previous study, ONSD values were significantly higher in patients diagnosed with secondary headache compared with those diagnosed with primary headache [20]. In another study, when the intracranial pressure was >20 mmHg, the cutoff value of ONSD was measured as >5.2 mm. At this value, the sensitivity and specificity were 83.3% and the specificity to be 100% [12]. Based on this finding, ROC analysis of ONSD was performed to identify patients with secondary headache. When the cutoff value of ONSD was predicted as 5.2 mm, the sensitivity and specificity were calculated as 98% and 100% (AUC: 0.998; 95% CI: 0.992-1.000), respectively. In some studies, in addition to ONSD, the differences in ONSD of both eyes were also evaluated. In a previous study, the ONSD difference was 0.97 mm in patients with pathology on CCT, whereas the ONSD difference was 0.45 mm in patients without pathology on CCT [7]. In another study, the difference in ONSD was 0.29 mm in patients with acute ischemic stroke, compared to 0.07 mm in healthy adults [9]. In another study contains 20 with idiopathic intracranial hypertension and 20 with intracerebral hemorrhage, the median asymmetry was higher in patients than in healthy subjects (0.45 mm vs. 0.23 mm) [16]. In a study conducted in patients with headache, the ONSD value on the same side as the lesion was found to be higher on the opposite side [10]. In our study, the difference in ONSD among patients with secondary headache was higher than that among the others. The ONSD difference was 0.30 mm in patients with secondary headache, 0.21 mm in patients with primary headache, and 0.20 mm in healthy volunteers. This result shows that differences in ONSD can also be used in differential diagnosis.

The GCS was used to evaluate the patients' consciousness status and intracranial lesions. Studies have shown that GCS decreases as ICP increases. Kshirsagar et al. [21] conducted a study. According to this study, compared with CT, bedside USG ONSD had 86.42% sensitivity and 64.29% specificity for detecting elevated ICP. A highly significant association was found among the GCS, CT results, and ONSD measurements. Patients with low GCS had higher mean ONSD values (6.4±1.0 mm) [21]. Güzeldağ et al. [22] measured the ONSD by US in acute middle cerebral artery stroke patients. They found that ONSD was negatively correlated with GCS at 24 hours. In a recent study, it was determined that ONSD increased as GCS decreased. In a study conducted in the ED, the ONSD of patients with a GCS of 14-15 was measured at 4.9 mm. The ONSD of patients with a GCS of 3-13 was measured as 5.8 mm [7]. Benhur et al. [23] investigated ONSD and GCS. In total, 57 patients underwent elective craniotomy for intracranial tumors. They measured ONSD and GCS at 12th, 24th and 48th hours after surgery. A negative correlation was observed between baseline ONSD and 12-h GCS. There was a significant change in GCS scores based on the ONSD status (raised or normal) at 12 hours postoperatively [23]. In our study, the median GCS score of patients with primary headache: 15 (15-15), whereas the median GCS score of patients with secondary headache was 13 (5-15). A statistically significant negative correlation ($r=-0.669$, $p<0.001$) was found between GCS and ONSD. These results suggest that ONSD can be used in addition to GCS to evaluate intracranial lesions. Red flags should be considered when differentiating high-risk patients for headache. Red flags include altered state of consciousness, seizure, fever, neurological symptoms, no previous headache, change in headache severity or worsening within weeks/months, progression, and most severe headaches in life. Neuroimaging should be performed when red flags are detected [24]. Therefore, assessment of pain intensity is important for diagnosis and treatment. The VAS is frequently used to evaluate pain severity in the ED. There is no study in the literature investigating the relationship between VAS scores and ONSD. In this study, we observed no difference between the VAS scores of patients with primary and secondary headaches. The VAS score was 10 in both groups. In addition, VAS score was not correlated with ONSD and GCS. These results show that GCS and bedside ONSD measurement may be more useful than the severity of pain before neuroimaging. As the ICP increases, brain herniation occurs, followed by brain death. In many studies, ONSD was found to be enlarged in patients with brain herniation and death [7,25,26]. In one study, the ONSD was 5.3 mm in patients who developed MLS and 4.42 mm in patients who did not develop MLS. In this study, the ONSD cutoff value for MLS was determined as 5.3 mm [7]. In a study of patients with head trauma, a positive correlation was found between midline shift and ONSD ($r=0.761$ ($p<0.0005$) [27]. In another study, ONSD was found to be 8.34 mm in patients with brain death. In addition, the ONSD cutoff value for brain death was determined to be 7.1 mm in this study [25]. In another study, ONSD changes in patients with middle cerebral artery infarction or malign middle cerebral artery infarction were investigated. The mean ONSD on admission was already larger

in patients who had developed a malignant middle cerebral artery infarction (5.99±0.32 mm) compared to patients with middle cerebral artery infarction (4.98±0.53 mm) [28]. In our study, the ONSD of patients who developed MLS was 6.3 mm, whereas that of patients who did not develop MLS was 5.2 mm. In addition, the ONSD of the non-survivor patients were 6.9 mm, and the ONSD of the survivor patients were 5.1 mm. In addition, the ONSD cutoff value for mortality was determined to be 6.5 mm in our study. At this value, the sensitivity was 100% and the specificity was 92%. These results indicate that ONSD can be used as a predictor of prognosis and mortality in patients with headache.

In our study, only CCT imaging was performed, and MRI could not be performed. We did not take into account the laboratory values of our patients for whom we recorded vital signs (blood pressure, pulse, fever and oxygen saturation values), visual pain scale, GCS, ONSD measurements, CCT imaging interpretations, final diagnosis, and outcome patterns of the patients. Additionally, CCT imaging was not performed in healthy volunteers. These are the limitations of our study.

CONCLUSION

In conclusion, there is a difference in SBP, DBP, GCS, ONSD, and ONSD between eyes in patients with primary and secondary headache. These parameters can be used in the differential diagnosis of patients with headache after CCT imaging. In addition, ONSD can be used to predict the prognosis and mortality of patients with headache.

Ethics

Ethics Committee Approval: University of Health Sciences Türkiye, Antalya Training and Research Hospital Clinical Research Ethics Committee (approval number: 3/17 date: 31.01.2019).

Informed Consent: It was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.İ.Y., F.S., S.Y., M.A., G.Ç.G., N.K., Concept: A.İ.Y., F.S., S.Y., M.A., G.Ç.G., N.K., Design: A.İ.Y., F.S., S.Y., M.A., G.Ç.G., N.K., Data Collection or Processing: A.İ.Y., F.S., S.Y., G.Ç.G., N.K., Analysis or Interpretation: F.S., M.A., G.Ç.G., N.K., Literature Search: F.S., M.A., N.K., Writing: A.İ.Y., S.Y., M.A., N.K.

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