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Ultrasound of Optic Nerve Sheath Diameter and Stroke Outcomes

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OBJECTIVES: We aimed at utilizing ocular ultrasound to determine its utility in predicting outcomes among stroke patients.

DESIGN: Single-center prospective observational study.

SETTING: Emergency department and ICUs.

PATIENTS: Patients suspected of stroke.

INTERVENTIONS: None.

MEASURES AND MAIN RESULTS: Bilateral optic nerve sheath diameter was measured on arrival and within the first 2 days of admission. Outcomes were inpatient survival, Cerebral Performance Category, and modified Rankin Scale at 3 and 6 months. Analysis was conducted using descriptive statistics, paired *t* test, chi-square test. Eighty-six patients were enrolled with ischemic or hemorrhagic stroke. Mean age was 67.2 years (± 15 yr), and 54.7% of patients were male. There was no difference between left and right eye measurements ($p = 0.467$ and $p = 0.903$, respectively) or between longitudinal and transverse measurements (transverse $p = 0.163$ and longitudinal $p = 0.270$). Mean optic nerve sheath diameter differed in patients who survived versus died prior to discharge in both ischemic (0.53 vs 0.58 cm; $p = 0.009$) or hemorrhagic stroke (0.57 vs 0.62 cm; $p = 0.019$). For every 0.1 cm increase in optic nerve sheath diameter, odds ratio for death were 4.2 among ischemic stroke (95% CI, 1.32–13.64; $p = 0.015$), and odds ratio 6.2 among ischemic or hemorrhagic patients (95% CI, 1.160–33.382; $p = 0.033$). Increased optic nerve sheath diameter correlated ($r = 0.44$; $p < 0.0001$) with poor functional outcomes measured as modified Rankin Scale scores of 3–6 at 6 months.

CONCLUSIONS: Elevations in optic nerve sheath diameter were associated with increased inhospital mortality and poor functional outcome at 6 months. Optic nerve sheath diameter may serve as a noninvasive marker of inhospital mortality and functional outcome. Further multicenter prospective trials for evaluating and treating optic nerve sheath diameter in ischemic and hemorrhagic strokes are warranted.

KEY WORDS: hemorrhagic stroke; ischemic stroke; optic nerve sheath diameter; point of care ultrasound; stroke; ultrasound

Stroke represents the second most frequent cause of death in people over the age of 60 years, the most frequent cause of permanent disability, the second most common cause of dementia, and uses approximately 3–7% of total healthcare expenditure in high-income countries (1). The American Heart Association predicts a 5.1% increase in stroke cases among Americans 45–64 years old by 2030. Worsening edema in stroke patients can lead to midline shift, compression, and eventual injury of previously unaffected brain structures. Significant cerebral edema occurs in approximately 10–15% of all middle cerebral artery occlusions requiring intensive care monitoring and treatment (2, 3). The risk of neurologic deterioration or death due to malignant cerebral edema ranges from 40% to 80% (4–6). Failure to identify these patients at risk can

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result in cognitive decline, hemorrhagic conversion (ischemic strokes), herniation, and death (7).

Cerebral edema associated with stroke may increase intracranial pressure (ICP). The current gold standard for monitoring ICP includes the placement of an invasive intraparenchymal probe or intraventricular catheter, which has risk and requires special expertise (8). CT scan findings such as midline shift and effacement of basal cisterns and sulci may be used to detect signs of elevated ICP; however, this may require frequent imaging that exposes the patient to increasing levels of ionizing radiation and transferring critically ill patients outside of the ICU affecting patient safety (9, 10). Regarding the use of imaging as a marker for increased ICP, estimation techniques have yielded a sensitivity of only 65% and specificity of 73% based on CT characteristics after trauma (11–13). In stroke patients, CT predictors of increased ICP on initial scan include pineal displacement (horizontal displacement of 0–3 mm from the midline was associated with alertness, 3–4 mm with drowsiness, 6–8.5 mm with stupor, and 8–13 mm with coma) or hypodensity greater than 50% of middle cerebral artery territory in the setting of both internal carotid and middle cerebral artery occlusion (14, 15).

Ultrasound is a widely used modality that has broad applications in clinical settings (16). Optic nerve sheath diameter (ONSD) evaluation using ocular ultrasound (OUS) is a portable noninvasive method to assess for elevated ICP. In a single-center prospective study of various acute brain-injured patients, an ONSD greater than or equal to 0.48 cm was associated with an ICP greater than 20 mm Hg; however, in this study, 17% of subjects were diagnosed with intracerebral hemorrhage and 1.5% of subjects with ischemic stroke (17). The clinical consequences of elevated ICP have demonstrated the duration of time with an ICP greater than 20 mm Hg is associated with worse functional outcomes in acute brain-injured patients (18, 19). Previous studies have investigated ONSD associated with clinical deterioration and mortality after stroke; however, no published studies have measured functional outcomes using both modified Rankin Scale (mRS) and Cerebral Performance Category (CPC) (20–23). Our objective was to determine the role of ONSD measurement in the acute setting of ischemic and hemorrhagic stroke patients and evaluation of functional outcomes. We also aimed to determine the optimal method for ONSD measurement (both eyes vs one, transverse vs longitudinal orientation) and to define ONSD thresholds associated with poor outcomes.

METHODS

Setting

The study was conducted in a single tertiary care academic center from June 1, 2013, to November 30, 2013. Suspected acute stroke patients in the emergency department or patients directly transferred from another hospital to the neurological ICU with an admitting diagnosis of stroke (ischemic or hemorrhagic [ICH]) were included.

Screening and Enrollment

Adults (≥ 18 yr old) who were identified as potential stroke patients were included in this prospective observational study. Patients were excluded if they had suspected globe trauma, known retinal or optic nerve disease, previous enucleation, were pending emergent surgery or if enrollment into the study would conflict with clinical management or interventions. A convenience sample of patients was enrolled based on the availability of the principal investigator, who performed or supervised all ultrasounds performed. Sample size calculation estimates using confidence interval analysis were performed prior to Institutional Review Board (IRB) approval. The University of Florida IRB (approval number IRB201300137) approved this study. Enrollment through delayed consent (96 hr) was approved from the IRB due to the high safety profile of ultrasound, critical timing of the intervention, and the high likelihood patient's mental status altered due to the conditions being studied. All enrolled subjects were provided written consent. Informed consent was obtained from all individual participants included in the study.

Data Collection

Demographic details including age, sex, and race, medical history, and clinical data including type of stroke, Glasgow Coma Score, National Institutes of Health Stroke Scale (NIHSS), time of admission CT with ICH volume, tissue plasminogen activator (tPA) administration, and outcome data were collected from the patient, clinical team, or abstracted from the medical records.

Measurement of Optic Nerve Sheath Diameter and Ocular Ultrasonography Technique

OUS was performed on the day of admission (usually within the first 6 hr of arrival to emergency department or ICU). ONSD measurements of right and left eyes were performed in both the transverse and longitudinal orientation for a total of four measurements. The times of all studies performed were recorded relative to the time of hospital arrival. On day 2 of hospital admission, a subsequent measurement of ONSD was performed and recorded in similar method. Most patients had eight measurements, unless they were discharged from the ICU on the second day and therefore had the initial four measurements.

OUS examination was performed using a Sonosite M-Turbo with a 7.5 MHz linear array transducer on first and second day of admission using standard techniques described in the literature and was adjusted to obtain orbital sonography with musculoskeletal presets software, as orbital software presets was not available (24). The OUS examination was performed by the study's principal investigator and research team members under the investigator's direct supervision. All sonographers underwent a training session with the principal investigator and had to demonstrate proficiency in obtaining images. All images were reviewed for quality and repeated during the supervision process if they did not meet standards for inclusion in the study. In previous studies, it was found that minimal interobserver variation exists among individuals trained to conduct OUSs (8, 25, 26). Sterile ultrasound gel was applied to the closed eyelid while the patient was in supine position, with their head in a neutral position (15–30° elevation). The probe was oriented in the transverse and longitudinal positions to obtain an axial cross-sectional image of the optic nerve. The optic nerve sheath appears as a hypoechoic band behind an anechoic globe (**Supplemental Figs. 1** and **2**, http://links.lww.com/CCX/A847) (27, 28). Measurements were taken 0.3 cm behind the optic disc in the transverse and longitudinal planes to obtain two measurements per eye during hospital days 1 and 2 for a total of eight measurements per patient (18).

Assessment of Outcomes and Orientation

Subjects who survived to discharge were contacted via telephone to assess mRS and CPC scores at 3 and 6 months after discharge. The primary outcome was inpatient death. Secondary outcomes were functional outcomes at 3 and 6 months using the mRS and the CPC (29–32). For the mRS, good outcomes were scores 0–2 (having no symptoms to having slight disability), while poor outcomes were scores 3–6 (moderate disability to death). For the CPC, category 1 represents good cerebral performance; category 2, conscious patients with moderate cerebral disability; category 3, conscious patients with severe cerebral disability; category 4, coma or vegetative state; and category 5, brain death. Patients with favorable neurologic outcome were CPC of 1 or 2. Comparison of measurement variability between right and left eyes was performed as well as between probe orientations of transverse and longitudinal.

Statistical Analyses

Descriptive statistics (i.e., mean, SD, and 95%) were used for the continuous variables. Student *t*/Mann-Whitney *U*/Kruskal-Wallis tests were conducted to assess differences between groups for continuous variables. For categorical variables, frequencies and percentages were calculated; chi-square and/or Fisher exact tests were used to evaluate associations between categorical variables. We used Research Electronic Data Capture to collect the study data, and SAS Version 9.4 (Statistical Analysis Software; SAS Institute, Cary, NC) was used to analyze the data.

RESULTS

During the study period, we screened 1,124 acute ischemic stroke and 278 acute intracranial hemorrhage patients, with enrollment of 86 subjects. Mean age was 67.2 years (± 15.04 yr), and 54.7% of patients were male. Thirty out of 57 ischemic stroke subjects received IV tPA, and 29 subjects had an intracerebral hemorrhage. Two of the ischemic stroke subjects underwent mechanical thrombectomy. There was no difference in location of ischemic or hemorrhage lesions (**Table 1**). Three subjects had infratentorial lesions, which were all ischemic stroke subjects. Thirty-two of the 57 ischemic stroke patients (56%) had NIHSS scores documented. The mean NIHSS score was 10.15 (range, 0–35). Eight of 29 subjects (28%) with ICH had an ICH volume and ICH score documented. The mean ICH volume was 53 mL (range, 5–90 mL), and mean ICH score was 2 (range, 1–4) (Table 1).

TABLE 1.
Characteristics of the Patients (*n* = 86)

Variables	Ischemic Stroke	Stroke With Tissue Plasminogen Activator	Intracerebral Hemorrhage	*p*
Continuous measurements				
Age, mean (SD)	68.96 (12.35)	65.30 (13.22)	68.21 (18.84)	0.624
Gender, *n* (%)				0.99
Male	15 (31.3)	17 (35.4)	16 (33.3)	
Female	12 (31.6)	13 (34.2)	13 (34.2)	
Ethnicity				0.99
White	27 (34.6)	24 (30.8)	27 (34.6)	
Non-White	0	6 (87.5)	2 (14.3)	
Location				
Emergency department	22 (33.3)	25 (37.9)	19 (28.8)	0.21
Neurosurgical ICU	5 (25.0)	5 (25.0)	10 (50.0)	
Location of injury on CT				0.14
Diffuse	10 (43.5)	10 (43.5)	3 (13.0)	
Right	6 (22.2)	11 (40.7)	10 (37)	
Left	11 (32.4)	9 (26.5)	14 (41.2)	
National Institutes of Health score, mean (SD)	10.93 (10.2)	10.08 (6.61)	7.25 (7.54)	0.754
ICH				
ICH volume (mean in mL)			53	
ICH score (mean)			2	
Survival				0.03
Survived	18 (30)	26 (43.3)	16 (26.7)	
Expired	9 (34.6)	4 (15.4)	13 (50)	

ICH = intracerebral hemorrhage.

All enrolled subjects had ONSD measured bilaterally in the longitudinal and transverse planes upon arrival to emergency department or ICU (if directly transferred from outside hospital) and the following day after admission. There was no difference between left and right eye measurements among all stroke subjects (*p* values of right and left eye were $p = 0.903$ and $p = 0.467$; respectively), nor between longitudinal and transverse measurements (transverse $p = 0.163$, longitudinal $p = 0.270$) (**Supplemental Table 1**, http://links.lww.com/CCX/A847). Subjects with ICH had a significantly larger ONSD (average 0.59 cm left eye; $p = 0.040$, average 0.60 cm right eye; $p = 0.001$, and mean 0.59 cm for both eyes; $p = 0.001$) on day of admission compared with ischemic stroke subjects (Supplemental Table 1, http://links.lww.com/CCX/A847). Measurements of ONSD, of both right and left optic nerves, on second day of admission were not significantly different between groups ($p = 0.142$).

There was no significant difference in the time to first ($p = 0.43$) or second ($p = 0.42$) ONSD measurements across ischemic stroke patients receiving tPA, ischemic stroke patients not receiving tPA, or ICH subjects. The time interval between first and second ONSD measurements was not significantly different ($p = 0.71$) (**Table 2**).

The primary outcome of this study was inpatient mortality. Subjects that expired during their hospitalization had significantly larger ONSD based on first (95% CI, 0.58–0.62; $p < 0.001$) and second (95% CI, 0.60–0.65; $p < 0.001$) ONSD measurements (**Table 3**). The mean ONSD of subjects that expired during hospitalization was 0.60 cm assessed on first measurement and 0.63 cm assessed on second measurement.

TABLE 2.
Interval Between Arrival Time (in min) and Optic Nerve Sheath Diameter Measurements

Stroke Types for Time Measurements	*n*	Mean (SD)
Time difference between arrival and first ONSD measurement		
Ischemic stroke without tPA	27	247.63 (272.06)
Ischemic stroke with tPA	30	295.77 (379.34)
Intracerebral hemorrhage	29	362.45 (327.03)
Total	86	303.14 (330.4)
p	0.43	
Time difference between first and second ONSD measurement		
Ischemic stroke without tPA	20	1,336.15 (180.01)
Ischemic stroke with tPA	19	1,281.21 (317.22)
Intracerebral hemorrhage	25	1,262.08 (360.91)
Total	64	1,290.91 (298.59)
p	0.71	
Time difference between arrival and second ONSD measurement		
Ischemic stroke without tPA	20	1,597.95 (374.29)
Ischemic stroke with tPA	19	1,441.32 (426.78)
Intracerebral hemorrhage	25	1,607.36 (508.07)
Total	64	1,555.13 (445.19)
p	0.42	

ONSD = optic nerve sheath diameter, tPA= tissue plasminogen activator.

Among ischemic stroke subjects that did not receive tPA, for every 0.1 cm increase in ONSD, the odds of death were 4.457 (95% CI, 0.790–25.147; $p = 0.0905$). Among ischemic stroke subjects who received tPA, for every 0.1 cm increase in ONSD, the odds of death were 4.052 (95% CI, 0.678–24.217; $p = 0.1250$). There was a significant difference in mean ONSD in subjects who survived to discharge in both ischemic stroke (0.53 vs 0.58 cm; $p = 0.0092$) and hemorrhagic stroke subjects (0.57 vs 0.62 cm; $p = 0.0187$). Overall, for every 0.1 cm increase in ONSD, the risk of mortality was increased 4.239-fold among ischemic stroke subjects (95% CI, 1.317–13.642; $p = 0.0155$), and increased 6.222-fold among intracerebral hemorrhage subjects (95% CI, 1.160–33.382; $p = 0.0329$).

TABLE 3.
Inpatient Survival by Optic Nerve Sheath Diameter Measurements (in cm)

	First Measurement (*n* = 86)	Second Measurement (*n* = 63)
Status	**Mean (95% CI)**	**Mean (95% CI)**
Survived	0.54 (0.53–0.56)	0.53 (0.51–0.55)
Expired	0.60 (0.58–0.62)	0.63 (0.60–0.65)
p	< 0.001	< 0.001

Functional outcomes were assessed using CPC and mRS at 3 and 6 months, which showed significantly worse functional outcomes (mRS 3–6) in the ICH group at 6 months (Table 4). Elevated ONSD measurements show a correlation ($r = 0.44$; $p < 0.0001$) with poor functional outcomes as assessed using mRS scores (mRS 3–6) at 6 months (Table 5). Poor functional outcomes, as assessed using CPC and mRS at 6 months both demonstrated significantly higher ONSD at first measurement (0.59 vs 0.54 cm; $p = 0.001$ and 0.57 vs 0.54 cm; $p = 0.003$, respectively) and at second measurement (0.62 vs 0.53 cm; $p < 0.001$ and 0.59 vs 0.53 cm; $p = 0.003$, respectively).

DISCUSSION

This study is the first to demonstrate an association between mortality and functional outcomes using two

TABLE 4.
Cerebral Performance Category Scores and Modified Rankin Scale at 3 and 6 Months by Injury Type

Scores	Ischemic Stroke	Stroke With Tissue Plasminogen Activator	Intracerebral Hemorrhage	*p*
CPC score at 3 mo				0.74
Poor (3–5)	2 (25)	4 (50)	2 (25)	
Good (1–2)	24 (33.3)	26 (36.10	22 (30.6)	
CPC score at 6 mo				0.08
Poor (3–5)	9 (30)	8 (26.7)	13 (43.3)	
Good (1–2)	16 (33.3)	22 (45.8)	10 (20.8)	
Modified Rankin score at 3 mo				0.81
Poor (3–6)	5 (38.5)	5 (38.5)	3 (23.1)	
Good (0–2)	21 (31.3)	25 (37.3)	21 (31.3)	
Modified Rankin score at 6 mo				0.02
Poor (3–6)	10 (25.6)	12 (30.8)	17 (43.6)	
Good (0–2)	13 (37.1)	17 (48.6)	5 (14.3)	

CPC = Cerebral Performance Category.

different time points measuring ONSD in acute stroke patients. Our primary outcome of inpatient mortality was associated with significantly increased ONSD in patients with ischemic and hemorrhagic strokes. Furthermore, increased ONSD was associated with poor functional outcomes at 6 months, assessed by both mRS and CPC. To our knowledge, this adds to current literature that long-term outcomes may be correlated with inpatient ONSD measurement.

Normal ONSD in adults is approximately 0.5 cm, more specifically, Geeraerts et al (33) measured ONSD in healthy controls finding 0.49 cm (± 0.03 cm) for the right eye and 0.48 cm (± 0.05 cm) for the left eye. In patients with stroke, elevated measurements of ONSD range from 0.59 to 0.63 cm (34). The ONSD is a promising marker of elevated ICP due to the unique anatomy of the optic nerve sheath. The optic nerve is wrapped and surrounded by a nerve sheath that consists of the three layers of meninges, that is, anatomically continuous with that of the brain's three layers of meninges—dura mater, arachnoid mater, and pia mater. Due to this communication, cerebrospinal

TABLE 5.
Cerebral Performance Category Score and Modified Rankin Scale at 6 Months by Optic Nerve Sheath Diameter Measurements All Types Combined

Scores	First Measurement (*n* = 86)	Second Measurement (*n* = 63)
Cerebral Performance Category score at 6 mo	Mean (95% CI)	Mean (95% CI)
Poor (3–5)	0.59 (0.56–0.61)	0.62 (0.58–0.64)
Good (1–2)	0.54 (0.52–0.55)	0.53 (0.51–0.55)
p	0.001	< 0.001
Modified Rankin Scale at 6 mo	Mean (95% CI)	Mean (95% CI)
Poor (3–6)	0.57 (0.55–0.59)	0.59 (0.56–0.62)
Good (0–2)	0.54 (0.52–0.56)	0.53(0.50–0.55)
p	0.003	0.003

fluid can travel freely between the intracranial subarachnoid space and that within the optic nerve sheath. Thus, a rise or drop in pressure within the cranium should translate to the same pressure changes within the optic nerve sheath (35). This expansion of ONSD can be measured noninvasively with point of care ultrasound to assess ICP (12, 17, 25–27). When measuring ONSD with ultrasonography, a position 3 mm behind the globe is commonly chosen because the ultrasound contrast is greatest here and the anterior nerve is also most distensible at this location (36). Anatomically, the sheath is wide in this area due to the bulging dura mater region (37). In cadaver studies it was noted that the ONSD increased by up to 60% at a distance 3 mm behind the globe as opposed to only 35% 10 mm behind the globe. On ultrasound, the optic nerve appears homogenous with low internal reflectivity compared with the high reflectivity of the nerve sheath (36). Thus, the contrast in reflectivity allows for improved ONSD measurement. Vaiman et al (37) did not find any significant changes in ONSD that correlated with age.

Clinicians that have reliable serial neurologic examinations can identify changes signifying potential intracranial alterations. However, when clinicians do not have reliable serial neurologic examinations due encephalopathy, intubation, sedating medications, detecting subtle changes can be difficult. For the assessment of brain edema in a patient with an equivocal or worsening clinical examination, the clinician may obtain a CT scan or MRI. We demonstrate that OUS can be performed repeatedly at the bedside, with equipment present in most emergency departments and ICUs.

Our results show that in regard to this technique, it is statistically significant that measurements made between right and left eye yield similar results, so that on a serial basis only one eye needs to be measured, regardless of the brain hemisphere of injury. Our results also show that measurements between transverse orientation measurements versus longitudinal orientation measurement are also similar, so the clinician may measure one instead of both.

The effect of tPA in ischemic stroke patients did not affect ONSD. When comparing increases in ONSD between patients who received tPA and those that did not, those that received tPA had less odds of death. This might suggest that ONSD measurements can be made without having to correct any of the measurements for tPA status of the patient and can be used in all patients who have a stroke.

Limitations include enrollment on a convenience sample of the sonographer. All of ultrasounds were performed/supervised by the principal investigator who underwent extra training in all ultrasound modalities and may not be extrapolated to all operators. There have been studies with a primary aim of looking at interobserver variability that reported there was minimal variability (8, 25, 26). Another limitation is this study was conducted at a single site experienced with various ultrasound modalities, which may not be present at all facilities.

At our institution, we evaluated 1,124 acute ischemic stroke and 278 acute intracranial hemorrhages over the course of this study. This high volume helps to have a diversified patient cohort. This study is missing control groups consisting of ICU patients who are not brain injured, although previous studies evaluated optic nerve sheath in healthy controls 0.49 cm (± 0.03 cm) for the right eye and 0.48 cm (± 0.05 cm) for the left eye (33). However, a strength was obtaining eight measurements per patient over 2-day period and outcome follow-up at 6 months. Image acquisition for the patient from the emergency department to the ICU was performed by the same individual (R.P.), and so there was consistency in the operator.

Our study did not correlate ONSD with invasive measurements of ICP. There remains ambiguity in thresholds of ONSD in regards to using this noninvasive modality to monitor ICP. A meta-analysis of 10 studies measuring ONSD and ICP in a total of 1,035 patients suggested high accuracy with an area under the receiver operating characteristic of 0.94. However, variability in thresholds used in these studies was noted to contribute to lack of general applicability of using ONSD to identify elevated ICP. In addition to lack of consensus on optimal ONSD to detect elevated ICP, as defined as greater than 20 mm Hg, there are no guidelines on monitoring ICP after acute ischemic stroke from the American Heart Association/American Stroke Association (38).

Withdrawal of life-sustaining treatment (WLST) may have been a factor in the mortality rates among both hemorrhagic and ischemic stroke subjects. The mortality rate among subjects in our study with hemorrhagic stroke was 45% and 23% with ischemic stroke,

which is higher than previously reported mortality rates of 30–33% and 3–9%, respectively (39). Previous studies have reported rates of WLST from 0.9% to 25% among stroke patients (40, 41). Our study is limited due to lack of reported data regarding inpatient and outpatient WLST that may have contributed to the mortality rates in our study.

CONCLUSIONS

Our study demonstrated that increase in ONSD measurement was associated with increased hospital mortality and poor functional outcomes at 6 months. ONSD measurements may be performed using just one eye and one probe orientation to make the serial examinations easier to adopt and perform. ONSD may be used to screen stroke patients at risk of poor prognosis, especially when used in conjunction with abnormal clinical examination and CT imaging. Prospective randomized controlled studies need to be performed to identify interventions that may affect outcomes.

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