Optic Nerve Sheath Diameter Detects Intracranial Hypertension in Acute Malignant Middle Cerebral Artery Infarction

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Objectives: To evaluate optic nerve sheath diameter in the acute phase of patients with malignant ischemic middle cerebral artery stroke submitted or not to decompressive craniectomy surgery. *Materials and Methods:* Forty patients participated in the study and were evaluated bilaterally by ultrasound on admission and at 24h, 48h and 72 h after admission. Optic nerve sheath diameter values were correlated with tomographic and/or clinical criteria compatible with severe intracranial hypertension. *Results:* A Receiver Operating Characteristic curve was drawn for each eye, determining a cut-off value for severe intracranial hypertension in the right eye of 5.4 mm (sensitivity: 62%; specificity: 100%; AUC: 0.82) and in the left eye 5.4 mm (sensitivity: 76%; specificity: 84%; AUC: 0.77). In patients undergoing craniectomy, there was a decrease in the mean value of 1.04mm in the right eye (pre: 5.84 ± 0.47 mm; post: 4.80 ± 0.84 mm; p = 0.001), while in the left, it decreased around 0.86mm (pre: 5.59 ± 0.69 mm; post: 4.73 ± 0.74 mm; p = 0.003). Patients with fatal outcome showed a persistent high mean ocular nerve sheath diameter. *Conclusions:* Monitoring optic nerve sheath by ultrasound can be considered a reliable method for identifying severe intracranial hypertension in patients with large vessel occlusion, as well as for monitoring patients undergoing craniectomy. Additional studies will be necessary to include this parameter in craniectomy indication algorithms in the future.

Key Words: Optic nerve—Intracranial hypertension—Ultrasound imaging, Middle cerebral artery stroke—Decompressive craniectomy

Introduction

The term “malignant hemispheric cerebral infarction” was initially described in 1996 by Hacke et al.[1] as an area of extensive infarction with surrounding cerebral edema. Currently, it is defined as ischemia of more than 50% of the middle cerebral artery (MCA) territory detectable on computed tomography (CT) and/or magnetic resonance imaging (MRI) of the skull, associated with compatible symptoms.[2]

Once the compensatory mechanisms for cerebral oedema have been exhausted, deterioration of consciousness and increased intracranial pressure (ICP) may occur, with consequent midline shift, cerebral herniation and death.[3] Decompressive craniectomy (DC) has been a major rescue therapy in this setting, with an impact on reducing mortality, which is still high among patients who present this condition.[4]

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Early detection of intracranial hypertension (ICH) is very important in the prevention of potentially devastating brain injuries.[5] Although the gold standard for monitoring ICP is based on the use of invasive devices, in some conditions they are not indicated (coagulopathies, post-craniectomy, acute ischemic stroke); in addition, they are associated with complications such as infections, bleeding, and displacement or blockage of the catheter.[6]

For these reasons, numerous non-invasive methods have been described for measuring ICP, such as CT/MRI of the skull, fundoscopy and transcranial doppler sonography.[7,8] Among alternatives, measuring the optic nerve sheath diameter (ONSD) using point-of-care ultrasound (POCUS) has become an interesting option, since it is a simple, accessible and feasible diagnostic method at the bedside, besides its safety, not exposing patients to radiation.[9]

Growing evidence suggests that monitoring of ONSD is a reliable method for determining ICH,[9,10] as well as being useful in assessing the neurological prognosis of patients after cardiac arrest.[11] More recently, its use on stroke due to large vessel occlusion is being discussed.[12,13] Although there may be some similarities between conditions that cause cerebral edema, it is important to determine ONSD values on conditions with different physiopathological mechanisms, such as stroke, since different cerebral autoregulation mechanisms may play a key role in cerebral edema in each condition.[14–16] The objective of this study was to evaluate optic nerve sheath diameter during the acute phase of patients with malignant MCA infarction submitted or not to decompressive craniectomy surgery.

Methods

Study design and participants

This observational and prospective study was carried out in the emergency department and stroke unit of a comprehensive stroke center in the state of Ceara, Brazil, a reference hospital for neurology and neurosurgery, from November 2018 to August 2019.

The study population was initially constituted by a sample, of 48 patients admitted to the emergency unit and diagnosed with large (>50%) MCA ischemic stroke detected by computerized tomography (CT), within 72 h after hospital admission. The study excluded patients under age 18, previously diagnosed with diseases that affected the optic nerve (for example glaucoma, optic neuritis and uveitis) or not bearing both eyes; patients who evolved with severe clinical or ophthalmological complications that impaired the interpretation of the data obtained by optic nerve sheath ultrasound (sepsis with hemodynamic instability and vitreous hemorrhage); patients whose ultrasound follow-up was less than 4 evaluations in the first 72 h after hospital admission; and patients with insufficient medical record data for the study (Fig. 1).

The study was approved by the local Research Ethics Committee of the institution and, and Informed Consent was obtained from a family member or their legal representative.

Study protocol

Patients were followed up in the first 72 h after hospital admission by ultrasound measurement of the optic nerve sheath diameter of the right and left eyes. To ensure uniformity, the first measurements were performed within 4 h after admission, and others were performed within 24, 48 and 72 h +/- 2 h, from the first measurements.

To determine the ONSD, a SonoSite M-Turbo® equipment was used together with its linear transducer (5-10 MHz). A single medical professional, with training in emergency medicine and experience in the exam

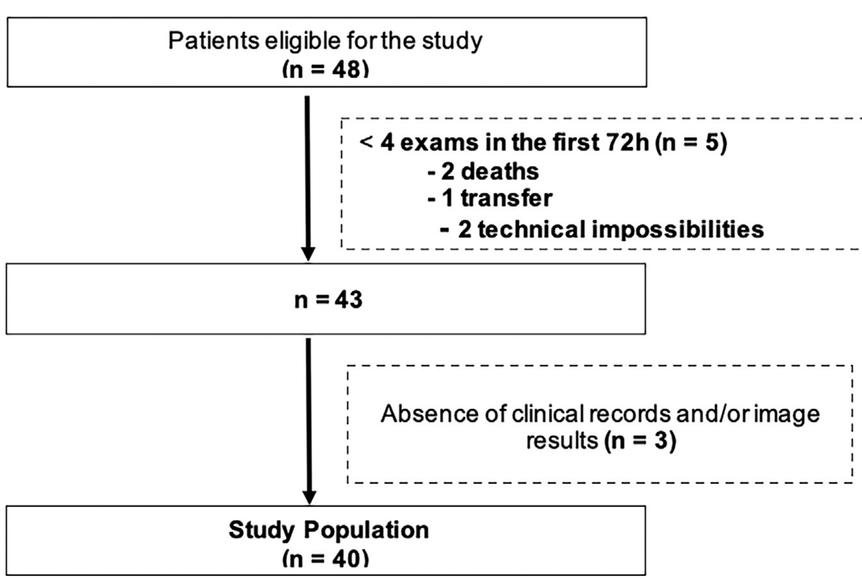

Fig. 1. *Flowsheet of the study population before first POCUS measurement.*

technique for at least 4 years, was responsible for POCUS execution.

For each measurement, the patient was placed in supine position, with the head of the bed at an angle of 30° and the head in a neutral position. The technique was performed in accordance with the new criteria for ultrasound quality of the optic nerve[10] by placing the transducer horizontally on the closed upper eyelid and measurements performed at a depth of 40 mm. Thus, measurement of ONSD was performed precisely 3 mm from the posterior eyeball, where the sheath is thinner and is more easily distended with the increase in ICP. The final ONSD value for each eye was defined by the average of three consecutive measurements in each eye.

The definition of life-threating or severe ICH to correlate with ONSD was based on the identification of clinical findings frequently associated with herniation (such as anisocoria, papilledema, Cushing's triad or worsening of the level of consciousness without any other apparent cause) and/or tomographic findings (midline deviation; ventricular system dilation; collapse of the lateral ventricles, third ventricle and perimesencephalic cisterns; intracranial subfaulcine herniation; and effacement of cortical sulci). All patients included were referred to neurosurgical evaluation for decompressive craniectomy consideration due to large core infarcts. The neurosurgical team was independent to indicate surgical intervention at any point. The results were categorized into two groups: patients undergoing DC (surgical) versus patients not undergoing DC (non-surgical).

Statistical analysis

Continuous data were presented as average and standard deviation, while categorical data were presented with absolute and percentages. Shapiro-Wilk was used to test for normality of the data. To compare the groups, we used the unpaired Student’s t-test for variables with normal distribution, and the Mann-Whitney test for variables with non-normal distribution. Categorical variables were compared with the chi-square or Fisher’s exact test as appropriate. ROC curves analysis and the Youden index were used to select the best cut-off of optic nerve sheath associated with severe intracranial hypertension levels. SPSS 22.0 program (IBM, Armonk, NY, USA) was used for analysis. The significance level was set at $p < 0.05$.

Results

Patients’ profile is described in Table 1. Among the comorbidities, hypertension was more prevalent in the group of patients who did not undergo craniectomy (72.4%; p = 0.027). Thrombolysis was performed in 32.5% (n = 13) in patients in general, with no significant difference between surgical and non-surgical groups. Of the thrombolysed patients, 30.7% (n = 4) died, while the outcome was favorable (no death) in all those who underwent thrombolysis associated with DC (n = 4). In the referred study, DC was indicated in 11 patients (28.2%) and was performed, mostly, in the first 24 h after admission (n = 6; 54.5%), with no indication after 72 h of admission. The average surgical duration time was approximately 202.8 ± 59.77 minutes.

Using ONSD as predictor for the definition of severe ICH, through comparative analysis with cranial CT and/or clinical criteria suggestive of herniation, two ROCs curves were constructed (Fig. 2), one for each eye, with the objective of finding a cut-off value of the optic nerve diameter bilaterally. A 5.4 mm cut-off was found for the right eye (Sensitivity: 62%; Specificity: 100%; AUC: 0.82; CI: 0,67-0,96) and a 5.4 mm cut-off for the left eye (Sensitivity: 76%; Specificity: 84%; AUC: 0.77, CI: 0,63-0,94).

By correlating the cerebral hemisphere affected with the ONSD of 22 patients who presented values compatible with severe ICH (ONSD> 5.4 mm), it was observed that regardless of the injured cerebral hemisphere, simultaneous changes were seen in both optic nerves (68.2% / n = 15). For patients with left hemisphere injury (n = 3), all presented alteration of the ONSD ipsilaterally, while the remainder with right hemispheric injury (n = 4), a predominance of contralateral optic nerve involvement was recorded. Thus, in almost all cases (95.4% / n = 21), the presence of a change in the left optic nerve was observed, regardless of the affected hemisphere.

Fig. 3 shows an evolution of the mean of the ONSD up to 72 h after admission, in both eyes of patients who underwent DC, as well as in the non-surgical patients. In the group of surgical patients, there was a reduction in the ONSD at the end of 72 h of admission, to an approximately similar value in both eyes. In contrast, in the non-surgical patients, there was a continuous rise of ONSD in the left eye over 72 h, while in the right eye, over 3 days after admission, the final value of ONSD corresponded to the value on admission.

After evaluating the ONSD in both eyes, before and after surgery, a significant difference was observed in the values referring to the right eye before (5.84 ± 0.47 mm) and after surgery (4.80 ± 0.84 mm), with a decrease in the average value of 1.04 (p = 0.001). Similarly, statistically significant difference was found for the left eye between the mean values before (5.59 ± 0.69 mm) and after surgery (4.73 ± 0.74 mm), with a decrease in the mean value of 0.86 (p = 0.003), as seen on Fig. 4.

Mortality of malignant MCA infarct patients in this study was 35% (n = 14). By specifying surgical and non-surgical patients within this percentage, death occurred in only 2 patients (18,2%) in the first group, while 12 patients (41,4%) died on the non-surgical group. The analysis of distinct mortality in each of the two groups showed that only 18.2% of surgical patients died, while 41.4% of non-surgical patients presented this unfavourable outcome.

Correlating the ONSD with patient outcome (died vs. survived), a similar behaviour in the rise of the ONSD in

Table 1. *Sociodemographic and clinical profile by group (surgical vs. non-surgical).*

	Total (n = 40)	Surgical (n = 11)	Non-surgical (n = 29)	*p*
Sex (male)	20 (50.0%)	7 (63.6%)	13 (44.8%)	0,29[b]
Age (years)	61 ± 19	50 ± 14	65 ± 19	0.02[a]
Hypertension	24 (60.0%)	3 (27.3%)	21 (72.4%)	0.03[c]
Diabetes	8 (20.0%)	0 (0.0%)	8 (27.6%)	0.08[c]
Smoking	20 (50.0%)	7 (63.6%)	13 (44.8%)	0.29[b]
Alcoholism	15 (37.5%)	6 (54.5%)	9 (31.0%)	0.27[c]
Previous Ranking Score				>0.99[c]
0-2	36 (90.0%)	11 (100%)	25 (86.2%)	
3-6	4 (10%)	0 (0%)	4 (13.8%)	
Admission up to 1st skull CT (min)	28.75 ± 27.88			
Admission to Thrombolysis (min)	33.27 ± 16.08			
SBP (mmHg) (Admission)				0.48[c]
< 220	38 (95.0%)	10 (90.9%)	28 (96.6%)	
>= 220	2 (5.0%)	1 (9.1%)	1 (3.4%)	
DBP (mmHg) (Admission)				0.55[c]
< 120	37 (92.5%)	11 (100.0%)	26 (89.7%)	
>= 120	3 (7.5%)	0 (0.0%)	3 (10.3%)	
Glycemia on admission (mg/dL)				0.32[c]
< 140	27 (67.5%)	9 (81.8%)	18 (62.1%)	
Glasgow Coma Scale (Admission)				0.47[c]
3-8	5 (12.5%)	0 (0.0%)	5 (17.2%)	
9-12	21 (52.5%)	7 (63.6%)	14 (48.3%)	
13-15	14 (35.0%)	4 (36.4%)	10 (34.5%)	
NIHSS (Admission)				>0.99[c]
0-7	0 (0.0%)	0 (0.0%)	0 (0.0%)	
8-15	5 (12.5%)	1 (9.1%)	4 (13.8%)	
16-42	35 (87.5%)	10 (90.9%)	25 (86.2%)	
ASPECTS Score (1st head CT)				0.89[c]
1-3	11 (27.5%)	3 (27.3%)	8 (27.6%)	
4-6	23 (57.5%)	7 (63.6%)	16 (55.2%)	
7-10	6 (15%)	1 (9.1%)	5 (17.2%)	
Thrombolysis	13 (32.5%)	4 (36.4%)	9 (31.0%)	>0,99[c]

Legend: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; NIHSS: National Institutes of Health Stroke Score; ASPECTS: Alberta Early Stroke Program CT Score; CT: computerized tomography. Data presented in n (%) and mean ± standard deviation; a: Student's t test; b: Pearson's chi-square test; c: Fisher's exact test.

the first 24 h, mostly on the left, followed by a slight decrease within 48h and a slight rise after completing 72h of admission, was observed in the right and left eyes of the patients who died. In patients who survived, a similar behaviour was also observed between the eyes, with a continuous drop in the ONSD value in the first 72 h after admission (Fig. 5).

Among survivors, on surgical patients 44.5% remained with severe disabilities, with mild functional deficits seen in 11.1%. In the non-surgical cases, 29.4% remained severely disabled, in contrast, 53% presented moderately disability while another 17.6% had some autonomy.

Discussion

This study shows that optic nerve sheath diameter obtained with point-of-care ultrasound in patients with malignant MCA infarcts is a valuable tool in detecting severe intracranial hypertension that may lead to death if not treated with DC. Early diagnosis of severe ICH is essential for patient survival; therefore, a simple, fast, inexpensive, non-invasive, easily reproducible and low cost and harmless method should be emphasized for clinical application in emergency and intensive care environments.[17]

In the present study, the cut-off value that represented greater sensitivity and specificity in detecting changes in the ONSD compatible with severe ICH confirmed by clinical and/or tomographic criteria was 5.4 mm for the right eye (sensitivity: 62%; specificity: 100%) and 5.4 mm to the left (sensitivity: 76%; specificity: 84%). Lochner et al performed a similar study, including 29 MCA patients, comparing to a control group. His findings were close to the cut-off value found in the present study, suggesting a 5,6mm, with a sensitivity of 100% and specificity of 90%.[13] Differences in this determination may be related to sample size used, criteria to determine a severe ICH related to MCA stroke and methods in calculating the cut-

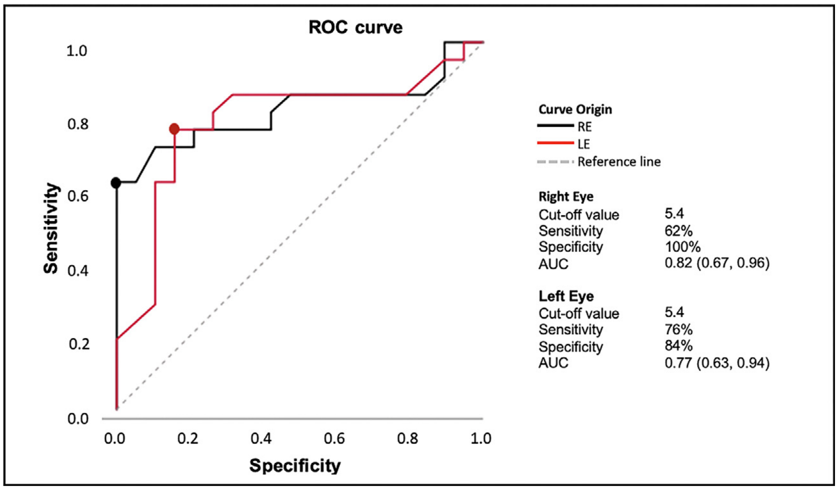

Fig. 2. *ROC curve of the optic nerve sheath diameter of the right and left eyes to predict intracranial hypertension. Legend: RE – right eye; LE – left eye; AUC – area under curve.*

off value. In our study, severe ICH was considered when clinical and/or imaging signs suggestive of herniation were we detected, which differs from the ones considered by Lochner et al. Also, in our study separate ROC curves for each eye were performed to allow a separate analyzes, since this is a not well-explored phenomena and more detailed information is needed.

Several published studies have correlated the ultrasound measurement of ONSD with ICH, proposing a single cut-off value, for both eyes, with different sensitivity and specificity (Table 2). The variations in the cut-off points of these studies can be justified by the non-standardization of the profiles of patients studied with ICH (traumatic causes, non-traumatic causes, idiopathic causes, cerebrovascular diseases, among others), sizes of the study populations, correlations with identification methods of ICH (intracranial catheter, skull CT, skull MRI, lumbar puncture and clinical criteria), in addition to the measurement technique used.[17] In a recent study to evaluate the presence of intracranial hypertension in ischemic stroke patients after IV thrombolysis, a value of 5,5mm was used to split groups, and a positive correlation was found with NIHSS and a negative correlation to Glasgow scale.[12]

We believe that, although the ICP represents a general condition of everything inside the skullcap, there could be a more specific correlation between the affected cerebral hemisphere and the specific changes in the optic nerve ipsilaterally or contralateral to the injury. Upon literature review on the measurement of ONSD by other methods,

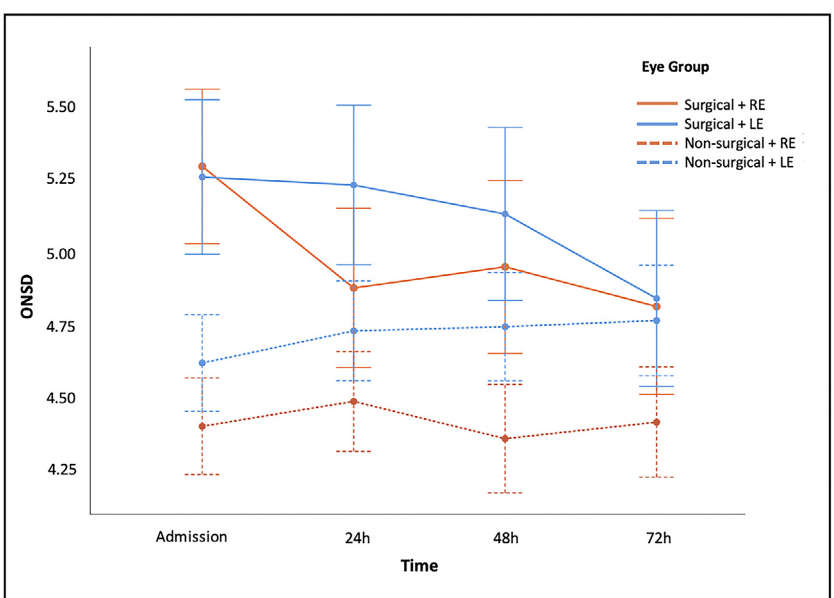

Fig. 3. *Evolution of the mean optic nerve sheath diameter in the right and left eyes of surgical and non-surgical patients. Legend: RE – right eye; LE – left eye; ONSD – optic nerve sheath diameter.*

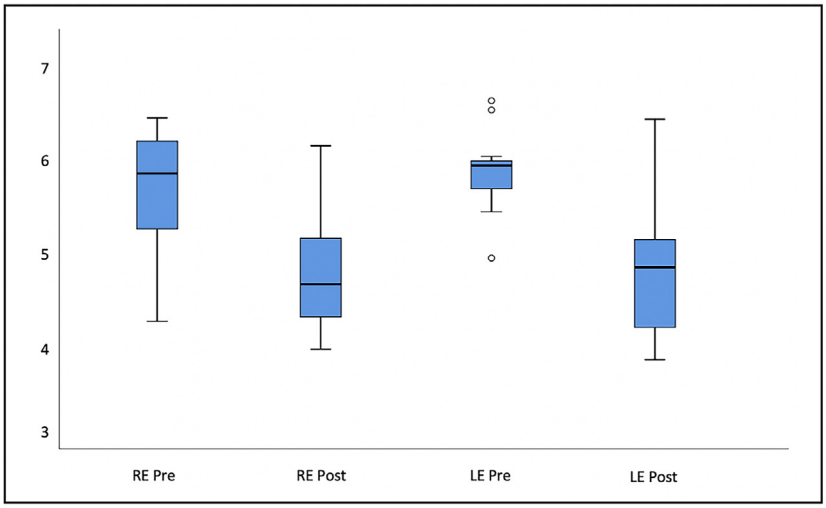

Fig. 4. *Optic nerve sheath diameter in the left and right eyes pre and post decompressive craniectomy. Legend: RE Pre – right eye pre-decompressive craniectomy; RE Post – right eye post-decompressive craniectomy; LE Pre – left eye pre-decompressive craniectomy; LE Post – left eye post-decompressive craniectomy. The markings beyond the ONSD column of the left eye before DC represent outliers.*

we found a study that documented changes in ONSD using cranial CT, according to subgroups based on the Bamford clinical classification. In that particular study, an analysis of both eyes was performed with results very similar to what we found in our study. The cut-off point for the right eye was 5.4 mm with a sensitivity of 75% and specificity of 91%, while the cut-off of the left eye was 5.3 mm with a sensitivity of 80% and specificity of 84%.[18] It was also observed that of all the studied subgroups, patients classified as total anterior circulation stroke syndrome (TACS) had the highest ONSD in both eyes, which corroborates the relevance of studying this patient profile. It is important emphasize that our objective was not to determine the ONSD as a predictor of MCA infarct, but to determine a value that could be a marker for severe ICH related to MCA infarct.

In the case of the affected hemisphere correlation with the altered optic nerve with respect to ICH (ipsilateral and / or contralateral), there are few literature data for comparison. In our study, a dominance of the left optic nerve alteration was observed, even though the lesion was not located ipsilaterally, as well as a predominance of bilateral optic nerve alteration. Although unilateral involvement is described as a rare event,[19] in this study, the alteration of a single optic nerve, regardless of the affected hemisphere, represented almost one third of the

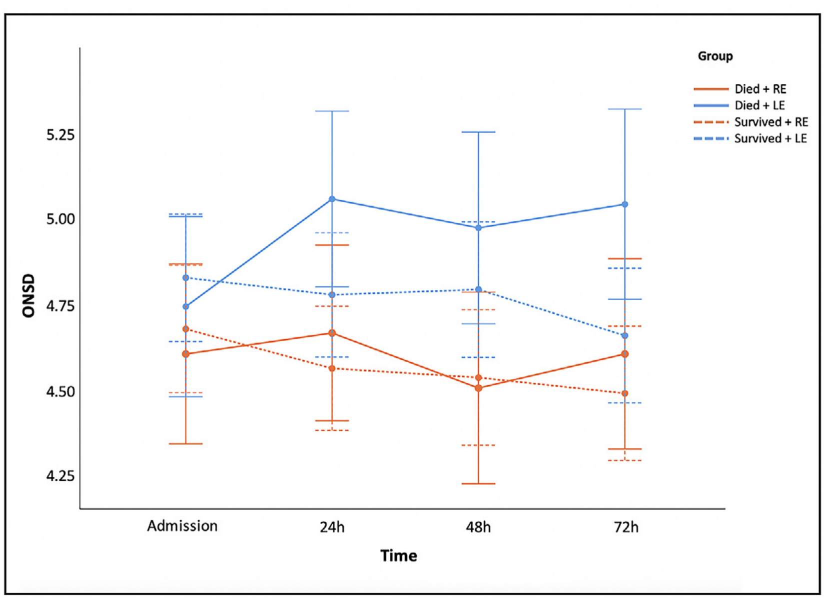

Fig. 5. *Outcome of patients with malignant middle cerebral artery infarction, surgical, non-surgical, according to the evolution of the optic nerve sheath diameter of the right, and left eyes. Legend: RE – right eye; LE – left eye; ONSD – optic nerve sheath diameter.*

Table 2. *Studies that measured the intracranial hypertension by ultrasonography measurement of optic nerve sheath diameter.*

Authors (Year)	Patients' Profile	Sample size	Correlation	*Cut-off*	Sensibility	Specificity
Rejajee *et al.* (2011)[18]	CVD	65	CIC, TC e RNM	4.8 mm	98.0%	94.0%
Tayal *et al.* (2007)[19]	TBI	59	CT	5.0 mm	100.0%	63.0%
Aduaui *et al.* (2015)[14]	EL	160	CT	5.2 mm	81.2%	100.,0%
Raffiz; Abdullah (2016)[20]	TBI / CVD	41	ICC	5.2 mm	95.8%	80.4%
Munawar et *al.* (2019) (21)	TBI	100	CT	5.8 mm	94.0%	96.0%
Lee *et al.* (2015) (22)	Suspect ICH/Stroke	134	CT	5.9 mm	98.7%	85.1%
Kishk *et al.* (2018) (23)	IICH	134	LP	6.0 mm	73.2%	91.4%
Del Saz-Saucedo *et al.* (2016) (24)	IICH	30	LP	6.3 mm	94.7%	90.9%
Soliman *et al.* (2018) (25)	TBI	40	ICC	6.4 mm	85.3%	82.6%
Lochner et al (2020)[13]	Stroke	29	CT	5.6 mm	100%	90%

Legend: CVD: cerebrovascular diseases; TBI: traumatic brain injury; EL: expansive lesions; ICH: intracranial hypertension; IICH: idiopathic intracranial hypertension; ICC: intracranial catheter; CT: computed tomography; MRI: magnetic resonance; LP: lumbar puncture.

cases. Larger sample documenting separately single eyes measurements are needed to confirm this phenomenon. Important to notice that, even though single-eye curves had different measurements on follow-up, cut-off values were similar for predicting intracranial hypertension.

All patients who underwent DC presented changes in the ONSD of the right and or left eyes, compatible with ICH. In addition, after craniectomy, 72.7% (n = 8) of the patients had normalized ONSD. Of the three patients who remained with altered ONSD, 02 persisted with progression of cerebral edema and the other evolved with hemorrhagic transformation and cerebral edema. A study carried out with 33 patients submitted to hemicraniectomy undergoing invasive ICP monitoring and ocular ultrasonography, showed that, after hemicraniectomy, the ONSD measured by ultrasound was not reliable to assess ICP, despite having shown a prognostic value for a bad neurological evolution. They also stated that the increase in ONSD induced by ICH before DC could also play an important role in neurological prognosis.[20] In our study, due to small sampling, it was not possible to establish whether the ultrasound method for determining ONSD would interfere with the follow-up of patients after craniectomy.

The identification of different follow-up pattern of ONSD, among patients who survived, was also an important data demonstrated in this study, suggesting that patients with decreases in the value of ONSD in the first 3 days after admission, may evolve with a better clinical outcome. This data is similar to the one described by Lochner et al, described as a persistent high binocular ONSD measurements on patients with malignant MCA infarct over 3 days of follow-up.[13] On the other hand, patients who died had higher measurements on the left eye that raised in the 24h evaluation window. This is an interesting result that needs to be better explored to determine if ONSD could be used as a parameter to indicate DC in the first 48h after an MCA ischemic stroke.

One of the main limitations of the present study was related to the small number of research participants, which limited the possibility of other statistical analyzes, such as a multivariable regression analysis. In addition, the failure to use a direct and more reliable ICP measurement method for comparison with ultrasound measurements, may have generated false-negative results. Even though a DC protocol is routinely adopted at this center, the neurosurgical team was allowed to perform surgery using individual interpretations of criteria, with controversial decisions on some DC cases. As strengths of the study, we would like to point out the followings: (a) the examination by a single experienced physician; (b) use of a single ultrasound device; and (c) carrying out the study on a single patient profile.

Conclusion

Our study shows that ultrasound measurement of ONSD in patients with MCI infarction is a useful method for defining severe ICH, through the cut-off point of 5.4 mm for both eyes, in addition to serving to monitor patients undergoing decompressive craniectomy. Additional studies will be necessary to determine the use of ONSD on the DC protocols, possibly using lower cut-off values as to avoid herniation performing early decompressive craniectomy.

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None.

Declaration of Competing Interest

None.

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