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Original article

Measurement of Optic Nerve Sheath Diameter and Optic Nerve Sheath Diameter to Eyeball Transverse Diameter Ratio using Ultrasonography in Patients with Neuro-critical Illness and their correlation with raised Intracranial Pressure and functional outcome – A Prospective Observational Study

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ABSTRACT

Background and Aims - The primary objective of this study was to assess the diagnostic utility of bedside USG guided ONSD and ONSD/ETD ratio in patients with neuro-critical illness and its correlation with functional outcome. Material and Methods-All patients meeting the inclusion criteria were studied after obtaining written informed consent and ensuring that they do not fall in the exclusion criteria. The disease course of the study patients was monitored closely in ICU with respect to hemodynamic parameters. ONSD and ETD were measured at admission and on the 3rd, 5th, 7th, 14th, and 28th days. USG-based ONSD and ETD measurements were compared, and initial ONSD/ETD and other readings were averaged over the study period and compared with functional outcomes using GOS criteria. Mann Whitney U test for continuous variables and Pearson correlation were used for analysis.Results-ROC graph showed ONSD on Day 1 as a slightly better predictor of raised ICP as compared to the ONSD/ETD ratio on Day 1. The ONSD/ETD ratio before Death/Discharge was significantly higher in the unfavorable outcome group (GOS 1-3) as compared to the favorable outcome group (GOS 4-5). ONSD at day 1 and ONSD/ETD ratio at Day 1 showed a weak negative correlation with the GOS while before death/discharge, they showed a moderately negative correlation. Conclusion- Ocular ultrasonography can be used as an early test for diagnosing raised ICP and can be repeated for re-evaluation. We suggest ONSD measurement be adopted as a point-of-care test in ICU patients.

Introduction

Serious neurological illness is life-chaning for the patient and family. Traumatic brain injury (TBI), Intra-Cranial Hemorrhage (ICH), stroke, septic encephalopathy, metabolic encephalopathy, meningitis, and meningoencephalitis are some of the neurological illnesses commonly seen in Intensive care units. Neurocritical patients require comprehensive medical and specialized neurological support in addition to standard interventions.

Areas of expertise unique to neurocritical care include the management of intracranial pressure, hemodynamic augmentation to improve cerebral blood flow, therapeutic hypothermia, and advanced neuromonitoring.[1]

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Increased Intracranial Pressure (ICP) causes brain insult, possibly associated with increased mortality and poor neurological outcomes. Early diagnosis and prompt treatment of raised ICP is lifesaving.[2] Monitoring of ICP has been used for decades in the fields of neurosurgery and neurology and can be measured using both invasive and non-invasive means. Invasive techniques are ventriculostomy, lumbar puncture manometry, and micro-transducers, ventriculostomy being the gold standard in terms of accurate measurement. Non-invasive techniques are Transcranial Doppler Sonography (TCD), Tympanic Membrane Displacement (TMD), Magnetic Resonance Imaging (MRI), Computed Tomography (CT) & Ultrasonography.

Increased ICP may be detected on ocular fundoscopy / Computed Tomography (CT) of the brain and invasive monitoring (which requires professional expertise and may not be available all the time at all places). Dependence on imaging studies to diagnose a cerebral insult requires the shifting of critically ill patients from the ICU to imaging centers and may endanger the lives of critically ill and hemodynamically unstable patients. [3] Invasive (ICP) monitoring is challenging as it requires the expense and availability of trained personnel.

Also, others concern include patient instability and risks of infection and bleeding,[4] Overall, in India, most of the neurocritical patients do not have invasive monitoring in place because of one of the reasons stated above.

Optic nerve sheath diameter (ONSD)measurement is a noninvasive and bedside method of diagnosing raised ICP. The optic nerve is myelinated and has three meningeal layers covering it. Its subarachnoid space is continuous with that of the brain. Hence, the intra-orbital subarachnoid space surrounding the optic nerve is responsive to the same pressure changes as the intracranial compartment. This makes the human optic nerve sheath elastic enough to allow a detectable dilatation in response to increased Intracranial Pressure (ICP). Raised ICP leads to increased CSF Pressure around the brain which then is transmitted around the optic nerve and increases the optic nerve sheath diameter. Various studies have shown that ONSD increases within seconds of a raise in ICP which can be detected early with ocular sonography.[5]

The upper limit of normal ONSD in Indian adults is considered to be 4.8 mm.[6] Eyeball Transverse diameter (retina to retina) is the maximum distance of the eyeball obtained by scanning the eyeball from the superior to the inferior side. Few studies showed that the ultra-sonographic ONSD/ETD ratio may be a better marker of elevated ICP as compared to ONSD alone.[7] In healthy adults, the ONSD/ETD index equals 0.19 ± 0.02 if measured in the middle third of the optic nerve intra-orbital path (the point where the ophthalmic artery crosses the optic nerve serves as an anatomical landmark).[2]

Persisting disability after brain damage may include both mental and physical handicaps. A five-point scale called GOS (Glasgow Outcome Scale)**(Table 1)**

Score	Rating	Definition	Interpretation
1	Dead	Non survival	Unfavorable outcome
2	Vegetative state	Minimal responsiveness	Unfavorable outcome
3	Severe disability	Conscious but disabled; dependent on others for daily support	Unfavorable outcome
4	Moderate disability	Disabled but independent; can work in sheltered setting	Favorable outcome
5	Good recovery	Resumption of normal life despite minor deficits	Favorable outcome

which was first introduced in 1975 by Jennett and Bond[8] describes the objective degree of recovery - death, persistent vegetative state, severe disability, moderate disability, and good recovery. The same scale has been used in this study to assess the patient's outcome. The primary objective of this study is to assess the diagnostic utility of bedside USG-guided ONSD and ONSD/ETD ratio in patients with neuro-critical illness and its correlation with functional outcomes. The secondary objective of the study is to establish a correlation of USG-guided ONSD and ONSD to ETD ratio with clinical and radiological signs of raised ICP.

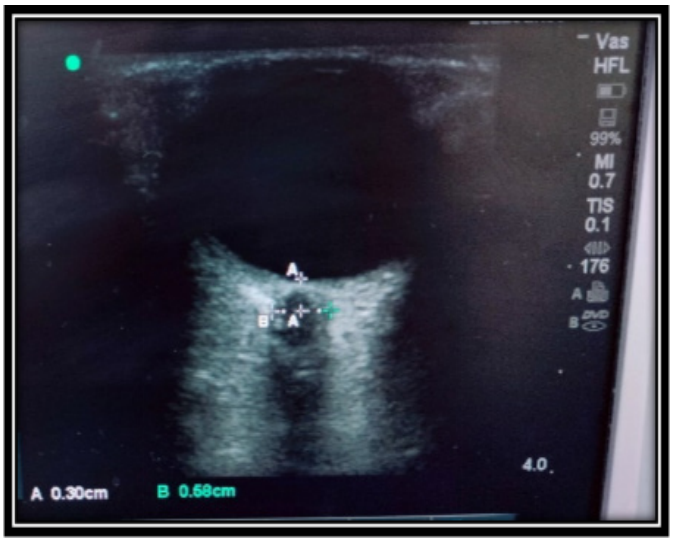
Methods

This prospective, monocentric, observational study was conducted in a tertiary care hospital in India after taking institutional ethical committee approval and in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2013. Adult patients (aged>18years)withneurocriticalillnessadmittedtoICUbetweenJune2021 andJune2022 wereincludedinthestudywhilepatientswithanyhistoryof glaucoma, optic neuritis, arachnoid cyst of the optic nerve, high myopia, optic nerve trauma, anterior orbital or cavernous sinus mass, ocular trauma, conjunctival edema, or orbital edema, hypercarbia (PCO_2 > 45 mm of Hg), cardiopulmonary resuscitation after cardiac arrest, spinal cord injury, diabetic ketoacidosis, thyroid disorders, and uncooperative patients were excluded from the study. Written informed consent to participate in the study and consent to publish was obtained from the next of kin or legally authorized representative and documented in the patient's medical record, as approved by the ethical review committee. The detailed history of patients was taken from next of kin. Signs and symptoms like headache, vomiting, drowsiness, anorexia, neck pain, convulsions, pulsatile tinnitus, new onset sensory or motor loss, blackouts, altered sensorium, coma, visual disturbances (blurred vision, visual field loss, double vision) were considered to be positive and clinically suggested of raised ICP. Ultrasound-guided ONSD and ETD were performed on the 1st, 3rd, 5th, 7th, 14th, and 28th day wherever possible or till death/discharge (if earlier). Baseline HR, blood pressure (SBP, DBP, MAP), respiratory rate (RR), oxygen saturation (SpO_2), and GCS were recorded on arrival at ICU. The disease course of the study patients was monitored closely in ICU with respect to the above-mentioned parameters.

Measurement of ONSD - Patients were examined in the supine position with (20–30) degree head end up using a Sono Site M-Turbo® system with a high resolution (7.5-11) MHz phased linear array probe on the closed eyelids. The structures of the eye were visualized to align the optic nerve directly opposite the probe, with the ONSD width perpendicular to the vertical axis of the scanning plane (Figure 1 a).

Figure 1 (a) Ultra sonographic image of abnormal ONSD measurement: From A to A is the distance (0.3 cm) behind the optic disc where the ONSD is measured in its width. Distance 2 is the ONSD (0.58 cm).
Figure 1 (b): Between the two arrows is the eyeball transverse diameter.

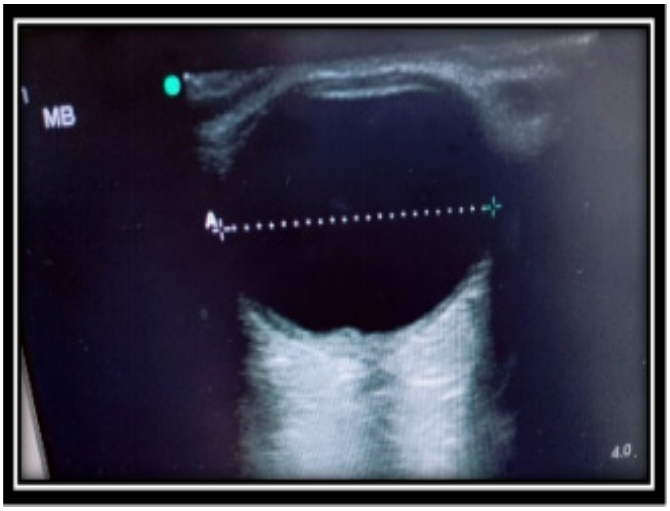
1(a)



Three measurements were taken for each optic nerve using the digital cursor and measurement software of the ultrasound machine. The ONSD measurements were obtained averaging three readings from each eye to create a binocular ONSD measurement by calculating their average. The measurements above 4.8 mm were considered to have increased ICP. ETD was also measured, and ONSD/ETD ratio was calculated (Figure 1 b).

All patients detected to have ONSD >4.8 mm during the study were re-evaluated by Neurosurgeon/Neuro-physician. Repeat CT Head and orbit was done only in specific cases depending on GCS and ONSD/ETD ratio

1 (b)



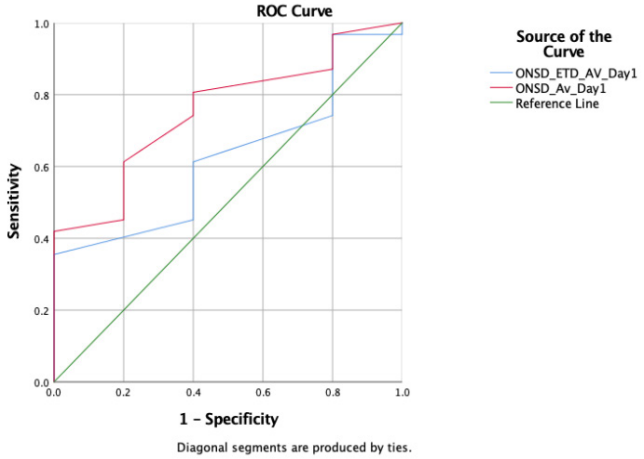
and neurosurgery/neurology review. USG-based ONSD and ETD measurements were compared, and initial ONSD/ETD and other readings were averaged over the study period and compared with functional outcomes using GOS criteria (Table 1). CT imaging result was considered to be positive if findings suggested a radiologic diagnosis of raised ICP such as midline shift of >3 mm, effacement of ventricles/ basal cisterns, significant cerebral edema/subarachnoid hemorrhage, mass effect, the collapse of ventricles, loss of white and grey matter differentiation, compression of cisterns, effacement of sulci, hydrocephalus and brain herniation.

Results

Receiver Operating Characteristic (ROC) curve showed ONSD on day one as a slightly better predictor of raised ICP as compared to the ONSD/ ETD ratio on day one. The Area under the curve (AUC) for ONSD on day one (0.755) turned out to be higher than the AUC value for ONSD/ETD ratio on Day one (0.626) (Figure 2).

Figure 2: ROC analysis of ONSD & ONSD/ETD ratio (day one) with the radiological signs of raised ICP
a) Under the nonparametric assumption
b) Null hypothesis: true area = 0.5

Further, the coordinates table from the Statistical Package for the Social Sciences (SPSS) provided the cut-off



values and their respective Sensitivity and Specificity data. At cut-off 0.45 (ONSD) and 0.19 (ONSD/ETD), the parameters had 96.8% sensitivity to predict raised ICP. Similarly, when ONSD parameters were evaluated to identify raised ICP one day prior to death/discharge, the AUC for ONSD at/before Death/Discharge was 0.765, and for the ONSD/ ratio it was 0.632 (Figure 3).

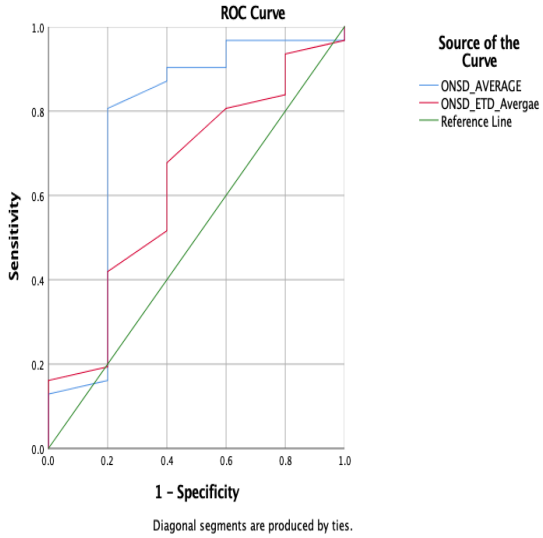
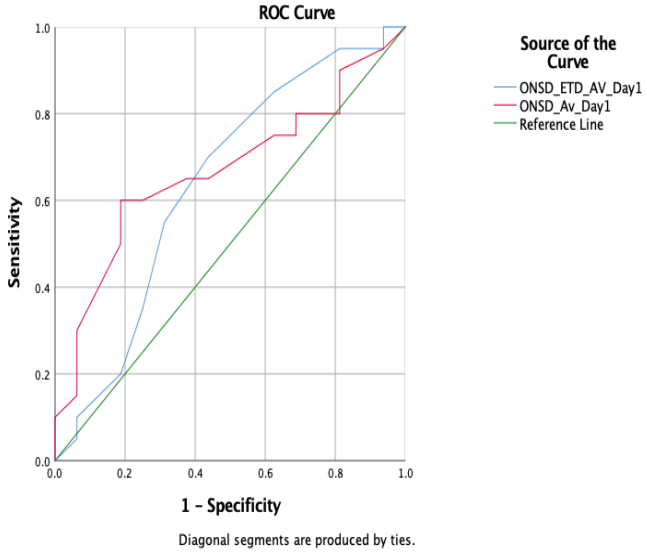


Figure 3: ROC analysis of ONSD & ONSD/ETD (Death/Discharge) with the radiological signs of raised ICP

The ROC curve analysis for the ONSD parameters and the GOS outcomes was assessed. The ROC curve analysis for the ONSD parameters and the GOS outcomes revealed AUC for ONSD at day one to be 0.669 and an



ONSD/ETD ratio of 0.639 (Figure 4). Further, the coordinates table from the SPSS provided the cutoff values and their respective sensitivity and specificity data. At cutoff 0.45 (ONSD) and cutoff 0.20 (ONSD/ETD), the parameters had 95% sensitivity each to predict unfavorable outcomes on Day one. A similar comparison was done one day prior to death/ discharge which revealed the AUC for ONSD and ONSD/ETD at Death/ Discharge was 0. 68 Further, the coordinates table from the SPSS provided the cut-off values and their respective Sensitivity and Specificity data. At a cut-off of 0.45 (ONSD) and 0.19 (ONSD/ETD), the parameters had 95% and 90% sensitivity respectively. The Association of the GOS (favorable and unfavorable outcomes) showed that it was significantly

as sociated with the GCS score with GCS being significantly high er in the favorable outcome category. (14.9 vs 5.8, (p=0.023). Further, ONSD & ONSD/ETD before death/discharge were significantly associated with and significantly higher in the unfavorable outcome group. The ONSD parameters on Day One were not found to be significantly associated with the GOS outcomes. The Pearson Correlation analysis showed that GOS was negatively correlated with the ONSD parameters before death/discharge. The Pearson correlation analysis showed that ONSD and ONSD/ETD showed a moderate negative correlation (-0.463 & -0.510) with the GOS score which was highly significant i.e., when the GOS score increased the ONSD parameters decreased (Death/Discharge).

GOS	GCS	GOS score	ONSD Day 1	ONSD (Death/ Discharge)	ONSD/ETD Day 1	ONSD/ETD (Death/ Discharge)
Unfavorable Outcome (1-3)	5.8 + 4.06 _	1.75+ 0.85 _	0.57+ 0.06 _	0.54+ 0.07 _	0.24 + 0.02 _	0.230 + 0.02 _
Favorable Outcome (4-5)	14.9+ 0.25 _	4.8+ 0.34 _	0.53+ 0.05 _	0.49+ 0.02 _	0.23+ 0.02 _	0.21+ 0.01 _
P value	P <0.05*	P <0.05*	P >0.05	P < 0.05*	P > 0.05	P < 0.05*

Table 2: Comparison of Favorable/Unfavorable Outcome on GOS with GOS scale, ONSD and ONSD/ETD (Day 1/ Death or Discharge)

***-Significant at 5%, Mann Whitney U Test.**

Discussion

Invasive ICP monitoring is not widely available across the ICUs, especially in resource-limited settings. A 2022 survey in India showed that only 36.42% patients had access to exclusive neurocritical care units, and 63.4% of consultants did not monitor ICP. Amongst the physicians who monitored for raised ICP, 60.32% used CT/MRI scans, 28.57% intraventricular catheter with external transducer, and 11.11% used Codman microsensor.[9] This shows the extent of the deficit in terms of advanced neuro-monitoring facilities across ICUs in resource-limited settings. USG ONSD is a good alternative to the available methods for ICP monitoring. We conducted a prospective study with the primary objective of validating ONSD by bedside ultrasound compared to features of raised ICP on the CT/MRI. The current study showed a higher mean ONSD at Day 1 (0.57+ 0.06) cm in the unfavorable outcome as compared to patients with unfavorable outcome (0.53 + 0.05) cm. However, the difference was statistically insignificant. This was in line with the study done by Donovan et al.[10] where initial ONSD was higher in the participants who died (0.56) versus those who survived (0.52). He concluded that ONSD ultrasound had a potential role as a noninvasive, affordable bedside tool for predicting brain pathology and death in TBM. Lovrenčić-Huzjan A et al study revealed that the patients with favorable outcomes had mean ONSD 5.64 + 0.61 mm compared to 5.94 + 0.77 mm in patients with unfavorable outcomes (p=0.06) and increased ONSD was also associated with increased ICP.[11] Physical findings of raised ICP are nonspecific and lack accuracy in diagnosing raised ICP. Diagnosis of raised ICP is essential as it may be associated with poor clinical outcomes. Early intervention using osmotherapy with hypertonic saline or mannitol has been shown to be effective in lowering ICP.[12-14]

ROC analysis of ONSD parameters in our study showed that ONSD at Day1 was a slightly better predictor of raised ICP as compared to the ONSD/ETD ratio at Day1 since the area under the curve (AUC) for ONSD was more as compared to AUC for ONSD/ETD ratio. The sensitivity for the ONSD parameters in the current study was 96.8% which was higher as compared to the study done by Caffery et al. who showed that the sensitivity of the optic nerve sheath diameter in detection of the elevated ICP was 75%. The contrasting results with the study conducted by Caffery et al. could be because they only examined the non-traumatic causes of the ICP whereas we considered all the causes.[15] Apart from the isolated studies, one meta-analysis has also shown that ONSD had a good level of diagnostic accuracy for detecting the ICP and thus aid in clinical decision-making and monitoring of the ICP.[16] The systematic review and meta-analysis composed of 231 patients from 6 studies found a pooled sensitivity of 0.90, a specificity of 0.85, and a diagnostic odds ratio of 51, for the ONSD to detect raised ICP. We opine that due to the high sensitivity of ONSD parameters in detecting raised ICP, it can be used as a bedside test as a primary investigation in the ICU setup. Confirmatory imaging tests can be done as a secondary test to confirm the findings and rule out false positives of the earlier test. This will go a long way in minimizing adverse events in shifting hemodynamically unstable patients for imaging and also help in providing early diagnosis and management of raised ICP which is vital to patient outcomes.

The correlation analysis showed that ONSD and ONSD/ETD ratio had a negative correlation with the GCS and GOS, which were similar to the results of Bekerman et al. [17] In our study, ONSD parameters showed a weak negative correlation with GOS on day 1, however, they showed moderate negative correlation before death/discharge which was significant at 1%. The strength of correlation was higher in the ONSD/ETD before death/discharge (Figure 4). Ultrasonographic measurement of ONSD is noninvasive, safe, quick, and can provide early detection of raised which will help in preventing secondary brain injury. Most of the hospital ICUs in our country do not practice invasive monitoring and in suspicion of raised ICP in patients, repeated CT scans are done. In such healthcare facilities, ONSD can be very helpful in the early detection of raised ICP so that measures to reduce ICP can be initiated quite early. Therefore, ONSD is a valuable modality in determining the severity of raised ICP, deciding the next line of treatment, referring to higher centers, in disasters, or when a CT scan is unavailable and where the referral center or a tertiary care center is at a longer distance.

Limitations

This novel study explored the ONSD and ONSD/ETD ratio and their ability to predict the ICP. The study also explored the ability of the above-mentioned variables to predict the outcome of the patient in terms of GOS. However, the study has several limitations. First, the factors affecting the ONSD are still unclear. Secondly, the normal range or threshold of ONSD for diagnosing intracranial hypertension is uncertain, and the two ranges may overlap. Thirdly the reliability of ONSD needs to be improved. USG-guided ONSD measurement has limitations such as lacking standardization of technique and value interpretation. Moreover, due to recent COVID-19 restrictions, it was not possible to follow up with participants after discharge. Also, patients need to be followed up for a longer duration of around 3 to 6 months instead of 28 days (as in the current study) for better correlation of optic parameters with the functional outcome of neurocritical patients. Further, the study should be extrapolated to multicenter, and large-sample studies need to be conducted to avoid insufficient statistical power due to low sample size.

Conclusion

Ocular ultrasonography can be used as an early test for diagnosing raised ICP and can be repeated for re-evaluation. We suggest ONSD measurement be adopted as a point-of-care test in ICU patients. It will help detect cerebral insults, monitor neurological status, guide treatment strategy, and predict prognosis.

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