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Advancements in Non-Invasive Intracranial Pressure Monitoring via Optic Nerve Sheath Diameter Measurement

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Intracranial pressure (ICP) monitoring is the mainstay of treatment for patients with brain tumors, hydrocephalus, cerebral edema, and traumatic brain injury (TBI). At present, there are 2 main monitoring methods: non-invasive and invasive. Although invasive monitoring of ICP is the criterion standard, non-invasive approaches based on measurement of optic nerve sheath diameter (ONSD) are becoming increasingly popular because of their simplicity, low cost, and accuracy. Ultrasound (US) measurement of ONSD is especially useful because it allows dynamic evaluation of ICP over the hospital and treatment period in a real-time manner and can be performed bedside for better patient acceptance. This paper reviews the research progress, and highlights the advantages, performance, and results of various ONSD measurement approaches, including US-based ONSD measurement, with regard to its principles, operation method, and clinical applications, as well as ONSD measurement by other techniques such as computed tomography (CT) and magnetic resonance imaging (MRI). New developments, including use of the ONSD/ocular transverse diameter (ETD) index and possible future studies on ONSD-based/assisted therapy and treatment for patients with TBI, stroke, and other conditions that can increase ICP will also be discussed.

Keywords: Brain Concussion • Intracranial Hemorrhages • Intracranial Hypertension • Nerve Tissue

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Introduction

Severe brain tissue damage, intracranial space-occupying lesions, cerebral hemorrhage, intracranial inflammation, and hydrocephalus can disrupt the compensatory mechanisms in the brain, resulting in rapid elevation of intracranial pressure (ICP), particularly in patients with intracranial hemorrhage or extensive cerebral infarction, subsequently causing deterioration of the condition and prognosis, leading to brain herniation and death in severe cases [1,2]. Elevated ICP (>15 mmHg) is an early sign of intracranial complications and is the main cause of death. Therefore, early and rapid determination of ICP is of very important for controlling ICP and preventing secondary brain injuries [3]. Currently, there is no single intervention modality that can prevent ICP elevation; however, optimizing the brain metabolic environment and cerebral perfusion pressure (CPP) using hypertonic saline (HTS) and mannitol can attenuate secondary brain injury and improve prognosis [4]. With advancements in technology and science, various invasive and non-invasive modalities for monitoring ICP have become available [5,6]. Invasive modalities, such as lumbar puncture and transducers connected to the extra-ventricular drainage, remain the criterion standard for ICP monitoring [6]. However, they are associated with the risk of hemorrhage, infection, and other complications, as well as high cost [7-9]. This is particularly true for children, and especially infants.

With the development of high-frequency ultrasonography, non-invasive ICP monitoring techniques based on optic nerve sheath diameter (ONSD) measurement, venous ophthalmodynamometry, tympanic membrane displacement, tissue resonance analysis, tonometry, acoustoelasticity, transcranial Doppler, electroencephalogram, near-infrared spectroscopy, pupillometry, anterior fontanelle pressure monitoring, skull elasticity, jugular bulb monitoring, visual evoked response, and radiological assessment of ICP are gaining popularity or being assessed as a replacement or alternative to the criterion standard [10,11]. Among them, ONSD measurement has been used clinically as a safe, fast, effective, portable, and dynamic non-invasive technology for monitoring ICP in patients with cerebral conditions, including brain injuries and tumors [11,12]. Studies have shown that as a result of an increase in ICP, ONSD will increase. Therefore, it was proposed that ICP could be monitored based on ONSD measurement [13]. However, ONSD is not intended to replace invasive ICP monitoring modalities like external ventricular drains (EVDs) or intraparenchymal monitoring, because the accuracy of ONSD depends on many factors, such as the skill and experience of the person performing the ultrasound, patient variability such as age and sex, and underlying conditions. Therefore, ONSD can serve as a screening or complementary tool in specific scenarios and patient populations.

In this paper, we review and discuss the research progress and advantages of ultrasound (US)-based ONSD measurement, including its principles, operation method, and clinical applications. New developments, including the use of the ONSD/ocular transverse diameter (ETD) index, and future studies on ONSD-based therapy for patients with traumatic brain injury (TBI) and other cerebral conditions such as tumor, hydrocephalus, and cerebral edema are also discussed.

Neuromonitoring for Neurologically Critically Ill Patients

Neurologically critically ill patients require multimodal and specialized functional assessments, including heart rate, blood pressure, respiration, blood oxygen, and specialized neurological examinations. Brain tissue damage, impaired autoregulation of cerebral blood flow, and associated complications due to altered brain metabolism caused by inflammatory mediators, oxidative stress, and vascular spasm can lead to secondary brain injuries, such as ischemia, edema, epileptic seizures, and hydrocephalus [14,15]. Secondary brain damage is the main cause of death among critically ill patients. For these patients, monitoring ICP, cerebral perfusion pressure (CPP), cerebral hemodynamics, cerebral metabolism, electroencephalogram, and brain oxygenation can help reduce secondary brain injury, among which ICP and CPP are the most important parameters to monitor. ICP and CPP can, to some extent, reflect cerebral blood flow (CBF), which is stabilized through static and dynamic self-regulation mechanisms to prevent secondary brain damage due to ICP elevation, ischemia, congestion, and hypoxia [16]. An elevated ICP can also cause brain ischemia or herniation damage [17]. ICP monitoring and early intervention are effective in reducing the mortality rate and improving the prognosis of patients in neuro-intensive care units. For example, Talving et al found that TBI patients receiving ICP monitoring had significantly lower mortality rates compared to those who did not receive ICP monitoring (32.7% vs 53.9%) [18]. Without ICP monitoring, the mortality rates due to cerebral herniation also significantly increased (21.7% vs 12%) [19] because increased ICP will result in increased mortality rates, as shown by Balestreri et al [19], who found that when ICP exceeded 20 mmHg, the mortality rate increased from 17% to 47%. Saul et al found that for TBI patients undergoing ICP monitoring, the mortality rate for patients starting treatment with ICP at 15 mmHg was 28%, whereas for those starting treatment at 20-25 mm Hg, the mortality rate was 46%, highlighting the importance of ICP monitoring [20].

ICP Monitoring

Based on the Monroe-Kellie doctrine, the space of the cranial cavity is fixed in volume and contains fixed proportions of brain matter, blood (approximately 150 ml), and cerebrospinal

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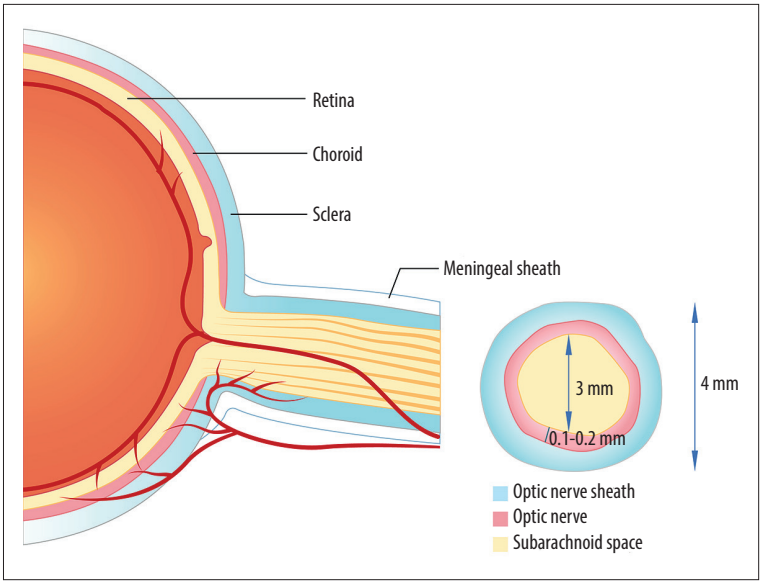

Figure 1. Transverse section of optic nerve sheath.

fluid (CSF) (approximately 150 ml). Because of this fixed space, an increase in the volume of one of these components must lead to the loss of another component in equal amounts [21]. Among these, CSF and intracranial blood are the easiest to regulate [22]. However, once the compensatory reserve reaches its limit, the ICP increases [23]. When ICP increases, CSF enters the subarachnoid space of the optic nerve through the optic canal, leading to an expanded intrathecal space of the optic nerve and an increased ONSD (**Figure 1**) [24-26].

ICP monitoring methods can be divided into invasive and non-invasive methods. In invasive methods, monitoring devices are inserted into the ventricles, parenchyma, subarachnoid space, and extradural space to monitor ICP. Ventricular drainage (EVD) is the criterion standard for monitoring the increase in ICP [6,27], where a ventricular drainage catheter is placed in the lateral ventricle at the interventricular foramen for external pressure sensors for measurement, enabling high accuracy and real-time ICP monitoring of ICP and other clinical parameters such as heartbeat, blood pressure, and central venous pressure. EVD can also be used to reduce ICP by draining the CSF. However, the drainage catheter needs to be accurately positioned, and advanced technical skills are required. When the ventricles are displaced, compressed, or become smaller, placing a drainage catheter becomes difficult and can also lead to various complications such as infection, hemorrhage, and CSF leakage [6]; among them, infections associated with ventriculostomy are common in EVD [28]. A meta-analysis of 60-year data from MEDLINE by Lozier et al showed that the incidence of infections related to ventriculostomy was between 0% and 22%, mostly around 10%, in different studies [29]. Some studies also suggest that invasive ICP monitoring is not suitable for long-term monitoring because infection increases over time [30].

Non-invasive ICP monitoring includes ONSD measurement, electroencephalogram, transcranial Doppler ultrasound (TCD), cerebral blood flow velocity, near-infrared spectroscopy (NIRS), evoked potential, pupil measurement, and other methods. NIRS utilizes the difference in absorption spectra between oxygenated hemoglobin (HbO_2) and deoxyhemoglobin (DHb) in the cerebral cortex to determine ICP based on brain tissue oxygenation, cerebral blood volume (CBV), and CBF [31]. When ICP changes, NIRS parameters can predict an increase in ICP earlier than EVD parameters [32]. Weerakkody et al found that relevant changes in DHb and HbO_2 can be used noninvasively to monitor ICP [33]. However, more studies are needed to investigate the sensitivity of NIRS for monitoring ICP changes.

TCD windows are located in areas with thin skull bone and can be used for real-time monitoring of hemodynamics and physiological parameters, such as blood flow direction, flow velocity (FV), pulsatility index (PI), and impedance index in the main cerebral arteries. When ICP increases, CPP and FV decrease, and blood flow resistance and PI increase. Therefore, TCD can be used to monitor ICP. It has the advantages of noninvasiveness, safety, high repeatability, and bedside procedures. The correlation coefficient between ICP and PI is 0.31 to 0.82 [34,35]. However, a meta-analysis by Fernando et al found that the area under the curve (AUC) value for TCD to predict PI was relatively low, at 0.550-0.718. In addition, TCD monitoring of brain blood flow requires high technical skill of operators, because slight changes in the direction of the ultrasound probe will have a remarkable impact on the results. When patients have severe skull trauma or increased ICP due to disturbance in cerebrospinal fluid circulation or an increase in brain parenchymal volume, TCD monitoring of ICP may be restricted. On other hand, the AUC value for assessing the elevation in ICP by ONSD could be as high as 0.94 (95% CI: 0.91-0.96). ONSD is not related to ICP in

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subarachnoid hemorrhage (SAH) because it does not accurately estimate ICP in SAH patients in the intensive care unit [36].

ONSD Measurement

Although ultrasonic (US) assessment of ONSD is well-evaluated, it is desirable to combine information gained from different imaging techniques for better differential diagnosis and cross-validation [37]. ONSD can be monitored using one or more of these techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), in addition to US, to monitor ICP. Recently, automatic ONSD measurements is being explored using US videos to improve diagnosis [38], and standard ONSD point -of-care ultrasonography is still not under development [39].

US Measurement of ONSD

US measurement of ONSD can be performed using a US scanner with a linear array probe. During scanning, patients are positioned with the head raised to 30° and in a neutral position, with the neck positioned for venous return. Coupling gel should applied to the probe before being placed on the upper eyelid just below the supraorbital rim. B-mode scans should be acquired in an axial plane to detect the eyeball and the optic nerve surrounded by its sheath and centered along its longitudinal axis. For each examination, at least 2 operators are suggested to perform ONSD measurements independently [40]. On a two-dimensional US scan, the optic nerve sheath is clearly visible and easy to distinguish. ONSD can be scanned horizontally, vertically, and axially to display different structures. Both horizontal and vertical scans can capture and clearly show the optic nerve sheath and intrathecal tissue and the three-layer structures surrounding the dark area of the optic nerve with high-low-high echoes from the inside out [41]. In the case of increased ICP, changes in the optic nerve can take several hours to occur [42], and US can detect changes in ONSD in the early stage [42].

US measurement of ONSD is a reliable way to determine admission eligibility to the ICU due to elevated ICP [12]. Chen found that subjects diagnosed with intracranial hypertension through lumbar puncture had higher ONSD based on US measurement than controls with normal ICP (4.53±0.40 mm vs 3.97±0.23 mm, $P<0.001$), indicating a clear correlation between ICP and ONSD [43]. Robba et al found that among the 320 patients, ONSD cutoff between 4.80 and 6.30 mm has excellent prediction ability for patients with elevated ICP (AUC 0.94) [13]. It is generally agreed that ONSD >5 mm is the cutoff for elevated ICP [44], which can differ with age. In children, when ICP is ≥20 mmHg, ONSD is 5.5 mm. As US measurement of ONSD can help estimate ICP and improve prognosis and outcomes, it is a useful monitoring method.

ONSD Measurement with CT

With the emergence of CT, the diagnosis and treatment of head diseases have become increasingly dependent on this technique. Currently, CT is the preferred imaging method for diagnosing intracranial space-occupying lesions. It can not only locate lesions but also detect the presence of hydrocephalus and cerebral edema in the ventricular system. CT imaging also contributes to the diagnosis and treatment of elevated ICP [45]. When ICP is elevated, CT can reveal pathological changes in the brain, such as edema, compression of the sulci and gyrus, reduced ventricles, and a series of changes in the optic nerve. When monitoring ICP in a female patient over 30 years of age with suspected encephalitis, repeated CT scans showed brain swelling with increased stenosis of the midbrain cerebellar cistern. The ONSD measured by CT was 7.1 mm at this time, whereas in the initial CT scan, the ONSD was 4.6 mm, showing a high consistency between the increase in ONSD and ICP [46]. Su et al measured ONSD in 88 neurological patients using CT reconstruction and found that ONSD was positively correlated with ICP and had a predictive value for intracranial hypertension [47]. Major et al showed that any increase in ICP caused by acute intracranial abnormalities has 100% specificity (95% CI: 76-100%) and 60% sensitivity (95% CI: 27-86%) in ONSD [48].

Turkin et al evaluated 41 patients with severe TBI within 48 hours after head injury by CT scan and found that the optimal ONSD for acute TBI patients was 6.35 mm with a sensitivity of 0.93 and a specificity of 0.80. The AUC was 0.87 [49]. Through a retrospective study of CT data from 1766 adult patients, Bekerman et al confirmed that using CT to measure the ratio of ONSD to eyeball transverse diameter (ETD) to evaluate ICP is more accurate, and the most accurate correlation can be obtained within an ICP range of 15-30 mmHg. They also pointed out that the position of the CT measurement of ONSD is different from that of US, with CT located 8-12 mm behind the eyeball and US located 3 mm behind the eyeball [50]. CT provides an opportunity for non-invasive ICP monitoring, making the examination more comprehensive. At the same time, CT examination is more easily accepted by patients and can be used as a supplement to US. Compared to US, CT can present higher-resolution images and measure ONSD more accurately. However, owing to its radiation, large size, inconvenient mobility, and high cost, its clinical use remains limited.

MRI-Based ONSD Assessment

With the development of medical imaging technology, MRI has become increasingly popular in optic nerve research owing to its non-invasive nature, clear imaging, and high resolution of soft tissues. It is currently the preferred method for displaying the anatomical details of the optic nerve and retrobulbar tissue.

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Tabe 1. Optimal ONSD threshold for evaluating ICP elevation.

Study	Country	Year	ONSD cutoff (mm)	Sensitivity (%)	Specificity (%)
Geeraerts et al [63]	France	2007	5.9	87	94
Kimberly et al [64]	USA	2008	5.0	88	93
Soldatos et al [65]	Greece	2008	5.7	74	99
Moretti et al [66]	Italy	2009	5.2	93	74
Strumwasser et al [67]	USA	2011	6.0	36	38
Rajajee et al [68]	USA	2011	4.8	96	94
Shirodkar et al [69]	India	2014	4.6	85	99
Wang et al [56]	China	2015	4.1	95	92
Rajajee et al [68]	USA	2011	4.8	96	94
Lochner et al [70]	Germany	2016	5.93	93	67
Kishk et al [71]	Egypt	2018	6.05	73.2	91.4

However, relatively few studies have used MRI to measure ONSD and evaluate ICP. On T2-weighted MRI, the optic nerve appears to be surrounded by the dura mater with low signal intensity and cavities with high signal intensity. Geeraerts et al found a positive correlation (r=0.71) between MRI-measured ONSD and invasively measured ICP, and ONSD measured based on MRI was highly reliable for monitoring ICP (AUC=0.94 and NPV of 92%) [51]. Kang et al also confirmed an excellent correlation between MRI-derived ONSD and ICP with an ONSD threshold of 5.99 mm, sensitivity of 90.0%, and specificity of 98.0% when ICP was above 20 mmHg [52]. Due to developmental differences in anatomical structures, such as skull rigidity and subdural space, between children and adults, the impact on intracranial compliance is still uncertain. However, in adults, when children have TBI, an increase in ICP can lead to severe secondary ischemic injury owing to restricted cerebral blood flow. Steinborn et al measured ONSD 3 mm behind the eyeball of clinically normal children and adolescents (5-18 years old) using axial T2W MRI and found that it was 5.96±0.31 mm, irrespective of age [53]. Similarly, Young et al found a linear relationship between ONSD and ICP in children diagnosed with intracranial hypertension, similar to adult patients [10]. In MRI, the specificity and sensitivity of ONSD in children for ICP are high, indicating that ICP monitoring could be set up for pediatric patients with TBI when ONSD is > 6.1 mm.

MRI has the advantages of being non-radiative and non-invasive, with high spatial resolution, strong soft-tissue contrast and specificity, good depth penetration, multiple sequences, and multi-plane reconstruction [54]. Therefore, there is great potential for non-invasive ICP monitoring using MRI-based ONSD measurements. However, the disadvantages of this method are its relatively high cost, lack of portability, long examination time, high dependence on patient compliance, and need to sedate young children.

Although many studies have demonstrated the feasibility of measuring ONSD using US, CT, and MRI to evaluate ICP [10], there is still a lack of standardized diagnostic protocols using the 3 methods and a lack of uniformity threshold values for ONSD across the 3 methods. Further experimental verification is needed to link the 3 methods and to develop guidelines for clinical practice.

Threshold of US ONSD for Elevated ICP

Many studies have examined the threshold of US ONSD for elevated ICP, and it is generally agreed that the threshold is between 5.0 and 5.9 mm, although the cutoff varies in different studies [55,56] (**Table 1**). It has been reported that the normal ONSD value was within 5 mm for patients older than 4 years, within 4.5 mm for patients between 1 and 4 years, and within 4 mm for patients less than 1 year old [57]. Using CT and clinical symptoms, the threshold for elevated ICP was determined to be 5.3 mm [58]. Chen Yan et al [59] analyzed the correlation between ICP obtained by direct catheterization through the lateral ventricle and US ONSD and concluded that the threshold was 5.1 mm [59]. Blaivas et al measured ONSD in patients with increased ICP assessed by CT and found that there was an excellent correlation between the ONSD and suggested increase in ICP by CT [60], and that ONSD was able to predict elevated ICP with a sensitivity of 87.5%, specificity of 94.1%, and AUC of 0.90 (95% CI: 0.85-0.96). Although MRI, CT,

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and US can be used to monitor ICP elevation [61], the first 2 are expensive, time-consuming, and involve a small amount of radiation, whereas US is inexpensive, simple to operate, easy to learn, has good repeatability, and has few intra-operator errors [62].

Measurement Method

The expansion of ONSD is most pronounced 3 mm behind the eyeball; therefore, it is suggested to be measured at this position [72]. However, the sensitivity of the optic nerve sheath to increased ICP varies among individuals and can differ between the left and right eyes [73]. Some diseases can also affect the ONSD. Therefore, congenital eye defects or microphthalmia should be excluded before ONSD measurement. Patients with diseases related to eye injury, optic nerve injury, optic canal fracture, optic neuritis, or abnormal intraocular pressure should also be excluded. Some studies suggest that the operator has little effect on the US measurement of ONSD, but during the operation, attention is needed to avoid the impact of artifacts and eye position on ONSD [74]. The movement of the subjects' eyes affects the optic nerve and consequently influences the optic nerve sheath [75]. Therefore, patients should be instructed to look straight ahead for an accurate ONSD.

Advantages of US ONSD Measurement for Detection of ICP Elevation

Although ONSD obtained with US, MRI, and CT are highly consistent and can be used for non-invasive screening to assess ICP elevation in patients to preliminarily evaluate ICP [76,77], US ONSD measurement is simple, inexpensive, and can be performed at the bedside with little intra- and interobserver variation [78]. Furthermore, US ONSD measurement can dynamically observe changes in ICP elevation in real time, especially in conditions in which invasive ICP monitoring is not available or not applicable, such as at trauma scenes [79]. Since the ONSD cutoff for predicting ICP elevation is not affected by sex, age, body mass index (BMI), waist circumference, head circumference, diastolic blood pressure (DBP), or other related factors, it could be quantitatively applied to predict ICP in patients [80].

Ultrasonography is now available in hospitals, medical institutions, and community health centers at all levels [81]. US ONSD measurement is simple and easy to learn, making it a widely used tool to monitor ICP elevation. As a commonly used and preferred non-invasive examination for ICP elevation, it can be used as a quick and non-invasive screening tool for ICP before or upon admission of the patient and offer suggestions for patient transfer to higher-level hospitals or to perform invasive ICP monitoring.

New Approach in ONSD Measurement

Although ONSD measurement is useful for monitoring ICP elevation, it was recently reported that the accuracy of ICP monitoring based on the ONSD method is not high [82] because the measurement does not take into account variations of forms and sizes of the eyeball and the optic canal. To solve this problem, the eyeball transverse diameter (ETD) and ONSD index (ONSD/ETD ratio) have been proposed [75]. There was a significant correlation between ETD and ONSD, and the standard error for the OND/ETD ratio was small, indicating that the index had a better diagnostic ability. For example, ONSD and ETD were measured in 312 cases, and the ONSD/ETD index was strongly related to ICP (r=0.77, $p<0.05$) and was not affected by age, sex, or other factors. The average index for the normal ICP group was 0.19±0.02, while for patients with high ICP, it was 0.29±0.05 [75,83]. Bekerman et al measured ONSD and ETD in 1766 patients, and the results showed that the ONSD/ETD index was significantly correlated with ICP [50]. Studies have used MRI and US to measure ONSD and ETD in 314 and 585 healthy Koreans, respectively; the OND/ETD index based on MRI and US was 0.22 and 0.18, respectively, which was not affected by sex, height, weight, or head circumference [84,85]. Du et al [29] used US and CT to determine ONSD and ETD, and the results showed that the US-ONSD, US-ONSD/ETD index, and CT-ONSD/ETD index were consistent with ICP obtained by intraventricular measurement, and the US OND/ETD and CT-OND/ETD indices were also consistent (Kappa=0.757, $P<0.001$) [86]. Youm et al found that the US ONSD and US ONSD/ETD ratio are related to actual ICP, and the ONSD/ETD index can be a more accurate predictor of ICP. An ONSD/ETD index of 0.264 was the optimal cutoff to increase ICP [87]. Guo et al found that the ONSD/ETD index can also be used to predict malignant progression in patients with middle cerebral artery ischemic stroke, where the optimal cutoff was 0.25 with a sensitivity of 84.2% and specificity of 92.5% [88].

In another study, ONSD and ETD were measured in 83 patients with different types of stroke and it was found that the mortality rate significantly increased when the ONSD was greater than 5.0 mm or the ONSD/ETD ratio was greater than 0.25, and the prediction of ONSD/ETD ratio was more accurate than ONSD alone [89]. Furthermore, automated ONSD and ETD ratio measurement is being developed to predict raised ICP [90].

In a study of children with diabetic ketosis, ONSD/ETD ratios were found to be significantly different before and after treatment, suggesting that this ratio is helpful in identifying brain edema related to diabetic ketosis and may be used as a potential risk stratification method [91]. Taken together, the normal range of the ONSD/ETD ratio in healthy adults and the mean and standard deviation of the threshold for the diagnosis of intracranial hypertension are smaller, suggesting that the index

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is a more stable and accurate measurement than the ONSD. However, in most studies, the subjects were patients with severe traumatic brain injury (TBI). Therefore, studies on patients with other diseases that cause elevated ICP are needed to further validate the efficacy and consistency of these methods.

Conclusions

Extensive studies have demonstrated that US ONSD measurement is a non-invasive and accurate method for monitoring ICP. Owing to its high accuracy, rapidity, effectiveness, and reproducibility, it is highly recommended for clinical use as a preferred non-invasive method for evaluation of intracranial hypertension for better management and treatment of patients with conditions such as TBI, large-artery ischemic stroke, intracranial hemorrhage, intracranial neoplasms, and diffuse cerebral disorders such as meningitis and encephalitis and other conditions, including Chiari malformation type 1 [92] and post-dural puncture headache [93]. It can serve as a screening tool in settings where invasive monitoring is unavailable, or be used to identify patients requiring urgent intervention in emergency departments or trauma settings. Furthermore, ONSD will not replace other approaches to become the standard of care because the cutoff of the ONSD threshold varies according to race, region, disease, and other related factors, and its accuracy relies on the skill and experience of the person who perform the US scan. Congenital eye conditions and prior ocular trauma will also impact its accuracy. Multimodal imaging should be further applied to ONSD measurements to enhance the sensitivity, accuracy, and reliability for early detection of ICP elevation and improvement of prognosis. In addition, more studies on perioperative ICP monitoring are needed, especially in elderly patients and patients with stroke, to control and treat increased ICP-derived brain function damage and improve prognosis and long-term quality of life.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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