Transorbital measurement of the optic nerve sheath diameter (ONSD) as a screening tool for raised intracranial pressure (ICP) in an acute care setting in children.

By

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Abstract

Background:
Acute care management of pediatric traumatic brain injury (TBI) can be challenging. Early and reliable diagnosis of intracranial pressure (ICP) in children following TBI is vital in optimizing outcome. Clinical findings of raised ICP can be non-specific and are often missed in minor injuries, leading to severe consequences. The use of a simple, quick, accurate, non-invasive technique to assess ICP can be invaluable in this setting. Based on the hypothesis that acutely raised ICP will result in an enlargement of the optic nerve sheath diameter (ONSD), this study aimed to demonstrate the efficacy of transorbital measurement of the ONSD as a routine screening tool in pediatric TBI.

Methodology:

This was a prospective observational analysis of a pediatric cohort of patients with head injury, treated in the trauma unit. All children included in the study were clinically assessed, and had indications for cranial computer tomography (CT) scan. All optic nerve sheath imaging was conducted by a single investigator, experienced in the use of ultrasound for emergency care. ONSD measurements were conducted using a high frequency, linear array probe. Patients were sedated and ONSD measurement was performed prior to or immediately after CT imaging. A total of 12 images were obtained in each patient, 3 axial and 3 sagittal images in each eye and the mean ONSD was calculated. ONSD measurements were analyzed in relation to clinical severity, CT findings of raised ICP and outcome of the patient.

Results:

A total of 82 patients were included in the study. The median age was 65.5 months (IQR 31-105), male to female ratio of 1.83:1. Etiology was motor vehicle accidents (50%), and falls (30.5%) in the majority of cases. The mean GCS was 11.4 (SD 4.9). The mean binocular ONSD in 45 children with out features of raised ICP on CT was 4.85 mm (SD 0.54), and the mean ONSD in 37 children with features of raised ICP on CT was 5.98
Diagnostic accuracy testing revealed an optimal ONSD cut-off value of 5.36 mm for detecting raised ICP, with a sensitivity of 86.5% and specificity of 80%. An increase in the ONSD measurement was noted as clinical severity increased i.e. mild - 5.02 mm (SD 0.68), moderate - 5.50 mm (SD 0.86) and severe - 5.98 mm (0.61). ONSD in relation to patient outcome also demonstrated a steady increase. Age related variation was considered by separately analyzing data in children over the age of 1 year. Analysis was conducted on 71 children in this part of the study. 37 of these patients had no features of raised ICP, with a mean ONSD of 4.84 mm (SD 0.56). 34 patients had features of raised ICP on CT, with a mean ONSD of 6.05 mm (SD 0.53) (p < 0.001). This resulted in a better sensitivity and higher odds ratio.

**Conclusion:**

Transorbital ultrasound measurement of the ONSD is a reliable marker of raised ICP demonstrated on initial CT imaging. It is a quick, accurate bedside technique, which can be used to screen children requiring a cranial CT scan or neurosurgical referral. It could reduce the incidence of morbidity related to missed TBI in minor head injuries and prevent unnecessary radiation exposure in minor TBI’s.
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<tr>
<td>AF</td>
<td>anterior fontanelle</td>
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<tr>
<td>ALARA</td>
<td>as low as reasonably achievable</td>
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<td>AUROC</td>
<td>area under the receiver operating characteristic</td>
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<tr>
<td>BOS</td>
<td>base of skull</td>
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<td>BTF</td>
<td>Brain Trauma Foundation</td>
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<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
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<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<td>CPP</td>
<td>cerebral perfusion pressure</td>
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<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>CT</td>
<td>computerized tomography</td>
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<tr>
<td>ED</td>
<td>emergency department</td>
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<tr>
<td>EFSUMB</td>
<td>European Federation of Societies for Ultrasound in Medicine and Biology</td>
</tr>
<tr>
<td>EI</td>
<td>elastance index</td>
</tr>
<tr>
<td>EVD</td>
<td>external ventricular drain</td>
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<tr>
<td>FAST</td>
<td>focused assessment with sonography for trauma</td>
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<tr>
<td>GCS</td>
<td>Glasgow coma scale</td>
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<tr>
<td>ICI</td>
<td>intracranial injury</td>
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<td>ICP</td>
<td>intracranial pressure</td>
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<td>ICU</td>
<td>intensive care unit</td>
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<td>IOP</td>
<td>intraocular pressure</td>
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<td>IQR</td>
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<td>MAP</td>
<td>mean arterial pressure</td>
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<td>magnetic resonance imaging</td>
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<td>MVA</td>
<td>motor vehicle accident</td>
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<td>NIRS</td>
<td>near infrared spectroscopy</td>
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<td>NPV</td>
<td>negative predictive value</td>
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OCT  optical coherence tomography
ON   optic nerve
ONS  optic nerve sheath
ONSD optic nerve sheath diameter
OR   odds ratio
PCC  Pearson’s correlation coefficient
PECARN Pediatric Emergency Care Applied Research Network
PI   primary investigator
PICU pediatric intensive care unit
POCUS point of care ultrasound
PPV  positive predictive value
RCWMCH Red Cross War Memorial Children’s Hospital
SAS  subarachnoid space
SCC  Spearman’s correlation coefficient
SD   standard deviation
STROBE strengthening the reporting of observational studies in epidemiology
SVP  spontaneous venous pulsations
TBI  traumatic brain injury
TCD  transcranial Doppler
TI   thermal index
VPS  ventriculo-peritoneal shunt
WHO World Health Organization
Chapter 1. Introduction and objectives

According to the Brain Trauma Foundation (BTF), traumatic brain injury (TBI) is a major cause of disability, death and economic cost to modern society. In South Africa, TBI alone accounts for 25.2% of non-natural deaths in children younger than 15 years of age. TBI is the most common cause of hospital admissions in children younger than 13 years of age. In Sub-Saharan Africa, 16.3% of children presenting to an emergency department with minor TBI require admission.

TBI can be defined as an alteration of brain function, which can manifest as confusion, altered level of consciousness, seizure, coma or focal sensory and motor neurologic deficit resulting from blunt or penetrating force to the head. The moment of impact (primary injury) is an independent factor that cannot be controlled, however it is the sequelae of events after this impact (secondary injury) that result in neurologic deterioration. Early management of secondary insults occurring during the pre-hospital and emergency department (ED) period, play a crucial role in determining outcome. Within hours following TBI, brain swelling can cause an increase in intracranial pressure (ICP), impairing cerebral perfusion and resulting in cerebral ischemia. The need to prevent, recognize and manage elevation of ICP is central to improving outcome in TBI patients.

Although the current gold standard for diagnosing raised ICP involves placement of an invasive intracranial monitoring device, computed tomography (CT) scanning remains the standard reference for assessing extent of injury in the acute setting. In an emergency care environment, the initial CT scan may help demonstrate evidence of increased ICP, the presence of hematomas or bony fractures. However, this valuable diagnostic tool is not always available, especially in an environment where resources are limited. A further concern regarding CT scanning relates to the liberal use of this technique for diagnosis, management and prognosis of TBI in children. This increases exposure to ionizing radiation and subsequently increases the lifetime risk of developing cancer.
Ultrasound has become an indispensable diagnostic tool for the management of many medical conditions. It is an excellent risk reducing tool, shortening time to definitive therapy and decreasing the rate of complications from invasive procedures.\textsuperscript{16} The practice of focused emergency ultrasonography is a goal-directed technique that has grown over the years both in adults and children, assisting in diagnostic dilemmas regarding particular signs or symptoms.\textsuperscript{17} Point-of-care ultrasound (POCUS) machines are widely available and form an integral component of trauma resuscitation with applications for vascular access, detection of fractures, detection of vascular and testicular injuries and especially for focused assessment with sonography for trauma (FAST) examinations.\textsuperscript{16-18} These machines are portable, rapid, low cost, non-invasive, widely available, and do not involve exposure to ionizing radiation.\textsuperscript{17}

Measurement of the optic nerve sheath diameter (ONSD) has recently emerged as an attractive non-invasive method of diagnosing raised ICP. This has been demonstrated by multiple studies using transorbital sonography,\textsuperscript{18-24} CT scans\textsuperscript{25-27} and magnetic resonance imaging (MRI).\textsuperscript{28-30} The anatomical relationship of the optic nerve (ON) and optic nerve sheath (ONS) to the brain and the direct cerebrospinal fluid (CSF) connection, provide the perfect portal to assess changes in ICP using transorbital ultrasonography. An increase in ICP results in displacement of CSF from the intracranial subarachnoid space (SAS) to the SAS surrounding the optic nerve causing dilatation of the ONS. This relationship was first described by Ossoinig, using an A-scan technique in 1979.\textsuperscript{31} Later Hansen and Helmke expanded on this to describe the current B-scan technique of transorbital ultrasonography to evaluate the ONSD.\textsuperscript{32-34}

This study aimed to analyse the diagnostic accuracy of sonographic measurement of the ONSD as a screening method for detecting raised ICP in children with TBI. A quick, reliable, non-invasive technique would be especially valuable where resources such as CT scanners, access to neurosurgeons and invasive monitoring are limited. ONSD measurement could potentially reduce the number of unnecessary cranial CT scans, especially in minor head injuries, limiting the radiation exposure to these children.
Chapter 2. Brief overview of pediatric traumatic brain injury

2.1. Epidemiology and etiology

TBI is a global phenomenon, and a critical public health problem, with dire implications for the individual and family. Limited data are available on TBI, yet this “silent epidemic” continues to be a major source of economic and social concern. The World Health Organization (WHO) predicts that TBI will surpass many diseases as the major cause of death and disability by the year 2020. It is estimated that TBI affects over 10 million people annually. In children the global incidence of TBI has been reported at 193 per 100,000, with higher rates in developing countries, as high as 359 per 100,000 in Sub-Saharan Africa.

The etiology of TBI varies between developed and developing nations, however motor vehicle accidents (MVA) remain the most common cause globally, accounting for up to 60%, followed by falls accounting for 20-30%. The South African road traffic fatality rate was twice the global average even in children. A study from the Red Cross War Memorial Children’s Hospital (RCWMCH) showed that pedestrian-related MVA’s accounted for 54.74% of severe TBI’s in children. The added challenge of poor health care services, unreported mild TBI’s and death due to severe injury en-route to hospital might further underestimate the true incidence of this condition.

2.2. Pathophysiology

TBI can be differentiated into primary and secondary injury. The primary injury is due to direct physical damage to the brain. The extent of this injury is directly related to the mechanism and force of impact, and is usually irreversible. The neurological damage after the impact may evolve over the next few hours or days resulting in secondary brain injury.
Secondary brain injury is the leading cause of morbidity and mortality.\textsuperscript{8,42,45} It is the sequence of metabolic events that take place after the initial impact which causes further damage to vulnerable parts of the brain. In trauma, most secondary brain injury is due to cerebral oedema, haematoma formation and ischemia.\textsuperscript{6} The Monro–Kellie doctrine proposed that any change to the fixed volume of the intracranial space occupied by the brain, CSF and blood could cause a change in ICP dynamics. Once the compensatory mechanisms to displace CSF have reached their limit, any further increase in intracranial volume will result in an increase in ICP.\textsuperscript{46} Increased ICP results in a decrease in cerebral perfusion pressure (CPP), which is the effective pressure that results in blood flow to the brain, calculated using the formula: \( \text{CPP} = \text{mean arterial pressure (MAP)} - \text{ICP}. \)\textsuperscript{9,47-49} The Monro-Kellie doctrine, does not apply to children who still have open fontanelles and expanding cranial sutures.\textsuperscript{49} This is of particular relevance in our study, as it forms the underlying reason behind age related cut-off values.

Mechanical herniation and cerebral ischemia are the two major consequences of raised ICP, resulting in impaired cerebral blood flow (CBF), inadequate cerebral oxygenation, leading to neurological impairment and even death.\textsuperscript{50} The outcome of patients sustaining TBI is dependent not only on the intracranial insults, but also due to extracranial causes. It has been shown that autoregulation is impaired even in those with mild TBI, therefore treatment and prevention of hypoxia, hypotension, ischemia and metabolic irregularities are fundamental management principles in TBI.\textsuperscript{51,52} A better understanding of the pathophysiology of TBI has lead to the development of improved treatment guidelines.\textsuperscript{7,11} Mortality due to severe TBI has fallen from 55\% to 30\% over the past 30 years with the help of better critical care protocols, routine CT and monitoring of ICP.\textsuperscript{8,11}
2.3. Clinical assessment:

Pre-hospital:

Early identification of TBI is critical in optimizing management and decreasing the risks and long-term sequelae of TBI.
According to the BTF, proper initial assessment, acute care management and rapid transfer to an appropriate facility, have significantly improved care while reducing cost implications.7,53

Hypotension and hypoxemia must be prevented during the pre-hospital phase.51,54 Early airway management through endotracheal intubation or bag-valve and mask ventilation in children with a Glasgow coma scale (GCS) of < 8 is effective in preventing hypoxemia, hypercarbia and aspiration.
The underlying cause of hypotension in trauma patients is usually haemorrhage, best managed with early intravenous access and fluid resuscitation.54
Early decisions by emergency medical services regarding the most appropriate transfer facility, remains an important factor in improving outcome. Children should ideally be transported to a pediatric trauma center, where facilities, staff and equipment for immediate care are available.55

In Hospital:

An accurate history and a high degree of suspicion should guide the clinician in assessing for raised ICP.
Since Teasdale and Jennet described the Glasgow coma scale in 1974, it has been internationally recognized as the neurological scale for rating severity of TBI.56 Due its limitations in children, several authors have developed modifications to the scoring system.57-62 Preference of scoring system in pre-verbal children varies between centres, the most favorable ones are i) Pediatric GCS50 ii) Raimondi-Hirschauer Children’s Coma Score63 iii) Adelaide Pediatric Coma Scale62, and iv) Children’s Coma Scale.59
Assessing GCS remains an important component of evaluating patients, as raised ICP usually manifests with a depressed level of consciousness.\textsuperscript{64} In a child, clinical signs and symptoms alone, can be poor indicators of the extent of TBI, creating an uncertainty about the need for imaging and treatment.\textsuperscript{40,44,59,65} In order to overcome this uncertainty in clinical diagnosis and questions regarding the necessity for a cranial CT, numerous studies have aimed to develop guidelines to assist with clinical assessment.\textsuperscript{43,44,66,67} The Pediatric Emergency Care Applied Research Network (PECARN) head trauma clinical prediction rules aimed to analyse signs and symptoms in addition to mechanism of injury in TBI. It has been promising in identifying children at very low risk of intracranial injury.\textsuperscript{43,67} The indications for cranial CT according to PECARN are:

For children < 2 years of age: altered mental status, non-frontal scalp haematoma, loss of consciousness for > 5 seconds, palpable skull fracture, and parents noting a difference in child.

For children > 2 years of age: altered mental status, any loss of consciousness, history of vomiting, clinical signs of base of skull (BOS) fracture and severe headaches.\textsuperscript{43} These rules were further expanded to include, seizures, neurological deficit, scalp haematomas, any signs of skull fracture, any loss of consciousness, vomiting and any headache in any age group.\textsuperscript{67}

Cranial CT scan is the standard modality for diagnosing TBI in the ED, by identifying space occupying lesions and defining management plans.\textsuperscript{12} Classification of head injuries based on the initial CT scan was introduced by Marshall in 1991.\textsuperscript{45} Findings of raised ICP on CT scan in TBI include the following: \textsuperscript{12,13,45,68-70}

- Diffuse sulcal effacement
- Compression or effacement of the basal cisterns
- Ventricular compression
- Midline shift > 5mm
- Evidence of uncal or transtentorial herniation
- Loss of grey white matter differentiation.

CT scans are widely available and play a pivotal role in the evaluation of TBI, this will be discussed in further detail in chapter 3.
2.4. Acute care management:

An important part of the management of raised ICP in a child involves prevention of secondary brain injury, which includes hypoxia, hypercarbia, hyperglycemia, hyperthermia and seizures.\textsuperscript{7,11,53,71} Acute care management principles in TBI, include:

- Management of TBI in a child starts with maintaining the airway (endotracheal intubation if indicated), breathing (maintaining adequate oxygenation) and circulation (administration of isotonic crystalloid solution) to maintain MAP and CPP, while maintaining cervical spine precautions.
- Elevation of the head of the bed to 30° to improve venous and CSF drainage.
- Optimization of serum osmolarity using e.g. mannitol or hypertonic saline.
- Aggressive treatment of post-traumatic seizures with benzodiazepines.
- Neurosurgical consultation in children with raised ICP, for possible placement of an ICP monitor.
- Mass lesions such as subdural and extradural bleeds require surgical evacuation.
- Decompressive craniectomy for refractory intracranial hypertension.\textsuperscript{37}

In some children clinical examination alone is not sufficient to identify raised ICP.\textsuperscript{72} A simple, reliable technique, which can be used as an adjunct to routinely screen all TBI patients would be helpful. It is with this goal in mind that this study was undertaken, as appropriately managed children with severe TBI have a better prognosis than adults.\textsuperscript{73,74}
Chapter 3. CT Scanning in clinical practice and associated risks

An important component of the early evaluation of pediatric TBI is adequate imaging. Currently CT scans are the main imaging modality used to assess the extent of intracranial injury (ICI). Since the introduction and increased availability of the helical CT scanner there has been a steady increase in the number of CT scans performed for evaluating TBI in children.\textsuperscript{75} Helical CT scans have the advantage of being faster, more user friendly and reduce the need for sedation in children.\textsuperscript{14}

A number of studies have clearly demonstrated that certain features on CT scan are good surrogate markers of raised ICP.\textsuperscript{8,12,13,45,68,70} Eisenberg et al related CT findings with abnormal ICP, later Marshall et al developed a classification of head injuries on the basis of these initial findings.\textsuperscript{13,45} They suggested that the likelihood of patients developing intracranial hypertension was best predicted by early CT scans (within 24 hours of injury).\textsuperscript{13,45} Although these studies have their limitations, they are widely recognized and accepted.\textsuperscript{7,8,10,12,40,76}

The clinical relevance and optimal use of CT scans for neuroimaging in pediatrics has been a subject of much discussion.\textsuperscript{44,52,65,67,77} Between 1995 and 2005, the use of CT scans for TBI has doubled.\textsuperscript{65,77} The reasons for this include:

1. Obtaining a normal CT scan in a patient with mild head injury can facilitate safe discharge.\textsuperscript{78,79}
2. Duplication of CT examinations after transfer to pediatric trauma centers.\textsuperscript{80,81}
3. 40-60 % of neuroimaging are due to minor head injuries, with only 10% of these demonstrating findings of intracranial pathology.\textsuperscript{40,78,82}
4. The wide availability of the CT scanner has resulted in its overuse for imaging in patients with low risk of intracranial pathology.\textsuperscript{40,83,84}

In the USA it is estimated that around 62 million CT scans are obtained per year, with around 4 million of these for children.\textsuperscript{14,85,86} Brenner et al\textsuperscript{87} in 2001 challenged the laid back approach to CT scanning by analyzing data from atomic bomb survivors and exposed the relative risk of a child developing fatal cancer from radiation exposure.\textsuperscript{88,89}
A disadvantage of increased CT use is the inherent risk associated with exposure to ionizing radiation. This risk is more alarming in children due to the susceptibility of the developing brain to radiation-induced damage. The radiation dose from a single CT scan is significantly higher than that of a standard radiograph, estimated at between 5 to 20 mGy, which is 3-5 times more than the background radiation exposure in the USA. The risk associated with a single cranial CT scan is highest in children under the age of 2 years, estimated as a 1 in 1500 risk for developing cancer. It is also important to remember that radiation doses are cumulative, with the induction of cancer and genetic defects attributed to stochastic effects – implying that low levels of radiation exposure are not certain to produce an effect, but that this possible effect may manifest over years. In children the decision to request a CT scan must therefore be weighed very carefully, as the lifetime attributable risk of cancer from radiation exposure varies with age and time of exposure. There are a few ways to effectively reduce the radiation exposure from CT scans:

1. Reduce CT related doses in individual patients, by following the ‘as low as reasonably achievable’ (ALARA) principle and ‘image gently’ initiative.
2. When practical and appropriate, replace CT use with other imaging modalities such as ultrasonography and MRI.
3. Decrease the number of unnecessary CT studies performed.

The immediate benefits of CT outweigh the long-term risks in many settings, and it will remain in widespread practice for the foreseeable future, however CT dose reduction should be a priority.

To achieve this goal a reliable method of detecting raised ICP in order to further screen patients requiring a CT scan would be of great help. It is also with this goal in mind that this study was embarked upon.
Chapter 4. Intracranial pressure (ICP) monitoring

Raised ICP has been well recognized as a cause of morbidity and mortality in patients following TBI. ICP monitoring provides the only reliable way of confirming or excluding intracranial hypertension.

According to the BTF guidelines, ICP monitoring is indicated in all TBI cases with a GCS between 3-8 and an abnormal CT scan. Although the exact targets for ICP and CPP are debatable, sustained ICP of > 20 mmHg may severely compromise CPP and is considered an important cause of secondary brain injury, often resulting in cerebral ischemia and mechanical brain herniation, both of which are associated with poor outcome. In TBI, prompt recognition, monitoring and treatment of raised ICP are critical to optimizing outcome.

4.1. Invasive methods of assessing ICP

The current invasive ICP monitoring technique was initially described by Lundberg in the 1960’s, with intraventricular catheterization. Even though haemorrhage and infection remain important complications, ventricular catheterization remains the gold standard for continuous ICP measurement.

Types of invasive ICP monitoring:

- External Ventricular Drain (EVD) placement in the lateral ventricle through a burr hole is considered the gold standard technique for monitoring ICP. This is the most reliable method currently available. It has good accuracy, allows continuous readings and with the significant advantage of CSF drainage to control ICP. However this technique also has significant complications, such as infection, haemorrhage, misplacement, obstruction, over drainage of CSF and limited applicability in children with small ventricles and thin scalps.

- Intraparenchymal devices include fiber-optic microtransducer probes and electronic strain gauge devices. These devices can be placed intraparenchymally or subdurally. They can be placed easily in most clinical situations and have...
enjoyed increased popularity, especially in the pediatric population.\textsuperscript{101,103,104} This is largely due to the lower complication rate compared to EVD placement.\textsuperscript{55,99} These devices are fragile and expensive, with displacement or malfunction often requiring complete replacement of the probe.\textsuperscript{100,102}

- Subdural catheters and extradural devices are methods that have been described but are used less often. The disadvantages include blockage, inaccuracy and difficulty in placement and maintenance, especially in children.\textsuperscript{11,49,104}

Invasive ICP monitoring using a transduced EVD remains the most reliable brain monitoring modality for guiding treatment.

Mortality due to severe TBI has fallen over the past 40 years due to improved critical care, routine CT and ICP monitoring.\textsuperscript{7} However this requires designated trauma personnel, 24 hour CT scanner availability, neurosurgical referral, ICP monitoring and an experienced critical care management team. This is not always possible in a resource limited setting and can delay diagnosis and treatment, resulting in poor outcome.

The incidence of complications such as haemorrhage, infection and device malfunctions remain low, and should be weighed against the benefits of continuous monitoring in selected cases.

The pre-hospital and early hospital period are extremely important to patient outcome. It is here that a reliable, non-invasive assessment of ICP could be most useful, with the added benefit of screening patients who require invasive monitoring.
4.2. Non-Invasive methods of assessing ICP

Clinical methods

- History alone has limited specificity for predicting raised ICP. Important symptoms to be aware of include, headaches, nausea, vomiting and decreased level of consciousness.
- Physical examination in infants can be of particular importance. Palpating the anterior fontanelle (AF), and measuring the head circumference before fusion of the cranial sutures can be helpful in assessing for raised ICP. Papilloedema on fundoscopy is a reliable sign of raised ICP, but has a delayed presentation and can be quite difficult to examine in an uncooperative child, limiting its value in the acute situation.

Radiological Methods

- CT scanning is the most frequently used method for detecting features of raised ICP, especially in an acute care setting. Some of the features on CT scan suggestive of raised ICP include compression or obliteration of cisternal spaces, subarachnoid blood and midline shift due to contusion or haemorrhage. The wide availability of CT has lead to its liberal use, even for minor head injuries, exposing children to the inherent risk of ionizing radiation. Proper consideration is often not given to ensuring that the diagnostic advantage of the CT scan outweighs the associated risk. This imaging method was discussed earlier in Chapter 3.
- MRI is a useful tool for detecting elevated ICP. Intraorbital findings such as optic disc protrusion into the globe, flattening of posterior globe, tortuosity of optic nerve and prominence of the peri-optic nerve CSF spaces, have been associated with raised ICP. MRI provides excellent image quality but is an expensive and time consuming imaging modality for use in acute care.
Ophthalmic Methods

The optic nerve and the ONS are a direct extension, of the white matter tracts of the brain and the dura mater respectively. This allows CSF communication between the peri-optic subarachnoid space (SAS) and the cranial SAS.\textsuperscript{110} Numerous methods have been tested using the eye as a diagnostic window, these include:

- Assessment of spontaneous venous pulsation (SVP) is a method that measures the subtle, rhythmic pulsations of the central retinal vein seen on the optic disc, and cessation of these venous pulsations is a marker of raised ICP.\textsuperscript{111} However interpretation of this method can be complicated and therefore difficult to use in a clinical setting.\textsuperscript{112}

- Intraocular pressure (IOP) measurement using a handheld tonometer, as a rapid screening tool for raised ICP has also been described.\textsuperscript{113} While an increase in IOP appears to have a relationship to raised MAP, IOP does not appear sufficiently accurate for predicting ICP.\textsuperscript{114,115}

- Venous Ophthalmodynamometry is the study of the pressure in the central retinal vein due an increase in ICP. This causes an increase in IOP, which may decrease SVP. The presence of SVP is therefore a sensitive marker for normal ICP, but of limited value in raised ICP and should be interpreted in the context of the patient’s clinical presentation.\textsuperscript{116}

- Optical Coherence Tomography (OCT) is the use of broadband infrared light to differentiate papilloedema from other causes of disc oedema, however its value in acutely raised ICP is still unclear.\textsuperscript{112,117}

- Scanning laser tomography is a method of evaluating oedema of the optic nerve, described mostly in glaucoma. A relationship between CSF opening pressure on lumbar puncture and optic nerve volume has been described.\textsuperscript{117,118}
• Pupillometry measures pupillary constriction after stimulation by light. It has demonstrated that pupil reactivity reduces after head injury. These pupillometers are sensitive but this technique requires further investigation.\textsuperscript{119}

• Measurement of the ONSD to detect raised ICP is a promising technique. The direct communication between the perineural SAS and the intracranial SAS has been confirmed, therefore significant change in ICP results in expansion of the ONSD.\textsuperscript{33,120} Several studies have demonstrated that an increase in ONSD measured on ultrasound is related to an increase in ICP.\textsuperscript{18,20,22,24,107,121-125} Studies have also shown that enlargement of the ONSD measured either on CT or MRI was also associated with raised ICP.\textsuperscript{25,28,30,126,127} This topic will be discussed in detail in chapter 6.

• Two-depth transcranial doppler (TCD) ultrasonography analyses flow in the ophthalmic artery by application of pressure on the orbit. Studies have shown that arterial resistance increases with increased ICP. This method is operator dependent and has not shown great accuracy.\textsuperscript{112,117,128,129}

Audiological Methods

The auditory canal also provides a window for non-invasive assessment of ICP.

• Tympanic membrane displacement is altered when ICP is increased. Elevated ICP is communicated through the cochlear aqueduct to the perilymph altering the stapedial reflex. Although this method is reliable, it requires an audiologist and specific hardware. Testing takes up to 60 minutes and is limited by poor inter-subject variability, making it less feasible in an acute care setting.\textsuperscript{112,117,130}

• Otoacoustic emissions are the sounds produced by the inner ear through stapes displacements, which can be recorded with the help of auditory
probes. Changes in ICP alter these sounds produced. This method is also limited by poor inter-subject reliability.\textsuperscript{112,131}

Methods using Fluid Dynamics

- TCD is a method first described in 1982, for evaluating flow velocities in the basal cerebral arteries.\textsuperscript{132} Since then it has grown in interest as a non-invasive method of evaluating raised ICP. Measurement of cerebral blood flow parameters and the pulsatility index were found to correlate with ICP measurements.\textsuperscript{133-135} Measurements were mainly taken over the temporal region and through the orbit. It has been shown that TCD can be an excellent first-line diagnostic modality to determine who requires urgent treatment.\textsuperscript{136} Although this method is relatively easy and cost effective, it requires a skilled operator and satisfactory results have not been obtained in all patients.\textsuperscript{135}

- MRI has been used to measure the change in intracranial volume, CSF pressure and blood flow, using the net trans-cranial CSF and blood volumetric flow rates. The elastance index (EI) is then calculated from this ratio. This EI was shown to correlate well with invasive ICP measurements.\textsuperscript{109} However this method requires further research and would be difficult in an acute care setting.\textsuperscript{112,117}

- Near Infrared Spectroscopy (NIRS) is a method which monitors the change in cerebral oxygen saturation and cerebral blood volume. It has been demonstrated that oxygen saturation varies with changes in ICP. This technique also requires specialized equipment and has a prolonged testing time.\textsuperscript{137,138}

The search for a non-invasive technique of measuring ICP has been the quest of scientists for many years. However, no single method has provided a reliable alternative to invasive ICP measurement.\textsuperscript{104} A non-invasive technique that would enable early
detection of elevated ICP with a high sensitivity and reproducibility would be extremely appealing. Especially in children, a technique that would be well tolerated, avoid harmful consequences and prevent unnecessary radiation exposure would be invaluable. Poor accuracy, continuous monitoring inability, requirement of specialized equipment and disparity between investigators has limited the use of the current techniques. Of the non-invasive methods, ultrasound measurement of the ONS and TCD appear to be the most promising in selected situations. 24,104,117,139

In this study we evaluated transorbital ultrasound measurement of the ONSD as a surrogate marker of raised ICP in children. The advantage of using ONSD as a screening tool for selecting children who require a CT scan was also evaluated.
Chapter 5. The Optic Nerve Sheath

The first description of oedema of the optic disc was made by von Graefe in 1860.\textsuperscript{140} This was later investigated by Hayreh in 1964, using inflated balloons placed in the subdural space of rhesus monkeys to increase ICP. This work described the increase of CSF in the ONS as being essential for the development of oedema of the optic disc.\textsuperscript{141} Since then numerous studies have been published on the association between the ONSD and increasing ICP.\textsuperscript{21,32,142-145}

The hypothesis of this study was based on this association, aiming to describe the relationship between transorbital ONSD and its relationship to clinical and CT findings of raised ICP in children.

Anatomy of ONS:

The ON is a white-matter tract of the central nervous system (CNS) that extends to the orbit and is surrounded by CSF throughout its entire length.\textsuperscript{146} It originates from the diencephalic neural fold on day 22, and extends anteriorly and laterally through the optic canal into the orbit.\textsuperscript{147}

The ON is about 40 - 50 mm in length and is about 4 mm in diameter. It is surrounded by a SAS filled with CSF, which in turn is encased by the ONS. The ONS has a thickness of 0.4 mm, and the SAS surrounding the ON is a blind ending space containing about 0.1 ml of CSF and is about 0.1 - 0.2 mm wide.\textsuperscript{146,148} Since it is assumed that CSF communicates between the different CSF compartments, any significant change in ICP will reflect in the diameter of the ONS.\textsuperscript{33,106,110}

The ONS is a dural sheath, which originates at the level of the optic canal and courses along with the ON to the sclera, it can be divided into three segments:\textsuperscript{147}

  a) Intracranial- this is the shortest segment, where the dura invaginates to form the falciform ligament at the sphenoid planum, here it does not completely adhere to the bone, but protects the dorsal surface of the ON.
b) Intracanalicular- the ONS exits the base of the skull through the optic canal, here the sheath along with the nerve courses obliquely in a lateral and ventral direction. The carotid-oculomotor membrane, which is formed by the dural covering of the clinoid process, is in contact with the ONS. This is where the ophthalmic artery and the first intracranial branch of the internal carotid artery arise. The artery then transverses the optic canal and joins the orbit.

c) Intraorbital- the ONS in this segment is a dense structure which helps form the annular ligament, where various recti muscles attach. It is surrounded by adipose tissues, which facilitate movement of the eye. Five different structures cross the orbital segment of the ONS: trochlear nerve, frontal nerve, nasociliary nerve, ophthalmic artery and the superior ophthalmic vein.

The anatomy of the ONS and the communication of CSF between the ONS and the intracranial space are key to understanding the response of the ONS to increases in ICP. CSF produced by the choroid plexus in the ventricles communicates with the cisterns and SAS, including the SAS surrounding the ON’s. The SAS of the bulbar segment of the ON is a dense system of delicate trabeculae and septa arranged in a reticular fashion, this complicates the flow of CSF between different segments. This is also the widest area of the SAS surrounding the nerve, which comes to an end blindly behind the globe (cul-de-sac). Here CSF circulates, reversing its direction back to where it can be reabsorbed, therefore free flowing between the SAS of the ON and the intracranial SAS. Due to this complex system, CSF flow may be inconsistent. An increase in ICP is initially transmitted to the SAS surrounding the ON causing distension of the ONS. Subsequently this pressure results in impairment of the normal axoplasmic flow surrounding the ON, leading to papilloedema. The ONS is wider near the eyeball with a bigger SAS providing useful information on where the most appropriate area to measure the ONSD is.
Chapter 6. Transorbital Ultrasound

6.1. History and overview

The potential of medical diagnostic ultrasound imaging was recognized in the 1940’s, however it was only in the 1970’s that it truly captivated the interest of researchers, evolving as an important diagnostic tool.\textsuperscript{121} The modern ultrasound machine is portable, easy to use and sophisticated, providing high image quality.\textsuperscript{151}

Transorbital ultrasound of the ON and the dural sheath surrounding it, was pioneered by Ossoinig in the 1970’s using the A-scan technique. He identified the structures on ultrasound by describing the change in reflectivity between the ON and the ONS.\textsuperscript{31} Ossoinig later described the relationship between ICP and the fluid surrounding the ON.\textsuperscript{142} This was confirmed by many groups both in patient and cadaver studies, identifying the linear relationship between the SAS surrounding the nerve and ICP, it was also noted that the bulbous portion of the ONS dilates as ICP is increased.\textsuperscript{152-155}

In 1994, Hansen and Helmke, described the current technique of ONSD measurement using a B-scan technique.\textsuperscript{33} They went on to study the optimal location for ONSD measurement, by injecting gelatin into the SAS of post mortem ON specimens. These investigators demonstrated that the maximum increase in diameter occurred 3.0 mm behind the ON head rather than at 10 mm, confirming Liu’s observation on cadavers.\textsuperscript{32,154} These authors also described the technique of scanning the ONSD in clinical practice and the ease of reproducibility of this technique.\textsuperscript{32,34,120}

Since this ground breaking work in the 1990’s, the B-scan technique in its current form, has been improved using modern high frequency transducers which provide better penetration and better image quality. Numerous authors have studied this technique and the use of ONSD measurement as a non-invasive method of diagnosing raised ICP.\textsuperscript{18,21,143-145,156,157}
6.2. The technique of transorbital ultrasound measurement of the ONS

Transorbital ultrasonography is a quick and simple method. This technique has some general principles that help generate the best image quality of the ONSD.\textsuperscript{158}

- A high frequency linear array transducer is required, with the insonation programme set to “small parts” or “superficial”.
- Depth is set at 4 cm for children, which can be adjusted for different age groups.
- Patient is positioned supine, with head in neutral position, and eyes closed.
- Coupling gel is applied on the eyelid as a medium between the eyelid and transducer.
- The transducer is placed lightly over the upper eyelid on the temporal side in an axial or sagittal plane as required. (Figures 6.1 and 6.2)
- Stabilizing the hand by resting the little finger on the orbital ridge, allowing the least possible pressure on the globe.
- The beam is focused, with subtle movements caudally and medially, to obtain a view of the globe, lens, vitreous and the ON.
- The ONS is a bilateral thin hypoechoic line, which is lateral and parallel to the nerve. (Figure 6.3)
- Subtle changes to angulation will be required until this image is on the middle of the monitor, clear, with well demarcated lines of the ONS visible.
- Once the optimum image is acquired, it can be stored as an image or video.
- Once all the images have been acquired, the probe can be removed, ensuring minimal exposure to the ultrasound beam. Stored images can be measured later.
- Using the caliper function, cursors are placed parallel to and in the middle off the ON measuring 3.0 mm posterior to the papilla.
- The second measurement is done perpendicular to this line at the 3.0 mm mark, measuring the diameter of the ONS. (Figure 6.4)
- The zoom function can be used to allow for more precise measurement
Figure 6.1: Axial imaging technique

Figure 6.2: Sagittal imaging technique

Figure 6.3: Ultrasound image of eye and ONS

- Vitreous
- Optic disc
- Optic nerve sheath
- Optic nerve
Figure 6.4: Ultrasound image of ONSD measurement
6.3. Advantages, disadvantages and safety considerations

While measurement of the ONSD using ultrasound has some distinct advantages it also comes with a few disadvantages, technical and safety considerations that the clinician must be aware of.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Relatively low cost</td>
<td>All examinations must be performed by a trained operator</td>
</tr>
<tr>
<td>Non-invasive technique</td>
<td>Inexperience in technique leads to error in measurements</td>
</tr>
<tr>
<td>Equipment available in most ED's</td>
<td>Over exposure of the eye to the ultrasound beam can result in thermal injury</td>
</tr>
<tr>
<td>Portable equipment</td>
<td>ONSD cannot be used with ocular injury and diseases of ON</td>
</tr>
<tr>
<td>Rapid results</td>
<td>Pressure on globe should be avoided at all costs</td>
</tr>
<tr>
<td>Reproducible technique and measures</td>
<td>The small measurements can increase the chance of error</td>
</tr>
<tr>
<td>Well tolerated by patients</td>
<td></td>
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<tr>
<td>Avoidance of ionizing radiation</td>
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Table 6.1: Advantages and disadvantages of transorbital ultrasound

When used by a trained operator, ultrasound imaging is generally a safe modality. In order to prevent thermal injury, the time of interaction between the ultrasound beam and the scanned tissue should be limited. An ultrasound image is produced when sound waves pass through the probe to the scanned tissues and are reflected from the tissue interfaces creating an image. When some of this energy is absorbed it causes a thermal change, elevating local temperature of the tissues. Prolonged exposure to this thermal and non-thermal energy must be minimized by setting the ultrasound output power to minimal or by using the ALARA principle,\textsuperscript{93,94} without compromising the diagnostic value of the examination. The European Federation of Societies for Ultrasound in
Medicine and Biology (EFSUMB) guidelines recommend that the thermal index (TI) and mechanical index (MI) displayed on the monitor should be set to \(< 1.0\) and \(< 0.7\) respectively for diagnostic transorbital ultrasound, this allows 30 minutes of safe examination time before possible injury to tissues\(^{159,160}\). The TI is an on screen guide to potential tissue heating and the MI is a guide to the likelihood and magnitude of non-thermal effects. It is suggested that during transcranial investigations where higher acoustic output and longer monitoring time is required, monitoring is paused regularly to minimize exposure\(^{160}\).

It is important to understand these safety issues while using the ultrasound, to justify the use of this technique as a safe diagnostic tool.
6.4. Literature review of ONSD as a non-invasive method of assessing ICP in children

6.4.1. Literature supporting ONSD use

1. Helmke and Hansen\textsuperscript{34} in 1996 conducted one of the earliest pediatric prospective studies published on this topic. They demonstrated that ONSD increased not only in chronic experimental findings of raised ICP, but also in acute conditions of intracranial hypertension. They examined 39 children admitted to ICU and compared them to 51 control patients. Twenty-four of the children being treated in ICU had raised ICP, due to trauma or metabolic disorders. Raised ICP was assessed through clinical and radiological findings and 7 of them had invasive ICP monitoring with values over 20 mmHg. They suggested that in children over the age of 4 years, an ONSD of 4.5 mm be regarded as borderline for raised ICP, and 5.0 mm regarded as definitely enlarged. The authors also suggested an age related cut-off value of 4.0 mm be considered enlarged in children under the age of 4 years. In the control group and in patients in ICU who did not have raised ICP, they found the range of ONSD to be between 2.7 - 4.0 mm, concluding that ONSD could provide important information regarding increased ICP in an acute setting and that the upper limit of the ONSD differs in children below the age of 4 years.\textsuperscript{34}

2. In 1999, Ballantyne and colleagues\textsuperscript{156} conducted a prospective study on 102 control children, to establish a range of normal values for children up to the age of 15 years. They used a 7 MHz probe, measuring the ONSD 3.0 mm behind the optic nerve head as suggested by Helmke and Hansen.\textsuperscript{32} The authors took 3 measurements of the ONSD in each eye and calculated the mean value. Their study found no significant difference in ONSD between boys and girls, and between right and left eyes. Although the authors noted age related changes, their findings differed from those of Helmke and Hansen,\textsuperscript{34} describing a normal range for children under the age of 1 year as between 2.1 - 4.0 mm and the range for children over 1 year of age being 2.4 - 4.3 mm. The authors concluded that an
ONSD of 4.0 mm in children <1 year be considered abnormal and in children >1 year old, 4.5 mm was abnormal.\textsuperscript{156}

3. Newman and colleagues\textsuperscript{145} conducted a prospective study in 23 children with shunted hydrocephalus. The results were compared to the control group used in the Ballantyne study,\textsuperscript{156} as this study was performed by the same investigating group. The authors used a 7 MHz probe, measuring the ONSD 3.0 mm behind the optic nerve head, taking 3 measurements in each eye and calculating the average. The children were divided into four groups.

Group 1: 102 normal children from the Ballantyne study.\textsuperscript{156} Under 1 year of age, mean ONSD was 2.9 $\pm$ 0.4 mm and older than 1 year the mean ONSD was 3.1 $\pm$ 0.36 mm. Upper limit being defined as 4.0 mm in children under 1 year of age, and 4.5 mm for older children.\textsuperscript{156}

Group 2: 6 children with shunted hydrocephalus presenting for routine review. These children had the same values as the control group.

Group 3: 5 children with shunted hydrocephalus, who had clinical signs of raised ICP (irritability, tiredness, nausea and headache), but did not require shunt revision, as their symptoms resolved spontaneously. ONSD values in this group were all less than 4.5 mm.

Group 4: 12 children with symptoms suggestive of raised ICP and required surgical intervention. The mean ONSD was 5.9 $\pm$ 0.6 mm, these values were all more than 4.5 mm. Four of these children had serial measurements taken of their ONSD, obtaining values that decreased as symptoms improved.

The authors noted the dynamic relationship between ONSD and ICP, suggesting that ONSD measurement could be used for serial testing of variations in ICP. They also noted that an increase in ONSD was an earlier predictor of raised ICP than papilloedema in the acute situation.\textsuperscript{145}

4. In 2005, Malayeri et al\textsuperscript{107} conducted a prospective study consisting of 156 children. 78 children in the case group were neurosurgical patients, with etiologies varying from trauma, brain tumours, hydrocephalus and encephalopathy, and 78 children in the control group. The case group had findings of raised ICP, assessed either through clinical symptoms of nausea,
vomiting, altered mental state and papilloedema or signs of raised ICP on CT scan or sonography of the brain in children <1 year of age.

In the control group the mean ONSD was found to be $3.3 \pm 0.6$ mm, with a maximum diameter of 4.35 mm and a minimum diameter of 2.0 mm. In the case group, the maximum diameter was 7.6 mm and the minimum diameter was 4.55 mm, with a mean value of $5.6 \pm 0.6$ mm. These values were found to be statistically significant ($p < 0.001$). The authors used age at 4 years as a cut-off point, as suggested by Helmke and Hansen. This study also found that age related differences were only significant in the control group and not in the case group. With a mean value of $3.0 \pm 0.6$ mm in children < 4 years of age, and $3.6 \pm 0.4$ mm in children older than 4 years of age. The authors also suggest that this was probably due to the expansile structure of the ONS and its anatomic characteristics. They did not suggest an optimal cut-off value of the ONSD for raised ICP in children.

5. Tsung et al in 2005 used ONSD measurements in 3 cases of head injury in a pediatric ED. A 7 MHz probe was used to take measurements in the sagittal and axial planes. Case 1: an 8 month old infant with positive CT findings of raised ICP, ONSD measurements of 4.1 mm and 4.4 mm, for the right and left eyes respectively were in keeping with the upper limit of 4.0 mm in infants as suggested earlier by Ballantyne et al. Case 2: A 12 year old with a normal CT scan and lumbar opening pressures, with no findings of raised ICP was found to have ONSD measurements of 3.75 mm in the right eye and 3.8 mm in the left eye. Case 3: a 4 month old infant with averaged ONSD of 3.55 mm on the right and 3.4 mm on the left, was in keeping with the child’s good clinical condition, with no signs of raised ICP. It was concluded that transorbital ONSD measurement is a valuable, rapid, non invasive method to detect raised ICP in a pediatric emergency care setting, which may decrease the need for cranial CT scans in neurologically normal patients.

6. Beare and colleagues conducted a prospective analysis in African children in Malawi in 2008. The authors recruited a total of 51 children. Thirty were control patients, in hospital due to pneumonia, gastroenteritis, sepsis and malaria and 21
patients had neurosurgical disease. Fourteen of the 21 demonstrated clinical findings suggestive of raised ICP, 8 of which were confirmed through CT scanning. The mean ONSD in this group of 8 patients was 5.4 mm. Seven out of the 21 patients with neurological disease had no clinical or CT features of raised ICP, the mean ONSD value was 3.6 mm. The control group of 30 patients had a mean ONSD of 3.5 mm. The authors suggested an ONSD cut-off value of 4.2 mm as the upper limit of normal with a sensitivity of 100% and specificity of 86%, and a cut-off value of 4.5 mm as highly suggestive of raised ICP. They found their normal control data range of 2.5 to 4.1 mm, in keeping with Ballantyne and Malayeri’s finding.\textsuperscript{107,156} The limitations of this study were the small numbers in the disease group and the unknown effect of gastroenteritis and sepsis on ICP in the control group. Although the mean age in the study was 69 months, the age range was not specified and no age related variations were suggested.\textsuperscript{162}

7. McAuley et al\textsuperscript{122} in 2009 performed a retrospective study on 160 pediatric hydrocephalus patients, and noted that the baseline normal value in the asymptomatic shunted hydrocephalus patients was much higher than that reported by Newman et al.\textsuperscript{145} The authors conducted 331 examinations in 160 patients. Ninety two patients had a single examination, and 68 had multiple examinations. Fifty one of the 68 patients had complete clinical and ONSD data. The ONSD was of clinical relevance in 29 of those 51 and the ONSD measurement correlated with the blocked shunt in 24 of the 29 (82.8%). Nineteen of the 24 children required surgical shunt revision on the basis of clinical symptoms. Interestingly it was noted that although CT/MRI imaging in these 19 patients did not demonstrate a change in ventricular configuration, these patients did have increased ONSD measurements from their baseline. The control group in this study was the asymptomatic hydrocephalus patients consisting of 45 children. Twenty-six of the 45 patients demonstrated an ONSD measurement of > 4.5 mm, which was higher than that suggested by Newman et al.\textsuperscript{145} The authors concluded that ONSD measurement may have a predictive role when brain
imaging does not assist with diagnosing shunt malfunction, and that ONSD can increase from its own baseline in symptomatic patients.\textsuperscript{122}

8. Agrawal and Brierley\textsuperscript{23} described the first study in children correlating ONSD with simultaneously measured invasive ICP. An ICP of more than 15 mmHg was considered elevated and a previously described ONSD value of 4.5 mm was used as abnormal. The study included 11 children between 2 and 15 years, who had sustained TBI and required ICP monitoring in the pediatric intensive care unit (PICU). The median ONSD for children with raised ICP was 5.2 mm in the right eye, and 5.1 mm in the left eye. In patients with normal ICP, the median ONSD value was 4.0 mm for the right eye and 3.9 mm for the left eye. All children with clinically significant raised ICP had increased ONSD (\( p = 0.025 \)). While concluding that the numbers were small and required validation in a larger pediatric study, the authors suggested that ONSD could be useful in identifying children with normal ICP, therefore avoiding unnecessary invasive ICP monitoring.\textsuperscript{23}

9. In a more recent study Steinborn and colleagues\textsuperscript{125} described significantly higher ONSD values for detecting raised ICP. They also identified a cystic appearance of the SAS surrounding the ON related to an increase in ICP. The study was conducted on 81 children aged between 3 years and 17.8 years. Using a 17-5 MHz probe, obtaining two or three ONS images of each eye, measured 3.0 mm behind the papilla. 25 of these patients had elevated ICP, diagnosed either by invasive ICP monitoring with a value of > 15 mmHg (\( n = 10 \)), or lumbar puncture CSF opening pressure > 28 cmH20 (\( n = 5 \)) or features of raised ICP on CT and MRI (\( n = 10 \)). The mean ONSD in the raised ICP group was 6.85 ± 0.81 mm. Fifty-six patients without any signs of raised ICP were used as the control group. The mean ONSD in this group was 5.77 ± 0.48 mm. The suggested cut-off value for predicting raised ICP was 6.0 mm with a sensitivity of 82% and specificity of 74%. These values are significantly higher than those suggested by previous studies. The limitations of this study are that it did not include children under the age of 3 years, and combined acute and chronic causes of raised ICP.\textsuperscript{125}
<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Patients (n)</th>
<th>Etiology</th>
<th>Reference standard for comparison</th>
<th>Mean ONSD/cut-off value for raised ICP &amp; accuracy</th>
<th>Conclusion</th>
</tr>
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<tr>
<td>Helmke and Hansen, 1996&lt;sup&gt;14&lt;/sup&gt;</td>
<td>39 patients and 51 control</td>
<td>Head trauma and metabolic disorders</td>
<td>Clinical, radiological and invasive ICP measurements</td>
<td>&lt;4yrs – 4.0 mm, &gt;4yrs – 4.5 mm (borderline), 5.0 mm (abnormal), No accuracy testing</td>
<td>ONSD measurement is useful in acutely elevated ICP. With age related variations</td>
</tr>
<tr>
<td>Ballantyne et al, 1999&lt;sup&gt;156&lt;/sup&gt;</td>
<td>102 control</td>
<td>Normal patients</td>
<td>Normal patients</td>
<td>&lt; 1yr – 4.0 mm, &gt;1yr – 4.5 mm, No accuracy testing</td>
<td>Age related differences in normal range</td>
</tr>
<tr>
<td>Newman et al, 2002&lt;sup&gt;145&lt;/sup&gt;</td>
<td>23 patients and 102 control</td>
<td>Shunted hydrocephalus</td>
<td>Clinical signs and symptoms</td>
<td>&lt;1yr – 4.0 mm, &gt;1yr – 4.5 mm, No accuracy testing</td>
<td>ONSD is a useful tool for assessment and monitoring of raised ICP. Increased ONSD can act as a marker for raised ICP before the development of papilloedema</td>
</tr>
<tr>
<td>Malayeri et al, 2004&lt;sup&gt;107&lt;/sup&gt;</td>
<td>78 symptomatic and 78 control</td>
<td>Mixed</td>
<td>Clinical and radiological</td>
<td>Mean 5.6 ± 0.6 mm in raised ICP, 3.3 ± 0.6 mm in control, 4.55 mm irrespective of age</td>
<td>Reliable alternative to or in conjunction with other diagnostic modalities for raised ICP</td>
</tr>
<tr>
<td>Tsung et al, 2005&lt;sup&gt;161&lt;/sup&gt;</td>
<td>3 case studies</td>
<td>Head trauma</td>
<td>Clinical and radiological</td>
<td>Historical values by Newman</td>
<td>Reliable screening method</td>
</tr>
<tr>
<td>Beare et al, 2008&lt;sup&gt;162&lt;/sup&gt;</td>
<td>21 patients (8 with elevated ICP) and 30 control</td>
<td>Mixed</td>
<td>Clinical and radiological</td>
<td>4.2 mm cut-off value, 100% sensitivity and 86% specificity</td>
<td>ONSD is useful in a resource limited setting</td>
</tr>
<tr>
<td>McAuley et al, 2009&lt;sup&gt;122&lt;/sup&gt;</td>
<td>160 VPS patients</td>
<td>Shunted hydrocephalus</td>
<td>Clinical assessment</td>
<td>Historical values by Newman</td>
<td>ONSD is increased in symptomatic patients from their own baseline</td>
</tr>
<tr>
<td>Agrawal and Brierley, 2012&lt;sup&gt;33&lt;/sup&gt;</td>
<td>11 patients</td>
<td>TBI</td>
<td>Invasive ICP measurement</td>
<td>Historical values by Newman</td>
<td>All children with raised ICP had abnormal ONSD</td>
</tr>
<tr>
<td>Steinborn et al, 2016&lt;sup&gt;125&lt;/sup&gt;</td>
<td>25 patients and 56 control</td>
<td>Mixed</td>
<td>Clinical assessment, radiological and 15 with invasive measurements</td>
<td>6.0 mm with a sensitivity of 82% and specificity of 74%</td>
<td>Normal and raised ICP values much higher than previously suggested. Quick non-invasive tool for raised ICP estimation</td>
</tr>
</tbody>
</table>

Table 6.2: Summary of pediatric literature supporting ONSD measurement
6.4.2. Literature not supporting ONSD use

1. Le and colleagues\textsuperscript{163} conducted a study on 64 children aged 0 to 18 years of age, of which 24 had confirmed raised ICP on either cranial CT or with CSF opening pressure greater than 20 cmH\textsubscript{2}O measured via ventriculostomy or lumbar puncture. An ONSD cut-off value of 4.0 mm for children < 1 year of age, and 4.5 mm for children over 1 year of age were used.\textsuperscript{145} An 8–5 MHz probe was used, and an average of two measurements were used for the ONSD. The authors found ONSD measurement had a sensitivity of 83\% and specificity of 38\% for detection of raised ICP, which would not be sufficient to aid in decision making of a disease condition that has a high morbidity and mortality. It was concluded that measurement of the ONSD would not be an adequate screening tool for raised ICP.\textsuperscript{163}

2. A study by Driessen et al\textsuperscript{164} compared the use of ONSD to fundoscopy in children with craniosynostosis. The authors found that ONSD measurement was not able to replace conventional fundoscopy. This study was conducted on 128 patients with syndromic or complex craniosynostosis with suspicion of raised ICP. Age related cut-off values of ONSD suggested by Helmke and Ballantyne were used.\textsuperscript{34,156} The authors also validated 27 ONSD measurements on CT scan as well, showing a good correlation between ONSD measured sonographically and on CT scan (p < 0.001). 38 eyes had papilloedema, of them only 4 had an increased in ONSD. This study demonstrated a sensitivity of 11\% and a specificity of 97\%. It was concluded that ONSD measurement would not be able to replace fundoscopy as a screening tool in chronic cases.\textsuperscript{164}

3. Hall and colleagues\textsuperscript{165} performed a study on 39 children aged between 6 months to 18 years, aiming to assess the value of ONSD measurement as a screening tool for ventriculo-peritoneal shunt (VPS) failure. Confirmation of VPS failure was based purely on the neurosurgical decision to operate. Ultrasound imaging was performed by one of four ED physicians. Sensitivity and specificity were determined by using the standard age related cut-off values suggested in earlier studies by Newman et al.\textsuperscript{145} The mean ONSD was 4.5 ± 0.9 mm in patients with
clinical shunt failure and $5.0 \pm 0.6$ mm in patients without shunt failure ($p < 0.03$). The reported sensitivity of 61% and specificity of 22.2% in this study was even lower than that reported previously by Le et al.\textsuperscript{163} ONSD measurement was therefore found to be a poor predictor of VPS failure. This study also noted no statistical significance, when ONSD was measured by anterior transbulbar or lateral transbulbar approach.\textsuperscript{165}

6.4.3. Discussion

There are only few studies evaluating the ONSD and its relationship with raised ICP in children. The focus has been to describe an accurate ONSD cut-off value, which in children is further complicated by age related variability.

Earlier studies by Helmke and Hansen\textsuperscript{34}, Ballantyne et al\textsuperscript{156} and Newman et al\textsuperscript{145} had laid the groundwork for most pediatric studies suggesting optimal ONSD cut-off values for detecting raised ICP, summarized as follows:

- <1 year old: ONSD of 4 mm
- 1 to 4 years: ONSD of 4.5 mm
- >4 year old: ONSD of 5 mm

These cut off values have been used as the criterion by nearly all the pediatric studies, except Beare et al\textsuperscript{162} and Steinborn et al\textsuperscript{125} who found cut off values much lower at 4.2 mm and higher at 6.0 mm respectively, than those previously suggested. McAuley et al\textsuperscript{122} used the same cut-off values but found the mean ONSD value to be higher than those suggested in the earlier studies, pointing out that baseline ONSD in symptomatic patients is an important factor to consider.\textsuperscript{122}

Using previously described measurements, Driessen et al\textsuperscript{164}, Le et al\textsuperscript{163} and Hall et al\textsuperscript{165} found ONSD measurement to be a poor predictor of raised ICP. The limited understanding of the ONS anatomy and response in situations of chronically raised ICP has made it difficult to comment on these studies. Malayeri et al\textsuperscript{107} included a large number of patients, but unfortunately did not suggest cut-off values and did not conduct diagnostic accuracy testing. Although the mean ONSD value of 4.55 mm with elevated ICP, regardless of age, is in keeping with
Helmke’s ONSD measurement of 5.0 mm as abnormal. However unlike the Helmke study, this study did not find age related differences in this group, and suggested age related differences were significant only in the control patients.

Even though Agrawal’s study had small numbers, it was the only study that compared ONSD to invasive ICP monitoring in pediatrics, but unfortunately did not suggest cut-off values.

Steinborn et al suggested that the high resolution of modern probes, provide better image quality, which has led to a higher ONSD cut-off values, suggesting 6.0 mm as the optimal cut-off value for predicting raised ICP. This value is considerably higher than the cut-off values of 4.5 and 5.0 mm, suggested by other authors. Although the study did not suggest any age related variations, only children between the ages of 3 and 17.8 years were included, therefore not addressing the controversy around age.

These studies have demonstrated the positive relationship between raised ICP and enlargement of the ONSD, however the cut-off values and accuracy varies.

In our study we have attempted to address certain short falls by only including children with acute findings of raised ICP, examining the diagnostic accuracies in each of our findings and analysing age related variations.

6.5. Literature review of ONSD as a non-invasive method of assessing ICP in adults - brief overview in table format and discussion

The use of the ONSD as a non-invasive method to detect raised ICP, is a topic well investigated in adults. A lot more studies have been published in adults compared to children. Below in table 6.3, is a summary of a few studies performed on patients with acutely raised ICP. The standard reference used for detection of raised ICP in these studies was either clinical assessment, cranial CT scan findings or invasive ICP monitoring. The distinct advantage of these studies is that they have analysed the diagnostic accuracy of ONSD cut-off values and the reproducibility of this technique.
<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Patients (n)</th>
<th>Etiology</th>
<th>Reference standard for comparison</th>
<th>Mean ONSD/cut-off value for raised ICP &amp; accuracy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blavis et al 2002</td>
<td>35</td>
<td>Mixed</td>
<td>CT Scan</td>
<td>Prior literature cut-off of 5 mm considered abnormal, sensitivity of 100% and 95% specificity</td>
<td>Close correlation of ONSD on ultrasound and raised ICP findings on CT scan</td>
</tr>
<tr>
<td>Geeraerts et al 2007</td>
<td>31 cases (15 with high ICP), 31 control</td>
<td>TBI in ICU</td>
<td>Invasive ICP monitoring</td>
<td>5.9 mm Sensitivity 87% and specificity of 84%</td>
<td>ONSD is an accurate predictor of raised ICP in TBI patients in the first 48 hours, with good inter-observer reliability</td>
</tr>
<tr>
<td>Girisgin et al 2007</td>
<td>28 with raised ICP, 26 control</td>
<td>Mixed</td>
<td>CT Scan</td>
<td>6.4 (0.7) mm for raised ICP, 4.6 (0.3) mm in controls</td>
<td>ONSD measurement is a useful and practical method for evaluation and follow-up of ICP</td>
</tr>
<tr>
<td>Tayal et al 2007</td>
<td>59</td>
<td>Trauma patients</td>
<td>CT scan</td>
<td>Prior literature cut-off of 5.0 mm, sensitivity of 100% and specificity of 63%</td>
<td>ONSD has potential as a sensitive test for raised ICP in adult head injury</td>
</tr>
<tr>
<td>Goel et al 2008</td>
<td>100</td>
<td>Head Injury</td>
<td>Clinical findings of raised ICP and CT scan</td>
<td>Prior literature cut-off of 5.0 mm, sensitivity of 98.6% and specificity of 92.8% and NPV of 96.3%</td>
<td>ONSD is useful in head injury patients, could potentially avoid unnecessary CT scans, and predict the need for surgery</td>
</tr>
<tr>
<td>Kimberly et al 2008</td>
<td>15</td>
<td>TBI and intracranial haemorrhage</td>
<td>Invasive ICP monitoring</td>
<td>5.0 mm, had a sensitivity of 88% and a specificity of 93%</td>
<td>This technique could be useful while waiting for CT or to monitor change in ED and ICU</td>
</tr>
<tr>
<td>Soldatos et al 2008</td>
<td>58 cases, 26 control</td>
<td>TBI</td>
<td>Clinical, CT scan and Invasive ICP monitoring</td>
<td>5.7 mm, sensitivity of 74.1% and a specificity of 100%</td>
<td>ONSD can be applied as an additional diagnostic tool to alert clinicians of raised ICP</td>
</tr>
<tr>
<td>Major et al 2010</td>
<td>26</td>
<td>Mixed group of ED patients</td>
<td>CT scan</td>
<td>Prior literature cut-off of 5.0 mm, sensitivity of 86% and specificity of 100%</td>
<td>ONSD is a specific and sensitive measure of raised ICP in any patient undergoing urgent CT form the ED</td>
</tr>
<tr>
<td>Rajajee et al 2011</td>
<td>65</td>
<td>Mixed group in ICU</td>
<td>Invasive ICP monitoring</td>
<td>4.8 mm has a sensitivity of 96% and specificity of 94%</td>
<td>When performed by an experienced operator, measurement of the ONSD is a accurate, non-invasive technique for detection of raised ICP</td>
</tr>
</tbody>
</table>

Table 6.3: Summary of adult literature supporting ONSD measurement
**Discussion**

The studies selected above conducted on adults, have been used either in an ED or in trauma patients who had sustained TBI. The table above reflects the strong relationship between ONSD measurement and ICP in adults. However the difficulty in describing an optimal ONSD cut-off value that best detects raised ICP is highlighted. Some studies have used the previously described cut-off value of 5.0 mm, which has shown good diagnostic accuracy.\(^{18,20,22,166,167}\) The studies conducted in the ED have used clinical and CT scan findings as the reference standard for raised ICP. ONSD measurements in all these studies range from 4.8 mm to 6.4 mm.\(^{21,144}\) Kimberly et al\(^ {22}\), found the commonly suggested cut-off value of 5.0 mm provided the best diagnostic accuracy when compared with invasive ICP measurement. Studies that have used invasive ICP measurements as the criteria for raised ICP should provide the most accurate values, although in these studies the values are variable (4.8 mm, 5.0 mm, 5.7 mm and 5.9 mm).\(^ {19,22,143,144}\)

The general consensus is that sonographic measurement of the ONSD is a rapid, accurate, reproducible modality when used by an experienced operator. It is an efficient screening tool that could be used in the ED prior to performing a CT scan. It can also be a valuable imaging modality in a resource limited setting and in patients who have contraindications for invasive ICP monitoring.

This study analysed ONSD measurements to determine their efficacy of detecting raised ICP in an acute care situation. The potential use of this technique as an adjunct to current assessment methods in children with TBI is promising.
Chapter 7. Transorbital ultrasonography of the ONSD as a non-invasive screening tool for raised ICP:

7.1. Study Design and Research methods:

Objective:

A reliable, cost-effective, non-invasive technique that can be used in an emergency care setting as a screening tool for raised ICP would be a valuable adjunct.

Based on the hypothesis that acutely raised ICP will result in an enlargement of the ONSD, this study aimed to demonstrate the efficacy of transorbital measurement of the ONSD as a routine screening tool in pediatric TBI.

Study Design:

This was a prospective, observational analysis of a pediatric cohort of patients (under 13 years of age). All patients included in this study had sustained TBI and presented to the trauma unit within 24 hours of injury. These children were clinically assessed and had indications for a cranial CT scan. For all the children included in the study, clinical severity was assessed, CT scan was analysed for features of raised ICP, measurements of the ONSD were performed and outcome of the patient was noted.

This data was reported according to the ‘strengthening the reporting of observational studies in epidemiology’ (STROBE) guidelines.¹⁶⁸
**Setting:**

All patients were recruited from the trauma unit of the Red Cross War Memorial Children’s Hospital, which is a tertiary referral center for pediatric TBI. Children were recruited to the study from December 2012 to June 2014. All history taking, clinical assessments, imaging, admission and follow-up were conducted at the same center. The hospital has a 24 hour emergency, radiological and neurosurgical service.

**Participants:**

A total of 99 patients under 13 years of age, who had sustained TBI and presented to the trauma unit, were included in this study.

17 of these patients were excluded due to:

- injury > 24 hours (n=2)
- uncooperative patients (n=4)
- inadequate ONSD imaging (n=6)
- extensive orbital injury (n=1)
- haemodynamic instability (n=4)

![Figure 7.1: Participants inclusion and exclusion criteria](image-url)
A total of 82 patients were included in the final analysis.

Appropriate informed consent was obtained from the parents/caregivers of children enrolled into the study. Enrollment into the study did not influence the medical care of the patients.

**Variables:**

ONSD measurements were analysed in relation to the main variables i) clinical severity, ii) CT features of ICP and iii) outcome of patients

Other sub-analysis were conducted on the following variables:

1. Due to previous studies suggesting age as a possible confounding variable, a subgroup analysis using an age cut off of 1 year was performed.

2. The axial ONSD and the sagittal ONSD were evaluated for any variation in measurement between these planes.

3. As BOS fractures can cause a CSF leak, this clinical finding was included as a potential confounding factor.

4. Operator reliability in emergency care would be an extremely important factor. To assess the reproducibility of this technique, inter-observer reliability was examined, by comparing measurements performed on 25 randomly selected patients by two users experienced in the used of transorbital ultrasound.
Data sources/measurements:

Data collection and clinical assessment was performed by a pediatric trauma physician, who is also the primary investigator (PI) of this study. Data was collected and saved onto a secure and confidential Microsoft® Excel® for Mac 2011 database. The following general data was collected: age, gender, date of birth, date of injury, mechanism of injury, date of examination, clinical signs and symptoms, examination findings including GCS, CT scan findings, outcome data and ONSD measurements.

Clinical Examination

All clinical examinations were conducted by the PI. Enrollment into the study was based on one or more of the following findings, which were indications for a cranial CT scan. These indications were based on the PECARN TBI clinical prediction rules.43

- Loss of consciousness, amnesia, altered mental status, post traumatic seizures, extensive headaches, excessive vomiting, dizziness, sensory deficit, GCS less than 15, skull defects on examination and evidence of BOS with findings of either rhinorrhea, CSF otorrhoea, battle sign, peri-orbital ecchymosis and haemotympanum.

GCS in children under 2 years of age was assessed according to the Pediatric GCS.60,64 GCS in children over 2 years of age was assessed according to the standard GCS.56

Clinical severity of patients was recorded according to initial GCS:76

- GCS 14-15 = Mild
- GCS 9-13 = Moderate
- GCS 3-8 = Severe
CT Analysis

All CT imaging was performed by the radiology department and findings of raised ICP on CT were based on radiology reports and neurosurgical opinion.

Features of raised ICP on CT scan were made using one or more of the following criteria:\textsuperscript{12,68,70}

- Diffuse sulcal effacement - one or both hemispheres
- Effacement of basal cisterns
- Ventricular compression
- Midline shift > 5mm
- Evidence of uncal or transtentorial herniation
- Loss of grey white matter differentiation.

Ultrasound ONSD imaging and measurements

All imaging was performed by a single investigator, experienced in the use of emergency care ultrasound. Imaging was done using a SonixOne, Ultrasonix machine, BK Ultrasound® (Canada) and a L14-5 linear transducer with a frequency range of 14 – 5 MHz. The TI and MI on the ultrasound machine were set to < 1.0, in accordance with the EFSUMB recommendations and imaging time was kept to a minimum.\textsuperscript{159}

All ONSD measurements were performed with patients in a supine position with the head central. The transducer was gently placed on the superior and lateral aspect of the closed upper eyelid, using coupling gel as a contact medium. Care was taken not to apply pressure to the globe, by using the little finger and hand to rest lightly on the superior orbital ridge for stability. The depth was set at 4 cm predetermined for “small organs”, but this was then adjusted along with the angle (caudally and medially) of the probe to provide the most suitable image quality of the ONS. Static images were then labeled and saved. Three axial images followed by three sagittal images were taken for each eye. Measurements were performed at a later stage. Each ONSD measurement was taken 3.0 mm behind the papilla, perpendicular to the ON.\textsuperscript{32} These measurements were
then averaged to obtain a mean ONSD for each eye. These mean ONSD measurements were used to determine the relationship with clinical, radiological and outcome findings.

**Bias:**

All ONS imaging was done either just before or just after the cranial CT scan. While the investigator was blinded to the CT result at the time of imaging, the investigator was also the primary clinician of the patient, therefore some bias may still exist. Inter-rater reliability testing was performed to address potential bias in this regard.

**Study Size:**

Based on results from existing studies in literature, the sample size estimate for comparison of means was calculated at 82 patients, to achieve 80% power, with an alpha of 5 (p < 0.05). Based on the available literature the results were expected to differ according to age category, with described age-related variation at 1 year. With an estimated 10% loss due to exclusion criteria and data loss, the study aimed to recruit 90 patients.

**Quantitative variables:**

The data were analysed according to age, gender, GCS score, clinical severity, cranial CT findings of ICP and patient outcome.

The main results of the ONSD measurements were correlated and compared with the following:
1. Clinical severity - each patient was placed into a clinical severity category based on initial GCS findings: GCS 14-15 = Mild, GCS 9-13 = Moderate, GCS 3-8 = Severe. These clinical categories and the CT scan features were then analysed, as described in table 7.3.

2. Features of raised ICP on CT - patients were divided into those without features of raised ICP on CT scan (Group 1), and those with features of raised ICP on CT scan (Group 2). There were 45 patients in Group 1, and 37 patients in Group 2.

3. Outcome - outcome was categorized as i) discharged home, ii) admitted to trauma unit for observations, iii) referred to neurosurgery for monitoring/surgery, or iv) died.

An age related cut-off value (at 1 year of age), as suggested in the pediatric literature, was also investigated. 11 children under the age of 1 year were then excluded from this part of the analysis, and the relationship between ICP and ONSD was analysed on the remaining 71 children.

The relationship between BOS fractures and ONSD measurements was also analysed. BOS fractures were assessed clinically and diagnosed by the presence of CSF rhinorrhea or otorrhoea, battle sign, peri-orbital ecchymosis and haemotympanum.

The entire patient cohort was used for this part of this analysis.

Inter-observer reliability was calculated by comparing measurements independently performed by two observers experienced in the use of transorbital ultrasound.

**Statistical Methods:**

Testing for normality of data distribution was performed using the Shapiro-Wilks test. Normally distributed (parametric) data were reported using means and standard deviations (SD) and abnormally distributed (non-parametric) data were reported using
medians and interquartile ranges (IQR). The general association between means of numeric variables was tested by applying either Pearson’s (PCC) or Spearman’s correlation coefficient (SCC), depending on normality of data distribution. The independent Student t-test was used for comparing mean values, and the Wilcoxon sum rank test/Mann-Whitney test was used to compare median values.

Bland-Altmann analysis was used to test inter-observer reliability, using limits of agreement and mean differences. The diagnostic accuracy of transorbital ultrasound measurement of the ONSD for detecting features of raised ICP on CT scan was described using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the receiver operating characteristic (AUROC) curves and odds ratios (OR), as well as their 95% confidence intervals (CI). Statistical significance was set at p < 0.05 and all significance testing was two sided. All analyses were done using Stata IC version 12.0 (Stata Corporation LP, College Station, Texas, USA) statistical software.

Approval for this study was granted by, Human Research Ethics Committee of the University of Cape Town (HREC Ref: 674/2013).

Approval for this study was also granted by, Research Committee of the Red Cross War Memorial Children’s hospital. Consent was obtained from parents/caregivers for all children included in the study.
7.2. Results and Discussion

General Results:

Participants:

A total of 99 patients were eligible for this study (Figure 7.1) Finally data analysis was conducted on 82 patients, who had ONSD measurements, clinical severity scoring, cranial CT scan and outcome documented. Data was also analysed using the age cut-off of 1 year, which excluded 11 children and included 71.

Descriptive data:

A total of 82 children aged between 0 and 13 years were enrolled in this study, all had ONSD measurements, clinical severity scoring, assessment of ICP using CT features, and outcome of patient was documented. A total of 984 ONSD measurements were acquired from 82 patients (3 axial images, and 3 sagittal images in each eye, for each patient).

The median age was 65.5 months (IQR 31-105)
This included 53 males and 29 females with a ratio of 1.8:1.
The most common etiologies were: motor vehicle accidents (MVA) in 41 (50%), falls in 25 (31%), struck by/against object in 6 (7%) and miscellaneous in 10 (12%) (gunshot wounds, non-accidental injuries, train injuries).
Figure 7.2: Etiology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>82</td>
</tr>
<tr>
<td>Age (median age in months)</td>
<td>65.5 (31-105)</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>Motor vehicle accident (passenger)</td>
<td>15</td>
</tr>
<tr>
<td>Motor vehicle accident (pedestrian)</td>
<td>26</td>
</tr>
<tr>
<td>Falls</td>
<td>25</td>
</tr>
<tr>
<td>Struck by object</td>
<td>6</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>10</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 7.1: Demographic details
Outcome data:

- The mean GCS over the entire cohort was 11.4 (SD 4.9)
- The patients were divided according to clinical severity of injury. 50 (60.98%) patients had mild injury, 6 (7.31%) patients had sustained a moderate injury and 26 (31.71%) had sustained a severe TBI.
- Diagnosis of raised ICP was made on the basis of CT scan result, with 45 (54.8%) children demonstrating no features of raised ICP (Group 1) and 37 (45.12%) children with positive features of raised ICP (Group 2).
- Outcome included 12 (14.63%) children who were discharged home, 39 (47.56%) admitted to the trauma unit for observations, 27 (32.93%) admitted to neurosurgery for surgery or invasive monitoring, and 4 (4.88%) children died in the ED.

<table>
<thead>
<tr>
<th>Number</th>
<th>No features of raised ICP (Group 1)</th>
<th>Features of raised ICP (Group 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>42 (19-92)</td>
<td>78 (39-108)</td>
</tr>
<tr>
<td>Mean GCS</td>
<td>14.3 (2.27)</td>
<td>7.84 (4.91)</td>
</tr>
<tr>
<td>Mean ONSD (mm)</td>
<td>4.85 (0.54)</td>
<td>5.98 (0.60)</td>
</tr>
<tr>
<td>Clinical severity score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>41</td>
<td>9</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Admission for observation</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Refer to neurosurgery</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 7.2: Parameters according to CT features of raised ICP
Main Results:

1. ONSD and clinical severity

There were 50 patients with mild TBI, 6 with moderate TBI and 26 with severe TBI. The mean ONSD in each group was 5.02 mm (SD 0.68), 5.50 mm (SD 0.86) and 5.98 mm (SD 0.61) respectively. These findings and the relevant statistical analyses are summarized in table 7.3. The difference between ONSD measurement in the mild and moderate TBI groups was not significant, p = 0.12. In the moderate and severe TBI, the ONSD measurements was also not statistically significant, p = 0.12. However the increasing mean ONSD as clinical severity increases is visible in the box and whisker plot (Figure 7.3).

<table>
<thead>
<tr>
<th>Clinical severity</th>
<th>Number (%)</th>
<th>No features of raised ICP on CT</th>
<th>Features of raised ICP on CT</th>
<th>Mean ONSD (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>50 (60.9)</td>
<td>41</td>
<td>9</td>
<td>5.02 (0.68)</td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (7.3)</td>
<td>3</td>
<td>3</td>
<td>5.50 (0.86)</td>
</tr>
<tr>
<td>Severe</td>
<td>26 (31.8)</td>
<td>1</td>
<td>25</td>
<td>5.98 (0.61)</td>
</tr>
</tbody>
</table>

Table 7.3: Mean ONSD values in relation to clinical severity

Figure 7.3: Box and whisker plot of ONSD for clinical severity, 1 = mild, 2 = moderate, 3 = severe
2. **ONSD and features on CT scan**

45 patients had no features suggestive of raised ICP on CT, and 37 patients had features suggestive of raised ICP. The mean ONSD in group 1 was 4.85 mm (SD 0.54), and the mean ONSD in group 2 was 5.98 mm (SD 0.60) (p < 0.001). Diagnostic accuracy analysis revealed an optimal ONSD value of 5.36 mm with a sensitivity of 86.5 % (95% CI: 71.2 - 95.5), specificity of 80% (95% CI: 65.4 – 90.4), PPV of 78% (95% CI 62.4 – 89.4), NPV of 87.8% (95 CI: 73.8 – 95.9). The AUROC curve was 0.83 (95% CI: 0.75 – 0.91) and the diagnostic OR was 25.6 (95% CI: 7.93 – 82.2). (Table 7.4 and Figure 7.4).

<table>
<thead>
<tr>
<th>ONSD cut-off value (mm)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>AUROC (95%CI)</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.36</td>
<td>86.5% (71.2 - 95.5)</td>
<td>80% (65.4 – 90.4)</td>
<td>78% (62.4 – 89.4)</td>
<td>87.8% (73.8 – 95.9)</td>
<td>0.83 (0.75 – 0.91)</td>
<td>25.6 (7.93 – 82.2)</td>
</tr>
</tbody>
</table>

Table 7.4: ONSD cut-off value for detecting raised ICP over the entire cohort.

![Figure 7.4: Box and whisker plot of ONSD for: 0 = no features of raised ICP, 1 = positive features of raised ICP](image-url)
3. **ONSD and outcome**

Twelve patients were discharged (grade 0), 39 patients were admitted for observation (grade 1), 27 patients were referred to neurosurgery (grade 2), and 4 patients died (grade 3). The mean ONSD measurement in each of these groups has been summarized in table 7.5.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number of patients</th>
<th>No features of raised ICP on CT</th>
<th>Features of raised ICP on CT</th>
<th>Mean ONSD in mm (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>4.83 (0.4)</td>
</tr>
<tr>
<td>1</td>
<td>39</td>
<td>32</td>
<td>7</td>
<td>5.05 (0.7)</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>2</td>
<td>25</td>
<td>5.98 (0.6)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>5.72 (0.5)</td>
</tr>
</tbody>
</table>

Table 7.5: Mean ONSD values in relation to outcome

Figure 7.5: Box and whisker plot of mean ONSD for outcome of patient. 0 = discharged, 1 = observation, 2 = neurosurgery, 3 = died
Other analyses:

Age group >1, ONSD cut off value

Eleven children were under the age of 1 and in accordance with previous studies were excluded, leaving 71 children between the ages of 1 to 13 years for this part of the analysis. Of these, 37 children had no features of raised ICP, and 34 had CT features suggestive of raised ICP. The mean ONSD measurements were 4.84 mm (SD 0.56) and 6.05 mm (SD 0.53), respectively. The optimal ONSD measurement for detecting raised ICP in this group was 5.4 mm, with a sensitivity of 91.2% (95% CI: 76.3 – 98.1), specificity of 78.4% (95% CI: 61.8 – 90.2), PPV of 79.5% (95% CI: 63.5 – 90.7), NPV of 90.6% (95% CI: 75 – 98). The AUROC curve was 0.85 (95% CI: 076 – 0.93), with a diagnostic OR of 37.5 (95% CI: 9.4 – 145).

<table>
<thead>
<tr>
<th>ONSD cut-off value (mm)</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>PPV (95%CI)</th>
<th>NPV (95%CI)</th>
<th>AUROC (95%CI)</th>
<th>OR (95%CI)</th>
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</thead>
<tbody>
<tr>
<td>5.40</td>
<td>91.2 (76.3 – 98.1)</td>
<td>78.4 (61.8 – 90.2)</td>
<td>79.5 (63.6 – 90.7)</td>
<td>90.6 (75 – 98)</td>
<td>0.85 (0.76 – 0.93)</td>
<td>37.5 (9.4 – 145)</td>
</tr>
</tbody>
</table>

Table 7.6: ONSD cut-off value for detecting raised ICP in children older than 1 year of age

Figure 7.6: Box and whisker plot of mean ONSD for: 0 = no features of raised ICP, 1 = positive features of raised ICP in children > 1 year of age
Relationship of ONSD between Axial and Sagittal views

The mean ONSD in the axial and sagittal planes were 5.41mm (SD 0.76) and 5.31mm (SD 0.86) respectively, demonstrating an excellent correlation (r = 0.94, p < 0.001). The mean binocular ONSD was 5.36 mm (SD 0.79).

Figure 7.7: Box and whisker plot of mean ONSD between axial and sagittal views

Figure 7.8: Scatterplot of mean ONSD of axial and sagittal views
Base of skull fractures

In group 1, with no features of raised ICP on CT, 6 patients had a confirmed BOS fracture, the mean ONSD measurement in this group was 4.69 mm (SD 0.59). In group 2 with features of raised ICP, 11 patients had a confirmed BOS fracture with a mean ONSD measurement of 5.75 mm (SD 0.62). While both these ONSD measurements were lower than the mean ONSD measurement in their respective groups, neither was statistically significant.

Inter-observer reliability

25 randomly selected patients had repeat measurements of their ONS images. The inter-observer reliability was tested by comparing the mean ONSD measurements. The data were correlated using PCC and Bland-Altman analysis to test for agreement between the observers. The mean ONSD measurement by observer 1 was 5.79 mm (SD 0.73) and by observer 2 was 5.86 mm (SD 0.78). Bland-Altman analysis revealed a mean difference between the two observers of 0.07 mm (95% CI: -0.231 – 0.087), with limits of agreement between -0.84 – 0.69 (Figure 7.9). Correlation between the 2 observers was very good (r = 0.90, p < 0.001).
Figure 7.9: Bland-Altman plots for inter-observer reliability. Outer solid lines represent limits of agreement

Figure 7.10: Scatterplot of mean ONSD measurements for observer 1 and observer 2
Discussion:

Key results:

Our study demonstrates that transorbital measurement of the ONSD shows a good relationship with features of raised ICP on CT scan. Clinical assessment of raised ICP in a child has always been difficult and non-specific.\textsuperscript{40,52,65} Blunt head trauma may go unrecognized, increasing the possibility of morbidity, which could otherwise be prevented. As ICP increases it results in a decrease in the level of consciousness and increased severity grading. This can be detected on initial cranial CT scan and will require admission to hospital. Early detection of raised ICP through sonographic measurement of the ONSD would help better management of these cases. The results of the ONSD measurements and key variables are as follows:

Relationship between ONSD and clinical severity score

In our study we noted 50 children with mild clinical TBI (GCS 14-15), of these 9 (18\%) children had features of raised ICP on CT and 41 (82\%) did not. In the moderate TBI group (GCS 9-13), 3 out of 6 (50\%) did not have features of raised ICP on CT. These findings are consistent with the uncertainty surrounding the clinical assessment of elevated ICP. Measuring the ONSD as an additional screening method combined with clinical assessment, could potentially reduce this uncertainty. The relationship between clinical severity grading and measurement of the ONSD was not statistically significant, p < 0.12. However, there was a steady increase in the mean ONSD value as clinical severity increased, i.e. mild - 5.02 mm (SD 0.68), moderate-5.50 mm (SD 0.86) and severe 5.98 mm (0.61). The box and whisker plots represent this trend in Figure 7.3.
Relationship between ONSD measurement and ICP features on CT

The linear relationship between ICP and ONSD has been described by many authors.\textsuperscript{18,19,21,23,32}

Analysing the entire cohort of patients, 37 had features of raised ICP on CT demonstrating a mean ONSD of 5.98 mm (SD 0.60) and 45 patients had no features of raised ICP with a mean ONSD of 4.85 mm (SD 0.54). Diagnostic accuracy testing revealed an optimal ONSD cut-off value of 5.36 mm for detecting raised ICP, with a sensitivity of 86.5% and specificity of 80% (p < 0.001). The diagnostic OR was 25.6, suggesting the chances of detecting raised ICP with an ONSD of more than 5.36 mm was 25.6 times higher than in children without raised ICP. It is suggested that a high sensitivity is preferred, in order to reduce the chances of false negatives.\textsuperscript{24}

The ONSD measurements in our study are slightly higher than those previously reported in children,\textsuperscript{34,107,145,156} although not as high as the most recent study by Steinborn et al.\textsuperscript{125}

Relationship between ONSD and outcome

In this part of the analysis we looked at the outcome of patients. Children with features of raised ICP should ideally be referred to neurosurgery or in the least be admitted for observation.

In our study 12 children were discharged home, the mean ONSD in this group was 4.83 mm (SD 0.42). 39 children were admitted to the trauma unit for observation, the mean ONSD in this group was 5.05 mm (SD 0.74). 27 children were referred to neurosurgery for an operation or monitoring, the mean ONSD in this group was 5.99 mm (SD 0.61). 4 children died with a mean ONSD of 5.72 mm (SD 0.56). There is a positive relationship between outcome and ONSD measurement in this analysis, as demonstrated by the box and whisker plot in Figure 7.5.

These values might be in keeping with those suggested by Helmke,\textsuperscript{34} that an ONSD measurement of more than 5.0 mm is suggestive of raised ICP, as children with an ONSD measurement of more than 5.0 mm in this study required hospital admission.
Relationship between ONSD and ICP features on CT in children over 1 year of age

The age related ONSD thresholds in children are still unclear. According to Luerssen, the Monro-Kellie doctrine does not apply to children with an open fontanelle and expanding cranial sutures. Bearing this in mind we excluded children under the age of 1 year and analysed the remaining 71 children. 37 of these had no signs of raised ICP, with a mean ONSD of 4.84 mm (SD 0.56) and 34 patients had features of raised ICP on CT, with a mean ONSD of 6.05 mm (SD 0.53). Diagnostic accuracy testing revealed the optimal ONSD measurement for detecting raised ICP in this group was 5.4 mm, with a sensitivity of 91.2% and a specificity of 78.4%. Diagnostic OR of 37.5 was much better than the OR of 25.6 over the entire cohort of patients. A better sensitivity means fewer false negatives, which is preferable, given the devastating potential of missing patients with raised ICP. It is also noted that the mean ONSD value for children without raised ICP in this subgroup analysis was the same as the value over the entire cohort, i.e. 4.84 mm (SD 0.56) and 4.85 mm (SD 0.54) respectively.

Limitations:

- While the investigator was blinded to the CT result at the time of imaging, she could not be blinded to the clinical condition, as the investigator was the primary clinician of the patient.
- Papilloedema was not assessed, as this was difficult in an acute trauma setting.
- The reference standard used for raised ICP is not the gold standard, as CT features of raised ICP are also surrogate markers. In emergency care setting access to invasive ICP monitoring is not feasible.
Interpretation and discussion:

The evaluation of pediatric TBI in an acute care setting can be very challenging. Clinical findings of raised ICP are often non-specific and may be missed in minor injuries. This limitation is exacerbated by concomitant injuries, sedation, paralysis and intubation. Although cranial CT scans are widely available, it requires time and transport away from the resuscitation area and can be risky in unstable patients. In our study we have demonstrated that transorbital measurement of the ONSD has a linear relationship with ICP, and is a good predictor of raised ICP in children. The use of a bedside, emergency ultrasound machine (which is widely available in emergency and pre-hospital settings) to detect raised ICP as a routine screening tool in all head injury patients would be very beneficial. A simple, rapid, portable, non-invasive, diagnostic tool used as an adjunct to clinical examination would allow earlier detection of raised ICP and prevention of unnecessary cranial CT scan in minor head injuries and neurologically normal patients.

The reasonably high sensitivity of this imaging modality, suggests that this can be used as a diagnostic tool in routine trauma care. The modern high quality transducers and small portable ultrasound machines, make this method patient and user friendly, providing excellent imaging even for a newly trained clinician. This method is easy to learn with minimal training and is relatively quick.

Measurement of the ONSD can be used in mass casualty to triage patients who require immediate transfer to neurosurgical facilities or CT scans for assessment of ICP. A portable machine can also be used in long transfers to monitor patients. This method can help for routine monitoring of ICP in children who have intracranial injury on CT but do not require neurosurgical intervention and are admitted for neuro-observations, therefore reducing the number of follow up CT scans.

POCUS machines are generally available even in resource limited settings. The use of transorbital measurement of the ONSD, can be used where neurosurgeons and invasive ICP monitoring are not available or contraindicated.
Conclusion:

Transorbital measurement of the ONSD is a reliable bedside screening tool to detect raised ICP in pediatric TBI. The cut-off values and age variations are the limitations of this technique however when used in conjunction with current clinical examination methods, it could provide better management of the patient.
Appendices:

Appendix 1

PECARN TBI clinical prediction rules used for clinical assessment of patients and guidelines for indications for cranial CT scan.

**Table 1** PECARN TBI age-based clinical prediction rules (high, intermediate and very low TBI risk groups) for children with minor blunt head trauma and initial GCS ≥14

<table>
<thead>
<tr>
<th>Indication criteria</th>
<th>CT recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;18 years of age</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-trivial head trauma within 24 h</td>
<td>Yes</td>
</tr>
<tr>
<td>Neurological abnormalities</td>
<td>Yes</td>
</tr>
<tr>
<td>Bleeding disorders</td>
<td>Yes</td>
</tr>
<tr>
<td>Suspected child abuse</td>
<td>Yes</td>
</tr>
<tr>
<td>Previous neuroimaging</td>
<td>Yes</td>
</tr>
<tr>
<td>Outcome measure: clinically important TBI</td>
<td>Yes</td>
</tr>
<tr>
<td>Death, Intubation ≥24 h, neurosurgery, or two or more nights in the hospital for management of the head injury</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**PECARN TBI risk groups**

<table>
<thead>
<tr>
<th>Age ≤2 years</th>
<th>Age &gt;2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Age ≤2 years</td>
<td>Age &gt;2 years</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>Altered mental status</td>
</tr>
<tr>
<td>Severe injury mechanism</td>
<td>Severe injury mechanism</td>
</tr>
<tr>
<td>Loss of consciousness &gt;5 s</td>
<td>Loss of consciousness &gt;5 s</td>
</tr>
<tr>
<td>Not acting right as per parent</td>
<td>Not acting right as per parent</td>
</tr>
<tr>
<td>Very low risk</td>
<td>Very low risk</td>
</tr>
<tr>
<td>No predictors</td>
<td>No predictors</td>
</tr>
</tbody>
</table>

*Ground-level falls or running into stationary objects with no signs of TBI other than scalp abrasions and lacerations.*

**Figure 3** Suggested CT algorithm for children younger than 2 years (A) and for those aged 2 years and older (B) with GCS score of 14-15 after head trauma.

**GCS** Glasgow Coma Scale, **TBI** traumatic brain injury, **LDC** loss of consciousness. *Data are from the combined derivation and validation populations. Other signs of altered mental status, agitation, somnolence, repetitive speaking, or slow response to verbal stimuli. Eleven mechanism of injury: motor vehicle crash with patient ejection, death of another passenger or rider, pedestrian or bicyclist without helmet struck by motor vehicle, fall of >3 feet for children >2 years of age or >5 feet for children ≤2 years or head struck by high impact object.*

**GCS, Glasgow Coma Scale; PECARN, Pediatric Emergency Care Applied Research Network; TBI, traumatic brain injury.**
Appendix 2

Glasgow Coma scale used for grading of severity of injury for children under 2 years of age and over 2 years of age.

Standard Glasgow Coma Scale⁵⁶

<table>
<thead>
<tr>
<th>Eye Opening</th>
<th>Best Verbal Response</th>
<th>Best Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>Oriented</td>
<td>Follows commands</td>
</tr>
<tr>
<td>To verbal stimuli</td>
<td>Confused</td>
<td>Localizes pain</td>
</tr>
<tr>
<td>To pain</td>
<td>Inappropriate words</td>
<td>Withdraws to pain</td>
</tr>
<tr>
<td>None</td>
<td>Incomprehensible sounds</td>
<td>Flexion to pain</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Extension to pain</td>
</tr>
</tbody>
</table>

Pediatric Glasgow Coma Scale⁶⁰,⁶⁴

<table>
<thead>
<tr>
<th>Eye Opening</th>
<th>Best Verbal Response</th>
<th>Best Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>Coos, babbles</td>
<td>Normal spontaneous movement</td>
</tr>
<tr>
<td>To speech</td>
<td>Irritable, cries</td>
<td>Withdraws to touch</td>
</tr>
<tr>
<td>To pain</td>
<td>Cries to pain</td>
<td>Withdraws to pain</td>
</tr>
<tr>
<td>None</td>
<td>Moans to pain</td>
<td>Abnormal flexion</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Abnormal extension</td>
</tr>
</tbody>
</table>
Appendix 3

Strobe guidelines used for reporting of study.

The STROBE Statement—checklist of items that should be addressed in reports of observational studies

<table>
<thead>
<tr>
<th>Item number</th>
<th>Title and Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract.</td>
</tr>
<tr>
<td></td>
<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found.</td>
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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (briefly available on the websites of PLoS Medicine at www.plosmedicine.org, Annals of Internal Medicine at www.annals.org, and Epidemiology at www.epidem.com). Separate versions of the checklist for cohort, case-control and cross-sectional studies are available on the STROBE website at www.strobe-statement.org.

* Give such information separately for cases and controls in case-control studies, and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Reference List


46. Monro A. Observations on the structure and functions of the nervous system. . 1783.


88. Brenner DJ, Elliston CD, Hall EJ, Berdon WE. Estimates of the cancer risks from pediatric CT radiation are not merely theoretical: Comment on "point/counterpoint: In x-ray computed
tomography, technique factors should be selected appropriate to patient size. against the proposition". Med Phys. 2001;28(11):2387-2388.


