Optic Nerve Sheath Ultrasound to track changes in Intra Cranial Pressure. The OPTIC-ICP study.

Short Title: Optic-ICP study

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1. Background and rationale

Severe Traumatic Brain Injury (TBI) is significant problem accounting for approximately 160,000 admissions to critical care annually in the UK (www.centreformentalhealth.org.uk, 2014). Management of patients with TBI in tertiary neuroscience centres frequently involves the use of intra parenchymal monitoring of intracranial pressure (ICP). However, not all patients are initially managed in such facilities and in some situations it can be many days before such management can be initiated.

Optic nerve sheath diameter ultrasound (ONSD US) is a non-invasive method of quantifying ICP which has been found to have an acceptable correlation during the acute phase of TBI. The optic nerve is continuous with the coverings of the brain and any increase in brain swelling is transmitted via cerebral spinal fluid to the optic nerve sheath, causing dilatation of that structure. Studies have shown this phenomenon to occur within minutes of acute changes in ICP. However, an important caveat is that ONSD estimation of ICP relies on normal intracranial flow dynamics to allow for adequate displacement of the sheath. Following a severe TBI, the dynamics of CSF flow can alter over time and there is no data relating to the continuing use of ONSD US to track changes in ICP over a more prolonged time course. Many of the reported studies have taken one off measurements of ONSD / ICP, usually early in the clinical course. To our knowledge, no study has sequentially tracked ICP in individual patients over time, as opposed to stratifying groups of patients based on the presence of high ICP at a single time point and examining the mean ONSD value.

2. Aims

The principal research question is whether changes in Optic Nerve Sheath Diameter (ONSD) are correlated with invasive measurements of ICP and whether this correlation is preserved over the first 5 days following traumatic brain injury.

3 Study design

3.1 Overview

Prospective longitudinal observational study. Serial measurements will be made of the optic nerve sheath diameter over time using ultrasound.

3.2 Population

Adult patients admitted to Critical Care with diagnosed severe TBI, requiring invasive ICP monitoring. It is expected that 50 patients will be required for this study.

3.2.1 Inclusion criteria

- Adult patients over 18 years old
- Patients with traumatic brain injury
- Established intra-cranial pressure monitoring within 24 hours of ICU admission.

3.2.2 Exclusion criteria

- Not expected to survive 24 hours in whom the treatment focus is palliative.

- Any peri-orbital injury precluding placement of ultrasound probe, e.g. penetrating globe injury or severe exophthalmos.

3.2.3 Co-enrolment

Co-enrolment is permitted with both observational and interventional studies.

3.2.4 Screening

Patients will be identified by members of the direct care team. Once identified members of the research team will be alerted to a potential participant. Members of the research team will promote regular awareness of the inclusion and exclusion criteria for the study amongst clinical staff.

Daily screening will take place and details of eligible patients will be entered into a screening log. Reasons for non-recruitment of eligible patients will be recorded in the screening log.

3.3 Recruitment and consent

3.3.1 Overview & rationale

Intubated, ventilated patients with confirmed TBI, eligible for inclusion in the study are critically unwell, invariably receiving sedative medications and exhibiting both a reduced level of consciousness and inability to effectively communicate. For all these reasons they lack capacity to provide prior informed consent. The point of maximal scientific interest and potential for future treatment developments occurs in the first hours of critical illness during this period of mental incapacity. For these reasons any attempt to obtain either prior informed consent from the patient, or the opinion of their Personal Consultee (i.e. relative or close friend), prior to study enrolment would be inappropriate.

Once an eligible patient has been identified who fulfils the inclusion criteria they will be entered into the study after taking advice from the referring clinician, acting as a nominated consultee. Subsequent opinion will be sought from a friend or relative (personal consultee) and ultimately consent for use of data will be sought from the patient after they regain capacity.

3.3.2 Role of Nominated Consultee

The clinician referring the patient will also assume the role of nominated consultee. This individual will not be a member of the research team. The role of the nominated consultee will be to express an opinion as to whether the patient is suitable for inclusion in the study. They will receive information relating to the nature of the study in the form of an information sheet. Nominated consultees will be asked to indicate agreement for enrolment in the study.

3.3.3 Role of Personal Consultee

As out lined in Section 3.3.1 it will not be possible to involve trial participants in the consenting process at study recruitment. Instead, consent will be obtained from patients once they have stabilised and are deemed to have capacity.

In the interim, once notified of the enrolment of a patient into the study, a delegated member of the research team will approach a close friend or relative, known as a personal consultee,

as soon as appropriate and practically possible to discuss the trial and to seek advice as to the patients' likely wishes and feelings regarding participating in research. Ideally, this approach would take place within 24-48 hours of study enrolment, once the patient's medical situation is no longer an emergency and initial meetings between the consultee and treating clinicians have occurred.

The Personal Consultee will be provided with a Personal Consultee Information Sheet, containing all of the information provided on the PIS, supplemented by information about why the Personal Consultee has been approached at this stage. A Personal Consultee Opinion Form will be provided indicating that: the information given, orally and in writing, has been read and understood; the patients' participation is voluntary and can be withdrawn at any time without consequence; and that, in the Personal Consultees opinion, the patient would not object to taking part in research. Personal Consultees will also be asked to indicate on the Personal Consultee Opinion Form whether, in their opinion, the patient would agree to access to medical records for data collection.

Personal Consultees will be given time to read the Personal Consultee Information Sheet and have an opportunity to ask any questions they may have about the patients' participation in the study. After verifying that the Personal Consultee Information Sheet and Opinion Form are understood, the person seeking opinion will invite the Personal Consultee to sign the Personal Consultee Opinion Form and will then add their own name and countersign it. A copy will be given to the Personal Consultee, a copy placed in the patient's medical notes and the original kept in the Site File.
If a Personal Consultee advises that, in their opinion, the patient would not choose to participate in research, then no further data collection will occur.
If and when patients regain the physical and mental capacity to give consent, information will be provided to them and written informed consent will be sought for use of collected data.

3.3.4 Informed consent from participants

Following enrolment, patients will be approached once they have been deemed to have full capacity to provide informed consent. At this stage study measurements will have concluded and consent will be related to the use of collected data. A Participant Information Sheet (PIS) will be provided to the patient. The PIS will provide information about the purpose of the study, what participation means for the patient, confidentiality and data security, and the future availability of the trial results.

A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File. If the patient is unable to physically sign the Consent Form (e.g. due to physical incapacity), an independent witness can sign on their behalf.

3.3.5 Event of patient death

In the situation where the patient dies any data collected will be used in analysis. There will be no requirement to make further approaches to a consultee in this instance.

3.3.6 Event of discharge / transfer prior to recovery of capacity

In the rare situation where the patient is transferred to another hospital prior to consent being sought, then the most appropriate member of the site research team will liaise with the receiving hospital to establish at which point capacity has been regained and when discharge is probable. If possible, patients will be approached by researchers in person at the other site to provide informed consent for data use. Patients will not be contacted remotely (e.g. by letter).

3.4 Measurements

ONSD US measurements will be prospectively recorded two times daily for the first 5 days following severe TBI.

Measurements will be obtained using an Affiniti Ultrasound System (Philips, UK).

All patients will be in a supine position, with head elevated to 30°. A standardised insonation technique will be utilised. A linear transducer will be applied to each globe in turn following liberal application of ultrasound gel medium over a closed eyelid. The transducer will be manipulated to visualise the ONSD in a vertical orientation at or near the centre of the optic nerve head. The ONSD will be measured at a point 3 mm behind the insertion of the optic nerve into the globe in 3 planes; sagittal, coronal and 45°. 3 separate measurements will be made for each eye, 1 for each plane of visualisation. After rejecting images that do not reach sufficient quality the mean of ONSD measurements for the remaining images will be calculated.

Training in the technique will be provided by expert users.

Ultrasound images will be saved and reviewed offline, for quality, by an independent researcher. Co-efficients of correlation will be calculated relating to the values of invasive ICP and optic nerve sheath diameter at each time point.

3.5 Outcome measures

3.5.1 Primary Outcome

Correlation between ONSD and ICP at each time point over time.

3.6 Data collection

This trial will be coordinated from the ACET research team at KCH. Data will be collected by local investigators. Only data as set out on the CRF will be collected for this study.

All participant data collected will be entered onto a paper CRF before being transferred to an electronic spreadsheet. The site PI will oversee and be responsible for data collection, quality and recording.

Security of the electronic spreadsheet is through restricted access permissions. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act.

3.7 Data handling and management

The study complies with the principles of the Data Protection Act, 1998 and General Data Protection Regulations, 2018. At all times researchers will act to preserve the confidentiality of patient identifiable data.

Patients will be de-identified by allocation of a unique study number and collected data will be referred to this study number rather than to personal identifiable information. Personal data, including full name, contact details, date of birth and NHS number will be required to successfully follow up enrolled patients and will be linked to collected data on a separate electronic spreadsheet. Only members of the immediate research team will have access to personal identifiable data. Personal data will not be retained after follow up is complete and will be deleted at this time. The research team will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified.

All physical data, such as Clinical Report Forms and Consent Forms, will be securely stored in a locked research office.

All electronic data will be maintained on a secure electronic database accessible only by members of the research team.

4 Safety Monitoring

The risk of ocular ultrasound approaches zero as long as certain precautions are observed.

The eye is vulnerable to thermal hazards as the lens, aqueous and vitreous humours have no cooling blood supply. The British Medical Ultrasound Society (BMUS, 2009) has published a mechanical index (MI) which is an on-screen indicator of the relative potential for ultrasound to induce an adverse bio effect by a non-thermal mechanism including cavitation. The recommendation is to ensure the value remains between 0-0.3. This allows for unlimited scanning time but operators should adhere to the ALARA principles (as low as reasonably achievable) by setting the lowest acoustic power that can allow visualisation and measurement of the ONSD.

4.1 Definitions

Adverse Event

Any untoward medical occurrence affecting a trial participant during the course of a clinical trial.

For this observational study using a non-invasive technique AEs related to the study protocol are considered unlikely. The risk of thermal injury to the globe has been reduced to negligible levels by the precautions outlined above.

Any suspected ocular trauma or injury resulting from insonation of the globe will be recorded as an AE and referred to the CI for attribution of causality.

Serious Adverse Event

A Serious Adverse Event (SAE) is any adverse event that:

· Results in death
· Is a life-threatening situation

· Requires prolongation of hospitalisation
· Results in persistent or significant disability or incapacity

4.2 Recording and reporting AEs

AEs relating to suspected or actual globe injury will be recorded and reported to the CI who will assess causality. AEs attributed to the study will be reported to the REC and will trigger a suspension of the study pending further investigation.

In the context of the clinical setting patients with severe TBI will be expected to have some or all of the above SAEs occurring as part of their clinical condition. For the purposes of this study such SAEs will be recorded and assessed by the CI who will determine whether there is any relationship with involved in the OPTIC ICP study. In the event that there is a suspicion of linkage then the SAE will be reported to the REC and the Sponsor's representative.

5. Study closure

5.1 Data archiving

Data will be held in accordance with the requirements of the sponsor. Hard copy will be held securely in an archiving facility within King's College Hospital. Electronica data will be stored in password protected files on King's College Hospital or King's College London computer systems.

6. Statistics and data analysis

6.1 Statistical analysis plan

The relationship between invasive ICP and ONSD-US measurements will be examined using appropriate coefficients of correlation. Comparisons will be referred to the time point after injury. Receiver operator curves will be constructed in order to determine the optimum ONSD threshold for predicting an ICP of > 20 mmHg. In order to assess the validity of the test over time analysis will be performed with patients defined by time after insertion of ICP monitoring. The exact cut off for these groups will be determined after analysis of data from the first pilot study, but our initial intent is to group patients by day after study inclusion.

7. Ethical compliance and standards

Patients eligible for enrolment in this study will lack capacity to provide informed consent. The ethical procedures followed by this study will be based on the guidance provided in the Mental Capacity Act 2005 and adhere to the principals laid down within the Declaration of Helsinki. Advice regarding the suitablity of a potential patient for study enrollment will be sought from a nominated consultee, who will be the consultant responsible for the patient's medical management. At the earliest possible opportunity we will seek to obtain approval from the patient’s surrogate decision maker (e.g. close friend or relative) to allow continuing participation in the study. Once the patient regains capacity they will be approached to consent for use of data. We have used this approach in two previous research studies involving critically ill patients, which both received ethical approval.

8. Data protection

Identifiable patient data, including hospital number and condition, will be held by study team. The PI is responsible for ensuring preservation of participant confidentiality and will not disclose or reproduce any information by which participants could be identified. Data will be stored securely.

The study team will seek consent to share patients' anonymised data.

All data will be securely stored in a locked cabinet or in an encrypted electronic file.

9. Declaration of interests

All trial investigators have confirmed that they do not have any financial or other conflicts of interest to declare in relation to this trial.

10. Funding source

Funding provided by Ministry of Defence.

11. Dissemination of results

The results of the Optic ICP trial will be widely and actively disseminated through publication in peer reviewed medical journals and presentations at national and international meetings.