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Assessment of brain and eye blood flow after traumatic brain injury

Submission date
03/06/2025

Recruitment status
Recruiting

Registration date
26/08/2025

Overall study status
Ongoing

Last Edited
01/09/2025

Condition category
Injury, Occupational Diseases, Poisoning

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Traumatic brain injury (TBI) is a leading global cause of disability and death among military personnel. In the military, severe head impacts, explosions, and wounds to the head cause TBI. Brain injury occurs in two stages. The initial injury is called the primary injury, and secondary injury, which occurs in response to injury, leads to delayed brain damage. In secondary injury, brain damage may be worsened by reduced blood flow, low oxygen levels, increased pressure in the brain, and brain swelling. To prevent secondary injury occurring, early and accurate assessment of the brain's blood supply is crucial. However, current techniques to monitor brain blood supply are invasive, limited in effectiveness, or slow, especially in emergencies. A non-invasive and quicker intervention may allow early treatment and therefore improve patient recovery and survival.
This study explores whether eye imaging techniques can reflect brain damage and brain health after TBI. The eye and the brain share blood vessels. In healthy individuals, blood flow in the back of the eye, known as the retina, and the brain vary together. Optical coherence tomography angiography (OCTA) is an imaging technique widely used in eye clinics and images blood vessels in the retina. We, therefore, aim to determine if blood flow in the retina, measured by OCTA, can be used as a proxy measure for brain blood flow after TBI.
Retinal venous pulsations (RVPs) are blood flow movements in retinal veins. RVPs are affected by brain pressure. TBI commonly increases brain pressure, causing RVPs to be altered or absent. Assessing RVPs will allow us to determine whether we can use it to assess brain pressure.
A protein called aquaporin-4 (AQP4) controls water movement in the brain and eye. Increased AQP4 levels have been linked to brain swelling after TBI and may be connected to retinal swelling. We will assess the relationship between brain swelling and retinal swelling after TBI by comparing brain imaging and AQP4 levels with retinal thickness measurements.

Who can participate?
The study will include a control group of healthy individuals and an acute TBI group. Control participants must have no previous history of TBI, degenerative disease affecting the brain or eye, be willing and able to follow the protocol, have capacity to consent and have two eyes. Individuals in the TBI group will be admitted to the Queen Elizabeth Hospital, Birmingham, UK with moderate to severe TBI, with preplaced or planned placement of invasive neuromonitors. Participants of both groups must be over 18 years of age with at least one eye available for

retinal imaging. Individuals under 18 years of age and pregnant females are excluded from the study.

What does the study involve?
For the acute TBI group, eye and brain imaging, invasive brain monitoring, and the collection of blood and fluid from the brain and spine will occur at enrolment, 24, 48, 72 hours and 28 days later, or until the invasive monitors are removed. A disability rating measurement will occur at 28 days. For the control group, an initial assessment involving eye and brain imaging, blood collection, and a disability rating measurement will occur.

What are the possible benefits and risks of participating?
There is no increased risk in participating in this study as the techniques are non-invasive or occurring as part of routine care.

Where is the study run from?
Queen Elizabeth Hospital, Birmingham, UK

When is the study starting and how long is it expected to run for?
January 2024 to August 2029

Who is funding the study?
United States Department of Defence

Who is the main contact?
1. Lt Col. Prof. Richard Blanch, r.j.blanch@bham.ac.uk
2. Prof. Antonio Belli, a.belli@bham.ac.uk

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
339540

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
RG_24-008, CPMS 63262

Study information

Scientific Title
Real-time assessment of retinal perfusion and blood flow as a surrogate measure for cerebral perfusion in severe traumatic brain injury

Acronym
RETINA-TBI

Study objectives
1. Retinal perfusion, measured by optical coherence tomography angiography (OCTA), mirrors cerebral blood flow after traumatic brain injury (TBI).
1.1. Higher injury severity, assessed by extended IMPACT score, is associated with lower retinal perfusion.
1.2. Lower retinal perfusion acutely after injury and greater retinal neurodegeneration at follow up associates with worse early functional outcomes after TBI.
2. The magnitude of retinal venous pulsation is associated with intracranial pressure (ICP) after TBI.
3. Retinal oedema is associated with cerebral cellular oedema, mediated by aquaporin 4 upregulation.

Ethics approval required
Ethics approval required

Ethics approval(s)
submitted 28/05/2024, Wales Research Ethics Committee 2 Cardiff (Health and Care Research Wales, Cardiff, CF11 9AB, United Kingdom; +44 (0)2922941119; +44 (0)2922 940959; Wales.REC2@wales.nhs.uk), ref: 24/WA/0196

Study design
Single-centre observational study

Primary study design
Observational

Study type(s)
Diagnostic, Prevention

Health condition(s) or problem(s) studied
Acute severe traumatic brain injury

Interventions
Patients will have cerebral and retinal perfusion assessed after TBI. Invasive neuromonitoring will assess cerebral oxygenation and intracranial pressure and collect cerebral microdialysis. Ocular imaging techniques, optical coherence tomography and optical coherence tomography angiography, will assess retinal oedema and retinal perfusion, respectively. Non-invasive measures of cerebral perfusion will include transcranial Doppler ultrasound and Near Infra-red Spectroscopy. Biofluids such as blood, CSF, and microdialysate will be collected to assess AQP4 expression. The disability rating scale will assess early functional outcomes.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
N/A

Primary outcome(s)
The primary outcome is the correlation between retinal perfusion and invasive neuromonitoring data:
1. Retinal perfusion will be assessed by OCTA at the time invasive neuromonitors are inserted, 24, 48, 72 hours (if neuromonitoring remains in situ), and 28 days later.
2. Cerebral perfusion pressure will be calculated as the difference between mean arterial pressure and intracranial pressure at the time invasive neuromonitors are inserted, 24, 48, and 72 hours later, or until invasive monitors are removed.
3. Cerebral oxygenation will be measured by brain tissue oxygen tension at the time invasive neuromonitors are inserted, 24, 48, 72 hours later or until the monitors are removed.
4. Cerebral microdialysis lactate to pyruvate ratio will be measured at the time invasive neuromonitors are inserted, 24, 48, 72 hours later or until invasive neuromonitors are removed.

Key secondary outcome(s))
1. Middle cerebral artery Doppler will measure mean velocity, peak velocity, end diastolic velocity, and pulsatility index at the time of neuromonitors insertion, 24, 48, 72 hours, and 28 days later
2. Near infrared spectroscopy will assess cerebral cortical perfusion (total haemoglobin, oxyhaemoglobin, and deoxyhaemoglobin) at the time invasive neuromonitors are inserted, 24, 48, 72 hours, and 28 days later
3. 28-day mortality
4. 28-day neurological outcome assessed by the disability rating scale
5. The amplitude of retinal venous pulsation will be measured on video fundoscopy at the time invasive neuromonitors are inserted, 24, 48, 72 hours, and 28 days later
6. Microdialysate, CSF, and blood AQP4 expression will be assessed at the time invasive neuromonitors are inserted, 24, 48, 72 hours, or until the removal of invasive neuromonitors; primarily by ELISA
7. Total retinal, ganglion cell layer, and retinal nerve fibre layer thickness in the macula and peripapillary retina will be assessed with OCT at the time of neuromonitor insertion, 24, 48, 72 hours, and 28 days later

8. Intracranial pressure will be assessed by an invasive ICP monitor at the time of neuromonitor insertion, 24, 48, 72 hours later or until invasive neuromonitoring removal

Completion date
08/08/2029

Eligibility

Key inclusion criteria
Patients with acute TBI:
1. Moderate to severe TBI
2. Over 18 years of age
3. Planned invasive neuromonitoring or insertion of invasive neuromonitoring consistent with the study protocol within the prior 24 hours
4. At least one eye with optically clear media to allow retinal imaging

Healthy control participants:
1. Over 18 years of age
2. Two eyes
3. Capacity to consent
4. Willing and able to follow the protocol
5. No prior history of moderate to severe TBI
6. No prior history of retinal or optic nerve degenerative disease
7. At least one eye with optically clear media to allow retinal imaging

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Under 18 years of age
2. Pregnancy

Date of first enrolment
01/06/2025

Date of final enrolment
08/07/2029

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
U.S. Department of Defense

Alternative Name(s)
United States Department of Defense, Department of Defense, U.S. Dept of Defense, US Department of Defense, US Dept of Defense, DOD, USDOD

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The final deidentified dataset will be made available on reasonable request subject to data transfer agreement. Please contact Lt Col Prof Richard Blanch (r.j.blanch@bham.ac.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes