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Finding the best time to give blood thinning drugs to prevent clots from forming in the legs or lungs, in patients with traumatic brain injury

Submission date
21/11/2024

Recruitment status
Recruiting

Registration date
11/12/2024

Overall study status
Ongoing

Last Edited
18/06/2025

Condition category
Injury, Occupational Diseases, Poisoning

[X] 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
Patients who have suffered a traumatic brain injury (TBI) due to falls, assaults, road traffic accidents etc are at risk of VTE and this will complicate their recovery from TBI, could lead to long-term reduction in quality of life and occasionally can be fatal. Doctors typically give TBI patients blood thinning medication to reduce the chances of developing VTE but some doctors worry that these drugs could increase the risk of further bleeding in the brain if given too soon following the injury. Several studies have shown that giving blood thinning medication within 72 hours of injury does not increase the risk of further bleeding compared to giving the medication later than 120 hours or not giving it at all if deemed clinically unnecessary. This study will recruit patients with TBI and compare the timing of giving blood thinning medication (within 72 hours vs more than 120 hours following TBI or not at all) and guide the best practice in the future for initiating the drugs to reduce the risk of VTE without introducing complications from further bleeding.

Who can participate?
Patients ≥16 years of age with acute TBI

What does the study involve?
For this trial patients, following informed consent and eligibility screening, will be randomly allocated (by a computer) into one of two groups. The "early" group will start blood thinning medication within 72 hours of injury while the "late" group will have their medication deferred by at least 120 hours from injury or not given at all. Patients will be given the medications while they are in hospital. The study aims to ascertain the optimal timing of VTE prophylaxis in TBI patients by comparing the two groups in terms of development of VTE within 30 and 90 days from trial enrolment, mortality at 7 and 30 days and 12 months and quality of life following discharge from hospital. Patients will be asked about their quality of life at 30 days and then at 6 and 12 months via postal questionnaire, email or phone call.

What are the possible benefits and risks of participating?
There is no guarantee that the patient will benefit from taking part in this trial. The timing of

initiating the blood thinning medication following TBI may prevent the patient from developing a clot without introducing complications from further bleeding. As a consequence of participation in the trial, patients may be seen more often and/or feel more supported. Information gained from this trial may help improve treatment for adults with TBI in the future.

The study drugs (blood thinning medication) given to patients within this trial are standard-of-care drugs that are routinely given to TBI patients so there is no additional risk. As with any medication, blood thinning drugs can give rise to some side effects but patients will be closely monitored and if they suffer any serious unforeseen reactions the drug will be stopped immediately. The risk of bleeding will be assessed before patients are randomised to either the early or late arm of the trial.

An additional burden to participants is that they will be asked to complete some questionnaires at 30 days, 6 and 12 months, this may coincide with a routine clinical appointment if possible, otherwise, the questionnaires will be sent to participants to complete via post or email and can also be completed via telephone by the central research team.

Where is the study run from?
Cambridge Clinical Trial Unit (CCTU), UK

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

Who is funding the study?
NIHR Health Technology Assessment Programme (HTA)

Who is the main contact?
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Contact information

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1009812

Protocol serial number
TOP-TPI

Study information

Scientific Title
Timing Of venous thromboembolism Prophylaxis for adult patients with Traumatic Brain Injury (TOP-TBl): a pragmatic, randomised trial

Acronym
TOP-TBI

Study objectives
Recruit 1512 patients in a randomised trial (150 in the internal pilot, 1362 in the substantive study) to estimate the absolute difference in the proportion of patients developing VTE between the two arms (early vs late PTP administration).

1.Compare the consequences of early versus late PTP administration on functional neurological outcome (assessed using the Glasgow Outcome Score Extended) and quality of life using the EQ-5D-5L
2.Compare all-cause mortality between the two arms
3.Compare intracranial haemorrhage progression and all serious adverse events between the two arms
4.Undertake a detailed economic evaluation.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 03/12/2024, North East – Newcastle & North Tyneside 1 Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8077; newcastlenorthtyneside1.rec@hra.nhs.uk), ref: 24/NE/0202

Study design

Randomized controlled open-label parallel-group study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Medical condition: Traumatic Brain Injury (TBI)
Medical condition in lay language: Severe brain injury following an accident
Therapeutic areas: Diseases [C] - Injuries, poisonings, and occupational diseases [C21]

Interventions
Early pharmacologic thromboprophylaxis (PTP) arm - defined as administration of PTP within 72 hours of TBI
Late PTP arm - defined as administration of PTP after a minimum of 120 hours from TBI or PTP not administered at clinical discretion.

· IMP
o Low molecular weight heparin (LMWH),
o Low molecular weight sulphated glycosaminoglycuronans
o DOAC (Direct Oral Anticoagulants)
o Synthetic pentasaccharide
o Heparin

The dose, dose frequency, and route of administration to be used are at the discretion of the doctor managing patient care using NICE guidelines. Sealed Envelopes will be used for the randomisation.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Fondaparinux sodium [fondaprinux sodium], dabigatran etexilate (as mesilate) [dabigatran etexilate], danaparoid sodium [danaparoid sodium], heparin sodium [heparin sodium], enoxaparin sodium [enoxaparin sodium], dalteparin sodium [dalteparin sodium], tinzaparin sodium [dalteparin sodium]

Primary outcome(s)
Symptomatic DVT or PE will be investigated as per standard clinical practice either by compression Doppler ultrasound of the femoral and popliteal veins or CTPA, as appropriate, within 30 days from randomisation

Key secondary outcome(s))
1. Any asymptomatic proximal DVT as part of symptomatic screening ultrasound diagnosed from the day of randomisation up until day 29 post-randomisation
2. Progression of intracranial haemorrhage requiring neurosurgical intervention measured using

CT brain scans within 14 days after randomisation
3. Progression of intracranial haemorrhage on routinely performed imaging. All CT brain scans will be used for measurement from admission to discharge.
4. Adverse events, of special interest (AESI) including major and clinically relevant bleeding events (assessed and reported in accordance with criteria published by the International Society of Thrombosis and Haemostasis) will be measured throughout the trial
5. VTE will be investigated as per standard clinical practice either by compression Doppler ultrasound of the femoral and popliteal veins or CTPA, as appropriate, at 90 days
6. Mortality measured using data collected in medical notes on day 7, day 30 and month 12
7. Patient functional outcome measured using the Glasgow Outcome Scale-Extended (GOSE) questionnaire and using data collected during telephone interviews at 6 and 12 months
8. Quality of life measured using the EQ-5D-5L questionnaire at day 30 or discharge, 6 and 12 months
9. Length of stay of index admission measured using data collected in medical notes at one time point
10. Economic analysis measured using data collected in medical notes at several time points

Completion date
31/03/2029

Eligibility

Key inclusion criteria
1. Adult patients (≥16 years of age)
2. Acute TBI (defined as acute traumatic changes on CT brain, either in isolation or in the context of polytrauma)
3. Patients admitted to hospital within 72 hours of injury

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 years

Sex
All

Key exclusion criteria
1. Patients with recent Venous Thromboembolism (VTE) - within 3 months before TBI
2. Known hypersensitivity to any VTE prophylaxis agents to be used in this trial
3. Patients not expected to live beyond 72 hours
4. Time interval from injury to randomisation exceeding 72 hours
5. Participation in the same study within last 12 months
6. Current use of anticoagulation for an alternative indication, with a clinical decision to continue

7. Acute bleeding deemed serious enough that the treating clinical team lack equipoise for the study question
8. Progression of early traumatic intracranial haemorrhage or unstable neurological condition, such that the treating clinical team lack equipoise for the study questions

Date of first enrolment
02/06/2025

Date of final enrolment
15/01/2028

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Cambridge Clinical Trial Unit (CCTU)
Hills Road
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CB2 0QQ

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Organisation
University of Cambridge

ROR
https://ror.org/013meh722

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.1	27/11/2024	24/01/2025	No	Yes