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ACIT-2: An observational study investigating the systemic inflammatory, coagulation and genomic response in humans to severe injury and bleeding after major trauma

Submission date
15/03/2021

Recruitment status
Recruiting

Registration date
31/03/2021

Overall study status
Ongoing

Last Edited
04/04/2025

Condition category
Injury, Occupational Diseases, Poisoning

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Within minutes of injury, up to 25% of badly injured patients display a change in their ability to make a blood clot. This change is called Acute Traumatic Coagulopathy (ATC). Patients who develop ATC also show changes in their immune system, which alter the body's ability to fight off infections and heal itself. We now know that patients who develop ATC bleed more meaning they need more blood transfusions. Patients who develop ATC are also less likely to have a good recovery from their injury by developing multiple organ dysfunction and are more likely to die. It is hoped that the data and blood samples collected from patients in ACIT II will help us to understand the changes that happen in the body after injury that lead to the development of ATC and changes in the immune system.

Who can participate?
Trauma patients brought to the hospital in London's air ambulance or those patients who require treatment by the trauma doctors on arrival in the emergency department.

What does the study involve?
All participants should be recruited within 2 hours of their injury. Data will be collected up to 28 days following injury. Blood samples will be collected during the first 72 hours and again at 7 days after injury to allow for blood clotting and immune cell measurements to be investigated.

What are the possible benefits and risks of participating?
Benefits – None
Risks – Blood sampling is limited to some potential bruising at the site of venepuncture and some discomfort.

Where is the study run from?
1. The Royal London Hospital (UK)
2. John Radcliffe Hospital (UK)
3. Salford Royal (UK)

When is the study starting and how long is it expected to run for?
November 2007 to January 2037

Who is funding the study?
National Institute for Health Research (NIHR) (UK).

Who is the main contact?
Dr Charlotte Lindsay, c.lindsay@qmul.ac.uk

Study website
https://www.c4ts.qmul.ac.uk/research-programmes/acit

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
071328

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 071328, CPMS 05637

Study information

Scientific Title
A prospective, observational study investigating the molecular and cellular responses to traumatic injury (and resuscitation) in severely injured and bleeding adults and children and how these influence patient outcomes such as mortality, organ dysfunction, blood transfusion requirements and quality of life: Activation of Coagulation and Inflammation in Trauma II

Acronym
ACIT II

Study objectives
AIM 1: Coagulopathy and Massive Transfusion
Characterize the key derangements and describe trauma specific phenotypes in coagulation, fibrinolytic, platelet and endothelial cell function following major injury; determine the response to blood component therapy and anti-fibrinolytic medication; and further characterize the subsequent hypercoagulable state.

Hypothesis ACIT: 1A
Acute traumatic coagulopathy is caused primarily by tissue hypoperfusion which leads to systemic activation of anticoagulant and fibrinolytic pathways as well as global platelet dysfunction. Pathways of activation and dysfunction vary according to patient specific (e.g. age) and injury specific (e.g. site of injury, presence/duration of hypoperfusion) factors.

Hypothesis ACIT:1B
Subsequent transfusion of red cells, blood component therapy and antifibrinolytic drugs (e.g. tranexamic acid) have specific effects on the acute coagulopathy, which may be beneficial or harmful dependent on the current clinical state.

Hypothesis ACIT: 1C
Early coagulopathy leads to exhaustion of the anticoagulant system, up-regulation of

antifibrinolytic systems and altered platelet function, resulting in a hypercoagulable state which is associated with thrombotic events and organ dysfunction.

Hypothesis ACIT 1D:
Children develop an acute traumatic coagulopathy that is distinct from that observed in adults. The coagulopathy can be identified and characterized with viscoelastic testing and coagulation biomarkers and platelet function assays.

Hypothesis ACIT 1E:
Acute traumatic coagulopathy occurs within minutes after injury and can be detected in the prehospital phase of care. Diagnostics for hyperacute identification can stratify patients for targeted treatment of precise derangements in coagulation.

AIM 2: Development of Organ Injury
To elucidate the effect of derangements in coagulation, fibrinolytic, platelet and endothelial cell function on the inflammatory response and the development of acute organ injury (e.g. lung, kidney, cardiac), multiple organ dysfunctions (MODS), and death.

Hypothesis ACIT: 2A
There is a dose-dependent effect of the severity of trauma on coagulation, fibrinolytic, platelet and endothelial cell function. These correlate with activation of a pathological systemic inflammatory response that leads to acute organ injury (e.g. lung, kidney, cardiac) and MODS.

Hypothesis ACIT: 2B
There is a dose-dependent effect of the degree and duration of tissue hypoperfusion on coagulation, fibrinolytic, platelet and endothelial cell function. These correlate with activation of a pathological systemic inflammatory response that leads to acute organ injury (e.g. lung, kidney, cardiac) and MODS.

Hypothesis ACIT: 2C
While tissue trauma (ACIT:2A) and cellular hypoperfusion (ACIT:2B) are different initiators, the resulting activation of the coagulation and inflammatory systems is identical and is the final common pathway in acute organ injury and MODS. Tissue trauma and cellular hypoperfusion have an additive effect on the development of organ injury and MODS. The acute lung injury caused by tissue trauma and tissue hypoperfusion can be temporally separated.

Hypothesis ACIT:2D
Children with major trauma exhibit a specific immunological signature in response to tissue damage and blood loss that differs from adults. Particular responses are either associated with or protective for developing organ injury and MODS.

Hypothesis ACIT 2E:
Cellular pathways and biochemical signalling that produce organ injury and MODS occurs within minutes after injury and can be detected in the prehospital phase of care. Diagnostics for hyperacute identification can stratify patients for organ protective or organ restorative therapies.

Added 04/04/2025: Hypothesis ACIT 1F:
Patients with traumatic brain injury develop a coagulopathy that is distinct from that observed in bleeding trauma patients. The coagulopathy can be identified and characterised with viscoelastic testing, coagulation biomarkers and platelet function assays.

AIM 3: Prediction models in major trauma
To develop a prediction model for massive transfusion requirements and the development of organ injury in following trauma in adult and paediatric patients.

Hypothesis ACIT:3A
Massive transfusion requirements can be predicted by initial physiological variables and immediate analysis of coagulation parameters. Conversely, the requirement for blood component therapy might be reduced by targeted measurement of coagulation function and biomarkers during transfusion.

Hypothesis ACIT:3B
Acute organ injury (e.g. lung, kidney, cardiac) can be predicted in the first hours after trauma based on trauma severity scores, tissue damage, severity and duration of tissue ischemia, with biochemical markers of coagulation or inflammation. Identify specific markers which may be clinically relevant.

AIM 4: Genomic, proteomic and lipidomic analysis
To process and store samples for subsequent proteomic, transcriptomic, lipidomic and genomic techniques to identify new loci for investigation, targeting drug discovery and identification of genetic susceptibility to poor outcome following trauma.

Hypothesis ACIT:4A
There are signature transcriptomic, proteomic and lipidomic profiles associated with the risk of post-traumatic MODS and other adverse outcomes. Specific changes in circulating leukocytes and parenchymal cells occur in organs remote from the injured site and are associated with MODS.

Hypothesis ACIT: 4B
Children develop a specific transcriptomic and proteomic response to tissue trauma and hypoperfusion that is protective against post-traumatic organ injury and MODS.

AIM 5: Trauma DNA Bank
To process and store samples for subsequent DNA typing and analysis. There appears to be a background race and genetic susceptibility to the effects of trauma. These alterations may well lie within the coagulation and inflammatory systems. Early identification of patients at risk may, in the future, allow therapy to be targeted depending on patients' racial background or even specific genetic make-up.

Hypothesis ACIT:5A
There are genetic mutations of coagulation and inflammatory genes (e.g. Factor V Leiden, Prothrombin 20210, Mannose Binding Lectin) that may protect against or increase susceptibility to the effects of tissue trauma and hypoperfusion.

Hypothesis ACIT:5B
There are Haplotype-specific (and thus race-related) variations in susceptibility and response to tissue trauma and hypoperfusion.

Ethics approval required
Ethics approval required

Ethics approval(s)

Approved 13/11/2007, London – City & East Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 (0)207 104 8284; cityandeast.rec@hra.nhs.uk), ref: 07/Q0603/29

Study design
Prospective observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
https://www.c4ts.qmul.ac.uk/downloads/pdf-downloads/participant-information-sheet-a---participant-v6.0---clean.pdf

Health condition(s) or problem(s) studied
Molecular and cellular responses to traumatic injury in severely injured adults and children

Interventions
Participants are enrolled at pre-hospital (Adults) or in the Emergency Department (Adults and Children). Patient data will be collected for the first 28 days and blood samples will be taken for first 72 hours and then at Day 7.

Intervention Type
Other

Primary outcome measure
Measured using patient records throughout the study:
1. Blood products transfused in the first 24 hours
2. Incidence & severity of acute organ injury & MODS

Secondary outcome measures
Measured using patient records throughout the study:
1. 28-day mortality
2. Ventilator-free days
3. Length of hospital and critical care stay
4. Thrombotic events
5. Requirement for organ support (artificial ventilation, renal replacement therapy, inotropic support)
6. Infection – organ-specific and each episode detailed

7. Transfer destination at discharge e.g. home, other medical facility, rehabilitation unit
8. Quality of life at 28 days and 1 year measured using EQ5D questionnaire and extended Glasgow Outcome Scale (adults); added 04/04/2025: and PedsQL (children)

Overall study start date
13/11/2007

Completion date
07/01/2037

Eligibility

Key inclusion criteria
All trauma patients regardless of age can be screened for inclusion in hospital (adults only in prehospital care)

Participant type(s)
Patient

Age group
All

Sex
Both

Target number of participants
5,000

Key exclusion criteria
1. Transfers from other hospitals
2. Burns >5% total body surface area
3. More than 120 min have lapsed since time of injury
4. Deemed inappropriate for recruitment by an independent clinician

Date of first enrolment
23/01/2008

Date of final enrolment
01/01/2037

Locations

Countries of recruitment
England

United Kingdom

Study participating centre

The Royal London Hospital
Barts Health NHS Trust
Whitechapel Road
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Study participating centre
John Radcliffe Hospital
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Sponsor type
University/education

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ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF) RP-PG-0407-10036 (2008 – 2013)

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
01/06/2037

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Abstract results		01/12/2015	31/03/2021	No	No
Interim results article		14/01/2020	31/03/2021	Yes	No
Interim results article		01/03/2014	31/03/2021	Yes	No
Interim results article		01/05/2013	31/03/2021	Yes	No
Interim results article		01/06/2019	31/03/2021	Yes	No
Interim results article		01/01/2013	31/03/2021	Yes	No
Interim results article		01/01/2017	31/03/2021	Yes	No
Interim results article		01/02/2015	31/03/2021	Yes	No
Interim results article		23/11/2012	31/03/2021	Yes	No
Interim results article		01/06/2021	31/03/2021	Yes	No
Interim results article			31/03/2021	Yes	No
Results article	Secondary analysis	01/11/2021	02/11/2021	Yes	No
Protocol file	version 8.0	16/07/2024	04/04/2025	No	No