Pre-hospital **A**nti-fibrinolytics for **T**raumatic **C**oagulopathy and **H**aemorrhage (The PATCH Study)

A multi-centre randomised, double-blind, placebo-controlled trial of pre-hospital treatment with tranexamic acid for severely injured patients at risk of acute traumatic coagulopathy.

Statistical analysis plan

Version 1.0

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ABBREVIATIONS

AE	Adverse event
ATC	Acute traumatic coagulopathy
CDC	Centers for Disease Control and Prevention
CONSORT	CONsolidated Standards of Reporting Trials
DSMC	Data Safety and Monitoring Committee
DVT	Deep vein thrombosis
GOSE	Glasgow Outcome Scale Extended
IEAC	Independent Endpoints Adjudication Committee
ITT	Intention-To-Treat
NHMRC	National Health and Medical Research Council
PI	Principal Investigator
SAE	Serious Adverse Event
SD	Standard deviation
SSI	Surgical site infection
TXA	Tranexamic acid
WHODAS	World Health Organisation Disability Assessment Schedule 2.0, 12 item

Study synopsis

Study design

Prospective, multi-centre, randomised, double-blind, placebo-controlled trial.

Study hypothesis

TXA given early to injured patients who are at risk of acute traumatic coagulopathy (ATC) and who are treated in advanced trauma systems reduces mortality and improves recovery at 6-months after injury.

Primary Objective:

To determine the effect of early administration of tranexamic acid (TXA), compared to placebo, on mortality and favourable outcomes (moderate disability or good recovery) at six months in severely injured adults at risk of ATC who are treated in advanced trauma systems.

Secondary Objectives:

(1) To determine the effect of early administration of TXA, compared to placebo, on coagulation and fibrinolysis, and on clinical outcomes that are mediated through other putative inflammatory, immune, and neurological effects of plasmin.
(2) To determine whether early administration of TXA, compared to placebo, is associated with excessive vascular occlusive events, especially among potentially higher risk patients (e.g., aged >50 years old).

Inclusion criteria

- Adult patients (aged ≥18 years).
- Injury through any mechanism.
- Coagulopathy of Severe Trauma score ≥3.
- First dose of study drug can be administered within 3 hours of injury.
- Patients to be transported to a participating trauma centre.

Exclusion criteria

- Suspected pregnancy.
- Nursing home residents.
- Age <18 years.

Further details of the trial design are available in the published PATCH protocol paper. (1)

Outcome Definitions

Primary outcome

Dichotomised Glasgow Outcome Scale Extended (GOSE) at 6 months: A favourable outcome is defined as GOSE scores 5-8 (moderate disability or good recovery) as opposed to GOSE scores 1-4 (died=1, severe disability 2-4).

Secondary outcomes

1. Units of blood products used (packed red blood cells, fresh frozen plasma, platelets, prothrombin complex concentrate, recombinant factor VIIa, cryoprecipitate) in the first 24 hours
2. Blood lactate concentration at patient arrival to hospital
3. Coagulation profile (international normalised ratio, activated partial thromboplastin time, fibrinogen, platelet count) at:
    a. hospital arrival;
    b. end of treatment with study drug (i.e., immediately after administering the second dose of the study drug by 8-hour infusion);
    c. 24 hours after the first dose of study drug.
4. Vascular occlusive events (deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke) up until 28 days or hospital discharge (whichever occurs first).
5. Ventilator-free days in first 28 days.
6. Mortality at:
    a. 24 hours;
    b. 28 days;
    c. 6 months.
7. Proportion of deaths due to:
    a. bleeding;
    b. vascular occlusion (pulmonary embolus, stroke or acute myocardial infarction);
    c. multiorgan failure;
    d. brain/neurological injury.
8. Cumulative incidence of sepsis up until 28 days or hospital discharge (whichever occurs first).
9. Quality of life (World Health Organisation Disability Assessment Schedule (WHODAS) 2.0 and EuroQol 5-Dimension (EQ-5D)) at 6 months.

Randomisation

Trial packs are prepared by an independent pharmaceutical packaging company with either TXA or placebo. Packs are consecutively numbered, opaque, foil parcels with a tamper proof seal. Upon confirmation of eligibility, patients are randomised (1:1) to TXA or placebo, with the randomisation stratified by state and country participating in the study, and additionally by the presence of severe traumatic brain injury (TBI) defined by a Glasgow Coma Scale (GCS) <9 assessed at the time of randomisation.

Interim Analyses

Two planned interim safety analyses for potential harm have been performed by the independent data and safety monitoring committee (DSMC) at 25% and 50% patient enrolment. Both analyses examined in-hospital and 28-day mortality using the Haybittle-Peto conventional 3-SD threshold of a standardised statistic (ie, $|Z|>3$), corresponding to two-tailed p-value of 0.003. Based on the observed effects of the study drug and adherence to the study protocol in these analyses, the members of the DSMC were unanimous in recommending to the management committee continuation of the study to full enrolment.

Sample size

Targeting 90% power to detect an increase in a favourable GOSE outcome (scored 5–8) from 60% to 69% with TXA, this trial would require 592 patients in each arm (1184 total) with a two-sided 5% significance level. In a protocol amendment (PATCH Protocol ANZIC-RC/ V.1.6 3 February 2020) accommodation for a 10% loss to follow-up, the required sample size was increased to 658 patients in each arm (1316 total).

STATISTICAL ANALYSES

General principles

The analysis and reporting of the results will follow the CONSORT guidelines. (2) Baseline characteristics will be tabulated by using appropriate summary statistics. Data for the primary outcome will be analysed using the intention-to-treat (ITT) and per protocol (PP) populations (see definitions and details below), with the ITT analysis regarded as the principal analysis. All secondary and tertiary outcomes will be analysed using the ITT population only. A nominal two-tailed 5% significance level will be employed. No adjustment to the 5% level is required for the two interim analyses due to their conservative boundaries having negligible impact on the overall Type I error rate. No correction for multiple testing will be performed.

Analysis Populations

A. Intention-To-Treat (ITT) population

The ITT population will consist of all randomised patients.

B. Per Protocol (PP) population

The PP population will consist of all randomised patients with the exception of those who did not receive both doses of study drug or received open label TXA or did not meet the inclusion/exclusion criteria: age <18 years, had a COAST score <3, received their study drug >3 hours after injury, were pregnant, were residents at an aged care facility or did not attend a participating study centre.

Primary outcome analysis – favourable 6-month GOSE score

ITT analysis

The binary primary outcome of favourable GOSE (scores 5-8) will be compared between treatment groups using a risk ratio together with a 95% confidence interval and p-value, estimated by a log-binomial regression model. If model convergence is not achieved, then Poisson regression with robust standard errors will be applied. Supplementary analyses will adjust for the randomisation stratification variables of country/state and GCS<9 as fixed effects in the regression model. These analyses will use the 6 month GOSE regardless of the actual duration at the time of measurement. The number of patients with 6 months GOSE assessed prior to 4 months or beyond 8 months will be tabulated, and sensitivity analyses excluding these patients will be performed.

If the proportion of patients missing the primary 6 month GOSE outcome exceeds 5%, a supplementary analysis using multiple imputation of the missing outcomes using chained equations will be employed using relevant baseline and postbaseline variables in the imputation models that are predictive of GOSE, or of GOSE being missing, and constructed separately for each treatment arm. Patients who withdrew consent for any data to be used will not be included in these imputations. This multiple imputation analysis will be regarded as supplementary.

Post hoc sensitivity analyses will make adjustment for any variables exhibiting substantial imbalance across treatment arms at baseline.

Per Protocol analysis

The Per Protocol analysis will use the same methods as the ITT analysis, confined to the patients meeting the per protocol population definition. Because the patients not meeting the PP population definition have been excluded, there may no longer be balance in patient characteristics between treatment groups. The baseline characteristics in the TXA and placebo arms will be tabulated and compared for the 'compliant' (PP) patients. Any variables exhibiting imbalance will be adjusted for as covariates in the risk-ratio regression models.

Secondary and tertiary endpoint analyses

The binary secondary outcomes of vascular occlusive events (#4), mortality at 24 hours, 28 days and 6 months (#6) and incidence of sepsis to 28 days (#8) will be analysed using the same log-binomial regression modelling approach as the primary outcome. Cumulative mortality to 6 months will also be displayed with Kaplan-Meier curves. Blood product usage (#1) will be dichotomised as any/none and also analysed with log-binomial regression. The quantity of blood product usage among patients receiving the product will be summarised with medians and interquartile ranges, and compared between treatment groups using quantile (median) regression, reporting the difference in medians between treatment arms together with 95% CIs and p values. Analyses of blood lactate concentration (#2) (regardless of assay method) and coagulation profile variables at each time point (#3) will similarly use quantile regression to compare medians between treatment groups. Blood lactate concentration (#2) obtained by venous and arterial samples will each also be dichotomised at >3mmol, and a composite measure of >3mmol for either sampling method will be calculated. INR (#3) will be dichotomised at >1.3 IU, and fibrinogen (#3) at <1 g/L and at <2 g/L. These dichotomised variables will be analysed as binary variables as above. Ventilator-free days in the first 28 days (#5) will assign a value of 0 to patients dying within 28 days regardless of location at time of death, and a value of 28 days if never ventilated in ICU or never admitted to ICU. This will be analysed using quantile regression to estimate the difference in median ventilation-free days. The 4 causes of death (#7a,b,c,d) in patients that died at any time up to 6 months will be tabulated and reported descriptively. The cumulative incidence of each cause of death to 6 months will be displayed graphically taking into account the other competing causes of death, and with cause-specific hazard ratios estimated using Cox regression with censoring at the time of all other causes of death. A composite cause of 'potentially preventable death' will be calculated as any of bleeding, vascular occlusion and multi-organ failure. Comparison of median quality of life outcomes at 6 months (#9) between treatment arms will be analysed using quantile regression, with patients not alive at 6 months treated as having missing values (and see below), and with EQ-5D calculated using Australian weights (3).

Additional analyses of each of the vascular occlusive events (#4) and sepsis (#8) at 28 days will be performed to take into account the competing risk of death. This will use cumulative incidence functions with estimated incidence at 28 days, with the incidence compared across treatment groups using risk ratios with 95% CIs derived using the delta method. For analysis of quality of life outcomes at 6 months, for patients not alive at that time a value of 0 will be imputed for the EuroQol 5-Dimension (EQ5D) summary and VAS scores (3). For the WHODAS scale, in the absence of published guidelines for addressing mortality, a score of 61 will be imputed, placing death as worse than the maximum scale score of 60. These modified quality of life outcomes will also be analysed using quantile regression. Supplementary analyses of these outcomes will use inverse probability of death weighting rather than imputation of values to accommodate truncation by death.

Subgroup analyses

Planned sub-group analyses will assess consistency across subgroups of differences between TXA and placebo arms with respect to the primary outcome in the intention to treat population only. These will be assessed using regression models with interaction term(s) between the particular subgroup and treatment arm. These analyses will provide a risk ratio

and confidence interval for the effect of randomised arm in each subgroup and the interaction p-value. The subgroup variables are:

- Age, dichotomised to >= 50 years
- Time from injury to first dose (<1 hour, 1-<2 hours, 2-<3 hours, >=3 hours)*
- First valid recorded systolic blood pressure categories (<=75, 76–89, >=90 mm Hg)
- Mechanism of trauma (penetrating, blunt, blast/burns*)
- Baseline GCS<9.

**If there are <10 patients in any single category then this category will be tabulated but not included in the regression modelling.*

PUBLICATION PLAN

The principal manuscript will analyse all endpoints apart from the quality of life secondary endpoints #9. These will be analysed in a separate manuscript.

CHANGELOG

Version 1.0. August 19 2022.

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