Tranexamic acid for hyperacute spontaneous IntraCerebral Haemorrhage (TICH-3)

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Short title: Tranexamic acid for IntraCerebral Haemorrhage

Acronym: TICH-3

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SYNOPSIS

Title	Tranexamic acid for Hyperacute Spontaneous Intracerebral Haemorrhage (TICH-3)
Acronym	TICH-3
Short title	Tranexamic acid for Hyperacute Spontaneous Intracerebral Haemorrhage
Chief Investigator	Professor Nikola Sprigg
Objectives	To assess the clinical effectiveness of TXA after ICH and determine whether TXA should be used in clinical practice. Primary objective: To assess the effect of TXA on early death (≤7days) Secondary objective: To assess the effect of TXA on dependency 6 months after ICH.
Trial Configuration	Pragmatic phase III prospective blinded randomised placebo-controlled trial.
Setting	Emergency departments, acute stroke services/units across the UK and worldwide.
Sample size estimate	2750 participants per group would allow detection of a difference of 2.57% in the proportion of deaths at day 7 between the placebo and TXA groups (7.74% deaths on TXA, OR of 0.73), at the 5% significance level (2-sided) with 90% power. As the primary outcome is death we anticipate there will be minimal loss to follow up.
Number of participants	At least 5500
Eligibility criteria	**Inclusion criteria:** Adults within 4.5 h of onset of acute spontaneous ICH (confirmed on brain imaging). When onset of symptoms is unknown patient must be within 4.5 hours of symptom discovery and have no other exclusion criteria. **Exclusion Criteria**: i. Patient with a known indication for TXA treatment (e.g. traumatic brain injury). ii. Patient with contraindication for TXA treatment iii. Patient known to be taking anticoagulation at time of enrolment

	iv. Massive ICH for which haemostatic treatment seems futile (This would ordinarily be when haematoma volume is estimated as larger than 60ml) v. Severe coma (Glasgow Coma Scale <5) vi. Decision already taken for palliative (end of life) care with withdrawal of active treatment
Description of interventions	Intravenous tranexamic acid 2g: 1g loading dose given as 100 mls infusion over 10 minutes, followed by 1g in 250 mls infused over 8 hours. Comparator – matching placebo (normal saline 0.9%) administered by an identical regimen.
Duration of study	7.25 years project; approximately 5.25 years participant recruitment in the UK, 4.75 years in international sites, Start date 1 April 2022 Duration of study per participant: 6 months.
Randomisation and blinding	Randomisation will be to TXA vs. placebo in a 1:1 ratio. Due to the emergency situation, a straightforward randomisation process will be used, where sites will simply select the next available treatment pack, which will be a numbered box containing either TXA or placebo according to a computer-defined sequence. Boxes will be identical with the exception of the treatment pack number. Randomisation will be stratified by site with supply to each site balanced for TXA and placebo, using random permuted blocks of varying size. The IMP manufacturer will prepare blinded individual treatment packs containing four 5ml glass ampoules of TXA 500mg or sodium chloride 0.9% which will be very similar in appearance.
Outcome measures	**Primary outcome:** mortality at 7 days, Secondary functional outcome: modified Rankin Scale at (mRS) 180 days. Other secondary outcomes: Death at 2 days. Safety outcomes**:** Recorded in the first 7 days (or death if sooner): venous thromboembolism; ischaemic events (arterial thrombosis at any site, ischaemic stroke, transient ischaemic attack peripheral artery embolism, myocardial infarction, acute coronary syndrome); seizures. Quality of Life (EuroQol(Devlin, Shah, Feng, Mulhern, & van Hout, 2018), EQ-5D-5L, VAS), and cognition (AD-8)(Galvin, Roe, Coats, & Morris, 2007) at day 180.
Resource and Cost Measures	Hospital resource and cost at discharge, to include: length of stay, days in ICU and treatments. Usual residence: Disposition at discharge and day 180. Patient level Health Resource Use Questionnaire at day 180.
Statistical methods	The analysis and presentation of the trial results will be in accordance with the CONSORT guidelines. The primary outcome will be compared analysing as randomised without imputation of missing data. Due emphasis will be placed on the confidence intervals for the between arm comparisons. A full Statistical Analysis Plan (SAP) will be developed prior to database lock. The evaluation of the primary outcome will be performed using regression models for binary outcomes, with adjustment for key prognostic factors. The model will be fully specified in the SAP. Absolute and relative measures of effect and 95% confidence intervals will be presented. The primary outcome will also be investigated in pre-specified subgroups using appropriate interaction terms. The subgroups will be specified in the SAP and will, at a minimum include age, sex, systolic blood pressure, HV, GCS, the start of treatment (≤2 or >2 hours, ≤3 or >3 hours) and intraventricular haemorrhage (yes, no).

Health Economic Analysis	Cost effectiveness of TXA versus usual care. Incremental cost effectiveness ratios (ICERs), net monetary benefit and cost effectiveness of usual care versus TXA
Simplicity of Trial Procedures	To reflect the time critical emergency nature of ICH, and to facilitate rapid enrolment in emergency departments, even in hospitals affected by the pandemic, patient enrolment (simple randomisation) and all other trial procedures are greatly streamlined. Informed consent is simple and data entry is minimal. Randomisation via taking the next treatment pack is simple and quick. Follow-up information is recorded at a single timepoint and may be ascertained by contacting participants, by post, phone or electronically, or by review of medical records and databases.