

Intravenous tranexamic acid for hyperacute primary intracerebral hemorrhage: Protocol for a randomized, placebo-controlled trial

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Abstract

Rationale: Outcome after intracerebral hemorrhage remains poor. Tranexamic acid is easy to administer, readily available, inexpensive, and effective in other hemorrhagic conditions.

Aim: This randomized trial aims to test the hypothesis that intravenous tranexamic acid given within 8 h of spontaneous intracerebral hemorrhage reduces death or dependency.

Design: Phase III prospective double-blind randomized placebo-controlled trial. Participants within 8 h of spontaneous intracerebral hemorrhage are randomized to receive either intravenous tranexamic acid 1 g 10 min bolus followed by 1 g 8 h infusion, or placebo.

Sample size estimates: A trial of 2000 participants (300 from start-up phase and 1700 from main phase) will have 90% power to detect an ordinal shift of the modified Rankin Scale with odds ratio 0.79.

Study outcomes: The primary outcome is death or dependency measured by ordinal shift analysis of the 7 level mRS at day 90. Secondary outcomes are neurological impairment at day 7 and disability, quality of life, cognition, and mood at day 90. Safety outcomes are death, serious adverse events, thromboembolic events, and seizures. Cost outcomes are length of stay in hospital, readmission, and institutionalization.

Discussion: This pragmatic trial is assessing efficacy of tranexamic acid after spontaneous intracerebral hemorrhage. Recruitment started in 2013; as of 15th January 2016 1355 participants have been enrolled, from 95 centers in seven countries. Recruitment is due to end in 2017. TICH-2 Trial is registered as ISRCTN93732214.

Keywords Hyperacute intracerebral hemorrhage, tranexamic acid, randomized trial, placebo controlled

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Introduction and rationale Intracerebral hemorrhage (ICH) is a devastating form of stroke, with high early mortality; of those who survive, the majority remain disabled. Despite advances in management of ischemic stroke, outcome following ICH has remained static for decades.¹ Around a quarter of ICH are complicated by hematoma expansion (HE); this most often occurs within the first few hours, but can occur up to 24 h from spontaneous ICH (sICH) onset and is associated with poor outcome.^{2–4} Recent evidence has shown that intensive early blood pressure lowering can improve functional outcome, and this has been incorporated into clinical guidelines.⁵

Hemostatic drug therapies aimed at limiting HE have been tested in SICH, with recombinant factor VIIa being the most widely studied. Meta-analysis of these and other hemostatic therapies found no significant benefit on outcome.⁶

Tranexamic acid, an antifibrinolytic drug, significantly reduced mortality, with no increase in vascular occlusive events, in patients with major bleeding following trauma.⁷ In a subgroup analysis of patients with traumatic ICH, tranexamic acid showed a nonsignificant trend to reduce mortality and death or dependency.⁸

A meta-analysis of the only two trials of tranexamic acid in traumatic intracranial hemorrhage showed a significant reduction in posttraumatic intracranial bleeding.⁹ However, the confidence interval is wide and a larger trial is ongoing.¹⁰

Tranexamic acid has also been tested in aneurysmal subarachnoid hemorrhage, where it reduced the risk of rebleeding at the expense of increased risk of cerebral ischemia.¹¹ However, prolonged administration of tranexamic acid for seven days, and the known risk of delayed cerebral ischemia without tranexamic acid after aneurysmal subarachnoid hemorrhage, may explain the greater risk of vascular occlusive events.

In two small nonrandomized studies, tranexamic acid was reported to restrict HE following ICH.^{12,13} In a subsequent small pilot randomized study, administration of tranexamic acid was feasible and well tolerated after ICH.¹⁴ There have been recent calls for large trials to evaluate tranexamic acid in ICH,¹⁵ and several phase II studies are ongoing.¹⁶

Methods

Aim

Tranexamic acid for hyperacute primary intracerebral hemorrhage (TICH-2) aims to test the hypothesis that intravenous tranexamic acid is superior to placebo by reducing death or dependency at day 90 when given within 8 h of SICH.

Design

TICH-2 is an international pragmatic double-blind randomized placebo-controlled parallel group, phase III trial. The pragmatic design ensures that the TICH-2 trial tests whether tranexamic acid is effective in clinical practice, balancing generalizability of results in real life with a sound scientific rationale in academic terms. We have designed the study to include participants who reflect the broad population with acute SICH and have kept exclusion criteria to a minimum.¹⁷ Participants are randomized (1:1) to receive either tranexamic acid or matching placebo (0.9% saline). Outcome is assessed face to face at the end of treatment (day 2) and day 7; central telephone follow-up determines outcomes at days 90 and 365. Brain imaging (CT) is performed as part of routine care prior to enrolment; a second research CT scan is performed after 24 h of treatment to assess HE (Figure 1).

Patient population

Inclusion criteria. Adults with acute SICH within 8 h of stroke symptom onset or time last seen well.

Exclusion criteria .

1. Patients with ICH secondary to anticoagulation, thrombolysis or known underlying structural abnormality such as arteriovenous malformation, aneurysm, tumor, or venous thrombosis. An underlying structural abnormality does not need to be excluded before enrolment, but where known, patients should not be recruited.
2. Contraindication to tranexamic acid.
3. Premorbid dependency (mRS > 4).
4. Concurrent participation in another drug or device trial. Participants enrolled in TICH-2 may be enrolled into the RESTART trial¹⁸ after 21 days.
5. Prestroke life expectancy

Informed consent

All participants who have capacity need to provide consent before they enter the trial. However, the need for urgent treatment means that it would be inappropriate to delay treatment when either impaired capacity (e.g. in cases of dysphasia or reduced conscious level) or lack of time prohibit obtaining written consent. If the potential participant lacks capacity to give informed consent permission will be sought from a relative, or if no relatives are available, a doctor unconnected with the trial, acting as an independent legal representative.

If the time window does not allow investigators to seek full informed written consent, and if the attending clinicians consider it appropriate, patients or relatives (if the participant lacks capacity) will be approached to give oral assent. If oral assent for recruitment is given, participants (or relatives if the participant lacks capacity) will be approached to give written consent as soon as possible after recruitment.

Randomization

All patients eligible for inclusion are randomized using a secure internet site in real time. Trial web application/ database programmers at University of Nottingham are responsible for the randomization processing and security of the internet site in conjunction with University of Nottingham IT Services. Randomization involves minimization on key prognostic factors: age, sex, time since onset, systolic blood pressure, stroke severity (National Institute Health Stroke Scale (NIHSS)), presence of intraventricular hemorrhage, known history antiplatelet treatment used immediately prior to stroke onset. Randomization is stratified by country but not by site (to protect allocation concealment in small sites). The randomization algorithm code calculates an imbalance score to decide to which group the new subject must be allocated, to have the minimum amount of imbalance, in terms of prognostic factors. In the case that the groups are evenly matched, a group is selected at random. At random, the opposite group will be selected approximately 5% of the time to reduce predictability and bias.¹⁹ Out of the treatment packs available at the participant's hospital, one is selected at random which matches the selected treatment group. Randomization generates a unique number corresponding to a treatment pack. The selected treatment pack is then allocated to

the participant's unique trial number. Balance between the treatment groups is monitored by programmers and statisticians during the recruitment phase.

Treatment

Blinded individual treatment packs contain four 5 ml glass ampoules of tranexamic acid 500 mg or sodium chloride 0.9%, which are identical in appearance. Trial treatment is administered as 10 ml (tranexamic acid 1 g or placebo) in 100 ml sodium chloride 0.9% infusion bag intravenously as a loading dose infusion over 10 min, followed by infusion of 10 ml (tranexamic acid 1 g or placebo) in 250 ml sodium chloride 0.9% infusion bag over 8 h.

Allocation concealment. Clinicians, patients, and outcome assessors (research nurse and radiologist) are blinded to treatment allocation for the duration of the study. Unblinding should be done only in those rare cases when the doctor believes that clinical management depends importantly upon knowledge of whether the patient received antifibrinolytic or placebo. In those few cases when urgent unblinding is considered necessary, the emergency telephone number should be contacted, giving the name of the doctor authorizing unblinding and the treatment pack number. Unblinding will be monitored and audited.

Primary outcome

Death or dependency using the seven-level modified Rankin Scale (mRS) at day 90.

Secondary outcomes

1. Neurological impairment (NIHSS20) at day 7 (or discharge if sooner).
2. Outcome: Disability (Barthel index²¹), dependency (mRS²²), Quality of Life (EuroQol, EQ-5D, and EQ-VAS²³), Cognition (Telephone Interview Cognition Score-Modified²⁴), and mood (Zung Depression Scale²⁵) at days 90 and 365.
3. Costs: Length of stay in hospital, readmission, institutionalization.
4. Radiological efficacy/safety (CT scan): Change in hematoma volume from baseline to 24 h scan, hematoma location, and new infarction. Details of hematoma volume calculation to be given in statistical analysis plan.
5. Safety endpoints recorded until day 90: Death (cause), venous thromboembolism, vascular occlusive events (stroke/transient ischemic attack/myocardial infarction/peripheral artery disease), seizures. Serious adverse events (SAEs) in first seven days.
6. MRI substudy: Prevalence of remote diffusionweighted imaging hyperintense lesions, perihematoma edema volume and diffusion restriction on day 5 MRI scan, and combined volume of the residual hematoma cavity and abnormal signal on the day 90 MRI scan.

Serious adverse events

SAEs are defined as any untoward medical occurrence or effect that at any dose results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Important

medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. SAEs and safety endpoints are reported in line with expedited reporting regulations and then adjudicated by an independent panel.

All SAEs occurring within the first seven days will be recorded and reported to the competent authority Medicine Healthcare Regulatory Authority (MHRA) and Regional Ethics Committee (REC) as part of the annual reports. Suspected Unexpected Serious Adverse Reactions will be reported within the statutory timeframes to the MHRA and REC.

Data monitoring

An independent Data and Safety Monitoring Committee (DSMC) receives safety reports every six months, or more frequently if requested, and assesses unblinded efficacy and safety data. The DSMC will perform a formal interim analysis after 800 participants have been recruited and followed up at 90 days. A DSMC Charter contains details of membership, terms and conditions, and guidelines for stopping the trial. The DSMC reports their assessment to the independent chair of the trial steering committee (TSC), (with a copy to the chief investigator (CI)) and a copy is then sent to the funder (National Institute for Health Research (NIHR), Health Technology Assessment (HTA)).

With respect to safety, the following outcomes will initiate discussion for recommending early stopping or continuation of the study:

- . The primary outcome (“shift” in mRS) favors the active group (benefit), $P < 0.001$ (two-sided);
- . The primary outcome (“shift” in mRS) favors the control group (hazard), $P < 0.02$ (two-sided);
- . Analysis of death favors the control group (hazard) with $P < 0.02$ (two-sided).

Sample size estimates

The null hypothesis (H_0) is that tranexamic acid does not alter death or dependency at day 90, in participants with acute SICH. The alternative hypothesis (H_A) is that death or dependency at day 90 differs between those participants randomized to tranexamic acid versus placebo. A total sample size of 2000 (1000 per group) participants with acute SICH are required, assuming overall significance (α) $\frac{1}{4}$ 0.05, power ($1 - \beta$) $\frac{1}{4}$ 0.90, ordinal odds ratio of 0.79, increases due to losses to follow-up of 5%, and a reduction of 20% for baseline covariate adjustment. 26

Statistical analyses

Detailed information regarding analyses will be in the statistical analysis plan, which will be finalized before database lock.

Primary outcome. Death or dependency (ordinal shift analysis of the seven-level mRS) at day 90 will be compared between tranexamic acid and placebo by intention to treat, without imputation, using ordinal logistic regression, with adjustment for minimization factors. The assumption of proportional odds will be tested using the likelihood ratio test.

Subgroup analyses. The comparison of tranexamic acid and placebo on the primary outcome will be performed in prespecified subgroups, including the minimization criteria, and: start of treatment (3, >3 h), CT angiography (yes, no), spot sign (yes, no), hematoma location (lobar, deep, infra-tentorial), geographical region (UK, other), and ethnicity (white, other). The interpretation of any subgroup effects will be based on interaction tests (i.e. evidence of differential treatment effects in the different subgroups). The scientific rationale for the subgroup analysis and predicted direction of effects will be covered in detail in the statistical analysis plan.

Secondary analyses. Binary logistic regression will be used for binary outcomes, including SAEs and thromboembolic events. Cox regression will be used for time-to-event analyses, including death. Analysis of covariance will be used for continuous measures, including HE. Wilcoxon rank sum test will be used for continuous measures which are not normally distributed, including Barthel Index. Regression analyses will be performed with adjustment for minimization factors.

Study organization and funding

The University of Nottingham is sponsor for the study with funding from National Institute of Health Research Health Technology Assessment (NIHR HTA project code 11_129_109). The study has been adopted in the UK by the NIHR Clinical Research Network (CRN) portfolio and participants will be recruited from acute stroke units at NIHR CRN sites in the UK and acute stroke units in participating centers worldwide. UK sites have dedicated Stroke CRN staff to facilitate recruitment and follow-up. Trial coordination will be performed by staff at the University of Nottingham. Outside the United Kingdom, international sites will have a National Coordinating Centre and the National Coordinators will form the International Advisory Committee. The study received approval from the MHRA on 23rd October 2012, REC on 23rd November 2012, and the respective National Health Service Research & Development (R&D) department on 15th February 2013. The study was prospectively registered with the ISRCTN on the 17th January 2013 (No. 93732214). Recruitment started in 2013; as of 15th January 2016, 1355 participants have been enrolled, from 95 centers in seven countries. Recruitment is due to end in 2017. Additional funding for conductance of the trial in Switzerland was provided by a grant from the Swiss heart foundation.

Discussion

ICH is a medical emergency for which treatment needs to be given urgently. HE is most likely to occur in the first few hours after ICH, but extends up to 24 h later³ and is associated with poor functional outcome. Tranexamic acid is inexpensive and easy to administer, and potentially safe, based on data from other studies. In CRASH-2, tranexamic acid was most effective when given rapidly; delayed administration was associated with lack of efficacy and potential harm.²⁷ TICH-2 will include patients as soon as possible after stroke onset, but allow a pragmatic time window of 8 h.

Contrast extravasation within the hematoma during contrast-enhanced CT, and CT angiography (the “spot sign”) predict HE,^{28–30} although there is currently wide variation in the use of these techniques in routine clinical practice. Nevertheless, other clinical trials assessing tranexamic acid in ICH are selecting participants on the basis of contrast extravasation, recruiting “spot positive” patients.¹⁶ However, as the spot sign has limited specificity for HE, and CTA is not used routinely in many patients with ICH, we chose not to limit selection to those with spot sign positive ICH.

The dosing regime used in TICH-2 produces plasma concentrations sufficient to inhibit fibrinolysis; higher doses do not provide any additional hemostatic benefit.³¹ In the emergency situation administration of a fixed dose is more practicable and the fixed dose chosen is efficacious for large patients and safe for small patients.

Summary and conclusion

SICH is a devastating form of stroke, in which HE plays a key role in high morbidity and poor outcome. TICH-2 is a large pragmatic randomized controlled trial assessing the efficacy of tranexamic acid, an anti-fibrinolytic drug, on death and dependency in SICH. If effective, tranexamic acid is inexpensive, easy to administer, and widely available—and could be combined with other treatments such as antihypertensives, which are now recommended in clinical guidelines,⁵ in an attempt to target multiple pathophysiological targets to improve outcome from SICH.

Authors' contribution

NS, KR, and PB drafted the manuscript. All authors reviewed and commented on the final manuscript.

Declaration of conflicting interests

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