Tranexamic acid to improve functional status in adults with spontaneous intracerebral haemorrhage: the TICH-2 RCT

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Scientific summary

The TICH-2 RCT

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Scientific summary

Background

Although intracerebral haemorrhage (ICH) accounts for only 10–15% of all strokes, it is the most devastating type of stroke, with a 30-day fatality rate of 40–50%. One year after ICH, 70–80% of survivors remain dependent.

Haematoma expansion occurs in up to 38% of patients with ICH, mostly within the first few hours. Haematoma expansion leads to higher mortality and worse functional outcome. The most widely researched haemostatic agent in ICH, recombinant factor VIIa (rFVIIa), does not significantly reduce death or dependency. Although a reduction in haematoma expansion has been reported, the benefit of this is probably offset by an increase in thromboembolic events.

Tranexamic acid is an antifibrinolytic agent that acts on the plasmin-mediated pathway to prevent the breakdown of a blood clot. It is an effective haemostatic agent in many bleeding conditions. In the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage – 2 [CRASH-2; CRASH Trial Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;**376**:23–32] trial, involving 20,211 patients with major bleeding due to trauma, treatment with tranexamic acid significantly reduced mortality [adjusted odds ratio (aOR) 0.91, 95% confidence interval (CI) 0.85 to 0.97], especially when given within 3 hours of trauma. A subgroup analysis of patients with traumatic intracranial haemorrhage in the trial showed a non-significant trend to reduced mortality (aOR 0.47, 95% CI 0.21 to 1.04), and death or dependency (aOR 0.66, 95% CI 0.32 to 1.36). The CRASH-3 study is an ongoing randomised controlled trial (RCT) that is assessing the effect of tranexamic acid on risk of death or disability in patients with traumatic brain injury.

Treatment with tranexamic acid reduced bleeding-related death in women with postpartum haemorrhage in the WOrld Maternal ANtifibrinolytic (WOMAN) trial [WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017;**389**:2105–16] [n = 20,060; risk ratio (RR) 0.81, 95% CI 0.65 to 1.00], with the greatest effect in women given treatment within 3 hours of childbirth (RR 0.69, 95% CI 0.52 to 0.91). Furthermore, an individual patient data meta-analysis of the CRASH-2 and WOMAN trials highlights the need to administer tranexamic acid immediately. Immediate treatment improved survival by > 70% and the survival benefit decreased by 10% for every 15 minutes of treatment delay until 3 hours, after which there was no benefit to the patient. There was no increase of thromboembolic events with the treatment of tranexamic acid in both trials, although the patients were younger and had fewer comorbidities than those with ICH.

The use of tranexamic acid in spontaneous ICH (SICH) has been studied in two small RCTs (Law ZK, Meretoja A, Engelter ST, *et al.* Treatment of intracerebral haemorrhage with tranexamic acid – a review of current evidence and ongoing trials. *Eur J Stroke* 2016;**2**:3–22; Al-Shahi Salman R, Law ZK, Bath PM, et al. Haemostatic therapies for acute spontaneous intracerebral haemorrhage. *Cochrane Database Syst Rev* 2018;**4**:CD005951). The Tranexamic acid in IntraCerebral Haemorrhage (TICH) trial was a feasibility trial that randomised 24 patients to receive intravenous tranexamic acid or placebo. Arumugam *et al.* (Arumugam A, Rahman NAA, Theophilus SC, Shariffudin A, Abdullah JM. Tranexamic acid as antifibrinolytic agent in non traumatic intracerebral hemorrhages. *Malays J Med Sci* 2015;**22**:62–71) was a single-centre, single-blind RCT that allocated 30 patients to treatment with intravenous tranexamic acid or placebo. Two recent systematic reviews concluded that there is no evidence for tranexamic acid treatment in SICH, although there are six ongoing RCTs, including the TICH-2 trial.

Objectives

The primary objective of the trial was to assess whether or not tranexamic acid is safe and improves the functional status (i.e. reduces death and dependency) of patients after SICH. The secondary objective was to assess the effect of tranexamic acid on secondary outcomes: clinical outcomes (disability, quality of life, mood, cognition), safety outcomes, costs and radiological efficacy.

Methods

The TICH-2 study was an international, double-blind, randomised, placebo-controlled Phase 3 trial. The trial included adult patients (aged ≥ 18 years) with SICH presenting within 8 hours of symptoms onset. Exclusion criteria were ICH secondary to anticoagulation, thrombolysis, trauma or a known underlying structural abnormality; patients for whom tranexamic acid was contraindicated; prestroke dependence (i.e. patients with a modified Rankin Scale [mRS] score of > 4); a life expectancy of < 3 months; and a Glasgow Coma Scale (GCS) score of < 5. Patients were recruited by investigators from acute stroke services in 124 hospitals in 12 countries. Ethics approval was obtained in each site and country prior to the commencement of the study. The study was designed to be performed in two phases, an 18-month start-up phase (with the aims to activate 30 centres and to recruit a minimum of 300 participants) and then a main phase (with 120 centres and to recruit to a total of 2000 participants), with no break in recruitment between the two phases, as the prespecified stopping criteria were not met.

Investigators obtained written informed consent from each participant if they had the capacity to provide it. If participants could not give consent, a relative or representative gave proxy consent. When consent was deferred or given by a proxy, we informed the participant about the trial as soon as possible and sought their consent for ongoing follow-up.

Participants were randomised centrally using a secure internet site in real time. Randomisation involved stratification by country and minimisation on key prognostic factors: age, sex, time since onset, systolic blood pressure (SBP), stroke severity [as measured using the National Institutes of Health Stroke Scale (NIHSS)], presence of intraventricular haemorrhage (IVH) and known history of antiplatelet treatment used immediately prior to stroke onset. Participants were assigned to receive either an intravenous 1-g tranexamic acid loading dose in 100 ml of 0.9% normal saline infused over 10 minutes, followed by another 1 g of intravenous tranexamic acid in 250 ml of 0.9% normal saline that was infused over 8 hours, or a matching placebo (i.e. 0.9% normal saline), which was administered with an identical regimen. Individual masked treatment packs comprised four 5-ml glass ampoules containing either 500 mg of tranexamic acid or 0.9% sodium chloride. Packs were made identical in appearance and were labelled with a unique pack number. The randomisation system allocated each participant a unique number corresponding to a treatment pack containing either tranexamic acid or placebo. Treatment allocation was concealed from all staff and patients involved in the trial.

At randomisation, investigators recorded participants' age, sex and medical history, as well as their assessment of ICH location, presence of IVH, whether or not advanced imaging had been performed and, if applicable, presence of spot sign. Investigators assessed prestroke dependence with the mRS, and stroke severity using the NIHSS and GCS. Participants were reviewed at days 2 and 7 and on the day of death or hospital discharge, whichever came first, to gather information on clinical assessment (NIHSS), the process-of-care measures (e.g. blood pressure-lowering treatment, neurosurgical intervention), and discharge date and destination (e.g. home or institution).

Central assessors who were trained and certified in administration of the mRS and masked to treatment allocation carried out the final follow-up at 90 days by telephone from the co-ordinating centre in each country. If the participant or carer could not be contacted, they received a questionnaire by post, covering the same outcome measures.

Brain imaging by computed tomography (CT) scanning was done as part of routine care before enrolment; a second research CT scan was done 24 hours after treatment to assess haematoma expansion. When multiple scans were done, the scan closest to 24 hours after randomisation was used. Central independent expert assessors, who were masked to treatment assignment, assessed CT scans for the location of the ICH using a web-based adjudication system. Semi-automated segmentation of the ICH was done on Digital Imaging and Communications in Medicine [DICOM®; Medical Imaging & Technology Alliance (MITA), Arlington, VA, USA]-compliant images to give ICH volumes. The user-guided three-dimensional active contour tool in the itk-SNAP software (version 3.6; www.itksnap.org/pmwiki/pmwiki.php, accessed 3 May 2019) was used for segmentation and one of three assessors did, as required, manual editing. All assessments were masked to treatment assignment. Haematoma expansion was defined as an absolute increase of > 6 ml or a relative growth of > 33%.

The primary outcome was functional status at day 90, as assessed with the mRS, which was administered by telephone or by postal questionnaire, and was masked to treatment allocation. Secondary outcomes included:

- neurological impairment at day 7 or discharge (whichever came first), as assessed by the NIHSS
- health-related quality of life, as measured by the EuroQoL-5 Dimensions (EQ-5D) health-utility status and visual analogue scale
- activities of daily living, as assessed according to the Barthel index
- cognition, as assessed via the Telephone Interview Cognitive Score – Modified (TICS-M), and verbal fluency
- mood, as assessed by the Zung Depression Scale
- costs (length of hospital stay and discharge destination)
- radiological efficacy [change in haematoma volume (HV) from baseline to 24 hours and haematoma expansion].

Prespecified safety outcomes were death, venous thromboembolism, ischaemic events (stroke, transient ischaemic attack, myocardial infarction (MI), acute coronary syndrome, peripheral artery disease) and seizures. These safety outcomes were reported up to day 90, along with all serious adverse events (SAEs) in the first 7 days. Safety outcomes and SAEs were independently adjudicated and masked to treatment assignment. Serious adverse events were categorised in accordance with the Medical Dictionary for Regulatory Authorities (MedDRA).

Results

In total, 2325 participants were recruited from 124 hospitals in 12 countries over 55 months, from which 1161 participants were randomly assigned to receive tranexamic acid (n = 1161) or placebo (n = 1164). Most participants were recruited in the UK (1910, 82%). The mean age of participants was 68.9 years [standard deviation (SD) 13.8 years] and 1301 (56%) participants were male. The median time from stroke onset to randomisation was 3.6 hours [interquartile range (IQR) 2.6–5.0 hours] and 833 (36%) participants were recruited within 3 hours. The mean baseline SBP was 173 mmHg (SD 27.5 mmHg) and the mean baseline diastolic blood pressure was 93 mmHg (18.4 mmHg). A total of 1371 (59%) participants had a haematoma that was supratentorial deep, whereas 738 (32%) participants had one that was supratentorial lobar; 745 (32%) participants had IVH. The mean HV was 24.0 ml (SD 27.2 ml) and the median HV was 14.1 ml (IQR 5.9–32.4 ml). Contrast-enhanced imaging in the form of computed tomography angiography (CTA) scanning was done in 249 (11%) participants. Of these individuals, 24 (20%) of 121 in the tranexamic acid group and 32 (25%) of 128 in the placebo group were spot positive. Treatment groups were well balanced at baseline.

The primary outcome of mRS score, at day 90, was assessed in 2307 (99%) of 2325 participants; nine (< 1%) were lost to follow-up and nine (< 1%) withdrew from follow-up. There was no difference in the

distribution in the mRS score at day 90 after adjustment for stratification and minimisation criteria, with an aOR of 0.88 (95% CI 0.76 to 1.03; $p = 0.11$). A formal goodness-of-fit test showed no evidence that the proportional odds assumption was violated ($p = 0.97$). In a sensitivity analysis, no difference was detected between the trial groups in the proportion of participants who were dead or dependent at day 90 (i.e. a mRS score of > 3) and the aOR was 0.82 (95% CI 0.65 to 1.03; $p = 0.08$). In the prespecified subgroup analysis, the only significant interaction was between mRS score and baseline SBP (interaction $p = 0.019$). Participants in the tranexamic acid group, with a baseline SBP ≤ 170 mmHg had a favourable shift in mRS score, compared with those participants with a baseline SBP > 170 mmHg. There was no heterogeneity of treatment effect by time of administration, whether dichotomised as < 3 hours versus ≥ 3 hours (interaction $p = 0.75$) or as < 4.5 hours versus ≥ 4.5 hours (interaction $p = 0.28$) or when analysed as a continuous variable (aOR 0.98, 95% CI 0.90–1.07; $p = 0.69$).

Fewer participants in the tranexamic acid group had haematoma expansion at day 2 [265 (25%) of 1054 participants] than in the placebo group [304 (29%) of 1058 participants; aOR 0.80, 95% CI 0.66 to 0.98; $p = 0.030$]. The mean increase in HV from baseline to 24 hours was also smaller in the tranexamic acid group [3.72 ml (SD 15.9 ml)] than in the placebo group [4.90 ml (SD 16.0 ml); adjusted mean difference (aMD) –1.37 ml, 95% CI –2.71 to –0.04 ml; $p = 0.043$].

Neurological impairment (as assessed via the mean NIHSS score) at day 7 did not differ between the tranexamic acid group and the placebo group (aMD –0.43, 95% CI –0.94 to 0.09; $p = 0.10$).

There were no significant differences in any of the day 90 functional outcomes between treatment groups, that is, activities of daily living, mood, cognition or quality of life. Length of hospital stay and discharge disposition did not differ between treatment groups.

By day 7, fewer patients had died in the tranexamic acid group [101 (9%) of 1161 participants] than in the placebo group [123 (11%) of 1164 participants]. However, the number of deaths by day 90 did not differ between the tranexamic acid group [250 (22%) patients] and the placebo group [249 (21%) patients]. Survival did not differ between the treatment groups over 90 days (adjusted hazard ratio 0.92, 95% CI 0.77 to 1.10; $p = 0.37$).

Participants in the tranexamic acid group had fewer predefined safety outcomes and SAEs than those in the placebo group at days 2 [379 (33%) patients vs. 417 (36%) patients; $p = 0.027$], 7 [456 (39%) vs. 497 (43%); $p = 0.020$], and at 90 days [521 (45%) vs. 556 (48%); $p = 0.039$]. There was no increase in venous thromboembolic events [39 (3%) patients in the tranexamic acid group vs. 37 (3%) in the placebo group; $p = 0.98$], seizures or arterial occlusions (MI, acute coronary syndrome or peripheral arterial occlusion) in the tranexamic acid group compared with the placebo group.

Conclusions

Tranexamic acid did not have a significant benefit on functional status at day 90, although potential benefits were seen with significant modest reductions in haematoma expansion, early death and SAEs. The observed effect size was smaller than anticipated and is compatible with a lack of efficacy or the presence of a smaller treatment effect than expected.

Implications for health care

Based on current evidence, tranexamic acid cannot be recommended for routine treatment of patients with SICH. Tranexamic acid is inexpensive, easy to administer, seems to be safe and is widely available, so even a modest treatment effect could have an important impact on a global scale.

Recommendations for research

Although there is insufficient evidence to support the routine use of tranexamic acid in clinical practice for SICH, the results do not exclude a modest beneficial effect. The reductions in haematoma expansion and early deaths may reflect an antifibrinolytic effect and are promising, but further large randomised trials are needed to confirm or refute a clinically significant treatment effect. Future research should focus on enrolling participants earlier after ICH onset and investigate which subgroups of patients are most likely to benefit.

Trial registration

The trial is registered as ISRCTN93732214.

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