Tranexamic Acid for Spontaneous Intracerebral Hemorrhage: A Randomized Controlled Pilot Trial (ISRCTN50867461)

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Background: Spontaneous intracerebral hemorrhage (ICH) can be devastating, particularly if hematoma expansion (HE) occurs. Tranexamic acid (TA), an antifibrinolytic drug, significantly reduced mortality in bleeding patients after trauma in the large CRASH-2 trial. The CRASH-2 ICH substudy found that TA nonsignificantly reduced mortality and dependency in traumatic ICH. The aim of this study was to assess the feasibility of performing a randomized controlled trial of tranexamic acid in spontaneous ICH, ahead of a definitive study. *Methods:* We performed a single-center, prospective, randomized (2:1), double-blind, placebo-controlled blinded endpoint trial of TA (intravenous 1 g bolus, 1 g infusion/8 h) in acute (<24 hours) spontaneous ICH. The primary objective was to test the feasibility of recruiting to the trial. Other objectives included tolerability (adverse events) and the effect of TA on HE and death and dependency. *Results:* The trial was feasible, with 24 patients enrolled (TA, n = 16; placebo, n = 8) between March 2011 and March 2012, and acceptable—only 3 patients declined to participate. All patients received the correct randomized treatment; 1 patient in the TA group did not complete the infusion because of neurologic deterioration. There were no significant differences in secondary outcomes including adverse events, HE, death, and dependency. One patient in the TA group had a deep vein thrombosis . *Conclusions:* This, the first randomized controlled trial of TA in ICH, found that the protocol could be delivered on schedule (2 patients/mo) and was feasible. Larger studies are needed to assess safety and efficacy of TA in ICH. **Key Words:** Acute stroke—intracerebral hemorrhage—tranexamic acid—randomized controlled trials.

Introduction

Spontaneous intracerebral hemorrhage (ICH) is a common cause of death and disability worldwide. Outcome after ICH is closely related to both hematoma size and hematoma expansion (HE), which is associated with a bad outcome (death and disability).[1] Extravasation of arterial blood can be visualized as a white "spot" using contrast-enhanced computed tomography (CT) and/or CT angiography (CTA); the presence of

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Disclosure: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

Conflict of interest: None.

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spot-positive hematoma predicts HE and a poor outcome.[2-5]

Hematoma volume can be reduced surgically although whether this improves outcome was unclear in the STICH[6] and STICH-2[7] trials. Acute blood pressure lowering appears to be safe and may improve outcome in ICH although this was not conclusively demonstrated in the INTERACT studies.[8,9] This study focuses on a hemostatic approach to ICH.

Hemostatic drug therapies have been tested in spontaneous ICH, with recombinant factor VIIa (FVIIa) being the most widely studied agent. Although phase II study of FVIIa appeared promising,[10] the subsequent and larger FAST trial was neutral with respect to functional outcome.[11] A meta-analysis of these and other trials of hemostatic therapies was similarly neutral.[12] In a small case series, platelet infusion therapy for patients with ICH while on antiplatelet therapy did not prevent death or improve outcome[13]; a larger study, PATCH,[14] is ongoing.

Tranexamic acid is a licensed antifibrinolytic drug that can be administered intravenously or orally and is used to reduce bleeding in several conditions including menorrhagia and during cardiac surgery.[15,16] In a recent megatrial (CRASH-2) in 20,000 patients with major bleeding after trauma, tranexamic acid (TA) significantly reduced mortality, with no increase in vascular occlusive events.[17] Treatment was most effective when given rapidly; delayed administration was associated with lack of efficacy and potential harm.[18] In a subgroup analysis of patients with traumatic ICH, TA showed a nonsignificant trend to reduce mortality and death or dependency.[19] However, patients in CRASH-2 were younger and had less comorbidities than those with spontaneous ICH. In another randomized controlled trial in traumatic ICH, TA nonsignificantly reduced death and death or dependency, without increased thromboembolic events.[20]

Tranexamic acid has been tested in aneurysmal subarachnoid hemorrhage, where it reduced the risk of rebleeding at the expense of increased risk of cerebral ischemia.[21] However, administration was prolonged, conferring prolonged exposure to risk of ischemic events. A trial of immediate short-term (72 hours) TA treatment showed a trend to improved outcome,[22] and a trial of ultra-acute (within 6 hours) administration is currently ongoing.[23]

Additionally, TA has been found to restrict HE in several small case series involving patients with spontaneous ICH.[24,25] There have been recent calls in the literature for large clinical trials to examine the use of TA in ICH.[26] The aim of the present study was to test the feasibility of performing a randomized controlled trial of TA in ICH and assess initial safety, ahead of a definitive study.

Methods

We performed a prospective, randomized, placebo-controlled, blinded end point single-center phase IIa trial of TA in patients with acute spontaneous ICH. The study was approved by Cambridgeshire 2 Research Ethics Committee (November 1, 2010, ref: 10/H0308/80), had a Medicines and Healthcare Products Regulatory Agency Clinical Trial Authorization (03057/0044/0010001, October 4, 2010), was registered with a trial number (ISRCTN 50867461), and performed according to the Declaration of Helsinki and Good Clinical Practice.

Subjects

Adult patients with acute (<24 hours after ictus) spontaneous ICH were identified and enrolled from the stroke service at Nottingham University Hospital NHS Trust. The principal exclusion criteria included secondary ICH (anticoagulation, known vascular malformations), previous venous thromboembolic disease (VTE), recent (<12 months) ischemic events (ischemic stroke [IS], myocardial infarction, peripheral artery disease [PAD]), renal impairment (estimated glomerular filtration rate <50 mmol), and pregnancy or breast feeding.

Full written informed consent was obtained from patients before randomization, or proxy consent was taken from a relative/carer if the patient lacked capacity because of being obtunded, confused, or dysphasic.

Intervention

Patients were randomized to receive either intravenous TA (Cyklokapron; Phamacia Limited, Kent, UK) administered as a 1-g loading dose infusion for 10 minutes followed by a 1-g infusion for a period of 8 hours or matching placebo (.9% saline) administered by identical regime. This regime has been used in other studies[17] and has been shown to inhibit fibrinolysis in vitro.[27] Computerized randomization was performed 2:1 (TA:-placebo) with minimization on age, sex, baseline severity (National Institutes of Health Stroke Scale [NIHSS]), and time from stroke onset.

Outcomes

The primary outcome was trial feasibility (surrogate for trial acceptability:number of patients screened who are eligible for enrollment and who gave informed consent).

Secondary outcomes included tolerability (adverse events occurring during or after administration of TA) and safety (clinical information on ischemic events [IS, transient ischemic attack, acute coronary syndrome, PAD] and VTE were also recorded). The Data Safety Monitoring Committee reviewed unblinded safety data after 6, 12, and 18 patients have been recruited and followed for 7 days.

Clinical measures: impairment (NIHSS) at day 7 (or discharge from hospital) and day 90 (end of follow-up); dependency (modified Rankin Scale shift), disability (Barthel Index), quality of life (EuroQoL), mood (Short Zung

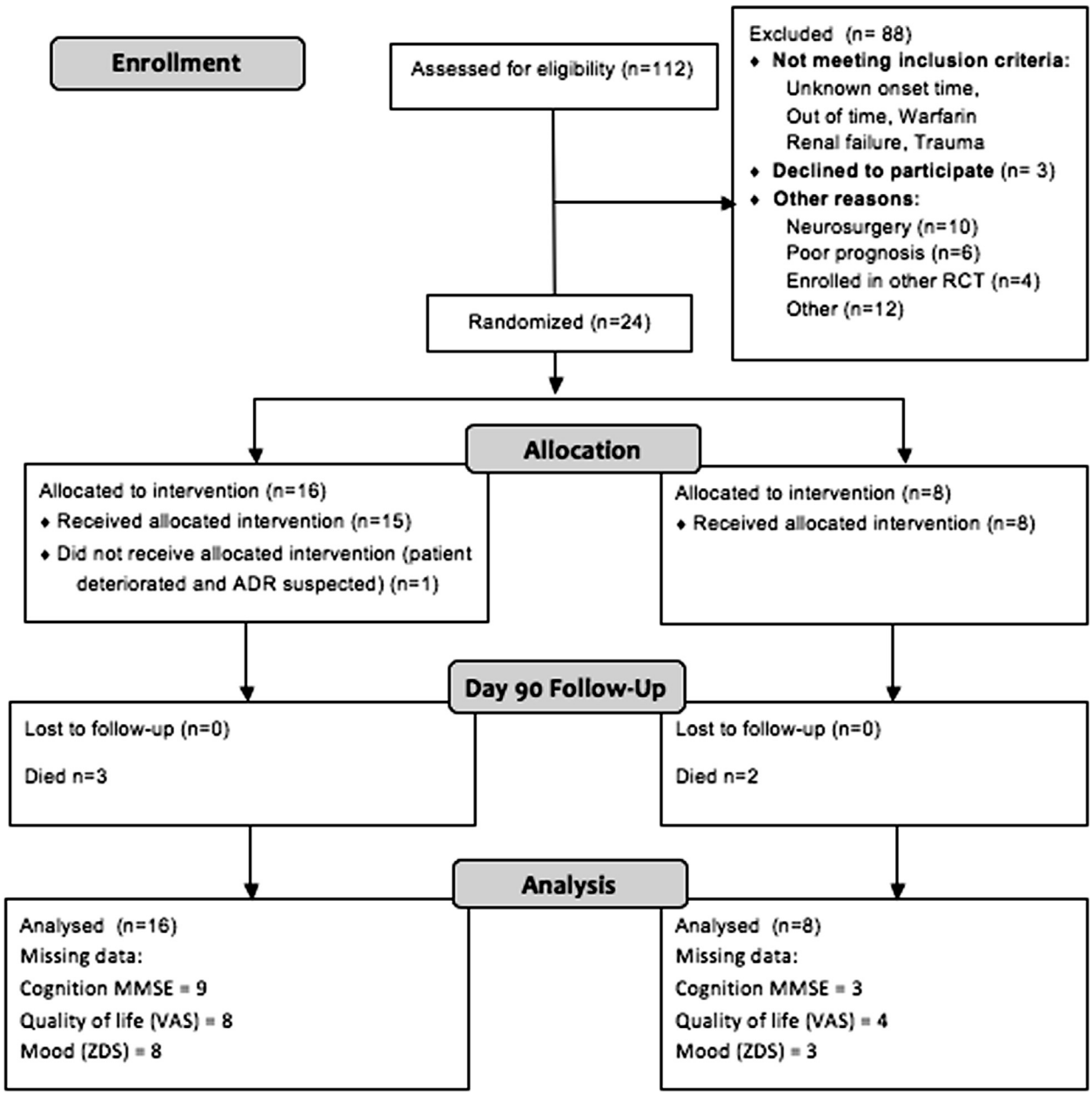

Figure 1. *Consort flow diagram. Abbreviations: ADR, adverse drug reaction; MMSE, Mini-Mental State Examination; RCT, randomized controlled trial; VAS, visual analog scale; ZDS, zung depression scale.*

Depression Scale score), and cognition (telephone MMSE) at day 90.

Radiological measures: percentage hematoma volume change on brain imaging day 1 to day 2 and HE (defined as greater than 6-mL absolute increase in hematoma volume[28]). All image analyses were performed blinded to clinical status and treatment allocation. CT scan data were exported from the Nottingham University Hospitals Picture Archiving and Communication System in DICOM format to an offline image analysis workstation. The data were converted to analyze format before volumetric analysis using 3DSlicer software.[29]

Manual outlining of ICH, IVH, and edema was performed as described previously[30] by a single investigator (Y.K.) in all cases. In a subset of 8 cases, the ICH volume on the baseline and follow-up scans (hence 16 scans) was measured by a second experienced observer (R.A.D.) allowing interobserver variability measurement for ICH volumes and for the calculated change in ICH volume between the 2 scans. Additionally, difference in ICH volume measurement between the 2 readers was calculated as a type A intraclass correlation using an absolute agreement definition.

Statistical Methods

Data were analyzed using Fisher exact test, *t* test, and Mann–Whitney *U* test, as appropriate. All analyses were

Table 1. *Baseline characteristics*

	Active	Placebo	Total
Number of patients	16	8	24
Age, mean	67.9 (13.2)	68.5 (12.9)	68.1 (12.8)
Sex (male %)	10 (62.5)	4 (50)	15 (62.5%)
Systolic blood pressure (mm Hg)	166.6 (19.6)	165.5 (27.5)	166.3 (21.9)
NIHSS (/42)	14.8 (8.9)	15.9 (9.1)	15.1 (8.8)
Glasgow Coma Scale (/15)	12.7 (3.1)	12.8 (2.7)	12.7 (2.9)
History of previous stroke (%)	2 (12.5)	0	2 (8.3%)
History of hyperlipidemia (%)	5 (31.3)	0	5 (20.8%)
History of hypertension (%)	10 (62.5)	5 (62.5)	15 (62.5%)
History of IHD (%)	0	0	0
History of PAD (%)	0	0	0
History of TIA (%)	1 (6.3)	2 (25)	3 (12.5%)
History of AF (%)	1 (6.3)	0	1 (4.2%)
History of diabetes mellitus (%)	2 (12.5)	0	2 (8.3%)
History of previous antiplatelet use (%)	4 (25%)	1 (12.5)	5 (20.1%)
Ethnicity (%)			
African	2 (12.5)	0	2 (8.3%)
South Asian	1 (6.3)	0	1 (4.2%)
White British	13 (81.3)	8 (100)	21 (87.5%)
Sinus rhythm on ECG	15 (93.6)	8 (100)	
Atrial fibrillation of ECG	1 (6.3)	0	1 (4.2%)
Smoking, current (%)	3 (18.7)	0	3 (12.5%)
Modified Rankin Scale (/6)	.5 (1.0)	.1 (.4)	.4 (.9)
Onset to randomization (h)	11.3 (7.4)	15.2 (9.4)	12.6 (8.1)

Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; IHD, ischemic heart disease; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral artery disease; TIA, transient ischemic attack.
Data are number (%) or mean (SD).

performed using SPSS (Apple Mac, version 11; SPSS Inc., Chicago, IL). Analysis was by intention-to-treat; significance was taken at P less than .05. As this was a feasibility study, no formal sample size calculation was performed.

Results

Of 107 patients who were screened between March 2011 and April 2012, 24 were enrolled (Fig 1). The commonest reason for non-enrollment was inability to randomize within 24 hours of onset because of unknown time of onset. Other reasons included need for immediate neurosurgery (10) and deep coma (6). Of eligible patients, 3 declined to consent.

The baseline characteristics were matched for age, sex, systolic blood pressure, and baseline stroke severity (Table 1); patients randomized to TA had a trend to larger hematoma volumes, earlier randomization, and were more likely to have had previous stroke and be on antiplatelet therapy.

All patients received all their bolus injection, and 1 patient in the tranexamic group did not receive their infusion because of rapid deterioration, which initially was thought to be an allergic reaction but was later confirmed as because of HE.

No patients were lost to follow-up; however, cognition, mood, and quality of life data were missing in a number of participants who were unable to answer questions because of communication problems. There were no significant differences in functional outcomes between the groups (Table 2); point estimates variably favored TA or placebo but with no apparent trends.

Six patients in the TA group and 2 in the control group had SAEs (Table 3). One patient had a deep vein thrombosis 8 days after treatment with TA; there were no other episodes of VTE or arterial thrombosis (IS, transient ischemic attack, acute coronary syndrome, or PAD); 5 patients in the TA group and 2 in the control group had neurologic deterioration (NIHSS score >1).

Basal ganglia hematoma were more common than lobar hematoma in both groups (Table 4). Only 4 patients had CTA before randomization, and none of these were positive for contrast extravasation (ie, all "spot negative").

The intraclass correlation coefficients of .997 (95% confidence interval .989-.999, $P < .0005$) and .953 (95% confidence interval .803-.990, $P < .0005$) were obtained for absolute ICH volume and for the calculated change in ICH volume. The mean difference in absolute ICH volume measurement between the 2 readers was 1.75 mL (range .01-4.91 mL).

Table 2. *Secondary outcomes at day 90*

Outcome	Tranexamic acid	Placebo	Total	2*P*
Modified Rankin Scale (/6)	3.6 (1.9)	3.4 (2.1)	3.5 (1.9)	.82
Barthel Index (/100)	59.2 (39.7)	81.7 (18.1)	66.3 (35.5)	.11
MMSE (/30)	21.3 (.8)	18.6 (4.0)	20.2 (2.8)	.21
Zung Depression Scale (/40)	21.3 (12.6)	18.2 (6.8)	20.1 (10.5)	.63
EuroQoL: HUS	.5 (.5)	.54 (.27)	.51 (.44)	.89
EuroQoL: Visual analogue scale (/100)	76.8 (14.3)	66.3 (17.0)	73.3 (15.3)	.28
Length of stay (d)	19.4 (24.5)	10.8 (14.0)	16.6 (21.7)	.37
Day 90 disposition (%)				
Living at home	10 (62.5)	6 (75)	16 (66.7)	.22
In-patient	2 (12.5)	0	2 (8.3)	1.0
Nursing home	1 (6.3)	0	1 (4.2)	1.0
Death	3 (18.8)	2 (25)	5 (20.8)	.72

Abbreviations: HUS, health utility score; MMSE, Mini-Mental State Examination.
Data are number (%) or mean (SD).

Four patients had radiological HE, 3 in the TA group and 1 in the control group. There was a trend to greater percent HV increase in the control group (9.7%) versus the TA group (5.4%).

Discussion

There is an urgent need for effective treatments for ICH. We have shown here that administration and testing of the prohemostatic agent TA in ICH is feasible. However, the numbers enrolled in this study are too small to draw any conclusions on safety or efficacy, and as expected, no trends were seen for or against TA.

Twenty-four patients were recruited over 2 years (2 patients/mo), the intended rate. All patients bar 1 received the full dose of TA/placebo. With respect to safety, no significant differences between TA and placebo were seen for rates of death, serious adverse events, neurologic deterioration, or VTE. The commonest adverse event was neurologic deterioration, often associated with HE, although in a number of patients, it was associated with a systemic cause, such as aspiration pneumonia or atrial fibrillation. With respect to VTE, a potential complication with TA, 1 patient had a deep vein thrombosis 8 days after treatment with TA; larger numbers are needed to assess safety; however, no increase in VTE was seen in CRASH-2.[17]

Table 3. *Serious adverse events*

Event (%)	Tranexamic acid	Placebo	2*P*
Number of patients	16	8	
Any serious adverse event	6 (37.5)	2 (25)	1.0
Venous thromboembolism	1 (6.3)	0	1.0
Neurological deterioration	5 (31.3)	2 (25)	1.0
Aspiration pneumonia	3 (18.8)	0	.56
Craniotomy	1 (6.3)	0	1.0
Death	3 (18.8)	2 (25)	.722

Data are number (%).

We used a definition of HE of greater than 6-mL absolute increase. Five patients had more than 33% increase in hematoma volume, but in only 3 of these, the volume increase was greater than the 3-mL absolute increase. Again, there was no difference between TA and placebo. Patients in the treatment group were more likely (nonsignificant) to have been taking antiplatelet therapy, a risk factor for HE.[31]

Recent studies have suggested that clinical trials of prohemostatic agents should enroll patients who are more likely to be prone to HE,[28] for example, using the CTA "spot sign."[5] We did not include patients on the basis of CTA; first, CTA is not a standard of care in stroke patients in the United Kingdom (in our study, only 4 patients had a CTA), and second, spot-negative patients can still go on to suffer HE.[32]

There was no increase in cerebral edema, an important finding, as an experimental model of warfarin-induced ICH demonstrated that TA-treated animals had increased cerebral edema. This warrants further investigation in a larger study.[33]

The limitations of this study are 3-fold. First, it was a very small pilot study, designed only to test the feasibility of performing a randomized control trial of TA in ICH. Second, patients were recruited at an average time of 10-15 hours postonset, that is, in the acute rather than hyperacute phase after ICH. The window for recruitment of up to 24 hours was deliberately chosen because this was a feasibility study. Nevertheless, it is likely that any prohemostatic agent will need to be given much earlier if it is to be effective by reducing HE because expansion occurs early after onset.[34] All the patients who underwent HE

Table 4. *Radiological measures between TA versus placebo*

Radiological measures	TA	Placebo	Total
Baseline CT patients	16	8	24
Time from onset to scan (h:min)	05:32 (6:24)	04:48 (4:54)	05:17 (5:51)
Hematoma volume median (IQR)	27.0 (6.7-61.2)	14.3 (4.8-51.1)	17.4 (6.8-60.0)
Hematoma location (%)			
Thalamic	6 (37.5)	4 (50)	10 (41.7)
Basal ganglia	5 (31. 25)	1 (12.5)	6 (25)
Lobar	5 (31.25)	3 (37.5)	8 (33.3)
IVH present at baseline (%)	4 (25)	2 (25)	6 (25)
CTA performed (%)	3 (12.5)	1 (12.5)	4 (16.7)
CTA dot sign ''positive''	0	0	0
24 h CT, patients	16	7	2*P*
Time from onset to scan (h:min) (SD)	40:20 (14:13)	41:59 (29:09)	.842
Percentage change in HV from baseline, mean	5.4 (23.8)	9.7 (17.5)	.656
Hematoma expansion* (%)	3 (18.8)	1 (12.5)	1.00
Change in cerebral edema from baseline	6.6 (13.3)	7.7 (7.3)	.302

Abbreviations: IVH, intraventricular hemorrhage; CTA, computed tomography angiography; HV, hematoma volume; TA, tranexamic acid. Data are number (%), mean (SD or median [interquartile range]. Comparison by chi-square test, *t* test, or Mann–Whitney *U* test.
*Greater than 6-mL absolute increase in HV.

were enrolled greater than 4 hours after stroke onset, and 5 of 6 received treatment more than 12 hours after ictus. Patients in the treatment group were enrolled somewhat earlier and had somewhat larger baseline hematoma volumes although both observations were nonsignificant; these findings are not surprising because earlier randomization is expected to be associated with more severe stroke presentations.[35] The feasibility of recruiting patients to a hyperacute (short time window), multicenter trial was not addressed by this pilot study; however, other studies suggest that this will be feasible.[9] Third, although we did not confirm that fibrinolysis was inhibited in vitro, the dose regime used for administering TA here has been demonstrated to have antifibrinolytic action in other studies.[27]

In conclusion, we found it was feasible to administer TA in acute ICH. Larger studies, recruiting patients much earlier, are now needed to determine safety and efficacy. A number of such studies are in preparation with 2 studies currently recruiting patients. One such phase III trial, TICH-2,[36] started in March 2013 and aims to recruit 2000 patients. In parallel, the STOP-AUST[37] phase II trial will assess the effect of TA on hematoma expansion in "spot-positive" patients.

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