The STOP-AUST trial: a test for the spot sign in intracerebral haemorrhage?

David J Werring

Stroke Research Centre

UCL Queen Square Institute of Neurology

First Floor

Russell Square House

10-12 Russell Square

London WC1B 5EH

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Comprehensive Stroke Service, National Hospital for Neurology and Neurology, Queen Square, University College London Hospitals NHS Foundation Trust, London WC1N 3BG

d.werring@ucl.ac.uk

Spontaneous intracerebral haemorrhage (ICH) – nontraumatic bleeding into the brain substance - is the least treatable and most deadly form of stroke, accounting for 5% of all human deaths and causing major disability for 18 million survivors.[1] By contrast with the major advances in treating ischaemic stroke there are still no proven effective treatments for acute ICH, making it a major and urgent unmet clinical need.

Haematoma growth is strongly associated with functional outcome and mortality after ICH, making it a key target for intervention. The "spot sign" describes extravasation of contrast seen on CT angiography, hypothesised to be a small arterial bleeding point.[2] The spot sign has been reported in about 25% of acute ICH and is associated with an increased risk of haematoma expansion; in an early report 60.7% of patients with a spot sign had haematoma growth compared to 21.6% of those without.[2] In a larger pooled analysis the spot sign modestly improved the predictive value of baseline ICH volume and pre-ICH antithrombotic use in predicting hematoma expansion.[3]

Unfortunately, neither intensive blood pressure lowering,[4,5] nor haemostatic agents (recombinant Factor VII[6] or tranexamic acid)[7] – both interventions that target haematoma expansion - significantly reduced death or disability in randomised controlled trials. The spot sign has been suggested as a way to select participants for trials of interventions targeting haematoma expansion, with the aim of reducing the sample size needed to detect a treatment effect. This approach was tested in the STOP-AUST trial of tranexamic acid, an antifibrinolytic agent that appears safe in patients with acute ICH[7] and effective in traumatic brain injury. Participants were eligible if they had a non-traumatic ICH with a spot sign, were treatable within 4·5 hours of symptom onset and within 1 hour of CT angiography, and who did not have a low conscious level or very large (>70 mL) haematoma.

Across 13 stroke centres in Australia, Finland, and Taiwan, 100 participants with median ICH volume 14.6 ml were randomised. The primary outcome of ICH growth occurred in 26/50 (52%) placebo and 22/50 (44%) tranexamic acid group participants (adjusted odds ratio [aOR] 0·72, 95% CI 0·32–1·59, p=0·41). There were no differences in mortality, thromboembolic complications or functional outcome distribution (adjusted generalised OR 1·01, 0·63–1·61, p=0·97) between the placebo and tranexamic acid groups. A post hoc analysis found evidence of a time-by-treatment interaction favouring early administration (p=0.059) The STOP-AUST investigators should be commended on perseverance in completing this trial. The results confirm that tranexamic acid is safe, and might be more effective if given early, but do not provide evidence of efficacy in a population selected by the presence of a spot sign.

The most obvious explanation for this neutral result is that any treatment effect size for tranexamic acid is too small to detect using the recruited population. In the much larger TICH-2 trial in 2325 participants (half treated within 4 hours), the proportion with haematoma growth was only 4% lower in the tranexamic acid group (25% v 29%, p=0.03)[7] while STOP-AUST was powered for a much larger 30% absolute risk difference in the proportion of patients with ICH growth, based on data from Factor VII trials.[6] Second, in STOP-AUST, the median delay from baseline CT to treatment was 41 minutes, so that substantial haematoma growth may have already occurred before treatment.[8]

What are the lessons for future trials in acute ICH? STOP-AUST took 6 years to recruit 100 participants from 13 centres; this challenge may have been in part due to the requirement to obtain urgent CTA and evaluate for a spot sign, which is not currently part of routine care for acute ICH. The added value of this additional imaging is uncertain: even in those with a spot sign, only about half had haematoma growth, in line with observational studies, while previous

small trials of rFVIIa (n=69) using the spot sign as a selection criterion (STOP-IT and SPOTLIGHT) did not demonstrate significant reductions in ICH growth.[9] Furthermore, only 10% of the 2325 participants in TICH-2 had a spot sign, with no indication that this affected the response to tranexamic acid. Since baseline haematoma volume seems to be a key predictor of expansion[3] future trials could potentially select participants based on this much simpler criterion.

In summary, future trials of haemostatic therapies in acute ICH need to: be large enough to detect a realistic effect on haematoma expansion; be simple (avoiding additional imaging to maximise recruitment and speed of administration); and exclude participants with either very small or very large volume ICH. Several further tranexamic acid trials are underway and an individual patient data meta-analysis is planned.[10] The true (tranexamic) acid test will be whether well-powered and pragmatic trials in acute ICH can improve not only haematoma expansion but also mortality and longer term clinical outcomes that are important to patients, carers and their physicians.

References

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