December 2010

What are the current therapeutic options for haemorrhagic strokes

Maria Khan
Aga Khan University

Ayeesha Kamran Kamal
Aga Khan University

Evidence Based Medicine

What are the current therapeutic options for haemorrhagic strokes?

Maria Khan, Ayeesha Kamran Kamal
Department of Neurology, Director Stroke Service and Vascular Fellowship Program, Aga Khan University Hospital, Karachi, Pakistan.

The Factor Seven for Acute Haemorrhagic Stroke Trial (FAST) and Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage trial (INTERACT).

Why are these studies important and noteworthy?

Intracerebral haemorrhage (ICH) is the most devastating form of stroke carrying a mortality of up to 40% at one month. In our part of the world the levels of uncontrolled hypertension pose a greater risk of ICH for our population where ICH is about 30% of all strokes compared to 14% in developed countries.

There is evidence to suggest that haematoma expansion occurs in as many as 70% of patients. This expansion translates into increased disability and death. Most of this expansion is within the initial three hours. Also early elevation of blood pressure (BP) is very common after ICH and many studies have highlighted an association between elevated BP post ICH and poor outcomes. The reason for this is postulated to be an increase in both the size of the haematoma and perilesional oedema.

Factor VIIa activates factor X on the surface of activated platelets and leads to accelerated coagulation and thus limits rebleed and haematoma expansion. A prior study (published in NEJM in 2005) had demonstrated that recombinant activated Factor VII (rFVIIa) when given within four hours of symptom onset limited the growth of ICH. In the FAST trial, the investigators evaluated the effects of two dose of rFVIIa on rates of death and disability after ICH.

The Intensive Blood Pressure Reduction In Acute Cerebral Haemorrhage Trial (INTERACT) was a randomized controlled trial undertaken to determine the effects of early intensive BP lowering on haematoma growth and perihaematomal oedema. A pilot phase of this study had demonstrated that such lowering of BP was safe and limited haematoma expansion in patients treated within six hours of symptom onset. In the next phase the authors have reported the effects of early intensive BP lowering on haematoma growth over 72 hours and also investigated the effects of this treatment on perihaematomal oedema. A third phase of the study is currently underway to assess whether this therapy translates into clinical benefit or not.

Who were the participants?

The FAST trial was a multicenter, randomized, double- blind, placebo- controlled trial conducted between May 2005 and February 2007 at 122 sites in 22 countries. Most of these were European countries and the US, with no contribution from South East Asia. China and Singapore contributed small numbers. Patients older than 18 years with acute ICH documented by CT within 3 hours of symptom onset were eligible to get enrolled. They excluded patients who had a GCS of 5 or less (indicating severe ICH), those who had a surgical evacuation planned within 24 hours, those who were on anticoagulation and those who had a history of recent thromboembolism (and therefore contraindication to rFVIIa).

For INTERACT 404 patients were recruited form a network of hospital sites in China, South Korea, and Australia during 2005 and 2007. They include patients >18 years of age with CT confirmed spontaneous ICH and elevated systolic BP (>2 readings of >150 and <220 mm Hg recorded >2 min apart). A prerequisite was the capacity to start randomly assigned treatment within 6 hours of ICH in a monitored environment. They excluded patients with a clear indication or contraindication to BP lowering, those with a recent ischaemic stroke, those who were deeply comatose or were planned for an early

neurosurgical intervention.

What was the intervention?

In FAST the patients underwent block randomization according to site to receive a single intravenous dose of placebo (268 patients) or of rFVIIa at a dose of 20 µg (276 patients) or 80 µg (297 patients) per kilogram. Treatment was administered within 1 hour after the baseline CT scan and no later than 4 hours after the onset of symptoms. Follow up CT scans were performed at 24 and 72 hours and volumes of intracerebral haemorrhage, intraventricular haemorrhage, and oedema were calculated. The primary outcome measure was the score on mRS at day 90.

In INTERACT, patients were randomly assigned to receive either an early intensive BP-lowering treatment strategy (203 patients) or the recommended best practice standard of BP lowering (201 patients) at the time that of the American Heart Association guidelines published in 1999. For patients allocated to the intensive group, the goal was to achieve a systolic BP of 140 mm Hg within 1 hour of randomization and subsequently to maintain this target level for the next 7 days. For patients allocated to the guideline group, treatment was recommended to achieve a target systolic BP of 180 mm Hg. The outcomes for the present investigation were the absolute and proportional increases in haematoma and perihaematomal oedema volumes during the first 72 hours after ICH. CT was repeated at 24 and 72 hours of symptom onset. For this 151 patients were included from the intensive arm and 145 from the standard care arm, as the rest did not have 3 CT scans.

What was the outcome?

In FAST the estimated mean increase in the volume of intracerebral haemorrhage was 26% in the placebo group and 11% in the group receiving 80 µg of rFVIIa per kilogram thus proving that factor VI does limit haematoma expansion. The increase in the volume of haematoma was 3.8 ml less in the group receiving 80 µg of rFVIIa than in the placebo group (95% confidence interval [CI], 6.7 to 0.9; P = 0.009). The intraventricular haemorrhage volume doubled in the placebo arm but remained unchanged in the factor VII arms, but this difference did not reach statistical significance and the final lesion volumes were also similar in the three groups. Despite the significant haematoma expansion in the placebo arm compared to the active arm, the primary outcome measure (the proportion of patients who died or were severely disabled) did not differ significantly among the three groups. The distribution of outcomes on the modified Rankin scale and the median scores on the Barthel index were similar among the three groups. However, there was an absolute increase of 5% in the frequency of arterial thromboembolic serious adverse events in the group receiving 80 µg of rFVIIa per kilogram as compared with the placebo group (P = 0.04).

In INTERACT, early intensive BP lowering significantly reduced BP levels during the treatment. Compared with the guideline group, the intensive group showed significant differences of 3.15 mL (95% CI, 1.00 to 5.30 mL; P=0.004) and 2.45 mL (95% CI, 0.75 to 4.16 mL; P=0.005) less mean absolute haematoma growth at 24 and 72 hours, respectively. The mean difference in absolute increase over 72 hours was 2.80 mL (95% CI, 1.04 to 4.56 mL; P=0.002). However, there was no significant difference in the mean perihaematomal oedema growth between the two groups.

What were the conclusions?

In FAST, rFVIIa given within 4 hours after the onset of symptoms of intracerebral haemorrhage significantly reduced growth of the haematoma but failed to improve survival or functional outcome at 90 days. There was also an absolute increase of 5% in arterial thromboembolic serious adverse events in the group receiving 80 µg of rFVIIa per kilogram as compared with the placebo group (9% vs. 4%). Although this is a negative trial there are some important things that need to be considered. Firstly, there were important randomization imbalances in the trial. Secondly, the patients who were included had relatively small haemorrhages (mean volume~22-24 ml) and were neurologically very intact with GCS of 14 and NIHSS of around 13. What is not known is whether those with larger haemorrhages or those with higher risk of re-bleed for various reasons would benefit more from this therapy.

INTERACT has demonstrated that early intensive BP lowering does attenuate haematoma growth in patients with ICH. It does not have a significant effect on the growth of perihaematomal oedema. Whether this radiological finding translates into clinical benefit is yet to be evaluated.

Do corticosteroids have a role in ICH?

A Cochrane review published in 2008 on use of corticosteroids in primary ICH concluded that there is no evidence of a beneficial or adverse effect of corticosteroids in patients with ICH whereas there is some evidence that corticosteroids increase the risk of serious adverse effects.

How does this impact our clinical practice?

Before FAST and INTERACT, there was little data regarding therapy in ICH. Now at least targets have been identified. Recombinant factor VIIa shows promise but it needs to be evaluated in patients with larger haematomas and in those with higher risk of re-bleed. Till then its use is not recommended.

Early intensive BP lowering also has impact on limiting haematoma growth. But till the next phase of this trial is completed, we cannot conclude whether this translates into clinical benefit or not. Besides this kind of aggressive BP management requires dedicated stroke units which in our current setup are not available. Till more data comes out, standard recommendations for ICH management should be followed.

Corticosteroid use is very frequent in our setup. What must be borne in mind is that there is no evidence to suggest their benefits and they carry a risk of adverse effects. Therefore their use is not recommended in patients with ICH.

Recommended Reading

1. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T; FAST Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med 2008; 358: 2127-37.
2. Anderson CS, Huang Y, Arima H, Heeley E, Skulina C, Parsons MW, et al. INTERACT Investigators. Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). Stroke 2010; 41: 307-12.
3. Feigin VL, Anderson N, Rinkel GJE, Algra A, Jan van Gijn, et al. Corticosteroids for aneurysmal subarachnoid haemorrhage and primary intracerebral haemorrhage Cochrane Review, October 2008.