

Medical Management of Haemorrhagic Stroke

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ABSTRACT

Intracerebral haemorrhage (ICH) is much less common than ischaemic stroke (15% versus 85% in most Western studies), but is associated with a significantly worse prognosis. ICH is much more common in Asian populations, probably reflecting higher rates of small vessel disease, hypertension and genetic factors. Overall, ICH mortality rates approach 50% and there has been little effective treatment to date, except for the overall benefit from stroke unit care. Surgery for supratentorial ICH was not shown to be beneficial in a large recent trial of over 1000 patients, although controversies remain. For example, it still has an important role in selected patients with cerebellar ICH. Medical therapies to reduce brain edema and intracranial pressure, including glycerol and mannitol, are not of proven value. It is accepted that corticosteroids should not be used in ICH and may worsen outcomes. The management of acute hypertension is controversial and guidelines are based on little direct evidence. (Critical Care and Resuscitation 2005; 7: 185-188)

Key words: Intracerebral haemorrhage, medical management, recombinant activated factor VII, review

Intracerebral haemorrhage (ICH) is much less common than ischaemic stroke (15% versus 85% in most Western studies), but is associated with a significantly worse prognosis. ICH is much more common in Asian populations, probably reflecting higher rates of small vessel disease, hypertension and genetic factors. Overall, ICH mortality rates approach 50% and there has been little effective treatment to date, except for the overall benefit from stroke unit care.¹ Surgery for supratentorial ICH was not shown to be beneficial in a large recent trial of over 1000 patients, although controversies remain. For example, it still has an important role in selected patients with cerebellar ICH.² Medical therapies to reduce brain edema and intracranial pressure, including glycerol and mannitol, are not of proven value. It is accepted that corticosteroids should not be used in ICH and may worsen outcomes.³ The management of acute hypertension is controversial and guidelines are based on little direct evidence.

Prognostic determinants and the dynamic evolution of ICH

The positive results of a proof of concept trial using

a novel medical therapy for ICH by Mayer and colleagues⁴ with the haemostatic agent, recombinant activated Factor VII (rFVIIa), raises the real possibility of a widely applicable medical therapy for patients who can be treated within the first 4 hours of the onset of symptoms. Unlike other experimental approaches to acute stroke therapy, the use of rFVIIa was not based on preclinical models, but rather new insights into the pathophysiology of ICH in observational human studies. First, the volume of ICH and conscious state measured with the Glasgow Coma Scale were recognised as critical prognostic determinants. For example, in patients with an ICH volume of 60 cm³ or greater on the initial CT scan and a Glasgow Coma Scale (GCS) score of 8 or less, there is a 30 day mortality of 91%.⁵ The volume of an ICH can readily be measured on a CT scan without sophisticated technology, by simply multiplying the three axes (x,y,z) in cm and dividing by two, approximating an ellipsoid.⁵ In addition to haematoma volume and conscious state, poor outcomes are amplified by advancing age, infratentorial location of the ICH, and intraventricular haemorrhage.⁶

Second, ICH is not a static phenomenon, as was

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once believed. It was previously considered that the volume of a cerebral haematoma was usually maximal at onset and then contained by hydrostatic forces and elevated intracranial pressure. This view contrasted with developments in the understanding of the dynamic pathophysiology of ischaemic stroke, where it was recognised that the infarcted core typically expands over the first few hours due to progressive failure of cerebral blood flow. In ischaemic stroke, this is due to occluded arteries and progressive loss of potentially viable tissue in the ischaemic penumbra. This insight led to the introduction of thrombolytic therapy, aimed at arterial recanalisation with resultant reperfusion of the critical penumbral region.⁷ In contrast to ischaemic stroke, research by our group and others have shown that there is no ischaemic penumbra in ICH.⁸ However, ICH patients also exhibit an evolution of pathophysiology and a substantial proportion demonstrate significant haematoma expansion into surrounding brain tissue, early after the onset of stroke symptoms. This was first shown in observational retrospective studies using CT^{9,10} and will be familiar to many clinicians treating patients with ICH, when repeat CT scans are performed at the time of a clinical deterioration (Figure 1.).

A landmark prospective study by Brott et al, published in 1997, showed that 38% of patients exhibited substantial growth (defined as greater than one third increased volume) if first imaged with CT within 3 hours and then re-scanned 24 hours later.¹¹ Most of this growth (26%) appeared within one hour of the first scan. This volume increase probably reflects continued bleeding or rebleeding. This finding confirmed that, like ischaemic stroke, ICH is a dynamic process and might be amenable to a therapeutic intervention with a haemostatic therapy that could attenuate this bleeding and reduce the eventual volume of the haematoma.¹²

Recombinant factor VIIa and haemostasis

Most patients with ICH do not have an underlying coagulopathy. The exception of course is warfarin-related ICH, accounting for about 10% of cases in most series.^{13,14} Therapy with rFVIIa is effective in coagulopathic patients and was introduced as a treatment for haemophilia. However, it also arrests continued bleeding in patients without coagulopathy. It is thought to act by stimulating a thrombin burst on the surface of activated platelets, catalysing the development of fibrin clot. It is therefore being investigated as a haemostatic agent in various conditions where life-threatening bleeding is the common theme, such as perioperative bleeding and major trauma.^{15,16}

Trials with recombinant factor VIIa in stroke

Safety and dose-escalation studies were performed in two preliminary ICH trials.¹⁷ The further development of the compound involved a proof of concept study in 400 patients (100 placebo-treated and 100 each receiving doses of 40, 80 and 160 µg/mL).⁴ Patients with ICH were scanned with CT within 3 hours of stroke onset and then treated no later than one hour after the baseline scan. Because the study was aimed at proof of concept, the primary outcome was haematoma growth over 24 hours. Secondary clinical outcomes included mortality and standard functional outcome scales, including the modified Rankin Scale and the Barthel Index. Safety, particularly the incidence of thromboembolic events, was monitored by an Independent Data Safety Monitoring Committee.

Proof of concept was confirmed with a haematoma growth of 29% in the placebo group reduced by about one half in the rFVIIa-treated groups. However, the secondary clinical endpoints were also positive. Mortality was significantly reduced from 29% at 90 days in the placebo group, to 18% in the pooled treated groups. There is always concern that a stroke therapy that reduces mortality might result in highly disabled survivors, but the trial showed that functional outcomes were also significantly improved in survivors. There was a small increase in thromboembolic events with therapy, particularly arterial events including myocardial and cerebral infarction. These adverse effects were substantially outweighed by the overall benefits from therapy, with only 5 - 6 patients needed to treat to avoid one bad outcome. Based on these results, a second and hopefully confirmatory phase III study, the FAST (Factor 7 in Acute hemorrhagic Stroke Trial) trial, is underway.

Conclusions and future trials

While off-label use of rFVIIa is very tempting, a confirmatory study is necessary to confirm the safety and efficacy of the therapy. Other ICH trials would be worthwhile. These could include a study of patients with ICH due to warfarin, excluded in the current rFVIIa trials in ICH. It would also be important to assess treatment in patients with slightly longer time windows. Given that the poor results of surgical evacuation could be due to rebleeding, a trial of rFVIIa in combination with stereotactic evacuation seems appealing. A trial in subarachnoid haemorrhage would also be a priority.

The other critical issue in the medical management of ICH is the management of blood pressure. There is some evidence linking high blood pressure and rebleeding. There is currently little evidence to support

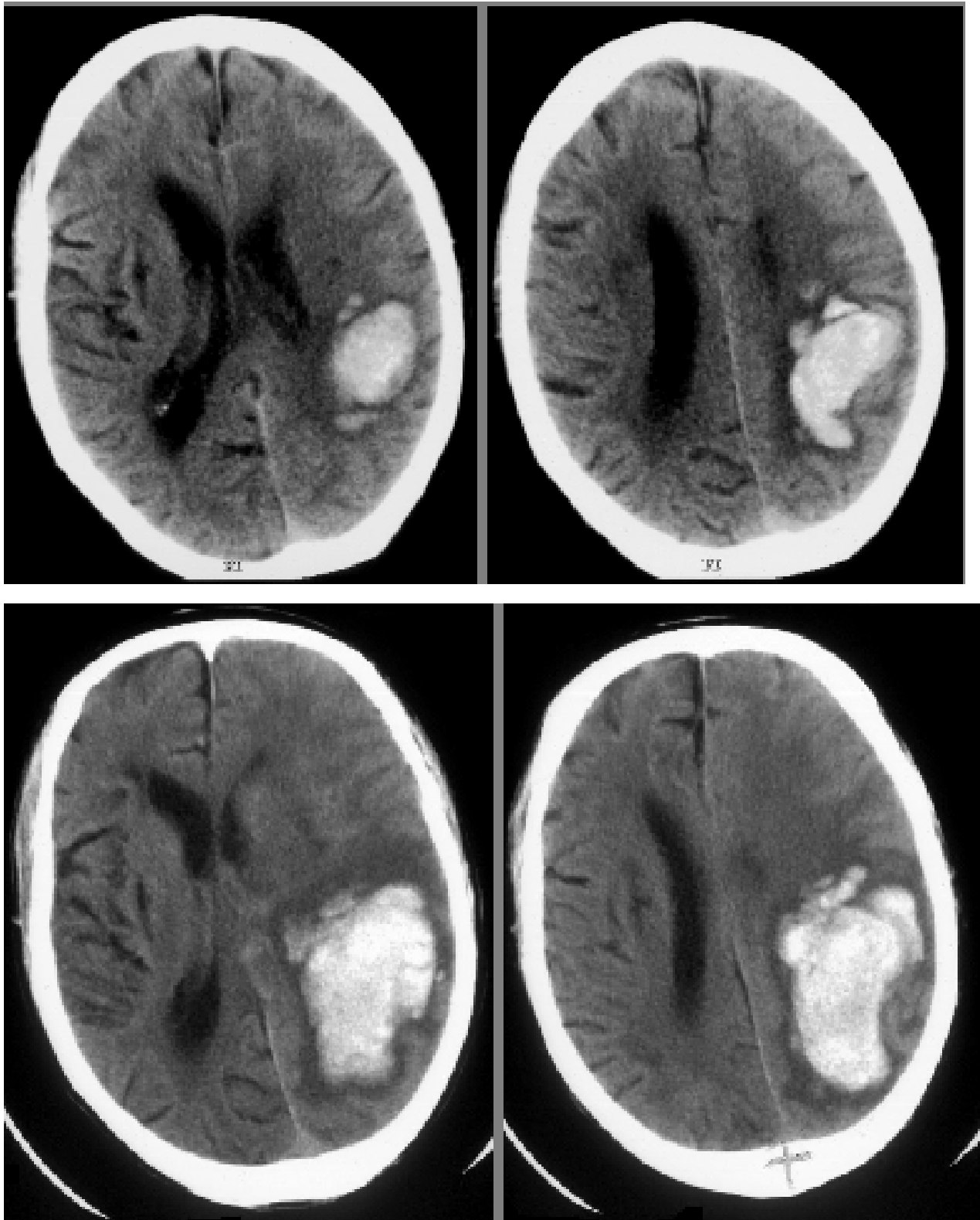


Figure 1. The top two scans were performed three hours after hospital admission. The bottom two scans were performed six hours later because of clinical deterioration and demonstrate substantial growth in the intracranial haemorrhage (Reproduced with permission from Davis SM, Kaye AH. Therapy for intracerebral haemorrhage. *J Clin Neurosci* 2005;12:219-220.)

any approach to blood pressure management. An innovative trial INTERACT (Anderson *et al* 2005 – personal communication) is aiming to randomise patients to either rapid normalisation of blood pressure using intravenous therapy, versus the rather conservative approach advocated in current guidelines.

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