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CLEAR Intraventricular Hemorrhage More Than a Glimmer of Hope

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See related article, pages 3009–3016.

Stroke unit care, intravenous thrombolysis, and endovascular treatment of acute ischemic stroke have changed stroke medicine dramatically. In the past decades, the chances of surviving acute ischemic stroke without severe handicap have increased substantially for the majority of stroke patients. However, the outlook for patients with intracerebral hemorrhage is still gloomy. There has been only little progress for treatment of acute intracerebral hemorrhage.

Cerebral hemorrhage that is not related to trauma or coagulopathy, neoplasm, or vasculopathy accounts for 10% to 20% of the stroke burden worldwide. Treatment of arterial hypertension is the most effective means to reduce this part of the stroke burden. Both primary and secondary preventive studies have shown the effectiveness of blood pressure lowering to decrease the risk of so-called spontaneous or primary hemorrhage.^{1,2} Nevertheless, acute intracerebral bleedings do occur, even if prevention is optimized.

Several interventions in the acute stage that aimed at reduction of hematoma enlargement, improvement of perihematoma perfusion and hypometabolism, and reduction of vasogenic edema raised hope that modern medicine would become effective to improve outcome after cerebral hemorrhage. This hope was generated because of uncontrolled or small randomized studies, but it did not come true after larger trials. The most illustrative examples are the phase II and phase III trials with recombinant factor VIIa.^{3,4} Treatment with recombinant factor VIIa within 4 hours after the onset of intracerebral hemorrhage limited the growth of the hematoma, reduced mortality, and improved functional outcomes at 90 days in the phase II trial but failed to improve survival or functional outcome in the larger phase III study. Nevertheless, there is still a small glimmer of hope that a subgroup of patients might benefit from recombinant factor VIIa.⁵ This and many other intervention trials for acute intracerebral hemorrhage taught us that there is not a similar intervention for cerebral hemorrhage like intravenous thrombolysis for ischemic stroke, which helps more or less all the patients. Treatment of acute intracerebral hemor-

rhage turns out to be more complicated and needs to be tailored according to the clinical presentation and individual hemorrhage characteristics.

At present, there are several targets of intervention undergoing evaluation in large randomized hemorrhage trials. A phase II randomized study has shown that aggressive lowering of blood pressure reduces hemorrhage growth and improves outcome. This is currently investigated in INTERACT II, a large phase III study.⁶ In patients with a spot sign on CT who are at high risk for hemorrhage, growth recombinant factor VIIa is further tested in a phase II study, the STOP IT or SPOTRIAS trial.⁶ In STICH, early surgical evacuation of a supratentorial hematoma did not provide a benefit as expected and there was no overall benefit, but subgroup analyses indicated an advantage for patients with lobar bleedings that are <1 cm away from the brain surface.⁷ Whether this will turn out to be correct when prospectively studied will be answered by STICH II.⁸ Unlike subcortical bleeding, hemorrhages with a deep location did not benefit at all in STICH. However, these hemorrhages have a propensity to rupture into the ventricles and, according to animal studies and open series outcome, seem to improve when the blood is cleared from the ventricles more rapidly.

Intracerebral hemorrhage with rupture into the ventricles is the most frequent cause of intraventricular hemorrhage, more frequent than intraventricular hemorrhage from aneurysm rupture or the rare bleedings from intraventricular arteriovenous malformations or tumors. A recent study showed that 45% of intracerebral hemorrhages rupture into the ventricles.⁹ Patients with larger hematomas and caudate or thalamic locations tend to bleed more often into the ventricles, and patients with intraventricular extension have a worse outcome. The volume of intraventricular hemorrhage is an important determinant of outcome in supratentorial intracerebral hemorrhage.¹⁰

In this issue of *Stroke*, Naff et al¹¹ report the results of a phase II trial to clear blood from the ventricles in patients with small supratentorial intracerebral hemorrhage (<30 mL) and massive intraventricular bleeding. All patients had an extraventricular drainage and were randomized within 24 hours to receive 3 mg/3 mL of recombinant tissue-type plasminogen activator (rtPA) or 3 mL of normal saline injected via the extraventricular drainage into the ventricular spaces every 12 hours until CT evidence of clot resolution was sufficient to remove the catheter. With 18% per day, the blood clot resolution was significantly higher in the rtPA-treated patients compared to 8% per day for the placebo-treated patients ($P<0.001$), and treatment duration was shorter. Mortality and complications such as bleeding events were similar in both treatment arms, although there was a

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trend toward more bleedings with use of rtPA. Mortality was 19% in the rtPA-treated group and 23% in the placebo group. Ventriculitis occurred among 8% and 9%, respectively, and symptomatic bleeding was reported for 23% of the rtPA-treated group and 5% of the placebo group. There was also a trend toward better clinical outcome at 30 days. The prespecified functional outcome measures were all improved in the rtPA group: Glasgow Outcome Scale was <2 (57% rtPA versus 64% placebo); modified Rankin Scale score was <4 (52% rtPA versus 27% placebo); National Institutes of Health Stroke Scale score was <10 (54% rtPA versus 29% placebo); and Barthel Index was >80 (19% rtPA versus 18% placebo).

Questions that arise or remain after this successful phase II study are whether rtPA is the right thrombolytic agent and whether the right dose has been selected. Most of the work using animals has been performed with urokinase, and most of the reported patients before this study were treated with urokinase, even by the principal investigators of this study. Experimental and clinical work has shown that rtPA might be toxic, enhances edema formation, and might potentially not be the best choice among thrombolytic agents.^{12–14} The principal investigators of this trial were forced to terminate an earlier study because commercial withdrawal of urokinase in the United States precluded additional enrollment of patients.¹⁵ Was the choice of rtPA in this study a regulatory issue, or is there a good scientific reason for the selection of rtPA?

Nevertheless, the investigators have made a great achievement and they have to be congratulated for this successful phase II trial. With their study they have given more than a glimmer of hope to patients with cerebral hemorrhage and rupture into the ventricles. They have shown the feasibility and safety of accelerated clearing of blood from the ventricles with the help of rtPA, and this treatment has to be and will be studied further in a phase III trial. CLEAR III, a phase III study, and DITCH, a smaller trial in the Netherlands, are already underway.⁶ However, the current phase II study also shows the slippery slope of using thrombolytics in cerebral hemorrhage. It is nothing else but logical to accelerate clot removal with rtPA, but there is a trend toward more bleeding complications with rtPA. This could be a signal that the expected benefit of rtPA might easily turn into harm. Let us hope that this will not be the case!

Disclosures

None.

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KEY WORDS: intracerebral hemorrhage ■ intraventricular hemorrhage ■ extraventricular drainage ■ cerebral hemorrhage treatment ■ randomized trial