From Medscape Education Clinical Briefs

Low-Dose rtPA Hastens Clot Removal in Brain Hemorrhage

News Author: Fran Lowry
CME Author: Hien T. Nghiem, MD Faculty and Disclosures
CME Released: 11/15/2011; Valid for credit through 11/15/2012

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CLINICAL CONTEXT

Cerebral hemorrhage that is not related to trauma, coagulopathy, neoplasm, or vasculopathy accounts for 10% to 20% of stroke burden worldwide. The most effective means to reduce this part of the stroke burden is the treatment of arterial hypertension. However, even if prevention is optimized, acute intracerebral hemorrhage (ICH) occurs. Patients with ICH and intraventricular hemorrhage (IVH) have a reported mortality rate of 50% to 80%. Animal models have demonstrated significant benefits associated with early removal of blood clots from either the ventricle or the intraparenchymal spaces. Currently, limited attention has been devoted toward measuring the efficacy of clot removal.

The aim of this study by Hanley and colleagues was to evaluate a clot lytic treatment strategy for these patients regarding mortality, ventricular infection, bleeding safety events, and its effect on the rate of intraventricular clot lysis.

STUDY SYNOPSIS AND PERSPECTIVE

A clot lytic treatment strategy with low-dose recombinant tissue-type plasminogen activator (rtPA) speeds clot removal in patients with ICH that is complicated by IVH, results of a phase 2 trial confirm.

Moreover, it does so with an "acceptable safety profile compared to placebo and historical controls," the authors, led by Neal Naff, MD, from Johns Hopkins University, Baltimore, Maryland, write.

One caveat with the novel treatment, however, is that it appears to be associated with more bleeding, senior author Daniel F. Hanley, MD, also from Johns Hopkins, told *Medscape Medical News*. Still, the aim in treating this condition, which can be almost 100% fatal, is to reduce the patient's exposure to blood, thereby reducing injury to the brain.

"This drug has to be used carefully because of the increased risk of bleeding, but it will dissolve the blood clot that has formed in the intraventricular space," Dr. Hanley said. "Most of the blood clot is like an iceberg that sits under the water, doing nothing. Getting that blood clot out eliminates one big part of that iceberg that can damage the brain."

Results of this phase 2 trial were published in the November issue of *Stroke*.

Clot Resolution

The current study was done to assess the safety of low-dose rtPA administered via extraventricular drainage catheter for the treatment of ICH with massive IVH with regard to mortality, ventricular infection, and bleeding events.

The study also tested whether administration of 3 mg of rtPA via external ventricular device (EVD) every 12 hours increased the rate of intraventricular clot lysis compared with placebo (normal saline)-irrigated catheters.

The study included 48 patients aged between 18 and 75 years with a small supratentorial ICH of 30 mL or less and massive IVH. All had an EVD already placed for the treatment of obstructive hydrocephalus.

A computed tomography scan was done to ensure that the EVD had been properly placed and that the clot was stable.

The patients were then randomly assigned to receive either 3 mg/3 mL of rtPA (n = 26 patients) or 3 mL of normal saline (n = 22 patients) injected into the ventricular spaces via the EVD. This continued every 12 hours until computed tomography showed that clot resolution was sufficient for safe removal of the catheter or until the

occurrence of symptomatic bleeding, infection, or death.

The median duration of dosing was 7.5 days for rtPA and 12 days for placebo.

The researchers report that the frequency of death and ventriculitis was substantially lower than expected.

The predicted 30-day mortality was 75% for both treatment groups. The actual mortality was 19% in the rtPA-treated group and 23% in the placebo group. Ventriculitis occurred in 8% of the rtPA-treated group and 9% of the placebo group.

Symptomatic bleeding was higher with rtPA, affecting 23% of patients compared with 5% of patients receiving placebo (P = .1).

The study showed that the greatest amount of lysing activity in patients receiving rtPA occurred during the first 3 days.

There was a significant beneficial effect of rtPA on the rate of clot resolution. The authors report that the estimated resolution for rtPA-treated patients during the first 3 days was 22.3% per day (95% confidence interval, 16.7% - 28.0%), and for patients receiving placebo, it was 9.9% per day (95% confidence interval, 3.5% - 16.2%).

As a result of these findings, the researchers concluded that low-dose rtPA for the treatment of ICH with IVH has an acceptable safety profile and call for more data from a "well-designed phase 3 clinical trial, such as [Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR)] III," to fully evaluate the treatment.

"We concluded that because there was no difference in infection, no difference in death rate, and the difference in bleeding rate was not statistically significant," Dr. Hanley explained.

He added that the dose of rtPA should probably be lower, "or at least lower doses should be tested," because of the increased bleeding that was seen in this study.

This treatment strategy for ICH with IVH has been explored in other studies by the same group.

In 2008, at the 17th European Stroke Conference, Dr. Hanley presented results of the CLEAR-IVH trial, which showed that administration of 1 mg of tissue plasminogen activator every 8 hours for up to 4 days reduced expected mortality by 70% and also resulted in a dramatic improvement in functional outcomes in patients with IVH.

The next year, at the American Stroke Association International Stroke Conference 2009, Dr. Hanley announced that the National Institutes of Health was set to fund a multicenter, 500-patient study to expand on the findings of the CLEAR-IVH trial.

Finally, in July 2010, the American Heart Association/American Stroke Association released a new guideline on the management of spontaneous ICH, emphasizing that ICH is a very treatable disorder.

The new guideline makes mention of the CLEAR-IVH trial, noting that the efficacy and safety of intraventricular rtPA in IVH are still "uncertain and considered investigational."

"Great Achievement"

In an accompanying editorial, Heinrich P. Mattle, MD, and Andreas Raabe, MD, from the University of Bern in Switzerland, point out that the results raise the issue of whether rtPA is the best thrombolytic for this application. Most of the animal and early patient work with this approach was done with urokinase, and there is some evidence to suggest rtPA may be toxic or enhance formation of edema, they write.

In fact, they note, "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. Was the choice of rtPA in this study a regulatory issue, or is there a good scientific reason for the selection of rtPA?"

Nevertheless, they conclude that Dr. Naff, Dr. Hanley, and their team "have made a great achievement and they have to be congratulated for this successful phase 2 trial."

The editorialists concur with the researchers that the treatment must be studied in further phase 3 trials and point out that CLEAR III is already underway, as is the Dutch Intraventricular Thrombolysis after Cerebral Hemorrhage study (DITCH), a smaller trial being conducted in the Netherlands.

They also voice concern about the bleeding that was seen in the rtPA-treated patients.

The current study "shows the slippery slope of using thrombolytics in cerebral hemorrhage," they note. "It is nothing else but logical to accelerate clot removal with rtPA," but the trend toward more bleeding "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!" they conclude.

The trial was supported by grants from the Office of Orphan Products Development, US Food and Drug Administration. Johns Hopkins has applied for a use patent, and Genentech has licensed this patent, for use of rtPA. Dr. Naff reports receiving funding from the American Heart Association. Dr. Hanley, Dr. Mattle, and Dr. Raabe have disclosed no relevant financial relationships.

Stroke. 2011;42:2999-3000, 3009-3016. Abstract, Editorial

STUDY HIGHLIGHTS

- In this phase 2 trial, 48 patients were enrolled at 14 centers and were randomly assigned to treatment with 3 mg of low-dose rtPA (n = 26) or to placebo (n = 22).
- Inclusion criteria were patients 18 to 75 years old who experienced a small supratentorial ICH (≤ 30mL) with massive IVH. Also, these patients must already have had an EVD placed for treatment of obstructive hydrocephalus per standard of care, and could be randomly selected within 24 hours of diagnostic CT scan showing an IVH.
- CT scans were performed daily to monitor for asymptomatic bleeding and measure clot resolution while the patients received rtPA or placebo administration, and once between days 28 and 32 after enrollment.
- Genentech provided the Activase for the trial. Those administering the study medication and nursing personnel were blinded to whether the patient received rtPA or placebo.
- The rtPA/placebo administration was continued every 12 hours until CT evidence of clot resolution was sufficient to remove the catheter or until the safety endpoint (symptomatic bleeding, infection, or death) occurred, whichever came first.
- All adverse events and endpoints were reviewed in an unblinded manner by an independent Data Safety and Monitoring Board consisting of 2 neurologists, a neurosurgeon not associated with the study, and the study statistical consultant.
- The following criteria were prespecified to trigger early Data Safety and Monitoring Board analysis and possible study suspension: 30-day survival rate of less than 25%, rate of symptomatic rebleeding (clot enlargement with concurrent decline in Glasgow Coma Scale of > 2) of more than 35%, and a rate of infection (fever and positive result on cerebrospinal fluid culture) of more than 30%.
- Demographic characteristics, severity factors, safety outcomes (mortality, infection, bleeding), and rates of clot resolution were compared in the 2 groups.
- Results demonstrated a significant beneficial effect of rtPA on the rate of clot resolution (18% per day vs 8% per day for placebo-treated patients; $P < .001$).
- This effect was associated with a higher rate of successful removal of the catheter at the end of the rtPA vs placebo administration (50% vs 20%), less reliance on 3 or more EVDs (4% vs 32%), and shorter length of treatment.
- The median duration of dosing was 7.5 days for rtPA and 12 days for placebo.
- Improved 30-day outcomes for rtPA-treated patients were observed for all prespecified functional outcomes:

- Glasgow Outcome Scale was 2 or less (57% rtPA vs 64% placebo).
- The modified Rankin Scale score was 4 or less (52% rtPA vs 27% placebo).
- The National Institutes of Health Stroke Scale score was 10 or less (54% rtPA vs 29% placebo).
- The Barthel Index was 80 or higher (19% rtPA vs18% placebo).

- Severity factors, including the admission Glasgow Coma Scale, ICH volume, IVH volume, and blood pressure were evenly distributed. Adverse events were also evenly distributed, except for an increased frequency of respiratory system events in the placebo-treated group.
- Neither intracranial pressure nor cerebral perfusion pressure differed substantially between the treatment groups on presentation, with EVD closure, or during the active treatment phase.
- Frequency of death and ventriculitis were substantially lower than expected, and bleeding events remained below the prespecified threshold for mortality (18% rtPA vs 23% placebo), ventriculitis (8% rtPA vs 9% placebo), symptomatic bleeding (23% rtPA vs 5% placebo, which approached statistical significance [*P* = .1]).
- Mortality rate was 19% in the rtPA-treated group and 23% in the placebo group.

CLINICAL IMPLICATIONS

- Mortality rates for patients with ICH with associated IVH range from 50% to 80%.
- Low-dose rtPA for the treatment of ICH with accompanying IVH has an acceptable safety profile compared with placebo and historical controls.

CME TEST

To receive *AMA PRA Category 1 Credit*™, you must receive a minimum score of 70% on the post-test.

A 70-year-old woman with a history of hypertension and diabetes mellitus presents to the hospital with an ICH with associated IVH. You are making rounds at the hospital and meet her family at the bedside. They ask you what the mortality rate is for this type of stroke. You inform them that the *most* accurate range is from:

- ○ 10% to 20%
- ○ 30% to 50%
- ○ 50% to 80%
- ○ 80% to 100%

According to this study by Hanley and colleagues, compared with the placebo group, treating the patient in Question #1 with low-dose rtPA would lead to higher rates of the following outcomes *except*:

- ○ Blood clot resolution per day
- ○ Ventriculitis
- ○ Symptomatic bleeding
- ○ Improved 30-day outcomes

Save and Proceed