MAYO CLINIC

REVIEW

Update on Intravenous Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke

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Abstract

The controversial field of interventional stroke neurology has attracted considerable interest within the stroke community, but no endovascular interventional therapies have proved to be superior to intravenous (IV) recombinant tissue plasminogen activator (rtPA), the standard of care for patients with acute ischemic stroke. In this article, we review the evidence and background of IV thrombolysis for stroke, the clinical application of IV rtPA in practice, and the management of potential complications after thrombolysis. We conducted this review using a search of PubMed for articles published from January 1, 1995, to October 31, 2013, with the following terms: *ischemic stroke*, *tissue plasminogen activator*, *TPA*, *alteplase*, *thrombolysis*, and *intracranial hemorrhage*. Articles were also identified through searches of reference lists and the authors' files. In nearly 2 decades since the publication of the transformative National Institute of Neurological Disorders and Stroke trials, the efficacy and safety of IV rtPA has been consistently verified in international real-world clinical practice. Time from stroke symptom onset to thrombolysis is crucial and probably the most important determinant of success of IV therapy. Thus, optimal care of patients with acute stroke should include community education and standardized protocols to guide immediate patient assessment and triage to medical centers with capability for efficient neurologic assessment, brain imaging, drug administration, and specialized postthrombolysis care.

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The availability of intravenous (IV) recombinant tissue plasminogen activator (rtPA) has dramatically transformed the approach to acute ischemic stroke. As recently as just 2 decades ago, no emergent therapies for stroke were proven to be safe or effective in improving outcomes, and patient care was focused on supportive measures, rehabilitation, and secondary stroke prevention. Progress in preventive measures for cerebrovascular disease and in acute care have helped lower stroke from the third to the fourth leading cause of death in the United States, but it remains a major cause of long-term disability.[1] The cumulative poststroke disability burden is likely to become a growing problem for society as an increasing number of people survive their strokes because of developments in the medical field. Since the publication of the pivotal National Institute of Neurological Disorders and Stroke (NINDS) IV rtPA trials in 1995,[2] IV rtPA has become standard therapy for patients presenting within 3 hours of onset of acute ischemic stroke. Recent advances in the field center around interventional stroke neurology and direct intra-arterial therapies, which have captured considerable interest of researchers, clinicians, and medical device companies. Yet despite a sound pathophysiologic rationale and promising results from nonrandomized studies, treatment of patients with endovascular therapy has not proved to be superior in improving patient outcomes compared with IV rtPA.[3,4]

In this article, we review the evidence and background of IV thrombolysis for stroke, the clinical application of IV rtPA in practice, and the management of potential complications after thrombolysis. We conducted this review using a search of PubMed for articles published from January 1, 1995, to October 31, 2013, with the following terms: *ischemic stroke*, *tissue plasminogen activator*, *TPA*, *alteplase*, *thrombolysis*, and *intracranial hemorrhage*. Articles were also identified through searches of reference lists and the authors' files.

REVIEWING THE EVIDENCE

Results of the NINDS rtPA Stroke Study[2]—a trial of 624 patients randomized to receive IV rtPA (0.9 mg/kg, maximum 90 mg) or placebo within 3 hours of ischemic stroke onset—revealed that IV rtPA increases the chance of achieving a

ARTICLE HIGHLIGHTS

- Intravenous (IV) recombinant tissue plasminogen activator (rtPA) remains the only proven therapy for acute ischemic stroke and is most effective when given early.
- There is evidence that the "therapeutic window" for IV rtPA can be extended to 4.5 hours for most patients with stroke who are less than 80 years old, but efficacy and safety are greatest when thrombolytic therapy is administered within the first 3 hours.
- Factors most predictive of prognosis include onset to treatment time, stroke severity (National Institutes of Health Stroke Scale score), age, and blood glucose levels.
- The most feared complication of IV rtPA is symptomatic intracranial hemorrhage, which occurs in 2% to 6% of patients.
- Postthrombolysis intracranial hemorrhage should prompt neurosurgical evaluation, strict blood pressure control, and consideration of antifibrinolytic agents, cryoprecipitate, and platelet transfusion.

3-month complete or nearly complete neurologic recovery by at least 30%. The proportion of patients achieving 3-month favorable outcome (modified Rankin Scale score of $\leq$1) was 39% in the rtPA group and 26% in the placebo group (P=.019). Intracranial hemorrhage (ICH) occurred more often in the rtPA-treated group (6.4% vs 0.6%), and the rate of severe systemic hemorrhage was less than 1%. Mortality rates were not significantly different between the groups (21% vs 17%). Absence of hemorrhage on noncontrast computed tomography (CT) was the only radiologic condition for proceeding with thrombolysis in this trial. However, on US Food and Drug Administration approval of IV rtPA for acute stroke, an additional radiologic exclusion criterion, the presence of multilobar low-attenuation changes on baseline CT, was added on the basis of exclusion criteria from the early European Cooperative Acute Stroke Study (ECASS) trials.[5-7] Intravenous rtPA is most effective when given shortly after symptom onset. In the NINDS study sample, after adjustment for stroke severity, patients treated within 90 minutes had significantly increased odds of improvement at 24 hours and favorable 3-month outcome compared with patients treated beyond 90 minutes (odds ratio [OR], 2.11 vs 1.69).[8] This result has been consistently found in subsequent studies. In a recent analysis of 58,353 IV rtPA—treated patients from the national Get With The Guidelines—Stroke registry, faster onset to treatment time, in 15-minute increments, was associated with reduced mortality (OR, 0.96; 95% CI, 0.95-0.98), reduced symptomatic ICH (OR, 0.96; 95% CI, 0.95-0.98), and increased rate of independent ambulation at hospital discharge (OR, 1.04; 95% CI, 1.03-1.05).[9]

Following approval of IV rtPA for the treatment of acute ischemic stroke by the US Food and Drug Administration in 1996, rtPA gained international acceptance, and its effectiveness and safety have been repeatedly confirmed by several postmarketing observational studies of real-world clinical practice. One of the largest was SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study), which included 6483 patients from nearly 300 centers in 14 European countries.[10] The rate of symptomatic ICH (sICH) in this population at 24 hours was only 1.7%, and the 3-month mortality rate was 11.3%. These unfavorable events occurred at lower rates than those reported in the pooled analysis of earlier randomized trials of IV thrombolysis for stroke, and even centers with very limited IV thrombolysis experience achieved good results. The lower rate of sICH is likely due to a different definition of sICH in this study (parenchymal hemorrhage in >30% of infarcted area with substantial mass effect combined with neurologic deterioration of $\geq$4 points on the National Institutes of Health Stroke Scale [NIHSS] or leading to death).[10] Although treatment with IV rtPA has become standard of care for patients with acute ischemic stroke, only 3% to 5% actually receive the therapy.[11-13] Utilization is increased in academic teaching medical centers—particularly those with neurology training programs—but still is generally less than 5%.[14] The main reason for this low rate is that many patients present for medical attention beyond 3 hours after symptom onset. This delay has led to interest in expanding the therapeutic window for IV rtPA. In 2004, a pooled analysis of 6 trials of IV rtPA administered up to 6 hours after symptom onset suggested that a clinical benefit may exist even when rtPA was administered beyond 3 hours.[15] This analysis confirmed that efficacy is greatest when IV rtPA is given within 90 minutes of symptom onset but showed similar efficacy between time to treatment of 91 to 180 and 181