Thrombolytic Therapy Within 3 to 6 Hours After Onset of Ischemic Stroke
Useful or Harmful?
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Background—The use of recombinant tissue plasminogen activator (rtPA) within 3 hours after onset of an ischemic stroke is an established therapy. Because the use of intravenous rtPA beyond a time window of 3 hours after stroke onset is still a matter of debate, we sought to review the evidence for the use of thrombolytic therapy in a time window up to 6 hours after onset of symptoms of ischemic stroke.

Summary of Review—The meta-analyses of the major trials (National Institute of Neurological Disorders and Stroke rtPA Stroke Study, European Cooperative Acute Stroke Study [ECASS] I, ECASS II) showed a benefit of thrombolytic therapy with intravenous rtPA even within 6 hours after onset of symptoms of ischemic stroke. The rate of intracerebral hemorrhage was slightly increased in the 6-hour time window compared with the 3-hour time window (odds ratio, 3.23 versus 2.68), but this was without statistical significance because of wide confidence intervals. A positive effect of 37% relative odds reduction with the use of a dichotomization of ≤2 versus ≥3 on the modified Rankin Scale remains for rtPA treatment within 6 hours. However, the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) Study, in which a 3- to 5-hour time window was used, failed to show a benefit of rtPA. Still, when the results of ATLANTIS are included into meta-analyses such as the Cochrane Library, the positive effect of rtPA treatment in the 6-hour time window remains, with a "number needed to treat" value of 11. Treating patients only within a 3- to 6-hour time window would lead to a number needed to treat value of 25.

Conclusions—Consequently, from our point of view it appears unjustified to limit thrombolytic therapy to 3 hours. Because of lack of approvals for 3 to 6 hours, thrombolytic therapy within this time window should be done only as part of an institutional protocol after extensive information is obtained from the patient and the patient’s relatives. Better methods for patient selection are required; in particular, newer MRI techniques, such as diffusion- and perfusion-weighted imaging, can play a key role. The aim is to qualify and individualize the time window according to the findings in each patient’s imaging results rather than to use a strictly time-defined therapeutic window. (Stroke. 2002;33:1437-1441.)

Key Words: stroke, ischemic ▪ thrombolysis ▪ time factors ▪ tissue plasminogen activator

The management of stroke has undergone significant development over the past decade. Perhaps the single most important landmark has been the approval of recombinant tissue plasminogen activator (rtPA) for the intravenous treatment of ischemic stroke by the Food and Drug Administration and several other institutions.

This approval was based primarily on the results of the National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Study, which used a 3-hour time window. In addition, the Stroke Council of the American Heart Association in 1996 stated that intravenous rtPA treatment within 3 hours was a grade A recommendation. The benefit of intravenous rtPA for acute ischemic stroke beyond 3 hours from onset of symptoms has not been established. The European Stroke Initiative, however, concluded in 2000, as level I evidence, that the benefit from the use of intravenous rtPA for acute ischemic stroke beyond 3 hours after onset of symptoms is less than in the first 3 hours but is present in selected patients.

Because the use of intravenous rtPA beyond a time window of 3 hours after stroke onset is still a matter of debate, we sought to review the evidence for the use of thrombolytic therapy in a time window up to 6 hours after onset of symptoms of ischemic stroke.

Important Trials and Meta-analyses of Thrombolytic Therapy in Stroke

NINDS rtPA Stroke Study
In the NINDS rtPA Stroke Study, 624 patients were treated with rtPA (0.9 mg/kg) or placebo within 3 hours of onset of
symptoms. As a part of the protocol, half of the patients were treated within the first 90 minutes after stroke onset. The primary end point was the clinical outcome after 3 months measured by Barthel Index, modified Rankin Scale (mRS), Glasgow Outcome Scale, and National Institutes of Health Stroke Scale (NIHSS). In addition, the results of these 4 scales were combined into a global statistic. Regarding this primary end point, there was a significant improvement in outcome after 3 months in patients treated with rtPA. The rtPA-treated patients had a 30% higher probability of recovering with little or no deficit after 3 months. The absolute percent difference in the rtPA-treated patients was 11% to 13% compared with placebo.1

After adjustment for NIHSS as a covariate, an onset-to-treatment interaction was detected (P=0.09): the adjusted odds ratio (OR) for a favorable 3-month outcome associated with rtPA was 2.11 (95% CI, 1.33 to 3.35) in the 0- to 90-minute stratum and 1.69 (95% CI, 1.09 to 2.62) in the 91- to 180-minute stratum.4 The positive effect of rtPA treatment was seen despite a 5.8% increase in the absolute risk of symptomatic intracerebral hemorrhage (ICH) within 36 hours among rtPA-treated patients (6.4% versus 0.6%). In a secondary analysis, the only variables independently associated with an increased risk of symptomatic ICH in the NINDS trial were the severity of the initial neurological deficit, as measured by the NIHSS, and the presence of brain edema or mass effect by CT before treatment. The bleeding rate was not influenced by the time to treatment.4,5

**European Cooperative Acute Stroke Study**

The European Cooperative Acute Stroke Study (ECASS) randomized 620 patients to either treatment with intravenous rtPA (1.1 mg/kg) or placebo within 6 hours after stroke onset. The intention-to-treat analysis failed to show a significant difference in functional outcome measured by the Barthel Index and the mRS after 90 days. After exclusion of the patients with protocol violation, a significant improvement was seen in this prospectively defined target population.6

If the global end point analysis of the NINDS trial is applied to the data of the ECASS patients, ECASS is positive in the intention-to-treat analysis. The global end point statistic shows a significant increase of favorable outcome in the rtPA-treated patient group (OR, 1.5; 95% CI, 1.1 to 2.0; P=0.008).7

ECASS did not evaluate symptomatic ICH but evaluated hemorrhagic events divided into hemorrhagic infarction and parenchymal hemorrhage. Recent analysis demonstrated that only parenchymal hematomas of larger extent (>30% of the ischemic lesion volume), so-called parenchymal hemorrhage type 2, were associated with an increase of morbidity and mortality after 3 months.8 The risk of parenchymal hematoma of larger extent was increased by 8.8% in patients receiving rtPA (11.1% versus 2.3%) in the intention-to-treatment population of ECASS. Treatment with rtPA did not increase the risk of hemorrhagic infarction. A severe clinical deficit before treatment and the presence of early ischemic changes on CT scan were related to the risk of hemorrhagic infarction. Advanced age was associated with increased risk of parenchymal hemorrhage. For both types of hemorrhagic events, there was no correlation between risk and time to treatment.9

**ECASS II**

ECASS II was a nonangiographic, randomized, double-blind, placebo-controlled trial evaluating the use of 0.9 mg/kg rtPA in 800 patients at 108 centers in Europe as well as Australia and New Zealand.10 Patients were randomized in a stratified manner to receive treatment 0 to 3 or 3 to 6 hours after onset of symptoms. The primary end point was the mRS 90 days after treatment, dichotomized into favorable (score 0, 1) and unfavorable (score 2 to 6) outcome. Furthermore, another dichotomization for independence (mRS score 0 to 2) versus dependence or death (mRS score 3 to 6) was calculated. There was a nonsignificant 3.7% absolute difference (10% relative difference) in the primary end point in favor of rtPA treatment, but the increase of independent patients was significant (54.3% versus 46.0%; P=0.024). The rate of parenchymal hematoma type 2 was increased 10-fold in rtPA-treated patients (8.1% versus 0.8%); this difference did not lead to an excess in mortality in the rtPA group because of a higher rate of fatal outcomes due to space-occupying edema in the placebo group.

The absolute treatment differences in ECASS II were very similar in those patients treated in the first 3 hours of stroke compared with those treated between 3 and 6 hours. This is also true for the bleeding rate (parenchymal hematoma type 2), which was 7% within the first 3 hours and 8.3% between 3 and 6 hours in rtPA-treated patients. However, these results should be viewed with caution because only 158 patients (19.9%) were enrolled in ECASS II within 3 hours of stroke onset (81 rtPA, 77 placebo).

**Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke**

The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study was initially designed to assess efficacy and safety of intravenous rtPA in the time window 0 to 6 hours after symptom onset. Because of safety committee concerns and the results of the NINDS trial, the time window was modified to 3 to 5 hours in February 1996. Primary efficacy end point was an excellent neurological recovery at day 90, defined as a score of ≤1 on the NIHSS. In total, 613 patients were enrolled, 547 of these treated between 3 and 5 hours after symptom onset. In this target population, 32% of the placebo group and 34% of rtPA-treated patients had an excellent recovery at day 90 (P=0.65). An additional analysis of the percentage of patients with independent recovery, defined as a mRS score of ≤2, also showed no treatment effect (54% with rtPA versus 56% with placebo; P=0.75). In the first 10 days, treatment with rtPA significantly increased the rate of symptomatic ICH (7.0% versus 1.1%; P<0.001). Mortality at day 90 was not significantly different (11.0% with rtPA versus 6.9% with placebo; P=0.09).11

**Prolyse in Acute Cerebral Thromboembolism**

The Prolyse in Acute Cerebral Thromboembolism (PRO-ACT) trials evaluated the use of intra-arterial local applica-
tion of recombinant prourokinase versus intra-arterial heparin in patients with angiographically proven proximal middle cerebral artery occlusion. Part 1 tested safety and recanalization rate, and part 2 tested safety and clinical efficacy within a time window of 6 hours. The primary outcome measure of PROACT II was the proportion of patients with slight or no neurological disability at 90 days, as defined by a mRS score of ≤2. Secondary outcomes included middle cerebral artery recanalization, the frequency of ICH with neurological deterioration within 24 hours, and mortality. A meta-analysis included data of several thrombolysis trials.

Meta-analyses

Two meta-analyses included data of several thrombolysis trials. Hacke et al. evaluated the data of the NINDS trial and both ECASS trials, including 2044 patients (1034 rtPA, 1010 placebo). The effects of rtPA treatment on reducing disability and death (mRS score ≤2 versus ≥3), on the occurrence of symptomatic intracerebral bleeding, and on mortality were evaluated. The analyses were stratified for both time windows: 0 to 3 and 0 to 6 hours. It should be kept in mind that comparing bleeding complications between ECASS and the NINDS trial is difficult because of differences in the definition of hemorrhagic events. Accordingly, for this meta-analysis the symptomatic ICH of the NINDS trial and the parenchymal hemorrhages (type 1 and 2) of ECASS were pooled.

For the 6-hour time window, ICH was significantly more frequent in rtPA-treated patients (OR, 3.23; 95% CI, 2.39 to 4.37), but mortality was not different between rtPA-treated patients and placebo patients (OR, 1.07; 95% CI, 0.84 to 1.36). Additionally, within the 3-hour time window the risk for ICH was significantly increased among rtPA-treated patients (OR, 2.68; 95% CI, 1.56 to 4.62); mortality again was not increased (OR, 0.91; 95% CI, 0.63 to 1.32). rtPA treatment led to a significant 37% reduction of disability and death (mRS score ≥3) within 6 hours (OR, 0.63; 95% CI, 0.53 to 0.76) and to a 45% reduction of unfavorable outcome in the 3-hour time window (OR, 0.55; 95% CI, 0.41 to 0.72) (Figure).

In the Cochrane Library, all randomized, placebo-controlled trials of any thrombolytic agent in patients with ischemic stroke were included (NINDS trial, ECASS I and II, ATLANTIS A and B, PROACT I and II, Australian Streptokinase [ASK] Trial, Multicenter Acute Stroke Trial–Europe [MAST-E], Multicenter Acute Stroke Trial–Italy [MAST-I], and several smaller trials). There were 5216 patients in 17 trials, 2889 of them from rtPA trials. Thrombolytic therapy significantly increased the odds of death within the first 10 days (OR, 1.85; 95% CI, 1.48 to 2.32). The main cause of the increase in deaths was fatal ICH after thrombolysis (OR, 4.15; 95% CI, 2.96 to 5.84). Despite this, thrombolytic therapy, administered up to 6 hours after onset, significantly reduced the proportion of patients who were dead or dependent (mRS score ≥3) (OR, 0.83; 95% CI, 0.73 to 0.94). For patients treated within 3 hours of stroke, thrombolytic therapy appeared to be more effective (OR, 0.58; 95% CI, 0.46 to 0.74). Trials testing intravenous rtPA suggest that it may be associated with a lower mortality when given up to 6 hours after onset (OR, 1.24; 95% CI, 0.85 to 1.81).
A meta-analysis with only the data of trials using intravenous rPA for thrombolytic therapy in the 3- to 6-hour time window has not yet been published. The Table shows an analysis of the appropriate data for this time window concerning dependence or death (mRS ≥3) from ATLANTIS, ECASS, and ECASS II, leading to an OR of 0.79 (95% CI, 0.66 to 0.96) in favor of rPA.

### Conclusions for Clinical Practice

Thrombolytic therapy, like other therapies, is associated with both benefit and risk, and it is the balance between these 2 that determines the usefulness of a treatment in clinical practice. The most important risk of thrombolytic therapy is the occurrence of ICH and mortality. The definition of benefit is somehow more difficult. On the basis of the aforementioned trials, a reasonable and meaningful definition of benefit is the reduction in disability and death. This can be evaluated by dichotomizing the data of the mRS; the advantage of this approach is that this information is available from every major trial. For clinical decisions, the “number needed to treat” (NNT) is a convenient and informative way in which to compare the clinical benefits of different therapeutic interventions.

The utility of intravenous thrombolytic therapy within 3 hours after symptom onset in patients with ischemic stroke has been clearly demonstrated; the NNT to prevent 1 death or disability is 7 in this time window. To conclude whether thrombolytic therapy is more harmful the later it is initiated, it is important to know whether an onset-to-treatment effect exists in this time interval. Marler et al² found a decreasing benefit between the first and the second 90-minute time windows of the NINDS trial patients after adjusting for initial stroke severity. In contrast, Demchuk et al¹⁶ could not find this effect in a large cohort of 1025 patients treated with thrombolytic therapy according to the NINDS protocol. In this trial, however, no placebo group existed.

The meta-analyses of the major trials¹⁴,¹⁵ both showed a benefit of thrombolytic therapy with intravenous rPA even within 6 hours after symptom onset of ischemic stroke. The risk of ICH was not increased by time in ECASS or the NINDS trial.⁴,⁹ In the meta-analysis, the rate of ICH was slightly increased in the 6-hour time window compared with the 3-hour time window (OR, 3.23 versus 2.68), but this was without statistical significance because of wide CIs.¹⁴ A positive effect of 37% relative odds reduction with the use of a dichotomization of ≤2 versus ≥3 on the mRS remains for rPA treatment within 6 hours. ATLANTIS, however, failed to show such a positive effect of rPA treatment within 3 to 5 hours after symptom onset. When the patients’ baseline characteristics between ECASS II and ATLANTIS are compared, there were only minor differences in the study population. In particular, the initial stroke severity was not different (median NIHSS score 11 in ECASS II and 10 in ATLANTIS). In both trials, 54% of the rPA-treated patients achieved a favorable outcome (mRS score ≤2). In ECASS II, however, only 46% of the placebo patients had this favorable outcome compared with 56% in ATLANTIS. Thus, no difference exists in ATLANTIS between rtPA-treated and placebo patients. Perhaps the different outcome of the placebo patients is based on a higher rate of ICH in the ECASS placebo group. Still, when the results of ATLANTIS are included into meta-analyses such as the Cochrane Library, the positive effect of rPA treatment in the 6-hour time window remains, with a NNT of 11. Treating patients only within a 3- to 6-hour time window would lead to a NNT of 25.¹⁴ This evidence is supported by several case series.¹⁷–¹⁹

Another argument for the usefulness of thrombolytic therapy within 6 hours after symptom onset is the result of the PROACT trials. The limitation of beneficial effect to only the patients with moderate stroke severity (NIHSS score 11 to 20) and an occlusion of the proximal middle cerebral artery shows that, with growing knowledge, the decision involves not only whether or not to offer thrombolytic therapy but also which modality is the best choice for the individual patient.

Consequently, from our point of view it appears unjustified to limit thrombolytic therapy to 3 hours. Because of lack of approvals for 3 to 6 hours, thrombolytic therapy within this time window should be done only as part of an institutional protocol after extensive information is obtained from the patient and the patient’s relatives.

As demonstrated, in addition to the time window, other variables determine the risk of thrombolytic therapy. In particular, these are initial clinical severity as measured by the NIHSS, the extent of early infarct signs on CT, and patient age.⁵,⁹ Thus, to improve the utility and to decrease the risk of thrombolytic therapy, appropriate patient selection, especially for bleeding prevention, is important. Improvements in neuroradiological methods such as diffusion- (DWI) and perfusion-weighted MRI (PWI) or perfusion CT are very useful.

For risk stratification, it might be helpful to know as early as possible the location and size of an area of irreversible ischemic brain damage, whether there is any additional tissue at risk, and the location of a possible vessel occlusion. Some studies have reported incidences of early CT signs of infarction between 53% and 92% within the first 6 hours for all acute stroke patients.²¹,²² However, conventional CT is not able to show tissue at risk. The advent of new MRI techniques such
as DWI and PWI has revolutionized diagnostic imaging in stroke. DWI may delineate infarcted brain tissue in <1 hour after symptom onset, probably within minutes, although evidence is accumulating that in the very early stage of stroke there may be reversible DWI changes, while PWI defines the area of cerebral hyperfusion. The absolute volume difference or ratio of PWI and DWI reveals the ischemic tissue potentially at risk of irreversible infarction. In addition, MR angiography can reliably assess the cerebral vessel status. Several studies have reported early findings of stroke on MRI within the first 6 to 12 hours, demonstrating the feasibility and practicality of this method in the setting of acute stroke and thrombolytic therapy.

In essence, the presence of a vessel occlusion according to MR angiography is associated with a PWI/DWI mismatch, and the investigation of stroke on MRI may perhaps define the ideal candidate for thrombolysis. Thus, the rather strictly defined therapeutic window may be qualified and individualized according to the findings in each patient’s imaging results. However, because of lack of evidence regarding the usefulness of thrombolytic therapy after 3 hours, it is probably not appropriate for most centers to apply this therapy beyond this time until definitive data are available. Therefore, further studies should be done to answer these underlying questions. Currently, the desmoteplase in acute ischemic stroke trial tests the use of desmoteplase (another lytic agent with longer half-life than rtPA) in a 3- to 6-hour time window for patients with proven vessel occlusion and a significant mismatch revealed by early stroke findings on MRI.

Nevertheless, even if there might be a benefit of thrombolytic therapy in the 6-hour time window as well, it is important to treat patients as early as possible. In particular, the achievement of short onset-to-hospital and door-to-needle times should play a key role in local stroke programs.

References

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