Should the Window for Intravenous Administration of Tissue Plasminogen Activator in the Treatment of Acute Ischemic Stroke be Extended to 4.5 Hours?

THE "PRO" SIDE

In Canada, 50 000 people receive a diagnosis of stroke annually, and 80% of these strokes are ischemic in nature. Every year, more than 14 000 Canadians die as a result of stroke.[1] In the 10 minutes it will take to read this article, approximately 1 person will have a stroke. In the 2 h that one might take out of the day to peruse this journal and read some of the papers, 12 people will have a stroke, of whom perhaps 1 will recover completely, 1 or 2 will die, and 8 or 9 will have restrictions on their activities and will need assistance with the activities of daily living such as dressing, bathing, grooming, feeding, and maintaining personal hygiene.[2]

Until 1995, treatment for acute ischemic stroke was limited to supportive care, a strategy that consisted of watching and waiting. In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) investigated the effects of IV administration of tissue plasminogen activator (tPA) on 624 patients who presented with acute ischemic stroke within 3 h of symptom onset. In that study, there was a 30% relative increase in the likelihood of complete recovery at 3 months for those who received tPA.[3] Unfortunately, the incidence of symptomatic intracerebral hemorrhage was also significantly greater among the patients who received tPA (6.4% vs 0.6%, $p < 0.001$, number needed to harm 17).

Regrettably, only 4% of patients with stroke receive tPA within 3 h of symptom onset.[4] The most quoted reasons for this dismal rate are delays in arrival at the emergency department—only a quarter of stroke victims arrive within 3 h—and fear of higher incidence of symptomatic intracerebral hemorrhage in nonacademic or low-volume institutions, where clinicians are typically less experienced with this type of therapy.[4,5]

Several subsequent investigations and analyses of data in tPA registries have established that the results of the NINDS study can be replicated in clinical practice. In Canada, 37% of patients with acute ischemic stroke who were treated with IV tPA within 3 h of onset had excellent clinical outcomes[4] (indicated by scores of 0 to 1 on the modified Rankin scale, where a score of 0 represents no disability and a maximum score of 6 represents death). In the same registry, symptomatic intracerebral hemorrhage occurred in just 4.6% of patients,[4] a lower rate than in the NINDS study.[3] Most importantly, this investigation demonstrated no differences in rates of excellent outcome or symptomatic intracerebral hemorrhage between high-volume and low-volume centres or between tertiary care and community hospitals. Investigations in the United States and Europe have yielded similar results in terms of both effectiveness and safety, with no significant differences between centres with experienced and inexperienced clinicians.[6-9]

Although the NINDS study demonstrated the efficacy of tPA in the treatment of acute ischemic stroke within 3 h, 3 other studies showed no benefit when tPA was infused 3–6 h after the onset of stroke.[10–12] However, these studies had several limitations. For example, although 80% of the patients were enrolled 3–6 h after onset, with a mean time to treatment of 4.3 h, one of the studies (the European Cooperative Acute Stroke Study or ECASS[10]) did not find a difference in favour of tPA, possibly because of a higher tPA dose (1.1 mg/kg) and significantly more protocol violations in the tPA arm, such that more patients with larger infarcts were assigned to receive tPA than were assigned to receive placebo. Consequently, there was also a significantly higher incidence of parenchymal hemorrhage in the tPA arm.

In the second ECASS study (ECASS II)[11] and the Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study,[12] tPA doses of 0.9 mg/kg were infused. In ECASS II, 80% of the patients received the dose within 3–6 h of stroke onset; in ATLANTIS, a similar percentage received it within 4–5 h of stroke onset. Both studies enrolled patients whose stroke severity was significantly lower than that of patients in the NINDS study. The baseline median score on the National Institutes of Health Stroke Severity score (NIHSS; a measure of stroke severity in which scores range from 0 to 42 and where scores above 25 indicate severe neurological impairment) was 11 in ECASS II, 10 in ATLANTIS, and 14 in the NINDS study. As a result, a greater percentage of patients randomly assigned to receive placebo in ECASS II and ATLANTIS had modified Rankin Scale scores of 0 to 1 than was the case in the NINDS study (37% in ECASS II, 41% in ATLANTIS, 26% in NINDS). Conversely, the percentage of patients with modified Rankin Scale scores of 0 to 1 who were assigned to receive tPA was similar in the 3 studies: 40% in ECASS II, 42% in ATLANTIS, and 39% in NINDS. Both ECASS II and ATLANTIS would have required larger samples sizes to find statistical significance with a smaller difference in outcomes for patients with acute ischemic stroke and lower NIHSS scores. It was encouraging that the rates of symptomatic intracerebral hemorrhage did not increase with the longer time to treatment but remained similar to the NINDS study (6.4% in tPA arm versus 0.6% in placebo arm in the NINDS study and 6.7% in tPA arm versus 1.3% in placebo arm in the ATLANTIS study).

To investigate the relationship between time to treatment with tPA in acute ischemic stroke and functional outcome and clinically relevant hemorrhagic complications, investigators for the NINDs, ATLANTIS, and ECASS studies conducted a pooled analysis.[13] The results indicated that the odds of a favourable outcome at 3 months decreased with increasing time to receipt of treatment, but was significantly different from the odds of a favourable outcome with placebo up to 4.5 h after the onset of stroke. The odds of a favourable outcome were 2.8 (95% confidence interval [CI] 1.8–4.5) among patients who received tPA within 90 min after onset of stroke, 1.6 (95% CI 1.1–2.2) for those who received tPA between 91 and 180 min after onset, 1.4 (95% CI 1.1–1.9) for those who received tPA between 181 and 270 min after onset, and 1.2 (95% CI 0.9–1.5) for those who received tPA between 271 and 360 min after onset. In terms of safety, substantial intracerebral hemorrhage was observed in 5.9% of patients who received tPA but only 1.1% of those who received placebo. Parenchymal hematoma was associated with tPA treatment and age but not with time to treatment.

The recently published ECASS III study[14] examined the effects of tPA in patients with acute ischemic stroke who presented 3 to 4.5 h after stroke onset. Ten percent of the patients received tPA between 3 and 3.5 h after stroke onset, 46.8% between 3.5 and 4 h, and 39.2% between 4 and 4.5 h. Compared with the NINDS study, the patients in ECASS III had milder stroke severity overall (median NIHSS score 9–10). In ECASS III, 52.4% of the patients in the tPA arm and 45.2% of those in the placebo arm had a favourable outcome (modified Rankin Scale score 0–1) (odds ratio 1.34, 95% CI 1.01–1.34; $p = 0.04$). In the adjusted analysis, the odds ratio for a favourable outcome was 1.4 (95% CI 1.02–1.98; $p = 0.04$). It is striking that this odds ratio for a favourable outcome is similar to that calculated for the same treatment period (3 to 4.5 h) in the pooled analysis.[13] The incidence of symptomatic intracerebral hemorrhage was reported as 2.4% in the active treatment arm and 0.3% in the placebo arm (odds ratio 9.85, 95% CI 1.26–77.32; $p = 0.008$). Although this appears to be a much lower incidence of symptomatic intracerebral hemorrhage than the NINDS study criteria, when the NINDS criteria for this complication were applied, the rates were 7.9% in the tPA arm and 3.5% in the placebo arm (odds ratio 2.38, CI 1.25–4.52; $p = 0.006$).[14]

Administration of tPA is the only treatment for acute ischemic stroke that has been shown to increase the likelihood of complete recovery. ECASS III was designed to detect an odds ratio of 1.4 in favour of tPA with 90% power.[14] ECASS II and ATLANTIS would have required much larger samples to show similar results. Furthermore, 80% of the patients in ATLANTIS were enrolled between 4 and 5 h after stroke onset.[12] ECASS III has shown that the therapeutic benefit of tPA diminishes substantially beyond 4.5 h.[14]

The administration of tPA will increase the likelihood of a full recovery if administered within 4.5 h of stroke onset without a substantial increase in symptomatic intracerebral hemorrhage. Applying the study-specific eligibility criteria and extending the time interval will increase the number of patients eligible to receive tPA.[14] However, it cannot be emphasized too strongly that extending this interval should not be an invitation to slacken the timely infusion of tPA. Time is, after all, brain.

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THE "CON" SIDE

Recently, 2 sets of data have fuelled a rush in the stroke community to extend the window for administration of tissue plasminogen activator (tPA) in cases of acute ischemic stroke from 3 to 4.5 h: the Safe Implementation of Thrombolysis in Stroke — International Stroke Thrombolysis Register (SITS-ISTR) study[1] and the European Cooperative Acute Stroke Study (ECASS) III trial.[2] Both studies were published in September 2008, and by December 2008, the Canadian Stroke Network and the Heart and Stroke Foundation of Canada had updated and published their Best Practice Recommendations for Stroke Care[3] to mention only 4.5 h as the relevant treatment window for thrombolysis, removing any mention of the decade-old 3-h window.

This enthusiasm is understandable, but changing thrombolysis criteria deserves careful scrutiny because the benefit-to-harm ratio is razor-thin under the best of conditions.[4] Since 1996, the practice of thrombolysis has been based almost exclusively on trying to replicate the methods and results of the National Institute of Neurological Disorders and Stroke (NINDS) trial.[4] That study showed that 1 of every 8 meticulously selected patients would experience a benefit of thrombolysis (manifested as "minimal or no disability" at 90 days among people who otherwise would have been "slightly disabled" or worse), whereas 1 in 16 would experience thrombolysis-induced symptomatic intracerebral hemorrhage, a condition associated with immediate death in 75% of cases in Canada.[5] This is a narrow therapeutic index of rare gravity in pharmacotherapeutics.

Subordinate to the ECASS III randomized trial, the SITS-ISTR prospective observational study deserves only brief comment.[1] It showed no significant differences in efficacy or toxicity between patients who received thrombolysis before the 3-h mark and those treated between 3 and 4.5 h. This result is not surprising, considering that 60% of the "late" patients were treated within 20 min of the 3-h cutoff, which made the "late" group more like a 3-h group than a 4.5-h group. The younger age and lower stroke severity of these patients might also have obscured clinically meaningful differences. Furthermore, the adjusted odds of symptomatic intracerebral hemorrhage (1.32, 95% confidence interval [CI] 1.00–1.75) suggested that being treated beyond 3 h carried a high probability of being less safe than being treated within 3 h. SITS-ISTR inspires little confidence that treatment within the 3- to 4.5-h window presents a benefit–risk prospect similar to that of earlier treatment.

It was the ECASS III trial, however, that really relaxed the timekeeper's vigil.[2] In this randomized controlled trial, tPA was superior to placebo when given in the 3- to 4.5-h window, with 1 in 14 treated patients achieving a "favourable outcome" as defined in the NINDS trial[4] and 1 in 22 patients experiencing treatment-induced symptomatic intracranial hemorrhage. Setting aside the fact that the patients who received tPA had less severe stroke symptoms at presentation and half as many prior strokes as those in the placebo group (a difference that, by itself, could have explained the barely significant difference in efficacy between the groups), the wisdom of extending the treatment window to 4.5 h on the basis of this trial is faulty for 2 reasons.

First, on the basis of the ECASS III data, the overall clinical benefit of extending the therapeutic window by 90 min will be minimal. In Canada, 80% of the 50 000 strokes that occur each year are ischemic, and only 13% of potentially eligible patients present to a centre that can administer thrombolysis in the 2- to 3.5-h window—that's 5200 patients.[6] This is the population that will be affected by the change in the tPA administration window, because the goal thereafter is 60 min "from door to needle".[3] According to the ECASS III data, treating all of these patients would produce a "favourable outcome" at 90 days in 380 patients, but would also cause 229 cases of symptomatic intracranial hemorrhage, 172 of which would be fatal in the short term.[5] Therefore, the net benefit would extend to only 151 patients. Given that ECASS III showed that 61.4% of patients would have slight, minimal, or no disability following their stroke without tPA, 141 of the 229 patients who would experience treatment-induced intracranial hemorrhage and 106 of the 172 who would die as a direct result of tPA would otherwise survive with slight, minimal, or no disability in a tPA-free world. Even this best-case (least likely) scenario raises serious ethical concerns related to nonmaleficence.

Second, consideration of all of the trials examining thrombolysis beyond the 3-h window reveals meaningful potential for net harm to occur if the window is extended. To focus exclusively on ECASS III is to ignore the results of ECASS I, ECASS II, and the Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study. Combining the results of these 4 trials (and a few other small trials) reveals a more ominous view of treatment beyond 3 h: it benefits 4% of patients and harms 6%.[7] This analysis and others have shown that treatment with tPA beyond 3 h results in a drop in efficacy to roughly one-third of that within the 3-h window.[8] In Canada, this means that treating the 5200 additional patients would result in benefit for 208 and harm to 312, 234 of whom will die as a direct result of the therapy. This does not appear to be a favourable benefit–risk ratio, unless you assume that all patients left with moderate disability or worse consider it a fate worse than death.

In a nutshell, the totality of evidence indicates that the window of 3–4.5 h for thrombolysis has an even narrower benefit–risk ratio than earlier treatment, and under some plausible scenarios the harm exceeds the benefit. Even its most enthusiastic supporters must acknowledge that the uncertainty over the therapeutic tradeoff is greater in the 3- to 4.5-h window than with earlier treatment.

In conclusion, extending the therapeutic window for tPA administration in acute ischemic stroke to 4.5 h is a flawed policy from the viewpoint of the evidence on which it is based and the implications of its practice in Canada. The overall impact would range from minimally beneficial to harmful. Exposing any stroke patient who would have otherwise had a good outcome to an intervention that carries a significant probability of harm (in the form of short-term death) is unacceptable.

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