abstract

Despite the fact that stroke is both common and devastating in older patients, very little randomized controlled data is available on the efficacy or safety of thrombolysis in older age groups. We review literature from both randomized control studies and case series data treating older patients, and look at the hemorrhage rate and mortality associated with thrombolysis. In addition, we examine risk markers, other than age, for a poor outcome. We suggest that older age alone is not a contraindication to thrombolytic therapy.

Key words: *ischemic stroke, tPA, thrombolysis, hemorrhage risk*

Can Older Patients with Acute Ischemic Stroke Be Treated Safely with Thrombolysis?

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Stroke is a major cause of death and disability in older Canadians and the risk of stroke doubles every ten years after the age of 55.[1] Older patients more frequently experience coma, paralysis, swallowing problems, and urinary incontinence in the acute phase of stroke compared to younger patients, as well as a one-month mortality estimated at 21% without thrombolysis.[2] Thrombolysis with recombinant tissue plasminogen activator (tPA) is a licensed treatment for use within three hours of symptom onset in acute ischemic stroke. It offers the prospect of rapid reperfusion and improved outcomes compared to placebo. Key evidence of its efficacy came from the National Institutes of Health Neurological Disorders and Stroke (NINDS) tPA stroke trial, which found that the number needed to treat (NNT) was eight for one additional favourable outcome over placebo. Favourable outcome was defined as a modified Rankin Scale score[3] (mRS) of zero to one (i.e., little or no disability) at three months.[4]

Hemorrhage is the main danger with thrombolysis; in NINDS, the absolute risk of symptomatic intracranial hemorrhage (ICH) was 6% compared to 1% with placebo. Despite the high prevalence and severity of stroke in older people, NINDS was the only one of three major randomized trials of stroke thrombolysis[5,6] to include any patients over the age of 80 years and the number included was just 42 of a total 624 subjects. This makes it difficult to extrapolate directly the risk or benefits of treatment in those over 80 years of age.

Evidence in Older Age Groups

Some evidence is available from retrospective case series studies. Tanne *et al.* compared 30 patients over 80 years of age with 159 younger patients treated with tPA.[7] They found no significant difference in the symptomatic ICH rate between these groups, nor between improvement measured on a stroke scale rating (NIHSS),[8] although the older patients were more likely to be discharged to a nursing care facility (17% vs. 5%, P=0.005). We examined a series of 62 tPA-treated patients aged over 80 years old[9] (Figure 1) and again found a similar rate of symptomatic ICH to NINDS as long as treatment protocols[10] were followed exactly. Encouragingly, a 10-point improvement in NIHSS was seen in 34% of patients; however, at 24% the in-hospital mortality rate was high in our series. Tanne *et al.* also found a high in-hospital mortality of 20% in those aged over 80 years vs. 8% in younger patients (P=0.04), although when they adjusted for baseline characteristics such as stroke severity, there was no statistical difference between the death rate in older and younger patients. Stroke is a devastating occurrence in older adults. The high mortality seen in these tPA-treated series is probably not in excess of the natural history.[1]

A recent, large German stroke registry study of tPA-treated patients[11] included

396 patients who were over 75 years of age out of a total 1,658. As expected, they found that increasing age over 75 years was associated with an increased mortality (multivariate adjusted OR 3.2, 85%CI 1.8–5.7), and a decreased level of consciousness at presentation was associated with higher mortality. They did find an increased risk of symptomatic ICH in older patients of 10.3% in patients >75 years old vs. 4.9% in patients < 55 years old (test for trend, P=0.02). In addition, they reported that the in-hospital mortality rate for those over 75 years of age was 38.6% with tPA treatment compared to only 7.7% in the same age group in the registry who had not been treated with tPA. Importantly, these figures were not adjusted for stroke severity or other patient factors, so it is inappropriate to interpret this as tPA treatment increasing mortality.

Like so many other conditions and treatment options in older patients, we are left to infer the risks and benefits from imperfect data from younger populations. Older patients clearly have a high mortality and morbidity from stroke and they may therefore have the most to gain from prompt reperfusion. The easiest conclusion we can draw from all these studies is that to better assess the efficacy and risk of thrombolysis in older patients we require an older-age–specific randomized controlled trial. However, as Wardlaw *et al.* pointed out in their review of the thrombolysis literature, "treatment effects may differ in magnitude but rarely change direction (e.g., from benefit to harm) in different subgroups of patients."[12] It is likely that patients selected on the basis of their premorbid conditions and without contraindications to tPA have the potential to derive benefit from thrombolysis regardless of their chronological age.[13] What factors other than age, therefore, can guide us in risk stratification for an individual patient?

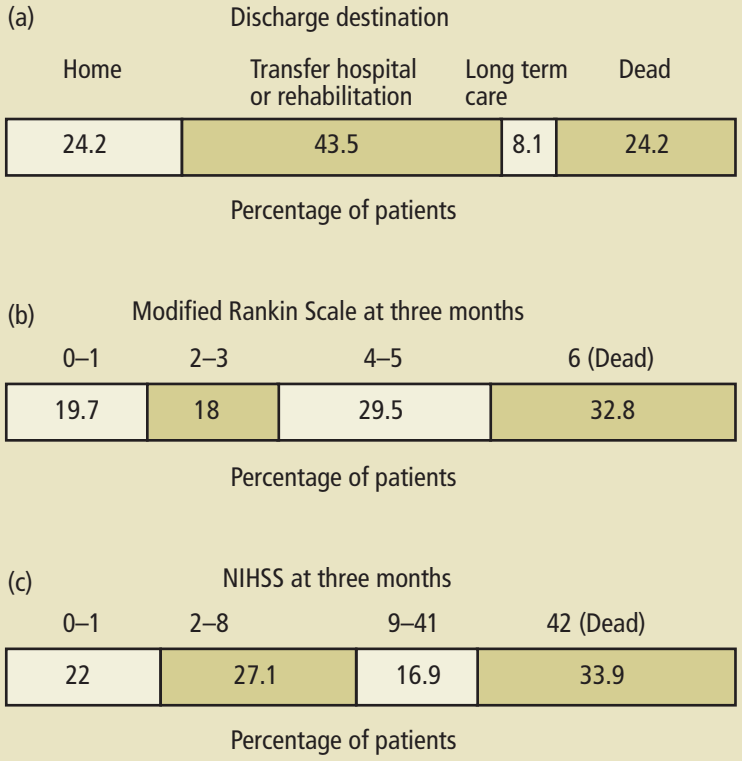

Figure 1: Percentage of Patients by Outcome in a Series of 62 Patients Aged Over 80 Years Old Treated with tPA.
(a) Destination at discharge from Hospital, (b) mRS at three months, (c) NIHSS at three months. The percentage of those dead is not the same as for the mRS because two patients had no NIHSS recorded at follow-up).

Source: Reprinted with permission from Simon JE et al.[9]

Risk Stratification

There are several contraindications to thrombolysis, such as platelet count less than 100,000/mm^3 or INR greater than 1.4, which could predispose a patient to ICH.[10] There are also a number of clinical factors that have been associated with an increased symptomatic ICH rate and a poorer outcome after thrombolysis. These include high glucose, high blood pressure and, in particular, presenting stroke severity,[14,15] although an interaction has been reported between increasing age and both blood pressure and stroke severity.[16] It may be possible to select low hemorrhage-risk older patients by avoiding tPA treatment in those with these added risk factors. The issue of who to treat remains complex, however, because older patients with these hemorrhage risk factors are also the most likely to die or be disabled by their ischemic stroke. The NNT for one additional favourable outcome in such patients may be higher, and the number needed to harm lower, than in younger patients. A NINDS subgroup analysis found no benefit from tPA treatment of patients over 75 years of age with an NIHSS>20, but the number of subjects studied was small.[16]

Imaging factors can also help to stratify risk. Increasing size[15] and hypodensity of early ischemic lesion on CT are predictive of subsequent hemorrhage.[17] Leukoaraiosis is commonly seen on CT or MRI of older patients and raises concern, but although it is associated with primary ICH[18] and with warfarin-related ICH after ischemic stroke,[19] there is only limited current evidence to support that leukoaraiosis indicates an increased risk of hemorrhage after thrombolysis.[20] More specific MR markers for predicting hemorrhage, or to indicate salvageable tissue, are the subjects of ongoing research.[21]

Conclusions

Thrombolysis is only one element in stroke care. All patients, regardless of age, require access to investigations, supportive stroke unit care, rehabilitation, and secondary prevention as appropriate to their individual clinical state. Importantly, age, as a predic-

tor of poor outcome, is much less important than the severity of stroke and the degree of early ischemia seen on acute CT or DWI-MRI brain imaging. Researchers should recognize the high prevalence of stroke in the older age group and abandon upper age limits for enrollment in favour of more biologically relevant exclusion criteria (such as the presence of severe renal or cardiac failure). Not only would these measures be likely to increase the speed at which studies are completed, they would also make the findings more readily applicable to the largest target demographic of stroke therapies. Such data may become available when the International Stroke Trial-3, which aims to enroll 6,000 patients, is completed.

Thrombolysis offers the potential for improved recovery from stroke in a previously nihilistic field. Currently, with the limited evidence available, there is no reason to exclude patients from treatment on the basis of age alone. ◆

In the past five years, Dr. Hill has received honouraria for speaking at educational symposia from Hoffmann-La Roche Canada Ltd., who hold the license for marketing alteplase in Canada.

References

1. The Heart and Stroke Foundation. Statistics & background information—stroke statistics. heartandstroke.on.ca 2002; ww2.heartandstroke.on.ca/Page.asp?PageID=33&ArticleID=1078&Src=news&From=SubCategory.
2. Bhalla A, Grieve R, Tilling K, et al. BIOMED II European study of stroke care. Age Ageing 2004;33:618–24.
3. Rankin J. Cerebral vascular accidents in patients over the age of 60, II:prognosis. Scott Med J 1957;2:200–15.
4. National Institute of Neurological disorders and stroke rt-PA stroke study group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581–7.
5. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). JAMA 1995;274:1017–25.
6. Clark WM, Wissman S, Albers GW, et al. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset: the ATLANTIS study. JAMA 1999;282:2019–26.
7. Tanne D, Gorman MJ, Bates VE, et al. Intravenous tissue plasminogen activator for acute ischemic stroke in patients aged 80 years and older: the tPA stroke survey experience. Stroke 2000;31:370–5.
8. Spilker J, Kongable G, Barch C, et al. Using the NIH Stroke Scale to assess stroke patients. The NINDS rt-PA Stroke Study Group. J Neurosci Nurs. 1997;29:384-92.
9. Simon JE, Sandler DL, Pexman JH, et al. Calgary stroke programme: is intravenous recombinant tissue plasminogen activator (rt-PA) safe for use in patients over 80 years old with acute ischaemic stroke? Age Ageing 2004;33:143–9.
10. Adams HP Jr, Adams RJ, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. Stroke 2003;34:1056–83.
11. Heuschmann PU, Kolominsky-Rabas PL, Roether J, et al. Predictors of in-hospital mortality in patients with acute ischemic stroke treated with thrombolytic therapy. JAMA 2004;292:1831–8.
12. Wardlaw J, Berge E, Del Zoppo G, et al. Thrombolysis for acute ischemic stroke. Stroke 2004;35:2914–15.
13. Gorman MJ, Tanne D, Lewandowski CA. Centenarian stroke treated with tissue-type plasminogen activator. Cerebrovasc Dis 2002;13:285–7.
14. Demchuk AM, Tanne D, Hill MD, et al. Predictors of good outcome after intravenous tPA for acute ischemic stroke. Neurology 2001;57:474–80.
15. Tanne D, Kasner SE, Demchuk AM, et al. Markers of increased risk of intracerebral hemorrhage after intravenous recombinant tissue plasminogen activator therapy for acute ischemic stroke in clinical practice: the multicenter rt-PA acute stroke survey. Circulation 2002;105:1679–85.
16. The NINDS tPA stroke study group. Generalised efficacy of-PA for acute stroke: Subgroup analysis of NINDS t-PA stroke trial. Stroke 1997;28:2119–25.
17. Dubey N, Bakshi R, Wasay M, et al. Early computed tomography hypodensity predicts hemorrhage after intravenous tissue plasminogen activator in acute ischemic stroke. J Neuroimaging 2001;11:184–8.
18. Hiroki M, Miyashita K, Oe H, et al. Link between linear hyperintensity objects in cerebral white matter and hypertensive intracerebral hemorrhage. Cerebrovasc Dis 2004;18:166–73.
19. Smith EE, Rosand J, Knudsen KA, et al. Leukoaraiosis is associated with warfarin-related hemorrhage following ischemic stroke. Neurology 2002;59:193–7.
20. Derex L, Hermier M, Adeleine P, et al. Clinical and imaging predictors of intracerebral haemorrhage in stroke patients treated with intravenous tissue plasminogen activator. J Neurol Neurosurg Psychiatry 2005;76:70–5.
21. Hsia AW, Tong DC. New magnetic resonance imaging and computed tomography techniques for imaging of acute stroke. Curr Atheroscler Rep 2003;5:252–9.