PAPER

Thrombolysis in patients older than 80 years with acute ischaemic stroke: Canadian Alteplase for Stroke Effectiveness Study

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See Editorial Commentary, p 812

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Background: The benefit of intravenous tissue plasminogen activator (tPA) given within 3 h of acute ischaemic stroke to patients over 80 years of age is uncertain.
Aim: To examine the clinical characteristics and complications and the predictors of outcome after intravenous tPA treatment in patients aged ⩾80 years.
Methods: Data (n = 1135) prospectively collected from the Canadian Alteplase for Stroke Effectiveness Study were reviewed and patients aged ⩾80 years (n = 270) treated with intravenous tPA for acute ischaemic stroke were compared with those aged <80 years (n = 865).
Results: The risk of symptomatic intracerebral haemorrhage did not differ between patients aged ⩾80 years and <80 years (4.4% (95% CI 2.3 to 7.6) *v* 4.6% (95% CI 3.3 to 6.2), p = 1.0). Favourable outcome, defined as a modified Rankin Score of 0–1 at 90 days, was seen in 26% of patients aged ⩾80 years and in 40% of those <80 (p<0.001). The following baseline characteristics were found to be more common in those aged ⩾80 years than in those aged <80 years: atrial fibrillation (37% *v* 18%; p<0.001); congestive heart failure (11% *v* 6%; p = 0.004); hypertension (59% *v* 48%; p = 0.002); and severity of stroke with a median National Institutes of Health Stroke Scale (NIHSS) score of 16 *v* 14 (p = 0.004). In the multivariable logistic regression analysis, age ⩾80 years, stroke severity, baseline Alberta Stroke Program Early CT Score and glucose level were found to be the major independent predictors of outcome.
Conclusion: In carefully selected elderly patients, the use of intravenous tPA was not found to be associated with an increased risk of symptomatic intracerebral haemorrhage. Age-related differences were seen in the clinical characteristics and outcome in the elderly population.

Thirty per cent of strokes occur in patients aged ⩾80 years but the role of intravenous thrombolysis in this age group is not well defined.[1] No randomised trials have focused specifically on elderly patients with acute ischaemic stroke. Recent studies analysed the risks and outcome of using intravenous tissue plasminogen activator (tPA) in elderly people and reported no increase in the risk of intracerebral haemorrhage, but the outcomes were not as favourable as in younger patients.[2 3] The number of patients studied, however, was very small, thereby preventing definitive conclusions from being drawn.

People older than 80 years represent the fastest growing segment of the population in developed countries,[4] and in view of the increased incidence of stroke with advancing age, stroke-related disability is expected to increase.[5–7] We sought to examine the clinical characteristics, complications and predictors of outcome in patients aged ⩾80 years who were treated with intravenous tPA.

METHODS

We analysed the data prospectively collected from the Canadian Alteplase for Stroke Effectiveness Study.[8] This was a national prospective cohort study, which led to the licensing of alteplase for the treatment of acute ischaemic stroke in Canada. Data were collected from 60 participating centres in Canada over a period of 2.5 years. Each centre obtained institutional ethics approval for data collection. Briefly, according to the National Institute of Neurological Disorders and Stroke Alteplase Study protocol, patients with acute ischaemic stroke were treated with intravenous alteplase within 3 h of stroke.[9] The final decision to treat the patient was made by the neurologist at each centre. The severity of the neurological deficit at admission was assessed with the National Institute of Health Stroke Scale (NIHSS). The outcome was measured by using the modified Rankin Scale at 90 days and a favourable outcome was defined as a score of 0–1. All the patients underwent a follow-up computed tomography (CT) scan at 24–48 h. Baseline and the follow-up CT scans were centrally reviewed by a stroke neurologist and neuroradiologist, and the Alberta Stroke Program Early CT Score was applied.[10 11] Haemorrhagic transformation was assessed in the follow-up CT scan and classified into parenchymal haematoma and haemorrhagic infarction, according to definitions in the European Cooperative Acute Stroke Study trials.[12 13] Symptomatic intracerebral haemorrhage (ICH) was defined as a haemorrhage documented on the CT scan and was associated with decline in the neurological status, judged by the local investigator, in the first 24 h of thrombolytic treatment. Asymptomatic ICH was defined as a haemorrhage documented in the follow-up CT scan, without associated clinical deterioration. Fatal ICH was defined as a haemorrhage documented on the CT scan, associated with the death of the patient. The patients were stratified into two groups,

Abbreviations: CT, computed tomography; ICH, intracerebral haemorrhage; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator

Table 1 Clinical characteristics of patients treated with tissue plasminogen activator

Variable	Age <80 years (n = 865)	Age ⩾80 years (n = 270)	p Value
Age (years, mean (SD))	65.6 (11.7)	84.7 (3.6)	
Sex (male, %)	60	37	0.001
Vascular risk factors (%)			
Hypertension	48	59	0.002
Atrial fibrillation	18	37	0.001
Smoking (current)	19	3	0.001
Hyperlipidaemia	22	10	0.001
Ischaemic heart disease	23	30	0.05
Valvular heart disease	3	5	0.1
Congestive heart failure	6	11	0.004
Prior stroke/TIA	23	27	0.2
Pretreatment mRS>1	20	28	0.005
Pretreatment systolic BP (mm Hg, mean (SD))	150 (21.6)	155 (21.3)	0.001
Pretreatment glucose level (mol/l, mean (SD))	7.4 (3.1)	7.3 (2.2)	0.46
Pretreatment ASPECTS	8.3 (2.1)	8.1 (2.4)	0.34
NIHSS (mean (SD))	13.9 (6.2)	16 (6.4)	0.004
Protocol violations, all causes (%)	14	12	0.26
Onset to needle time (mean (SD))	150 (38.6)	146 (33.5)	0.12
Type of stroke	0.073		
Total anterior circulation	27	30	
Partial anterior circulation	62	64	
Posterior circulation	4	1	
Lacunar	7	4	

ASPECTS, Alberta Stroke Program Early CT Score; BP, blood pressure; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack.

those aged ⩾80 years and those aged <80 years. We compared the baseline characteristics, complications, in-hospital mortality and outcome at 90 days between the groups.

Statistical analysis

Fisher's exact test and Student's *t* test were used to compare the two groups. Multivariable logistic regression was used to identify predictors of outcome. The final model was a parsimonious model developed by backwards stepwise elimination. In the assessment of final outcome, we adjusted for baseline (pre-stroke) estimated modified Rankin Scale.

RESULTS

Baseline characteristics

Among the 1135 patients treated with tPA, 270 (23.8%) were ⩾80 years. Table 1 shows the baseline characteristics of the two groups of patients. Patients aged ⩾80 years were more likely to have atrial fibrillation, congestive heart failure, ischaemic heart disease and hypertension. Current smoking and hyperlipidaemia were more often observed in the patients aged <80 years. Violations of the protocol occurred in 154 (13.6%) patients, of which 132 (85.7%) were due to the treatment beyond the 3 h time window. The time to treatment from onset of symptoms, deviations from protocol, pretreatment Alberta Stroke Program Early CT Score and the baseline serum glucose level were comparable between the two groups. The baseline stroke severity was significantly greater in the patients aged ⩾80 years (median NIHSS, 16 *v* 14; p = 0.004).

Complications and outcome

The rate of symptomatic ICH did not differ between the patients aged ⩾80 years and those aged <80 years (4.4% *v* 4.6%; p = 1.0). Of the 12 patients aged ⩾80 years with symptomatic haemorrhages, 11 (91.6%) were fatal. Table 2 shows the haemorrhagic complications and the outcomes. In the multivariable analysis, increased pretreatment glucose level and protocol violations were independent predictors of symptomatic intracranial haemorrhage. Age ⩾80 years was not a predictor of symptomatic haemorrhage (odds ratio (OR) 1.12, 95% CI 0.57 to 2.2).

Figure 1 shows the clinical outcomes. The proportion of patients with favourable outcome at 90 days, defined as having a modified Rankin Scale of 0–1 was significantly greater in the patients aged <80 years (40% *v* 25%; p = 0.001). At 3 months' follow-up, more patients aged ⩾80 years were dead than their younger counterparts (35% *v* 18%; p = 0.001).

In multivariable analysis, predictors of death in the patients ⩾80 years were baseline NIHSS score, baseline serum glucose level and congestive heart failure. Predictors

Table 2 Outcome and haemorrhagic complications in patients treated with tissue plasminogen activator

Variable	Patients aged <80 years (n = 865)	Patients aged ⩾80 years (n = 270)	p Value
Intracranial haemorrhage, n (%, 95% CI))			
All	93 (10.8, 8.8 to 13.0)	39 (14.4, 10.5 to 19.2)	0.1
Symptomatic haemorrhages	40 (4.6, 3.3 to 6.2)	12 (4.4, 2.3 to 7.6)	1.0
Fatal	30 (3.6, 2.4 to 5.0)	11 (4.1, 2.1 to 7.3)	0.4
Outcome at 90 days, % (95% CI)			
Excellent outcome (modified Rankin Scale<2)	40.2 (36.8 to 43.6)	25.9 (20.8 to 31.6)	0.001
Death from all causes	18.2 (15.7 to 21.0)	35.3 (29.6 to 41.4)	0.001

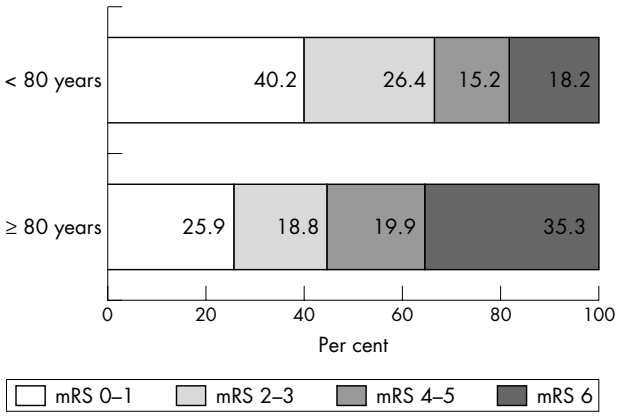

Figure 1 Patient outcome at 90-day follow-up. mRS, modified Rankin Scale; mRS 0–1, excellent outcome; mRS 2–3, moderate disability; mRS 4–5, severe disability; mRS 6, dead.

of favourable outcome at 90 days in this group were a higher baseline ASPECTS and a lower baseline glucose level.

DISCUSSION

All six of the alteplase stroke trials have included very few elderly patients. Therefore, we have very limited class 1 evidence to support its use in elderly people. But as the aged population is increasing,[14 15] doctors attending to patients with stroke will have greater opportunity to use thrombolysis in elderly patients. This study provides observational data on the risk of ICH and predictors of outcome after treatment with intravenous tPA in elderly people.

Advancing age was consistently found to be an independent predictor of ICH after thrombolytic treatment for acute stroke and myocardial infarction.[16 17] A recent study on in-hospital mortality in patients treated with tPA showed that the rate of ICH after using tPA increased with age from 4.9% in patients <55 years to 10.3% in patients aged ⩾75 years.[18] Two case series on the use of tPA treatment in patients aged ⩾80 years reported a risk of ICH between 10% and 13%.[19 20] These smaller observational studies have led to a fear in using thrombolytic treatment in these patients. Our study refutes these past observations, showing that the risk of ICH after tPA was the same in the patients aged <80 as those aged ⩾80 years; age ⩾80 years was not an independent predictor of symptomatic haemorrhage.

Patients with acute stroke aged ⩾80 years have a higher in-hospital and 3 month morbidity and mortality.[1] A recent study observed very old age to be a strong predictor of short-term and long-term outcome and mortality, independent of other clinical characteristics.[15] Analysis of all the studies on the use of tPA in elderly people reported an increased mortality at discharge and at 90 days (20–33%) and a less favourable outcome (26–30%) compared with that in the younger patients. These results are similar to the mortality and the less favourable outcome seen in our study. The average mortality of 44% at 3 months was reported in elderly patients not treated with tPA.[1] The above studies suggest that, rather than age alone, a complex interplay of stroke severity, comorbid conditions and pre-existing disability accounts for poor overall outcome in elderly people.

As in previous studies,[3 18 20] age, baseline NIHSS and baseline glucose level were predictors of death at 90 days among all patients. Among elderly patients alone, only baseline NIHSS, glucose level and congestive cardiac failure were predictors of mortality at 90 days.

Overall, the safety profile of thrombolytic treatment in the population under study suggests that it is possible to select patients appropriately for treatment. Taking into account that elderly patients are the most at risk for poor outcomes without thrombolysis, and that they can be treated safely, suggests that an aggressive approach to acute stroke care is warranted in elderly patients.

Our report has certain limitations. Our data do not result from a randomised controlled trial and hence should be interpreted cautiously. As the final decision to treat was made by the doctor at the each centre, selection bias may have influenced the results. In addition, of the 13.5% protocol violations, 85% were due to treatment beyond the 3 h time window and hence the results cannot be strictly compared with trials in which all the patients were treated within 3 h.

In conclusion, this is the largest study to report on the risk of intravenous tPA as well as the predictors of outcome in elderly people with acute ischaemic stroke. By careful selection of patients, tPA can be given safely to elderly people without increased risk of ICH within the 3 h time window. Further randomised data from the Third International Stroke Trial Study will permit more definitive conclusions on the use of tPA in elderly people.

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