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Stroke thrombolysis in the very elderly

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Summary

Acute ischaemic stroke is common in older people and is associated with a higher morbidity and mortality compared with younger patients. Intravenous thrombolysis with recombinant tissue plasminogen activator (r-tPA) has become the mainstay of treatment and is the only evidence-based specific treatment for acute ischaemic stroke. However, little data are available on the safety of thrombolysis in the over-80 years age group due to under-representation of this group in trials and the upper age limit for licensing of the drug. In this review, we look at the pathophysiology of stroke and recent advances in neuroimaging techniques. We also look at the evidence base for use of thrombolysis in stroke and in particular analyse the trials that include the very elderly as subjects. Finally, issues around ongoing trials and future research are discussed.

Key words: elderly, stroke, thrombolytic therapy.

Introduction

Stroke is currently the second leading cause of death in the Western world, ranking after heart disease and before cancer, and causes 10% of deaths worldwide. Acute ischaemic stroke accounts for approximately 80% of total cases, the remainder being haemorrhagic in nature. Stroke is common in older people and is associated with a higher morbidity and mortality compared with younger patients. In the United Kingdom, 30,000 people aged 80 and over present with ischaemic stroke, and this number is likely to rise as the proportion of elderly people reaching advanced age is expected to increase.

In recent years, intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (r-tPA) has become the mainstay of treatment, and apart from aspirin[1] is the only evidence-based specific treatment for acute ischaemic stroke.[2,3] However, little data are available on the safety of thrombolysis in older patients. r-tPA use for ischaemic stroke has been licensed in European countries in adults older than 18 years up to 75 years of age, and recently the licence was extended to 80 years. The age restriction results from the higher risk of intracranial haemorrhage (ICH) in the elderly and as a result of this, it is possible that thrombolytic therapy may be withheld from many older patients with acute stroke. However, a number of studies advocate the use of thrombolysis in the elderly and have found that the risks of ICH post-r-tPA for acute ischaemic stroke are similar in patients above and below 80 years.

This review covers the use of thrombolysis in the elderly including previous data regarding pathophysiology, neuroimaging, prevalence and prognosis of stroke in this group of patients.

Pathophysiology

Ischaemic strokes are caused by an occlusion of cerebral blood vessels resulting in ischaemia to the dependent area of the brain and subsequent infarction. About four-fifths of ischaemic strokes are the result of thrombosis and emboli. The most common sites of thrombotic occlusion are the atherosclerotic large cerebral arteries (e.g. carotid, middle cerebral and basilar arteries) or atherosclerotic small cerebral arteries (e.g. lenticulostriate, basilar penetrating and medullary arteries). Arterial stenosis precipitated by turbulent blood flow, atherosclerosis and platelet adherence cause blood clots to form.[4] Less common causes of thromboses, particularly seen in younger stroke patients, include cervical artery dissection, polycythemia, sickle cell anaemia and thrombophilia syndromes.

Emboli may arise from the heart, the extracranial arteries or rarely, the venous circulation (paradoxical emboli) and can occlude the vasculature. The sources of cardiogenic emboli include mural thrombi (post-myocardial infarction, dilated cardiomyopathy, severe congestive cardiac failure and atrial fibrillation (AF) and valvular thrombi

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(subacute bacterial endocarditis, prosthetic valve). Atrial fibrillation is strongly associated with ageing, and, with the projected increase in the elderly population, the US prevalence of this condition is expected to more than double by the year 2050.[5] The attributable risk of stroke from atrial fibrillation is estimated to be 1.5% for those aged 50–59 years, and approaches 30% for those aged 80–89 years. However, there is a low rate of anticoagulation in elderly patients, perhaps due to the inconvenience associated with coagulation monitoring and dose adjustment. Small vessel disease within the brain causes a further 20% of ischaemic strokes. These are usually in patients with generalized small vessel disease – for example, hypertensive and diabetic patients. Multiple small emboli or an *in situ* process called lipohyalinosis (in which multiple microatheromata occlude the vessels) are thought to be responsible for this small vessel disease.

Endothelial dysfunction has also been implicated as a cause of atherosclerosis and subsequent thrombus development. It is characterized by a shift of the actions of the endothelium towards reduced vasodilatation, a pro-inflammatory state, and pro-thrombotic properties.[6] It is associated with most forms of cardiovascular disease including stroke. Mechanisms that participate in the reduced vasodilatory responses in endothelial dysfunction include reduced nitric oxide generation, oxidative excess, and reduced production of hyperpolarizing factor. Up-regulation of inflammatory cytokines and production of plasminogen activator inhibitor-1 participate in the inflammatory response and contribute to a prothrombic state and may in fact trigger plaque rupture. A recently published Scottish study implicates increased arterial stiffness as a poor prognostic factor in patients with stroke; Soiza *et al.*[7] examined the relationship between measures of arterial function obtained from pulse wave analysis, stroke type and in-hospital outcome after ischaemic stroke. The authors found a positive correlation between augmentation index and increased length of stay along with worsening Barthel score.

Neuroimaging

Neuroimaging techniques have transformed the investigation and delivery of stroke care. Currently, computed tomography (CT) is commonly used to select patients who have had an acute stroke for thrombolytic therapy on the basis of the absence of haemorrhage and, more controversially, the presence of early CT changes of ischaemia. In a phase IV North American study, a quantitative system to define ischaemic changes was developed (the Alberta Stroke Programme Early CT Score, or ASPECTS).[8] In this study, the extent of early ischaemic changes was related to high rates of intracerebral haemorrhage as well as to poor clinical outcomes at three months. The ASPECTS system is a simple way to quantify early ischaemic changes. The changes are described as either parenchymal hypoattenuation (defined as a region of abnormally low attenuation of brain structures relative to that of other parts of the same structure or of the contralateral hemisphere) or focal brain swelling (defined as any focal narrowing of the CSF space due to compression by adjacent brain structures such as effacement of the cortical sulci or ventricular compression). The extent of early ischaemic changes is measured on two standard CT cuts, one through thalamic and basal ganglia and the other above these structures and including the lateral ventricles. The total territory of the middle cerebral artery represents 10 points, and one point is subtracted for early ischaemic change of each of ten areas. The baseline ASPECTS value predicts functional outcome and symptomatic intracerebral haemorrhage, and a sharp increase in dependent or fatal outcomes occurs with ASPECTS of 7 or less.

The ischaemic penumbra describes a functionally impaired but potentially viable tissue that (normally) surrounds an area of recent cerebral infarction. Since patients with ischaemic penumbra are more likely to respond to therapy, identification of patients with this feature is essential in deciding which patients may be more likely to respond to thrombolysis. Perfusion CT may play a useful role in the selection of patients for therapy with published thresholds of relative regional blood flow to identify the infarct core and regional cerebral blood volume to identify the penumbra, but this technique has the disadvantage of allowing only one slice to be assessed and is associated with a relatively large dose of radiation in comparison with a conventional non-contrast CT brain scan. Although several imaging modalities can identify the penumbra, the most suitable is magnetic resonance imaging (MRI) showing perfusion-weighted and diffusion-weighted imaging mismatch.[9]

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Multi-tracer PET has been invaluable in defining the pathophysiology of acute stroke, but the technique is confined to research use because of several factors, including the requirement for arterial access to produce quantitative data which is increasingly difficult in the thrombolytic era.[10]

Ringleb *et al.* looked at whether older patients selected for stroke thrombolysis by MRI had better outcomes than those selected by CT.[11] The authors found that the use of MRI to select octogenarians for thrombolytic therapy appeared to decrease the risk of symptomatic intracranial haemorrhage (sICH) (rate of sICH in MRI *vs.* CT, 0 *vs.* 9.4%, $P = 0.10$). However, the use of MRI did not influence the overall outcome after 3 months.

A 2006 study looking at predictors of cerebral microbleeds in acute stroke and transient ischaemic attack (TIA) suggested that T2 gradient echo sequences on MRI might be more effective than CT for selecting suitable patients for thrombolysis.[12] Gradient echo MRI is more effective at visualizing microbleeds which can indicate poorly controlled hypertension or amyloid angiopathy. Leukoariosis is an indicator of secondary chronic vascular brain injury and is more prevalent in older people. It is best visualized on MRI T2 sequences. There has been some conflicting evidence as to whether there is an association between leukoariosis and intracerebral haemorrhage post-thrombolysis. In a retrospective multicentre analysis of just under 450 stroke patients, the authors found that symptomatic intracerebral haemorrhage post-thrombolysis was more frequent when moderate to severe leukoariosis was present than when there was no leukoariosis (10.5 *vs.* 3.8%, $P = 0.015$).[13]

As previously mentioned, intravenous thrombolysis is restricted to treatment within 3 h of stroke onset, necessitating prompt assessment and referral for neuroimaging. The ECASS-III study suggested that use of intravenous r-tPA between 3 and 4.5 h after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke.[16] Thomalla *et al.* reviewed published data regarding thrombolysis beyond the 3 h time window in patients aged 80 and over, and concluded that IV thrombolysis in MRI-selected patients was safe within an extended time window of up to 6 h.[14]

The Cochrane review published in 2009 did not find any evidence that the use of MRI, perfusion or angiographic studies were likely to improve patient selection in the older patient group.[15]

Evidence for thrombolysis

The evidence base for thrombolysis in stroke includes 21 completed randomized controlled clinical trials enrolling 7152 patients, using various agents, doses, time windows, and intravenous or intra-arterial modes of administration.[15] Four trials used intra-arterial administration alone, with the rest using the intravenous route. Most data come from trials that started treatment up to 6 h post-stroke, and approximately 55% of the above trials were using IV r-tPA. Thrombolytic therapy, which was mainly administered up to 6 h post-stroke, significantly reduced the proportion of patients who were dead or dependent (modified Rankin score 3–6) at 3–6 months (odds ratio (OR) 0.81, 95% confidence interval (CI) 0.73 to 0.90). Treatment within 3 h of stroke was associated with lower rates of death and dependency (OR 0.71, 95% CI 0.52 to 0.96). Thrombolytic therapy increased the risk of symptomatic intracranial haemorrhage (OR 3.49, 95% CI 2.81 to 4.33) and death by 3–6 months after stroke (OR1.31, 95% CI 1.14 to 1.50).

Age limits

The evidence for use of thrombolysis is less clear for older stroke patients as they have thus far been excluded or under-represented (0.5% of total subjects) in the randomized controlled trials (RCTs) of IV r-tPA. The NINDS trial only included patients aged 80 and over ($n = 42$) in the second part of the trial.[2] Furthermore, two large European studies have excluded subjects aged 80 and over from their investigations. The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITSMOST) had an upper age limit of 80 years, as did the ECASS-3 (European Co-operative Acute Stroke Study).[16,18]

Post-thrombolysis outcomes

A number of smaller observational studies carried out in single centres or collaborations between centres show similar results with regard to outcomes post-thrombolysis in older people. A Dutch study looked at 184 patients who received IV thrombolysis, 45 of whom were 80 years of age or older. The authors found that although numbers were small, there was a significant increase in the risk of sICH in the older cohort (11.1 *vs.* 2.9%).[18]

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In a Swiss multicentre cohort study all r-tPA-treated stroke patients ⩾ 80 years old were compared with their younger counterparts.[19] Outcome measures included death (all causes), ICH (asymptomatic, symptomatic/fatal) and favourable *versus* poor outcome measures (Rankin scale). None of the five centres included in the study applied an upper age limit for r-tPA treatment. Among 325 r-tPA-treated subjects, 38 (12%) were ⩾ 80 years old. After 3 months 32% (12/38) of older *versus* 12% (35/287) of younger patients had died ($P < 0.01$). The rate of ICH did not differ significantly between older and younger patients. Furthermore, a favourable outcome occurred in 29% of older and 37% of the younger patients ($P > 0.1$). Age was not found to be an independent predictor of outcome as either a dichotomized categorical variable (⩾80 *vs.* <80 years) or a continuous variable. Limitations of this study include the fact that exclusion criteria which differed from the NINDS trial[2] were applied and that the study was observational rather than a randomized study.

Pundik *et al.* analysed a database of 477 consecutive patients with ischaemic stroke who received thrombolytic therapy to determine whether factors that included age > 80 years were associated with symptomatic ICH.[20] The odds of symptomatic ICH after thrombolytic therapy for patients over 80 years after adjusting for route of administration, NIHSS (National Institutes of Health Stroke Scale score), mean arterial pressure and glucose was not significantly different from that of the younger age group (OR 1.64; 95% CI 0.729–3.66). The authors concluded that the decision to thrombolyse in ischaemic stroke should not be solely based on the patient's age.

Vatankhah *et al.* identified all patients over 75 years with middle cerebral artery ischemia treated with intravenous r-tPA over a 5-year period from 1999 until 2004.[21] Clinical course and outcome until day 5 in addition to mortality after 3 and 6 months were analysed. Twenty-nine patients aged 75 and over were given IV thrombolysis with a mean age of 80.8 years. After 5 days, 13/29 (44%) showed a good recovery (NIHSS improvement ⩾ 4 points). In 10.3% non-symptomatic and in 3.4% symptomatic cerebral bleeding was found.

A systematic review of the non-randomized cohort studies comparing outcome after r-tPA treatment in patients aged under 80 compared with those aged over 80 found that the latter group had a higher overall mortality, but that imbalances in predictive baseline variables to the disadvantage of the older patients may have contributed to the findings.[22] Engelter *et al.* found that the reported symptomatic intracerebral rate was not significantly increased in the over-80 group (5.6 *vs.* 5.2%).

In a retrospective review, Zeevi *et al.* compared patients >80 years ($n = 341$) admitted to a community stroke centre with acute ischaemic stroke with their younger counterparts.[23] Older patients were not delayed in reaching the hospital within 3 h of stroke onset (182/690 (26%) in the <80 cohort *vs.* 98/341 (29%) in the > or = 80 cohort). Although the overall rates of r-tPA use were similar in both the young and aged cohort, older patients were less likely to be treated with r-tPA because of reasons not elucidated (17% in the <80 cohort *vs.* 32% in the > or = 80 cohort). The older group did not have an excessive risk of intracranial haemorrhage following r-tPA infusion despite equivalent NIHSS on admission (13.5 in the <80 cohort *vs.* 12.4 in the > or = 80 cohort). Both groups showed improvement in NIHSS following thrombolytic treatment with a drop of 7.7 points in the younger age group and 5.6 points in the older group. Elderly patients treated with r-tPA had a comparable 12-month modified Barthel Index score to younger cohorts. The authors concluded that early treatment with r-tPA in patients >80 years appears to be both safe and efficacious.

Intra-arterial (IA) thrombolysis

IA thrombolysis has also been investigated as a treatment for acute ischaemic stroke compared with intravenous therapy. IA therapy offers several advantages, including a higher concentration of lytic agent delivered to the clot target, a lower systemic exposure to the medication, and higher recanalization rates. Disadvantages include additional time required to initiate therapy, limited availability in specialized centres only, and mechanical manipulation within potentially injured vessels. As a result of the practical limitations, the use of intra-arterial thrombolysis is less common. There are limited data available on its use in elderly patients. Kim *et al.* reported on a study comparing complications and outcomes between intra-arterially treated ischaemic stroke patients aged ≥80 years and their younger counterparts.[24] The authors found

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that intra-arterial fibrinolysis in the elderly can be accomplished with recanalization rates and haemorrhage rates equal to that in younger patients. Although mortality rates are higher and good functional outcomes are lower than in younger people, non-disabling outcomes may be achieved in a quarter of patients.

Clot retrieval

Acute ischaemic stroke caused by thrombus within large vessels (middle cerebral, basilar artery, and carotid terminus) are relatively resistant to dissolution from plasminogen activators delivered intravenously providing a reason to pursue direct endovascular techniques to open vessels.[2] Endovascular mechanical thrombectomy may be used during acute ischaemic stroke due to large vessel intracranial occlusion. Endovascular mechanical thrombectomy may be employed, either as a stand-alone therapy or as an adjunct to IV r-tPA, and has several potential advantages, including a wider time window (up to 8 h), the capacity for use in coagulopathic patients and higher recanalization rates. The Mechanical Embolus Removal in Cerebral Ischemia (MERCI)[25] and Multi MERCI trials[27] evaluated the safety and efficacy of thrombectomy in the treatment of intracranial arterial occlusions within 8 h of symptom onset. The MERCI trial used a novel embolectomy device (Merci retriever) and found that recanalization was achieved in 46% (69/151) of patients on intention to treat analysis, and in 48% (68/141) of patients in whom the device was deployed.[25] Good neurological outcomes (modified Rankin score ≤ 2) were more frequent at 90 days in patients with successful recanalization compared with patients with unsuccessful recanalization (46 *vs*. 10%; relative risk (RR) 4.4; 95% CI 2.1 to 9.3; $P < 0.0001$), and mortality was less (32 *vs*. 54%; RR 0.59; 95% CI 0.39 to 0.89; $P = 0.01$).

The Multi MERCI trial found that mechanical thrombectomy after IV r-tPA seems as safe as mechanical thrombectomy alone. Mechanical thrombectomy with both first- and second-generation Merci devices is efficacious in opening intracranial vessels during acute ischaemic stroke in patients who are either ineligible for IV fibrinolytic therapy or have failed IV fibrinolytic therapy.[26]

Although neither of the aforementioned MERCI trials had an upper age limit, the mean age (±SD) of their subjects was 67.0 ± 15.5[25] and 68 ± 16 years.[26] There have been no thrombectomy studies to date on the very elderly population.

Cost effectiveness of thrombolysis

There have been few studies into the cost effectiveness of thrombolysis and none have focused on thrombolysis in the elderly. Sandercock *et al.* looked at the health economic impact of limited use of thrombolytic therapy and to assess whether it was likely to be cost effective when used more widely in the UK National Health Service (NHS).[27] The model suggested that compared with standard care, if eligible patients were treated with r-tPA up to 6 h, there was a 78% probability of a gain in quality-adjusted survival during the first year, at a cost of £13,581 per quality-adjusted life-year (QALY) gained. Over a lifetime, r-tPA was associated with cost savings of £96,565 per QALY. However, the estimates were imprecise and highly susceptible to the assumptions used in the economic model.

Future research

A number of factors including changes in demographics, increased survival after first stroke and improved secondary prevention in younger years are leading to increased rates of stroke in the over-80s. Despite this fact, older patients continue to be under-represented in clinical trials, in particular those involving the use of thrombolysis for acute strokes. While the FDA (Food and Drug Administration) placed no upper age limit on the use of r-tPA, the European licensing agency suggested a limit of 80 years as the original submission for approval only included 42 patients over this age limit.

The SITS (Safe Implementation of Thrombolysis in Stroke) Register, of which 10% are >80 years, shows a mortality rate and outcome similar to that reported in the published meta-analysis. The rate of symptomatic haemorrhage (2%) was not significantly greater than the 1.5 seen in <80-year-olds.[28]

The Third International Stroke Trial (IST-3, www.ist3.com) is ongoing and aims to determine whether administration of intravenous r-tPA within 6 h of ischaemic stroke increases the proportion of independent survivors at 6 months.[29] It has no upper age limit and at the time of

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writing has included more than 800 patients aged 80 and over. This trial will provide unique data on the balance of risk and benefit in this older patient group, and results will be reported in early 2012.

A further multicentre randomized control trial has begun in Italy (TESPI) with the aim of collecting efficacy and safety data on IV thrombolysis in patients aged 80 and over. This trial started in 2008 and so far has 66 of an estimated 600 recruits.[30]

Although age is but one factor which influences the risks and benefits of thrombolysis, it is clear that further research is necessary with regard to evidence for inclusion of older patients as candidates for thrombolysis given the demographic changes that are taking place. Whilst the use of thrombolysis in selected patients >80 years is warranted (albeit off licence), we await further randomized clear evidence on the balance of risk *versus* benefit in this patient population in order to optimize stroke care.

On the basis of the current evidence, there is limited justification for routine thrombolysis in very old patients with acute ischaemic stroke. However, clinicians are encouraged to consider inclusion of potentially thrombolysable older patients into clinical trials such as IST-3 so that the evidence base for thrombolysis can be developed.

Conflict of interest

None of the authors has any conflict of interest.

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