

Thrombolytic treatment in the oldest-old patient with acute ischemic stroke: an update on current evidence

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ABSTRACT

The incidence of ischemic stroke rises exponentially with age, with a steep increase in the age interval between 75 and 85 years. Thrombolytic therapy restores cerebral blood flow in patients with acute ischemic stroke of any etiology by using drugs that dissolve blood clots. Infusion for 1 h of alteplase at the dose of 0.9 mg/kg within 3 h of the start of the symptoms is associated to a 30% increase in the likelihood of gaining a favorable outcome with respect to placebo. There is strong evidence that selected patients with ischemic stroke may benefit from intravenous thrombolysis when treated within 3 h. The aim of the study was to evaluate available evidence for the efficacy and safety of thrombolytic therapy in patients with ischemic stroke aged 80 years and over. Compared to younger stroke patients treated with thrombolytic therapy, those aged 80 years and over have higher acute mortality due to symptomatic intracranial hemorrhage. However, functional outcome at six months is significantly better for over-80-year-olds than younger patients. There is a need for screening tools that take into account pre-stroke functional and cognitive status that are able to identify those over-80-year-old patients with ischemic stroke who can most benefit from thrombolytic treatment. Available evidence supports further recruitment of oldest-old patients into ongoing trials of thrombolysis.

Introduction

Each year approximately 22 million people have a stroke worldwide. Therefore, stroke is one of the main public health issues with important consequences for the organization of healthcare systems.¹ Ischemic stroke incidence in all its forms (lacunar, atherothrombotic and cardioembolic) is largely related to age. In order to improve health-related quality of life in very old patients with ischemic stroke, it is crucial to optimize the organization of stroke care from referral to rehabilitation.

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Treatment of stroke in patients aged 80 years and over is difficult^{2,3} for various reasons. Firstly, there is the issue of limited admission to stroke units and/or stroke care. Hospitalization in stroke units is particularly beneficial for the elderly patient and the oldest-old patient because of the higher prevalence of early complications in these age groups. However, the limited number of beds in these units often prevents the admission of the most elderly patients. Also, there is a low proportion of elderly ischemic stroke patients receiving thrombolytic therapy. The benefits of intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) is demonstrated in a Cochrane systematic review of 11 trials including a total of 3977 patients.⁴ However, older people were under-represented in those trials, with only 79 over-80-year-olds included. As a result, in all main international guidelines (in Europe and the USA)⁵ thrombolytic therapy with rt-PA is restricted to the treatment of patients younger than 80 with acute ischemic stroke who could be treated within 3 h of onset, even though 40% of strokes occur in very elderly patients. In the last few years, many patients aged over 80 have been enrolled in trials.^{5,6}

Elderly patients and thrombolysis treatment: a difficult decision

Every day clinicians have to decide whether to treat very old patients affected by comorbidities or to exclude them from thrombolysis treatment. Age itself

is the most significant independent risk factor for stroke-associated mortality, mainly due to the fact that elderly persons are more prone to complications and have more comorbidity than their younger counterparts. A systematic review of 6 studies comparing intravenous alteplase in stroke patients over 80 years old *versus* younger ones found no increased risk of symptomatic intracranial hemorrhage in the older age group and also a better prognosis.

Despite a worse outcome of stroke in over-80-year-olds, patients who were treated with thrombolysis have better outcomes than untreated patients and this effect is independent of age.⁷ On the contrary, some studies demonstrated that treatment with thrombolysis is associated with significantly more favorable distribution scores on the modified Rankin scale at three months compared with younger patients. The oldest age beyond which it is reasonable to perform treatment is uncertain. There are case reports of treatment in patients aged over 90, and even on over-95-year-olds. However, so far no safety studies have been conducted on these patients and this issue will need to be dealt with in the future. In the randomized IST3 study,⁸ half of all patients were over 80 years of age. In this study, there is evidence that rt-PA improved functional outcomes by six months in this group compared with younger patients.

Other aspects of very elderly patients' care include the analysis of baseline autonomy, cognitive status and comorbidities. A comprehensive geriatric assessment has been proposed to screen for frailty but such an assessment is difficult to carry out. An important test to perform is the Identification of Seniors At Risk (ISAR),⁹ a questionnaire developed and validated in Canada and successfully used in Belgium and Italy. A positive test result suggests increased risk of experiencing adverse events such as death, repeated Emergency Unit visits, and hospital admission within six months. The ISAR score includes activities such as daily living, social condition, cognitive status and comorbidities (Table 1).

At the end of the 1980s, angiographic studies suggested the use of thrombolytic therapy in acute is-

chemic stroke patients. Five randomized studies of intravenous thrombolysis were published in 1995: ASK (Australian Streptokinase), MAST-E (Multicentre Acute Stroke Trial, Europe), MAST-I (Multicentre Acute Stroke Trial, Italy), ECASS (European-Australian Acute Stroke Study), and NINDS (National Institute of Neurological Disorders and Stroke). These studies have shown the efficacy of intravenous thrombolysis in the disintegration of thrombi in 30-60% of cases. The NINDS study shows that treatment with alteplase (rt-PA) in a single 1-h infusion (0.9 mg/kg) within 3 h of stroke onset enhances the chance of a favorable outcome (approx. 30% more recoveries than the control group). This benefit was observed in all kinds of strokes, embolic, atherothrombotic, and in small vessel occlusion.¹⁰ The other three studies (ASK, MAST E, MAST I) based on streptokinase use were interrupted due to excessive mortality in the treated group.

Following these results, intravenous thrombolysis with alteplase (rt-PA) was approved as therapy of acute ischemic stroke within 3 h of stroke onset in selected patients first in the USA and Canada (1996) and then in Europe and Italy (2002).¹¹ A meta-analysis has demonstrated that the use of rt-PA in approximately 1000 patients produces an excellent outcome attributable to treatment in 140 patients.¹⁰

Large intracranial hemorrhage is the most severe complication of thrombolytic therapy and occurs in approximately 7% of treated patients. This complication occurs more often in patients with an elevated diastolic pressure value and is dependent on the time between stroke onset and treatment and on rt-PA dose.

The ECASS III study (2008) has, therefore, demonstrated the effectiveness of intravenous thrombolysis within 4-5 h of stroke onset.¹²

Very elderly people in stroke trials

Thrombolytic therapy with intravenous rt-PA, when approved in the USA (American Heart Associ-

Table 1. Identification of Seniors At Risk criteria.

ISAR	Score No/Yes
1. Before the illness or injury that brought you to the Emergency Unit, did you need someone to help you on a regular basis?	0/1
2. Since the illness or injury that brought you to the Emergency unit, have you needed more help than usual to take care of yourself?	0/1
3. Have you been hospitalized for one or more nights during the past six months (excluding a stay in the Emergency Unit)?	0/1
4. In general, can you see well?	0/1
5. In general, do you have serious problems with your memory?	0/1
6. Do you take more than three different medications every day?	0/1

ISAR, Identification of Seniors At Risk. Screening scores >2 are considered positive.

ation/American Stroke Association)¹³ and Europe was restricted to patients younger than 80 years of age with acute ischemic stroke. As the number of very elderly individuals is rapidly growing worldwide, the burden of ischemic stroke among the elderly is increasing.⁵

The first results on effectiveness of thrombolysis in over-80-year-old patients were published from 2000 onwards (Tables 2 and 3).¹⁴⁻²⁰ These results seemed to show that advanced age reduces therapy safety and efficacy, increases mortality, and produces less favorable outcomes.

The study by Mishra *et al.*⁷ compared the outcome at 90 days among patients who received intravenous thrombolysis with the control group; the comparison was performed among patients of various age groups to illustrate the strength of evidence across full age ranges. The authors collated the data from stroke patients who underwent thrombolysis through the SIST-ISTR registry. The control group was made up of untreated stroke patients from neuroprotection trials held within VISTA archives. A total of 29,500 were en-

rolled patients: 23,334 in the treated group, 6166 in the control group. Of these patients, 3472 (11.8%) were aged over 80 years. In Mishra's analysis, patients who were treated with intravenous alteplase had better outcomes than untreated patients and this effect was not dependent on age. In particular, patients aged over 80 derived similar benefits from treatment to younger patients. These results suggest that there is no *a priori* reason to suspect a diminished effect on these elderly patients compared with younger people. Furthermore, there are reassuring safety data on the risk of intracerebral hemorrhage. Selection bias cannot be excluded, due to the observational design of the study. However, data for mortality and incidence of spontaneous intracerebral hemorrhage are similar to those previously published in the literature. This suggests the study sample is fairly representative of ischemic stroke patients. As far as the findings in the study sample as a whole are concerned, differences in demographics may partially explain the higher benefit of treated patients compared to controls. However, this explanation does not apply

Table 2. Current published evidence on mortality at three months.

Author	No. of study sample	% >80 yrs	Type of study	OR* of mortality at 3 months: <80 yrs vs >80 yrs	Mortality at 3 months >80 yrs (%)
Engelter, 2006 ¹⁴	2244	21	Meta-analysis of observational studies	3.09 (2.37-4.03)	21-40
Sylaja, 2006 ¹⁵	1135	24	Prospective registry	-	35.3
Ringleb, 2007 ¹⁶	468	19	Prospective registry	3.37 (1.79-6.32)	28.9
Uyttenboogart, 2007 ¹⁷	142	22	Prospective registry	6.3 (2.1-19)	45.2
Toni, 2008 ¹⁸	248	16	Prospective	-	34.1
Alsheklee, 2010 ¹⁹	7950	20.9	Retrospective	-	-
Ford, 2010 ²⁰	21,242	8.6	Retrospective	1.53 (1.43-1.65)	30

yrs, years; OR, odds ratio. *OR>1 and 95% of confidence interval in over-80-year-olds.

Table 3. Current published evidence on disability outcomes (Rankin scale) and symptomatic intracerebral hemorrhage in patients aged over 80 years.

Author	OR* by RS≤1-3 months <80 yrs vs >80 yrs	OR* by SICH <80 yrs vs >80 yrs	Incidence of SICH >80 yrs (%)
Engelter, 2006 ¹⁴	0.53 (0.42-0.66)	1.22 (0.77-1.94)	5.87
Sylaja, 2006 ¹⁵	-	-	4.4
Ringleb, 2007 ¹⁶	0.38 (0.23-0.6)	1.28 (0.50-3.28)	6.7
Uyttenboogart, 2007 ¹⁷	-	-	9.7
Toni, 2008 ¹⁸	-	1	2.4
Alsheklee, 2010 ¹⁹	-	1.31	5.7
Ford, 2010 ²⁰	-	0.96 (0.87-1.06)	9.5

OR, odds ratio; RS, Rankin scale; SICH, symptomatic intracerebral hemorrhage; yrs, years. *OR and 95% confidence interval.

to the older subgroup, which includes treated patients and controls of similar age.

A recent meta-analysis²¹ showed that treated patients over 80 years old have a lower probability of gaining a favorable functional outcome and a higher mortality rate compared to younger patients. However, the same meta-analysis found that the rate of intracranial hemorrhage did not differ between over-80-year-olds and younger patients. This supports recruitment of over-80-year-olds into ongoing trials of thrombolysis *versus* standard treatment.

A recent study of combined intravenous alteplase (i.v.) and endovascular therapy (intraarterial, i.a.) in octogenarians²² showed that, in this age group, the i.v.-i.a. approach was associated with lower efficacy at three months and higher mortality and asymptomatic hemorrhagic complications (defined as an increase in National Institute of Health Stroke Scale, NIHSS, score < 2) than in patients under 80 years of age.

In the international, multicenter, randomized, open-treatment trial IST-3,⁸ 3000 patients were allocated either to the 0.9 mg/kg intravenous rt-PA group or to the control group. In IST-3, 53% of all these patients were over 80 years of age (1407 patients aged 81-90 years and 210 patients aged over 90 years). At six months, 36% of treated patients were alive and living independently *versus* 35% of those in the control group. The biggest benefit was seen in patients treated within 3 h of onset of acute ischemic stroke. More deaths occurred within seven days in the rt-PA treated group than in the control group, but at six months similar numbers had died both in the rt-PA group and in the control group.

In a subsequent meta-analysis (2012) of 12 trials (including IST-3), the effectiveness of rt-PA treatment was confirmed in over-80-years-old patients treated within 3 h (96 alive and independent out of 1000 treated) as well as in the younger patients' group. No benefit was demonstrated in over-80-years-old patients treated 3-6 h after onset (in the younger group this benefit was consistent: 23 alive and independent out of 1000 treated).

New thrombolytic therapies

Despite substantial advances in stroke research, with several therapeutic drugs being able to enhance clinical outcomes in people with stroke, the use of rt-PA is still limited because of economic and logistical problems. The stroke community is, therefore, making an effort to identify patients who might benefit from this treatment. In Italy, the use of rt-PA is limited to 2.5% of ischemic strokes. Improving the risk *versus* benefit ratio may be obtained in different ways: i) the development and use of more effective and less expensive thrombolytic agents (desmoteplase and

tecteplase); ii) trials based on combined intravenous and intraarterial tr-PA therapy (bridging) that can achieve higher recanalization rates; iii) widening the therapeutic window up to 6 or 9 hours in selected patients screened by neuroimaging (diffusion/perfusion-weighted magnetic resonance imaging and perfusion computed tomography); iv) reduction of symptomatic intracerebral hemorrhage (now occurring in 3-7% of patients) by adoption of new inclusion criteria based upon neuroimaging or use of different thrombolytic agents or regimens along with alternative biomarkers and neuroprotectors.

In the meantime, in order to maximize the number of older patients receiving therapy and optimize their clinical results within the currently recommended time-window, pre- and intra-hospital stroke management needs to be significantly improved. Elimination of pre- and intra-hospital delays in thrombolytic therapy is a major priority, as well as public education campaigns aimed at increasing thrombolysis adoption and diffusion.²³

Ultrasound thrombolysis

Transcranial doppler ultrasonography that is aimed at residual obstructive intracranial blood flow may help expose thrombi to rt-PA. In the Combined Lysis Of Thrombus in Brain Ischemia Using transcranial ultrasound and Systemic TPA Study (CLOTBUST),²⁴ a total of 126 patients were randomly assigned to receive 2-MHz continuous ultrasonography (n=63) or placebo (n=63) after treatment with intravenous rt-PA within 3 h of onset of symptoms. Continuous transcranial Doppler augments rt-PA-induced arterial recanalization (36%) with a non-significant trend toward an increased rate of intracranial hemorrhage.

The ARTHUS (Acceleration of Thrombolysis by Ultrasound) study²⁵ and TRUMBI (Transcranial low-frequency US mediated thrombolysis in Brain Ischemia) study (TRUMBI, unpublished data, 2005) would have shown an even higher risk of intracerebral hemorrhage compared with arterial recanalization. The TRUMBI study has been interrupted for this reason. Other clinical data and experimentation demonstrated that rt-PA efficacy could be increased by using gas-filled microbubbles associated to dual-frequency transcranial ultrasound. Ultrasound thrombolysis may be a viable alternative for patients outside the time-window for i.v. treatment (after 3 h from the start of the symptoms) and when an intracranial artery re-occludes after i.v. thrombolysis (20% of cases).

Intra-arterial thrombolysis

For a significant number of patients, mainly in stroke caused by proximal vessel obstruction, systemic thrombolysis was proven to be ineffective be-

cause of the low recanalization rate. No thrombolytic agent other than rt-PA (reteplase, tenecteplase or desmoteplase) has yet shown a higher efficacy than alteplase.

The endovascular approach (disintegration or mechanical extraction of thrombi), the combined i.v.-i.a. thrombolysis (bridging therapy), and the use of endovascular stent increase the efficacy and improve the arterial recanalization.²⁶

In highly specialized stroke units, direct intraclot injection of thrombolytic agents (rtPA, streptokinase, urokinase) by a superselective microcatheter is also performed. Thrombus dissolution rates with this procedure are higher than reported for standard i.v. thrombolysis (60-80%). Literature data suggest a clinical benefit but there is a lack of randomized studies confirming efficacy of the approach in older patients.

Conclusions

From a safety point of view, there seem to be no reason to exclude ischemic stroke patients from thrombolysis based on a pre-defined upper age limit. It is expected that we will learn more from future randomized placebo-controlled studies in which elderly people are also included.

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