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Original article

Intravenous Thrombolysis for Acute Ischemic Stroke in the Elderly: An Italian Cohort Study in a "Real World" Setting☆

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SUMMARY

Background: Thrombolysis in the elderly is still a matter of debate. Recently, the Third International Stroke Trial (IST-3) suggested that recombinant tissue plasminogen activator (rt-PA) improves functional outcome, without a substantial absolute increase in symptomatic intracranial hemorrhage, even in older patients. The aim of the current prospective study is to describe safety and functional outcome in a cohort of patients treated by intravenous rt-PA in an Italian stroke unit "real world setting".

Methods: All the consecutive patients treated with rt-PA between 2006 and 2010 in an Italian province with 290,000 inhabitants were enrolled. Total and symptomatic (associated with a 4-point worsening on the National Institutes of Health Stroke Scale [NIHSS] score) hemorrhages were evaluated, as safety measures, along with disability (at 3-month modified Rankin scale) as effectiveness measure.

Results: One hundred and eighty-seven patients were treated with rt-PA; 90 males (48.1%); average age 75.1 (±11.9) years; 79 (42.2%) patients aged ≥80 years. Patients aged ≥80 years had a higher NIHSS score at stroke onset (13.5 vs. 10.9). No significant difference was found between patients aged <80 years and ≥80 years in mortality rate ($p = 0.1$), total or symptomatic intracranial hemorrhage ($p = 0.52$ and $p = 0.085$, respectively), whereas the 3-month disability was higher in octogenarians ($p = 0.004$).

Conclusion: Thrombolysis in patients aged ≥80 years was not associated with significantly increased intracranial hemorrhage. The higher 3-month disability rate observed in octogenarians may be explained by the more severe stroke and higher poststroke disability. Based on the current, "real world setting" study, we advocate the need for a randomized clinical trial to better clarify the efficacy and safety of intravenous thrombolysis for acute ischemic stroke in the elderly.

1. Introduction

Thrombolysis in the elderly is still a matter of debate: whether people aged ≥80 years may benefit, or are at increased risk of intracerebral hemorrhage after recombinant tissue plasminogen activator (rt-PA treatment), remains controversial.[1] Indeed, previous comparative cohort studies, carried out on stroke patients aged ≥80 years and <80 years treated with intravenous (i.v.) rt-PA, yielded conflicting results.[2–4] A lower probability of a favorable outcome and a higher mortality rate in patients aged ≥80 years has been reported, even if there was no statistically significant increase in the symptomatic intracerebral hemorrhage (SICH) rate.[2] However, a controlled comparison study[5] aimed at assessing the effect of age on rt-PA response in acute ischemic stroke demonstrated that the association between thrombolysis and improved outcome was maintained even in the elderly.

Such discrepancy is most likely due to the differences in methods and baseline populations. First, the definition of SICH varies among comparative studies [hemorrhage accompanied by any decline in neurological status or by a 4-point National Institutes of Health Stroke Scale (NIHSS) deterioration, according to European Cooperative Acute Stroke Study (ECASS) criteria[6]]. Second, older

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people show a higher burden of comorbidities, an increased likelihood of preexisting disability, and a poorer functional ischemic stroke outcome.[7,8] Third, the percentage of octogenarians, who usually represent about 37% of all ischemic stroke populations,[9] is only 12–31% in cohort studies,[10] suggesting a selection bias.

The results of the Third International Stroke Trial (IST-3)[11] have recently been published: that is, to date, the only randomized, controlled trial to have investigated into the benefits and safety of thrombolysis in the elderly. The IST-3 was carried out by randomizing 3,035 patients (1,617 i.e., 53%, were ≥80 years) to rt-PA treatment versus placebo within a 6-hour time frame. According to the IST-3 results, the benefit of thrombolysis did not seem to be diminished in elderly patients. However, this trial was not designed *ad hoc* to unravel this specific issue, but to clarify outcome and safety of thrombolysis in a wider range of patients previously excluded from treatment with rt-PA.

A subsequent meta-analysis[12] reported that the benefit of thrombolysis in the elderly was similar to that observed in patients aged <80 years, especially when treated within 3 hours of symptom onset.

This study aimed to evaluate the safety and effectiveness of thrombolysis, in terms of total and symptomatic intracranial hemorrhage and disability, respectively, at 3 months, in a large single-center "real world setting" cohort of patients, aged ≥80 years and <80 years, treated consecutively with i.v. thrombolysis for ischemic stroke in an Italian hospital in Piacenza, from 2006 to 2010.

2. Participants and methods

2.1. Study design and participants

This is a prospective, single-center, cohort study, carried out in the neurology unit (NU) of the Guglielmo da Saliceto Hospital in Piacenza, the administrative center of a northern Italian province with about 289,875 inhabitants, covering a territory of 111,940 km.[2] Guglielmo da Saliceto Hospital is the main Italian Public Health Care System Hospital in this province ("District Hospital", with 529 beds). The study enrolled all the consecutive stroke patients treated by rt-PA between 2006 and 2010.

2.2. Procedures

The province of Piacenza has four hospitals that admit a total of about 800 stroke patients per year into their emergency departments (ED), but there is only one NU, in the "District Hospital", where thrombolysis is performed by six general and two cerebrovascular neurologists. This NU has 21 beds (including 4 stroke-dedicated beds), and a yearly admission rate for stroke of about 350 patients.

A territorial network for acute stroke care was set up. During weekdays, i.e., Monday to Saturday, any patient complaining of acute neurological dysfunction suggestive of stroke underwent a computed tomography (CT) scan of the brain and routine laboratory tests on admission to any of the four EDs. Patients eligible for rt-PA were quickly transferred to the NU for neurological examination and i.v. rt-PA, if they fulfilled the ECASS III protocol inclusion criteria,[6] except for age. Exclusion criteria were based on the ECASS III protocol[4] and/or having suffered a previous stroke with a significant residual disability [modified Rankin scale (mRS) ≥ 3]. Patients admitted to any of the four EDs for acute neurological deficit at night, or on Sundays, were sent directly to the NU for neurological examination and brain CT scan.

Patients fulfilling the aforementioned inclusion criteria were admitted to the NU and administered rt-PA. The patients' demographic characteristics, medical history, exact stroke timing, neurological examination, blood pressure, glucose level, Glasgow Coma Scale score, and NIHSS score were recorded in an *ad hoc* clinical file. The mRS,[13] NIHSS, and Barthel index at 7 days and at 3 months were also noted. Any preexisting functional disability was also evaluated as dependence in at least one activity of daily living (ADL), or instrumental activity of daily living (IADL), prior to stroke. Routine brain CT scan was performed 24 hours after treatment and whenever there was clinical worsening. Any violations of the set protocol were reported and taken into account in the statistical analysis.

2.3. Outcome measures

The effectiveness outcome measure was based on disability at three months. Patients aged <80 years were compared to those aged ≥80 years. The primary endpoint was the proportion of subjects with mRs ≤1 (no disability) at 3 months; the secondary endpoint was the proportion of patients with mRs ≤2 (no or mild disability). The safety outcome measures were the mortality rate, the total (TICH) and symptomatic (SICH) intracerebral hemorrhage rate. Patients aged <80 years were compared to those aged ≥80 years. The primary endpoint was symptomatic hemorrhage, defined as the presence of hemorrhagic infarction, or a parenchymal hematoma, associated with a 4-point increase on the NIHSS score.[6] Secondary endpoints were mortality rate and TICH.

2.4. Statistical analysis

Any differences between the two groups (<80 years and ≥80 years) were evaluated by the Students *t* test (or Mann–Whitney *U* test, when appropriate) and the Chi-square test for continuous, or categorical variables, respectively. A multivariate stepwise logistic regression model was adopted to determine the independent association of significant variables for the TICH outcome. The following covariates were used: age, sex, NIHSS score at stroke onset, time from stroke onset to treatment, history of hypertension, diabetes, atrial fibrillation, and previous stroke. Age was chosen because the primary objective of the study was to clarify the safety and effectiveness of rt-PA in the octogenarians in a "real world setting"; the effect of hypertension on TICH was documented in the echoplanar imaging thrombolytic evaluation trial (EPITHET) trial[14] and some studies revealed an association between TICH and diabetes, cardioembolism, stroke extension, and time from stroke onset to rt-PA administration.[15]

Statistical analysis was performed by SPSS 16.0 for Mac (SPSS Inc., Chicago, IL, USA). The study protocol was approved by the local Ethics Committee and all participants gave written informed consent.

3. Results

From January 2006 to December 2010, a total of 2,331 stroke patients from the province of Piacenza were referred to the NU; 187 (8%) patients fulfilled the ECASS III protocol criteria[6] (8.4% of those <80 years and 7.5% of those ≥80 years) and were treated by rt-PA within 4.5 hours from stroke onset; 90 (48.1%) males and 97 (51.9%) females.

The average age was 75.1 (±11.9), age range 27–97 years; 79 (42.2%) patients were aged ≥80 years. The demographic characteristics, prevalence of vascular risk factors, NIHSS score at stroke onset, door-to-needle time, and stroke onset to treatment time in the study population are shown in Table 1. There was a higher frequency of prestroke disability, measured by the ADL/IADL dependence, in at least one activity, in patients aged ≥80 years

Table 1
The demographics of the study population and of patients aged <80 years compared to those aged ≥80 years.

Feature	Total sample	<80 y group	≥80 y group	*p*
Average age (yr ± SD)	75.1 (11.9)	67.9	84.9	
Females	51.9	40.7	67.1	<0.000
Atrial fibrillation	30.1	18.7	45.6	<0.001
Diabetes	21	27.1	12.7	0.02
Hypercholesterolemia	25.3	31.8	16.5	0.03
Hypertension	66.7	62.6	72.2	0.21
Smoking habit	16.1	19.6	11.4	0.16
Previous TIA/stroke	14.6	15	14.1	1
Anticoagulants	2.7	1.9	3.8	0.65
Antiplatelets	32.8	35.5	29.1	0.43
NIHSS (± SD)	12 (6.14)	10.9	13.5	0.004
Door-to-needle time (min ± SD)	97.9 (38)	98.7	96.7	0.71
Onset-to-treatment time (min ± SD)	161.2 (44.28)	160.9	161.7	0.91

Data are presented as % unless otherwise indicated.
NIHSS = National Institutes of Health Stroke Study; SD = standard deviation; TIA = transient ischemic attack.

[20.8% vs. 7.7%; $p = 0.01$; odds ratio (OR): 3.16; 95% confidence interval (CI): 1.26–7.91].

3.1. Disability at 3 months

Disability at 3 months in the entire study population and in the <80 years and ≥80 years groups is reported in Table 2. A total of 28 participants (35.4%) had no or mild disability (mRS 0–2) in the group ≥80 years, compared to 62 (57.4%) in the group <80 years ($p = 0.003$; OR: 2.51; 95% CI: 1.38–4.57). In the subgroup of patients with no disability prior to the onset of stroke (153 patients, 62.7% <80 years and 37.3% ≥80 years), 22 patients ≥80 years (38.6%) had no poststroke disability (mRS 0–1), compared to 56 (58.3%) patients in the <80 years group ($p = 0.02$; OR: 2.23; 95% CI: 1.14–4.35).

3.2. Mortality at 3 months

There was a 15.1% overall 3-month mortality rate (Table 2), without any statistically significant difference between patients aged <80 years and ≥80 years ($p = 0.1$; 95% CI: 0.89–4.54).

3.3. Rate of TICH and SICH

There was a 14% rate of TICH (26 patients) in the entire study population (Table 2), 16.5% (13 patients) in the ≥80 years group and 12.1% (13 patients) in the <80 years group, without any statistically significant difference between the groups ($p = 0.52$). There was a 3.2% rate of SICH in the entire sample (6 patients, 5 in the ≥80 years group and 1 in the <80 years group). Although there was no statistically significant difference between the two groups ($p = 0.085$), a trend toward a major risk was observed in the ≥80 years group.

Table 2
Proportion (%) and odds ratio of main outcomes at 3 months for patients aged <80 years compared with those aged ≥80 years.

Outcome	Total sample	<80 y group	≥80 y group	*p*	OR (95% CI)
No disability (mRS 0–1)	43	52.3	30.4	$p = 0.004$	2.52 (1.37–4.64)
No or mild disability (mRS ≤2)	48.4	57.4	35.4	$p = 0.003$	2.51 (1.38–4.57)
Mortality	15.1	11.2	20.3	$p = 0.1$	2.01 (0.89–4.54)
TICH	14	12.1	16.5	$p = 0.52$	1.42 (0.62–3.27)
SICH	3.2	0.9	6.3	$p = 0.085$	7.16 (0.82–2.57)

CI = confidence interval; mRS = modified Rankin scale; OR = odds ratio; SICH = symptomatic intracerebral hemorrhage; TICH = total intracerebral hemorrhage.

3.4. Violations of protocol

There were protocol violations in 14 (9%) patients, 6 (6.7%) in the <80 years group and 8 (11.9%) in the ≥80 years group ($p = 0.27$; 95% CI: 0.63–5.76). All violations were due to rt-PA administration after 4 hours and 30 minutes; however, the maximum time from symptom onset to treatment was 4 hours and 42 minutes.

3.5. Multivariate analysis

A logistic regression analysis was performed on TICH because the very few patients presenting with SICH were poorly representative (Table 3). A statistically significant correlation was observed between the NIHSS score prior to treatment and TICH ($p = 0.02$).

4. Discussion

The results of the recent randomized controlled trial IST-3[11] and a meta-analysis[12] on rt-PA for acute stroke suggest that i.v. thrombolysis seems to be both effective and relatively safe in those aged ≥80 years; consequently, age alone should no longer be considered a barrier to treatment. Furthermore, recent studies indicate that intravenous rt-PA within 4.5 hours represents a cost-effective intervention for acute ischemic stroke in most patient subgroups and is a good economic value versus no treatment.[16,17]

A noteworthy finding of our study is that the 3-month disability rate was higher in patients aged ≥80 years receiving i.v. thrombolysis for ischemic stroke. This seems to be in line with a worse outcome of i.v. thrombolysis in elderly patients, as reported by most comparative cohort observational studies.[2] Conversely, the recent IST-3 study[11] suggests that age does not have a negative effect on benefit. However, some factors should be taken into consideration, because as major confounders could minimize rt-PA efficacy when comparing people aged <80 years and ≥80 years in open-labeled, nonrandomized clinical studies.

It is well known that elderly patients do tend to have a worse poststroke functional outcome than younger patients, a difference that remains despite adjustment for baseline differences in stroke risk factors and other comorbidities.[7,8,18] Also in the current study, the NIHSS mean score at stroke onset was significantly higher in patients ≥80 years, in agreement with previous findings[7,18,19] that disability after stroke is higher in the elderly even in the absence of rt-PA treatment not only because of age, but also because of the

Table 3
Multivariate analysis for the total intracerebral hemorrhage outcome.

Variable	*p*
Age	0.38
Sex	0.22
Hypertension	0.10
Atrial fibrillation	0.09
Diabetes	0.17
Previous TIA/stroke	0.99
Onset-to-treatment time	0.95
NIHSS at stroke onset	0.02

NIHSS = National Institutes of Health Stroke Study; TIA = transient ischemic attack.

greater severity of stroke at onset, to premorbid disability and/or to more frequent medical complications in the acute phase.

Furthermore, some degree of disability prior to stroke onset was more frequently observed in the elderly patients in our study, as might be expected. However, in the subgroup without preexisting disability, the 3-month functional poststroke outcome was poorer in the group ≥80 years, as was the case for the entire study group; therefore, the presence/absence of preexisting disability did not seem to significantly affect the thrombolysis outcome in those ≥80 years.

Somewhat surprisingly, the statistical analysis carried out in the IST-3 study,[11] based on the adjusted effect of treatment on the primary outcome between patients aged <80 years or ≥80 years, seemed to demonstrate a greater ($p = 0.029$) benefit of thrombolysis in patients ≥80 years. However, about 44% of the patients aged ≥80 years (726 of 1617) were given i.v. rt-PA within 3 hours, compared to only 8.6% of those aged <80 years (123/1,418), a difference that bears a higher clinical relevance. Indeed, the more favorable time frame of rt-PA administration in the elderly is most likely to be responsible for the apparently greater benefit obtained by treatment in this group, whereas it turned out that the time to randomization significantly affected the primary outcome in the statistical analysis (0–3 hours: adjusted OR = 1.64 in favor of treatment).

A total of 3,035 patients from 156 centers were enrolled into the IST-3 study[11] over an 11-year period (277 patients per year, average 1.7 patients/center/y). Furthermore, all the patients with a clear indication for rt-PA were treated according to local guidelines and were excluded from the study: these selection criteria may well explain why this study enrolled a higher proportion of elderly people than what is normally encountered in clinical practice and a very low average number of patients per center per year.[2–9]

Another noteworthy finding of our study is that there was no difference either in mortality rate or in the TICH/SICH rate between the two age groups, in agreement with some previous studies[20,21] and with the IST-3 death rate at 6 months. However, there was an evident trend toward a higher frequency of symptomatic hemorrhage in the elderly. Such a trend may suggest that although the elderly are not more prone to hemorrhage after rt-PA than younger patients, they do run a higher risk of becoming symptomatic after hemorrhage, due to premorbid conditions/treatments and/or stroke severity/subtype, or reduced neuronal reserve.

Something that should not be underestimated in this study is that it was carried out in a "real world" setting, as another fundamental question is the reproducibility of the results achieved in randomized controlled trials in everyday routine, where the selection of stroke patients, based on more restrictive criteria, makes the cohorts more homogeneous and generally younger than in clinical practice. Moreover, although there were some protocol violations, they were similar in patients aged <80 years and ≥80 years and were, therefore, not significant.

We are also aware of some methodological shortcomings of the study that should be taken into consideration: first of all, the population reported is small and was collected in a single-center, so it could be poorly representative of the elderly population in other settings. Furthermore, the design was observational prospective, did not compare elderly people treated or not treated with rt-PA, and was not randomized. Indeed, caution is always wise when analyzing the safety and efficacy of a treatment through this type of nonrandomized, noncontrolled study, as the numerous biases and confounders may render any conclusion unreliable. Hence the design of the current study only makes it possible to formulate a hypothesis about a good safety and efficacy of thrombolysis for acute ischemic stroke in the elderly, but a randomized clinical trial is mandatory to confirm such hypothesis. We welcome the data from the ongoing Italian Thrombolysis in Elderly Stroke Patients in Italy open-label, randomized trial,[22] which has been specifically tailored to address the use of thrombolysis within 3 hours in the elderly stroke patients, in the hope that it may clarify this important issue.

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