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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