Effect of Intravenous Thrombolysis on Stroke Associated with Atrial Fibrillation

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Background: Data based on randomized clinical trials regarding the efficacy and safety of intravenous thrombolysis (IVT) versus placebo or any other antithrombotic agent in the treatment of stroke associated with atrial fibrillation (AF) are unavailable. *Methods:* Prospectively collected data on AF-associated stroke patients treated in a 3-year period were analyzed to assess the effect of IVT treatment. Outcome measures were modified Rankin Scale (mRS) score for functional outcome, death, and symptomatic intracerebral hemorrhage (sICH). *Results:* Of 787 patients diagnosed with an acute ischemic stroke in the observed period, 131 (16.6%) had AF. Multivariate logistic regression analysis after adjustment for confounders demonstrated that independent predictors of excellent outcome (mRS 0-1) in patients with AF-associated stroke were lower baseline National Institutes of Health Stroke Scale [NIHSS] score (adjusted odds ratio [$_{adj}$OR], .87; 95% confidence interval [CI], 0.81-.94; P = .000) and the use of IVT ($_{adj}$OR, 5.31; 95% CI, 1.90-14.82; P = .001), whereas independent predictors of death were higher baseline NIHSS score ($_{adj}$OR, 1.07; 95% CI, 1.02-1.12; P = .003), previous stroke ($_{adj}$OR, 4.11; 95% CI, 1.49-11.35; P = .006), absence of IVT use ($_{adj}$OR, .19; 95% CI, .05-.77; P = .021), sICH ($_{adj}$OR, 18.52; 95% CI, 1.59-215.37; P = .020), and higher serum glucose levels ($_{adj}$OR, 1.26; 95% CI, 1.06-1.50; P = .008). Thrombolyzed patients with AF were less severe at baseline and were less likely to have NIHSS >18. They were more likely to have excellent and good functional outcome (mRS 0-2) whereas less likely to have death as outcome at 3 months. Thrombolyzed AF patients had constantly lower probability of death regardless of the baseline NIHSS score values. *Conclusions:* These results should encourage the use of IVT in AF-associated strokes. **Key Words:** Stroke—atrial fibrillation—intravenous thrombolysis—outcome.

Introduction

Atrial fibrillation (AF) is the most prevalent sustained hearth rhythm disorder, which is associated with severe consequences that include heart failure, stroke, reduced quality of life, poor mental health, and death.[1] Around 2% of world population has AF and the situation is predicted to worsen because it is expected that the number of people with AF will double by 2050.[2,3] AF is an independent risk factor for stroke and thromboembolism, which increases the stroke risk by 5-fold and results in an independent increase in mortality per se.[4] It is estimated that AF is responsible for approximately 15%-20% of all strokes.[5] AF-associated strokes are more severe,[6] more

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often fatal,[7] and more likely to lead to disability.[8]They are also more likely to increase costs[9] and extended hospital care compared with non-AF strokes.[6]

Intravenous thrombolysis (IVT) is the only approved therapy in patients with acute ischemic stroke presenting within 4.5 hours after symptom onset.[10] However, data about its efficacy in the treatment of AF-associated strokes is still scarce because there have no't been many studies that were analyzing the issue whether stroke patients with AF are obtaining significant benefit from thrombolysis in comparison with non thrombolyzed stroke patients with AF. In randomized controlled trials of IVT use in treatment of ischemic stroke, baseline characteristics and outcomes of AF patients who were thrombolyzed have been detailed in only few trials.[11-13] However, their results are conflicting with a non-significant trend in favor of placebo in "Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ECASS III)" trial,[12] in favor of IVT in "The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke [IST-3])" trial,[11] and no effect of the treatment in "Tissue Plasminogen Activator for Acute Ischemic Stroke (NINDS)" trial.[13] Some studies that were analyzing in more detail, the baseline characteristics and outcomes of AF-associated stroke patients (with thrombolyzed and non-thrombolyzed ones included), have also reported contradictory results.[14-16] In Virtual International Stroke Trials Archive (VISTA) study, of 1631 AF patients with ischemic stroke, 639 received IVT. AF patients had more severe clinical deficits, were older than non-AF patients, and there was a benefit of IVT administration that was registered.[14] In another retrospective study that compared 22 AF patients who received IVT with 44 AF patients who did not, there was an association with a favorable outcome in thrombolyzed patients.[15] On the other hand, the study of Saposnik et al[16] that included 2185 patients with AF-associated stroke, from which 316 were thrombolyzed, has found no benefit of IVT use in patients with AF.

The aims of our study were the following: (1) to analyze baseline characteristics of AF patients with stroke and (2) to test the hypothesis that stroke patients with AF who receive IVT have better outcomes in comparison with non-thrombolyzed AF patients.

Materials and Methods

We analyzed prospectively collected data of patients with AF-associated stroke who were treated in the Department for Emergency Neurology of Neurology Clinic, Clinical Centre of Serbia, from January 2009 to June 2012. For the study, a specially designed protocol was used.

Setting

The general organization of this stroke center has already been described.[17]

Inclusion and Noninclusion Criteria

Inclusion and exclusion criteria were those of the NINDS recombinant tissue plasminogen activator stroke protocol.[18] To be indicated for IVT administration patients had to have the following: (1) an acute ischemic stroke with a clearly defined time of onset; (2) an acute neurologic deficit expected to result in significant long-term disability; and (3) a baseline computed tomographic scan of the brain showing no hemorrhage or well-established acute infarct.[18] IVT was performed according to the current guideline up to a 4.5-hour time window for hemispheric stroke and up to 12 hours for posterior circulation stroke.[19] Eligible patients received 0.9 mg of alteplase per kilogram of body weight (with a maximum dose 90 mg), administrated intravenously.[19]

Assessment of AF

In all patients medical history was recorded, an electrocardiogram (ECG) at admission was performed as well as a 48-72 hours continuous ECG monitoring and, if necessary because of the clinical symptoms, additional ECG recordings. AF was classified as previously known or de novo AF. AF was considered as previously known in cases where previous ECG with AF or atrial flutter was seen by a stroke team's physician or when there was a report of a cardiologist stating that AF had been previously detected on ECG or Holter ECG. AF was considered as de novo in cases when there was no medical history of previous AF or atrial flutter but this was found on either ECG recorded in the emergency department on admission or during hospitalization (on the 48-72 hours continuous ECG monitoring).

Clinical Assessment

The pretreatment stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) score[18] just before IVT administration and after 7 days. The outcomes at 3 months were assessed with the modified Rankin Scale (mRS) score.[20] All assessments were made by a senior neurologist. In survivors, when the visit after 3 months was not possible it was replaced by a telephone interview with the patient, caregiver, local neurologist, or general practitioner. The analyses of computed tomographic scans were performed by a neuroradiologist.

End Points

The primary end point was the proportion of patients who had an excellent outcome (defined as a mRS score of 0 or 1 at 3 months or similar to the pre-stroke mRS). Secondary end points were as follows: (1) after 7 days: symptomatic intracerebral hemorrhage (sICH, defined according to the ECASS III definition)[10] and death and (2) after 3 months: good outcome (defined as a mRS 0-2) and death.