SAFETY AND OUTCOME OF INTRAVENOUS THROMBOLYSIS WITH rtPA IN PATIENTS WITH ATRIAL FIBRILLATION

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ABSTRACT

Background and purpose. Intravenous administration of recombinant tissue plasminogen activator (rtPA) is approved for the treatment of patients with acute ischemic stroke. It is still controversial if in patients with ischemic stroke due to atrial fibrillation this treatment has the same efficacy as in patients with ischemic stroke due to other etiologies. The present study aimed to compare the safety and outcome of intravenous thrombolysis with rtPA between patients with stroke due to atrial fibrillation, due to other cardiac sources of emboli and due to large-vessel disease.

Methods. Retrospective analysis of 463 patients treated with rtPA in the Stroke Unit of Ramon y Cajal University Hospital, Madrid, between January 2004 and December 2011. Patients were divided in three subgroups according to stroke etiology: cardioembolic stroke due to atrial fibrillation, cardioembolic stroke due to a cardiac disease other than atrial fibrillation, stroke due to large-vessel disease. The outcome measures of the study were: symptomatic intracranial hemorrhage transformation, modified Rankin score and mortality at three months.

Results. The results of the multivariate analysis showed that stroke etiology has no influence on functional outcome ($p = 0.181$), symptomatic intracranial hemorrhage ($p = 0.093$) and mortality at three months ($p = 0.091$). Age and baseline NIHSS scores are independent predictors for both functional outcome and mortality.

Conclusion. Stroke outcome after intravenous thrombolysis with rtPA is not influenced by the stroke etiology.

Key words: thrombolysis, rtPA, atrial fibrillation, cardioembolic stroke, outcome, safety

INTRODUCTION

Intravenous administration of recombinant tissue plasminogen activator (rtPA) is approved for the treatment of patients with acute ischemic stroke. It is still controversial if in patients with ischemic stroke due to cardioembolism and particularly in those with atrial fibrillation this treatment has the same efficacy as in patients with ischemic stroke due to other etiologies.

METHODS

We performed a retrospective analysis in order to assess the safety and effectiveness of the treatment with intravenous rtPA in patients with atrial fibrillation.

The study included all the patients treated with rtPA in the Stroke Unit of Ramon y Cajal University Hospital, Madrid, between January 2004 and December 2011. Patients treated with intra-arterial rtPA or mechanical thrombectomy were excluded. Intravenous rtPA was administered in a standard dose of 0.9 mg/kg within 4.5 hours from stroke onset, according to the current European recommendations for thrombolytic treatment.

On admission, neurological examination was carried out. Blood analysis and a cranial CT scan were performed for all the patients, and in selected cases perfusion CT and CT angiography. A second

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CT scan was performed 24 hours after rtPA administration or earlier, in case of neurological worsening. Stroke severity was assessed with The National Institutes of Health Stroke Scale (NIHSS) at admission, 24 hours and 7 days after thrombolysis.

Other registered data included: age, sex, previous diseases (hypertension, diabetes, previous Stroke, atrial Fibrillation, history of heart failure, other cardiac diseases, dyslipidemia), arterial blood pressure (at admission and during the first 24 hours), level of plasma glucose, time from stroke onset to rtPA administration (stroke onset was defined as the last time when the patient was seen without new neurological deficit), the presence or absence of cerebral hemorrhagic transformation and the type of this transformation (symptomatic/asymptomatic), results of other paraclinical findings: (cervical and transcranial Doppler ultrasonography, ecocardiography, 24h ECG monitoring - in selected patients), modified Rankin score three month after thrombolysis, cause and time of death.

Hemorrhages were classified according to the SITS-MOST classification (hemorrhagic infarction type 1, hemorrhagic infarction type 2, parenchymal hematoma type 1, parenchymal hematoma type 2, remote parenchymal hematoma type 1 and remote parenchymal hematoma type 2). Symptomatic intracranial hemorrhage (sICH) was defined as local or remote type 2 parenchymal hematoma in patients with a neurological worsening of 4 or more points from baseline NIHSS score, or from the lowest NIHSS score between baseline and 24h, or any hemorrhage that lead to death (1).

For each patient stroke etiology was carefully analyzed (large-vessel disease, small-vessel disease, cardioembolism, other etiology, undetermined despite extensive evaluation, undetermined because of incomplete evaluation, undetermined with two possible causes). A special attention was paid to the cardioembolic etiology. For each patient with cardioembolic stroke the underlying cardiac disease was noted (atrial fibrillation, other arrhythmia, cardiomyopathy, rheumatic valvular disease, mechanical prosthetic valve, left atrial or ventricular thrombus, recent myocardial infarction). For further analysis were selected only the patients with atrial fibrillation (The Atrial Fibrillation Group – AF Group), the patients with cardioembolic stroke due to other cardiac diseases (The Cardioembolic Without Atrial Fibrillation Group – CE Group) and the patients with ischemic stroke due to large-vessel disease (The Large-Vessel Disease Group – LVD Group). Patients with stroke due to small-vessel disease, stroke of undetermined etiology and stroke due to cervical artery dissection were not included in the further analysis.

The outcome measures of the study were:

- symptomatic intracranial hemorrhage transformation;
- independence at three months defined as a modified Rankin score ≤ 2 at three months;
- mortality at three months

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS Software version 19.0.0 (SPSS Inc, Chicago, IL, USA). Comparisons between study groups were made using Chi-squared test or Kruskal – Wallis test, as appropriate. Multivariable analysis was performed using a multiple logistic regression model which included: baseline NIHSS score, age, sex, arterial hypertension, diabetes mellitus, history of heart failure and blood pressure higher than 185/110mmHg during the first 24h. Statistical significance was set at $p < 0.05$.

RESULTS

The final study group included 463 patients. The mean age was 74.6 ± 12.1 years and 47.7% were males. The patients were divided in 3 subgroups:

- patients with cardioembolic stroke due to atrial fibrillation (217 patients, 46.8% – further named AF Group)
- patients with cardioembolic stroke due to a cardiac disease other than atrial fibrillation (59 patients, 12.7% – further named CE Group)
- patients with stroke due to large-vessel disease (187 patients, 40.3% – further named LVD Group).

Baseline and demographic data of all three groups are expressed in Table 1.

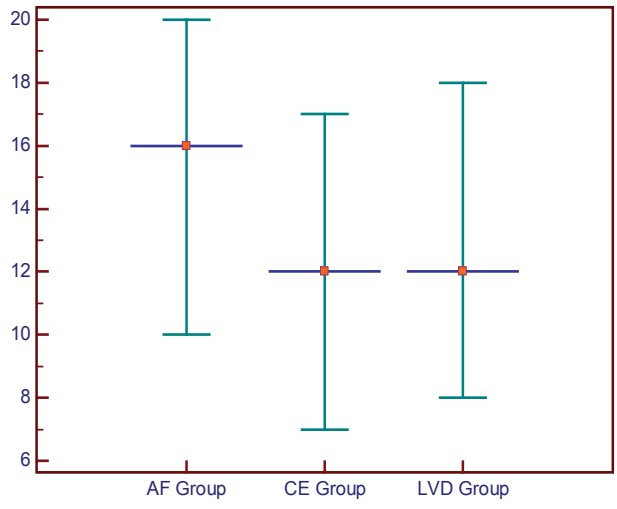
The AF Group contained a significantly higher proportion of women (61.7% vs. 45.7% in the CE Group vs. 43.3% in the LVD Group, $p = 0.06$), the patients in this group being significantly older (mean age 78.1 vs. 64.1 in the CE Group vs. 73.9 in the LVD Group, $p < 0.0001$). There were no differences regarding the prevalence of hypertension, diabetes mellitus, dyslipidemia and previous stroke between the three groups. As expected, the patients included in the CE Group more frequently had heart failure (27.1% vs. 17.5% in the AF Group vs. 3.2% in the LVD Group, $p < 0.001$). The proportion of smokers was significantly lower in the AF Group (7.8% vs. 15.2% in the CE Group vs. 21.3% in the LVD Group, $p = 0.0005$). High values of blood

TABLE 1. *Baseline characteristics of the patients*

	AF Group (*n = 217*)	CE Group (*n = 59*)	LVD Group (*n = 187*)	p value
Demographic data				
Age	78.1 ± 9.5	64.1 ± 15.9	73.9 ± 11.3	P < 0.0001
Female Sex	134 (61.7%)	27 (45.7%)	81 (43.3%)	P = 0.006
Previous mRS 0-2	203 (93.5%)	55 (93.2%)	180 (96.2%)	P = 0.2
Clinical characteristics				
Hypertension	170 (78.3%)	38 (64.4%)	134 (71.6%)	P = 0.06
Diabetes mellitus	63 (29%)	12 (20.3%)	51 (27.2%)	P = 0.4
Dyslipidemia	68 (31.3%)	21 (35.5%)	65 (34.7%)	P = 0.7
Heart failure	38 (17.5%)	16 (27.1%)	6 (3.2%)	P < 0.001
Previous Stroke	32 (14.7%)	7 (11.8%)	28 (14.9%)	P = 0.8
Baseline plasma glucose (mg/dl)	137.6 ± 40.9	134.4 ± 46.6	134.9 ± 45.67	P = 0.1
Smoking	17 (7.8%)	9 (15.2%)	40 (21.3%)	P = 0.0005
High blood pressure during the first 24h (*)	42 (19.3%)	6 (10.1%)	52 (27.8%)	P = 0.008
Baseline NIHSS	16 (6;23)	12 (5;21)	12 (5;21)	P < 0.0001
Time from stroke onset to rtPA administration (min)	151.1 ± 49	146 ± 60	164.1 ± 66.4	P = 0.1

* defined as a blood pressure > 185/110 mmHg during the first 24h from stroke onset; NIHSS National Institutes of Health Stroke Scale; Results are expressed as median and the 25th and 75th percentiles or mean and standard deviation for continuous variables (upon case) and as absolute values and relative frequencies for categorical variables.

pressure during the first 24h from stroke onset (defined as blood pressure higher than 185/110mmHg) were more frequently observed among patients included in the LVD Group (27.8% vs. 19.3% in the AF Group vs. 10.1% in the CE Group, p = 0.008). There were no significant differences regarding the time from stroke onset to rtPA administration between the groups. The baseline NIHSS scores were significantly higher in the AF Group (median NIHSS 16 vs. 12 in the CE Group vs. 12 in the LVD Group, p < 0.0001, Graph 1).



GRAPH 1. *Baseline NIHSS scores according to stroke etiology. Values are expressed as medians (horizontal lines) and 25-75 percentiles (vertical lines)*

The results of the bivariate analysis (Table 2) showed that the functional outcome (defined as a mRS ≤ 2 at three months) was worse in the AF Group (44.2% vs. 71% of the CE Group vs. 58.8% of the LVD Group, p = 0.0002). However, the multivariate analysis (logistic regression model which included stroke etiology, sex, age, baseline NIHSS score, hypertension, diabetes mellitus, history of heart failure, presence of high blood pressure levels during the first 24h as independent variables – Table 3) showed that stroke etiology has no influence on functional outcome (p = 0.181). Independent predictors for good clinical outcome were: age (OR 0.95, 95%CI 0.93-0.98, p = 0.000), baseline NIHSS score (OR 0.82, 95%CI 0.79-0.86, p = 0.000), hypertension (OR 1.8, 95%CI 1.06-3.14, p = 0.028) and blood pressure values higher than 185/110 mmHg during the first 24h (OR 0.46, 95%CI 0.26-0.81, p = 0.007).

TABLE 2. *Differences in stroke outcomes between subgroups: bivariate analysis*

	AF Group (*n = 217*)	CE Group (*n = 59*)	LVD Group (*n = 187*)	P
mRS 0-2 at three months	96 (44.2%)	42 (71.1%)	110 (58.8%)	P = 0.0002
sICH	9 (4.1%)	0	5 (2.6%)	P = 0.2
Mortality	51 (23.5%)	5 (8.4%)	19 (10.1%)	P = 0.0003

mRS: modified Rankin Scale; sICH: Symptomatic intracranial hemorrhage; results are expressed as absolute values and relative frequencies.

TABLE 3. *Independent predictors for good clinical outcome (mRS 0-2 at three months) after rtPA administration*

	P	OR	95% CI for OR
Stroke etiology	0.207	1.25	0.884-1.769
Age	0.001	0.959	0.938-0.980
Sex	0.136	0.706	0.446-1.116
Baseline NIHSS score	0.001	0.829	0.795-0.864
Hypertension	0.028	1.832	1.066-3.146
Diabetes Mellitus	0.488	0.811	0.449-1.466
BP > 185/110 mmHg during the first 24h	0.007	0.465	0.266-0.810
History of heart failure	0.193	1.576	0.794-3.129

Multivariate logistic regression analysis testing stroke etiology, sex, age, baseline NIHSS, hypertension, diabetes, blood pressure > 185/110 during the first 24h, history of heart failure as independent predictors

There were no differences regarding the symptomatic intracranial hemorrhage following rtPA administration between the study groups (p = 0.2). When multivariate analysis was performed (Table 4), the only independent predictor for this complication were the blood pressure levels higher than 185/110 mmHg during the first 24h (OR 3.73, 95%CI 1.2-11.62, p = 0.023).

TABLE 4. *Independent predictors for symptomatic intracranial hemorrhage after rtPA administration*

	P	OR	95% CI for OR
Stroke etiology	0.093	0.403	0.139-1.165
Age	0.228	0.968	0.918-1.021
Sex	0.960	1.029	0.333-3.186
Baseline NIHSS score	0.299	1.049	0.958-1.148
Hypertension	0.429	1.951	0.372-10.23
Diabetes Mellitus	0.522	1.517	0.424-5.429
BP > 185/110 mmHg during the first 24h	0.023	3.736	1.2-11. 626

Multivariate logistic regression analysis testing stroke etiology, sex, age, baseline NIHSS score, hypertension, diabetes mellitus, blood pressure > 185/110 during the first 24h as independent predictors

The mortality in the AF Group was higher according to bivariate analysis (23.5% in the AF Group vs. 8.4% in the CE Group vs. 10.1% in the LVD Group, p = 0.0003). However, the results of the multivariate analysis (Table 5) showed that stroke etiology has no influence on mortality rates (p = 0.09). The only independent predictors for mortality were age (OR=1.055, 95%CI 1.02-1.08, p = 0.001), baseline NIHSS score (OR = 1.2, 95%CI 1.13-1.27, p = 0.000), diabetes mellitus (OR 2.206, 95%CI 1.04-4.65, p = 0.017) and history of heart failure (OR 2.44; 95%CI 1.14-5.18; p = 0.02).

TABLE 5. *Independent predictors for mortality after rtPA administration*

	P	OR	95% CI for OR
Stroke etiology	0.091	0.66	0.408-1.068
Age	0.001	1.055	1.021-1.089
Sex	0.086	1.683	0.928-3.052
Baseline NIHSS	0.001	1.2	1.136-1.274
Hypertension	0.505	0.772	0.361-1.651
Diabetes Mellitus	0.038	2.206	1.046-4.653
BP > 185/110 mmHg during the first 24h	0.054	1.930	0.989-3.764
History of heart failure	0.02	2.44	1.14-5.18

Multivariate logistic regression analysis testing stroke etiology, sex, age, baseline NIHSS, hypertension, diabetes mellitus, history of heart failure and blood pressure > 185/110 mmHg during the first 24h as independent predictors

DISCUSSIONS

The NINDS Trial showed that rtPA treatment was effective regardless of the stroke subtype (small-vessel, large-vessel or cardioembolic stroke) (2). Since then, various studies questioning the effectiveness of thrombolysis with rtPA in patients with atrial fibrillation have been published.

The results of the present study, comparing the safety and effectiveness of intravenous thrombolysis with rtPA between patients with stroke due to atrial fibrillation, due to other cardiac sources of emboli and due to large-vessel disease, show that stroke etiology has no influence on functional outcome, symptomatic intracranial hemorrhage and mortality. Age and baseline NIHSS score are independent predictors for both functional outcome and mortality. In other words, we found that a stroke leading to a certain baseline NIHSS score will have the same three months functional outcome and the same mortality risk, regardless of the stroke etiology.

S. Rocha and her colleagues conducted a study that included 177 patients, categorized into patients with cardioembolic (81 patients) and non-cardioembolic stroke, showing that patients with non-cardioembolic stroke had better three months outcomes (mRS < 3). The authors raised the problem that the benefit of thrombolysis with rtPA can vary according to the size, composition and origin of the thrombus, old clots rich in platelets, well organized and formed in flow conditions being more resistant than fresh clots, rich in fibrin and blood cells, formed under conditions of stasis (3).

The results of our study argue against this assumption as we didn't find any association between stroke subtype (and accordingly thrombus composition) and functional outcome.

D. Sanak and his colleagues found that patients with AF had significantly worse 90-day clinical outcome after intravenous thrombolysis compared to those without AF, probably due to more severe baseline neurological deficits. His study included 157 patients, treated with rtPA within 3 hours from stroke onset, divided in two study groups according to the presence or absence of atrial fibrillation. He performed magnetic resonance angiography to all the patients and found that there are no differences regarding the recanalization rates between the study groups (4).

On the other hand, Molina et al. conducted a study that aimed to evaluate the timing and degree of rtPA induced recanalization in patients with different stroke subtypes. The study included 72 patients with acute stroke due to proximal middle cerebral artery occlusion divided in three subgroups according to stroke subtype (large-vessel disease strokes, cardioembolic strokes, strokes of undetermined origin). The authors of the study consider that cardioembolic stroke represents the stroke subtype with more uniform fibrin-rich clots in which rtPA penetrates and distributes homogeneously, leading to entire and rapid clot dissolution. The results of the study show that early recanalization was more frequent, faster and more complete in patients with cardioembolic stroke compared with other stroke subtypes. Consequently, the proportion of patients who became independent at three months (mRS score < 3) was significantly higher in the cardioembolic group (59%) compared with the undetermined group (40%) and the large-vessel disease group (11%). This proportion was assessed by bivariate analysis (Kruskall-Wallis test) without adjusting for confounding factors in a multivariate analysis model (5). The study groups of the present analysis are different from Molina's groups, since we excluded the patients with atrial fibrillation from the cardioembolic group and analyzed them separately. Even though the study groups didn't include the same patients (as mentioned), the results of the bivariate analysis of our study are in agreement with Molina's findings: 71,1% of the patients included in the cardioembolic group were independent at three months versus 58,8% of the patients included in the large-vessel disease group.

Kimura et al. conducted a study that included 85 patients, divided in two subgroups according to the presence or absence of atrial fibrillation. The conclusion of the study is that patients with ischemic stroke and atrial fibrillation more frequently had poor outcome after iv. rtPA therapy compared with those without atrial fibrillation. However, the multivariate analysis performed included only gender and age as confounding factors, and not the baseline NIHSS score and other factors that may have an impact on final outcome (6).

We must consider, however, certain limitations of our findings, the main being the retrospective design of the study and the post hoc analysis of the database.

CONCLUSIONS

Stroke outcome after intravenous thrombolysis is not influenced by the stroke etiology. Patients with higher baseline NIHSS scores will have a worse prognosis, but the three months functional outcome and the mortality risk will be the same for a certain baseline NIHSS score regardless of the stroke etiology.

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