SAFETY OF THROMBOLYSIS WITH IV RT-PA IN PATIENTS WITH ATRIAL FIBRILLATION RELATED ISCHEMIC STROKES AND PRIOR SUBTHERAPEUTIC USE OF COUMARINIC ANTICOAGULANTS

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ABSTRACT

Background and purpose. There are conflicting data in the literature regarding the safety of intravenous thrombolysis in patients with ischemic strokes receiving prior treatment with vitamin K antagonists. We aimed to assess the safety, short term outcome and mortality after rt-PA administration in patients with atrial fibrillation related strokes and prior subtherapeutic use of vitamin K antagonists.

Methods. The study included 210 patients with atrial fibrillation who received treatment with intravenous rt-PA for acute ischemic stroke. We compared the frequency of bleeding complications, including intracerebral hemorrhage of any type and symptomatic intracerebral hemorrhage in patients with and without preadmission acenocoumarol use. We also investigated whether there were differences regarding short term functional outcome (assessed with the modified Rankin score at three months after thrombolysis) and mortality rates between them.

Results. 48 patients (22.8%) were receiving acenocoumarol before admission and had international normal ratio (INR) ≤ 1.7. In this group, the median INR value was 1.4 (IQR 1.3-1.6). Preadmission coumarinic anticoagulants use was neither associated with secondary intracerebral hemorrhage of any type (p = 0.9), nor with symptomatic intracerebral hemorrhage (p = 0.9). Moreover, no differences regarding short term stroke outcome (p = 0.86), and mortality (p = 0.56) were observed between patients with or without prior acenocoumarol use. Using logistic regression analysis NIHSS score was found to be the only independent predictor for both short term stroke outcome (OR = 0.82; 95% CI 0.77-0.87; p < 0.0001) and mortality (OR = 1.18; 95%CI 1.09-1.27; p < 0.0001). Chronic heart failure was a second independent predictor for mortality (OR = 3.66; 95%CI 1.41-9.5; p = 0.007). Blood pressure values of more than 185/110 mmHg during the first 24 hours after stroke onset were independently associated with the short term stroke outcome (OR 0.37; 95% CI 0.15-1.88; p = 0.02).

Conclusion. In the present study the rates of intracranial hemorrhage and mortality following intravenous thrombolysis for atrial fibrillation related ischemic strokes were not different between the patients who were prior receiving subtherapeutic treatment with acenocoumarol and those who were not receiving coumarinic oral anticoagulants at all. As a result, the use of recombinant tissue plasminogen activator in this clinical setting seems to be safe. Further studies with larger number of patients and a prospective design are needed to confirm these findings.

Key words: ischemic stroke, atrial fibrillation, thrombolysis, recombinant tissue plasminogen activator, oral anticoagulation, intracerebral hemorrhage, short term stroke outcome, mortality

INTRODUCTION

Intravenous administration of recombinant tissue plasminogen activator (rtPA) is currently the gold standard in the treatment of acute ischemic stroke. However, besides increasing the probability of a favorable outcome this treatment has a potential associated risk of hemorrhagic complications,

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the intracranial hemorrhage being the most feared of them.

Atrial fibrillation is of considerable importance in the pathogenesis of ischemic stroke because of its high prevalence and its substantial risk of embolism. Despite the huge efforts that have been made over the last decade in order to improve the prevention strategies it still accounts for one fifth of all strokes. With over 6 millions of Europeans affected by this arrhythmia (1), the issue of anticoagulant use among patients presenting with acute ischemic stroke is not trivial and has raised further concerns regarding the hemorrhagic risk in patients receiving treatment with rt-PA.

Neither the NINDS study (2), nor the ECASS studies (3) (4) included patients who were taking oral anticoagulants or who had received heparin within the 48 hours preceding the onset of stroke and had an elevated partial thromboplastin time or a prothrombin time >15 seconds. Nevertheless, the current guidelines allow the treatment with intravenous rt-PA when the international normalized ratio (INR) preceding stroke is ≤ 1.7.

A few studies have investigated the benefits and risks of rt-PA administration in patients prior receiving treatment with coumarinic anticoagulants (5) (6) (7) (8) and even fewer have specifically assessed the safety profile in patients with strokes due to atrial fibrillation (9), which might be associated with an increased risk of hemorrhagic transformation even in the absence of thrombolysis (10).

PATIENTS AND METHODS

We performed a retrospective analysis in order to assess the safety of the treatment with intravenous recombinant tissue plasminogen activator (rt-PA) in patients with atrial fibrillation who were receiving treatment with coumarinic oral anticoagulants prior to thrombolysis.

The study included all the patients with acute ischemic stroke and atrial fibrillation treated with IV rt-PA in the Stroke Unit of Ramón y Cajal Hospital, Madrid, between January 2004 and December 2011. Intravenous rt-PA was administered in the standard dose of 0.9 mg/kg within 3-4.5 hours from stroke onset, according to the recommendations of the European Stroke Organization at the moment of the treatment. Stroke onset was defined as the last time when the patient was seen without new neurological deficits.

All clinical, imaging and laboratory data of the patients were recorded and documented according to the standardized acute stroke care protocol of the hospital: detailed neurological examinations with assessment of the National Institute of Health and Stroke score (NIHSS) at admission, 24 hours and 7 days after thrombolysis or at the moment of clinical worsening (if the case); time from onset of symptoms to initiation of rtPA treatment (further named time to treatment – TTT); assessment of cardiovascular risk factors; CT scans at admission and 24 hours after the treatment (range 22-36 hours) or if the case, at the moment of neurological worsening; ECG; Doppler ultrasonography of the cervico-cerebral arteries; transthoracic or transesophageal echocardiography and 24 hours ECG monitoring in selected cases; laboratory tests; modified Rankin score (mRS) 90 days after the stroke onset or, in case of death, time and cause of death.

For each patient all the previously mentioned data were carefully analyzed. All the patients with acute ischemic stroke and atrial fibrillation in which IV thrombolysis was performed were included in the study, irrespective of the type of atrial fibrillation (chronic or paroxysmal, non-valvular or valvular). Further on, the patients were divided in two groups according to whether they have received or not treatment with acenocoumarol prior to thrombolysis.

Functional outcome after thrombolysis was rated using the mRS at 90 days after treatment, and patients were considered to have good clinical outcome when the mRS was ≤ 2.

Intracranial hemorrhages, appreciated by CT scans at 24 hours (range 22-36 hours) after thrombolysis or earlier, in case of neurological worsening, were classified according to the SITS-MOST classification. Symptomatic intracranial hemorrhage (sICH) was defined as local or remote type 2 parenchymal hematoma that was associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death.

The mRS at three months, ICH, sICH and mortality at three months were the main outcome measures of the study.

STATISTICAL ANALYSIS

Statistical analysis was performed using MedCalc version 12.7.1.0. Categorical variables were compared using the Fisher's exact test and Pearson χ^2 test, as appropriate. Continuous variables were analyzed by Mann-Whitney test. For the investigation of predictors for the main outcome measures of the study multiple logistic regression was performed. Statistical significance was set at $p < 0.05$.

RESULTS

Over the study period 236 patients with atrial fibrillation and acute ischemic stroke received treatment with IV rt-PA. 26 patients were excluded from further analysis due to missing data. The final study group included 210 patients, from which 48 patients (22.8%) were found to receive subtherapeutic treatment with acenocoumarol (INR ≤ 1.7) prior to thrombolysis (Group further named *Group with OAT*) and 162 patients (77.2%) were not taking oral anticoagulants at that moment (Group further named *Group without OAT*).

Clinical characteristics and demographic data of the two subgroups of patients are expressed in Table 1.

TABLE 1. *Baseline characteristics of the patients**

	Group without OAT *(n = 162)*	Group with OAT *(n = 48)*	P value
Demographic data			
Age (years)	79 (74; 85)	79 (73-83)	P = 0.5
Male sex	63 (38.8%)	12 (25%)	P = 0.08
Clinical characteristics			
Previous mRS 0-2	152 (93.8%)	44 (91.6%)	P = 0.5
Arterial hypertension	123 (75.9%)	43 (89.5%)	P = 0.04
Diabetes mellitus	45 (27.7%)	16 (33.3%)	P = 0.4
Dyslipidemia	47 (29.01%)	21 (43.7%)	P = 0.07
Heart failure	19 (11.7%)	19 (39.5%)	P < 0.001
Previous stroke	20 (12.3%)	11 (22.9%)	P = 0.1
Smoking	14 (8.6%)	3 (6.2%)	P = 0.7
High blood pressure during the first 24 h**	33 (20.8%)	9 (19.5%)	P = 0.8
Baseline plasma glucose (mg/dL)	125.5 (109; 155)	133 (113;173.7)	P = 0.1
Baseline NIHSS	15.5 (10;19)	18 (10;23)	P = 0.057
Time to treatment (min)	145 (110;175)	160 (130;190)	P = 0.058

*Results are expressed as median and 25th and 75th percentiles for continuous variables and as absolute values and relative frequencies for categorical variable;
** defined as blood pressure > 185/110 mmHg

There were no significant differences between the groups regarding demographic data. The baseline neurological status of the patients, assessed with the mRS score before thrombolysis was similar. The *Group with OAT* contained a significantly higher proportion of patients with heart failure (39.5% vs. 11.7%, p < 0.001) and arterial hypertension (89.5% vs. 75.9%, p = 0.04). There were no differences regarding prevalence of diabetes mellitus, dyslipidemia and previous stroke between the groups. The proportion of smokers was similar in the two groups. The baseline plasma glucose levels were somewhat higher in the *Group with OAT* but the difference didn't reach statistical significance (125.5 vs. 133, p = 0.1). High values of blood pressure during the first 24h from stroke onset were observed with the same frequency in both groups. The median baseline NIHSS score (Figure 1) was higher in the group of patients receiving prior treatment with acenocumarol, reflecting more severe strokes, but the difference didn't reach statistical significance (median values 15.5 vs.18; 25-75IQR 10-19 vs.10-23, p = 0.057).

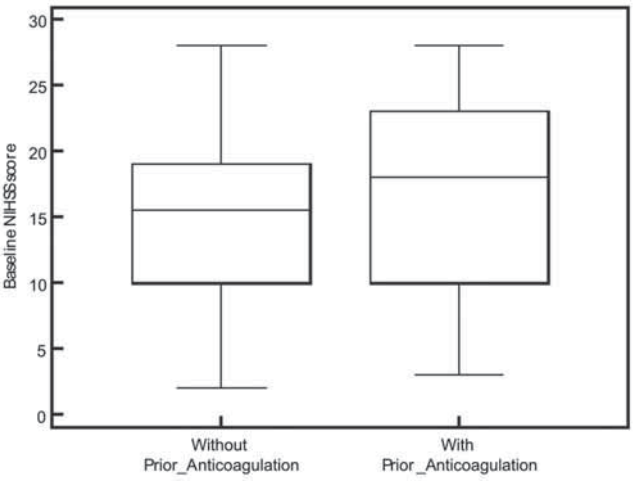

FIGURE 1. *Box-and-whisker plot representing the baseline NIHSS scores in the two groups.*

The patients receiving oral anticoagulants were treated later as compared to those who were not receiving such treatment (Figure 2), but the difference of the time periods was not statistically significant (median 145 minutes vs. 160 minutes, 25-75 IQR 110-175 vs. 130-190, p = 0.058).

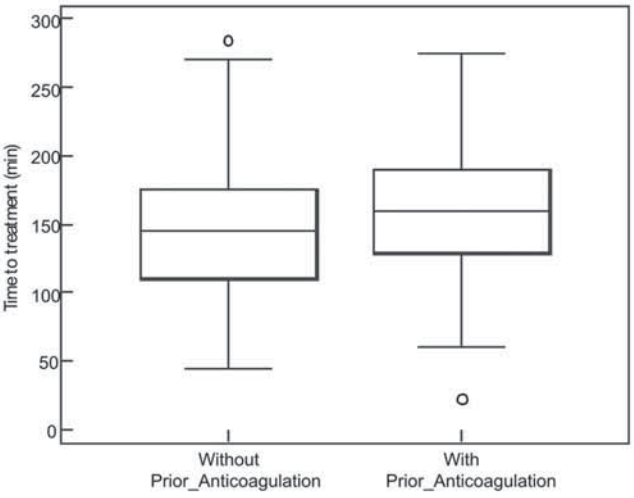

FIGURE 2. *Box-and-whisker plot representing the time from stroke onset to rt-PA administration (time to treatment) in the two groups*

The median INR value for those taking coumarinc oral anticoagulants was 1.4 (25-75 IQR 1.3-1.6). In 50% of the patients the INR was between 1.3 and 1.6 and in 20% of them the INR value was at the upper limit currently admitted (1.7) (Figure 3).

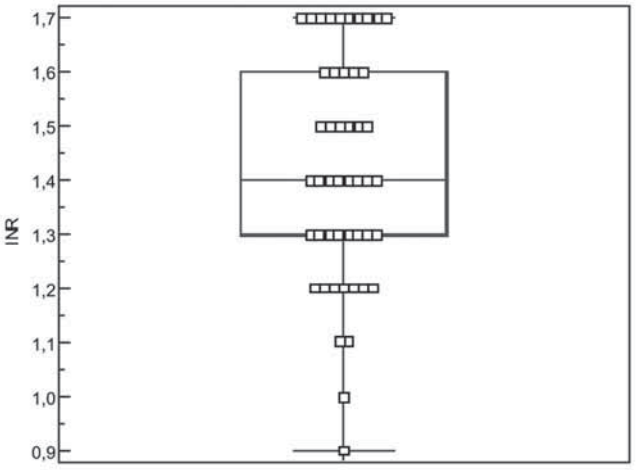

FIGURE 3. *The INR values of the patients receiving oral anticoagulant treatment prior to thrombolysis*

There were no significant differences regarding the main outcome measures of the study (ICH, sICH, mRS at three months and mortality) between the two study groups. The results of the bivariate analysis are presented in Table 2.

TABLE 2. *Differences in outcome measures between subgroups: bivariate analysis**

	Group without OAT *(n=162)*	Group with OAT *(n=48)*	P value
mRS 0-2 at 3 months	68 (41.9%)	21 (43.7%)	P = 0.86
ICH	26 (16.05%)	7 (14.5%)	P = 0.9
sICH	7 (4.3%)	2 (4.1%)	P = 0.9
Mortality	37 (22.8%)	13 (27.08%)	P = 0.56

* values are expressed as absolute values and relative frequencies

One of the two cases of sICH in the *Group with OAT* was in a male, 82 years old, with history of arterial hypertension, who was administered IV rt-PA 185 minutes after the stroke onset. The INR before thrombolysis was 1.3. He had high values of blood pressure during the first 24 hours after rt-PA infusion, for which he was administered intravenous antihypertensive treatment. His baseline NIHSS score was 17 and his worsening of 7 points observed several hours after thrombolysis was attributed to a parenchymal haematoma type 2. He died 6 days after the stroke onset. The other case was of a woman, 78 years of age, with history of arterial hypertension, who received treatment with rt-PA 160 minutes after the stroke onset. Her baseline NIHSS score was 18 and she had a pretreatment INR value of 1.7. She had blood pressure values greater than 185/110 mmHg during the first 24 hours after thrombolysis. She experienced a worsening of 5 points on the NIHS scale which was also attributed to a parenchymal hematoma type 2. She was discharged with a NIHSS score of 19 and the mRS score at three months was 5.

The seven sICH observed in the *Group without OAT* were in patients aged between 66 and 80 years, with a range of baseline NIHSS values between 4 and 24 points. 5 of them were taking previous treatment with aspirin and 1 with aspirin and clopidogrel. Only 1 of them had values of blood pressure above 185/100 mmHg during the first 24 hours. 4 of them were known with hypertension and one had more than 4 vascular risk factors. The time range between stroke onset and thrombolysis was 99-190 minutes.

For sICH as an outcome variable multivariate analysis was not performed due to the low number of cases observed. Independent predictors for the other three main outcome measures, were assessed in multivariate logistic regression models which included age, gender, chronic heart failure, arterial hypertension, blood pressure levels above 185/100 mmHg during the first 24 hours, baseline NIHSS score, time to treatment and prior anticoagulation status.

In the multivariate analysis prior subtherapeutic acenocoumarol use was not associated with either ICH (OR 0.55; 95% CI 0.19 – 1.59; p = 0.2), mortality (OR 0.85; 95% CI 0.33 – 2.18; p = 0.7) or good clinical outcome at three months (OR 1.27; 95% CI 0.53 – 3.04; p = 0.5). The only independent variable associated with both mortality and mRS 0-2 at three months was the baseline NIHSS score (OR 0.82; 95% CI 0.77-0.87; P<0.001 for mRS 0-2 at two months and OR 1.18; 95%CI 1.09-1.26; P < 0.001 for mortality). No independent predictor was found for ICH.

DISCUSSIONS

There are conflicting data in the literature regarding the safety of intravenous thrombolysis in patients with ischemic stroke receiving prior treatment with vitamin K antagonists (6,7,11). One of the main reasons for the paucity of information regarding this subject comes from the fact that the major clinical trials which led to the approval of rt-PA for the treatment of acute ischemic stroke didn't include patients prior receiving oral anticoagulants.

The increase in risk of intracerebral hemorrhage after rt-PA treatment is a well-known feature of this drug. The actual mechanism by which prior antico-

agulation, even at subtherapeutic levels, might further increase the risk of hemorrhagic transformation after thrombolysis is unclear, in part because of lack of adequate pathologic studies. However, several hypothesis have been proposed. First, the fibrinolytic effect of rt-PA may be enhanced by the anticoagulant effects of vitamin K antagonists. Higher recanalization rates with this combination may lead to a greater rate of reperfusion injury (5). Second, oral anticoagulants might enlarge initially minor bleedings that would otherwise occur without clinical consequence in individuals with normal coagulation function (12). Third, vitamin K antagonists use may be only a marker for patients with cardioembolic strokes in whom hemorrhagic transformation is more common and the infarct size is usually greater (7). On the other hand, the underlying mechanism of the majority of patients with acute ischemic stroke prior receiving treatment with oral anticoagulants is cardioembolic and the emboli arising from cardiac sources are thought to recanalyze better after intravenous administration of rt-PA due to their composition rich in fibrin loosely packed (13) (14). Prior use of oral anticoagulants in this situation, even at a subtherapeutic level, could additionally facilitate the recanalization by favoring the formation of a more fragile thrombus (5).

The results of the present study suggest that intravenous thrombolysis with rt-PA is not associated with an increased risk of intracerebral hemorrhage of any kind (symptomatic and asymptomatic) or death in patients with atrial fibrillation and acute ischemic stroke who are prior receiving treatment with coumarinic anticoagulants and have INR levels ≤ 1.7. The only predictor for both short term clinical outcome and mortality in our study was the baseline NIHSS score, reflecting the initial severity of stroke.

Similar results were reported by Kim et al. (9) which assessed the same issue in a study on 179 patients with high-risk cardioembolic sources that received intravenous thrombolytic agents or underwent intraarterial thrombolysis. Prior warfarin use in their study group was found in 28 patients (15.6%). The frequency of bleeding complications was not different between patients who received warfarin and those who did not. No differences were either observed regarding mortality and mRS at three months. However, even if the results are similar to ours, certain mentions have to be made. First of all, the study of Kim et al. included patients who either received treatment with intravenous rt-PA, either underwent intraarterial thrombolysis which is associated with different benefits and different hemorrhagic risks. Second, the median INR value observed in their study in patients prior receiving vitamin K antagonists was 1.14 (IQR 1.02-1.42), much lower than the median of our study which was 1.4 (IQR 1.3-1.6).

Vergouwen et al. (11) performed an analysis on 1739 patients with acute ischemic stroke treated with iv rt-PA of whom 125 (7.2%) were receiving warfarin before admission. The premorbid use of this coumarinic anticoagulant was not significantly associated with an increased risk of intracerebral hemorrhage, either symptomatic or asymptomatic. Furthermore, in this study warfarin use was independently associated with a reduced risk of poor functional outcome.

Several other retrospective studies have also reported that systemic thrombolysis was safe in patients previously anticoagulated with INR levels $\leq$ 1.7 (6) (8) (15) (16).

On the other hand, Prabhakaran et al. (7) performed a study on 107 patients with acute ischemic stroke who were administered iv treatment with rt-PA. Of these 13 patients were taking warfarin at baseline. A 10-fold increased risk of symptomatic ICH was observed in the group of warfarin compared to nonwarfarin users. The authors did not report if prior warfarin use was also independently associated with poor functional outcome or mortality. However, the results of this study, which to our knowledge is the only that has reported such a dramatic increase in the risk of intracerebral hemorrhage, must be carefully interpreted taking into account that the number patients receiving prior treatment with vitamin K antagonists was extremely low.

In conclusion, the results of the present study show that thrombolysis with intravenous rt-PA can be safely administered in patients with atrial fibrillation who are previously receiving subtherapeutic treatment with coumarinic oral anticoagulants, as we found no difference in terms of short term stroke outcome, hemorrhagic transformation and mortality between the patients who were previously treated with vitamin K antagonists and those who were not. However, we must consider certain limitations of our findings, the main being the retrospective design of the study and the relatively small sample size which led to a low number of symptomatic hemorrhages. Further studies with larger number of patients and a prospective design are needed to confirm these findings.

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