The Outcome of Patients with Mild Stroke Improves after Treatment with Systemic Thrombolysis

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Abstract

Introduction: In up to one third of patients with mild stroke suitable to receive systemic thrombolysis the treatment is not administered because the treating physicians estimate a good spontaneous recovery. However, it is not settled whether the fate of these patients is equivalent to those who are thrombolysed.

Methods: We analyzed 203 consecutive patients (134 men and 69 women, mean age 69±14 years) without premorbid disability and a NIHSS score ≤5 at admission [median 3 (IQR 2–4)]. Intravenous thrombolysis was administered within 4.5 hours from stroke onset (n = 119), or it was withheld (n = 84) whenever the treating physician predicted a spontaneous recovery. The baseline risk factors, clinical course, infarction volume, bleeding complications, and functional outcome at 3 months were analyzed and declared to a Web-based registry which was accessible to the local Health Authorities.

Results: Expectedly, not thrombolysed patients had the mildest strokes at admission [median 2 (IQR 1–3.75)]. At day 2 to 5, the infarct volume on DWI-MRI was similar in both groups. There were no symptomatic cerebral bleedings in the study. An ordinal regression model adjusted for baseline stroke severity showed that thrombolysis was associated with a greater proportion of patients who shifted down on the modified Rankin Scale score at 3 months (OR 2.66; 95% CI 1.49–4.74, p = 0.001).

Conclusions: Intravenous thrombolysis seems to be safe in patients with mild stroke and may be associated with improved outcome compared with untreated patients. These results support the evaluation of the efficacy of intravenous thrombolysis in mild stroke patients in randomized clinical trials.

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Introduction

Current guidelines offer no specific recommendations on the need of thrombolysis in stroke patients with mild or rapidly improving symptoms [1,2]. However, this issue is of great clinical interest as up to half of ischemic stroke patients manifest mild or rapidly improving symptoms at clinical onset [3,4], and around 30% of these patients are not treated with thrombolytic agents on the assumption that they may achieve an excellent recovery spontaneously [5–7]. However, according to some reports [5,6,8–11], up to one third of these patients fail to recover as much as it was anticipated by the responsible physician, and persist having symptoms as the result from a delayed growth of the infarction. The criteria used to define mild or rapidly improving symptoms are also weak and may encounter rather loose terms such as isolated sensory loss, ataxia, facial weakness, or dysarthria [12]. In most research studies, clinical deficits measured on the National Institutes of Health Stroke Scale (NIHSS) score of up to 3 or 5 were the most common definitions of mild stroke [13].

We analyzed the clinical and radiological course of patients with mild or rapidly improving stroke on admission in which the decision to administer intravenous recombinant tissue plasminogen activator (IV rt-PA) within 4.5 h of stroke onset was judged by the responsible physician according to his prediction of spontaneous recovery.

Methods

Ethics Statement

The study protocol was approved by the Clinical Research Ethics Committee of the Hospital Clinic de Barcelona (CEIC Hospital Clinic) and the patients or their legal representatives signed a written informed consent if age was over 80 years, or treatment was to be initiated >3 h of stroke onset.

Patients

All consecutive patients with ischemic stroke admitted at our institution from January 2009 to May 2012 which fulfilled all the following criteria: 1/ delay from the onset of symptoms to...
Results

Statistics

Normal distribution of all studied variables was assessed, and continuous variables were compared with Student's t-test, ANOVA, Mann-Whitney or Kruskal-Wallis tests as appropriate. Correlations were assessed with Spearman coefficients, and categorical variables were compared with the Fisher's exact tests. Ordinal regression analysis was used to increase the statistical power of the study [18], and analyze the independent effect of thrombolytic therapy on functional outcome at 3 months. As it was anticipated that patients not treated with thrombolytics would have the mildest strokes, the pretreatment NIHSS score was forced a priori into the model. In addition, exploratory analyses were also performed and which included the variables associated to outcome (p<0.2) on the univariate analysis and the variables with significant differences between treatment groups at baseline. The level of significance was established at a two-tailed value of p<0.05. All tests were performed using SPSS version 20.0.

Outcome

In the study, 53 of 203 patients referred from other centers were assessed only at hospital discharge (27 treated with thrombolysis and 26 not treated, p=0.247). The baseline traits of these patients did not differ from the patients with 3 months follow up (data not shown). At 3 months, 167 (82%) patients had excellent outcome (mRS 0 to 1). As shown in Figure 1, there were no significant differences in the proportion of patients that reached excellent outcome (83% in patients that received IV rt-PA versus 81% in patients that received standard care). In the ordinal regression analysis, we found a greater proportion of patients who shifted down on the modified Rankin Scale score at 3 months in the thrombolysed group than in patients receiving standard care (OR 2.66; 95% CI 1.49–4.74, p=0.001). The association also was significant (OR 2.02; 95% CI 1.02–3.98; p=0.042) in models adjusted for the effect of all variables associated to mRS score at 3 months on univariate comparison and for variables with differences at baseline: pretreatment NIHSS (OR 0.77; 95% CI 0.67–0.89; p<0.001), age (OR 0.97; 95% CI 0.95–1.00; p=0.023), prior mRS (OR 0.35; 95% CI 0.17–0.70; p=0.003), dyslipidemia (OR 0.62; 95% CI 0.33–1.20; p=0.157), coronary artery disease (OR 0.50; 95% CI 0.24–1.05; p=0.068), hypertension (OR 0.78; 95% CI 0.40–1.52; p=0.468), diabetes (OR 0.64; 95% CI 0.30–1.36; p=0.243), systolic blood pressure (OR 0.99; 95% CI 0.98–1.00; p=0.128) and glucose levels (OR 1.00; 95% CI 0.99–1.01; p=0.625). In exploratory analysis, there was also a trend in the same direction for thrombolysis (OR 1.85; 95% CI 0.90–3.86; p=0.100) after excluding patients without day 90 visit.

Discussion

The value of systemic thrombolysis in patients with mild or rapidly improving stroke is not settled. A post-hoc analysis of very few patients with mild stroke assessed in the NINDS trial suggested some benefit [19], and a subgroup analysis of the IST-3 trial did not show a significant effect of rt-PA in patients with mild stroke.
This study confirmed that in regular practice a significant proportion of patients with mild stroke are not deemed suitable to be thrombolysed. However, the major new finding of the study was that the administration of IV rt-PA was independently associated with a greater proportion of patients shifting down on the modified Rankin Scale score at 3 months compared with patients receiving standard care. Importantly, the association was obtained regardless that the patients who did not receive IV rt-PA had greater chances of recovery as they were in better neurological condition at baseline [21,22]. Indeed, this benign clinical course influenced the treating physician who withheld the therapy to avoid unnecessary risks in patients likable to make a full recovery spontaneously. Therefore, it is very likely that the true beneficial effects of IV rt-PA in patients with mild stroke might be even stronger.

The rate of excellent outcome was higher in this study than in previous reports of patients with minor stroke where the functional outcome was evaluated only at hospital discharge [8,10,11]. Most likely, the good results of the current study obeyed to the longer duration of follow up, the admission and management of all patients into a stroke dedicated unit, and the exclusion of patients with any degree of premorbid disability.

Table 1. General characteristics of the study population according to the treatment group.

|                          | Thrombolysis (n = 119) | No thrombolysis (n = 84) | P       |
|--------------------------|------------------------|--------------------------|---------|
| Age, years, mean (SD)    | 68.8 (13.8)            | 69.0 (13.2)              | 0.921   |
| Gender, %, male/female   | 68.9/31.1              | 61.9/38.1                | 0.300   |
| Hypertension, %          | 68.1                   | 67.5                     | 0.929   |
| Diabetes mellitus, %     | 24.4                   | 37.3                     | 0.047   |
| Dyslipidemia, %          | 38.8                   | 48.2                     | 0.186   |
| Coronary artery disease, %| 16.9                  | 18.1                     | 0.836   |
| Atrial fibrillation, %   | 15.3                   | 23.8                     | 0.115   |
| Prior mRS, median (IQR)  | 0 (0–0)                | 0 (0–1)                  | <0.001  |
| Onset to admission time, min, median (IQR) | 94 (58–143) | 108 (60–171) | 0.198 |
| SBP, mmHg, mean (SD)     | 157.5 (24.5)           | 163.1 (33.3)             | 0.221   |
| Glucose, mg/dL, mean (SD)| 138.3 (54.8)           | 141.7 (59.4)             | 0.683   |
| OCSP, %, Lacunar/Non-lacunar | 37.8/62.2       | 30.8/69.2                | 0.316   |
| NIHSS score, median (IQR) |                       |                          |         |
| Admission                | 3 (2–4)                | 2 (1–3.75)               | <0.001  |
| Pre-treatment/post neuroimaging | 3 (2–4)      | 1 (0–2)                  | <0.001  |
| Day 1                    | 1 (0–3)                | 0 (0–1)                  | <0.001  |
| Discharge                | 1 (0–2)                | 0 (0–1)                  | 0.027   |
| Day 90                   | 0 (0–1)                | 0 (0–0.75)               | 0.926   |
| Improvement in NIHSS during admission, median (IQR) | 1 (0–3) | 0 (0–1) | <0.001 |
| DWI volume, median (IQR), n = 152, cc | 0.69 (0–3.09) | 0.33 (0–2.46) | 0.165 |
| DWI lesion pattern, %    |                       |                          | 0.417   |
| Territorial              | 50.5                   | 50.0                     |         |
| Lacunar                  | 20.4                   | 14.3                     |         |
| watershed                | 2.2                    | 0                        |         |
| No lesion                | 26.9                   | 35.7                     |         |
| TOAST                    |                       |                          | 0.566   |
| Cardioembolic, %         | 28.4                   | 28.4                     |         |
| Large vessel, %          | 14.7                   | 6.8                      |         |
| Lacunar, %               | 20.2                   | 23.0                     |         |
| Undetermined, %          | 34.9                   | 39.2                     |         |
| Other, %                 | 1.8                    | 2.7                      |         |
| Stroke mimick, %         | 6.8                    | 8.6                      | 0.637   |
| Any ICH, %               | 6.7                    | 2.7                      | 0.323   |
| sICH, %                  | 0                      | 0                        |         |
| mRS at discharge, median (IQR) | 1 (0–2)       | 1 (1–2)                  | 0.966   |
| mRS at day 90, median (IQR) | 1 (0–1)       | 1 (0–1)                  | 0.023   |
| Death, %                 | 1.7                    | 3.6                      | 0.651   |

mRS: modified Rankin scale; SBP: systolic blood pressure, OCSP: Oxfordshire Stroke Project Classification; TOAST: Trial of Org 10172 in Acute Stroke Treatment; NIHSS: National Institutes of Health Stroke Scale; ICH: intracranial hemorrhage; sICH: symptomatic intracranial hemorrhage.
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The study also highlighted the safety profile of IV rt-PA in patients with mild or rapidly improving stroke as none of the actively treated patients suffered symptomatic bleeding complications. Therefore, any future clinical trial designed to compare the value of rt-PA versus standard care in patients with mild stroke must calculate the inclusion of a very large database.

While the patients included in this study represented only 8% of all the stroke admissions at our Stroke Unit, they also represented 24% of all the ischemic stroke patients which are candidates to receive IV rt-PA within 4.5 h. Therefore, these results may have important clinical implications for many of these patients who are currently not thrombolysed in regular practice on the assumption of their benign natural course. As the study showed, 19% of these patients failed to achieve a full recovery. Yet, while the study confirmed a high rate of excellent recovery in many of these patients, it also suggested that the benefits were enhanced after thrombolysis.

The main limitation of the study was its non-randomized design although several of its traits minimized the risk of bias. Thus, the effect of the lower stroke severity on the untreated group was important clinical implications for many of these patients are minimized by the appropriate adjustment of the NIHSS score in multivariate analysis. The validity of the study was also supported by the prospective collection of the data and its storage into a Web-based registry owned and monitored by the Catalan Health authorities [17]. Therefore, our results represented all the admissions at our institution that fulfilled the preestablished entry criteria. Alternatively, most of previous cohorts described the outcome in the Web based registry of stroke patients. We thank Dr Martha Vargas for all her work in collecting and introducing the information in the Web based registry of stroke patients.

Conclusions
Patients with mild or rapidly improving stroke seem to benefit from a timely administration of IV rt-PA. More patients receiving IV rt-PA shift down on the mRS at 3 months compared to patients receiving standard care. The risk of serious bleeding complications is very low in these patients while the probability of incomplete recovery is not negligible in untreated patients. While awaiting a definitive answer from a randomized clinical trial our results support the use of IV rt-PA in patients with mild or rapidly improving stroke when there are no contraindications.

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Author Contributions
XU, HA, A. Cervera. Wrote the paper: XU, HA, A. Cervera. Contributed reagents/materials/analysis tools: XU, HA, LL, SA, VO, A. Cervera. Conceived and designed the experiments: XU, HA, A. Cervera. Collected data: XU, HA, LL, SA, VO, A. Cervera. Reviewed the manuscript: XU, HA, A. Cervera. The main limitation of the study was its non-randomized design although several of its traits minimized the risk of bias. Thus, the effect of the lower stroke severity on the untreated group was minimized by the appropriate adjustment of the NIHSS score in multivariate analysis. The validity of the study was also supported by the prospective collection of the data and its storage into a Web-based registry owned and monitored by the Catalan Health authorities [17]. Therefore, our results represented all the admissions at our institution that fulfilled the preestablished entry criteria. Alternatively, most of previous cohorts described the outcome of either treated [23–25] or not treated patients [6–10], or used historical controls [26].

Currently, a randomized controlled clinical trial is being planned to evaluate the role of thrombolysis in patients with mild stroke [27]. In the meantime, our findings may be very informative for the treating physicians as they support a favorable benefit/risk ratio of thrombolysis in patients with minor stroke.

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Figure 1. Distribution of modified Rankin Scales scores at 3 months in patients with mild stroke and treated or not with intravenous thrombolytic therapy.
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Overall p value = 0.10
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