

Determinants of outcome in patients eligible for thrombolysis for ischemic stroke

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Objectives: Eligibility criteria for thrombolysis in ischemic stroke have been clearly defined. However, not all eligible patients benefit from this treatment. This study aimed to assess the determinants for clinical outcome in consecutive, eligible patients with ischemic stroke treated with thrombolysis in a single-center study.

Methods: Consecutive patients with ischemic stroke were treated with tissue plasminogen activator (t-PA) following the established eligibility National Institute of Neurological Disorders and Stroke (NINDS) and European Stroke Initiative (EUSI) criteria. Risk factors including blood pressure and pre-treatment glycemia were properly managed. Death and disability at 3 months were the study outcomes. Disability was evaluated by the Rankin-scale. Favorable outcome was defined as 0–2 and adverse outcome as 3–6 including death.

Results: Seventy-eight patients were included in the study in a single stroke unit. The mean age was 70.9 ± 13.2 years (range 36–94). Follow-up at 3 months was completed in 73 patients. A favorable outcome was observed in 37 patients (50%) and adverse outcome in 36 (36%). Nine patients (12.3%) died within 3 months. The presence of an occluded carotid artery was a strong predictor for adverse outcome ($p < 0.0001$). A low NIH Stroke Scale-Score (NIHSS) at admission was associated with a favorable outcome, while history of diabetes mellitus led to an unfavorable outcome.

Conclusion: Among patients eligible for thrombolysis, many do not benefit from this treatment. These include patients with carotid occlusion and diabetes.

Keywords: thrombolysis, stroke, outcome, diabetes, carotid artery occlusion

Introduction

Stroke is the third leading cause of death after myocardial infarction and cancer, and is the leading cause of permanent disability in western countries (WHO 1999). Furthermore, it is the leading cause of disability-adjusted loss of independent life-years. Aside from the tragic consequences for the patients and their families, the socioeconomic impact of more or less disabled stroke survivors is evident, as stroke patients with permanent deficits such as hemiparesis and aphasia will frequently not be able to live independently or pursue an occupation. The added indirect and direct cost estimates for a survived stroke vary between US\$35,000 and 50,000 per year. In the face of our ageing population and the skewed population pyramid, the incidence and prevalence of stroke is expected to increase. Up to 85% of all strokes are of ischemic origin and are mostly caused by the blockage of a cerebral artery by a blood clot. Occlusion of a brain vessel leads to a critical reduction in cerebral perfusion and, within minutes, to ischemic infarction, with a central infarct core of irreversibly damaged brain tissue and an area of variable size of hypoperfused but still vital brain tissue (the ischemic penumbra), which can potentially be salvaged by rapid restoration of the blood flow. Therefore, the underlying rationale for the introduction and application of thrombolytic agents is the lysis of a thrombus and the subsequent re-establishment of cerebral blood flow by cerebrovascular recanalization (Schellinger et al 2001).

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Although approved by North American and, conditionally, by European authorities, thrombolysis is rarely used in the acute treatment of stroke. Fear of bleeding and scepticism about efficacy are the main reasons of this underutilization. Indeed, difficulties in identifying those patients who may benefit from thrombolysis treatment limit the widespread use of this therapy (Demchuk et al 2001). The short interval between symptom onset to treatment makes the decision even more difficult. Other factors influencing the decision are direct and indirect costs. In addition to the crude cost of the thrombolytic agent, the cost of at least 24-hour patient monitoring should be considered as well as the necessity for specialized personnel in dedicated wards.

Based on the results of intervention studies, eligibility criteria for thrombolysis in ischemic stroke have been clearly defined. However, not all eligible patients benefit from this treatment. The aim of this study was to assess the determinants for clinical outcome in consecutive eligible patients with ischemic stroke treated with thrombolysis at single institution.

Methods

Consecutive patients eligible for thrombolysis for ischemic stroke according to the NINDS and EUSI criteria were included in this study at the Stroke Unit, University of Perugia. (The Stroke Unit is the only department where intravenous thrombolysis treatment within three hours was performed, and serves an area of approximately 160,000 inhabitants). The Italian emergency system 118 was organized to transport patients with acute stroke immediately to the Stroke Unit, because it was the referral hospital for thrombolysis treatment. All patients presented a NIH stroke scale-score (NIHSS) of 5–22, as foreseen by European stroke initiative (EUSI) guidelines (EUSI 2000, 2003) and National Institute of Neurological Disorders and Stroke (NINDS) criteria (NINDS 1995). These patients were divided into three groups according to clinical severity: NIHSS: 5–10 (mild-moderate stroke), 11–15 (moderate-severe stroke), >15 (severe stroke) (Golstein et al 1989).

Patients with a hypodensity larger than one third of the territory of middle cerebral artery (MCA) were excluded from treatment. Additionally, Alberta stroke program early CT score (ASPECTS) was used to measure early infarct signs: patients with an ASPECTS-score ≥ 7 were also excluded from thrombolysis-treatment (Pexman et al 2001). Standard blood examinations including hematocrit and fasting blood glucose were measured at admission. Duplex-examination was performed on all patients. The diagnosis of internal

carotid artery occlusion in the acute stage was done in case of absence of flow in the ICA at the level of carotid bifurcation. The Umbria Ethics Committee approved the protocol. The patients themselves or their relatives gave written informed consent for the treatment. This was the first time in the Stroke Unit of Perugia that patients had been treated with thrombolysis. The physicians of the center had no experience in thrombolysis-treatment.

Neurological examinations were repeated: every 15 minutes during infusion of t-PA, 1 hour after the end of infusion, after 24 hours and at discharge. Blood pressure was monitored every 15 minutes and measurements were repeated more frequently if systolic or diastolic pressures were >180 mm or >105 mm Hg, respectively. Antihypertensive drugs, such as intravenous labetalol or urapidil, were administered as needed in case of hypertension. All patients underwent CT-scan 24 hours after thrombolysis, except in cases of neurological deterioration. In these cases CT-scan was performed to exclude any possible cerebral hemorrhagic complications. The hemorrhagic transformations were classified according to the European Cooperative Acute Stroke Study I and II (ECASS and ECASS II) criteria (Hacke et al 1995, 1998).

Aspirin, heparin and warfarin were not administered for at least 24 hours following infusion. All protocol violations were registered and all extra-cranial hemorrhage were recorded. Data were collected on vascular risk factors: age, sex, hypertension (blood pressure of >160/90 mmHg found at least twice before stroke or already under treatment with antihypertensive drugs), diabetes mellitus (glucose levels >140 mg/dL preprandial from two examinations, glucose level >200 mg/dL postprandial, or HbA_{1c} > 8.5%), cigarette smoking (>10 cigarettes per day or cessation <5 years earlier), hyperlipidemia (cholesterol concentration of >200 mg/dL and/or triglyceride concentration >140 mg/dL the day after admission or if already under hypolipemiant therapy), history of ischemic heart disease (proven myocardial infarction, existence of multiple lesions from thallium heart isotope screening, or evidence of coronary disease from coronary artery catheterization), arrhythmia, or vascular claudication, family history of stroke and/or heart disease, or previous transient ischemic attacks (TIAs).

An experienced neurologist reviewed the medical records of each patient and assigned stroke subtypes on the basis of the Trial of ORG 10172 in Acute Stroke Treatment-criteria (TOAST): atherosclerotic (large artery disease), cardioembolic, lacunar (small artery disease), other determined etiologies and undetermined etiology (Adams 1993).

Atherothrombotic strokes are characterised by presentation with ischemic stroke and 50% stenosis or occlusion of the supplying cerebral artery. Patients with aortic plaques of >4 mm diameter or mobile aortic thrombi located before the ostium of the left subclavian artery, but in whom no signs of cardioembolic and other determined etiology of stroke were diagnosed at transoesophageal echocardiography, were also assumed to have atherothrombotic stroke. Cardioembolic strokes are characterized by presentation with an ischemic stroke and a potential cardiac source of embolism.

Lacunar strokes are characterized by presentation with one of the traditional clinical lacunar syndromes (pure motor hemiparesis, pure sensory syndrome, sensorimotor syndrome, ataxic hemiparesis, and dysarthria-clumsy hand syndrome), and (2) either normal brain computed tomography/MRI or an appropriate subcortical or brain stem lesion of diameter 1.5 cm. Strokes with another determined etiology refer to ischemic strokes caused by arterial dissection, fibromuscular dysplasia, vasculitis, hematological disorder, migraine, and other rare forms of stroke. Strokes of undetermined etiology are ischemic strokes where the underlying cause during diagnostic work up remains undetermined, or where there are multiple possible causes of stroke or an incomplete evaluation.

Patients were followed up prospectively over the first 3 months after stroke during which the time of occurrence and the cause of death were recorded. Death was categorized into neurological causes: oedema, herniation, status epilepticus, recurrence of stroke, and non-neurological: myocardial infarction, pneumonia, sudden death, other cardiovascular diseases, cancer, pulmonary embolism, gastrointestinal hemorrhage and other causes. At follow-up after 3 months, dependency was assessed with the modified Rankin Scale (mRS) (Van Swieten 1988). Favorable outcome was defined as 0–2 and adverse outcome as 3–6 including death (Hacke et al 1999).

Statistical analysis

Crude association between each of the categorical baseline variables and adverse outcome at three months was assessed by preliminary cross-tabulations with the χ^2 test or Fisher's exact test with Yate's correction when appropriate. Multiple logistic regression analysis was used to identify independent predictors for outcome at 3 months. The independent variables included in this analysis were selected from the bivariate analysis with a 0.25 level as a screening criterion for selection of candidate variables. Assumptions underlying the use of such a regression model were tested according to

recommended procedures (Leys 1989). Data were analyzed with the SPSS/PC – Win Package.

Results

From December 2001 to July 2004, 78 stroke patients were treated with thrombolysis. The mean age was 70.9 ± 13.2 years (range 36–94). Distribution of patient risk factors is shown in Table 1. Mean time from stroke onset to treatment was 160 minutes, while mean time from stroke to hospital arrival was 86 minutes.

Follow-up at three months was completed in 73 patients. A favorable outcome was observed in 37 patients (50.7%) and adverse outcome in 36 patients (49.3%) (Table 1). Nine patients (12.3%) died within three months: 2 malignant MCA infarcts, 3 internistic complications (pleuritis, pulmonary embolism), 2 sudden deaths, 2 acute myocardial infarctions, 1 contralateral stroke recurrence and 1 cerebral hemorrhage occurring 2 months after fibrinolytic treatment in a patient with a probable amyloid angiopathy. The baseline median NIHSS value was 10 (range 5–22): 38 patients (52%) presented a NIHSS of 5–10, 20 (27%) a NIHSS of 11–15 and 15 (21%) (>15). A high NIHSS-score before thrombolytic treatment was associated with increased risk of adverse outcome (Table 2), while a low score seemed to be associated with a favorable outcome. In the multivariate analysis only a low NIHSS-score seemed to be protective against adverse outcome. All patients underwent Duplex examination before thrombolysis treatment. Four patients underwent MRI-angiography, 5 CT-angiography within 3

Table 1 Vascular risk factors and outcome in patients receiving thrombolysis for ischemic stroke (univariate analysis)

Vascular risk-factors	Overall number/%	Favorable outcome	Adverse outcome	P value
Age (mean)	70.03 ± 13.05	67.11 ± 14.39	74.40 ± 10.03	p = 0.01
Male sex	44/60.2	22/59.9	22/61.1	p = ns
Hyperlipidemia	27/36.9	13/35.1	14/37.8	p = ns
Previous stroke	16/21.9	6/16.2	10/27.7	p = ns
Atrial fibrillation	21/28.7	11/29.7	10/27.7	p = ns
Peripheral artery disease	5/6.8	3/8.1	2/5.5	p = ns
Hypertension	56/76.7	30/83.3	26/70.2	p = ns
Diabetes mellitus	14/19.1	4/11.1	10/27.0	p = 0.081
Coronary disease	6/8.2	3/8.1	3/8.1	p = ns
Previous aspirin use	33/45.2	14/38.8	19/52.7	p = ns
Carotid artery occlusion	11/15.0	0/0	11/100	p < 0.0001
Smoking	14/19.1	9/24.3	5/13.8	p = ns
Cerebral hemorrhage	6/8.2	3/8.1	3/8.1	p = ns

Table 2 The NIHSS of thrombolysis treated patients and statistical significance for outcome in univariate analysis

NIHSS-score	Total number/ %	Favorable outcome	Adverse outcome	P value
0–10	38/52.0	27/71.0	11/28.9	$p < 0.0001$
11–15	20/27.3	6/30.0	14/70.0	$p = 0.038$
>15	15/20.5	4/26.6	11/73.3	$p = 0.046$

days of stroke onset while 2 patients died due to malignant MCA-infarct before further neuroradiological examinations could be performed. No patient presented recanalization of carotid artery and the two patients who died of malignant MCA-infarct were considered as not recanalized as well. No patient had occlusion due to cervical artery dissection. Eleven patients (14%) had carotid artery occlusions. Seven of these patients (63.7%) died or 4 (36.3%) were disabled at 3 months. The association between carotid artery occlusion and adverse outcome was statistically significant ($p = 0.0001$) in the univariate analysis. Multivariate analysis was not performed for carotid artery occlusion, because no patient with carotid artery occlusion had a favorable outcome. The presence of carotid artery occlusion was not statistically associated with NIHSS >15 ($p = 0.06$), while only two patients with a NIHSS 5–10 had a carotid artery occlusion ($p = 0.02$).

Age was significantly associated with stroke outcome in the univariate analysis, but not in the multivariate analysis. In the univariate analysis for diabetes there was only a tendency to be statistically significant ($p = 0.081$), while in the multivariate analysis diabetes was an independent risk factor for outcome (Table 3). Mean glycemia at admission was 131 ± 34 mg/dL and only 1 patient had hyperglycemia (250 mg/dL). The glucose levels at admission did not influence the outcome at three months in the multivariate analysis. Mean diastolic blood pressure was 83 ± 12 mm Hg and mean systolic blood pressure was 156 ± 24 mm Hg. The median ASPECT-score was 10 (65 of 78 patients had a normal CT-scan at admission). Aspirin pretreatment was not statistically associated with adverse outcome (Table 2). The stroke subtypes were distributed as following: 17 (21.7%) patients with large vessel disease, 30 (38.4%) with cardioembolic stroke, 13 (16.6%) with lacunar stroke, 3 (3.8%) other causes and 15 (19.2%) with undetermined stroke.

Table 3 Multivariate analysis of determining factors of outcome

	OR	95% CI	P value
NIHSS 0–10	0.19	0.05–0.41	$p = 0.006$
Diabetes	12.3	1.2–117.4	$p = 0.02$

None of the stroke subtypes was statistically associated with adverse outcome.

Cerebral hemorrhagic complications were observed in 6 patients: 3 symptomatic hemorrhages (RS = 2 at 3 months) and 3 asymptomatic cerebral hemorrhages. Cerebral hemorrhages were observed in the territory of cerebral anterior artery (2) and posterior cerebral artery (1). Extracranial hemorrhages had been observed in 10 patients: five had hematuria and five had subgingival hemorrhage.

Discussion

In our study 73 completed the 3-month follow-up and 50.7% had a favorable outcome. These results are in keeping with those from NINDS as well as post-marketing studies such as Canadian activase for stroke effectiveness study (CASES), standard treatment with alteplase to reverse stroke (STARS) and Colonia (Hill et al 2002; Albers et al 2000; Grond et al 1998). Additionally, the observed rate of hemorrhagic complications was not higher than in randomized controlled trials (RCT) (NINDS 1995; Hacke et al 1995, 1998; Clark et al 1999).

In our study population we identified sub-groups of patients who did not benefit from t-PA. All patients with carotid occlusion had an adverse outcome, the majority of patients died, while the remaining patients were disabled at follow-up. Trouillas et al (1998) observed that patients with atheromatous proximal carotid occlusion treated with thrombolysis within 7 hours had an adverse outcome ($p = 0.02$). These results should be interpreted with caution, because in this study patients were treated in a larger time frame. Indeed, in a recent meta-analysis of thrombolysis-trials Hacke et al showed that the benefit of thrombolysis-therapy decreases with the prolonging of time-frame and the net benefit was only evident until the fourth hour after onset (Hacke et al 2004).

Rudolf et al (2000) evaluated both 9 carotid artery occlusions due to atherothrombotic disease and 6 due to cervical artery dissection. In this study 3 out of 15 patients showed an excellent clinical outcome, so that the authors concluded that patients with carotid artery occlusion should not be excluded a priori from thrombolysis therapy (Rudolf et al 2000). Even so, prognosis of carotid artery occlusion due to cervical artery dissection is more favorable compared to atherothrombotic occlusion (Arnold et al 2001) so that these two patient groups could not be put together.

A recent study compared the outcome of patients with carotid artery occlusion to those with MCA occlusion (Linfante et al 2002) and found a higher recanalization rate in

patients with MCA-occlusion, although the effect on clinical outcome remains unclear. Probably MCA occlusion is more often embolic while carotid artery occlusion is more often atherosclerotic and complicated by embolic occlusion (Del Zoppo 1992; Mori 1992). Nevertheless, thrombolytic therapy could increase collateral flow leading to improved brain perfusion.

The limit of all the above mentioned studies including ours is the absence of an untreated control group. However, it is well known from RCT on thrombolysis that the main cause of death in the placebo group is MCA infarction. This leads to subsequent transtentorial herniation due to space-occupying brain oedema (Hacke et al 1996) which is likely in patients with a total anterior cerebral infarct following carotid artery occlusion (Hacke et al 1996). Whether a Duplex-examination should be performed in all patients before thrombolysis and those with carotid occlusion excluded remains to be established in properly designed clinical trials.

In our study, patient age did not seem to be an independent risk factor for adverse outcome, even if patients with adverse outcome were on average seven years older than patients with favorable outcome. Tanne et al (2000) in a recent study, compared the outcome of 30 > 80 year-old patients to younger patients. No significant difference in outcome was found, while Mouradian et al showed in another study that older patients presenting with more severe baseline stroke were much less likely to benefit from iv rt-PA as compared with their younger counterparts (Mouradian 2005). Data from the CASES-study showed that in carefully selected elderly patients, the use of intravenous tPA was not found to be associated with an increased risk of symptomatic intracerebral hemorrhage. The differences in outcome were age-related and had the clinical characteristics of outcome in the elderly population (Sylaja 2006). However, Heuschmann et al found a higher in-hospital mortality with for each 10 years of increasing age (Heuschmann et al 2004). The possibility that elderly patients could benefit from thrombolysis is clinically relevant since age is one of the major determining factors of disability and death in stroke patients (Weimar et al 2002; Henon et al 1995). Indeed mean life-expectancy in Western countries is prolonged, increasing the prevalence of cerebrovascular disease (Sarti et al 2002).

Consistent with other studies, milder baseline stroke severity and no history of diabetes mellitus were identified as independent predictors of favorable outcome in patients treated with tPA (Demchuk et al 2001). In our study the baseline NIHSS was 10, which could explain partially the good outcome of the patients.

Data from NINDS-study and from a recent Canadian open-label study showed that glycemia and uncontrolled blood pressure levels are markers of adverse outcome in patients treated with thrombolysis (Bruno et al 2002; Saposnik et al 2004; Demchuk et al 2001). Here, only one patient had glycemia higher than 200 mg/dL before treatment while no patient presented uncontrolled hyperglycemia. Additionally, blood pressure was monitored before and during thrombolytic treatment and in no patient thrombolysis was started if blood pressure was higher than indicated by protocol guidelines. In these cases, patients were treated with infusion of urapidil with an excellent control of blood pressure levels. Probably due to the low number of patients, the different variables did not reach statistical relevance.

Clinical studies showed that thrombolysis is beneficial in patients with acute stroke. However, doubts remain on which patients could most benefit from this therapy. Even in a limited number of patients we identified factors that were predictive of favorable or adverse outcome. Among the former, there was a milder baseline stroke severity and among the latter a presence of carotid artery occlusion and diabetes; the more that these data will be archived, the larger the benefit of thrombolysis will be in stroke patients.

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