J Neurol (2003) 250 : 320 – 324
DOI 10.1007/s00415-003-1004-5

ORIGINAL COMMUNICATION

R1 – Systemic thrombolysis in German stroke units

The experience from the German Stroke data bank

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Received: 11 February 2002
Received in revised form: 16 October 2002
Accepted: 22 October 2002

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Abstract *Background* Systemic thrombolysis with tissue plasminogen activator (t-PA) for treatment of acute ischemic stroke was approved in Germany in 2000. Up to now, only data from single centers have been available for the study of the use of thrombolysis in a hospital-based approach outside controlled trials. We therefore sought to determine the frequency of application and complications as well as the patient outcome after t-PA treatment in clinical routine of specialized stroke centers in Germany. *Methods* Within the German Stroke Data Bank Collaboration, 6234 consecutive patients with ischemic stroke were prospectively documented in 20 stroke centers between 1998 and 1999. The patients were centrally followed via telephone interview after 3 months and 1 year to assess global functional outcome using the Modified Rankin Scale. *Results* 250 patients (4 %) received systemic t-PA treatment during the study period. The baseline characteristics of these patients were comparable to large clinical trials and phase IV studies. Symptomatic and asymptomatic parenchymal hemorrhage occurred in 22 patients (8.8 %) and was fatal in 3 patients. Follow-up data after 3 months were obtained in 82.4 % of all patients, of which 35 % had a favorable functional outcome (mRS ≤ 1), while 23.8 % were severely disabled (mRS ≥ 4) and 17 % had died. *Conclusion* The results of our study agree with the assumption that thrombolytic therapy can be performed safely and effectively in daily clinical practice. Nevertheless, the small proportion of patients receiving thrombolysis even in specialized stroke centers calls for further improvement of acute stroke management in Germany.

Key words cerebral ischemia · stroke · thrombolysis · outcome

Introduction

After official approval of tissue-type plasminogen activator (t-PA) for treatment of acute ischemic stroke in the United States in 1996, several US studies on the use of t-PA in daily clinical practice revealed conflicting results with regard to safety and feasibility of this new therapeutic approach. Especially the risk of parenchymal hemorrhage (PH) after application of t-PA still raises concerns which have been fostered by a high rate of PH in non-stroke specialized hospitals in the United States [5]. In contrast, another survey in specialized stroke centers in the United States yielded low complication rates [2]. In Germany, t-PA for acute ischemic stroke has been increasingly used since 1996 [4]. However, reports providing information on the actual use of thrombolytic therapy in acute stroke care in Germany are still scarce and derive only from single center studies with relatively small patient numbers [4, 6, 8]. In this multicenter survey in specialized German stroke centers we therefore sought to determine to what extent thrombolysis had been implemented into daily clinical practice and to explore the hypothesis that its complication rates and outcome are comparable to randomized studies.

Subjects and methods

The German Stroke Data Bank (GSDB) of the German Stroke Foundation (Stiftung Deutsche Schlaganfall-Hilfe) is a multicenter hospital-based stroke registry that was initiated in 1997 in order to obtain data on etiology, management, and outcome of acute cerebrovascular diseases. Twenty-three Neurology departments from all geographic parts of Germany participated in data acquisition between January 1998 and December 1999. Participating hospitals are equipped with an acute stroke unit and are the main stroke care providers in their catchment areas of 100.000 up to 1 million inhabitants. All patients with acute stroke received cerebral imaging, and almost all patients underwent extra- and transcranial ultrasound or angiographic evaluation of brain supplying arteries, ECG or ECG monitoring, basic blood tests and additional laboratory investigations as required. Two thirds of all patients were examined by transthoracic or transesophageal echocardiography.

All data were collected on standardized questionnaires by the treating neurologists. The definitions of risk factors were as follows: arterial hypertension: history of elevated blood pressure above 160/90 mmHg at two independent readings or antihypertensive medication, diabetes mellitus – history of elevated blood glucose at two independent readings or elevated HbA1c (> 7.5 %) at admission or antidiabetic medication, hypercholesterolemia – history of elevated total cholesterol > 220 mg/dl at two independent readings or lipid-lowering medication. Neurological deficits were quantified on the National Institute of Health Stroke Scale (NIHSS) by local investigators who were familiar with the NIHSS from other clinical trials or the NIHSS training video. For assessment of etiological stroke subtypes we used the classification of the TOAST investigators [1]. As a slight modification we included an additional category for patients with competing potential etiologic mechanisms. The TOAST-classification was scored in the documenting hospital according to a standardized protocol [3]. Parenchymal (PH) hemorrhage was defined as symptomatic and asymptomatic secondary parenchymal bleeding diagnosed on cerebral imaging or autopsy. Complications were assessed until the day of discharge from the documenting hospital but in order to consider solely effects of t-PA treatment and to account for varying lengths of stay, only complications occurring within 7 days after admission were considered. After a final consistency check with the source data at site, questionnaires were sent to the data management centers at the University of Essen and the Stiftung Deutsche Schlaganfall-Hilfe, Gütersloh. Data were rechecked by two physicians for completeness and plausibility and entered in duplicate into the database by trained personnel. Missing or implausible data were queried to the treating neurologist. Data quality was furthermore ensured by monthly reports and clinical site visits.

Functional outcome according to the modified Rankin Scale [11] (mRS) was assessed by central telephone interview after a median of 97 (range: 71–175) days (surmised as status after 3 months) and 381 (range: 347–450) days (surmised as status after 1 year). If the patient did not consent to submission of personal data, the participating center forwarded only anonymous data to the data management center and performed the follow up interview at site upon bimonthly request. Otherwise, the follow up was performed by trained telephone interviewers at the University of Essen or the Stiftung Deutsche Schlaganfall-Hilfe. If a patient could not be reached via telephone or via his treating physician, a follow up letter was sent. If still no information on a patient's outcome could be obtained, a query at the citizen registry was made to check for current address or death. Aspects of data safety of the Stroke Data Bank were considered clarified by the responsible data protection officer and all patients gave informed consent if their personal data were to be transferred to the data management center.

In this analysis we included 6234 patients with ischemic stroke from 20 centers (12 university hospitals and 8 municipal hospitals) who had registered more than 100 patients each. For a comparison with the patients receiving systemic thrombolysis, we furthermore excluded 42 patients who had received intraarterial thrombolysis (Fig. 1). 46 thrombolyzed and 406 patients not receiving t-PA in one center have been the subject of a previous report [6].

The criteria for application of thrombolysis in all centers were adopted with individual modifications from the NINDS-protocol

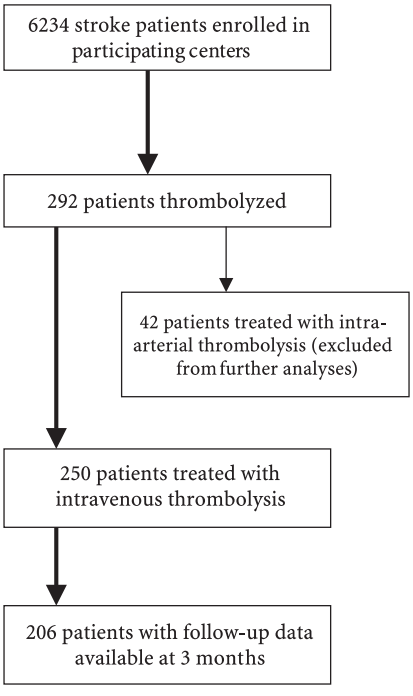

Fig. 1 Inclusion of patients

[10]. Thus, alteplase (Actilyse; Boehringer Ingelheim) was administered in a dose of 0.9 mg/kg body weight (maximum dose 90 mg), with 10 % given as a bolus followed by delivery of the remaining 90 % as a constant infusion over a period of 60 minutes. In certain centers proof of an intracranial artery occlusion on transcranial ultrasound or angiography was additionally considered a prerequisite for thrombolytic therapy. Infringements of the recommended 3-hour time window were left to the discretion of the attending neurologists.

Statistical analyses were performed using the program package SPSS version 9.0.

Continuous variables are presented as mean and standard deviation or as median and percentiles. Categorical variables are presented as percentages. In chi-square tests of categorical variables or ANOVA-tests of ordinal variables, a level of < 0.05 was considered significant.

Results

During the 2 year study period a total of 6234 patients with ischemic stroke were recruited. The number of patients enrolled per center ranged from 103 to 1084. Thrombolytic therapy was performed in 292 patients (4,9 %), of which 250 patients (4 %; range 0 %–11 % per center) were treated systemically. Since our study was focused on systemic thrombolysis, the 42 patients treated with intra-arterial thrombolysis were excluded from further analyses. The baseline characteristics of t-PA treated patients and those without thrombolysis are displayed in Table 1. In total, 1564 patients (25,4 %) were admitted within < 3 hours after symptom onset. Of these, 208 (13.3 %) received thrombolytic therapy. The distribution of the NIHSS on admission in patients who received thrombolysis compared to the STARS-study population [2] is depicted in Fig. 2. Median delay between symptom onset and hospital admission was 75 minutes for patients with systemic thrombolysis compared with 4 hours 45 minutes for patients without thrombolysis. In thrombolyzed patients the median time from admission to CT was 20 min, and the median door-needle-time (delay from admission to t-PA treatment) was 66 minutes (max. 360 min. in 2 patients with basilar artery occlusion). The majority of patients (89.7 %) were treated within 3 hours. Compared with patients without thrombolysis, t-PA treated patients significantly more often had a classification of cardioembolic stroke subtype while an inverse relation was seen for small vessel disease. With respect to large artery atherosclerosis and unknown etiologies there were only minor differences between these groups. 41.2 % of t-PA treated patients received full-dose intravenous anticoagulation within 24 hours after thrombolysis. The compliance with the NINDS-protocol [10] compared with other studies is displayed in Table 2.

Follow-up brain imaging studies (either CT or MRI) within 7 days after treatment were performed in 95 % of patients. Parenchymal hemorrhage was documented in 22 patients (8.8 %) of which 3 patients (13.6 %) died. 2.8 % of all patients with thrombolysis suffered any peripheral bleeding within 7 days (0.5 % of patients without thrombolysis) and 4.8 % underwent decompressive surgery (41.7 % of which had suffered a PH). The pro-

Table 1 Baseline characteristics of all patients with systemic thrombolysis and without thrombolysis

Variable	Systemic t-PA Treatment (n = 250)	Without Thrombolysis (n = 5942)
Mean age (median) (years)	62.5** (64)	66.7 (68)
Men (%)	60	57.8
Prior stroke (%)	14.6**	22.4
Prior TIA (%)	8.8	13
Arterial Hypertension (%)	58.6*	66.6
Diabetes mellitus (%)	17**	28.1
Hypercholesterolemia (%)	32.3	35.1
Smoking (%)	33.5	28.2
Prior platelet inhibitors (%)	24*	30.3
Modified Rankin Scale < 2 before stroke (%)	96.8**	87.3
Mean NIH-SS at admission (median)	14.1** (13)	7.2 (5)
Stroke subtype (%)		
Small vessel disease	2**	20.9
Cardioembolic	44**	24.7
Large artery atherosclerosis	17.6	21.4
Other etiology	2.8	2.9
Concurrent etiology	5.6	6.7
Unknown	28*	22.4

* significant at $p < 0.05$; ** significant at $p < 0.01$

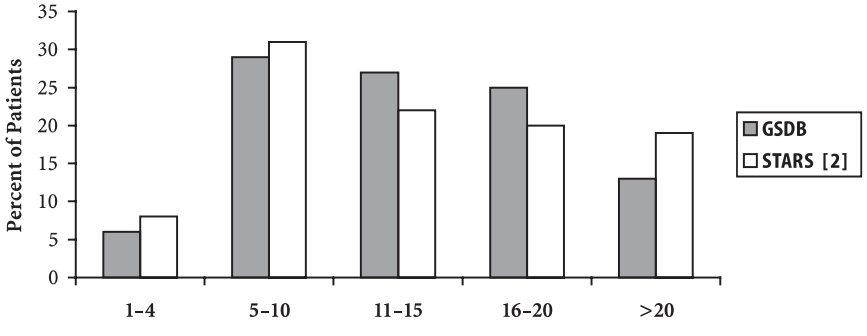

Fig. 2 National Institute of Health Stroke Scale (NIHSS) scores on admission (*GSDB* German Stroke Data Bank)

Table 2 NINDS [10] protocol violations

	GSDB	STARS [2]	Cleveland [5]
Treatment beyond 3 hours	10.3%	13%	13%
Full-dose Anticoagulation < 24h after t-PA	41.2%	9%	37%
Elevated BP (> 185 and/or 110 mmHg)	n. a.	8%	7%

GSDB German Stroke Data Bank

portion of patients suffering a PH did not significantly differ between patients with and without anticoagulant treatment within 24 hours after thrombolysis. Complications after systemic thrombolysis are summarized in Table 3.

Follow-up information after 3 months was obtained in 82.4% of t-PA treated patients. While 35% had a favorable outcome (mRS ≤ 1), 48.1% were functionally independent (mRS ≤ 2), 23.8% had a severe disability (mRS ≥ 4), and 17% had died. Baseline data of patients lost to follow-up did not significantly differ with respect to age, sex or initial severity on the NIHSS. Fig. 3 shows the global outcome according to the mRS after 3 months compared to outcome in the STARS-study [2] and the t-PA cohort of the NINDS-study [10].

Follow-up information after 1 year was available in 72% of t-PA treated patients. At this time, 33.8% had a favorable outcome (mRS ≤ 1) and 44.4% were functionally independent (mRS ≤ 2), while 21.7% had a severe disability (mRS ≥ 4), and 22.8% had died.

Discussion

This multicenter, hospital-based cohort study of t-PA treated patients from the German Stroke Databank constitutes the largest survey outside controlled trials in Germany and is most likely representative for thrombolysis in clinical routine in specialized stroke centers in Germany. The frequency of systemic thrombolysis is higher than in a community-based study in the Cleveland area which reported use of t-PA in 1.8% of all patients with ischemic stroke in 29 primary care centers not specifically specialized in stroke treatment [5]. While single center studies reported rates up to 9,4% [6], systemic thrombolysis rates per center in our study ranged from 0% to 11.5%. This illustrates the uncertainty about t-PA treatment before official approval and the efforts necessary to increase the rate of thrombolysis even in specialized centers. At the first follow-up after 3 months, the percentage of patients who had completely recovered (mRS ≤ 1) was lower than in the NINDS-study [10] and identical to the STARS-study [2], which reported almost 400 t-PA treated patients from experienced US stroke centers. Baseline NIHSS scores of our patients are quite comparable to the STARS-study and to the NINDS-study (Fig. 2). However, the rate of lacunar infarcts in our observations was extraordinarily low. As we know from the NINDS-trial these patients have the best outcome after systemic thrombolysis and contribute considerably to the share of completely restituted patients in this trial. When functional independence (mRS ≤ 2) was considered a favorable outcome (48.1% in our study), our results compare even favorably with the STARS-trial (43%).

Table 3 Complications

	GSDB	STARS [2]	CLEVELAND [5]	NINDS [10]
Symptomatic parenchymal hemorrhage	n. a.	3.3%	15.7%	6.4%
Asymptomatic parenchymal hemorrhage	n. a.	8.2%	6.3%	4.5%
Any parenchymal hemorrhage	8.8%	11.5%	22%	10.9%
Peripheral bleeding	2.8%	1.5%	n. a.	n. a.
In-hospital deaths	7.7%	n. a.	15.7%	n. a.
Mortality at 3 months after admission	17%	13.4%[1]	n. a.	17%

GSDB German Stroke Data Bank; [1] until 30 days after admission

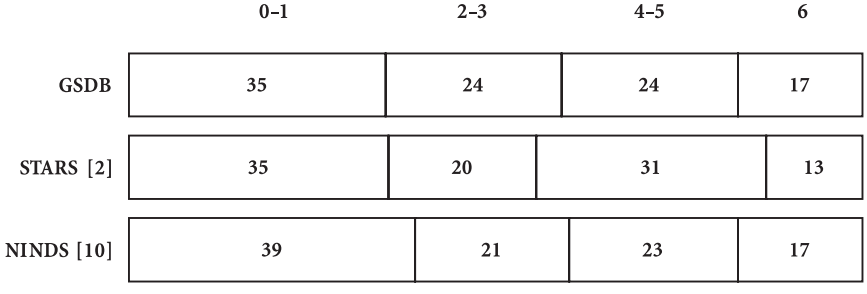

Fig. 3 Outcome after 3 months (STARS: 30 days) on the modified Rankin Scale (*GSDB* German Stroke Data Bank)

The median time from stroke onset to t-PA treatment in our study was shorter than in the STARS trial which is mainly due to the shorter delay from admission to t-PA treatment. Many patients, however, are clustered at the end of the 3 hour time window – confirming the observation of the STARS investigators of an inverse relationship between the delay of admission and the time from admission to treatment. Stroke teams need to be aware of this phenomenon, because an earlier administration of t-PA is known to be associated with a better outcome [7].

Regarding the proportion of patients with favorable (mRS ≤1) or functionally independent outcome (mRS ≤2), our follow-up results at 1 year did not differ significantly from the follow-up data at 3 months, thus indicating a sustained effect of t-PA treatment. These data correspond with the 1 year follow-up results of the NINDS-trial [10] and a single center study in Germany [9].

The methods for assessment of complications differed between STARS, NINDS, and our study in that we did not differentiate between symptomatic and asymptomatic parenchymal hemorrhage. In the NINDS-study, symptomatic hemorrhagic complications were defined as any intracranial hemorrhage leading to decline in neurological status [10]. Since 95 % of thrombolyzed patients in our study underwent follow-up brain imaging, it is unlikely that symptomatic hemorrhages were missed. Given our overall PH rate of 8.8 % and the experiences from other studies that approximately 30 % to 50 % of all PH are asymptomatic [2, 5, 10], the proportion of symptomatic PH in our study can be estimated between 4.4 % and 6,2 %. Considering the controversial discussion on the clinical usefulness of the term symptomatic hemorrhage [12], we might overestimate the influence of the hemorrhage itself on clinical deterioration. The above-mentioned definition of symptomatic hemorrhage neglects other causes of clinical deterioration such as ischemic edema. Regarding our PH rate from this point of view, it is well within safety limits.

Although a violation of the NINDS-protocol, full-dose intravenous anticoagulation within 24 hours did not seem to affect the rate of PH compared to patients without early anticoagulation.

Mortality of t-PA treated patients in our study was nearly identical to the NINDS trial but slightly higher than in the STARS-study, which is likely to be attributable to the longer follow-up interval in our study and the NINDS trial (90 days vs. 30 days in STARS).

In conclusion, the observed outcome after systemic thrombolysis with t-PA for acute ischemic stroke in specialized centers in Germany is well comparable to results from other uncontrolled and controlled studies in the US. The risk of t-PA associated PH under routine conditions is likewise comparable to optimized conditions of controlled studies. Our observations therefore further encourage the routine use of t-PA in acute ischemic stroke.

Acknowledgements We thank the Stiftung Deutsche Schlaganfall-Hilfe for financial support and support with data collection, as well as the following sponsors: Heinz-Nixdorf-Foundation, Bayer, Bristol-Myers-Squibb, Boehringer Ingelheim, Glaxo-Wellcome (now: Glaxo-SmithKline), Janssen-Cilag, Knoll, Sanofi-Synthelabo and Schering. No other than financial input has been received from these sponsors.

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