ORIGINAL ARTICLE

Lack of experience of intravenous thrombolysis for acute ischaemic stroke does not influence the proportion of patients treated

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Objectives: To determine the eligibility of patients with ischaemic stroke admitted to the 2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland, for intravenous thrombolysis; to identify the major exclusions and assess whether organisational changes in the in-hospital stroke pathway and informative campaign in the local community and medical services can increase the number of patients treated; and to establish whether lack of previous experience with thrombolytic treatment or trials is predictive of the low proportion of patients treated.

Methods: A survey of the database of patients with stroke admitted during the first 30 months after the introduction of intravenous thrombolysis for acute ischaemic stroke was conducted to search for all eligible patients. This included patients admitted within 2 h of symptom onset (assuming a 1 h door-to-needle time), age <80 years, National Institute of Health Stroke Scale (NIHSS) Score of 5–22, seizures at onset, platelet count >100 000/ml, glycaemia 50–400 mg/dl and international normalised ratio (INR) <1.6. The number of eligible patients was compared with the number actually treated.

Results: 745 patients with acute ischaemic stroke were admitted during the study period. 18.4% were admitted within 2 h of symptom onset, 71% were aged <80 years, 55.4% had an NIHSS score between 5 and 22, 96.1% had INR <1.6, 98.9% had a platelet count >100 000/ml, 99.4% had blood glucose concentrations of 50–400 mg/dl and 97.4% had no seizures at onset. After adjusting for all inclusion criteria, 7.1% of the patients were found to be potentially eligible and 8.7% were actually treated ($p=0.25$). Of the 65 treated patients, 63.1% were independent after 3 months, 16.9% died and none had a symptomatic intracranial haemorrhage.

Conclusions: The proportion of patients with ischaemic stroke treated with intravenous thrombolysis in a previously inexperienced centre was not lower than in other centres and in countries where this treatment has been provided for a longer period of time. The number of patients treated was higher than that estimated mainly owing to organisational changes introduced in our centre, allowing treatment of those admitted between 2 and 3 h after symptom onset.

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Recombinant tissue plasminogen activator (rt-PA, alteplase) is the first effective treatment for acute ischaemic stroke. The National Institute of Neurological Disorders and Stroke (NINDS) Trial showed a 16% absolute increase in independent survival with intravenous rt-PA versus placebo given within 3 h of onset and a number needed to treat of seven.¹ Despite its efficacy in reducing mortality and disability after stroke being proved, only 1.8–4.7% of the patients with ischaemic stroke were treated with rt-PA.^{2–3}

Alteplase was approved in Poland on the same terms as in the countries remaining under the authority of the European Agency for the Evaluation of Medicinal Products in November 2003. It was introduced in our department (Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland) in October 2003, initially as an experimental and, after licensing, as a routine treatment. Intravenous thrombolysis in Poland is implemented according to the Safe Implementation of Thrombolysis in Stroke (SITS) Protocol.⁴

Efficacious implementation of thrombolysis depends on several factors. Some of them can be modified to increase the proportion of patients treated with rt-PA. These include good organisation of "the in-hospital stroke pathway" and public awareness of stroke signs and treatment possibilities.⁵ Introduction of thrombolysis on a satisfactory level when at least 5% of all patients with ischaemic stroke should be treated may be a problem in some European countries and centres

without previous experience and not participating in trials with rt-PA—for example, the European Cooperative Acute Stroke Study I and II.^{6–7}

A previous report showed that a tertiary referral centre in Australia without previous experience achieved an 11% treatment rate with thrombolysis, resulting in effects comparable to the treatment arms of the NINDS Trial.⁸ It is important to perform such calculations, especially in countries with inadequate experience in the treatment of acute stroke. In Poland, as in other former communist countries of Eastern Europe, the availability of new developments in medical care was restricted, and clinical trials were neglected for many years from the end of the Second World War until the last decade of the 20th century. We therefore wished to assess whether this handicap could influence the implementation and effects of thrombolysis in ischaemic stroke.

We developed a treatment protocol for thrombolysis in our centre, and also made efforts to enhance the knowledge of stroke symptoms in the local community.

The aim of this study was to determine how many patients with stroke received thrombolytic treatment in our centre and

Abbreviations: INR, international normalised ratio; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; rt-PA, recombinant tissue plasminogen activator; SITS, Safe Implementation of Thrombolysis in Stroke

whether all those potentially eligible actually received rt-PA. We also wanted to investigate the reasons why patients with stroke did not receive alteplase in the centre with an active treatment protocol.

PATIENTS AND METHODS

The study was performed using a prospective registry of patients with stroke admitted to the 2nd Department of Neurology during the first 30 months after the implementation of thrombolysis. This computer database was designed according to the modified National Institutes of Health Stroke Data Bank Protocol.⁹

In Poland, almost all patients with stroke are treated in neurological departments. There was no selection bias as our department provides stroke services for several districts in Warsaw and suburban areas, and all patients from this area are admitted. The patients were also not selected according to the severity of stroke.

We analysed the data of patients with stroke admitted to our department within 7 days after stroke onset, diagnosed according to the International Classification of Diseases, 10th revision. The time of stroke onset was defined as the time at which the patient or a witness first noted signs of neurological deficit. If the symptoms were noted on awakening or, not witnessed, the time of onset was assumed to be the time when the patient was last seen well.

We have reviewed the records and specifically abstracted the information on the inclusion and exclusion criteria used in rt-PA treatment decisions specified in the SITS Protocol.

Patients were considered eligible for alteplase if they met the inclusion criteria as stated in the SITS Protocol. The arrival time limit was set at 2 h after stroke onset, because we accepted an additional 1-h door-to-needle interval. The inclusion criteria also included age between 18 and 80 years and a clinical diagnosis of stroke with symptoms persisting >30 minutes. The identifiable exclusion criteria are evidence of intracranial haemorrhage observed through computed tomography, INR value >1.5 in patients not receiving as well as those receiving oral anticoagulation, platelet count <100 000/ml, glycaemia <50 and >400 mg/dl and seizures at onset. Also, patients with minor (NIHSS Score <4) and severe (NIHSS Score >23) strokes were assumed to be ineligible. We considered that hypertension with systolic blood pressure >185 mm Hg or diastolic pressure >110 mm Hg is a conditional contraindication, because it can be potentially lowered in a short period of time. Data on other exclusion criteria—for example, recent major surgery, trauma or cancer—were not included in the database. We did not assess rapid improvement because patients in whom symptoms were resolved within 24 h of onset were classified as having a transient ischaemic attack and therefore not included in the database.

Owing to the introduction of thrombolytic treatment in our department, we made several changes in the organisation of emergency stroke admissions. These concerned the emergency department and included the following:

- blood samples are taken in the emergency department and not in the stroke unit (as was being done previously);
- after initial examination by the doctor on duty, the patient is immediately taken for a computed tomography scan.

Doctors' duties were also changed as follows:

- after an initial quick assessment, the doctor on duty notifies a doctor on call, who is specially trained in stroke medicine (including evaluation of early ischaemic and haemorrhagic changes observed on computed tomography) and who relieves the first doctor in taking care of the patient qualified

for thrombolysis. After his arrival, he takes over the care of the patient and after consultation with the head of the department makes the final therapeutic decisions.

We prepared separate posters and leaflets for patients, general practitioners and emergency services relating to early stroke signs and new treatment possibilities. Information was posted to every outpatient clinic and general practitioner in the districts of Warsaw, which were under the care of our department.

We calculated the eligibility of patients with ischaemic stroke for thrombolysis, after making adjustments for the above-mentioned inclusion criteria. We used χ^2 statistics to compare the number of patients eligible and those actually treated with rt-PA.

In patients actively treated, we assessed significant early improvement, defined as a decrease in the NIHSS Score of ≥ 4 during the first 24 h after treatment or full recovery, and independence after 3 months, defined as a modified Rankin Scale (mRS) Score of ≤ 2 . We also assessed the frequency of symptomatic intracranial haemorrhage and mortality at 3 months, and also tested the treated group for quality parameters, defining an ideal practice as an onset-to-treatment time of 90 min and a door-to-needle time of 45 min.

All analyses were performed using the STATISTICA V.6.0 PL software package.

RESULTS

A total of 847 patients with stroke were admitted to our department during the study period, 745 of whom were ischaemic (table 1).

In all, 135 (18.4%) patients arrived within 2 h of stroke onset, and the time window was the most important exclusion. Other important exclusions included age >80 years and too severe or too mild neurological deficits. Abnormal laboratory findings such as INR ≥ 1.6 and platelet count <100 000/ml were not frequent. Excessive systolic and diastolic blood pressure was also not found often. Arbitrarily, we did not consider high blood pressure an excluding factor, as it could be promptly and effectively treated (table 1).

After adjusting for the inclusion and exclusion criteria, we assessed that 53 (7.1%) patients with ischaemic stroke potentially fulfilled these criteria, and were thus potentially eligible for intravenous thrombolysis.

During the study period, a total of 65 patients with ischaemic stroke (8.7%, 95% CI 6.9 to 11.0) were treated with rt-PA. Three of them were > 80 years and nine were treated, although they

Table 1 Eligibility for recombinant tissue plasminogen activator treatment

	Valid cases (n)	Patients fulfilling inclusion (n)	% (95% CI)
Admission <2 h of symptom onset	733	135	18.4 (15.8 to 21.4)
Age <80 years	737	523	71 (67.6 to 74.1)
NIHSS Score 4–23	740	410	55.4 (51.8 to 58.9)
INR <1.6	637	612	96.1 (94.3 to 97.3)
Platelet count >100 000/mm ³	732	724	98.9 (97.9 to 99.4)
Glycaemia 50–400 mg	703	699	99.4 (98.5 to 99.8)
No seizures at onset	725	706	97.4 (95.9 to 98.3)
SBP <185 mm Hg	743	648	87.2 (84.6 to 89.4)
DBP <110 mm Hg	743	667	89.8 (87.4 to 91.7)
All criteria fulfilled	745	53	7.1 (5.5 to 9.2)

DBP, diastolic blood pressure; INR, international normalised ratio; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure

arrived after 2 h of symptom onset (but within the 3-h time window), so according to our criteria they were not considered eligible. The difference between the number of patients potentially eligible for intravenous thrombolysis and those actually treated was not significant ($p = 0.25$).

In the treatment group, we observed a considerable early improvement in 50.8% of the patients, and 63.1% were independent after 3 months. None of the patients had a symptomatic haemorrhage, but 16.9% were dead at the 3-month follow-up. Only 1.5% of patients were treated within 90 min of stroke onset, and the door-to-needle time was <45 min in 9.2% (table 2). The mean time from arrival in hospital to brain imaging was 18.6 min (95% CI 13.8 to 23.5).

DISCUSSION

This study showed that 8.7% of all patients with ischaemic stroke and 48.1% of those admitted within 2 h of onset to our department received thrombolytic treatment. We also found that all eligible patients with stroke received thrombolysis.

Patients with stroke should be handled with high priority.¹⁰ This is crucial because of the narrow time window. The time from onset to admission was the main excluding factor as in the other studies. In our population, 18.4% of patients were admitted within 2 h of symptom onset. In the Greater Cincinnati/Northern Kentucky study, 19% of the patients were admitted within 2 h of symptom onset, in Cleveland 17.1% arrived early enough to receive rt-PA and in the Copenhagen population, 14.2% of patients fulfilled the time criteria for thrombolysis.^{2 11 12} The main reasons for late arrival were delays in emergency transport and poor recognition of stroke signs. The older the patient, the worse the recognition of stroke signs.^{7 13 14}

Prehospital management, special education of emergency transport services and rising public awareness of stroke signs remain the weakest points in stroke treatment.

Prehospital management is as important as the in-hospital care and door-to-needle time. In our study, we assumed a 1-h door-to-needle time, but we also had patients treated within shorter times after arrival. The mean door-to-scan time for patients undergoing thrombolysis was 18.6 min, which allows for ideal treatment of patients within 1 h. In this time, the patients were initially assessed clinically and had a computed tomography scan assessed by a stroke physician. This could only be achieved because they were treated as high priority in the emergency and radiology departments. The mode of action introduced in our department in October 2003 allowed us to treat all eligible patients with stroke, but the quality parameters can still be improved so that more patients can be treated sooner after onset. This requires further work to reduce the prehospital and in-hospital delays. The second doctor on call, who takes care only of patients with acute stroke, could be recommended, at least in Polish hospitals. All patients with stroke arriving at the emergency department should also be

considered as being potentially eligible for thrombolysis in consultation with the head of the department, as is done in our centre.

Age was the second major exclusion factor from thrombolysis in our population. Nevertheless, the approach towards treating elderly people with rt-PA is still not consistent. For example, in the US study, in patients aged >80 years, there were comparable outcomes and no increase in haemorrhage risk versus patients <80 years, but in the study by Heuschmann *et al*¹⁶ those >75 years were more likely to have an intracranial haemorrhage than those <55 years (10.3% *v* 4.9%).^{15 16}

In our study, three women aged 80, 81 and 83 years were treated. None of them had any haemorrhagic side effects of thrombolytic treatment. As the population ages, the proportion of elderly patients with stroke increases. Evidence on the safety and efficacy of rt-PA in patients aged ≥80 years is sparse. The available studies compared the effects of treatment in those <80 and >80 years. In a study by Engelter *et al*,¹⁷ no differences between the two age groups were noted. Other studies reported that elderly patients benefited less and could be more susceptible to intracranial haemorrhage.^{18–20} Further studies are necessary to provide reliable data on thrombolytic treatment in older patients.

Mild and resolving symptoms were also a major exclusion from rt-PA treatment in our study. A study based on the NINDS Trial results showed a markedly higher rate of full recovery within 24 h of treatment onset in patients with mild neurological deficits treated with alteplase than in the placebo group.²¹ Barber *et al*³ reported that even patients with considerable early clinical improvement are likely to develop a persistent neurological deficit. A large number of patients with only slight signs are also at an increased risk of developing severe neurological deficits within days after the onset of a stroke.²² This means that the severity of a stroke should be reconsidered as an exclusion for rt-PA.

We found that all “eligible” patients with stroke received rt-PA, even in a hospital without previous experience in unlicensed treatment or in clinical trials with rt-PA. Changes in the organisation of the emergency department and doctors’ duties are efficient, and the thrombolysis rate in our centre is high. We observed an insignificantly higher rate of administration of rt-PA compared with the proportion estimated. The main reasons for exclusion from thrombolytic treatment were time from onset to arrival, age and severity of the stroke, which did not differ from the results of other centres.

The considerable early improvement rate in our patients was 50.8%, and is comparable to the treatment arm in the NINDS Trial—47%.¹ As for the outcome at the 3-month follow-up, the results are not compatible, because we accepted mRS ≤2 as favourable, whereas in the NINDS Trial it was ≤1. However, in our study, it was 63.1%, and only 39% in the NINDS Trial, and 60% after including patients with mRS 2–3. Surprisingly to date, we have not noted any symptomatic intracranial haemorrhage, and the 3-month mortality at 16.9% is almost the same as that in the NINDS Trial (17%).

Bray *et al*⁸ reported that 11% of patients were treated in their department after implementation of thrombolysis, but their thrombolysis protocol did not exclude patients aged >80 years.

Our study confirms that lack of experience with thrombolysis for acute ischaemic stroke before its broad implementation is not associated with a low treatment rate, if proper organisational changes are made.

Intravenous thrombolysis for acute ischaemic stroke is not only efficacious, but also cost effective, and generates cost savings with the increase in the proportion of patients treated.^{23 24} Therefore, medical authorities and health services should be interested in improving the organisation of acute stroke care and a widespread implementation of rt-PA treatment.

Table 2 Outcome events and quality parameters of recombinant tissue plasminogen activator treatment

	Patients (n)	% (95% CI)
Considerable early improvement	33	50.8 (38.1 to 63.4)
mRS ≤2 (3 months)	41	63.1 (50.2 to 74.7)
Symptomatic intracranial haemorrhage	0	0 (0 to 5.6)
Mortality (3 months)	11	16.9 (8.8 to 28.3)
Onset to treatment <90 min	1	1.5 (0 to 8.3)
Door-to-needle time <45 min	6	9.2 (3.5 to 19)

mRS, modified Rankin Scale.

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