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INTRAVENOUS rt-PA THROMBOLYTIC THERAPY IN FIFTY-SIX ISCHEMIC STROKE PATIENTS – A PROSPECTIVE FOLLOW-UP STUDY

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SUMMARY – Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) has recently reached the goal of becoming standard therapy in the acute stage of ischemic stroke in many countries. This appears to be one of the first pilot study reports from the region of Central and Eastern Europe. From January 1998 till October 2002, 56 consecutive patients underwent rt-PA thrombolysis at the University Department of Neurology, Nitra University Hospital, Slovakia. Selection criteria for the study were based on the NINDS study, with emphasis on the 3-hour therapeutic window. The mean baseline NIHSS was 14.5, mean therapeutic interval 167 minutes, and mean intravenous rt-PA dose 0.7 mg/kg body weight. At 3 months, mRS 0-1 was recorded in 33.9%, mRS 2-3 in 37.5%, and mRS 4-5 in 16.1% of study patients. Clinically relevant mRS 0-2 was achieved in 44.6% of study patients. The mortality was 12.5%. The rate of symptomatic and fatal intracerebral hemorrhage was 8.9% and 5.3%, respectively. Asymptomatic hemorrhagic transformation of a benign course was relatively frequently recorded (19.6%). Results of the study showed our stroke patients treated with intravenous rt-PA to have a favorable prognosis, and were comparable with those reported from the NINDS study and recent clinical studies.

Key words: *Cerebrovascular accident – drug therapy; Brain ischemia – drug therapy; Fibrinolytic agents – administration and dosage; Thrombolysis; Acute disease; Follow up studies*

Introduction

The last decade of the past century, attributed by neurologists as The Decade of Brain, was really characterized by a great progress in the prevention, diagnosis and especially acute therapy of ischemic stroke. The initial enthusiasm about recombinant tissue plasminogen activator (rt-PA) has grown into the use of modern thrombolysis in practice, according to standard therapeutic principles[1,2]. The saying "time is brain" has become great motivation for the public, emergency staff and stroke teams in hospitals, aiming to reach the shortest possible time interval from the first symptoms of stroke to the initiation of thrombolytic therapy. Despite the failures recorded in clinical trials with neuroprotectives, there are continuing efforts to develop new therapeutic methods for all types of stroke[3-7].

After recognizing a stroke by family members, the patient is immediately transported by ambulance to the nearest regional hospital or regional stroke center (Table 1). The required staff and equipment include 24-hour duty of emergency department, stroke unit, and computed tomography (CT) availability. The initial examination consists of electrocardiogram (ECG) and blood tests for blood count, platelet count, partial thromboplastin time (PTT), INR, and glucose. Although not obligatory, it is useful to perform blood tests for blood type, serum electrolytes, fibrinogen, and renal and hepatic function. An immediate vein access is necessary, preferably bilaterally. Upon internal and neurologic examination, cranial CT is indicated and

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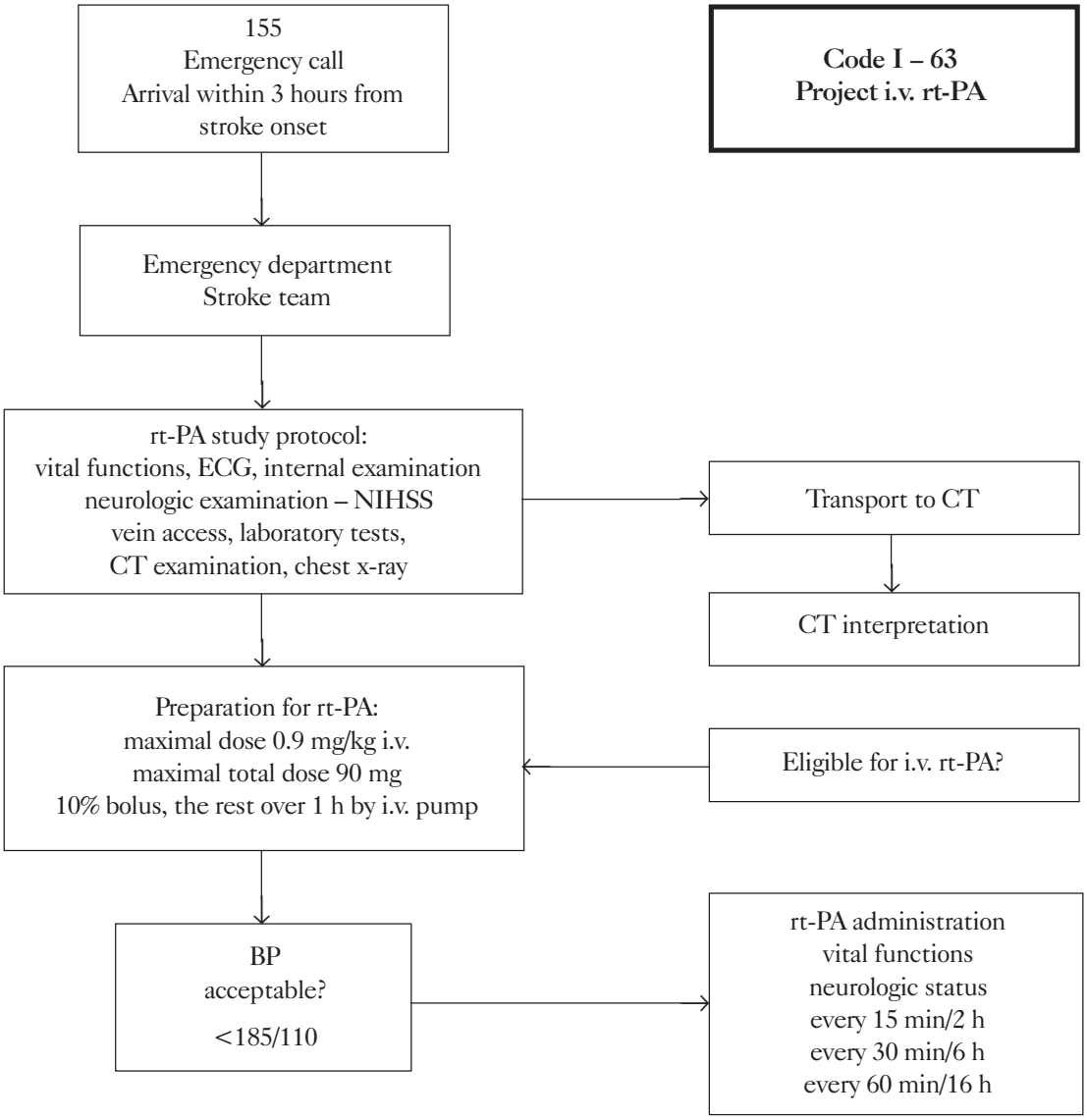
Table 1. Thrombolytic therapy in acute ischemic stroke patients – schematic presentation



readily performed. Chest x-ray is also recommended. During transportation, euvolia should be maintained by intravenous saline infusion. Cardiac monitoring is recommended; careful treatment of extreme hypertension should be performed to maintain systolic blood pressure (BP) <185 and diastolic BP <110[6,8]. At present, there are several diagnostic modalities available for recognizing the type of stroke, especially cranial CT, magnetic resonance (MR), single photon emission computed tomography (SPECT), angiography and sonography. The primary diagnostic goal is to differentiate ischemic stroke from intracranial hemorrhage as well as from other causes such as brain tumor, subdural hygroma, or inflammatory diseases. The secondary goal is to evaluate CT signs of early ischemia. The tertiary goal is to recognize the site of arterial occlusion to plan direct intra-arterial thrombolysis.

Cranial CT has now become the standard diagnostic test for the acute stage of stroke. Most important is diagnostic rapidity because the therapeutic interval for successful intravenous thrombolysis is limited to only 3 hours, and for intra-arterial thrombolysis to 6 hours of the onset of symptoms[3-5,7,8].

Table 2. Patients administered rt-PA at Stroke Unit, University Department of Neurology, Nitra University Hospital, Nitra, Slovakia, during the 1998-2002 period

Year	1998	1999	2000	2001	2002
No. of patients (N=56)	9	7	14	16	10

At our institution, we have been performing rt-PA thrombolysis for ischemic stroke patients since January 1998[9]. The diagnostic and therapeutic programs have been organized for several years now. In 1992, we started with CT and immediately ensured 24-hour availability of CT scanning. During the 1992-2002 period, nearly 2000 carotid endarterectomies with noninvasive transcranial Doppler (TCD) monitoring were carried out at our institution. We perform 1800-2000 duplex, cerebral flow monitoring (CFM) and transcranial color coded sonography(TCCS) ultrasound screening examinations *per* year. Since 1994, we have been performing percutaneous angioplasty of the carotid and subclavian arteries. Well trained stroke teams have been organized, consisting of emergency specialists, radiologists, internists and cardiologists, and experienced neurologists.

CT scan is evaluated by a radiologist and a neurologist. The rt-PA infusion can be started immediately upon CT evaluation. At the University Department of Neurology, there is an intensive care unit working almost as a 'stroke unit', i.e. providing acute therapy, vital sign monitoring, rehabilitation, neuropsychologic care and speech rehabilitation for all stroke patients.

Patients and Methods

From January 1998 till October 2002, 56 consecutive ischemic stroke patients were treated with intravenous rt-PA thrombolysis (Table 2). The study conducted as part of the thrombolysis project was approved by the Ethics Committee of the Nitra University Hospital. Treatment schedules were mainly based on the NINDS protocol, and partially on the ECASS protocol (Table 3). The main criterion was the therapeutic window limited to 3 hours from the onset of symptoms to the initiation of rt-PA therapy. In only several selected cases, rt-PA was started at 4 hours and exceptionally at 5 hours of the onset of stroke symptoms. From the ECASS study we have adopted the presence of early CT signs of ischemia of more than one third of the involved hemisphere as a contraindication. The study included patients with hemispheric and infratentorial ischemia. The initial neurologic deficit was assessed by the NIHSS scale. Patients with severe deficits of NIHSS >24 were not excluded. All patients were hospitalized

Table 3. Contraindications for rt-PA thrombolysis

- Patient taking anticoagulants (PTT >15 s, INR >1.7)
- Patinet taking heparin i.v. within the preceding 24 hours
- Platelets <100 000
- Blood pressure >185/110 after two therapeutic measures
- Previous stroke or serious head trauma in the preceding 3 months
- Isolated mild or quickly resolving neurologic deficit
- Suspected subarachnoid hemorrhage
- Major surgery within the preceding 14 days
- Known intracranial tumor, AVM or aneurysm
- Known hemorrhagic diathesis
- Arterial puncture at a noncompressible site within the preceding 7 days
- GIT or urogenital hemorrhage within the preceding 14 days
- GFS verified gastrointestinal ulcer within the preceding 3 months
- Aneurysm of the aorta, colitis, esophageal varices
- Acute pancreatitis
- Generalized malignancy
- Pregnancy
- Recent myocardial infarction
- Glucose <2.7 and >22.2 mmol/l
- Peritoneal dialysis and hemodialysis
- Extremely severe neurologic deficit (NIHSS >24)
- Epileptic seizure at the onset of stroke
- Age over 80
- Sopor and coma
- Septic febrility
- Ocular hemorrhage or surgery within the preceding 3 weeks
- Severe hepatic and renal insufficiency
- Subacute bacterial endocarditis

at the neurologic intensive care (stroke) unit and treated with intravenous rt-PA (Actilyse®, Boehringer, Ingelheim)[10], mean dose 0.7 mg/kg body weight, with 10% of the dose administered as a bolus, and the rest as pump infusion over one hour.

There were 34 men and 22 women, mean age 59.2 (range 22-82) years (Fig. 1). The initial neurologic deficit was 7-24 NIHSS scale, mean 14.5 NIHSS scale. The dominant hemisphere was involved in 38 (68%) and nondominant hemisphere in 13 (23%) patients. Infratentorial stroke was present in five (9%) patients. The most common risk factors were hypertension (41.1%) and cardiac ischemic disorders (51.7%); atrial fibrillation was present in 28.6% of cases. Cardioembolic stroke in the middle cerebral artery (MCA) territory was presumed in 21 (37.5%), thrombosis or thromboembolism into MCA in 28 (50%), and the latter associated with internal carotid artery (ICA) thrombosis in seven (12.5%) cases. Thrombosis of the basilar artery was presumed in four (7.1%), and thromboembolism into the choroidal arteries in two (3.5%) cases. One patient suffered severe thromboembolic stroke in the dominant hemisphere during Seldinger catheterization angiography. On TCCS, slowing of the blood flow in the left MCA was observed. In this patient, the neurologic status did not change during 3 hours, and right hemiplegia and complete aphasia persisted. The patient was treated with rt-PA during the fourth hour from the onset of symptoms. In one case, ischemic stroke after CEA caused by early postoperative carotid thrombosis was observed. This patient was successfully treated with rt-PA during the fifth hour of stroke onset. The youngest patient aged 22 suffered severe cardioembolic stroke in the dominant hemisphere, caused by the left atrial myxoma. He underwent an acute operative procedure on day 2 of stroke onset.

The mean time interval between the onset of ischemic stroke and administration of rt-PA therapy was 167 minutes (minimum 15 minutes, maximum 300 minutes) (Table 4).

Initial CT was negative in 41%, whereas media sign was present in 21% of cases. Early signs of ischemia were detected in 32% of CT scans, with media sign also observed in two thirds of positive scans. Previous infarcts were seen in 3 (5.3%) patient scans. In all patients, control CT was performed at 24 hours of thrombolysis. Another control CT during the next 3 months of the study was done in the majority of patients (70%).

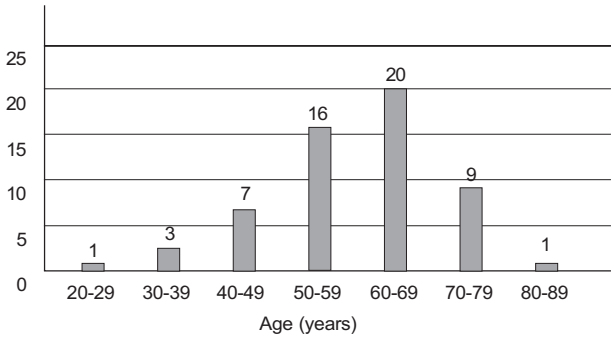


Fig. 1. Age distribution of stroke patients submitted to rt-PA thrombolysis at Nitra University Hospital during the 1998-2002 period (N=56)

Duplex (CFM) and transcranial (TCCS) ultrasound examination was performed in 30 (53.6%) patients during the acute stage of ischemic stroke. We identified 11 (19.6%) severe stenoses or occlusions of ICA and MCA each, 3 (5.3%) of the latter being associated with recent occlusion of ICA.

A modified Rankin scale (mRS) was used for functional status evaluation at 3 months of stroke.

Results

In our study, mRS 0-1 (without any deficit or with minimal deficit) was achieved in 33.9% and mRS 2-3 (moderate neurologic deficit) in 37.5% of patients. From the clinical point of view, it was very important to evaluate mRS 0-2 (patient independent, without severe neurologic deficit). This mRS grade was achieved in 44.6% of patients. Six (10.7%) patients were free from residual symptoms, with mean NIHSS 12.8, i.e. somewhat lower than in the group as a whole. The mortality was 12.5% (seven patients). Comparison of our results with those reported from the NINDS study is illustrated in Fig. 2.

Table 4. Therapeutic window (time interval) in stroke patients administered rt-PA thrombolysis

Time interval (min)	0-60	60-120	120-180	180-240	240-300
No. of stroke patients (N=56)	4	7	26	12	7

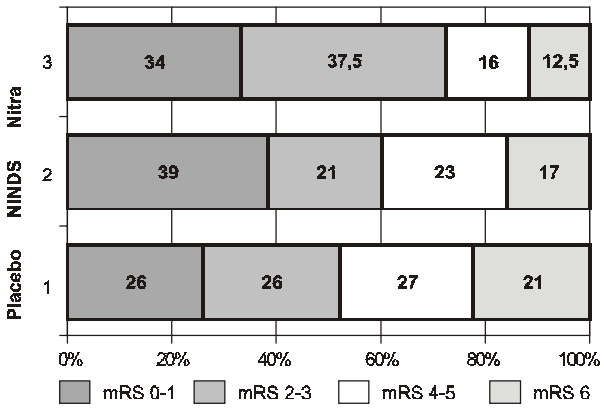


Fig. 2. Results of rt-PA thrombolysis therapy and comparison with NINDS groups

Post-thrombolytic intracranial hemorrhage occurred in five (8.9%), and was fatal in three (5.3%) patients. Retrospective analysis of these fatal cases revealed the following findings: initial platelet count of 95,000 and immediately repeated platelet count 115,000 (a male aged 66, NIHSS 12); evolving MCA infarct was underestimated and subsequently hemorrhagically converted (a female aged 67, NIHSS 18); and a history of two cardioembolic cerebral infarcts (a female aged 61, NIHSS 19) in one patient each. In these cases, therapeutic window was within the NINDS limits (180, 145 and 140 minutes, respectively); the initial mean NIHSS (16.3) was greater than in the group as a whole.

In two (3.6%) patients, the hemorrhagic transformation of the initial brain infarct was associated with the occurrence of brain parenchymal hematoma in the contralateral hemipshere, as observed on subsequent CT scans. In these cases, bilateral cardioembolic involvement of brain hemispheres occurred. In both of these patients, the vegetative state persisted.

It is of particular interest that 19 (33.9%) of our patients were successfully treated during the 4th and 5th hour of stroke. These patients were younger than the group mean (55.1 *vs.* 59.2 years). They had almost identical initial NIHSS (14.4 *vs.* 14.5). Fifteen (79%) of these patients suffered left hemisphere stroke and two (10.5%) had infratentorial stroke. In this subgroup, nine of 19 (47.4%) patients achieved mRS 0-2. Two patients from this group died during the period of hospitaliazation, i.e. one from acute myocardial infarction on day 17 of stroke, and one from fatal thrombocytopenia on day 7 of stroke.

In our study group, there were five (8.9%) infratentorial strokes treated by rt-PA. Three of these patients recovered to mRS 1 and two to mRS 2 during the first week of therapy. In four (80%) of them, clinical improvement persisted for several months after stroke. One patient died from basilar rethrombosis on day 7 of the first ischemic stroke. Basilar rethrombosis was confirmed on autopsy.

Asymptomatic hemorrhagic transformation of the initial brain infarction site, sometimes associated with minor central hemorrhage, was relatively frequently observed in our patients (19.6%). In these cases, the transformation was clinically silent, in some of them it could even be a sign of good prognosis.

Ultrasound monitoring (duplex, CFM, TCD, TCCS) verified early recanalization in 30.3% of cases. CT and TCD findings of three cases are shown in Figs. 3, 4 and 5.

Discussion

Acute thrombolytic therapy of ischemic stroke is considered to be a revolutionary goal of the last decade of the

Table 5. Comparison of results reported from rt-PA thrombolysis studies

Parameter	Nitra UH	Brno UH	NINDS*	ECASS II*	PROACT II*
No. of patients	56	31	312	407	121
Mean age (yrs)	59	65	68	68	67
Therapeutic interval (min)	167	136	–	–	318
NIHSS	14.5	13.6	14	11	17
ICH within 36 h – symptomatic	8.9%	6.4%	17.3%	10.6%	10.2%
ICH asymptomatic or malacia rubra	19.6%	3.2%	4.5%	–	–
Lethality	12.5%	12.9%	17.3%	10.6%	25%
Rankin 0-1	33.9%	38.7%	38.7%	40.3%	–
Rankin 0-2	44.6%	51.6%	–	54.3%	40%

*randomized studies; UH=University Hospital; ICH=intracranial hemorrhage; Rankin=modified Rankin scale

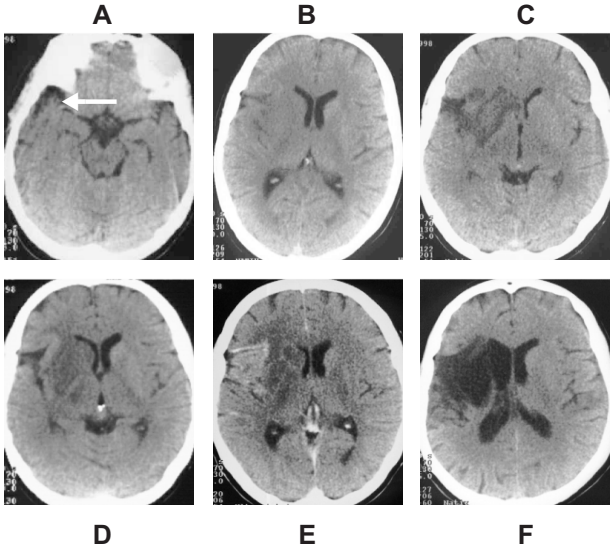


Fig. 3. Case 1 – CT scans

3A: Initial noncontrast CT scan with hyperdense media sign (arrow); 3B: early findings of cerebral ischemia in the temporoparietal region of the left hemisphere on noncontrast CT; 3C: ischemic cerebral changes with lateral ventricle compression on day 2; 3D: noncontrast CT, and 3E: hyperperfusion after administration of contrast media on day 12; 3F: regional temporoparietal hypodensity confirming the ischemic infarction in the postcentral region of the left hemisphere on day 23.

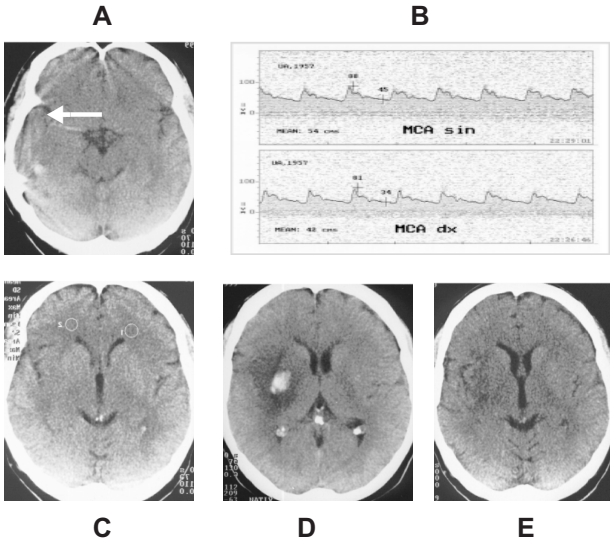


Fig. 4. Case 14 – CT and TCD scans

4A: The hyperdense media sign on initial CT; 4B: recanalization of the left MCA confirmed 8 h after rt-PA thrombolysis; 4C: normal findings on initial noncontrast CT scan; 4D: a small central post-thrombolytic hemorrhage on day 7; 4E: normal CT findings on day 17 of stroke.

20th century, with the ability to reopen recently occluded cerebral arteries. Soon after publishing the results of randomized studies[3-5], the therapeutic potential of intravenous rt-PA, and partially of intra-arterial prourokinase too, has been repeatedly documented in standard clinical settings[7,12,14]. It has been confirmed that early recanalization enables restoration of the cerebral function with longlasting clinical benefit[13]. For the first time it could be demonstrated that even patients with initial severe neurologic deficits could be cured from ischemic stroke without any sequels.

A great limitation of thrombolytic therapy still remains the time interval from the onset of stroke. It is generally accepted that intravenous thrombolysis can be safely performed during the first 3 hours of stroke. Our study confirmed that in individual cases, good results could be achieved with thrombolysis performed up to 5 hours of stroke onset. Nevertheless, the need to maintain standard protocols of thrombolytic therapy and urgent time limit

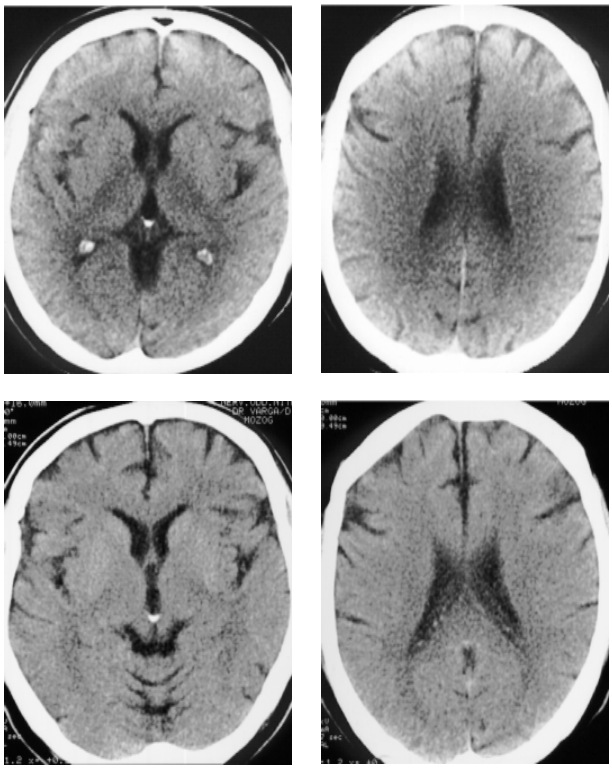


Fig. 5. Case 28 – CT scans

Upper panels: initial CT scans. Only small nonspecific hypodensity in the left parietal cortex is observed. Lower panels: follow-up scans after 10 days. Nonspecific hypodensity in the left parietal cortex seems to have slightly increased. The finding was interpreted as a residual ischemic zone.

have fastened and improved the diagnosis and therapy, and thus the outcome of stroke patients[6-8].

In many countries, a network of hospitals has emerged which are capable to evaluate and treat ischemic stroke patients immediately according to the internationally standardized protocols[8,12]. Ischemic stroke is not necessarily 'the brain apoplexy' with serious and untreatable consequences. The progress in stroke care has shown that interdisciplinary collaboration on the part of stroke teams is the basic precondition for early evaluation and successful therapy in stroke patients. The potential of new therapeutic methods has become a great motivation for the public whose awareness of stroke has gradually raised during the past years.

After publishing the results of randomized studies on thrombolysis in 1995[3,4] and FDA approval of intravenous thrombolysis in 1996, and especially after publishing the Proposal of Cerebrovascular Program for Slovakia in 1997[6], we embarked upon designing the project of intravenous thrombolysis in ischemic stroke patients at our hospital. The promising results of rt-PA therapy recorded in our first stroke patients were published soon thereafter[9]. From January 1998 till October 2002, the procedure of thrombolysis according to NINDS and ECASS protocols was performed in 56 patients, at a mean time interval of 167 minutes from stroke onset. The results were comparable to those published in the literature[3,4,14] according to three important clinical parameters: mRS 0-1was achieved in 33.9% and mRS 0-2 in 44.6% of patients, whereas symptomatic hemorrhages occurred in 8.9% of patients (Table 5). This means that almost half of our patients sustained no or only mild residual neurologic deficit following thrombolysis. More than 70% of patients were rendered self-sufficient, without the need of any help from their family members. Only 15% of patients sustained disability, with severe neurologic deficits, which is a considerably lower rate as compared with standard therapy and rehabilitation after stroke. As mentioned above, intravenous rt-PA therapy can only produce successful results if initiated by the 5th hour of stroke onset in severe cases. Promising results have also been observed in case of infratentorial stroke.

Serious hemorrhagic complications were recorded in 8.9% of study patients, i.e. almost a half as compared with NINDS study. The post-thrombolytic hemorrhage was fatal in only three (5.6%) patients. Our results confirmed the safety of appropriately used rt-PA thrombolysis. In our study, the rate of asymptomatic hemorrhagic transformation of the initial infarct (19.6%) was higher than those reported elsewhere[3-5]. It was partially due to the higher rate of CT controls in our patients. We believe that the occurrence of cardioembolic stroke in our patients could have exceeded that recorded in most of the published studies. In this stroke type, the hemorrhagic transformation of the infarct is part of its natural course. The CT appearance of partial hemorrhagic transformation is a sign of temporary interruption of the blood-brain barrier in the area of infarcted tissue and/or undergoing excessive hyperemia. Clinically, this transformation has no adverse effect, on the contrary, it could be interpreted as a sign of the possible good clinical prognosis.

In comparison with other studies[3-5,14], our patients were younger (mean age younger by 8-9 years). One of the reasons for this was a more active diagnostic and therapeutic approach to younger patients. On the other hand, the initial neurologic status of our thrombolysis patients was relatively severe (mean NIHSS 14.5) with frequent involvement of the dominant hemisphere (68%). That is why we consider our group of patients prognostically more severe than the randomized patients from the NINDS and ECASS studies. Older patients more often suffer lacunar infarction, and the natural course of this type of stroke is more favorable, even without any therapy. Younger patients usually have not developed adequate collateral cerebral circulation. Thus, when they suffer an MCA ischemic stroke, the malignant course seems to be quite common[6,11,12].

Another deviation from the NINDS protocol was the use of a lower rt-PA dose (mean 0.7 mg/kg body weight). There were two reasons for this: financial limitations, especially on launching the study, and TCD monitoring results that had indicated early recanalization of MCA or basilar artery after a lower dose of rt-PA than the recommended dose of 0.9 mg/kg used in the NINDS study. A similar experience has recently been reported by a group from France[7]. We considered the lower dose of rt-PA to be adequate for some of our patients with MCA or ICA thrombotic occlusion. In the next study, we plan to use a mean dose of 0.8-0.9 mg/kg rt-PA *per* patient.

In the region of Nitra, Slovakia, we were able to treat 10-15 patients with intravenous rt-PA thrombolysis *per* year, i.e. 3% to 5% of all ischemic stroke cases. The mean time elapsed from the onset of stroke symptoms to the admission to emergency hospital department was 60-90 minutes, whereas the mean door-to-needle interval (from the emergency department to therapy initiation) was usually about 60 minutes. During this interval, all blood tests, chest x-ray, ECG, cardiologic examination and cranial CT were performed and evaluated.

The recent experience from the USA, Canada, Germany and other European countries has shown that public education and perfect organization of transportation and hospital evaluation enable sophisticated and safe thrombolytic treatment to offer to nearly 10% of ischemic stroke patients[2,12,14]. In many regional hospitals, which serve as regional stroke centers, thrombolysis has become standard therapy, and hundreds of patients can be treated yearly. Several combinations of thrombolytic and neuroprotective therapies are experimentally under way. We hope that some of these experiments may prove successful, and the therapeutic window for efficacious and safe thrombolysis be longer than it is nowadays.

Acknowledgment. This study was performed as part of the large thrombolysis project.

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Sažetak

INTRAVENSKA TROMBOLITIČNA TERAPIJA POMOĆU rt-PA U PEDESETŠESTORO BOLESNIKA S ISHEMIJSKIM MOŽDANIM UDAROM – PROSPEKTIVNA STUDIJA PRAĆENJA

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Intravenska tromboliza pomoću rekombinantnog aktivatora tkivnog plazminogena (rt-PA) odnedavno je postigla svoj cilj i u mnogim zemljama postala standardnim načinom liječenja akutnog stadija ishemijskog moždanog udara. Ovo je, čini se, jedno od prvih objavljenih probnih ispitivanja u području središnje i istočne Europe. U razdoblju od siječnja 1998. do listopada 2002. godine je na Klinici za neurologiju Sveučilišne bolnice Nitra iz Nitre, Slovačka, 56 uzastopnih bolesnika podvrgnuto trombolizi. Kriteriji za odabir bolesnika zasnivali su se na studiji NINDS, poglavito terapijski prozor od 3 sata. Postignuli smo prosječan bazalni NIHSS od 14,5, prosječan terapijski interval bio je 167 minuta, a prosječna doza intravenskog rt-PA bila je 0,7 mg/kg tjelesne težine.

Nakon 3 mjeseca mRS 0-1 dostignulo je 33,9%, mRS 2-3 37,5%, te mRS 4-5 16,1% bolesnika. Klinički važan mRS 0-2 postiglo je 44,6% bolesnika. Smrtnost je bila 12,5%. Stopa simptomatskog unutarmoždanog krvarenja bila je 8,9%, a fatalnog 5,3%. Asimptomatska hemoragijska transformacija bila je relativno česta, tj. u 19,6% bolesnika s benignim tijekom. Zaključeno je kako bolesnici s moždanim udarom koji se liječe intravenskom rt-PA trombolizom u našoj bolnici imaju dobru prognozu, usporedivu s rezultatima studije NINDS i drugim novijim kliničkim studijama.

Ključne riječi: *Cerebrovaskularni ispad – medikamentno liječenje; Moždana ishemija – medikamentno liječenje; Fibrinolitični lijekovi – primjena i doziranje; Tromboliza; Akutna bolest; Studije praćenja*