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THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE – OUR EXPERIENCES AS PART OF SITS-MOST

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SUMMARY – Thrombolysis with intravenous recombinant tissue plasminogen activator (rt-PA) is the first evidence based treatment for acute ischemic stroke, which aims to reduce the cerebrovascular lesion. At University Department of Neurology, Sestre milosrdnice University Hospital, Zagreb, thrombolytic therapy with intravenous rtPA (alteplase) (Actilyse®) for acute ischemic stroke was introduced in 2004. We present our results referring to demographic, time logistics and clinical outcome data as part of SITS-MOST (Safe Implementation of Thrombolysis in Stroke – MOnitoring STudy) and compare them with the results from other centers in Croatia and all other participating centers. Up to now, 56 patients (61% of male and 39% of female, average age 67 years) have been treated at our department with intravenous rt-PA (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose given as a bolus followed by 60-minute infusion. Our experiences with thrombolytic therapy with intravenous rt-PA (alteplase) (Actilyse®) for acute ischemic stroke confirm the safety and the efficacy of this therapy.

Key words: *Brain ischemia – drug therapy; Stroke – drug therapy; Thrombolytic therapy; Fibrinolytic agents – therapeutic use*

Thromboembolic occlusion of an artery leading to the brain or in the brain is a major cause of ischemic stroke. The size and site of the occlusion and the efficiency of compensatory flow through collateral arteries determine the amplitude and extension of the drop in the blood flow. Reperfusion should be done as early as possible to avoid cerebral lesion and complications caused by ischemic injury to the blood vessel walls and blood-brain barrier[1]. Thrombolysis with intravenous recombinant tissue plasminogen activator (rt-PA) is the first evidence based treatment for acute stroke, which aims to reduce the cerebrovascular lesion[2].

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Thrombolytic therapy for stroke was first reported in 1958[3], and a subsequent small trial was reported in 1963 in the absence of brain parenchymal imaging but guided by angiography[4]. The later arrival of CT scanning was an enabling technological event and early dose-finding trials were begun in the 1980s[5], with large randomized trials conducted a decade later. Results of randomized trials of streptokinase therapy for ischemic stroke were uniformly negative[6-8]. Results of trials of tissue plasminogen activator (tPA) were mixed in their respective primary analysis[9-13], but generally showed a benefit that wanes as the time from symptom onset to treatment elapses[14,15]. A meta-analysis of randomized controlled trials showed that 55 fewer patients per 1000 treated with tPA within 6 hours after stroke would be dead or dependent at the end of follow up compared with patients admin-

Table 1. Demographic and baseline data

Demographic and baseline data	Sestre milosrdnice University Hospital	Croatia	All centers
Total number of patients treated	56	85	29616
Dose given *per* patient (mg) (median)	75.0	76.5	68.0
Dose given *per* kg (mg/kg)	0.9	0.9	0.9

Table 2. Rankin before stroke onset

Rankin before stroke onset	Sestre milosrdnice University Hospital	Croatia	All centers
No symptoms at all	69%	71%	79%
No significant disabilities	22%	19%	11%
Slight disabilities	6%	6%	5%
Moderate disabilities	0%	0%	3%
Moderate to severe disabilities	2%	2%	1%
Severe disabilities	0%	1%	1%

Table 3. Stroke risk factors

RISK FACTORS	Sestre milosrdnice University Hospital	Croatia	All centers
Hypertension	84%	84%	61%
Diabetes	22%	21%	17%
Hyperlipidemia	18%	33%	31%
Current smoker	20%	25%	21%
Previous smoker	8%	12%	17%
Previous clin. dg. ischemic stroke	20%	14%	11%
Atrial fibrillation	16%	22%	24%
Congestive heart failure	6%	12%	8%

Table 4. Baseline NIHSS

Baseline NIHSS	Sestre milosrdnice University Hospital	Croatia	All centers
Median NIHSS	13	13	12
NIHSS score 0-7	12%	8%	24%
NIHSS score 8-14	45%	41%	35%
NIHSS score 15-	43%	44%	36%

Table 5. Blood pressure at baseline

Blood pressure at baseline (mean, mm Hg)	Sestre milosrdnice University Hospital	Croatia	All centers
Systolic	154	154	148
Diastolic	90	88	81

Table 6. Stroke subgroups

Subgroup	Sestre milosrdnice University Hospital	Croatia	All centers
Large vessel disease with significant carotid stenosis	29%	23%	12%
Large vessel disease, other	29%	41%	27%
Cardiac source of emboli	16%	19%	34%
Small vessel disease (lacunar)	20%	12%	10%
Other/unusual cause	0%	1%	4%
None of the above (can be multiple causes)	0%	0%	0%

Table 7. Time delay

Time delay (minutes) (median)	Sestre milosrdnice University Hospital	Croatia	All centers
Stroke onset – arrival to hospital (door time)	78	75	66
Door to imaging study time	29	27	25
Imaging study to report time	15	15	5
Door to treatment/needle time	67	70	65
Stroke onset to treatment – needle time	152	155	145

Table 8. NIHSS changes within 24 h

NIHSS changes within 24 h	Sestre milosrdnice University Hospital	Croatia	All centers
Change in NIHSS 0-2 h (median)	–2	–2	–2
Change in NIHSS 0-24 h (median)	–3	–3	–3
Significant early improvements (%)*	39	43	51
Significant deterioration (%)*	5	7	12

*Significant early improvement – significant improvement based on NIHSS, i.e. change <= 4 between 0 and 2 hours, 0 and 24 hours, and 2 and 24 hours, or full recovery (end state NIHSS=0).
*Significant deterioration – significant deterioration based on NIHSS, i.e. NIHSS change >=4 between 0 and 2 hours, 0 and 24 hours, 2 and 24 hours or death <=24 h.

Table 9. Global outcome (24 h)

Global outcome (24 h)	Sestre milosrdnice University Hospital	Croatia	All centers
Improvement –NIHSS score changed <4	49%	38%	31%
Improvement – NIHSS score changed <2	24%	30%	32%
Unchanged NIHSS score	12%	20%	24%
Deterioration - NIHSS score changed >2	12%	9%	9%
Much worse	2%	4%	4%
Dead	0%	0%	1%

Table 10. Global outcome (7 days)

Global outcome (7 days)	Sestre milosrdnice University Hospital	Croatia	All centers
Improvement –NIHSS score changed <4	46%	46%	41%
Improvement – NIHSS score changed <2	29%	23%	30%
Unchanged NIHSS score	16%	19%	15%
Deterioration - NIHSS score changed >2	2%	2%	5%
Deterioration - NIHSS score changed >4	7%	4%	3%
Dead	0%	6%	7%

Table 11. Rankin 3 months

Rankin 3 months	Sestre milosrdnice University Hospital	Croatia	All centers
No symptoms at all	5%	3%	18%
No significant diasbility symptoms	15%	17%	18%
Slight disability	18%	18%	15%
Moderate disability	23%	17%	12%
Moderate severe disability	20%	20%	12%
Severe disability	8%	5%	5%
Dead	8%	17%	14%

istered placebo[16,17]. Systematic reviews of randomized controlled trials indicate that treatment with thrombolytics is highly beneficial when administered within 3 hours from the onset of stroke symptoms[18].

Current guidelines for the management of patients with acute ischemic stroke published by the American Heart Association Stroke Council include specific recommendations for the administration of recombinant tissue plasminogen activator (rtPA), on behalf of Science Advisory from the American Heart Association and American Stroke Association.

Despite its effectiveness in improving neurologic outcomes, the majority of patients with ischemic stroke are not treated with rtPA, largely because they arrive after the currently approved 3-hour time limit for administration of the medication. One of the potential approaches to increase treatment opportunities has been the designation of a longer time window for treatment.

A recent prospective study, the European Cooperative Acute Stroke Study (ECASS)-3, has provided new data on rtPA (alteplase) (Actilyse®) treatment within the 3-to-4.5-hour window. Patients that are eligible for treatment with rtPA within 3 hours of the onset of stroke should be treated as recommended in the 2007 guidelines[19]. Although a longer time window for treatment with rtPA has been tested formally, delays in the evaluation and initiation of therapy should be avoided, because the opportunity for improvement is greater with earlier treatment. rtPA should be administered to eligible patients that can be treated within the time period of 3 to 4.5 hours after stroke. The eligibility criteria for treatment in this time period are similar to those for persons treated at earlier time periods, with any of the following additional exclusion criteria: patients older than 80 years, those taking oral anticoagulants with an international normalized ratio ?1.7, those with a baseline National Institutes of Health Stroke Scale (NIHSS) score >25, or those with a history of both stroke and diabetes. The relative utility of rtPA in this time window compared with other methods of thrombus dissolution or removal has not been established. The efficacy of intravenous treatment with rtPA within 3 to 4.5 hours after stroke in patients with these exclusion criteria is not well established[20-23].

SITS (Safe Implementation of Thrombolysis in Stroke) is an academic-driven, non-profit, international collaboration. It is an initiative by the medical profession to certify excellence in acute stroke treatment. It

started as an initiative by participants in the European-Australian randomized stroke thrombolysis studies (ECASS) and then spread to many centers in several countries. SITS initiated an internet-based interactive thrombolysis register, to serve as an instrument for clinical centers to follow their own treatment results and compare with other centers in their countries and in the collaborating countries. The SITS register is now the technical basis for the International Stroke Thrombolysis Register (SITS-ISTR) and SITS Monitoring Study (SITS-MOST). SITS-MOST has strict entry criteria, with a limit of maximally three hours from the onset of symptoms to treatment. The aims of SITS-MOST are to evaluate the safety and efficacy of routine use of rt-PA for this well defined population, to evaluate the effect of rt-PA within defined subgroups of this population, at experienced clinical centers and centers with less experience but high-quality general stroke care, and to compare these results with those from randomized controlled trials. SITS-MOST also aims to prove that rtPA is as safe and as beneficial in routine clinical practice in a large number of European clinical centers as it has been shown to be in randomized clinical trials such as the National Institute of Neurological Disorders Stroke (NINDS) trial. Participation in SITS-MOST requires agreement of the National Coordinator. The International Coordinating center is at the Karolinska Hospital[24,25].

At University Department of Neurology, Sestre milosrdnice University Hospital, Zagreb, thrombolytic therapy with intravenous rtPA (alteplase) (Actilyse®) for acute ischemic stroke was introduced in 2004. According to recommendations for stroke management endorsed by Croatian Society for Neurovascular Disorders of Croatian Medical Association, Croatian Stroke Society and University Department of Neurology, Sestre milosrdnice University Hospital as Reference Center for Neurovascular Disorders of Croatian Ministry of Health, published in 2001, thrombolytic treatment for acute ischemic stroke within 3 hours of onset was indicated as therapy of choice for all patients that are eligible for treatment[26].

We present our results as part of the SITS-MOST study in order to compare them with the results from other centers in Croatia and all other participating centers. Up to now, 56 patients (61% of male and 39% of female, average-age 67 years) have been treated at our department with intravenous rt-PA (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose given as a bolus followed by 60-minute infusion. The average dose given per patient at our department was 75 mg (Table 1).

Demographic and Baseline Details

We present demographic and baseline details from our center as compared to other centers in Croatia and all centers, according to Rankin before stroke onset, stroke risk factors, baseline NIHSS, blood pressure at baseline and stroke subgroups (Tables 2-6):

Time Logistics/Time Delay

As far as the average time from the onset of stroke symptoms to rtPA treatment is concerned, we share the same results as other centers in Croatia, whereas in all other participating centers this time was shorter. Time logistics is present as shown in Table 7.

Results – Clinical Outcome

There were no differences in the early improvement as expressed by improvement of NIHSS score status between our patients and patients from other centers in Croatia and all centers. We report a lower percentage of early deterioration. The results related to clinical outcome considering NIHSS changes within 24 hours, global outcome within the first 24 hours and 7 days, and Rankin after 3 months are presented in Tables 8-11.

At our department, asymptomatic intracranial hemorrhage occurred in only 4 patients. Using patient selection according to the standard protocol, we recorded no death within 7 days of rt-PA treatment.

Our experiences with thrombolytic therapy with intravenous recombinant tissue-type plasminogen activator (alteplase) (Actilyse®) in acute ischemic stroke confirm the safety and efficacy of this therapy, showing that complications are minimal if the Croatian Society for Stroke Prevention (CSSP), European Stroke Organization (ESO) and AHA/ASA guidelines are strictly followed. Being a part of the SITS-MOST trial serves as an instrument to follow our own treatment results and compare them with other centers in our country and in the collaborating countries, all with the same goal to argue for more widespread development and training of stroke physicians to deliver thrombolytic therapy to people experiencing acute ischemic stroke.

In conclusion, we are very happy to take active part in the exciting time in neurology, stroke in particular, and to be able to convey our enthusiasm for our research and the results obtained so far.

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Sažetak

TROMBOLIZA KOD AKUTNOG ISHEMIJSKOG MOŽDANOG UDARA – NAŠA ISKUSTVA KAO DIO PRISTUPA SITS-MOST

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Tromboliza intravenskim rekombiniranim aktivatorom tkivnog plazminogena (rt-PA) je prvi dokazani učinkoviti način liječenja akutnog ishemijskog moždanog udara u svrhu smanjenja cerebrovaskularnog oštećenja. U Klinici za neurologiju Kliničke bolnice "Sestre milosrdnice", Zagreb, trombolitička terapija intravenskim rt-PA-om (alteplase) (Actilyse®) u bolesnika s akutnim ishemijskim moždanim udarom započela je 2004. godine. Predstavljamo naše dosadašnje rezultate, koji se odnose na demografske, vremenske i podatke o kliničkom ishodu bolesnika, prikupljene u sklopu SITS-MOST (Safe Implementation of Thrombolysis in Stroke – Monitoring STudy) istraživanja, u svrhu usporedbe rezultata dobivenih u našem centru s rezultatima iz drugih centara Hrvatske i svijeta. Do sada je u našem centru trombolizom intravenskim rt-PA-om (0,9 mg/kg tjelesne težine, do maksimalno 90 mg), 10% doze primijenjene u bolusu, 90% doze u infuziju u trajanju od 60 minuta, liječeno 56 bolesnika (61% muškarci, 39% žene, prosječne životne dobi 67 godina). Naša iskustva u trombolitičkoj terapiji (alteplase) (Actilyse®) u bolesnika sa akutnim ishemijskim moždanim udarom potvrđuju učinkovitost i sugurnost takvog načina liječenja.

Ključne riječi: *Moždana ishemija – terapija lijekovima; Moždani udar – terapija lijekovima; Trombolitična terapija; Fibrinolitici – terapijska primjena*