OUR EXPERIENCE WITH THROMBOLYTIC THERAPY – PRELIMINARY REPORT

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SUMMARY – Stroke is a rapidly developing clinical disturbance of focal or global cerebral function, lasting for more than 1 hour. It is an acute form of symptoms of brain function disorder, with no apparent cause other than vascular origin. It is the final phase of arterial disease, the main cause of disability, and the second leading cause of death. Today, ischemic stroke can be treated successfully by acting on its cause using a very powerful weapon, thrombolytic therapy. The aim is to present a preliminary report of our experiences with thrombolytic therapy in patients with ischemic stroke. Results recorded in 20 patients who received thrombolytic therapy within three hours of stroke onset are presented. Nineteen patients survived and one patient died from therapy side effects, i.e. intracerebral hematoma. Seventeen of 19 patients were released from the hospital without any neurologic deficit, while two patients had Rankin score 2 (minimum disability) three months after stroke onset. Our experience confirms that thrombolytic therapy is the treatment of choice in patients with ischemic stroke if administered in accordance with precise protocols.

Key words: *Stroke; Brain ischemia; Thrombolytic therapy*

Introduction

Cerebrovascular diseases are a serious health problem, increasingly common worldwide, causing severe disabilities and creating an enormous burden on the social and health care systems. Stroke is the second leading cause of death, responsible for 4.4 million (9%) of the total 50.5 million deaths each year, and it is the leading cause of adult disability. Globally, stroke death rates vary widely; the highest rates are in Portugal, China, Korea, and most of Eastern Europe, and the lowest rates are in Switzerland, Canada, and the United States. Acute ischemic stroke accounts for approximately 80% of all strokes, and occurs when a thrombus, or embolism, blocks a cerebral blood vessel. Resulting mortality and morbidity, particularly long-term disability, are high. Approximately 20% of patients will die within thirty days of stroke onset, and many are left permanently disabled[1].

In 70%-80% of cases, stroke is caused by brain infarctions. An ischemic type of cerebrovascular disease, simply called ischemic stroke, is more frequent than hemorrhagic stroke. In the European population, ischemic stroke accounts for up to 80% of all cerebrovascular events, is frequent in middle-aged and older individuals, and often leads to prolonged hospitalization, disability, or death. It is likely that the progressive aging of Western populations will raise the number of ischemic stroke events in the future. Therefore, the prevention and better treatment of ischemic stroke has considerable public health significance. The 3-month mortality rate from ischemic stroke is approximately 12%. However, patients who are candidates for thrombolytic stroke therapy tend to have more severe strokes than the average patient

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with ischemic stroke. The 3-month mortality rate in these more severe patients is approximately 21% when they do not receive thrombolytic therapy. This death rate is not increased by the use of thrombolytic treatment. Common acute complications of stroke include pneumonia, urinary tract infection, and pulmonary embolism. Long-term morbidity in survivors of stroke is common, with ambulation difficulty in 20%, need for assistance in activities of daily living in 30%, and vocational disability in 50%-70% of patients. Comparison of stroke rates among races is confounded by socioeconomic, environmental, and nutritional factors. The age-adjusted incidence rate for black men is 1.5 times higher than that for white men; that for black women is 2.3 times higher than that for white women. The male-to-female ratio for stroke is about 1.35:1. The incidence of stroke doubles in every decade after age 45, rising from 104 *per* 100,000 *per* year for adults aged 45-54 to 111.3 *per* 100,000 *per* year for adults aged 75-84. Two thirds of strokes occur in persons older than 65[2-5].

The most common risk factors for ischemic stroke are age, hypertension, diabetes, smoking, atrial fibrillation, hypercholesterolemia, and coronary artery disease. Mechanisms of ischemic stroke are in situ atherothrombosis, artery to artery embolism, cardioembolism, lipohyalinosis, and hypercoagulable state[6].

The thrombolytic agent, recombinant tissue plasminogen activator (rt-PA/alteplase) has been approved for the treatment of acute ischemic stroke within three hours of symptom onset. It is the first thrombolytic agent to be licensed for this indication and has the potential to radically change the early management of acute ischemic stroke and reduce resultant disability.

Recommendations for Thrombolysis

Intravenous rtPA (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose given as a bolus followed by a 60-minute infusion, is recommended within 4.5 hours of the onset of ischemic stroke (Class I, Level A), although treatment between 3 and 4.5 h is currently not included in the European labeling.

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- The use of multimodal imaging criteria may be useful in patient selection for thrombolysis but is not recommended for routine clinical practice (Class III, Level C)
- It is recommended that blood pressures of 185/110 mm Hg or higher is lowered before thrombolysis (Class IV, GCP)
- It is recommended that intravenous rtPA may be used in patients with seizures at stroke onset, if the neurologic deficit is related to acute cerebral ischemia (Class IV, GCP)
- It is recommended that intravenous rtPA may also be administered in selected patients under 18 and over 80 years of age, although this is outside the current European labeling (Class III, Level C)
- Intra-arterial treatment of acute MCA occlusion within a 6-hour time window is recommended as an option (Class II, Level B)
- Intra-arterial thrombolysis is recommended for acute basilar occlusion in selected patients (Class III, Level B). Intravenous thrombolysis for basilar occlusion is an acceptable alternative even after 3 hours (Class III, Level B)
- It is recommended that aspirin (160-325 mg loading dose) be given within 48 hours after ischemic stroke (Class I, Level A)
- It is recommended that if thrombolytic therapy is planned or given, aspirin or other antithrombotic therapy should not be initiated within 24 hours (Class IV, GCP)
- The use of other antiplatelet agents (single or combined) is not recommended in the setting of acute ischemic stroke (Class III, Level C)
- The administration of glycoprotein IIb/IIIa inhibitors is not recommended (Class I, Level A)
- Early administration of unfractionated heparin, low molecular weight heparin or heparinoids is not recommended for the treatment of patients with acute ischemic stroke (Class I, Level A)
- Currently, there is no recommendation to treat ischemic stroke patients with neuroprotective substances (Class I, Level A)

The recently published European Cooperative Acute Stroke Study III (ECASS III) has shown that intravenous alteplase administered between 3 and 4.5

hours (median 3 h 59 min) after the onset of symptoms significantly improves clinical outcomes in patients with acute ischemic stroke compared to placebo. The absolute improvement was 7.2% and the adjusted OR of favorable outcome (mRS 0-1) was 1.42, 1.02-1.98. Mortality did not differ significantly (7.7% *vs*. 8.4%), but alteplase increased the risk of symptomatic intracerebral hemorrhage (sICH) (2.4% *vs*. 0.2%). Treatment benefit is time-dependent. The number needed to treat to get one more favorable outcome drops from two during the first 90 minutes through seven within 3 hours and towards 14 between 3 and 4.5 hours[7].

The SITS investigators compared 664 patients with ischemic stroke treated between 3 and 4.5 hours, otherwise compliant with the European summary of the product characteristics criteria, with 11,865 patients treated within 3 hours[8].

In the 3-4.5 hour cohort, treatment was started on an average 55 minutes after the stroke onset. There were no significant differences between the 3-4.5 hour cohort and the 3-hour cohort for any outcome measures, confirming that alteplase remains safe when given between 3 and 4.5 hours after the onset of symptoms in ischemic stroke patients who otherwise fulfill the European summary of product characteristics criteria[9].

Materials and Methods

This preliminary report presents our experience with the first 20 patients who received thrombolytic therapy within the three-hour period following stroke onset at the Stroke Unit in Banjaluka, the first stroke unit in Bosnia and Herzegovina. We made our protocol for thrombolytic therapy according to the experience of our colleagues from Serbia.

Inclusion criteria are as follows: treatment must be initiated within 3 hours of symptom onset; to be considered for thrombolytic therapy, the patient must have more than a minimal neurologic deficit; neurologic deficit must be stable; patients with the National Institutes of Health Stroke Scale (NIHSS) score 4-22 are candidates for this treatment.

Exclusion criteria are: rapidly improving neurologic signs; systolic blood pressure (SBP) above 185 mm Hg or diastolic blood pressure (DBP) above 110 mm Hg; seizure at stroke onset; symptoms suggestive of subarachnoid hemorrhage; stroke or serious head trauma within previous 3 months; major surgery or serious bodily trauma within previous 2 weeks; history of ICH; intracranial neoplasm; arteriovenous malformation or aneurysm; gastrointestinal or urinary tract hemorrhage within 21 days; arterial puncture at a noncompressible site or lumbar puncture within 1 week; concomitant oral anticoagulant (INR >1.7); platelet count <100x10^9/L; prothrombin time (PT) >15 (INR >1.7); activated partial thromboplastin time (aPTT) elevated beyond reference range; glucose range between 2.7 and 22.2 mmol/L; and positive pregnancy test (in women of childbearing age).

Imaging studies: immediate head computed tomography (CT) scanning is an imperative. Any ICH is an absolute contraindication to thrombolysis; early signs of major infarction on initial CT scan are a reason for caution in the use of thrombolytic therapy because the risk of hemorrhage is increased.

Other tests: Transcranial Color Coded Duplex Sonography (TCCD); an electrocardiogram (ECG) is required before administering tPA.

Medical care: stabilize airway, breathing, circulation, and acute life-threatening conditions; identify time of and witnesses to stroke onset; place intravenous line en route, if possible; arrange for emergency head CT and laboratory studies and TCCD; monitor BP at least every 15 minutes before tPA; monitor for improvement of neurologic deficits; place a Foley indwelling catheter and nasogastric tube, if necessary, prior to starting tPA; during and after tPA infusion, monitor BP at least every 15 minutes for 2 hours; aim for a "door-to-needle time" (interval from patient arrival at emergency department to start of thrombolytic therapy) of 60 minutes.

Consultations: cardiologist and neuroradiologist.

Diet: nothing by mouth 24 hours after treatment.

Further inpatient care: no antiplatelet or anticoagulant therapy should be administered for 24 hours following tPA; obtain a repeat head CT scan 24 hours after tPA to rule out asymptomatic hemorrhagic transformation prior to initiating antithrombotic therapy; BP should be monitored closely and controlled (every 1 hour for the next 6 hours after treatment); physical, occupational, and speech therapy is initiated after the first 24 hours of bed rest.

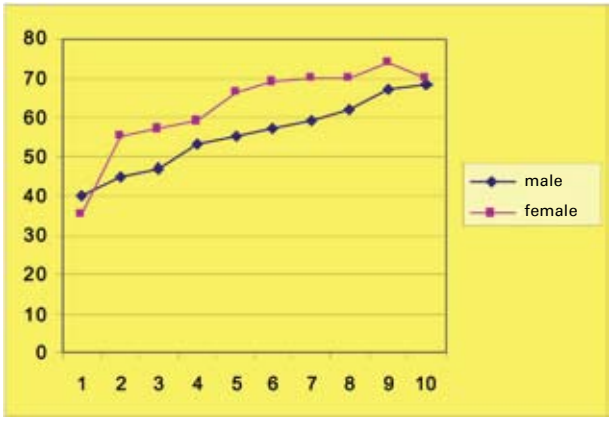

Fig. 1. Patient distribution according to age and sex.

Results

In the total number of patients (N=20) who received thrombolytic therapy, there were 10 male and 10 female patients. The youngest male patient was 40 and the youngest female patient 35 years old, while the oldest male patient was 68 and the oldest female patient 74 years old. The mean age of male and female patients was 55.3 and 62.50 years, respectively. The mean time of receiving Actilyse was 117.4 minutes after the onset of symptoms. The NIHSS on admission ranged from 5 to 18 (mean, 12.9) in male and from 5 to 17 (mean, 10.2) in female patients. In both male and female patients, the admission NIHSS was a predictor of poorer response to therapy received.

The NIHSS at discharge in male patients ranged from 0 to 11 (mean, 2.44). One patient who scored 11 had not received tPA within the 3-hour therapeutic window, as we found out later. In female patients, the NIHSS at discharge ranged from 0 to 11 (mean, 1.4). Overall, female patients showed better therapeutic response than male patients, although their NIHSSs on admission were lower.

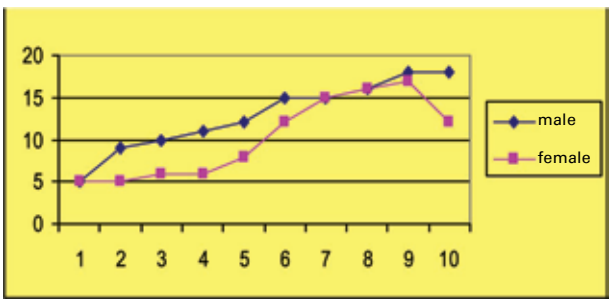

Fig. 2. National Institutes of Health Stroke Scale (NIHSS) score on admission in male and female patients.

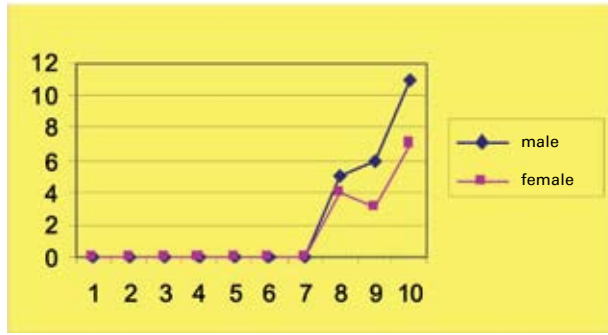

Fig. 3. National Institutes of Health Stroke Scale (NIHSS) score at discharge in male and female patients.

Rankin scores at discharge indicated that upon leaving the hospital, 13 patients were fully capable of self care and without any neurologic deficit, three patients had minimal deficit that completely resolved after three months, and one patient died within the first 24 hours following tPA. Out of 20 patients, 19 survived and one patient died from therapy side effect, i.e. intracerebral hematoma.

The most common risk factor in male patients was hyperlipidemia, followed by hypertension, smoking and diabetes, whereas in female patients the most common risk factors were hypertension, hyperlipidemia, smoking, obesity and arrhythmia.

The average duration of hospital treatment was 9 days.

Discussion

Thrombolytic therapy is of proven benefit for selected patients with ischemic stroke. Completion of

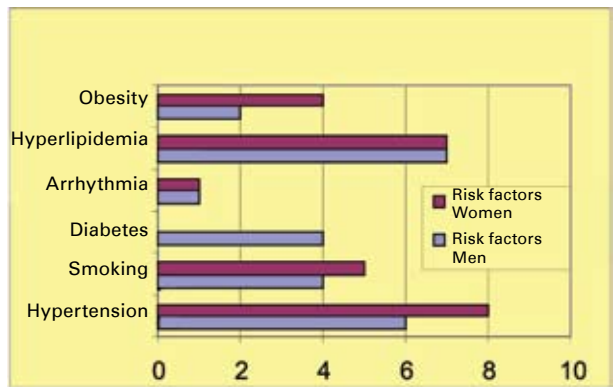

Fig. 4. Most common risk factors in male and female patients.

9 large phase III trials of intravenous thrombolytic therapy, which employed various agents, doses, and time windows, has provided a substantial database to guide clinical practice. However, a number of large multicenter randomized placebo controlled trials have shown an overall benefit for early treatment with rt-PA, despite an increased risk of early hemorrhage[10].

The pivotal National Institutes of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (tPA) trials were completed in 1995 and randomized 624 subjects within 3 hours of stroke onset to receive 0.9 mg/kg of intravenous tPA or placebo. These two trials found that patients treated with tPA within 3 hours of onset had a substantially better chance of functional independence with minimal or no disability 3 months after treatment. The proportion of patients with minimal or no disability increased from 38% with placebo to 50% with tPA, a 12% absolute improvement. The number needed to treat for 1 more patient to have a normal or near normal outcome was 8, and the number needed to treat for 1 more patient to have an improved outcome was 3.1[11].

The favorable results of the NINDS tPA trials have generally been duplicated in phase IV studies examining the use of intravenous tPA in routine clinical practice. The largest study of actual clinical practice evaluated 6843 patients treated at 285 centers in 14 countries and found the rate of complications and favorable outcomes similar to those of the NINDS tPA trials. These findings show that tPA is just as effective in clinical practice as in clinical trials when inclusion and exclusion guidelines are followed[12].

The European Cooperative Acute Stroke Study (ECASS) I was completed in 1995 and randomized 620 subjects within 6 hours of stroke onset to receive 1.1 mg/kg of intravenous tPA or placebo. This study failed to find a benefit for the use of tPA within 6 hours of stroke onset.

ECASS II was completed in 1998 and randomized 800 subjects within 6 hours of stroke onset to receive 0.9 mg/kg of intravenous tPA or placebo, and the outcome in the tPA group was significantly better than in the placebo arm.

Recently, pooled data from the six large randomized controlled trials (RCTs) of rt-PA involving 2775 patients were analyzed to gain better insight into the effect of time to treatment on efficacy. The findings reported recently confirm that the sooner the treatment is given to suitable stroke patients, the greater the benefit[10]. These results confirm the strong association between rapid treatment and favorable outcome[13-15].

A Cochrane review of thrombolysis for acute ischemic stroke analyzed 18 RCTs of any thrombolytic agent[8]. The review included 5727 patients given urokinase, streptokinase, recombinant pro-urokinase, or rt-PA. About half of the data come from trials testing rt-PA. There is a paucity of data on patients aged >80 years. Overall thrombolytic therapy, administered up to 6 hours after ischemic stroke, significantly reduced the proportion of patients who were dead or dependent (modified Rankin, 3-6) at 3- to 6-month follow up.

An independent reanalysis of the trials demonstrated a robust treatment effect in favor of tPA. The use of tPA for acute ischemic stroke was approved by the US Food and Drug Administration (FDA) in 1996 and subsequently by regulatory agencies in Canada, Europe, South America, and Asia. rt-PA was licensed under the brand name Actilyse for use in acute ischemic stroke in April 2003 in the UK. It must be administered within a 3-hour time window and was launched under strict licensing guidelines. Under these, it can only be used by a physician specialist in acute stroke care and with experience in the use of thrombolytic treatments and appropriate facilities to monitor its use and complications[13-15].

There have been a number of RCTs published from North America, Europe and Australia examining the role of thrombolysis in stroke. Many have used intravenous tPA but some have used intra-arterial infusion, especially for vertebrobasilar strokes. These studies include:

MAST-E Multicentre Acute Stroke Trial-Europe

MAST-I Multicentre Acute Stroke Trial-Italy

ASK Australian Streptokinase

NINDS National Institute of Neurological Disorders and Stroke (USA)

ECASS European Cooperative Acute Stroke Study

ECASSS II European and Australian Cooperative Acute Stroke Study II

ATLANTIS Alteplase Thrombolysis for Acute Noninterventional Treatment in Ischaemic Stroke

STAT Stroke Treatment with Ancrod Trial

Conclusion

The benefits of thrombolysis using rt-PA within three hours of stroke onset can be substantial. By promoting rapid recognition of stroke symptoms in the community, prompt transport of patients to specialized acute stroke units for early investigation, neuroimaging, stabilization and treatment, there would be substantial net benefit for all patients with stroke and not just for the small proportion (currently between 2.5% and 5%) eligible for thrombolysis. Clearly, we have a long way to go before "brain attack" is given the same degree of priority and urgency as "heart attack" currently is. The results are very encouraging, but complications from treatment can mean that the sooner tPA is given to patients, the greater the benefit.

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Sažetak

NAŠA ISKUSTVA S TROMBOLITIČKOM TERAPIJOM – PRELIMINARNO IZVJEŠĆE

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Moždani udar je naglo nastali, akutni oblik fokalnog ili globalnog poremećaja moždane funkcije, koji traje duže od jednog sata, poremećaja koji nema drugog vidljivog uzroka osim vaskularnog. Predstavlja završnu fazu bolesti lokalizirane na moždanim arterijama, glavni je uzrok onesposobljenosti i drugi uzrok smrtnog ishoda. U današnje vrijeme postoji mogućnost veoma uspješnog liječenja ishemijskog moždanog udara primjenom moćnog oružja, kauzalne trombolitičke terapije. Ovdje se daje preliminarni prikaz naših iskustava u primjeni trombolitičke terapije kod bolesnika s ishemijskim moždanim udarom. U radu se prikazuju rezultati liječenja 20 bolesnika koji su primili trombolitičku terapiju u prva tri sata od početnih simptoma moždanog udara, od kojih je 19 preživjelo, a jedan bolesnik je umro od sporednih učinaka terapije, tj. intracerebralnog krvarenja. Kod 17 bolesnika došlo je do potpunog oporavka bez neurološkog deficita, dok su dva bolesnika imala minimalnu onesposobljenost, Rankinov zbir 2, nakon tri mjeseca od događaja. Trombolitička terapija je i prema našim prvim iskustvima terapija izbora u liječenju ishemijskog moždanog udara, ako se primjenjuje strogo prema propisanim uputama.

Ključne riječi: *Moždani udar; Moždana ishemija; Trombolitička terapija*