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FUNCTIONAL OUTCOME AFTER THROMBOLYTIC THERAPY

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SUMMARY – In this paper, we report our experience from a prospective study in 40 ischemic stroke patients admitted during the last two years at University Department of Neurology Stroke Unit, Banja Luka Clinical Center, in order to assess the safety and efficacy of thrombolytic therapy, the impact of age, sex and risk factors, and functional outcome at 6 months of intravenous tissue plasminogen activator treatment. According to the National Institutes of Health Stroke Scale, there were 5 mild, 22 moderate and 13 severe stroke cases in the study group. The outcome measures at 6 months of thrombolytic treatment were taken in 38 (100%) patients, yielding a Functional Independent Measure score ≥90 (good clinical outcome) in 21 (52.50%) and modified Rankin Score ≤2 (good clinical outcome) in 22 (55%) patients. The rate of symptomatic intracerebral hemorrhage in tissue plasminogen activator treated patients was 5%, with a mortality rate of 17.50%. The outcomes were comparable with those found in the NINDS t-PA trial. Current guidelines recommend a 'door-to-needle' time of less than 60 minutes and emphasize that 'time is brain'.

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

Introduction

The 'time is brain' concept means that treatment of stroke should be considered as an emergency. In 1996, the Food and Drug Administration approved intravenous tissue plasminogen activator (tPA) for the treatment of acute ischemic stroke within 3 hours of onset. This approval was granted thanks to the favorable results obtained in the pivotal National Institutes of Neurological Disorders and Stroke (NINDS) tPA trial[1].

Stroke is sudden death of brain cells in a localized area due to inadequate blood flow, which is the result of thrombosis, embolism or hemorrhage, and one of the three most common and serious diseases with high medical, emotional and socioeconomic consequences to the elderly, their families and health care system. It is estimated that in 2002, the number of deaths due to stroke reached 5.51 million worldwide, with two-thirds of these deaths occurring in developing countries[2]. It is also a major cause of long-term disability[3], and the second most common cause of death, the first being heart attacks and the third cancer, with a tendency to become the leading cause of death worldwide[4].

Based on recent definitions of transient ischemic attack (TIA), both ischemic stroke and TIA, which are now considered to be a single entity, are defined as infarction of the central nervous system (CNS) tissue. Unlike TIA, ischemic strokes may be symptomatic

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or silent, i.e. asymptomatic. Symptomatic ischemic strokes are manifested by clinical signs of focal or global cerebral, spinal or retinal dysfunction caused by CNS infarction[5].

Within the areas of severely reduced blood flow, the 'core' of ischemic territory, excitotoxic and necrotic cell death occurs within minutes, and tissue undergoes irreversible damage in the absence of prompt and adequate reperfusion. However, cells in peripheral zones are supported by collateral circulation, and their fate is determined by several factors including the degree of ischemia and timing of reperfusion. In this peripheral region termed 'ischemic penumbra', cell death occurs relatively slowly *via* the active cell death mechanisms. Targeting these mechanisms provides therapeutic opportunities[6].

The goal of thrombolytic therapy is to restore brain blood flow in ischemic stroke. This is accomplished by clot lysis that results in reperfusion of affected but not yet infarcted tissue. The greatest risk of thrombolytic therapy is symptomatic intracerebral hemorrhage. Although the risk of hemorrhage increases with thrombolytic therapy, the risk is outweighed by improved functional outcome at 3 months of stroke onset. Randomized controlled trial sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) supported the view that tPA should be part of the management of acute ischemic stroke within three hours of onset in selected patients in experienced centers[1]. However, there is no full agreement. A study of tPA use in smaller community hospitals found a high rate of symptomatic intracerebral hemorrhage (15.7%), with 50% of patients treated without observing the NINDS guidelines[7]. Nevertheless, only 1% to 6% of all patients admitted for ischemic stroke receive a thrombolytic agent[8,9].

We report our experience with thrombolysis for stroke between April 2007 and April 2009.

Patients and Methods

This was a prospective study to assess the safety and efficacy of thrombolytic therapy, the impact of age, sex and risk factors, and functional outcome at six months. The patients were clinically assessed using the National Institutes of Health Stroke Scale (NIHSS) at the baseline, just before the administration of tPA, and at discharge from the hospital. The protocol was not formally approved by the Ethics Board of the Banja Luka Clinical Center because the study only observed outcomes after the standard treatment intervention. Data were collected prospectively by the Stroke Care Unit authorized personnel. We recorded baseline data, including patient demographic characteristics, time from symptom onset to arrival to the neurology department, time to tPA administration, NIHSS (on admission, atrial fibrillation past or current), pretreatment of blood pressure, full blood testing, serum glucose levels, length of hospital stay, and NIHSS score at discharge. All patients underwent follow up computed tomography (CT) imaging at 24 h or when clinically indicated. Intracerebral hemorrhage was considered symptomatic when it led to a 4-point or greater increase in the NIHSS score. The patients were followed up for six months. They were assigned a score on the modified Rankin Scale (mRS) and Functional Independent Measure (FIM) at six months of stroke.

Treatment protocol

All patients admitted to the hospital within three hours of symptom onset were immediately assessed by the competent stroke unit staff comprising of a stroke neurologist and trained nurse. The tPA protocol and inclusion and exclusion criteria were based on the protocols published by the American Heart Association and American Academy of Neurology[9,10]. The patients underwent pretreatment CT scans that were assessed by the attending neurologist and a radiologist. An informed consent was obtained after discussion of the potential benefits and significant risks.

Modified Rankin Scale is a simplified overall functional assessment in which score 0 indicates the absence of symptoms and score 5 severe disability[11]. The Functional Independence Measure is a widely accepted scale used to assess the functional abilities of patients undergoing rehabilitation. The outcome was assessed by the local rehabilitation team at Dr Miroslav Zotović Institute of Physical Medicine and Rehabilitation, Banja Luka, six months after treatment. We obtained clinical or telephone follow up with the patient or caregiver in all 38 cases and assessed the FIM score Activities of Daily Living Index and modified Rankin Disability Scale (mRS).

Telephone interview for assessing stroke outcome has been previously validated[12]. The inquiry was made regarding the number of weeks spent in the acute inpatient rehabilitation, outpatient rehabilitation, skilled nursing facilities, nursing homes, and professional home care. Good clinical outcome was defined as FIM values of 90/126 and mRS 0/1/2[13,14].

Results

Demographics

Forty patients were treated with intravenous tPA at Banja Luka Clinical Center between April 2007 and March 2009. During this period, around 1000 ischemic stroke patients were treated at Stroke Unit. Of these 1000 patients, 40 (4%) were treated with tPA. Most patients (60%) treated with tPA were male (n=24), and mean age was 61±9.1 (mean±SD; range, 35-74) years (Table 1).

Table 1. Demographic and baseline characteristics of patients in the study

Characteristic	Thrombolysis (n=40)
Age, y mean±SD	61.1±9.1
Sex, male (%)	60 (24)
Onset- needle time	122.6±37.8
Door- needle time	49.1±16.8
NIHSS (on admission) mean±SD	11.6±4.2
PACS, n (%)	17 (42.5)
TACS,	6 (15)
POCS	5 (12.5)
LACS	12 (30)
Smoker, n (%)	22 (55)
Diabetes mellitus, n (%)	9 (22.5)
Hypertension (current), n (%)	33 (82.5)
Hyperlipidemia (current), n (%)	25 (62.5)
Atrial fibrillation (past or current)	12 (30)
Length of stay, d±SD	10.6 ±5.0
NIHSS score on discharge, mean±SD	5.22±6.5

Abbrevations: SD: standard deviation, n: number, PACS: partial anterior circulation stroke, TACS: total anterior circulation stroke, POCS: posterior circulation stroke, LACS: lacunar stroke

We stratified the severity of strokes according to NIHSS into mild (0-6), moderate (7-12), and severe (≥13). There were 5 mild, 22 moderate and 13 severe strokes in this group. Pertinent medical history revealed that 82.50% had a history of hypertension, 22% had diabetes and 30% had a history of atrial fibrillation (Fig. 1).

According to the Oxfordshire Community Stroke Project classification of ischemic stroke (OCSP classification), 12.5% were posterior circulation syndrome (POCS), 30% lacunar circulation syndrome (LACS), 15% total anterior circulation syndrome (TACS), and

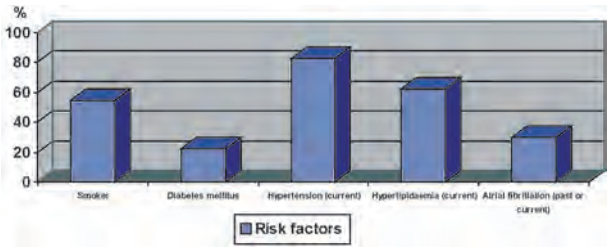

Fig. 1. Distribution of risk factors

42% partial anterior circulation syndrome (PACS) (Fig. 2).

We tested the hypothesis that the mean age was the same in both groups, survivors and dead, provided that there was no statistically significant difference with the reliability of 95%. However, *P* value was relatively small (0.0706) and less than 0.1, meaning that with the reliability of 90% the mean age was statistically significant higher in the group of dead than in the group of survivors (Fig. 3).

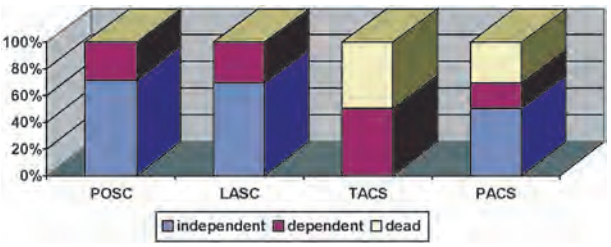

Fig. 2. OCSP classification and outcome of thrombolytic therapy

The maximum glucose levels ranged from 4.1 to 13.3 mmol/L, with a median of 6.9 mmol/L. There were no statistically significant differences when the maximum glucose levels were compared among patients stratified by admission stroke severity: 6.7±1.4 mmol/L in mild strokes, 7.3±2.3 mmol/L in moder-

ate strokes, and 7.6±2.1 mmol/L in severe strokes. Similarly, comparison of maximum glucose levels between patients that died and survivors at 6 months yielded no statistically significant differences either. The median cholesterol level was 5.83 mmol/L (range 3.3-9.61) and median triglyceride level 2.07 (range 0.49-6.06).

Hemorrhage occurred in 15 (37.5%) patients. Hemorrhage classified as petechial occurred in 10 (25%) and hematomatous in 12 (30%) patients. Major symptomatic intracranial hemorrhage occurred in two (5%) patients (NIHSS score at admission was 12).

The mean NIHSS score on admission was 11.6 (range 5 to 20) (Table 1). The median onset-to-treatment time was 122.6 min, SD 37.8 (IQR 45-195 min) and median door-treatment time 49.1±16.8 min; 20% of patients were treated with tPA within 90 minutes of the onset of stroke symptoms and two (5%) were given tPA after the recommended time of 180 minutes (190 and 195 min) (Fig 4).

The mean length of hospital stay was 10.6 (range 1 to?) days. Twenty-two (55%) patients were discharged for home care, ten (25%) to inpatient rehabilitation services, and five (12.5%) to nursing homes. Two (5%) patients died. Symptomatic intracranial hemorrhage occurred in two (5%) patients. At discharge, 45% of tPA treated patients had NIHSS score 0 or 1, while 70% had more than 4-point improvement on NIHSS as compared with admission scores. The mean discharge NIHSS score was 5.22 (range, 0-20) (Fig 5).

Survival could be evaluated in 38 (100%) patients; five of 38 (13.15%) patients died in the first six months. During the 6-month study period, the mortality rate was 17.5% (Table 2). Statistically significant differences were observed when NIHSS score at admission in patients that died was compared with 6-month survivors (ANOVA, F-ratio 9.71181; $P<0.05$; 95% confidence level).

At six months, FIM and mRS were performed in 38 (100%) patients. Scores 0, 1 and 2 on mRS, indicating no symptoms or minimal handicap, were recorded in 22 (55%) patients, FIM score 90/126 in 21 (52.5%) patients (Table 2).

Table 2. Outcome measures after 6 months

Outcome measure after six months	%	n(40)
% FIM score ≥90 (good clinical outcome)	52.5	21
% Modified Rankin Score <2 (good clinical outcome)	55	22
Mortality rate	17.5	7

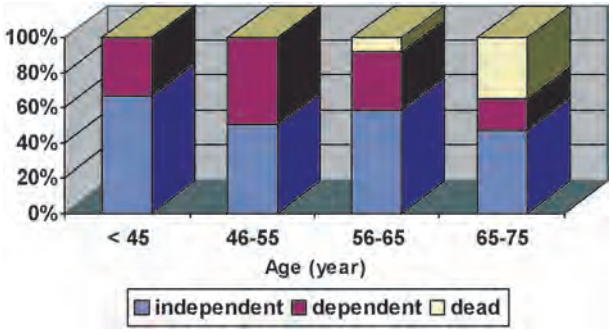

Fig. 3. Influence of age on the outcome of thrombolytic therapy

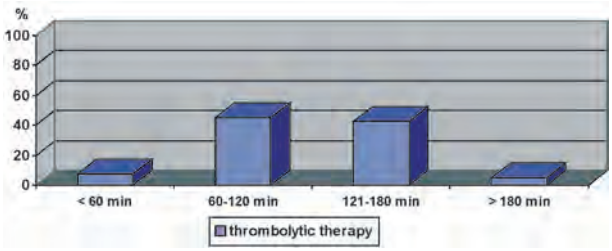

Fig. 4. Distribution of time from the onset of symptoms to the time of thrombolysis

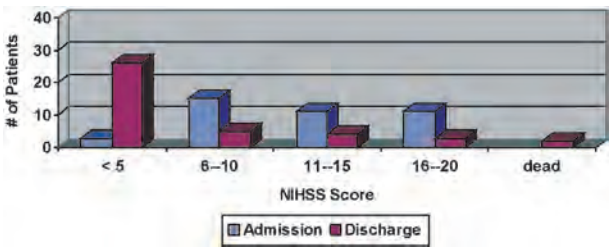

Fig. 5. NIHSS on admission and discharge.

Discussion

Study results showed the intravenous tPA therapy to be beneficial in ischemic stroke, when treatment was initiated within three hours of symptom onset. Outcomes were comparable to those found in the NINDS trial. One half of our tPA treated patients were functionally independent at follow up (mRS 0-2), compared with 49% of those in the NINDS trial. The rate of symptomatic intracerebral hemorrhage in our tPA-treated patients was 5%, similar to

that observed in the NINDS trial (6.4%). The mortality rate was quite comparable to the NINDS trial too (17.5% *vs.* 17%)[15,16]. Current guidelines recommend a door-to-needle time of less than 60 minutes and emphasize that 'time is brain'[17]. Our door-to-needle time median was 49 minutes. Of 40 patients, two were treated beyond the 180-min window, i.e. at 190 and 195 min, with no major complications. Of importance is also the degree of clinical improvement. The mRS and FIM score represent the entire range of function, from death and severe disability to complete recovery. The NIHSS assesses neurological deficit and not functional outcome. Complete recovery also means complete neurological recovery regardless of function. Higher NIHSS score, longer time to recanalization and elevated glucose proved to be important predictors of hemorrhage[17]. Further organization of stroke centers is required to address this inequity of access to thrombolytic treatment.

Intravenous thrombolysis represents the most effective acute stroke therapy. However, it is almost exclusively performed in stroke centers and is not available in wider community areas. The main rate-limiting step in provision of thrombolytic therapy is the three-hour time window. The possibility to administer this therapy outside the hospital is required before thrombolytic therapy for stroke is more widely applied. In areas where emergency services treat stroke with the same priority as acute myocardial infarction, admission to hospital is more rapid[18].

Although the success of acute thrombolytic therapy in urban hospitals is confirmed where neurologists are readily available, questions still arise as to the applicability and safety of tPA administration for acute ischemic stroke in the community and rural hospitals. Our center is recognized as a specialized Stroke Unit, with a dedicated and trained team available 24 hours a day. A low number of the treated compared to the total number of strokes suggests insufficiently developed infrastructure to support emergency arrival to the Stroke Unit. Our next challenge is to increase the percentage of patients that can be provided tPA therapy. Up to 10% of patients with stroke can be appropriately treated with tPA in well organized centers[11].

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 (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[19].

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[20].

In the 3- to 4.5-hour cohort, treatment was started on average 55 minutes later after symptom onset. There were no significant differences between the 3- to 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 that otherwise fulfill the European summary of product characteristics criteria[21].

Actually, thrombolysis treatment is recommended to administer within 4.5 hours of the onset of ischemic stroke (Class I, Level A). Our study was performed before changes of these recommendations in the European labeling, implemented as of January 29, 2009[22].

Conclusion

This prospective study included 40 ischemic stroke patients admitted during the last two years (April 2007 – March 2009) to the University Department of Neurology Stroke Unit, Banja Luka Clinical Center. The aim of the study was to assess the safety and efficacy of thrombolytic therapy, the impact of age, sex and risk factors, and six-month functional outcome with intravenous tPA therapy. Study results proved the benefit of intravenous tPA therapy when treatment was initiated within 3 hours of symptom onset. Our door-to-needle median time was 49 minutes. Of 40 patients, two were treated beyond the 180-minute window, i.e. at 190 and 195 minutes, with no significant complications.

Most patients (60%) treated with tPA were male (n=24), mean age 61±9.1 years; 82.5% had a history of hypertension, 22% had diabetes and 30% had a history of atrial fibrillation. According to NIHSS, the severity of stroke ranged from mild in five, moderate in 22 and severe in 13 patients.

Outcomes were comparable with those found by the NINDS trial; 52.5% of our tPA treated patients were functionally independent at follow up (mRS 0-2), compared with 49% in the NINDS trial.

The rate of symptomatic intracerebral hemorrhage in our tPA-treated patients was 5%, very similar to 6.4%, and the mortality rate was similar to that observed in the NINDS trial (17.5% *vs*. 17%). The mean age in the group of dead was statistically significantly higher than in the group of survivors. Of importance is also the degree of clinical improvement. The mRS and FIM score represent the entire range of functions, from death and severe disability to complete recovery. The NIHSS assesses neurologic deficit and not functional outcome. Complete recovery also means complete neurologic recovery regardless of function.

Higher NIHSS score, longer time to recanalization and elevated glucose proved important predictors of hemorrhage. Further organization of stroke centers is required to address this inequity of access to thrombolytic treatment.

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Sažetak

FUNKCIONALNI ISHOD NAKON LIJEČENJA TROMBOLIZOM

S. Miljković, D. Prtina, T. Rabi Žikić, Z. Vujković, D. Račić, V. Đajić, A. Ješić, M. Arbutina i *M. Žikić*

U radu iznosimo naša iskustva iz prospektivne studije kod 40 pacijenata sa ishemičnim moždanim udarom, liječenih u Jedinici za moždani udar Klinike za neurologiju Kliničkog Centra Banja Luka tokom posljednje dvije godine, da bi se procijenila pouzdanost i efikasnost trombolitičke terapije šest mjeseci nakon intravenske primjene aktivatora tkivnog plazminogena, kao i uticaj životne dobi, spola i faktora rizika na funkcionalni ishod nakon moždanog udara. Među njima je, prema skali za moždani udar Nacionalnog instituta za zdravlje SAD, bilo pet blagih, 22 umjerena i 13 teških oblika moždanog udara. Efikasnost terapije nakon šest mjeseci od trombolize kod 38 preživjelih pacijenata prezentirana je zbirom Nezavisnog funkcionalnog mjerenja ≥90 (dobar klinički ishod) kod 21 (52,50%) pacijenta, te kao modificirani Rankinov zbir ≤2 (dobar klinički ishod) kod 22 (55%) pacijenta. Učestalost intrakranijalne hemoragije bila je 5%, sa stopom smrtnosti od 17,50%. Rezultati funkcionalnog ishoda su upoređeni sa ishodom navedenim u studiji NINDS t-PA. Važeće preporuke savjetuju da vrijeme od "vrata do igle" bude kraće od 60 minuta, naglašavajući izreku "vrijeme je mozak".

Ključne riječi: *Moždana ishemija – dijagnostika; Moždana ishemija – terapija lijekovima; Moždani udar – dijagnostika; Moždani udar – terapija lijekovima; Fibrinolitički lijekovi – terapijska primjena; Trombolitička terapija – vremenski čimbenici*