Systemic thrombolysis with recombinant tissue plasminogen activator in acute ischemic stroke: first Croatian experiences

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Systemic thrombolysis with recombinant tissue plasminogen activator (rt-PA) in acute ischaemic stroke: first Croatian experiences

Abstract

In September 2003, recombinant tissue plasminogen activator (rt-PA) for acute treatment of ischaemic stroke was finaly approved by Croatian Ministry of Health. For the next five years, only three Stroke Units in the country implemented this therapy in their routine practice until summer 2008 when neurological wards in most Croatian hospitals started to treat acute stroke patients with systemic thrombolysis. We present a two years experience of thrombolytic therapy (2006-2008) in Stroke Unit of University Hospital in Zagreb, Croatian largest hospital, covering nearly 1/5 of Croatian citizens. Obtained data (vitals at admission and before administration of rt-PA; NIHSS and MRS scores at admission, 2 hours and 7th day after rt-PA treatment, "time to door" and "door to needle" intervals, duration of hospital treatment as well as outcomes and complications of our 66 thrombolysed patients) are presented and discussed. We also comment our results regarding benefits of this therapy as well as possible reasons for noticed complications.

Introduction

Stroke is the third leading cause of death and the leading cause of permanent disability in western countries.[1] Due to hypoxemia in hypoperfused brain, numerous neurons are within minutes irreversibly injured. However, in adjacent regions, which form, so called ischemic penumbra, blood supply still remains sufficient to keep neuronal cells alive for a longer period.[2] Thrombolytic treatment is aimed to save the penumbra, by possible recanalisation of occluded artery within 3-4,5 hours of symptom onset. Irrespective of ten-fold increase of risk for intracerebral haemorrhage, intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) greatly increases the rate of favorable outcome in acute stroke patients.[3] However, this kind of treatment is still applied to a relatively small group of patients even worldwide, due to at least three factors: quite narrow time window for treatment, very strict inclusion/exclusion criteria and fear of adverse effects.[4]

In 2003, Croatian Ministry of Health approved rt-PA for acute treatment of ischemic stroke. For next almost five years, only three centers in Croatia have started with this mode of treatment, among which our Stroke Unit covers the largest population group.

The aim of this article is to present the experience of implementing intravenous thrombolytic therapy for acute ischemic stroke in stroke unit of University Hospital Zagreb. In our work, we analyzed rates of patients receiving systemic thrombolytic therapy, safety and early clinical outcome in thrombolysed acute stroke patients admitted to our stroke unit in two-years-period (May 2006-May 2008). The patient's clinical data (blood pressures at admission and just before administration of rt-PA, NIHSS and MRS scores (at admission, 2 hours and 7th day after administering rt-PA), "time to door" and "door to needle" intervals, duration of hospital stay, as well as outcomes and complications during that time) are presented.

Methods

We retrospectively analyzed data of 66 patients who were admitted to Stroke Unit in Department of Neurology of University Hospital Zagreb, diagnosed as an acute ischemic stroke. Patients eligible for systemic thrombolytic treatment were selected according to inclusion and exclusion criteria of the strict protocol proposed by European Stroke Initiative[6] Selected data from each patient who received rt-PA treatment included: patient's age, gender, "time to door" (time interval from onset of symptoms to admission to our emergency room), "door to needle" (time interval from admission to our emergency room till administration of rt-PA), risk factors, blood pressure at the time of admission and just before administration of rt-PA, patient's score on the National Institute of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS) at the time of admission, 2 hours as well as 7th day after rt-PA treatment. We also compared findings of computed tomography (CT) and/or magnetic resonance imaging (MRI) of the brain at the time of admission and 2-24 hours after the administration of rt-PA therapy. In case of later clinical deterioration neuroimaging methods were optionally performed by that time. Data considering duration of hospital treatment and eventual complications during or after rt-PA treatment (death, intracerebral hemorrhage, malignant edema) were analyzed as well. Symptomatic intracerebral hemorrhage was defined as new sign of intracerebral hemorrhage in follow-up CT with clinical deterioration of at least one point in the patient's NIHSS score. The dose of rt-PA was 0.9 mg per kg body weight with a maximum of 90mg. According to protocol 1/10 of total dose of rt-PA was given intravenously in a bolus, the remaining 9/10 during one hour. Student's linked t-tests were performed for comparison of NIHSS and MRS scores at admission and on 7th day after rt-PA treatment administration. Non-linked student's t-tests were performed for comparison of single parameters between different years.

Results

During the period of two years (2006.-2008.) a total of 66 patients received intravenous thrombolysis (approximately 2% of all hospital admissions with diagnosis of acute stroke). All patients had symptoms of acute hemispheric stroke, and therapy was started within three hours of symptom onset. Mean age was 65 years (range 23-80) with male predominance (67%). The mean "time to door" (interval between symptom onset and arrival to the emergency room) period was approximately 62 minutes (range 10-120), while mean "door to needle" period was approximately 71 minutes (range 20-120). Mean blood pressure at admission was 152/89 (range of systolic blood pressure was 105-240, while range of diastolic blood pressure was 65-160). Mean blood pressure measured immediately prior administering rt-PA was 149/87 (range of systolic blood pressure was 108-210, while range of diastolic blood pressure was 60-122). Initial median NIHSS score was 10 (range 5-22), median NIHSS 2 hours post-thrombolysis was 5 (range 0-24) and seventh day after rt-PA treatment 3 (range 0-21). Initial mean MRS score was 3,99 (range 1-5), mean MRS 2 hours post-thrombolysis was 2,56 (range 0-5) and seven days post-thrombolysis was 2,52 (range 0-6). Thirteen cases of intracerebral hemorrhages or secondary hemorrhagic transformations occurred, among which 7 were symptomatic. Mean duration of hospital treatment was approximately 12 days (range 5-22 days).

In 2006/7, 21 of 1328 acute stroke patients admitted to Stroke Unit received rt-PA (1,43%) while that number in the next one-year period increased to 45 of total 1445 (3,11%).

Patients treated with rt-PA showed a significant reduction in NIHSS score during the acute phase (difference of NIHSS at admission and 7 days later). If NIHSS difference is compared between observed two years periods, no significant difference was revealed (Table 1).

Additionally, the duration of hospital admission was constant over the years and did not show any significant change (Table 1). During the time of hospitalization 12 patients died (18%), in range from second to tenth day after thrombolysis. Two patients died due to symptomatic ICH and two deteriorated in NIHSS score during first 7 days after thrombolysis. Lower rate of intracerebral bleeding was in the first observed year (26,7%), while percentage of lethal outcome in the same year was 19,04% (all patients died in range from 2-8 days); in the second year, percentage of lethal outcome didn't significantly change (17,8%); however six out of eight lethal outcomes had intracerebral hemorrhage and two patients died due to malignant infarction (Table 1).

Cost-to-benefit ratio showed no difference between two periods (Table 1). It should be emphasized that all thrombolysed patients are admitted into neurological intensive care unit, which anyhow has neurologist on duty, so there is no extra cost for thrombolysed patients.

All results of data comparison are presented in Table 1.

Discussion

Croatia has around 4,4 million inhabitants and about 22000 of patients with acute stroke per year. According to our Hospital registry, incidence of ischemic stroke is approximately 1,5-2,5 stroke per 1000 citizens and shows slow, permanent growth over the past few years. This is in contrary to western European countries where stroke incidence decreases over years due mostly to better primary prevention.[7] Majority of stroke patients in Croatia are still admitted to Neurological Wards while Stroke Units exist only in four University Hospitals. Systemic thrombolysis with rt-PA as treatment for acute ischemic stroke received the formal approval from Croatian Ministry of Health in September 2003. Since then thrombolytic treatment has been gradually introduced, but for first five years used only in three Croatian Hospitals (two

in Zagreb, and one in Rijeka). During last 12 months, thrombolytic treatment slowly begun to reach other parts of the country, and recently it is available in all University Hospitals and most of the Regional ones. According to our knowledge, from 2003 till end of May 2008, around 140 patients with acute stroke were thrombolysed in Croatia, 68 of them were treated in our Centre which covers a wide area of almost one fifth of Croatian population.

Number of treated patients significantly increased in 2007/8, compared to 2006/7 (from 21 to 45). There was not only increasing trend in absolute number of treated patients, but in thrombolysed ones, as well. In 2006/7 the rate was 1,4%, while in the next one-year period it raised to 3,11%. As our hospital started with the first thrombolytic therapy in December 2005, in those first months, only two patients (not included in this report) received rt-PA treatment. This fact was due to not yet well organized emergency ambulance service, (most of the patients didn't reach stroke unit within appropriate time-window) as well as slowness of emergency work-up once patient reached the hospital. Additional reason was also some reluctance of whole medical stuff, especially neurologists, to perform thrombolysis due to side effects fear.

However, from our data, it is evident that during the observed period intravenous thrombolysis was administered in increasing number of patients. This can be, in one way, explained by increasing number of admitted stroke patients, but this wouldn't explain a total increase of patients that received intravenous thrombolysis. Second reason is comprehensive education and reorganization of ambulance service in order to treat acute stroke as a medical emergency. Additionally, from relatively aggressive campaign general population became more sensible to this problem and sought a medical help more prompt then in previous years. Hence, decreased problems in obtaining informed consent were also noted. From the previously mentioned facts, it is evident that more and more patients reached neurological

emergency room in time-window for the thrombolytic treatment which leads to increased rate of thrombolysed patients.

Comparing results between 2006 and 2008, it is evident that age and initial NIHSS scores of the patients receiving rt-PA remained similar through these years. There wasn't significant difference between "time to door" "door to needle" time comparing first and second year of treatment. The drop in NIHSS range was significant (more than 7 points). The most significant drop did not occur soon (or in 24 hours) after treating, but after several (7 days) after treatment, suggesting that final conclusion about the efficacy of thrombolytic treatment can not be reached at least before the end of the 7th day after treatment.

Interestingly, during the first year, rate of hemorrhagic complications or lethal outcome was quite low (1 intracerebral hemorrhage and 4 lethal outcomes among 21 treated patients); however, in 2007 these rates increased disproportionately. That could be explained, by lower selectivity of patients, including also patients with more severe clinical presentations. Rate of hemorrhagic complications (intracerebral bleeding) and lethal outcome in 2007/8 were 26,6% and 17,7% respectively, and are much higher in our cohort then in previously published papers.[8] The fact that patients with more severe neurological presentation seek medical attention earlier and it's known that outcome of such patients is worse can partly explain the higher rate of complications during the second year. Another important factor is that we prolonged the therapeutic window from up to three hours to 4,5 hours, following the NEJM paper[9]. Patients with complication of intracerebral hemorrhage had more severe deficits on admission (median NIHSS score 19; range 8-20) then the rest of the study population (median NIHSS score 10; range 5-22). However, in National Institute of Neurological Disorders and Stroke trial[3], occurrence of symptomatic intracerebral hemorrhage was much lower (6,4%), but was estimated only for first 36 hours after the rt-PA therapy, while, in our case observation period last longer. In total, during analyzed two years, 7 of 12 lethal outcomes

were caused by intracerebral hemorrhage, while the others died probably due to malignant hemispheric edema (5^{th}-10^{th} day after thrombolysis). A high rate of lethal outcomes due to malignant infarction can be explained by clinically more severe stroke (higher NIHSS score). On the other hand, late onset of intracerebral hemorrhage can not be connected with thrombolytic treatment and should not be considered as a complication of treatment but of illness itself. Compared to SITS-MOST trial, our cohort was of similar age, with the significant prevalence of male patients.[10] We had somewhat lower NIHSS score at admission (11 compared to 13 in SITS-MOST trial) and systolic blood pressure was 153 mmHg compared to 156 in SITS-MOST trial and diastolic blood pressure was 90 compared to 84 mmHg in SITS-MOST trial. Compared to this trial we had significantly higher rate of symptomatic intracerebral hemorrhages and lethal outcomes. Some of the reasons are discussed above, but one of the reasons of high rate of intracerebral might be due to systolic blood pressure above recommended limits immediately before starting rTPA. In most of the cases blood pressure could not be lowered due to time limitations.

Over the two years, rate of thrombolysed patients in our centre increased, in fact, it doubled itself. However, these rates are still below the rate of other well organized stroke centers which can reach even the rate of more than 20% of admitted stroke patients. Still, positive trend is visible, that is the increasing number of medicated patients during the following year (3.11% vs 1.43% vs 2% SIST MOST average), the average NIHSS reduction (from 10 to 5). The main problem remains the high rate of symptomatic intracerebral hemorrhage. It should be mentioned that our study is retrospective in nature and there is no control group, so comparing this high rate with double blind, randomized controlled trials is difficult. The circumstances in the trial are strictly controlled which is not always possible in everyday practice.

The future aim of stroke management in Croatia is continuous organization and spreading network of stroke units which will cover all parts of Croatia and allow each patient to reach the nearest stroke unit within maximum of 60 minutes from onset of symptoms and, therefore, to be eligible for thrombolytic treatment. In other words, primary goal is to increase the rate of thrombolysed patients based on better accessibility of stroke units and education of medical stuff working in ambulance services as well as neurologists. Hence, we are about to establish a central stroke centre in our hospital which will cover comprehensive management approach, but also provide education for other medical employees included in acute stroke management all around Croatia.

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Table 1. Characteistics of patients teated with intavenous thombolysis and diffeences between two periods.

SBP systolic blood pressure, DBP diastolic blood pressure, NIHSS National Institute of Health Stroke Scale, MRS Modified Rankin Scale, ICH intracerebral hemorrhage; USD United States Dollar.

All data are presented as mean ± SD if not indicated differently in table.

Year	**2006/7**	**2007/8**	**2006-2008**
Number of patients treated with t-PA	21	45	66
Age, years	64,78±13,38	65,84±10,52	65,31±11,38
Gender (M:F); male (%)	18:3; 85,7%	26:19; 57,77%	44:22; 66,66%
Time to door (mean), minutes	61,56±33,75	60,24±20,00	61,90±26,88
SBP (at admission)	156,58±32,06	149,58±31,50	153,08±31,35
DBP (at admission)	91,58±16,25	88,42±14,50	90,00±15,38
NIHSS (at admission)	10,42±4,46	11,00±4,64	10,71±4,55
NIHSS (at admission, median, range)	10 (5-18)	10 (5-22)	10 (5-22)
MRS (at admission)	4,05±0,91	3,93±0,99	3,99±0,95
Door to needle (mean), minutes	72,94±19,93	69,88±23,36	71,41±21,65
SBP (immediately before t-PA)	145,84±25,99	152,40±23,43	149,12±24,67
DBP(immediately before t-PA)	87,95±13,07	86,80±15,74	87,38±14,41
NIHSS (2 hours after t-PA)	7,58±6,48	6,39±6,88	6,99±6,68
NIHSS (2 h after t-PA, median, range))	6 (0-23)	4 (0-25)	5 (0-24)
MRS (2 hours after t-PA)	3,00±1,70	2,27±1,63	2,64±1,67
NIHSS (7 days after t-PA)	4,75±5,07	3,97±4,99	4,36±4,99
NIHSS (7 days after t-PA, median, range)	3 (0-18)	3 (0-21)	3 (0-21)
MRS (7 days after t-PA)	2,79±2,18	2,25±2,04	2,52±2,11
NIHSS difference (at admission-after 7 days)	4,75±4,20	6,18±4,78	5,47±4,49
ICH	1	12	13
Death, day (mean, range)	4 (6,5; 5-10)	8 (5,0; 2-8)	12 (5,07; 2-10)
Hospitalization	11,26±4,04	12,13±6,06	11,70±5,05
Cost per average hospitalisation (USD)	6404±1616	6752±2424	6580±2020