Clinical Study

Experiences of Thrombolytic Therapy for Ischemic Stroke in Tuzla Canton, Bosnia and Herzegovina

Dževdet Smajlović, Denisa Salihović, Omer Ć. Ibrahimagić, Zikrija Dostović, Leila Avdić, and Mirjana Vidović

Department of Neurology, University Clinical Center Tuzla, Medical Faculty, University of Tuzla, Trnovac bb, 75000 Tuzla, Bosnia and Herzegovina

Correspondence should be addressed to Dževdet Smajlović; dzsmajlovic@hotmail.com

Received 6 January 2014; Accepted 4 February 2014; Published 11 March 2014

Academic Editors: F. Corea, H.-M. Kwon, and A. Shuaib

Copyright © 2014 Dževdet Smajlović et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Aim. To demonstrate our experiences of thrombolytic therapy in acute ischemic stroke. **Subjects and Methods.** Patients with ischemic stroke treated with rt-PA, admitted at the Department of Neurology, Tuzla, Bosnia and Herzegovina, in the period between April 1, 2008, and December 31, 2012, were included. **Results.** Between April 2008 and December 2012, intravenous rt-PA was given to 87 patients with acute ischemic stroke, which represents 3.2% of patients with acute ischemic stroke admitted to our department in that period. Hypertension was the leading stroke risk factor. The mean NIHSS score before thrombolysis was 12 (range 4–21). Large artery arteriosclerosis was the most common stroke etiology. The mean door-to-needle time was 72 minutes and onset-to-needle time 152 minutes. Half of patients (44/87) had a significant improvement within the first 24 hours. Parenchymal hemorrhage occurred in 5 patients (6%) and was fatal in two cases. At 3-month follow-up, 45% of patients (39/87) had good outcome (mRS 0 or 1). Sixteen patients were dead at 3 months, and mean baseline stroke severity was significantly higher in patients who died (NIHSS 16.5 versus 11, $P = 0.003$). **Conclusion.** The number of patients with acute ischemic stroke treated using rt-PA in the Department of Neurology, Tuzla, is lower than in developed countries. Thrombolytic therapy is safe and leads to favorable outcome in half of the patients.

1. Introduction

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.

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. Intravenous rt-PA given within 3–4.5 hours after the onset of acute ischemic stroke in the territory of the middle cerebral artery significantly increases

the proportion of patients left without handicap and without dependency after 3 months [1]. In the European Union, rt-PA was approved in 2002 and has been used widely since then [2, 3].

We present our results of thrombolytic therapy in acute ischemic stroke referring to demographic information, time parameters, and clinical outcome.

2. Subjects and Methods

Patients with ischemic stroke treated with thrombolytic therapy (rt-PA, Actilyse, Boehringer Ingelheim), admitted at the Department of Neurology, Tuzla, Bosnia and Herzegovina, in the period between April 1, 2008, and December 31, 2012, were included. All patients completely fulfilled in-hospital

protocol for the intravenous thrombolysis in acute ischemic stroke corresponding with SITS-MOST protocol. Thus, rt-PA was administered in a dose of 0.9 mg/kg body weight (maximum dose 90 mg), with 10% given as a bolus followed by delivery of the remaining 90% as a constant infusion over a period of 60 minutes.

Computed tomography of the brain was performed for all patients prior to treatment and 24 hours after thrombolysis. The performance of other diagnostic studies to determine stroke etiology was scheduled by treating neurologist. Records were reviewed to obtain demographic information, stroke risk factors, and time parameters. Stroke subtype was determined according to Treatment of Acute Stroke Trial (TOAST) criteria [4]. Stroke severity was measured by the National Institutes of Health Stroke Scale (NIHSS) before thrombolysis, 1 and 24 hours after treatment, and 7 days and at one month after the stroke onset.

Functional outcome was assessed by modified Rankin Scale (mRS) at three months after stroke onset. A good outcome was defined as an mRS of 0 and 1, a moderate outcome as an mRS of 2 and 3, and a poor outcome as an mRS of 4 and 5. The study was approved by the Ethics Committee of our University Clinical Center.

For the statistical analysis EpiInfo 8.0 software package was used.

3. Results

Between April 2008 and December 2012, intravenous rt-PA was given to 87 patients with acute ischemic stroke, which represents 3.2% of patients with acute ischemic stroke admitted to our department in that period (2667 patients). Baseline characteristics of the patients treated with thrombolytic therapy are given in Table 1. The mean age was 64 years (range 43–83), and two-thirds of the patients were males. Hypertension was the leading stroke risk factor, followed by smoking and diabetes. The mean NIHSS score before thrombolysis was 12 (range 4–21), implying an overall moderate stroke severity. Large artery arteriosclerosis was the most common stroke etiology.

The detailed logistics and timing of triage and treatment are summarized in Table 2. The mean onset-to-door time was 80 minutes, door-to-CT time 45 minutes, door-to-needle time 72 minutes, and onset-to-needle time 152 minutes.

The mean changes in NIHSS after thrombolytic therapy are given in Table 3. Immediately after thrombolysis the mean NIHSS score was lower for 3 pts. and 5 pts. 24 hours after thrombolytic therapy. Half of patients (44/87) had a significant improvement within the first 24 hours, defined by a decrease of ≥ 4 pts. on the NIHSS or complete recovery.

Parenchymal hemorrhage occurred in 5 patients (6%) and was fatal in two cases. Hemorrhagic transformation on CT was recorded in 10 cases (11%). Extracerebral bleeding complications occurred in 6 patients (7%): hematuria in 3 and gastrointestinal bleeding in 3 cases.

At 3-month follow-up, 45% of patients (39/87) had good outcome (mRS 0 or 1), and an analysis of independence (mRS 0–2) versus disability (mRS 3–5) or death showed that 56% of

TABLE 1: Baseline characteristics of the patients treated with thrombolytic therapy.

Characteristic	
Gender	
Female, <i>n</i> (%)	31 (36)
Male, <i>n</i> (%)	56 (64)
Age (y), mean $\pm$ SD	64 $\pm$ 10
Stroke risk factors, <i>n</i> (%)	
Hypertension	65 (75)
Diabetes mellitus	26 (30)
Atrial fibrillation	24 (28)
Heart failure	15 (17)
Hyperlipidemia	22 (25)
Current smoking	29 (34)
Previous stroke	8 (9)
Baseline NIHSS, <i>n</i> (%)	
0–7	15 (17)
8–14	46 (53)
≥ 15	26 (30)
NIHSS, mean $\pm$ SD	12 $\pm$ 4.0
Stroke etiology, <i>n</i> (%)	
Large artery arteriosclerosis	39 (45)
Cardiac embolism	17 (20)
Lacunar stroke	20 (23)
Undetermined	11 (12)

NIHSS: National Institutes of Health Stroke Scale.

TABLE 2: Time parameters in the patients treated with thrombolytic therapy.

Parameter	Minutes	Standard deviation
Onset-to-door	80 (15–180)	± 32
Door-to-CT	45 (15–80)	± 16
Door-to-needle	72 (45–135)	± 20
Onset-to-needle	152 (85–245)	± 30

Numbers in parenthesis denote range.

TABLE 3: Stroke severity in the patients treated with thrombolytic therapy.

NIHSS	Mean	Range
Baseline	12.0	4–21
After thrombolysis	9.0	0–20
After 24 hours	7.0	0–27
After 7 days	5.0	0–20
After one month	3.5	0–19

NIHSS: National Institutes of Health Stroke Scale.

patients treated in our centre were independent in self-care (Figure 1).

Sixteen patients (18%) were dead at 3 months. Causes of death were intracerebral hemorrhage in 2 patients, extent of initial stroke in 8, heart failure in 2, recurrent stroke in 1, myocardial infarction in 1, pulmonary embolism in 1, and pneumonia in 1 patient. Furthermore, mean baseline stroke

FIGURE 1: Three-month outcome of the patients treated with thrombolytic therapy.

severity was significantly higher in patients who died (NIHSS 16.5 versus 11, $P = 0.003$).

4. Discussion

Intravenous rtPA for acute ischemic stroke has recently been approved for use in our country. We formed Stroke Unit in April 2007 at our department and applied first thrombolytic therapy one year after. In our study the leading risk factors are hypertension and smoking, which is similar to the studies of Roje-Bedecković et al. [5] and Campbell et al. [6]. In the study of Bogosavljević et al. [7] distribution of risk factors is different than in our study, so that hyperlipoproteinemia is the leading risk factor followed by hypertension. In our study large artery arteriosclerosis was the most common stroke etiology, which is similar to the study of Roje-Bedecković et al. [5] and Litwin et al. [8], while cardioembolic stroke was the most common in the study of Bogosavljević et al. [7] and Chapman et al. [9].

Tuzla Canton counts around 500 000 citizens and our department is the only one which hospitalizes stroke patients and applies thrombolytic therapy in this canton. Onset-to-door time in the patients treated with thrombolytic therapy in our study is somewhat different in comparison with the results of our neighbors [5, 7]. One reason can be that some of municipalities in our Canton are very far from the clinic. Furthermore, patients and their families very often do not recognize the symptoms of stroke and do not go immediately to the first medical institution. We have initiated strategies to shorten the time to arrival at our department, including upgraded priority for ambulance response and stroke transfer combined with educational programs for local emergency physicians and nurses.

Our results showed that onset-to-needle time is similar to neighboring countries [5, 7]. Our hospital is very well organized but some departments (Department of Biochemistry and Transfusion) are working on standby basis which slows down providing results. Our main goal in future will be to improve these shortages and as result we will have shorter door-to-needle time. The study of Mikulík et al. [10]

showed that patients with longer door-to-needle time, in 60-minute increments, had less chance of achieving a modified Rankin Scale score of 0 to 1 at 3 months. According to the our results, almost half of patients showed significant improvement within 24 hours from applying thrombolytic therapy, which is similar to studies based on the same design [5, 7, 8, 11].

Parenchymal hemorrhage was present as one of complications in thrombolytic therapy which was present in 6% of our patients, as well as hemorrhagic transformation in 11%, which is similar to the results of others studies [2, 7, 12]. However, in Canadian and Poland studies the incidence of hemorrhagic complications was smaller [8, 9].

The available data show that treatment with iv rt-PA is associated with a 30% relative risk reduction of death or disability at 90-day follow-up [13]. The results of the SITS-MOST registry show that 54% of patients treated with rt-PA achieve favourable functional outcome with an mRS of 0–2 (2). Our results are very similar, as 56% of patients had favourable outcome at 3 months. At the other hand, 3-month fatality in our study (18%) is higher than in the SITS-MOST registry, as well as in the studies of our neighbors [2, 5, 7]. We think the reason for this can be high average of NIHSS at the onset of stroke and the relatively large number of our patients with severe stroke, who had NIHSS ≥ 15 (30%).

In spite of very promising results, intravenous thrombolysis can be given only to a small number of patients. We wish to emphasize that these are only the results from our department, not at the national level. Bosnia and Herzegovina is one of the few countries in Europe that does not have formed Stroke Registry yet, primarily because of the political situation. Therefore, we are limited in participation in multicenter studies. With this study we want to show that we are working according to established protocols and show that our results are similar to the results of other countries despite the aforementioned shortcomings.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

- [1] K. R. Lees, E. Bluhmki, R. von Kummer et al., "Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials," *The Lancet*, vol. 375, no. 9727, pp. 1695–1703, 2010.
- [2] N. Wahlgren, N. Ahmed, A. Dávalos et al., "Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study," *The Lancet*, vol. 369, no. 9558, pp. 275–282, 2007.
- [3] N. Wahlgren, N. Ahmed, A. Dávalos et al., "Thrombolysis with alteplase 3–4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study," *The Lancet*, vol. 372, no. 9646, pp. 1303–1309, 2008.

- [4] H. P. Adams Jr., B. H. Bendixen, L. J. Kappelle et al., "Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial," *Stroke*, vol. 24, no. 1, pp. 35–41, 1993.
- [5] M. Roje-Bedeković, V. Vargek-Solter, L. Čorić et al., "Thrombolysis for acute ischemic stroke—our experiences as part of SITS-MOST," *Acta Clinica Croatica*, vol. 48, no. 3, pp. 287–293, 2009.
- [6] B. C. V. Campbell, C. Costello, S. Christensen et al., "Fluid-attenuated inversion recovery hyperintensity in acute ischemic stroke may not predict hemorrhagic transformation," *Cerebrovascular Diseases*, vol. 32, no. 4, pp. 401–405, 2011.
- [7] V. Bogosavljevic, M. Bodenant, L. Beslac-Bumbasirevic et al., "Intravenous thrombolysis for acute cerebral ischemia in Belgrade, Serbia: comparison with Lille, France," *European Neurology*, vol. 66, no. 1, pp. 30–36, 2011.
- [8] T. Litwin, A. Kobayashi, M. Skowrońska, and A. Członkowska, "Thrombolysis in acute ischaemic stroke within 3 hours of symptom onset: a report of the first 100 cases," *Neurologia i Neurochirurgia Polska*, vol. 42, no. 1, pp. 1–5, 2008.
- [9] K. M. Chapman, A. R. Woolfenden, D. Graeb et al., "Intravenous tissue plasminogen activator for acute ischemic stroke: a Canadian hospital's experience," *Stroke*, vol. 31, no. 12, pp. 2920–2924, 2000.
- [10] R. Mikulík, P. Kadlecová, A. Członkowska et al., "Factors influencing in-hospital delay in treatment with intravenous thrombolysis," *Stroke*, vol. 43, pp. 1578–1583, 2012.
- [11] A. Dávalos, J. Alvarez-Sabin, J. L. Martí-Vilalta, and J. Castillo, "Intravenous tissue-type plasminogen activator for the treatment of acute cerebral ischemia," *Medicina Clínica*, vol. 120, no. 1, pp. 1–5, 2003.
- [12] N. Galldiks, O. Zaro-Weber, C. Dohmen et al., "Systemic thrombolysis with rt-PA in patients under 40 years of age: a subgroup analysis of the Cologne stroke experience," *Cerebrovascular Diseases*, vol. 30, no. 5, pp. 514–518, 2010.
- [13] J. R. Marler, "Tissue plasminogen activator for acute ischemic stroke," *The New England Journal of Medicine*, vol. 333, no. 24, pp. 1581–1587, 1995.