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Intravenous Thrombolysis for Acute Ischemic Stroke – Our Experiences

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A B S T R A C T

Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rt-PA) is the only available pharmacological therapy to improve the outcome of acute ischemic stroke. We compared 71 patients presenting with ischaemic stroke and given intravenous rt-PA (0·9 mg/kg total dose) within 3 h with 71 patients who present to the hospital more than 3 hours after stroke symptom onset. The primary endpoint was the modified Rankin scale (mRS) at 90 days, dichotomised for favourable and unfavourable (score 2–6). Outcome measures were symptomatic intracerebral haemorrhage within 36 h (haemorrhage associated with National Institutes of Health Stroke Scale [NIHSS] ≥4 points deterioration), and mortality at 3 months. More patients had favourable outcome with the rt-PA-treated group than with the control group (64.79% vs. 22.54%; p= 0.0001). The greater proportion of patients left with minimal or no deficit 90 days after rt-PA treatment, as compared with the control group. In the treated group symptomatic intracranial hemorrhage occurred in 1 patient who recovered to a level of functional independence, and asymptomatic intracranial hemorrhage was observed in 2 patients. Our experience of an acute stroke thrombolysis service shows that we are able to provide this treatment safely and in accordance with established treatment guidelines. We recommend thrombolytic treatment in acute ischemic stroke for selected population.

Key words: *stroke, thrombolysis, recombinant tissue plasminogen activator, outcome*

Introduction

Thrombolysis with intravenous (IV) recombinant tissue plasminogen activator (rt-PA) is the only available pharmacological therapy to improve the outcome of acute ischemic stroke. The aims of thrombolytic therapy are arterial recanalisation and salvage of the ischaemic penumbra, a region of critically hypoperfused but viable brain tissue around the irreversibly damaged infarct core[1]. Number of randomized, placebo controlled, clinical trials studying intravenous rt-PA in acute stroke have been conducted[2–5] and the US Food and Drug Administration (FDA) approved the use of IV rt-PA in 1996, on the basis of the results of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study[2]. Stroke specialists in many countries, including Croatia, adopted guidelines launched by the American Heart Association (AHA) in the management of acute ischemic stroke[6]. We describe the results of our controlled, parallel-group prospective study to investigate the clinical effectiveness of rt-PA administered in patients with acute ischemic stroke.

Patients and Methods

Protocol for rt-PA treatment

All acute ischemic strokes that presented at University Hospital Rijeka during 2000–2009 were screened for the eligibility for IV thrombolytic treatment. Inclusion criteria were hemispheric ischemic stroke and criteria that were published in the NINDS and ECAS II trial[2,3]. Control group represent the patients who present to the hospital more than 3 hours after stroke symptom onset.

Ethics committee approved the study protocol and the patient, next of kin, or legal representative, according to

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individual institutional protocols, provided written consent.

Initial assessments included a physical examination, brain CT and quantification of any neurological deficit with the use of the National Institute of Health stroke scale (NIHSS), a 15 item scale that measures the level of neurologic impairment: total scores range from 0 to 42, with higher values reflecting more severe stroke[7].

Patients allocated to the treatment had to receive rt-PA (Actilyse, Boehringer Ingelheim, Germany) in a dose of 0.9 mg/kg body weight (maximum 90 mg), started within 3 h of ischemic stroke onset. Of the total dose, 10% was administered as a bolus and the remainder was given by continuous intravenous infusion over a period of 60 min. Both groups were treated in the same way in all other respects.

After thrombolysis, treatment included preventive therapy of ordinary poststroke complications, initiation of secondary prevention, and early rehabilitation.

Repeat CT scan of the brain was scheduled at 24h after the thrombolytic therapy. In case of neurological worsening, CT scan would be performed soon after the detection of deterioration. Intracerebral hemorrhage was diagnosed by CT scan. Symptomatic hemorrhage was defined as hemorrhagic lesion on CT scan with clinical worsening of NIHSS ≥ 4 points.

Outcome measures

The primary outcome measure was the score on the modified Rankin scale (mRS) at day 90. The mRS evaluates global disability and handicap; scores range from 0 (no symptoms or disability) to 6 (death)[7]. The primary outcome was excellent functional outcome (mRS score 0–1) compared with disability or death (mRS score 2–6).

Secondary end points at day 90 included the Barthel index (BI) (ranging from 100 [independent in all activities of daily living] to 0 [completely dependent])[7], the NIHSS and the Glasgow Outcome Scale (GOS)[7]. Death within 3 months was also recorded.

Statistical analysis

All tests of significance were 2-sided and conducted at the p=0.05 level of significance. Differences in baseline characteristics were determined using t-test for continuous variables and χ^2-tests for categorical variables. Efficacy end points were tested using a 2-sample binomial test.

Results

Demographics

Between August, 2000 and August, 2009, there were 71 consecutive patients who fulfilled the thrombolysis criteria along with 71 patients from the control group. The mean age of the treated group was 60±36 years, with 58% males. The median initial NIHSS score was 14.41 (range, 7–29). Other baseline characteristics, including demographic data and risk factors, are given in Table 1.

TABLE 1
BASIC CHARACTERISTICS OF PATIENTS

	Control group (N=71)	rt-PA group (N=71)
Age (yr)	60.3±23.3	60±36
Gender (% of males)	58	58
Hypertension (%)	97	97
Diabetes (%)	38	35
Hyperlipidemia (%)	46	45
Atrial flutter or fibrillation (%)	24	25
Smoking status (%)	32	30
Alcohol abuse (%)	18	17

There was no significant difference between the group receiving rt-PA and the control group in regard to age, risk factors and NIHSS score prior to the treatment (p>0.05).

The median door-to-needle time (time interval from admission to our emergency room till administration of rt-PA) was 35 minutes.

Functional outcomes

Clinical outcomes are shown in Figure 1.

The number of patients with favorable outcomes for each of the four outcome measures three months after stroke was higher in the rt-PA group than in the control group.

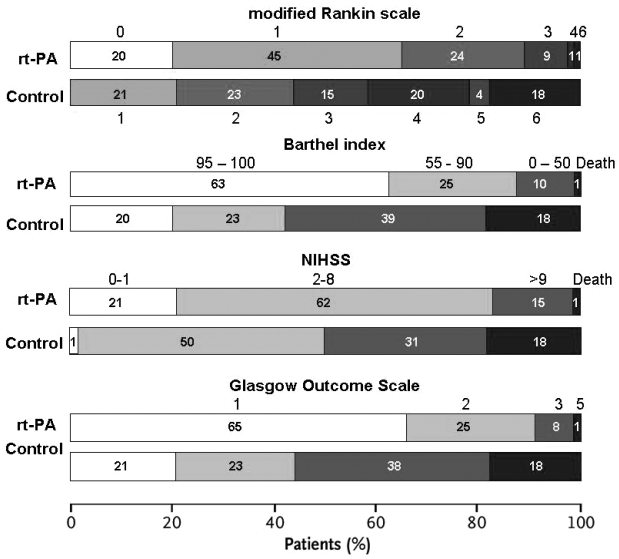

Fig. 1. The outcome at 90 days after the treatment. Scores of 0–1 on the mRS, 95–100 on the BI, 1 on the NIHSS, and 0–1 on the GOS were considered to indicate a favorable outcome. Values do not total 100 percent because of rounding. The results of all four outcome measures, statistically significant favor the rt-PA group. The greater proportion of patients left with minimal or no deficit 90 days after rt-PA treatment, as compared with the control group.

The observed rate of an excellent outcome in the treated group, the patients with no or minimal symptoms (mRS 0 to 1) was significantly higher in contrast to the control group (64.79% *vs*. 22.54%; p=0.0001).

On BI, 63.39% of patients were independent (BI 95 to 100) in the treated group in comparison to 19.72% in the control group (p<0.0001)

There was also an increase in the number of patients with an NIHSS score of 0 or 1 in the treated group than in the control group (21.13% *vs*. 1.41%; p=0.001).

A similar magnitude of effect was seen with respect to the improvement in the rt-PA group with the use of the Glasgow outcome scale (64.79% *vs.* 21.13%; p<0.0001). By 90 days after the onset of stroke, 1 of the 71 rt--PA-treated patients had died (1.41%), as compared with 13 of the 71 control patients (18.31%) (p=0.002.).

In the treated group symptomatic intracranial hemorrhage occurred in 1 patient who recovered to a level of functional independence, and asymptomatic intracranial hemorrhage was observed in 2 patients.

Discussion

We report our experience on rt-PA treatment in acute ischemic stroke. To our knowledge, this is the first report of prospective control-parallel group case series in Croatia. rt-PA is licensed treatment for acute stroke in the USA, Canada, Australia and the European Union, and cost-effectiveness analysis suggests that rt-PA for stroke is cost-saving due to reduction in nursing home and rehabilitation costs[3,5].

Researchers assessed the effectiveness of rt-PA as a routine treatment for acute stroke at many centres[1–4], and from year 2000 till 2004 in Croatia it was offered as a standard treatment only in our stroke unit.

A European community stroke study recorded that 25% of patients admitted to hospital with stroke had presented within 3 hours[8], and an American community stroke study recorded 20–28% of patients presenting within 2 hours of stroke onset[9]. In this study, we were able to administer thrombolytic agent within 3 h in all cases. Our mean door-to-needle time was comparable to other studies performed. Our major obstacle for getting more patients is the delayed in hospitalization. We believe that public health initiatives and education would increase the number of patients eligible for treatment in the future.

In our study, the rate of major improvement was higher than those previously reported. The overall excellent functional outcome (mRS score 0–1) rate was 64.79%. It is statistically higher than reported from the NINDS study (39%) and ECAS II study (40.3%). We believe that it is mainly due to the reason that in patients' selection, treatment, and evaluation provided protocol was strictly followed.

Our experience of an acute stroke thrombolysis service shows that we are able to provide this treatment safely and in accordance with established treatment guidelines. Direct comparison of our study with that of the NINDS and ECASS II studies is not possible. The baseline characteristics appear similar, but in our cohort we had less patients and all of them were from a single centre. In addition, the rate of symptomatic and asymptomatic intracerebral hemorrhages was much lower than in other studies. Death rate recorded was: 1.41% *vs.* 17% in NINDS rt-PA group and 10.6% in ECASS II rt-PA group.

Intracerebral bleeding occurred in three of our patients: it was clinically insignificant in one of the patients, while the other two patients appeared to have a net benefit from treatment with rt-PA, despite the bleed. Meta-analysis of community studies confirms that comparable outcomes to those of randomized trials can beachieved, especially when established treatment guidelines are followed[10–13].

Conclusion

In conclusion, thrombolytic treatment is recommended in acute ischemic stroke for selected population. Detailed published guidelines for use of thrombolytic therapy and management of patients post-thrombolysis are available and should be followed in order to reduce complications and to obtain the most effective treatment. It must be kept on mind that thrombolysis is specific therapy. Because of that arterial recanalisation and good outcome cannot be expected if arterial occlusion is not caused by thrombus.

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INTRAVENOZNA TROMBOLIZA U LIJEČENJU AKUTNOG MOŽDANOG UDARA: NAŠA ISKUSTVA

S A Ž E T A K

Intravenozna tromboliza (IV) s rekombinantnim tkivnim aktivatorom plazminogena (rt-PA) je jedina dostupna farmakološka terapija za poboljšanje ishoda liječenja akutnog moždanog udara. Usporedili smo 71 pacijenta s ishemijskim moždanim udarom koji su intravenozno primili rt-PA (0,9 mg/kg ukupna doza) unutar prva tri sata od nastupa moždanog udara sa 71 pacijentom koji su primljeni nakon 3 sata od nastupa moždanog udara. Primarni cilj je modificirana Rankin skala (mRS) nakon 90 dana, podjeljena na povoljan ishod (skor 0–1). Ishod je bio simptomatsko intracerebralno krvarenje u prva 24 sata (krvarenje povezano s pogoršanjem NIHSS za ≥ 4 boda) i moratlitet u 3 mjeseca. Više pacijenata liječenih s rt-PA u odnosu na placebo je imalo povoljan ishod (64,79% vs. 22,54%; p=0,0001). Veći postotak pacijenata liječenih rt-PA je napustio bolnicu s minimalnim ili nikakvim deficitom nakon 90 dana u usporedbi s kontrolnom grupom. U grupi liječenih imali smo jednog pacijenta s simptomatskim intracerebralnim krvarenjem koji se oporavio do nivoa funkcionalne neovisnosti, te dva bolesnika s asimptomatskim intracerebralnim krvarenjem. Naše iskustvo u liječenju bolesnika s akutnim ishemijskim moždanim udarom intravenoznom trombolizom pokazuje da smo sposobni pružiti sigurno liječenje prema važećim smjernicama. Preporučujemo trombolitičku terapiju kod ishemijskog moždanog udara kod selekcioniranih bolesnika.