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Hemorrhagic complications of thrombolytic therapy- eight years of experience from Banjaluka's University Hospital - Stroke unit

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ABSTRACT

Introduction. Intravenous thrombolysis with recombinant plasminogen activator is proven to be beneficial for patients with ischaemic stroke. Intracerebral hemorrhage represents the most serious complication of the treatment mentioned.

Aim of this study. The aim of this retrospective study is a detailed analysis of intracranial hemorrhagic complications treated with recombinanttissue plasminogen activator.

Patients and Methods. All intracerebral hemorrhage patients were classified according to the European Cooperative Acute Stroke Studyprotocol recommendations. A total of 188 patients were treated with thrombolytic therapy. Overall incidence of hemorrhagic complications was 22.3%, while the frequency of intracranial hemorrhagic events was 17%. The incidence of symptomatic intracranial hemorrhage was recorded in 6.9%, and the percentage of deaths after thrombolysis was in 5.3% of patients.

Conclusion. The most common cause of deterioration in patients treated with recombinant tissue plasminogen activator is the occurrence of parenchymal hematoma type 2. Other forms of intracerebral hemorrhage after thrombolysis did not lead to clinical deteriorations. If existing recommendations are followed, thrombolytic therapy is safe.

Key words:stroke, tissue plasminogen activator, intracranial hemorrhage

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Introduction

Acute ischemic stroke is one of the leading causes of death worldwide.[1] Annually, 15 million people worldwide suffer a stroke.[2] Stroke is the second leading cause of death in 2012, accounting for 6.7 million deaths.[3]

In 1996, the Food and Drug Administration (FDA) approved the use of recombinant tissue plasminogen activator (rt-PA) for the treatment of acute ischaemic stroke. The protocol is based on the results of the National Institute of Neurological Disorders and Stroke Recombinant

Tissue Plasminogen Activator (NINDS rt-PA) study.[4] So far it represents the only approved pharmacotherapy treatment for patients with acute ischaemic stroke and it includesrt-PA treatment protocol.[4] Administration of rt-PA within the three hours of stroke onset significantly improves the probability of a favorable outcome.[4]

Aim of this study

The aim of this retrospective study is a detailed analysis of intracranial hemorrhagic complications treated with recombinant tissue plasminogen activator in 188 patients.

Patients and methods

Intravenous recombinant tissue plasminogen activator therapy for acute ischaemic stroke was used from March 30, 2007 until May 18, 2014 in treatment of 188 patients. All patients were assessed by a stroke neurologist and admitted to Stroke unit where the rt-PA treatment was carried out. During the assessment, patients were evaluated using the protocol derived from NINDS rt-PA study recommendations.[4] All recorded intracranial hemorrhages were classified using the ECASS III study recommendations:

- Hemorrhagic infarction type 1 (HI 1), small petechiae along the margins of the infarct
- Hemorrhagic infarction type 2 (HI 2), more confluent petechiae within the infarcted area, but without space-occupying effect
- Parenchymal hematoma type 1 (PH 1), hemorrhage not exceeding 30% of the infarcted area with some mild space-occupying effect
- Parenchymal hematoma type 2 (PH 2), hemorrhage exceeding 30% of the infarcted area with significant space-occupying effect.

Additional criteria for extended time period of 3 to 4.5 hours were evaluated using relative contraindications suggested in ECASS III study.[4] Patients with diabetes and a previous stroke and those older than 80 years were excluded from the study. CT was performed for each patient upon admission to the hospital, while the controlled CT was conducted 24 hours after rt-PA application. Upon clinical indication, CT in some patients was performed several times.

Results

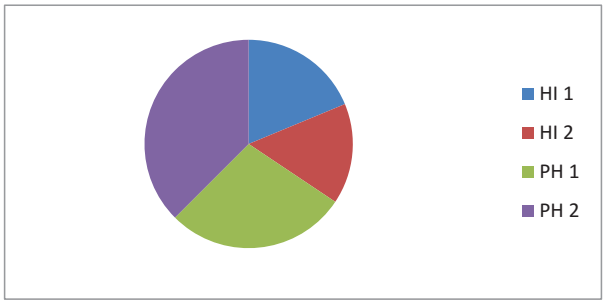
We studied a total of 188 patients: 100 men, 88 women. (Table 1.)

Table 1. Demographic data

	Number of patients	Middle age	Young	Old
Male	100	61.78	25	81
Female	88	65.29	33	79

We started with rt-PA treatments in 160 patients who had acute ischaemic stroke within 3 hours of stroke onset, while 28 treatments were started from 3 to 4.5 hour time window after stroke. Average time from symptom onset to arrival in neurological ambulance was 1 hour and 27 minutes. Mean time from arrival to neurological ambulance to initiation of rt-PA treatment was 51 minutes. Stroke severity on admission was evaluated using NIHS scale. At hospital discharge, NIHS scale was used to determine any possible presence and the level of neurological improvement. There was no neurological difference between men and women in stroke severity on admission, while women showed greater neurological improvementat discharge. Level of functional capacity at hospital discharge did not differ between sexes. Overall incidence of hemorrhagic complications was 22.3% (42/188). Frequency of all intracranial hemorrhagic events was 17% (32/188). (Figure 1.)

Figure1. Frequency of intracranial hemorrhagic events



HI 1- Hemorrhagic infarction type 1 (6 patients)
HI 2- Hemorrhagic infarction type 2 (5 patients)
PH 1- Parenchymal hematoma type 1 (9 patients)
PH 2- Parenchymal hematoma type 2 (12 patients)

Frequency of symptomatic intracranial hemorrhage (sICH) was defined as deterioration if the NIHSS score was 4 points or greater. Other (non sICH) hemorrhagic adverse events in patients were clinically manifested:subcutaneous hematoma (6 patients), transient hematuria (2patients),dental hemorrhage (1 patient) and hemorrhage to sphenoid sinus (1 patient). Mortality rate was 9% (17 patients), with 6.9% (12 patients) vs. 2.1% (5 patients) male to female ratio. There were 10 deaths

(5.3% patients)due to severe intracranial hemorrhage, detected on follow up CT scan of the head, after clinical deterioration was ascertained.

Discussion

Symptomatic intracerebral hemorrhage (sICH) causes high disability and death rate. In our retrospective study, which included 188 respondents, a detailed analysis of all hemorrhagic events and circumstances in which they occurred was conducted.

ECASS III study tested the efficiency and safety of rt-PA in the time window between 3 and 4.5 hours after stroke onset.4 After 90 days, significantly higher number of patients treated with rt-PA showed beneficial outcome in comparison with the patients who were given a placebo (52.4% vs. 45.2%; ratio, 1.34; 95% CI, 1.02 to1.76; P=0.04).[5]

sICH represents the most significant complication of thrombolytic therapy in acute stroke and it is linked to higher morbidity and mortality rate in patients treated with rt-PA. BothNINDS and ECAS III studies have shown a significant increase of overall incidence of intracerebral hemorrhage in patients treated with rt-PA in comparison with the placebo group (NINDS 11.9% vs.3.5%; ECAS III 27% vs.17.6%).[4,5]

sICH incidence was higher in rt-PA group (NINDS 6.4% vs. 0.6%; ECASS III 2.4% vs. 0.3%).[4,5] Certain markers are useful in the assessment of ICH hemorrhage caused with rt-PA in everyday clinical practice. They includestroke severity, higher blood pressure before treatment, history of diabetes mellitus and atrial fibrillation, older age, low level of thrombocytes in blood, usage of anti-thrombocyte therapy except aspirin before stroke occurrence and early signs of infarct changes at the baseline of CT.[6]

Intracerebral hemorrhage related to rt-PA does not necessarily produce neurological and functional deteriorations. Hemorrhagic infarction types(HI) 1 and 2 represent a marker of early successful recanalization which leads to reduced infarct size and improved clinical outcome.[8]

Data analysis showed that, in our study, sICH group was composed from all of the PH 2 patients and only one PH 1 patient, suggesting that HI type 1 and 2 patients did not deteriorate despite experiencing hemorrhagic complications. In this regard our research support the statement that hemorrhagic infarctions type 1 and 2 are strongly linked to good clinical outcome in patients treated with rt-PA.

Post-analysis of ECASS II data has confirmed the importance of the extent of hypoattenuation on the baseline CT, as a factor for significant hemorrhagic transformation in patients treated with rt-PA. Older patients and those who have used aspirin before stroke are at higher risk for sICH .[9]

Mean door–to-needle time (DTN) of 51 minutes ideally fits into the recommendations for treatment of all patients within an hour from arrival to emergency room.[10]

Therapeutic efficiency of rt-PA in treatment of acute ischaemic stroke is highly time dependent. Fonarow et al.11 suggested that rt-PA therapy from 77 to 67 minutes after acute stroke gives good clinical results.[11]

The authors of the article have mostly relied on the results of the NINDS and ECASS III studies, since the results of these studies are largely responsible for the creation of ongoing rtPA treatment protocols. This provides the usage of thrombolysis and treatment efficiency due to the expended time window and giving of rtPA to wider stroke population. The aim of the study was to check through clinical research and receive feedback from clinical practice based on the ECASS III recommendations.

Conclusion

If recommendations are followed,thrombolytic treatment is beneficial to stroke patients with acceptable proportion of hemorrhagic adverse events.

Adverse outcome of hemorrhagic complications treatment is found in patients with symptomatic intracerebral hemorrhage.

Thrombolytic therapy is safe if performed in specialized institutions, following the existing clinical guidelines made by educated expert teams of doctors.

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Hemoragične komplikacije trombolitičke terapije – osmogodišnje iskustvo banjalučke Univerzitetske bolnice-Jedinica za moždani udar

SAŽETAK

Uvod. Intravenska tromboliza sa rekombinatnim aktivatorom plazminogena je dokazano korisna za pacijente sa ishemijskim moždanim udarom. Intracerebralno krvarenje predstavlja najozbiljniju komplikaciju navedenog liječenja.

Cilj rada. Cilj ove retrospektivne studije je detaljna analiza intrakranijalnih hemoragičnih komplikacija liječenih sa rekombinantnim tkivnim aktivatorom plazminogena.

Ispitanici i metode. Svi ispitanici intracerebralnog krvarenja su klasifikovani prema preporukama iz European Cooperative Acute Stroke Study protokola Trombolitičkom terapijom liječena su 188 ispitanika. Ukupna incidenca hemoragijskih komplikacija iznosila je 22.3%, a frekvencija intrakranijalnih krvarenja 17%. Učestalost simptomatskog intrakranijalnog krvarenja evidentirana je u 6.9% ispitanika, a smrtost poslije trombolize kod 5.3% ispitanika.

Zaključak. Najčešći uzrok pogoršanja kod pacijenata liječenih rekombinatnim aktivatorom plazminogena je nastanak parenhimskog hematoma tip 2. Ostali oblici intracerebralnog krvarenja poslije trombolize nisu dovodili do kliničkog pogoršanja. Trombolitička terapija je sigurna ukoliko se prate postojeće preporuke.

Ključne riječi: moždani udar, tkivni aktivator plazminogena,intrakranijalno krvarenje