HEMORRHAGIC COMPLICATIONS OF THROMBOLYTIC THERAPY

Zoran VUJKOVIĆ, Duško RAČIĆ, Siniša MILJKOVIĆ and Vlado DJAJIĆ

Summary – Stroke is the most frequent neurological disorder, and the most common cause of severe disability compared to other diseases [1]. Recombinant tissue plasminogen activator (rt-PA) is the only approved specific therapy for acute ischemic stroke. Hemorrhage is a significant complication of thrombolytic treatment. When the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (rt-PA) Stroke Trial protocol is followed, this analysis suggests that the patients treated within 90 minutes from the stroke onset with rt-PA have an increased odds of improvement in 24 hours and favorable 3-month outcome compared to those treated more than 90 minutes after stroke [3]. Rt-PA has been shown to improve functional outcomes following acute ischemic stroke and can be administered to a selected group of patients up to 4.5h after the symptom onset. The main risk of treatment was symptomatic intracerebral hemorrhage, which occurred in 6.4% of patients treated with rt-PA versus 0.6% of patients who received placebo, but it did not result in an increase in mortality rate among rt-PA-treated patients. The presence of large early ischemic changes on baseline computed tomography (CT) scan was associated with a higher risk of symptomatic intracranial hemorrhage. The risk of intracranial hemorrhage, defined according to various criteria, was acceptably low. Substantial neurological decline from brain hemorrhage occurred in only 1.7% of patients. The adequate control of blood pressure before, during and after administration of intravenous fibrinolysis must be done to reduce the risk of intracranial bleeding. Most stroke specialists deem administration of fibrinolysis unsafe for patients who require sodium nitroprusside infusion to lower the blood pressure below 185/110mm Hg in the Emergency Department [4]. Remote cerebral hemorrhage is an infrequent complication after rt-PA treatment (3.3%); it is usually lobar and symptomatic and has a uniformly unfavorable outcome [5].

NINDS and European Cooperative Acute Stroke Study III (ECASS III) clinical trials demonstrated significantly improved outcomes in 3 months with the increased rates of intracranial hemorrhage, whereas ECASS II and the Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study showed increased hemorrhagic complications without improving outcomes. Meta-analysis of trial data from all ECASS trials, NINDS, and ATLANITIS suggest that thrombolysis within 4.5 hours improves functional outcomes [6-9].

Material and Methods

We had 100 thrombolytic treatments. Thrombolytic treatments were performed in the period from March 30th, 2007 to May 2nd, 2011. In all cases, thrombolysis was given at the Stroke Unit of the Department of Neurology, Clinical Center Banjaluka.

Upon admission to hospital, all patients were assessed immediately by the competent stroke neurologist and a trained nurse. The rt-PA protocol, as well as the inclusion and exclusion criteria were based on the protocols published by the American Heart Association and American Academy of Neurology. The patients underwent pretreatment CT scans, which were assessed by the attending neurologist and a radiologist. All patients underwent follow up CT imaging in 24 hours or when clinically indicated. Intracerebral hemorrhage was considered symptomatic when it had led to a 4-point or greater increase in the National Institutes of Health Stroke Scale (NIHSS) score.

Hemorrhagic transformations were classified as:
1. HI 1, hemorrhagic infarction type 1
2. HI 2, hemorrhagic infarction type 2
3. PH 1, parenchymal hematoma type 1
4. PH 2, parenchymal hematoma type 2

HI 1 is defined as small petechiae along the margins of the infarct, while HI 2 represents more con-
Results

There were 52 male and 48 female patients. The average age was 61.51 for male patients and 64.12 for female patients. The youngest male and female patient was 38 and 35, whereas the oldest male and female patient was 79 and 78, respectively (Table 1).

Table 1. Age of patients

<table>
<thead>
<tr>
<th>Average</th>
<th>The youngest</th>
<th>The oldest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/ Muškarci</td>
<td>61.51</td>
<td>38</td>
</tr>
<tr>
<td>Female/ Žene</td>
<td>64.12</td>
<td>35</td>
</tr>
</tbody>
</table>

We had 96 thrombolytic treatments within 3 hours from the symptom onset and 4 thrombolytic treatments within 3 to 4.5 hours.

82 patients had extracranial and transcranial color coded duplex scan (TCCD) before thrombolysis (82%). The average time from the symptom onset to arrival to the neurology department was 1 hour and 23 minutes.

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The average NIHSS on admission was 10.61 (for male) and 11.61 (for female) (Graph 1). The average NIHSS at discharge was 4.21 (for male) and 4.31 (for female) (Graph 2). The average Rankin score on admission was 3.6 (for male) and 3.9 (for female). The average Rankin score at discharge was 1.5 (for male) and 1.7 (for female).

The overall mortality was 6% (7.69% for male and 4.17% for female – Graph 3).

We had three deaths due to hemorrhage after thrombolysis, and three deaths due to cerebral infarction after thrombolysis without hemorrhage. The death rate related to hemorrhage after thrombolysis was 3%.

The frequency of hemorrhagic events (parenchymatous hematoma (PH) 1 and 2, hemorrhagic infarction (HI) 1 and 2) was 16%. Table 2 and Graph 4 show the distribution of PH and HI.

Table 2. Frequency of hemorrhagic events

<table>
<thead>
<tr>
<th>Hemorrhagic infarctions and intracerebral haematomas</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI 1</td>
<td>5</td>
</tr>
<tr>
<td>HI 2</td>
<td>3</td>
</tr>
<tr>
<td>PH 1</td>
<td>3</td>
</tr>
<tr>
<td>PH 2</td>
<td>5</td>
</tr>
<tr>
<td>Total/Ukupno</td>
<td>16</td>
</tr>
</tbody>
</table>

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Other adverse events were:
1. subcutaneous hematoma – 5 patients
2. hematuria – 1 patient
3. dental hemorrhage – 1 patient
The aim of the study was to assess the safety and efficacy of thrombolytic therapy. The frequency and risk factors for intracerebral hemorrhage (ICH) after ischemic stroke are well known. The rate of symptomatic intracerebral hemorrhage in our rt-PA treated patients was 5%, that being similar to the one observed in the NINDS trial (6.4%).

Perini found ICH frequency to be increased by the use of antithrombotic or thrombolytic drugs. Several experimental studies have demonstrated a relationship between ICH and hypertension after fibrinolysis, but the optimal blood pressure levels in patients treated with rt-PA are still unknown. Total cerebral hemorrhage occurred in eleven (12.7%), and symptomatic intracerebral hemorrhage occurred in seven (8.1%) patients. High blood pressure levels correlated with a worse outcome. Systolic blood pressure was significantly higher in ICH patients than in rt-PA-treated patients without hemorrhagic complications (p<0.03). This study indicates that rt-PA-induced hemorrhage is influenced by systolic blood pressure. More aggressive pharmacological reduction of hypertension during fibrinolysis and the subsequent 32 hours may reduce this complication [11].

We had one thrombolytic treatment in a patient with stroke on warfarin. This thrombolytic treatment was successful. This patient had international normalized ratio (INR) 1.3. Concerns have been raised about the risk of hemorrhage in patients having received warfarin. Therefore, different indications for thrombolytic treatment are in use for stroke patients on warfarin. However, it remains uncertain whether the prior warfarin use actually increases the risk of bleeding in patients treated with thrombolysis. Kim found that thrombolytic therapy for patients who had previously received warfarin and had an INR≤1.7 did not affect bleeding risk, clinical outcome, or recanalization rate. This data suggest that patients with a history of prior warfarin use may be treated safely with thrombolytic agents when their INR levels are low [12]. Hemorrhagic transformation (HT) after fibrinolytic therapy may be less common in patients with acute cerebral ischemia confined to single penetrating artery (SPA) territories than in patients with large artery ischemia. Previous investigations of HT diagnosed small vessel ischemia based on lacunar clinical syndromes, an approach known to yield misdiagnosis in one-third to one-half of cases. HT after lytic therapy in imaging-confirmed SPA infarcts is uncommon. Imaging demonstration of ischemia confined to SPA territory identifies this population at low risk for hemorrhagic complications better than clinical lacunar syndromes [13].

We had a large number of patients examined with transcranial color coded duplex scan before thrombolysis (82%). The unfavorable blood vessel arrangement may lead to occasional insufficiency of the blood supply, resulting in transitory neurological deficits. Neurosonology examination is a very important tool in treating ischemic disease of brain [14,15].

The care for patients with acute ischemic stroke has been revolutionized by the clinical application of fibrinolysis [16,17].

### Conclusions

In our experience, remote cerebral hemorrhage is an infrequent complication after rt-PA treatment.

The rate of symptomatic intracerebral hemorrhage in our rt-PA treated patients was 5%.

We had 3% death due to hemorrhage after thrombolysis.

The frequency of hemorrhagic events (hemorrhagic infarction type 1 and 2, parenchymal hematoma type 1 and 2) was 16%.

The overall mortality rate was 6%.

The study results have shown that the intravenous rt-PA therapy is safe.

## References

Sažetak

Uvod
Moždani udar je najčešći neurološki poremećaj i najčešći uzrok značajne nesposobnosti u poređenju s drugim bolestima. Rekombinantni tkivni aktivator plazminogena dokazana je specifična terapija za akutni ishemijski moždani udar. Hemoragija je značajna komplikacija trombolitičkog tretmana.

Materijal i metode

Rezultati
Smrt uzrokovana krvarenjem nakon trombolize bila je 3%, a ukupna smrtnost 6%. Učestalost svih hemoragičnih događaja bila je 16%. Učestalost simptomatske intracerebralne hemoragije u ovoj studiji (5%) slična je onoj koja je registrovana u studiji National Institute of Neurological Disorders and Stroke (6,4%).

Zaključak
Rezultati studije pokazali su da je intravenska rekombinantnim tkivnim aktivatorom plazminogena terapija sigurna. Smrtnost uzrokovana krvarenjem nakon trombolize bila je mala (3%).

Ključne reči: Krvenje; Moždani udar; Trombolitička terapija; Tkivni aktivator plazminogena; Muško; Žensko

Rad je primljen 18. VII 2011.
Prihvaćen za štampu 22. VIII 2011.
