Acute ischemic stroke (IS) is one of the leading causes of morbidity and mortality in the world. Intravenous thrombolysis with recombinant tissue plasminogen activator remains the standard treatment for acute ischemic stroke for any patient presenting within 4.5 hours from symptom onset. However, it is more effective and safe when treatment starts early. This therapy for acute ischemic stroke has been administered in Vojvodina since 2008. Various factors influence the outcome after intravenous thrombolysis. Timely recanalization and reperfusion is associated with better clinical outcomes. Mechanical thrombectomy – a New Therapeutic Modality for the Treatment of Acute Ischemic Stroke. Nevertheless, the rate of recanalization and favorable outcomes for patients with acute ischemic stroke due to large vessel occlusion are low after intravenous thrombolysis. In such patients mechanical thrombectomy has demonstrated significantly higher rates of recanalization and improved outcomes compared with intravenous thrombolysis alone. This endovascular reperfusion therapy began to be implemented in Vojvodina in 2016. Conclusion. Intravenous thrombolysis continues to play a key role in the treatment of all acute ischemic stroke patients, but mechanical thrombectomy should be the “gold standard” in the cases with large vessel occlusion.

Key words: Stroke; Brain Ischemia; Treatment Outcome; Endovascular Procedures; Thrombolytic Therapy; Thrombectomy; Tissue Plasminogen Activator; Reperfusion; Mechanical Thrombolysis

Ischemic stroke (IS) is one of the leading causes of morbidity and mortality in the world. IS is also the leading cause of disability in the world, and, in addition to health-related consequences, it has enormous socioeconomic significance for the society as a whole [1]. Reducing the effects of stroke and improving outcomes is the goal of treating patients with acute IS.
Abbreviations
IS – ischemic stroke
AIS – acute ischemic stroke
IV – intravenous
rtPA – recombinant tissue plasminogen activator
IVT – intravenous thrombolysis
NINDS – National Institute of Neurological Disorders and Stroke
NIHSS – National Institutes of Health Stroke Scale
SU – Stroke Unit
CCV – Clinical Center of Vojvodina
mRS – modified Rankin score
MRI – magnetic resonance imaging
sICH – symptomatic intracerebral hemorrhage
NNT – number needed to treat
OTT – onset to treatment time
SITS – Safe Implementation of Thrombolysis in Stroke
ICA – internal carotid artery
AF – atrial fibrillation
MCA – middle cerebral artery
MT – mechanical thrombectomy
MERCI – Merci Retrieval System
ESO – European Stroke Organization

occluded artery [3]. In this way, the size of the potential damage to the cerebral parenchyma can be reduced, neurological improvement can be achieved, and patient outcome after AIS can be improved.

Intravenous Thrombolysis in Acute Ischemic Stroke

Recanalization of a previously occluded artery can be achieved by intravenous (IV) administration of recombinant tissue plasminogen activator (rtPA), which remains the basis for treating patients with AIS [4]. Clinical efficacy of intravenous thrombolysis (IVT) was proved in 1995 after publication of the National Institute of Neurological Disorders and Stroke (NINDS) study [5]. This large randomized controlled study compared the AIS outcome in patients who received rtPA or placebo within 3 hours of the onset of symptoms. In the treated group, a relative increase in the percentage of patients with a favorable outcome was achieved, which meant the absence of disability after three months by 50% (modified Rankin score – mRS ≤ 1 after three months, 39% of the patients in the treated group compared with 26% of the patients in the placebo group). The following year, the Food and Drug Administration (FDA) approved rtPA in the treatment of AIS [6]. In 2008, the results of the randomized controlled study European Cooperative Acute Stroke Study III (ECASS III) showed that the therapeutic effect and clinical benefit of IVT exist even if rtPA is administered over a period of 180–270 minutes from the onset of symptoms [7]. This study showed that in the time window of 3–4.5 hours after the onset of IS symptoms, IVT administration resulted in an absolute increase of the percentage of patients with a favorable outcome after three months of 7% (52% of treated patients had mRS ≤ 1 three months after AIS versus 45% in the placebo group). The symptomatic intracerebral hemorrhage (sICH) occurred in these two studies in 6% and 8% of cases versus 0.6% in the placebo group, but the therapeutic benefit significantly exceeded the risks [5, 7]. To date, several large multicentre, controlled, double-blind, randomized studies have confirmed IVT’s efficacy in AIS, summed up in a single meta-analysis [8], which showed that the benefits of IVT use exist for all types of IS, regardless of the patient age, stroke severity, severity of neurological deficits expressed by the National Institutes of Health Stroke Scale (NIHSS), or the time of application of the therapy within the 4.5 hours time window.

Intravenous Thrombolysis for Acute Ischemic Stroke in Vojvodina

Intravenous thrombolysis with rtPA today represents a standard treatment of all patients with AIS within the first 4.5 hours after the onset of symptoms [9]. The first intravenous thrombolytic therapy in Serbia was performed in 2006 [10], and in Novi Sad two years later [11], when the first patient received IVT at the Neurology Clinic of the Clinical Center of Vojvodina (CCV). Since then, the number of patients treated with IVT has been increasing each year, to which contributed also the establishment of the new Emergency Center in the CCV, in which the Stroke Unit (SU) was formed. However, the percentage of patients who are treated with IVT today is only 5–8% of all patients who are examined for AIS in the CCV. The reason for this is, primarily, the small time window for the application of therapy [9], due to which the late recognition of patient’s symptoms, delay in calling emergency services, i.e. arrival to the hospital after the time window of 4.5 hours, prevent the use of this therapy. These percentages are similar in most countries, and higher percentages (> 10%) of all patients treated with IVT are recorded only in the most economically developed countries. Studies have shown that even if all patients with AIS would arrive within the appropriate time window, only one third would be eligible for IVT [9]. This may be explained by numerous contraindications, fear of complications, absence of the expected efficacy (severe clinical picture, high NIHSS score, occlusion of a large vessel, etc), but also by insufficient knowledge of both the general population and medical workers. A number of strategies have been considered to increase the number of patients with AIS who would be treated with IVT [9]. Today, it is known that in some conditions that were previously considered contraindications, such as seizures, age over 80 years, withdrawing symptoms and too mild or too severe stroke, IVT can be safely administered [8]. Recently, the American Heart Association and the American Stroke Association made clear recommendations on the use of IVT in the case of specific clinical conditions that can sometimes be considered relative contraindications [9]. In the case of a dilemma, the risk-benefit assessment should always be the first consideration in each individual case. Unknown time of symptom onset and the so-called wake-up stroke are still one of the main reasons for the decision not to perform IVT [12]. Magnetic
resonance imaging and diffusion-FLAIR mismatch techniques can enable selection of patients in whom the use of IVT would be justified.

With the help of telemedicine, doctors in outpatient centers who do not have access to the SU can be provided with expert assistance by neurologists and neuroradiologists when deciding on the application of IVT, which in many centers contributed to an increase in the percentage of patients with AIS treated with IVT, without increasing the risk of hemorrhagic complications [13]. Thanks to the Telestroke project, in some hospitals in Vojvodina the application of IVT under the supervision of the neurologists from the CCV started [14], and it is today routinely applied. In economically developed countries, mobile SU have been formed, thanks to which the therapy can also be applied in the field, but the justification of such models is still being tested [15].

**Time of Initiation of the Therapy**

Although IVT may be started within the first 4.5 hours following the onset of symptoms of IS, results of several studies have shown that the effect of therapy is time dependent and that the therapeutic response is better if the therapy is applied earlier [16, 17]. It has been shown that every additional 15 minutes of delay in IVT application reduces the chance of a patient’s discharge or his/her independent walking at discharge by about 4% [16]. Also, with every 15 minutes of delay in IVT, the risk of sICH is increased for about 4% and for about 4% of fatal outcome [16]. Furthermore, it has been shown that it is needed to treat 4.5 patients with AIS by intravenous thrombolysis in order to have one patient fully recovered (number needed to treat - NNT) if the drug is applied within the first 90 minutes after symptom onset. The number of patients needed to be treated is twice as high (NNT-2) if the IVT is applied within a period of 90 to 180 minutes, and if applied after 180 minutes, NNT is 14.1 [18].

In order to give the therapy to patients with AIS as soon as possible, rapid recognition of the symptoms, prompt response of emergency medical service, and efficient treatment after the patient has arrived to the hospital are necessary [19]. The average time from the onset of AIS symptoms to the application of IVT, onset to treatment time (OTT), in industrialized countries is about 140 minutes [20], and it is recommended that the door to needle time (DNT) should not be longer than 60 minutes [18]. In our conditions, in the CCV these periods are 10–15 minutes longer than the above mentioned, which suggests that it is necessary to optimize and improve each stage in the management of patients with AIS.

**Outcome after Administration of Intravenous Thrombolysis**

Since patients in daily clinical practice differ from those included in large clinical studies, in 2002 the Safe Implementation of Thrombolysis in Stroke (SITS) registry was established in order to evaluate the outcome and complications in patients with AIS treated with IVT in daily clinical work. The results showed that three months after AIS and IVT application, 40-45% of patients were without any disability (mRS ≤ 1), and 55–60% were functionally independent (mRS ≤ 2) [20]. With the same goal, from the beginning of IVT administration in Serbia, the Serbian Experience with Thrombolysis in Ischemic Stroke (SETIS) registry was established [21]. In the CCV, the results showed that 43.5% of patients three months after AIS and IVT had mRS ≤ 1, while 55.1% of patients had mRS ≤ 2 [22], which is in line with the results of the SITS registry.

In most studies, the predictors of unfavourable outcome (mRS 3–6) at three months despite the administration of IVT were older age, a more severe clinical picture (i.e. a higher NIHSS score on admission), glycemic status on admission rate, OTT, presence of early signs of brain ischemia, proximal occlusion, and absence of early recanalization [23]. In patients in the CCV, the occurrence of recanalization was associated with early neurological improvement and a favourable outcome at three months [24]. Among the patients who had computed tomography angiographically verified recanalization of previously occluded cerebral arteries, 54.6% had an early neurological improvement; 72.3% were functionally independent (mRS ≤ 2) at three months, compared with 15.0% of patients with early neurological improvement and 30% with mRS ≤ 2 at three months in the group of those who did not have recanalization. In the analysis of specific clinical conditions, earlier reports showed that patients with occlusion of extracranial parts of the internal carotid artery (ICA) had a worse outcome than patients without an ICA occlusion [21]. Furthermore, patients with atrial fibrillation (AF) had a worse outcome than those without AF [25]. However, in both cases after regression analyses, it was shown that independent predictors of poor outcome were older age and clinical picture, i.e. the NIHSS score on admission. Also, by comparing the types of infarction according to the Oxfordshire Community Stroke Project (OCSP) classification, it was shown that the patients with larger threatening strokes had worse outcomes despite the use of IVT [26]. Today, it is known that a higher NIHSS score on admission indicates larger infarction, that is, more proximal occlusion, when the chance of recanalisation after application of IVT is smaller, and therefore a chance of neurological improvement and a favourable outcome at three months is lower [24, 26]. Several studies have shown that IVT has a modest effect in case of large vessel occlusion (terminal ICA, M1 segment of the middle cerebral artery (MCA) or basilar artery). The failure of IVT in proximal occlusions has also been explained by the size of the thrombus itself [27–30].

Although several studies have shown that IVT contributes to a better outcome in all IS subtypes and in the entire range of severity of clinical picture, it is now clear that IVT alone is insufficiently effective in proximal occlusion caused by a large thrombus [29]. A higher percentage of recanalization was achieved by the intraarterial endovascular approach and mechanical extraction of the thrombus after IVT, which is today the standard treatment of patients with AIS caused by large vessel occlusion [30].
**Mechanical Thrombectomy - a New Therapeutic Modality for the Treatment of Acute Ischemic Stroke**

The introduction of mechanical thrombectomy (MT) in the clinical practice marks the beginning of a new era in the treatment of AIS caused by the occlusion of large vessels in the frontal cerebral circulation.

The Food and Drug Administration approved the use of the first endovascular device: Merci Retrieval System (MERCI®) in August 2004 [31]. Using this device, complete recanalization was achieved in 48% of patients with AIS and large vessel occlusion, treated within the first 8 hours after symptom onset and in 60.8% of patients in combination with adjuvant intra-arterial thrombolytic therapy. The occurrence of sICH was recorded in 7.8%. Using the modern generation of MERCI devices, 69.4% of patients had recanalization with additional thrombolyis (intra-arterial or intravenous), with favorable clinical outcome in 34% of patients; however, there was no control treatment group in this study [32].

The initial optimism for MT was shaken when three large randomized controlled studies failed to determine the beneficial effect of endovascular treatment compared with IVT [33–35]. However, the designs of these studies were criticized: inadequate patient selection (in one of the studies), no necessary evidence of large vessel occlusion, use of older technology (mainly the first generation “retriever” devices) and a longer period of time until the start of endovascular intervention. Nevertheless, a post hoc analysis of subgroups with CT angiographically verified occlusion in the frontal circulation, showed statistically significant benefit of this endovascular treatment within 90 minutes after IV rtPA administration [36].

To date, nine positive large randomized controlled studies have been published that compared the results of treatment of AIS patients using MT after IVT or only with MT versus treatment with IVT alone [30, 37, 38]. Publishing the results of these studies, which used mostly the new generations of stent retriever, made major changes: the clear superiority of this type of endovascular treatment was demonstrated compared with standard IV treatment, both in terms of improving the percentage of recanalization and in terms of increasing the percentage of patients without disability at 90 days (mRS ≤ 2). Clear evidence of safety and efficacy of MT was also confirmed by the collaborative meta-analysis HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke trials), which included the first five positive studies [39].

This meta-analysis showed that percentage of patients with good functional outcome (mRS ≤ 2) at 90 days was significantly higher in the group of patients treated with MT with or without prior IVT (46% of patients) than in the group of patients treated only with IVT (26.5%) [39]. In addition, the use of MT significantly reduced disability, i.e. the average mRS score at 90 days was reduced (adjusted CDR 2.49, 95% CI 1.76-3.53; p <0.0001). This meta analysis also showed that MT required the treatment of 2.6 patients in order to decrease the mRS by 1 or more points. Mortality in the first 90 days and the risk of sICH did not differ between patients who were treated with MT and IVT and those treated with only IVT. Another meta-analysis of the same five studies indicated that the clinical benefit of MT was also present if the intervention started within the first 7.3h (onset-to-expected arterial puncture time of 7 hours and 18 minutes) [40].

**Current Recommendations for the Treatment with Mechanical Thrombectomy**

Following re-evaluation of the AIS treatment protocol and the consensus opinion reached by members of the European Stroke Organization (ESO-Karolinska Stroke Update), supported by other European neurological associations at the end of 2015 [30], the following recommendations for the application of MT were given:

- Mechanical thrombectomy, in addition to IVT in the first 4.5 h, is indicated in case of occlusion of a large artery in frontal cerebral circulation up to 6h from the onset of symptoms (grade A, level of evidence 1a);
- Mechanical thrombectomy should not prevent IVT and vice versa, IVT should not delay the application of MT (recommendation grade A, level of evidence 1a);
- Mechanical thrombectomy should be performed as soon as possible and after establishing indications (grade A, level of evidence 1a);
- If IVT is contraindicated (e.g. in Warfarin-induced therapeutic INR, >1.7), MT is recommended as the first therapeutic modality (recommendation level A, level of evidence 1a);

The decision to initiate MT should be made jointly by a multidisciplinary team (neurologist, interventional radiologist, anesthesiologist) (grade C, level of evidence 4);

- The choice of anesthesia depends on individual situations; an effort should be made to avoid delaying MT (grade C, level of evidence 2b).

Patients with indications for MT are those in whom CT angiography has demonstrated a large blood vessel occlusion, primarily in the anterior circulation (M1 segment of the MCA or distal part of the ICA), NIHSS score on admission ≥ 6; Alberta Stroke Program early CT (ASPECT) score ≥ 6 [30].

**Mechanical Thrombectomy for Acute Ischemic Stroke at the Clinical Center of Vojvodina**

In the CCV, the era of the new therapeutic approach to AIS began in December 2016. So far, in the one-year period, a total of 17 AIS patients were treated with MT combined with IVT or without IVT, respecting the ESO-Karolinska recommendations [30]. The average age of our patients was 62 years. More patients were female (58% versus 42%). The average NIHSS score on admission was 14. The prevalence of risk factors...
was as follows: arterial hypertension (92%), smoking (50%), atrial fibrillation (42%), hypercholesterolemia (42%), and diabetes mellitus (25%). The onset to puncture time was 246 minutes, which does not differ significantly from the results of other clinical studies [39, 40]. The percentage of successful recanalization was 82.4%. Assessment of clinical outcome in the first 90 days is one of the key indicators of success of MT. A favorable clinical outcome depends on several factors. In the one-year follow-up period, 56.3% of patients had a favorable outcome (mRS ≤ 2).

Like after IVT, in the treatment of AIS by MT time remains the most important factor and key to success. Recent results suggest that any delay in achieving a 30-minute recanalization increases the risk of a worse clinical outcome by 12%, and that one-hour delay in achieving reperfusion reduces the chances of a favorable clinical outcome by 38%. The development of complications may also affect the outcome. The most severe periprocedural complications of MT are recurrent IS, occurring in about 6% of patients, and sICH, seen in about 8% [39, 40].

Conclusion and Future Guidelines

Intravenous thrombolysis continues to play a key role in the treatment of all patients with acute ischemic stroke. Today, there are quite obvious indicators that mechanical thrombectomy represents the “gold standard” in the treatment of patients with clinically most severe acute ischemic strokes due to occlusion of large blood vessels. The key challenge is to use this endovascular method in the safe and effective way. In the era of rapid development of endovascular devices for the treatment of acute ischemic stroke, it is necessary to make a balance between stricter patient selection and the benefits of treatment. Despite the varieties in time intervals, speed of revascularization and complications, our initial results in treating patients with mechanical thrombectomy are encouraging and do not differ significantly from the results of large studies.

However, there are fields that we can and must influence. In order to increase the number of patients with acute ischemic stroke who would be treated with this therapy and in order to apply the therapy as soon as possible, increased involvement is needed at all levels of management of acute ischemic stroke patients, as well as continuous education of the population. Provision of adequate re-education and cooperation with emergency medical teams is one of the prerequisites for the adequate treatment of these patients.

A significant clinical benefit can be achieved by relatively easy and simple implementation of what we already know: shortening the time from admission to the hospital to the application of recombinant tissue plasminogen activators. An improved coordination of the multidisciplinary team (neurologist, radiologist, anesthesiologist) would create conditions for shortening all significant time intervals until the initiation of endovascular intervention, i.e., until achieving the recanalization and reperfusion. With better selection of patients and greater experience, the shortening of the time from the onset of acute ischemic stroke symptoms to the application of therapy still remains the most important part of our efforts.

References


