Efficacy and Safety of Intra-Arterial Thrombolytic Therapy for Ischemic Stroke

ISS Early well-timed selective inter-arterial thrombolytic therapy (IATT) performed within 3-6 hour treatment window seems to be a promising method for early recanalization of the occluded vessel in acute stroke patients. We have performed the clinical trial to demonstrate efficacy and safety of IATT with streptokinase as a thrombolytic agent in 22 acute stroke patients hospitalized at the Republican Research Center of Emergency Medicine (Tashkent, Uzbekistan). At admission among 22 acute stroke patients atherothrombotic (n=16) and cardioembolic (n=6) subtypes were determined by means of color duplex sonography, clinical routine transcranial Doppler ultrasound examination and echocardiography. Post-IATT assessment by Glasgow Coma Scale, NIHSS and Rankin Scale demonstrated complete or significant neurological improvement and high degree of recanalization (72.7%).

Keywords: Acute stroke, intra-arterial thrombolytic therapy, streptokinase, treatment window

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Introduction

Recent achievements in elucidation of pathogenic mechanisms underlying ischemic stroke allowed determining main strategy of a pathogenic therapy for the most acute period, embodying improvement of the brain tissue perfusion by means of early occluded vessel recanalization. According to the last guidelines of the European Stroke Initiative (EUSI) and American Stroke Association a thrombolytic therapy (TT) performed within treatment window is a promising method for early recanalization of the occluded vessel in acute stroke patients (Suslina et al, 1997; AHA/ASA Scientific Statement Guidelines for the Early Management of Patients with Ischemic Stroke 2005 Guidelines Update, 2005; European Stroke Initiative Recommendations for stroke Management - Update 2003).

Plenty of prospective randomized multicenter studies have demonstrated efficacy and safety of TT in stroke patients triggering its wide use.

Today many neurovascular centers worldwide make use of the intravenous thrombolytic therapy (ITT). Performed in compliance with the conventional clinical guidelines it is a procedure with value and safety confirmed by meta-analysis (Clark, 1999; Hacke et al., 1995; 1998; 2004). Still intravenous thrombolytic therapy has some limitations. Thus, it is less efficient for thromboembolisms of large main arteries, such as, internal carotid artery and middle cerebral artery (MCA) M1 segment demonstrating more significant efficacy for small thromboembolisms occluding second level cerebral arteries. In most stroke patients due to frequent hemorrhagic complications ITT is counter-indicated. In addition, among up-to-date thrombolytic agents approved by health authorities only intravenous recombinant tissue plasminogen activator (rt-PA) is used as a systemic one. Due to frequent hemorrhagic complications streptokinase, urokinase (UK) and prourokinase (r-proUK) are not preferred (Multicentre Acute Stroke Trial - Italy (Mast-I) Group, 1995; Multicentre Acute Stroke Trial - Europe Study Group, 1996; Yasak, Chambers, Davis, and Donnan, 1998).

Selective intra-arterial thrombolytic therapy (IATT) with various thrombolytic agents is considered promising. According to some authors (Suslina, 1997; Furlan, 1999; Hacke et al., 1998) among its advantages high efficacy in recanalization of the occluded vessel (up to 80%), expediency for large artery occlusions and considerably less amount of
thrombolytic resulting in reduction of hemorrhagic ITT complications (Furlan, Higashida, Wechsler et al., 1999) can be enumerated.

We have performed the clinical trial to demonstrate efficacy and safety of IATT with streptokinase as a thrombolytic agent in ischemic stroke patients hospitalized at the Republican Research Center of Emergency Medicine (Tashkent, Uzbekistan).

**Materials and methods**

During the study period 22 ischemic stroke patients (12 males among them) were hospitalized at the Republican Research Center of Emergency Medicine within 6-hour treatment window. The age range was 22 to 85 years. According to clinical neurologic symptoms acute cerebrovascular event (ACE) in MCA basin in the right and left hemispheres was diagnosed in 14 and 7 patients, respectively, ACE in the posterior circulation system (vertebrobasilar basin) being registered in one. At admission all patients were taken for multidetector computed tomography (MDCT) with Brilliance 40-slice, CT Scanner (Philips, Netherlands). Ischemic stroke subtype was determined by means of color duplex sonography (CDS) on EUB-600 (Hitachi, Japan) with a 7.5 Hz transducer. Cerebral blood flow was assessed by clinical routine transcranial Doppler (TCD) ultrasound examination on MT-1010 apparatus (Mindray, China) with a 2 MHz transducer via temporal acoustic window. Sonoline-Omnia, a digital ultrasound system with 2-D, color flow, and Doppler imaging modes (Siemens, Germany) completed with a 4.0 MHz transducer was used to perform echocardiography. Fully automatic microprocessor-controlled contrast medium injector Angiomat (Illumena, Germany) with volume, flow and time control for intravenous bolus administration of 80-120 ml of an X-ray contrast medium (ultravist or omnipak) in the concentration of 300-350 mg/ml at the rate of 3.0-4.5 ml/s was used to accomplish MDCT angiography on Brilliance 40-slice, CT Scanner (Philips, Netherlands). The data was processed by means of the EBW (Extended Brilliance Workspace) platform (Philips, Netherlands). Philips Allura Xper FD20 fixed X-ray system was used to conduct cerebral angiography and IATT following common femoral artery puncture by Seldinger technique. Proximal internal carotid and vertebral arteries were catheterized by introducers and INFINITI, 5F diagnostic catheters (Cordis Inc., USA) to inject omnipak 300-350, a non-ionic X-ray contrast medium, (Nycomed, Switzerland) manually with 10-ml syringe. Upon digital subtraction angiography (DSA) standard, that is, anterior- posterior and lateral, images in most cases were usually taken at 2 - 3 frames per second, to involve arterial, parenchymal and venous phases. If necessary, additional series in various projections were taken. The angiographic findings were processed on Xcelera, an integrated multi-modality image management system for cardiovascular information (Philips, the Netherlands) to be jointly analyzed by an interventionalist, specialized in radiology, and a neuropathologist. In the patients eligible for IATT, the diagnostic catheter was substituted by the guide one (Envoy 5Fr, Cordis Inc., USA). Controlled by Roadmapping option Cordis microcatheter Prowler 10 by means of a micro-guide was navigated to the occluded area for 50,000 U of streptokinase bolus to be infused for 30 minutes. Following control angiography 30-minute infusion of 200,000 U of streptokinase was performed. The patients for thrombolytic therapy were selected in compliance with recommendations of American Academy of Neurology (European Stroke Initiative Executive Committee and UESI Writing Committee, 2003). To assess IATT efficacy and safety as well as the degree of recanalization by means of NIHSS scale the patients’ neurological status was monitored with the control cerebral MDCT, MDCT angiography and TCD in 2-3 days after the procedure.

**Results**

All patients were hospitalized at the Republican Research Center of Emergency Medicine within 6 hour interval starting from the onset of symptoms; the admission CT registered no organic changes in the brain to confirm the fact. Color duplex sonography (CDS), clinical routine transcranial Doppler (TCD) ultrasound examination and echocardiography
were used to diagnose atherothrombotic stroke in 16 patients. Thus, CDS demonstrated signs of atherosclerotic disease of major arteries of head with various degree of stenosis. TCD at admission revealed hemodynamically significant reduction of linear blood flow velocity in MCA on the side of occlusion, coefficient of interhemispheric asymmetry exceeding 50%. Cardioembolic subtype of stroke was diagnosed and confirmed by ECG and echocardiography in 6 patients. In one of them ischemic stroke was secondary to arrhythmic ischemic heart disease, in 5 it was related with various cardiac failures, such as, congenital heart disease (n=1), cardiac myxoma (n=1), cyanotic CHD with atrial fibrillation like heart rhythm disorder (n=3). Cerebral angiography established acute MCA occlusions in all cases (Figures 1-A, 2-A).

As to the time to treatment, that is, the interval between the onset of ACE symptoms and inter-arterial thrombolytic therapy it was up to 180 minutes in 3 patients, ranging from 181 to 240 minutes in 5, from 241 to 300 minutes in 5, from 301 to 360 minutes in 7 patients, exceeding 360 minutes in 2 patients.

Post-IATT control cerebral MDCT, MDCT angiography and TCD demonstrated complete, partial and absent MCA recanalization in 5, 11 and 7 patients, respectively (Figures 1-B, 2-B).

IATT efficacy assessment demonstrated improvement in mean parameters, that is, an increase from 11.45 to 13.0 scores in Glasgow Coma Scale, a decrease from 14.45 to 8.86 scores in NIHSS and a decrease from 4.36 to 2.86 scores in Rankin Scale. Complete and partial improvement of neurological symptoms could be observed in 5 (22.7%) and 11 (50%) patients, respectively, no effect being registered in 6 (27.3%).

The repeated CT demonstrated no organic changes of the brain in 5 patients indicating resolution of ischemic processes due to well-timed early MCA recanalization. Clinically it corresponds to complete resolution of neurological symptoms (Figure 3).
**Figure 2.** Cerebral angiogram of a male 54-year old patient present with acute cerebrovascular event of cardioembolic subtype in MCA carotid basin in the left hemisphere, (A) pre-IATT, (B) post-IATT (an arrow indicates occluded and recanalized MCA).

![Image of cerebral angiogram](image)

**Figure 3.** (A) Pre-IATT brain CT scan of a male 61-year old patient present with acute ischemic cerebrovascular event in the left hemisphere MCA basin.

![Image of brain CT scan](image)
The repeated CT revealed formation of small ischemic foci in the terminal MCA branches in 10 patients only, probably, due to main stem recanalization and occlusion of MCA terminal branches by fragments of the dissolved thrombus. Clinically it corresponds to significant improvement of neurological deficit (Figure 4).
FIGURE 4. (B) BRAIN CT SCAN OF THE SAME PERSON ON THE 3RD DAY AFTER IATT

FIGURE 5. BRAIN CT SCAN OF A MALE 22-YEAR OLD PATIENT PRESENT WITH ACUTE ISCHEMIC CEREBROVASCULAR EVENT IN THE RIGHT HEMISPHERE MCA BASIN, (A) PRE-IATT, (B) POST-IATT (AN ARROW INDICATES A HYPERDENSE (+45 HOUNSFIELD UNITS) 45 X 19 MM AREA
The repeated CT demonstrated no post-IATT effect in 6 patients present with major ischemic focus occupying the whole MCA basin vascularization. Hemorrhagic transformation of the focus was observed in 3 patients (13.6%) to be asymptomatic in all of them and present as small asymptomatic perdiapedetic and parenchymal hematomas with volume up to 5 cm³ (Figures 5, 6).

Among 6 patients with no recanalization there were 3 deaths attributed to extensive ischemic focus occupying the whole MCA vascularization area as well as to somatic worsening due to post-stroke pneumonia, acute coronary syndrome and pulmonary edema.

Thus, the findings above demonstrate high efficacy of IATT and high degree of MCA recanalization (72.7%, P<0.02), in acute stroke patients. Early thrombolytic recanalization within treatment window resulted in complete or significant neurological improvement in this category of patients.

**Conclusion**

Inter-arterial thrombolytic therapy with streptokinase as a thrombolytic agent is an efficient and comparatively safe method for recanalization of occluded vessel in ischemic stroke patients;

Inter-arterial thrombolytic therapy in ischemic stroke patients is an efficient and safe method within 6-hour treatment window, the highest efficiency observed within 3-hour range.

Asymptomatic perdiapedetic or parenchymal hemorrhagic transformation can be considered as a marker for efficient thrombolysis.
References


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