Signature: © Pol J Radiol, 2008; 73(4): 7-11

Polish Journal of Radiology
www.PolRadiol.com
ORIGINAL ARTICLE

Received: 2008.06.25
Accepted: 2008.10.27

Intra-arterial thrombolytic therapy in the acute ischemic stroke

Wojciech Poncyljusz[1], Aleksander Falkowski[2], Ewa Cebula[3], Leszek Sagan[4], Dariusz Jeżewski[4], Krzysztof Rzewuski[4], Monika Rać[5], Anna Walecka[1], Ireneusz Kojder[4]

[1] Department of Imaging Diagnostics and Surgical Radiology, PMU, Szczecin, Poland
[2] Department of General Diagnostics and Dental Radiology, PMU, Szczecin, Poland
[3] Department of Neurology with Intensive Neurological Care, Long-term Care and Postoperative Rehabilitation Subunit of the Ministry of Internal Affairs and Administration Hospital in Szczecin, Szczecin, Poland
[4] Department of Adult and Pediatric Neurosurgery, PMU, Szczecin, Poland
[5] Department of Biochemistry, Chair of Biochemistry and Medical Chemistry, PMU, Szczecin, Poland

Author's address: Wojciech Poncyljusz, Department of Imaging Diagnostics and Surgical Radiology, PMU, Unii Lubelskiej 1, 71-252 Szczecin, Poland, e-mail: wponcyl@poczta.onet.pl

Summary

Background: To evaluate the clinical efficacy and safety of local intra-arterial thrombolysis with rt-Pa in patients suffering from MCA acute brain infarction within 6 hours of the onset of symptoms

Material/Methods: Forty one patients with acute ischemic stroke of the middle cerebral artery (MCA) were qualified to the treatment (up to 6 hours after the beginning of the symptoms). Patient qualification was based on clinical examination, computed tomography (CT) and digital subtraction angiography (DSA). CT follow-up was performed after 24 hours and between 7–10 days. Continuous infusion of rt-Pa with a final dose of 40mg was administered. The patients were evaluated before, at discharge and 90 days after the procedure on the basis of modified Rankin and NIHSS scores.

Results: At the primary outcome, 22 (53%) of the patients achieved modified Rankin scores of 2 or less after 90 days. The secondary clinical outcome at 90 day follow-up: (NIHSS score ≤1) – 9 (22%) of the patients, (NIHSS score ≥50% decrease) – 24 (59%). A rate of recanalization was achieved in 76% of patients. Symptomatic hemorrhages occurred in 4 (10%). There were no deaths in the treated group after thrombolysis up to the time of discharge; however, the mortality during the 90-day follow-up period was 7%.

Conclusions: Intra-arterial thrombolysis with the use of rt-Pa, in the treatment of ischemic brain stroke within 6 hours after the onset considerably improved the clinical condition of patients after 90 days.

Key words: local intra-arterial thrombolysis • acute ischemic stroke

PDF file: http://www.polradiol.com/fulltxt.php?ICID=874000

Background

Cerabral stroke is an important clinical problem because of high incidence and long-term impact on the subjects' health. It is the third most common cause of mortality worldwide, after cardiovascular diseases and cancers, and the most frequent cause of permanent disability in patients above 40 years of age [1].

The literature describes a possibility of treatment of ischemic stroke with intravenous and intra-arterial fibrinolysis [2–3]. Intra-arterial thrombolysis is usually localized and can be combined with mechanical thrombectomy [4–16]. In clinical studies, anticoagulants were administered alone or in combination with fibrinolytic agents [17–19]. Because of controversial character of this method, as well as numerous diagnostic and therapeutic standards, this area is still being studied.

There are also problems with accurate prognosis before the institution of therapy using this method, based on modern imaging techniques – MR and CT, and estimation of clinical benefits for the patient associated with such procedures [20–26]. Fibrinolytic treatment of early ischemic stroke is currently available mainly in academic centers of Europe and USA, which have surgical neuroradiology and radiology teams. The benefits associated with this technique are more and more appreciated and it is gaining increasing acceptance [27].

The aim of the study was to assess the clinical efficacy and safety of local intracerebral fibrinolysis using recombinant tissue-type plasminogen activator (Actilyse-Boehringer Ingelheim) in patients with cerebral stroke in the area supplied by the middle cerebral artery within the 6-hour therapeutic window.

Material and Method

Between 2004 and 2007, forty one patients (26 women and 15 men) qualified because of early ischemic stroke (within 6 hours of the onset of symptoms) underwent local cerebral intra-arterial fibrinolysis procedures. The mean time elepsed between the onset of symptoms and the institution of treatment was 5.4 hours (range 1.5–6). The preliminary clinical qualification was performed by 2 neurologists familiar with the qualification criteria for fibrinolysis with rt-PA according to NIHSS. Additionally, the patients underwent laboratory tests: complete blood count with platelets, INR, APTT, ionogram, blood pressure and electrocardiography. After preliminary clinical qualification, the patients underwent multislice computed tomography of the brain, and from 2007 also perfusion CT. Tomography was performed to exclude intracerebral hemorrhage and to visualize the early symtoms of ischemic stroke providing contraindications for intra-arterial fibrinolysis.

After preliminary qualification based on neurological examination and CT, the patients were subjected to digital subtraction angiography (DSA), which allowed to make the ultimate decision concerning treatment or excludion from the study. Contraindications included NIHSS scores exceeding 30, coma, rapid improvement of neurological signs before the administration of the fibrinolytic drug, history of stroke within the preceding six weeks, seizures on admission, recent or past intracranial hemorrhage, suspected subarachnoid hemorrhage (SAH), a tumor, bacterial embolism, suspected lacunar stroke, a surgical procedure **within 30 days**, organic biopsy **within 30 days**, a trauma with internal injuries or lumbar puncture **within 30 days**, a head injury **within 90 days**, active bleeding or bleeding **within 30 days**, international normalized prothrombin time index (INR) higher than 1.7, partial thromboplastin activation time (APTT) exceeding 1.5-fold the normal value, platelet count lower than 100×10^9/L ($100\times10'$/pL), sensitivity to the contrast medium, arterial blood pressure higher than 185 mmHg with diastolic pressure exceeding 110 mmHg, measured 3 times at 10 min intervals, or requiring continuous intravenous infusion at 10 min intervals, or requiring continuous intravenous infusion.

Contraindications for intra-arterial fibrinolysis (IAF) detectable by CT included: brain tumors, intracerebral hemorrhages, considerable mass effect with displacement of midline structures, a new stroke area visualized as a hypodense focus, or obscured sulcus pattern on over 1/3 of the area supplied by the MCA (European Cooperative Acute Stroke Study criteria).

Contraindications for IAF after angiografphy included: delamination of the artery, arterial stenosis threatening safe microcatheter passage, non-atheromatous arteriopathy, invisible occlusiion.

Patients meeting the qualification criteria underwent the procedure performed by an intervention radiologist. In order to approach the thrombus site, a coaxial system with a guide tube with a 1.9 F microcatheter concentrically inserted on a steered microprobe 0.012″; under Road Map Digital System control. The microcatheter and the microprobe were introduced through the whole thrombosed segment, then partial fragmentation of the thrombus with the microprobe was performed, followed by injecting the thrombus with rt-Pa, starting fubrinolysis from its distal portion. Then the microcatheter was progressively shifted to the remaining part of the occluded artery. Intra- and postoperatively, control angiography was used to monitor the progress of the procedure. Patients treated with mechanical removal of the thrombus using Catch system (Balton) were excluded from the study. The procedure was usually unsuccessful if no progress in recanalization of the artery was obtained within 1 hour. Tissue-type plasminogen activator in the maximum dose of 40 mg was always used for recanalization. A 2000 U heparin bolus (Polfa Tarchomin) reducing thr risk of re-clotting and microembolization and early arterial occlusion at the site of fibrinolysis was administered. Control CT was performed after the first 24 h and then between days 7 and 10 after fibrinolysis. Blood flow in the vessel that had undergone recanalization was assessed with modified TIMI (thrombolysis in myocardial infarction) scale, primarily used for assessment of coronary blood flow, where TIMI 0 indicates blood vessel impatency, no flow (contrast enhancement) on DSA, TIMI 1 – significantly impaired flow, partial contrast enhancement of the blood vessel distally to the stenosis site, TIMI 2 – complete contrast enhancement with decelerated blood flow, TIMI 3 – normal flow. Recanalization was classified as complete (TIMI3) if blood flow in M1 and M2 segments of the MCA was demonstrated; as partial (TIMI2) if blood flow was detected in any previously occluded branch of the MCA. Clinical assessment based on modified Rankin and NIHSS scales was carried out before and on the day preceding the discharge, and 90 days after the procedure. Scores ≤2 achieved by the patient 90 days after fibrinolysis were regarded as primary clinical outcome. The average baseline stroke severity assessed by NIHSS before the procedure was 15. Secondary clinical outcome was defined by the following criteria: NIHSS ≤ on control examination after 90 days, recanalization detectable with DSA. Additional assessed parameters included clinical deterioration (including intracerebral hemorrhage) and mortality.

Results

Primary clinical outcome of ≤2 assessed with modified Rankin scale after 90 days was achieved by 22 (53%) of patients. Secondary clinical outcome assessed on the basis of NIHSS after 90 days of ≤1 was demonstrated in 9 patients (22%), NIHSS reduction by ≥50% was observed in 24 (59%)

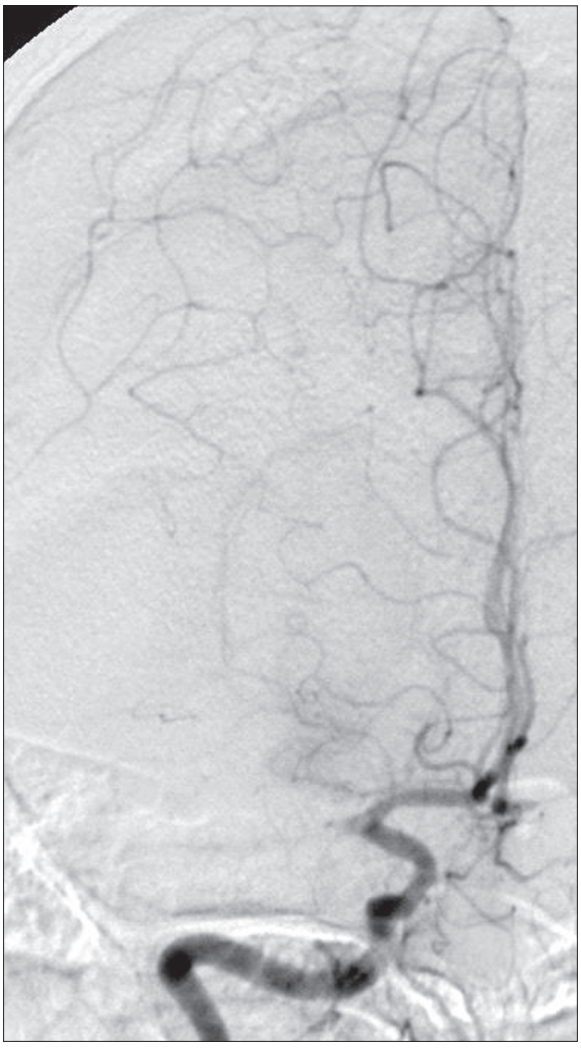

Figure 1. Angiography of the cerebral arteries in a 42-year-old patient with left-sided hemiparesis due to ischemic stroke. DSA (anterior projection, contrast administration to the right intermal carotid artery) confirms occlusion within the right MCA. Local administration of rt-PA to the thrombus through a microcatheter was started.

of patients. A relatively high MCA recanalization rate (TIMI 2 and 3) was obtained in 31 patients (76%). Mean time elepsed until recanalization was achieved was 81 minutes and ranged from 64 to 91 minutes. It was also demonstrated that the success of recanalization was dependent on the type of occlusion. The best clinical outcomes after fibrinolysis were observed in the middle and distal segments of the MCA. Among 5 complete MCA occlusions, recznalization was successful in 2 patients only (Figures 1,2). Intracranial hemorrhage occurred in 4 (10%). One patient underwent craniotomy because of the development of a hematoma. No deaths had been noted by the time of discharge, but after 90 days information concerning deaths of 3 patients (7%) was obtained.

Discussion

Intensive treatment of cerebral stroke, especially at the initial stage of the disease, is essential for reduction of its consequences and related mortality.

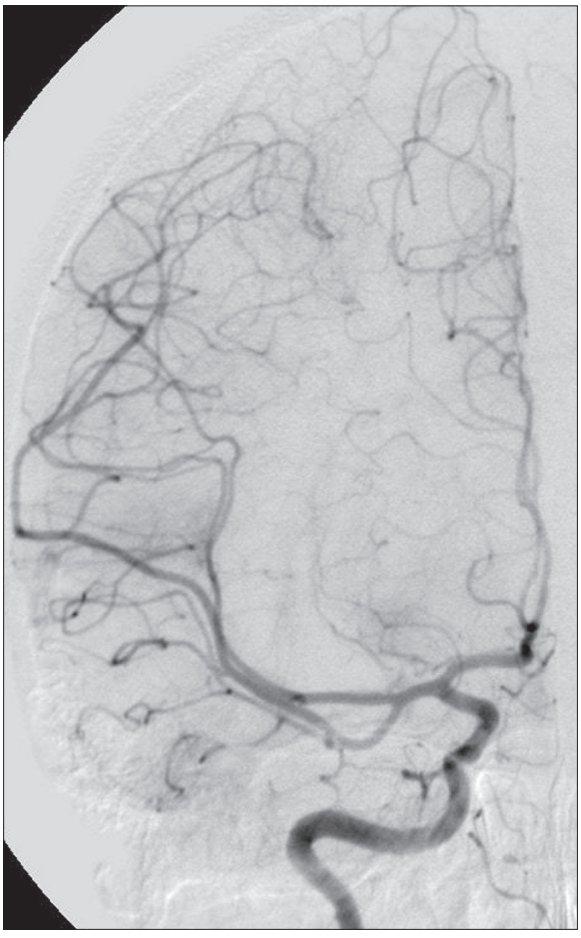

Figure 2. Control DSA demonstrated complete thrombolysis and normal flow within the MCA.

The literature includes studies concerning the treatment of early-stage cerebral stroke patients with intravenous and/or intra-arterial fibrinolysis. However, no clinical trials have compared both these methods of treatment yet. On the basis of currently available literature, intra-arterial fibrinolysis is considered to accelerate markedly recanalization of the cerebral arteries in comparison with intravenous fibrinolysis [3,6,7,9,10]. Despite the acceptance of intra-arterial fibrinolysis in the treatment of arterial occlusions due to stroke affecting the anterior cerebral circulation on the basis of PROACT I and II, it was not widely accepted in Europe because of the failures of European studies [7,9]. The therapeutic window for the anterior cerebral circulation is 6 h, but some authors, especially those using mechanical recanalization techniques, extends it to 8 h [13,15,22,28].

The presented study concerns the patients treated for strokes in the area supplied by the CMA with average TPA. In order to obtain a uniform group, „T-type" occlusions of the terminal portions of the internal carotid artery were not taken into consideration in this work because of a different course. Also the patients treated with local intra-arterial fibrinolysis combined with mechanical thrombectomy were excluded.

As we observed in our study, the recovery of patients with occlusions of the distal and/or medial branches of

the middle cerebral artery was better than in those with complete occlusion of the middle cerebral artery trunk. It is also known from the literature that recanalization is largely dependent on the type of occlusion and the method of treatment; however, the clinical condition of the patient obtained as a result of the therapy is difficult to predict [3,8].

In the present study, the patients were treated with rt-PA, in contrast to two large clinical studies PROACT I and PROACT II, using r-proUK. The recanalization rate in PROACT I reached 58% and was dependent on the administered heparin dose, but in the group of patients who received larger doses, intracerebral hemorrhages were observed in 27% of cases [7].

The PROACT II study used partially modified criteria and reduced heparin doses, obtaining 66% recanalization rate and 10% intracerebral hemorrhage rate [9].

In our research, in which the arterial occlusion type and the patients' condition was more similar to that in PROACT II, we demonstrated 76% recanalization rate with 10% intracerebral hemorrhage rate. Higher recanalization rate in comparison with PROACT II may be associated with a different fibrinolytic agent used in our study. Also the effect of thrombus injection through a microcatheter and its partial fragmentation with a microprobe may have played a role. Lower incidence of hemorrhages than in PROACT I, where the patients received 5000 U heparin, should be associated with a lower dose used in this study.

A study by Eckert et al, investigating the largest group of patients treated with local intra-arterial fibrinolysis in the anterior cerebral circulation area, included, according to the adopted criteria, no baseline clinical assessment of the patients before treatment [8]. The study demonstrated that in proximal type MCA occlusions the recanalization rates ranging from 50 to 80% in the group treated with high doses of rt-PA and rt-PA with lys-plasminogen. In the group receiving high rt-PA doses, CT demonstrated the traces of bleeding in 43% of patients and intracerebral hematomas in 5%; such a situation may have been associated with the use of specific heparin doses and hads been described before in PROACT I [7]. In another clinical study, Arnold et al, treating patients with early cerebral stroke associated with the MCA with urokinase, documented good clinical results in 59% of patients with occlusions in M_1 and M_2 segments, and 95% among those with occlusions in M_3 and M_4 ones, whereas symptomatic hemorrhages occurred in 7% of patients. The fact that most patients received 250–500 mg doses of aspirin instead of heparin is notable [3]. On the basis of the literature, it can be concluded that most intracerebral hematomas observed in patients treated with intra-arterial fibrinolysis were associated with more severe clinicsl condition, longer time between the onset of stroke and the institution of treatment, or differences in the doses and types of drugs. Some papers did not demonstrate any statistical correlation between recanalization of the artery and the risk of hemorrhage at the reperfusion site [14,16]. This was also the case in the present study.

The literature describes a few attempts to combine intravenous thrombolysis with tirofiban with mechanical thrombectomy and application of urokinase. However, this technique cannot be used on a larger scale until clinical studies enrolling a large cohort of patients are completed [18,19]. The remaining studies concerned with mechanical thrombectomy seem to be very promising, because in 30% of patients the arterial thrombus can be removed immediately and the recanalization rate, compared with local intra-arterial fibrinolysis, reaches 88% [24].

Additionally, in some patients, no complications in the form of intracerebral hemorrhages were observed [25]. The MERCI clinical study, using a special device for mechanical thrombectomy, noted only 46% of recanalizations (69/151) [13]. Additional administration of fibrinolytic agents increased the recanalization rate to 60% [13]. After improvement of the thrombectome used in the MERCI study, the recanalization rate increased to 57.3% (75/131), and eventually, in combinationm with a fibrinolytic agent, to 69.5% (91/131) [15]. Mechanical thrombectomy potentially reduces the time of arterial flow restoration and improves the recanalization rate in comparison with local intraarterial fibrinolysis. The latest studies of mechanical thrombectomy in cases of ischemic stroke indicate the possibility of recanalization of the infarct. However, the differences in design of these clinical studies make it impossible to compare different methods of treatment [15]. Continuation of the research is necessary to assess the role of this technique. The published clinical studies demonstrate that ischemic stroke should be treated as early as possible. Despite considerable knowledge of this area, there are still numerous questions which cannot be answered unequivocally. How should the residual thrombus remaining in the artery after local fibrinolysis be treated? Some neuroradiologists consider angioplasty to be the best solution in such situations when fibrinolysis alone is not successful [28]. There are also no explanations concerning the management of distal embolism, recurrence of the occlusion or stenosis during fibrinolysis. Other clinical studies, demonstrating the correlations between the successful outcome of fibrinolysis and the thrombus structure, are needed.

The presented study indicates that local intra-arterial fibrinolysis can be a relatively safe and effective method of treatment in stroke patients with middle cerebral artery occlusion.

Local intra-arterial fibrinolysis using rt-Pa at the early stages of ischemic stroke (within six hours from the onset of symptoms) can improve significantly the patients' clinical condition assessed after 90 days.

References:

1. American Heart Association. Heart and Stroke Facts Statistics: 1999 Statistical Supplement. Dallas, Tex: American Heart Association, 1999
2. Albers GW, Clark WM, Madden KP et al: ATLANTIS trial: results for patients treated within 3 hours of stroke onset: alteplase thrombolysis for acute noninterventional therapy in ischemic stroke. Stroke, 2002; 33: 493–96

3. Arnold M, Schroth G, Nedeltchev K et al: Intra-Arterial Thrombolysis in 100 Patients With Acute Stroke Due to Middle Cerebral Artery Occlusion. Stroke, 2002; 33: 1828–33
4. Berlis A, Lutsep H, Barnwell S et al: Mechanical Thrombolysis in Acute Ischemic Stroke with Endovascular Photoacoustic Recanalization. Stroke, 2004; 35: 1112–16
5. Clark WM, Albers GW, Madden KP et al: The rt-PA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study: thrombolytic therapy in acute ischemic stroke study investigators. Stroke, 2000; 31: 811–16
6. Clark WM, Wissman S, Albers GW et al: Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset: the ATLANTIS study: a randomized controlled trial: alteplase thrombolysis for acute noninterventional therapy in ischemic stroke. JAMA, 1999; 282: 2019–26
7. del Zoppo GJ, Higashida RT, Furlan AJ et al: PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke: PROACT Investigators: prolyse in acute cerebral thromboembolism. Stroke, 1998; 29: 4–11
8. Eckert B, Kuciński T, Neumaier-Probst E et al: Local intra-arterial fibrinolysis in acute hemispheric stroke: effect of occlusion type and fibrinolytic agent on recanalisation success and neurological outcome. Cerebrovasc Dis, 2003; 15: 258–63
9. Furlan AJ, Higashida R, Wechsler L et al: Intra-arterial prourokinase for acute ischemic stroke: the PROACT II study: a randomized controlled trial. JAMA, 1999; 282: 2003–11
10. Hacke W, Kaste M, Fieschi C et al: Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II): Second European-Australasian Acute Stroke Study Investigators. Lancet, 1998; 352: 1245–51
11. Higashida RT, Cullen SP, Malek R et al: Intraarterial Thrombolysis Trials in Acute Ischemic Stroke. J Vasc Interv Radiol, 2004; 15: 77–85
12. Lewandowski C, Frankel M, Tomsick T et al: The EMS Bridging Trial Investigators. Combined intravenous and intra-arterial r-rt-Pa versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial. Stroke, 1999; 30: 2598–605
13. Smith WS, Sung G, Starkman S et al: Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. Stroke, 2005; 36: 1432–38
14. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med, 1995; 333: 1581–87
15. Smith WS, Sung G, Saver J et al: Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. Stroke, 2008; 39(4): 1205–12
16. Poncyljusz W, Falkowski A, Kojder I et al: Treatment of acute ischemic brain infarction with the assistance of local intraarterial thrombolysis with recombinant tissue-type plasminogen activator. Acta Radiol, 2007; 48(7): 774–80
17. Adams HP Jr: Emergent Use of Anticoagulation for Treatment of Patients with Ischemic Stroke. Stroke, 2002; 33: 856–61
18. Mangiafico S, Cellerini M, Nencini P et al: Intravenous Glycoprotein IIb/IIIa Inhibitor (Tirofiban) followed by Intra-Arterial Urokinase and Mechanical Thrombolysis in Stroke. Am J Neuroradiol, 2005; 26: 2595–601
19. Mangiafico S, Cellerini M, Nencini P et al: Intravenous Tirofiban With Intra-Arterial Urokinase and Mechanical Thrombolysis in Stroke: Preliminary Experience in 11 Cases. Stroke, 2005; 36: 2154–58
20. Higashida RT, Furlan AJ, Roberts H et al: Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke, 2003; 34: 109–37
21. Oppenheim C, Naggara O, Arquizan C et al: MRI of acute ischemic stroke. J Radiol, 2005; 86: 1069–78
22. Randall T, Higashida RT, Furlan AJ: Trial Design and Reporting Standards for Intra-Arterial Cerebral Thrombolysis for Acute Ischemic Stroke. Stroke, 2003; 34: 1923–24
23. Röther J, Schellinger P, Gass A et al: Effect of intravenous thrombolysis on MRI parameters and functional outcome in acute stroke <6 h. Stroke, 2002; 33: 2438–45
24. Noser EA, Shaltoni HM, Hall CE et al: Campbell III Aggressive Mechanical Clot Disruption: A Safe Adjunct to Thrombolytic Therapy in Acute Stroke? Stroke, 2005; 36: 292–96
25. Wintermark M: Brain perfusion-CT in acute stroke patients. Eur Radiol, 2005; 15(Suppl.4): D28–31
26. Albers GW: Expanding the time window for thrombolytic therapy in acute stroke. The potential MRI trial role of acute MRI for patient selection. Stroke, 1999; 30: 2230–37
27. Poncyljusz W, Cyryłowski L, Sagan L: Local Intra-arterial fibrinolysis in a treatment of the acute ischemic stroke. Pol J Radiol, 2003; 68(4): 90–97
28. Ringer AJ, Qureshi AI, Fessler RD et al: Angioplasty for intracranial occlusion resistant to thrombolysis in acute ischemic stroke. Neurosurgery, 2001; 48: 1282–88