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APPLICATION OF SELECTIVE THROMBOLYTIC THERAPY FOR ISCHEMIC STROKE TREATMENT

Igor B. Kovalenko*, Zhanna Yu. Chefranova, Nadezhda S. Zueva, Vyacheslav D. Polyansky,
Belgorod State University 85 Pobeda St., Belgorod, 308015, Russia

Abstract:
The article deals with the review and analysis of the major study related to both applications of STLT and that compared to systemic thrombolysis which demonstrate good functional results after 90 days of STLT application and less number of intracranial hemorrhage during 24 hours.
The comparative analysis of the outcomes of ischemic stroke treatment based on systemic and selective thrombolysis by Actilyse was conducted in Belgorod Regional Clinical Hospital.
The procedure of selective thrombolysis was described. The analysis of the effectiveness and complications depending on medication dose and deterioration and thrombolysis period after initial neurological symptoms was conducted. The obtained results proved case fatality decrement and neurological symptoms amendment with patients after endovascular therapy.
Key words: *ischemic stroke, selective thrombolysis, hemorrhagic conversion, systemic thrombolysis*.

Corresponding author:
Igor B. Kovalenko,
Belgorod State University 85 Pobeda St.,
Belgorod, 308015, Russia
igor-kovalenko@mail.ru

QR code

The objective: *improvement of treatment results in case of patients with acute ischemic stroke (AIS) based on the comparison of two treatment methods.*

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INTRODUCTION:

Cerebral vascular diseases are the recent medical and social problem. High case fatality, death rate and disability are registered as the result of stokes [1-3]. Acute cerebrovascular disorders are one of the reasons of permanent disability of people in the world [4]. Having proved good treatment outcomes endovascular technologies are actively used for acute ischemic stroke treatment. Application of systemic thrombolytic therapy for proximal segments deterioration of middle cerebral artery has been proved effective by 13-18%, by 23% - in case of major arteries occlusion (internal carotid artery, vertebral artery, basilar artery) [5].

Application of intra-arterial thrombolysis resulted in recanalization in 60-70% of cases [6]. Three major studies have been conducted proving the effectiveness of selective thrombolytic therapy (STLT): PROACT I, PROACT II, MELT. The thrombolytic used in the study PROACT I и PROACT II – recombinant prourokinase (r-proUK, 6 mg in PROACT I and 9 mg in PROACT II).

Half of the thrombilytic was dosed into the proximal part of thrombus within one hour; in case the thrombus was lysed after one hour, the catheter was moved further into the thrombus, another half of the dose was introduced. In the two studies conducted the heparin was introduced alongside with thrombolysis.

In PROACT I the heparine dose was high: 100 U/kg of bolus dosing and then 1000 U/phr, later bolus dosing decreased to 2000, then 500 U/phr within 4 hours. Due to the high level of hemorrhage complications a reduced dose of heparine was introduced in ROACT II.

In MELT – the Japanese study, urokinase was used. The medication was introduced gradually in the distal part of thrombus either within 2 hours or before recanalization.

The same study also involved mechanical thrombus disruption by micro-guidewire which was impossible in the first two studies. The 5000 U of heparine was single dosed only before the operation [7].

In ROACT study patients with maximum 30 NIAHSS grade were involved, in MELT study – with the grade not exceeding 22. In PROACT study successful revascularization was defined as total recanalization (TIMI 3) in M1 segment and in all branch vessels of M2 segment; partial revascularization was defined as partial or total recanalization (TIMI 2 or 3) in M1 segment and in all branch vessels of M2 segment or TIMI 2 in one branch vessel.

In MELT study successful revascularization – reperfusion of all diseased segments including distal segments: 1. partial reperfusion by <50%, 2. partial reperfusion by ≥50%, 3. total reperfusion.

Table 1: Clinical outcomes.

First Author (Year)	Comparison	Favorable outcome, [a] %	Neurological deterioration, [b] %	Recanalization (TIMI 2+3), %	Intracranial hemorrhage, %	Mortality, %
Ciccone A (2013)	IAT vs. IVT	30.4 vs. 34.8	9 vs. 7	NA	6 vs. 6 (7 d) [§]	8 vs. 6 (day 7) 14.4 vs. 9.9 (day 90)
Ciccone A (2010)	IAT vs. IVT	56 vs. 31	0 vs. 4	NA	8 vs. 14 (7 d) [§]	20 vs. 14 (day 7)
Zhang B (2010)	IAT vs. IVT	82.6 vs. 56.4 [*]	NA	82.6 vs. NA	8.7 vs. 9.1 [§] 30.4 vs. 12.7	8.7 vs. 16.4 (day 90)
Sen S (2009)	IAT vs. IVT	NA	NA	100 vs. 0 [*]	0 vs. 25 (24 hrs) [§] 33 vs. 25 (24 hrs)	NA
Mattle HP (2008)	IAT vs. IVT	53 vs. 23 [*]	NA	71 vs. NA	1.8 vs. 0	7 vs. 23 (day 90)[*]
Ducrocq X (2005)	IAT vs. IVT	46 vs. 29	NA	All: 15	15 vs. 0 [§]	23 vs. 29 (day 90)
Furlan A (1999)	IAT vs. IVT	40 vs. 25 [*]	NA	66 vs. 18 (2hr)[*]	10 vs. 2 (24 hrs)	25 vs. 27 (day 90)
Lewandowski CA (1999)	IAT vs. IVT	47 vs. 67	NA	82 vs. 50 (2hr)	0 vs. 5.5 (24 hrs) [§] 11.8 vs. 5.5 (72 hrs) [§]	29 vs. 5.5 (day 90)

NA: not available; IAT: intra-arterial thrombolysis; IVT: intravenous thrombolysis; tPA: tissue plasminogen activator; TIMI: Thrombolysis In Myocardial Infarction

[a]*Favorable outcome was defined as a modified Rankin Scale score of 0 to 2 at 90 days after stroke.*

[b]*Neurological deterioration was defined as an NIHSS score ≥ 4 points on day 7.*

[*], P *value < 0.05. §, symptomatic intracranial hemorrhage.*

[§], *symptomatic intracranial hemorrhage.*

Application of selective thrombolytic therapy has a positive impact on development of symptomatic intracranial haemorrhage in the first 24 hours, functional outcome (mRS ≤2) [8]. There exist the data that selective thrombolysis, if compared to systemic thrombolysis, is more effective with the patients suffering from major artery occlusions who were admitted to hospital within 3 hours [9]. Systemic thrombolytic therapy applied with recombination tissue plasminogen activator (rt-PA) which is considered to be a standard treatment according to recommendations of European Stroke Organization (ESO) and American Heart Association and Stroke Association (AHA/ASA) is prescribed to patients in the first 4.5 hours after the initial neurological symptoms manifestation [10]. The time span of 4.5 till 6 hours is defined for selective thrombolytic therapy. As various studies proved, selective thrombolytic therapy can be an alternative for systemic thrombolysis (Table 1) [11].

Actilyse ® - recombinated human plasminogen tissue activator, glycoprotein which directly activates transformation of plasminogen into plasmin. The active substance is alteplase. After introduction alteplase remains relatively passive in the systemic blood. It is activated when bind to fibrin that leads to transformation of plasminogen into plasmine and the fibrin clot lysis.

MATERIALS AND METHODS:

Our study involved 110 patients with acute ischemic stroke. In order to define therapeutic approach all patients underwent computed tomography (CT) aiming at detecting ischemic segment, exclusion of cerebral hemorrhage.

Patients with a small ischemic segment (not exceeding 1/3 of the district) and cerebral hemorrhage were moved either to X-ray operation room or to intensive care unit of Neurology Department - CBFAD. All patients were divided into two groups. Group 1 included 54 patients with the average age of 62 who were treated with selective thrombolytic therapy (STLT). Group 2 included 56 patients aged 63 on the average who were treated with systemic thrombolysis. Table 3 specifies the period of selective thrombolytic therapy. STLT was applied by Actilyse ®. The average NIHSS grade upon hospital admittance was 8. According to focalization (Table 2):

Table 2: Deterioration focalization

Artery	Segment	Grade
internal carotid artery	Proximal 1/3 and supraclinoid segment	5
anterior vertebral artery	A2	1
medial vertebral artery	M1	7
	M1-M2	6
	M2	8
	M3-M5	10
vertebral artery, basilar artery, posterior vertebral artery		8
In 9 cases without documented occlusion, but with clinical picture		

Table 3: Period of selective thrombolysis

	Less than 3 hours	3-4 hours	4-5 hours	5-6 hours	> 6 hours
STLT	13	18	12	7	4

Table 4: Effectiveness of selective thrombolysis

	Less than 3 hours	3-4 hours	4-5 hours	5-6 hours	> 6 hours
STLT	40%	69%	75%	40%	50%

Table 5: Effectiveness of thrombolysis depending on the vessel segment

	ICA	M1-M2	M3-M5	ВББ	A2
2b-3	1	12	9	3	1
1-2a	2	4	1	2	0
0-1	1	5	0	3	0

Magistral artery angiography was conducted by femoral approach. Micro-guidewire and micro catheter were introduced through the distal flow. Occlusion recanalization was managed by the micro-guidewire, the micro-guidewire was introduced in the occlusion zone. Distal flow patency was tested by micro-guidewire angiography. Then, in order to prolong the contact of the active substance with fibrin, the thrombus tissue was bolus dosed with 5 mg, 10 mg in front of the thrombus through perfusor during 20 minutes. The medication dose introduced did not exceed 25% of the thrombolytics tolerance dose – 0.9 mg/kg of the patient's weight.

Thus, mechanical clot destruction combined with its lysis was performed. In 9 cases STLT did not demonstrate documented occlusion, but a clinical picture of acute ischemic stroke (6). The average NIHSS grade registered in Group 2 upon hospital admittance amounted to 11. The average period from the initial neurological symptoms manifestation to thrombolytics introduction lasted 2,5 hours. Thrombolysis was based on Actilyse ®. In one case observed the thrombolysis was terminated within the first few minutes due to the patient's sudden condition deterioration – worsening of cerebral symptoms (somnolent, blue lips, bad response to verbal communication, does not follow instructions).

RESULTS AND DISCUSSION:

The effectiveness of endovascular reperfusion therapy was evaluated according to TICI scale (The Thrombolysis in Cerebral Infarction): TICI 0 – the lack of recanalization; TICI 1 – recanalization outside initial occlusion, restricted blood flow in distal branch vessels; TICI 2a – recanalization with partial or delayed blood flow in less than 50% of the district of medial vertebral artery; TICI 2 b – recanalization with partial or delayed blood flow in more than 50% of the district of the medial vertebral artery; TICI 3 – total recanalization with the blood flow in all distal branch vessels of the medial vertebral artery including M3 and M4 segments.

Recanalization after the selective thrombolytic therapy TICI 2b-3 was successful in 57% of cases in Group 1, 1-2a - in 19% of cases, the lack of recanalization – in 17% of cases. The average NIHSS grade upon hospital release amounted to 4. In the postoperative period 6 patients from Group 1 developed hemorrhagic conversion of the ischemic focus in the form of hemorrhagic infarction of ECASS Type 1 and Type 2. The average NIHSS grade upon hospital release in Group 2 amounted to 4. In Group 2 hemorrhagic infarction of ECASS Type 1 and Type 2 were registered with 4 patients. Fatal cases in Group 1 were registered with 5 patients (9%), with 3 of them successful recatalization according to TICI 1-2a was performed. 2 patients after recatalization developed hemorrhagic conversion of the ischemic focus in the form of parenchymatous hematoma of ECASS Type 2. In Group 2 8 patients died (14%). One patient developed hemorrhagic conversion of the ischemic focus in the form of parenchymatous hematoma of ECASS Type 2. One patient had common miocardial infarction. 6 patients developed brain edema and dislocation of brain stem structures, cardiovascular collapse and respiratory failure.

CONCLUSION:

Application of selective and systemic thrombolysis to "a therapeutic window" of ischemic stroke is considered to be an effective method of patients' treatment. However, application of selective thrombolysis allows reducing fatal cases and frequency of fatal hemorrhagic conversion. This is achieved by the reduction of Actalise® dose introduced, mechanical thrombus disruption and partial recanalization during the outcomes establishing. The effectiveness of selective thrombolysis depends on the opening of the deteriorated vessel. During the occlusion of internal carotid artery, the recanalization of TICI 2b-3 was registered in 25% of cases while in case of deterioration of the proximal segments of medial vertebral artery recanalization of TICI 2b-3 was registered in 58% of cases, in case of distal deterioration of medial vertebral artery – in 90% of cases. In the cases when patients lack angiographic symptoms of intra- and extra cranial arteries occlusion and the clinical picture of ischemic stroke is obvious, the selective thrombolysis to "a therapeutic window" for the lysis of microembolus in distal extra cranial artery segments is required.

SUMMARY:

Considering the local impact and minimal medication dosing as well as "mechanical impact" on the thrombus and partial recanalization during instrumental manipulation, STLT has proved to be an effective and safe method of treatment. In case of medical conditions for reperfusion therapy, the selective thrombolysis rather than systemic one should be of choice. If the effectiveness is similar, the number of hemorrhagic complications is less in the group of patients treated with selective thrombolysis.

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