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## Intravenous thrombolysis in acute ischemic stroke – our experience

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**Abstract:** Stroke is a major health problem worldwide and nationally: the second leading cause of death and dementia, the most common cause of epilepsy in the elderly, and a common cause of depression. Stroke is associated with an increased rate of morbidity, but it is also the leading cause of long-term morbidity and disability in industrialized countries. Thrombolysis by administering intravenous recombinant tissue plasminogen activator (IV-rtPA) is the only treatment method "in the therapeutic window" recognized in international protocols. The benefit-risk ratio should be evaluated on a case-by-case basis, with the neurologist's decision being individual and often difficult.

The aim of our study was to analyze the outcome of this procedure in our hospital since 2015. We performed a retrospective clinical study of 77 patients with acute ischemic stroke subjected to IV-rtPA. Most patients with ischemic stroke undergoing intravenous thrombolysis did not receive chronic antithrombotic therapy. In most cases (76%) there was a decrease in the NIHSS score at 24 hours after thrombolysis and especially after 7 days (between 3 and 19 points), reflecting a reduction in poststroke disability in thrombolysed patients. In the series of patients undergoing i.v. thrombolysis 5 deaths (10%) were recorded, the lowest rate of data/death rate reported in the literature (14-18%).

**Key words:** stroke, thrombolysis outcome

### Introduction

Stroke is a bleak reality of the society we live in through its effects on the physical and mental status of the patient and his/her socio-professional reintegration. It is a major health problem worldwide and nationally: the second

leading cause of death and dementia, the most common cause of epilepsy in the elderly, and a common cause of depression. Stroke is associated with an increased rate of morbidity, but it is also the leading cause of long-term morbidity and disability in industrialized countries.

Thrombolysis by intravenous (IV) administration of recombinant tissue plasminogen activator (rtPA) is the only treatment method "in the therapeutic window" recognized in international protocols to which Romania adhered through the National Program of Intervention in acute ischemic stroke. Alteplaza is currently the only thrombolytic agent that has proven effective through in international clinical trials, with a real impact on dependence and disability or risk of death after stroke. At the same time, it is not a risk-free therapeutic method, the main risk being the hemorrhagic one, a major risk for elderly patients with elevated blood pressure, diabetes and severe stroke. The benefit-risk ratio should be evaluated on a case-by-case basis, with the neurologist's decision being individual and often difficult. Difficulty in dealing with each patient is not only due to medical particularities but also to collateral aspects such as: problems with obtaining informed consent in patients with speech disturbances or confusional syndrome, timely interaction with patient's family, difficulty in communicating essential information in clear and understandable terms to a moderately or poorly informed population under the pressure of the "time is brain" principle. The disability due to ischemic stroke in patients undergoing thrombolysis with IV-rtPA is reduced or absent 3 months after the acute ischemic event, a 30% reduction in this disability not being accompanied by a significant change in mortality [1].

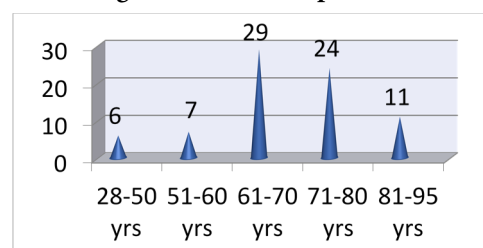
## Material and method

We performed a retrospective clinical study of 77 patients with acute ischemic stroke subjected to thrombolysis with IV-rtPA based on eligibility criteria assessed by neurologists on 24-hour duty between June 2015 and May 2017 at the Iasi "Prof.dr. N. Oblu" Emergency Hospital. The data were collected from the medical records, emergency medical records, and intensive care observation charts. The following parameters were assessed: vascular risk factors, prior cardio/cerebrovascular risk prevention therapy (antiplatelet, anticoagulant, statin), severity of neurological deficit assessed with the NIHSS scale at baseline and in dynamics, ASPECTS radiographic score at stroke onset, time from stroke onset to the initiation of thrombolytic therapy.

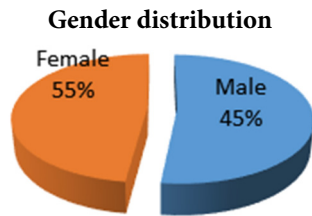
## Results

The age of enrolled patients ranged from 28 to 92 year.

**Age distribution of patients**



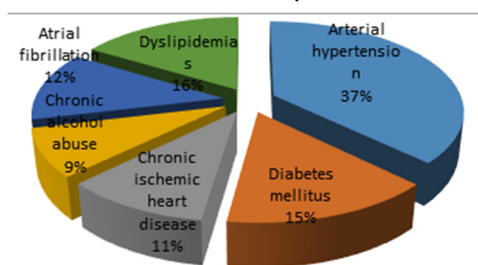
Gender distribution of patients subjected to thrombolysis revealed a female predominance.



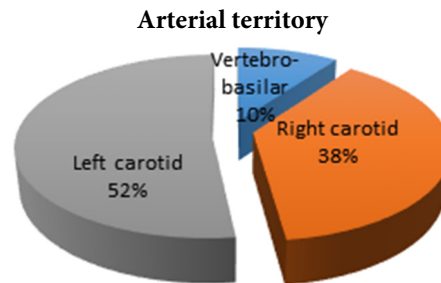
Most patients subjected to thrombolytic therapy had one or more vascular risk factors. Only 5 patients had an ischemic stroke of undetermined etiology, explained by incomplete laboratory assessment due to the logistic problem (lack of thrombophilia tests, absence of transthoracic or transesophageal echocardiogram, impossibility of Holter ECG monitoring).

Arterial hypertension was the main vascular risk factor in most patients, especially in the group at very high additional risk. Atrial fibrillation, chronic ischemic heart disease, dyslipidemias, diabetes mellitus and chronic alcohol abuse were also present in the panoply of vascular risk factors in patients undergoing thrombolysis.

**Vascular risk factors in the patients subjected to thrombolysis**

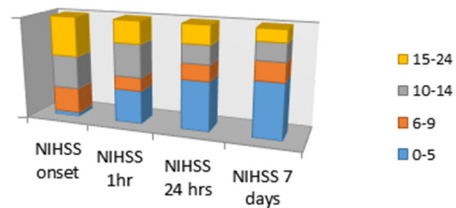


Most ischemic stroke treated by thrombolysis involved the carotid system territory mainly on the topography of the middle cerebral artery, and only 10% had a vertebrobasilar system location.



The average NIHSS score was 15 points, reflecting a significant percentage of cases with severe neurological deficits, most likely a consequence of the long time interval between stroke from to hospital presentation to the hospital, but also of the still long time from presentation to thrombolysis administration. In most cases (76%) a decrease of NIHSS score (between 3 and 19 points) was recorded at 24 hours and especially 7 days after thrombolysis, which reflects a reduction in poststroke disability in the thrombolysed patients.

**Clinical assessment**

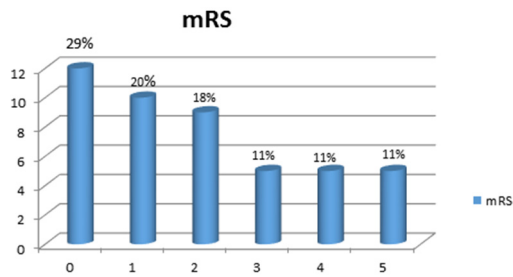


Imaging assessment. Native cerebral CT scan in emergency revealed a 10-point ASPECTS score in most patients subjected to thrombolysis (80%), only one fifth of patients having an ASPECTS score of 7-10 points. Evaluation of the remnant neurologic deficit after thrombolysis therapy was made, according to the protocol, at 3 months for 49 patients who underwent neuromotor

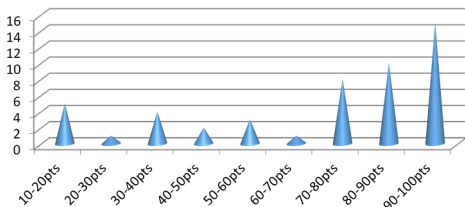
rehabilitation using the modified Rankin scale (mRS) and the Barthel capacity scale. Of these, the majority (34 cases) had low mRS scores and high Barthel index scores, signifying a reduced severity of the remnant neurologic deficit after stroke. These scores correlated with the decrease of NIHSS score during acute stroke.

Time intervals needed for the clinical and laboratory assessment of the patients eligible for thrombolytic therapy were compared with those specified in the national protocol; and international guidelines. The shortest time intervals were recorded for receiving the results of the compulsory tests specified in the thrombolysis protocol and result of imaging assessment, and the interval from presentation to emergency department (ED) to the initiation of thrombolysis was generally longer than recommended.

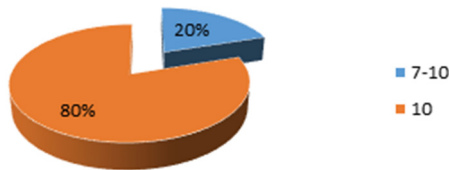
**Assessment at 3 month**



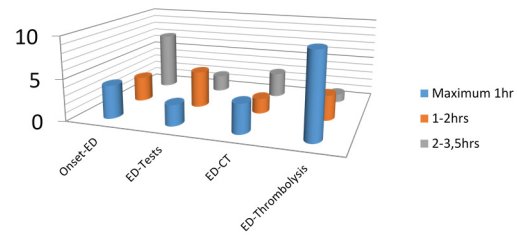
**Barthel Index**



**ASPECTS score**



**Laboratory efficacy**

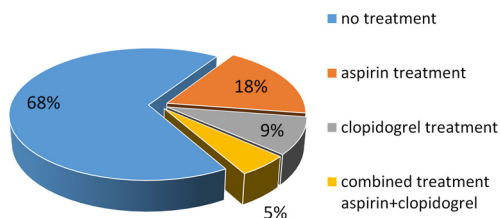


To illustrate we present the results of Priority Action for Interventional Treatment of Patients with Acute Stroke in accordance with data in the Romanian registry of Interventional Treatment for acute Stroke.

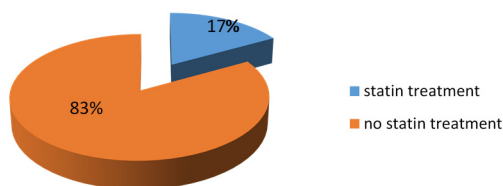
	Interval stroke onset- ED presentation	Interval ED presentation – brain CT scan	Interval ED presentation – receiving laboratory test results	Interval stroke onset –treatment administration	Interval ED presentation-treatment administration
2012-2014	75	30	53	150	75
2014-2015	65	30	44	135	70
2015-2016	86	34	50	165	79
2016 (Jan- Aug)	99	31	51.5	175.4	78.7
<b>Recommendations in international guidelines</b>		<b>25</b>	<b>45</b>		<b>60</b>

Most of the patients undergoing intravenous thrombolytic therapy were not on chronic antithrombotic treatment for secondary prevention at home.

**Home treatment prior to thrombolysis**



**Prior statin treatment**

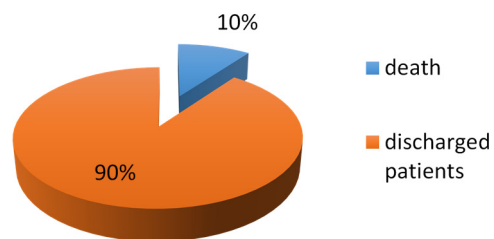


As to the patients on pre-stroke statin therapy, in only 5 of the 13 patients therapy was targeted at lowering LDL-cholesterol. Patients not on pre-stroke statin therapy

accounted for the majority of those with high onset NIHSS score (greater severity of neurological symptoms) and also tended to have lower e ASPECTS scores.

In the series of patients subjected to intravenous thrombolysis 5 deaths (10%) were recorded, rate lower than that reported in the literature (14-18%).

**Mortality rate**



**Discussions**

Ischemic stroke is produced by thromboembolic or hemodynamic mechanism. The pathogenesis of cerebral infarction is complex and consists of several stages, the processes involved in cellular injury determining an ischemic cascade. A multitude of factors are considered in cell dysfunction

and death. Seconds to minutes after the loss of glucose and oxygen supply to neurons, the ischemic cascade begins. This is a complex process that starts with the discontinuation of the normal electrophysiological function of neurons.

Pathophysiologically, the decrease in oxygen and glucose supply leads to inappropriate energy supply and thus to failure of energy dependent processes such as ion pumping. The result is the disruption of ionic homeostasis, with the influx of Ca and water into the cells and lactic acidosis. Finally cytotoxic edema occurs. The role of excitatory amino acids (especially glutamate liberated from ischemic cells) is a key element because they bind to NMDA receptors and excite neurons, causing an influx of Ca and Na that activates the enzymatic cascade ultimately leading to irreversible cellular lesions and neuronal death.

Other events induced by ischemia consist in free radical production, which causes lipid peroxidation and cell membrane rupture. Lactic acid accumulation and the consecutive biochemical changes are important in determining the extent of cellular lesions.

In terms of anatomopathological lesions, focal cerebral ischemia has two areas:

-1. "Core ischemic zone" at the center of the ischemic area where, through the depletion of energy reserves (blood flow  $<12$  ml /100 mg /tissue /min), neuronal death (necrosis) occurs.

-2. "Ischemic penumbra", present both at the margin of ischemic focus and even within the cerebral infarction for a short period of time contains functionally altered but still

viable cerebral tissue supplied with blood by arteries - the "luxury perfusion" - (BF = 12-23ml/100mg /tissue/min) [2]. At this level there is a risk of apoptotic-like cell death. IV-rtPA thrombolysis diminishes the extent of the infarct area towards the penumbral zone and also causes an increase of reperfusion processes, as shown by the studies (EPITHET - Echoplanar Imaging Thrombolytic Evaluation Trial) [3].

Ischemic penumbra:

-has a limited duration but may persist for over 12 hours after the occurrence of focalization signs due to ischemic stroke

-may progress to infarction due to neural lesions secondary to some biochemical cascades with cytotoxic and excitotoxic effects

-ion homeostasis and transmembrane potentials are maintained

-being a dynamic process, it has potential for reversibility if and reperfusion and neuroprotection therapies are initiated as early as possible.

The onset and time course of molecular processes are different. At the level of ischemic focus outbreak, increased excitotoxicity and secondary biochemical reactions cause necrosis in minutes to hours (within the first 24h), while at the level of ischemic penumbra excitotoxicity and secondary biochemical reactions cause apoptotic-like cell death which can last hours to days.

Thus, the earlier the initiation of the therapeutic strategy aimed at restoring blood flow and providing neuroprotection, the higher the percentage of saved penumbral zone with potential for reversibility. Imaging assessment by perfusion CT scans and

magnetic resonance imaging (MRI) and determination of diffusion-perfusion mismatch would allow a correct selection of patients who may benefit most from thrombolysis due to accurate quantification of the infarct zone versus potentially reversible ischemic penumbra. The use of these brain imaging techniques also allowed the expansion of the therapeutic window for i.v. thrombolysis from 3 to 4.5 hours [4, 5]

Revascularization therapy in acute ischemic stroke includes intravenous thrombolysis and endovascular treatment procedures (mechanical thrombectomy, intra-arterial thromboaspiration, intra-arterial pharmacological thrombolysis, combined pharmacological and mechanical treatment). Patients with acute ischemic stroke within the first 4.5 hours of the onset of neurological deficits may be eligible for systemic thrombolysis with rtPA administered intravenously, the recommended dose in the protocol being 0.9 mg/kg body weight, up to a maximum dose of 90 mg, of which 10% is administered bolus and the remainder is perfused over 1 hour [6].

The narrow therapeutic window, reduced efficacy for large artery occlusion, contraindications to this treatment in patients who associate a higher risk for bleeding complications are elements limiting this type of therapy. The main and most feared post-thrombolysis complication is intracerebral hemorrhage. It can be of varying degrees of severity, ranging from simple non-systematized petechiae to well-defined hematomas with mass effect, and which may be asymptomatic or symptomatic, by clinical

deterioration of more than 4 points on the NIHSS (National Institute of Health Stroke Scale). This major complication may occur early or late, more than 24 hours after thrombolytic therapy, and predictive factors are not clearly established. The increased risk of hemorrhage appears to be related to: advanced age, hypertension, diabetes, amyloid angiopathy, leukoaraiosis, severity of signs of early ischemia on CT scan, or cerebral ischemia volume evidenced by diffusion weighted MRI. According to some studies, the favorable post-thrombolysis course seems to correlate both with arterial rechanneling and with efficient collateral circulation [7,8, 9,10].

Although the therapeutic window for the rtPA treatment was extended to 4.5 hours, studies show that patients in whom thrombolysis was performed within the first 3 hours show a double benefit compared to those in whom this therapeutic intervention is performed within 3- 4.5 hours [11]. That is why it is imperative that all lines of care, emergency services and all involved factors to be maximally effective, so that patients with acute ischemic stroke to have rapid access to clinical and laboratory assessments in order to be eligible thrombolytic therapy. And this means functional collaboration protocols between emergency medical services, ambulance service dispatching system, emergency department medical staff, neurologists and neuroradiology unit. Increasing the number of hospitals with stroke and thrombolysis units as well as lines dedicated 24/24 to thrombolysis could lead to an increase in the proportion of patients with thrombolized acute ischemic stroke of all



stroke cases [12]. Other elements to be considered in order to extend the application and increase the benefit of thrombolytic therapy could be: increased number of stroke units, access to modern vascular imaging techniques, and extension of interventional neuroradiology services.

Another important aspect related to thrombolytic therapy in acute ischemic stroke is informed consent. Thrombolysis cannot be initiated without the patient's consent, which in many cases cannot be obtained because of language or understanding problems caused by stroke. Obtaining the consent from the patient's relatives may also be difficult, either because they are not present in due time in the hospital unit, or because the information given to them about the benefits vs. risk of thrombolysis is not sufficiently understood. Using and disseminating information materials about thrombolysis among the population or through media could shorten the time needed to obtain informed consent in order to save time until the actual initiation of thrombolytic therapy [13, 14, 15].

In conclusion the decision to initiate intravenous thrombolysis therapy in acute ischemic stroke during the therapeutic window remains an individualized and difficult one for the neurologist, because even when observing the indications in the national protocol, a number of decision-making elements remain incompletely clarified:

- thrombolytic therapy in patients with neurological symptoms occurring in the morning on waking or in elderly patients;

- use of the best neuroimaging method for assessing eligibility for thrombolysis and optimal benefit-risk assessment,

- the optimal organization model of structures and services involved in acute stroke management, so as to provide the fastest circuits in view of providing access to thrombolytic therapy for as many patients as possible.

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