MANAGEMENT OF PATIENTS WITH THROMBOLYSED ISCHEMIC STROKE

Osiceanu Alina*, Sabău Monica, Osiceanu Adrian

**University of Oradea, Faculty of Medicine and Pharmacy,
Parcul 1 Decembrie no. 10, Oradea, 410059
Romania, osiceanualina@yahoo.com**

Abstract

The purpose of this research is the tracking of the evolution of neurological and imaging status in patients with thrombolysis ischemic stroke with Actilyse (rt-PA) as measured by NIHSS and ASPECT scores, pre-and post-thrombolysis, the rate of morbidity and mortality.

Key words: ischemic stroke, NIHSS, ASPECTS, Actilyse

INTRODUCTION

Optimal management of a patient suspected of stroke requires a rapid and focused assessment. Early recognition of stroke symptoms, a rapid transfer to a medical center with stroke unit and the avoidance of any delay in correct diagnosis and treatment decisions is essential to save lives and prevent long-term disabilities. Thus, to avoid delays should be the primary goal in the management of acute stroke. Based on the concept of "time is brain", setting the elapsed time from onset of symptoms, achieving a targeted neurological examination and interpretation of auxiliary tests facilitates the right choice of therapy for acute stroke in eligible patients.

MATERIAL AND METHODS

This observational, prospective, interventional and cohort study was conducted in the Neurology Clinic in collaboration with the Radiology Clinic, Department of the Emergency Unit - SMURD and ATI Clinic of the Emergency County Hospital from Oradea in March 2012 - February 2014 a total of 125 patients hospitalized with a diagnosis of acute ischemic stroke.

These patients were divided into two groups:

- The study group (group S) - 61 patients eligible for the fibrinolysis of ischemic acute stroke with Actilyse (rt-PA), in which we assessed the changes in neurological deficits within 24 hours from the onset as a means of rt-PA action.
- control group (group C) - 64 patients with acute ischemic non-non-thrombolysed stroke treated with antiplatelet and anticoagulant therapy.

To test whether t-PA shows clinical activity, more exactly, if a greater percentage of patients treated with t-PA, have improved faster than those receiving placebo treatment. Faster recovery of neurological function was defined as the final neural deficit or as an improvement of the overall outcome in the score of the National Institute of Health regarding the strokes (NIHSS) by more than 4 points of recovery at 24 hours after the onset of the stroke . Each group was evaluated according to the time elapsed since the onset of the stroke and the beginning of treatment: 0-90 min, 91-180 min and 0-180 min after the onset of the stroke.

The management of thrombolysed patients was done according to the National Programme for fibrinolysis in acute ischemic stroke through which the "Standard operating procedure on the patient route and therapeutic protocol was made."

RESULTS AND DISCUSSION

This observational, prospective, interventional and cohort study was conducted in the Neurology Clinic in collaboration with the Radiology Clinic, Department of the Emergency Unit - SMURD and ATI Clinic within the Emergency Clinical County Hospital from Oradea in March 2012 - February 2014 on a total of 125 patients hospitalized with a diagnosis of acute ischemic stroke.

The 125 patients were divided into two groups:

 The study group (group S) - 61 patients eligible for the fibrinolysis of the - ischemic acute stroke with Actilyse (rt-PA), in which we assessed the changes in neurological deficits within 24 hours since the onset of stroke as a means of rt-PA action.

 control group (group C) - 64 patients with acute ischemic non-thrombolysed stroke treated with antiplatelet and anticoagulant therapy (placebo).

In the present study, modifiable risk factors were hypertension, carotid atheromatosis, artrial fibrillation, obesity, type II diabetes and myocardial infarct, in other words generalized atheromatous and thrombolytic disease is responsible for the increased risk of ischemic stroke. Their frequency was reatively equal between the two groups, but with statistically significant difference among the variables ($p < 0.05$) (Table no. 1).

Table. 1

Demographic characteristics and comorbidities in patients with acute ischemic stroke

Total of patients n=125		Study group n=61	Control group n=64	$p^{\dagger}$
Comorbidities	Myocardial infarction	3	1	*0.618724**
	Diabetes Type II	8	12	*0.468004**
	Obesity	10	16	*0.274884**
	Carotid atheromatosis	29	27	*0.592132**
	FIA	28	31	*0.858255**
	HTA	41	49	*0.319367**
		p < 0.0001**	***p < 0.0001*****	

*$^{\dagger}p < 0.05$ shows a statistically significant difference among the studied groups; * Fisher's exact test; ** Chi-square test; *** Comparison of means test*

Given the criteria indicating the opportunity of fibrinolytic therapy, in this study we monitored the weight, presence of hypertension, blood glucose, NIHSS and ASPECT score at the patient's arrival in the emergency department, pre-and post-thrombolysis. The statistical results show no significant differences between the two groups. We can mention that the average systolic and diastolic blood pressure was below 180/110 mmHg. The increase in blood pressure after the fibrinolytic therapy may also lead to the increase of the bleeding risk. A single patient had high oscillating high blood pressures, which have been kept under control by the administration of Urapidil 10 mg in intravenous bolus, repeated at 5 minutes depending on the blood pressure. The monitoring of the blood pressure was carried out every 15 minutes for 2 hours after ceasing the infusion of fibrinolytic perfusion, and then every 30 minutes for 6 hours and then every 60 minutes for 24 hours (Table 2).

The weight measurement was important for the administration of rt-PA dose. It had an average value of 76 ± 15 kg in the study group and 80 ± 18 kg in the control group (Table no. 2).

NIHSS score on arrival was divided into four categories of neurological severity: minor with NIHSS score between 1-4, mild with NIHSS score between 5-15, moderate / severe with NIHSS score between 15 to 20, severe with NIHSS score between 20 – 25. There were mainly

patients with neurological status ranging from moderate to severe, as measured by NIHSS score between 15-20, followed by those with severe and moderate neurological status (Table no. 2).

ASPECT score showed a parenchymal hypoattenuation in most patients in both groups. The computer tomography was performed within 30 minutes since the patient's arrival into the hospital, not before it is monitored hemodynamically, glycemically and clotting sampling (platelets and INR) and urinary tract sampling. A normal brain CT has an ASPECT score of 10, while an ischemic damage throughout the ACM has a score 0 In this study all patients had an ASPECT score between 5-10 points (Table no. 2).

Table 2
Clinical features in patients studied with acute ischemic stroke

Total of patients n=125		Study group n=61	Control group n=64	$p^{\dagger}$
Average weight (kg)		76±15	80±18	*0.1807**
HTA	Systolic	155±22	153±20	*0.5955**
	Diastolic	85±12	85±13	*1.0000**
Glycemia mg/dl		149±76	152±78	*0.8312**
NIHSS score	Minor 1- 4	0	5	*0.057876***
	Moderate 5-15	19	21	*0.850612***
	Moderate/Severe 15-20	22	20	*0.576768***
	Sever > 20 < 25	20	18	*0.697606 **
CT Aspect	Parenchymatous hypoattenuation	13	10	*0.491303***
	Focal edema or mass effect	5	3	*0.484787***
ASPECT score	5-10	61	64	*0.800345***
ASPECT score	0-5	0	0	

*$^{\dagger}p < 0.05$ shows a statistically significant difference between the studied groups; * Comparison of means test, Fisher's exact test ***

Analyzing the time from the onset of stroke until the initiation of fibrinolysis, it was found that time was directly proportional with the imagistic and clinical setting signs of acute stroke . If some of the 31 patients who arrived within 90 minutes since the stroke onset had a moderate and severe NIHSS score, after fibrinolysis the neurological

development has improved considerably, 10 patients having a NIHSS score between 1 and 4 ($p < 0.05$). Between 90 to 180 minutes after the onset of acute ischemic stroke, 26 patients had a NIHSS score between 5 and 25, and ten patients had post- thrombolysis NIHSS score 1-4 and two patients between 15-20 with statistic relevance. On arrival in hospital within 0-180 minutes, four patients had a NIHHS score of 5-20 and post- thrombolysis the neurological development showed a NIHSS score of 1-4 in a patient and of 5-20 in three patients , with no statistic relevance (Table no. 3).

Table no. 3 - Neurological evolution post-therapy 24 h

interval between stroke onset and treatment		Study group n=61	NIHSS value score at admission	Number of patients	NIHSS value score at discharge	Number of patients	P	Control group n=64	NIHSS value score at admission	Number of patients	NIHSS value score at discharge	Number of patients	P
0-90	31		1-4	0	1-4	9	0,002935	28	1-4	2	1-4	4	0,580323
			5-15	10	5-15	12	0,816192		5-15	10	5-15	12	0,816192
			15-20	12	15-20	5	0,133226		15-20	9	15-20	7	0,598055
			20-25	9	20-25	4	0,148656		20-25	10	20-25	6	0,290234
91-180	26		1-4	0	1-4	10	0,001362	25	1-4	2	1-4	4	0,580323
			5-15	8	5-15	9	1,000000		5-15	10	5-15	12	0,816192
			15-20	9	15-20	4	0,148656		15-20	6	15-20	5	0,760459
			20-25	9	20-25	3	0,071451		20-25	7	20-25	4	0,526319
			1-4	0	1-4	1	1,000000		1-4	2	1-4	2	1,000000
			5-15	2	5-15	3	1,000000		5-15	3	5-15	5	0,717782
			15-20	1	15-20	0	0,488000		15-20	5	15-20	3	0,488182
0-180	4		20-25	1	20-25	0	0,488000	11	20-25	1	20-25	1	1,000000

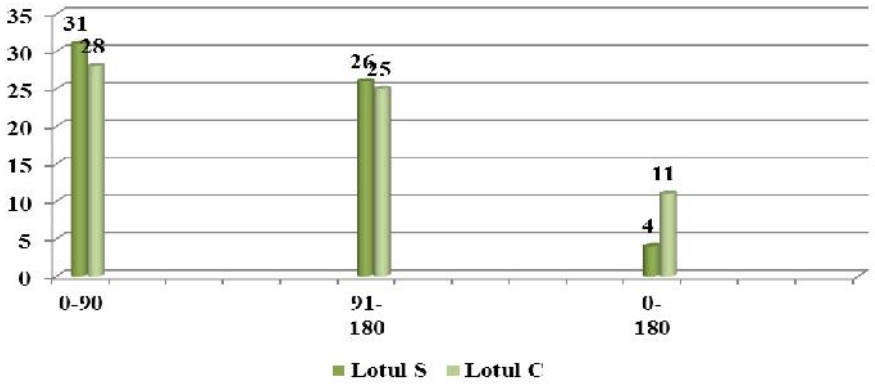


Diagram no. 1 Distribution of patients with acute ischemic stroke based on the time from the onset of stroke until the initiation of fibrinolysis

Patients were monitored neurologically throughout fibrinolysis and in case of obvious worsening (NIHSS increase of at least 4 points) the perfusion ceased and emergency CT was performed. All thrombolysed patients were re-evaluated neurologically and imagistically at 24 hours post-thrombolysis. Therefore, at the CT evaluation in 57 patients in the study group, the ischemia focus is highlighted in the Silvyan territory, three patients developed ischemia in the ACA territory and one in the PAC territory, with statistically significant differences. Compared with the study group, in the control group 55 patients developed ischemias in the MCA territory, six patients in ACA territory and three patients in PAC territory of statistical significance between variables. Comparatively, there were no statistically significant differences between the two groups.

Regarding the feared complication of this treatment, hemorrhagic transformation of acute ischemic stroke occurred in 14 patients in the study group, that is: 11 developed bleeding in the ischemia focus, only one patient developed it away from the ischemia, in the cerebellum hemisphere. The neurologic status worsened seriously in two patients by the appearance of vascular coma in 3 GCS points reflected by the computed tomography images, one in the development of ventricular hemorrhage, while in the second patient both ventricular hemorrhage and subarachnoid haemorrhage appeared (Table no. 4). The development of neurological status in the control group was significantly aggravated in 5 patients who developed vascular coma in 3 GCS points as evidenced by subarachnoid hemorrhage with ventricular hemorrhage in a patient and with ventricular hemorrhage in

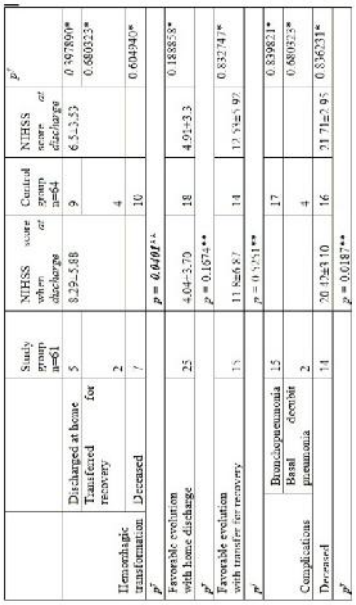
other patient. Nine patients had bleeding in the ischemia focus and two patients had it in the cerebellar hemisphere (Table 5). The statistical analysis shows no significant differences between the two groups. Normal appearance was identified in 7 patients in the total study group, 5 of the thrombolysed group and two in the control group .

Table 4.

Evolution of CT aspect at 24 hours after hospitalization

		Study group n=61	Control group n=64	$p^{\dagger}$
Delimitation of ischemia focus	ACM	57	55	*0.242517**
	ACA	3	6	*0.492564**
	ACP	1	3	*0.619323**
	$p^{\dagger}$	***p < 0.0001*****	***p < 0.0001*****	
Hemorrhagic transformation	in ischemia focus	11	9	*0.628914**
	in cerebellar hemisphere	1	2	*1.000000**
	Subarachnoid + ventricular hemorrhage	1	2	*1.000000**
	Ventricular hemorrhage	1	3	*1.000000**
	$p^{\dagger}$	***p = 0.0002*****	***p = 0.0284*****	
Normal aspect		5	2	*0.265586 **

*$^{\dagger}p < 0.05$ shows a statistically significant difference between the studied groups; * Fisher's exact test, Chi-square test ***



*$^{\dagger}p < 0.05$ shows a statistically significant difference between the studied groups; * Fisher's exact test; ** Chi-square test; *** Comparison of means (t - test)*

The morbidity rate in patients from the study group was significantly lower than those in the control group. On one hand, this was due to hemorrhagic transformation of the post- thrombolysis ischemic stroke and on the other hand to the unfavourable evolution of the cadiorespiratory status, 17 patients developing sepsis state with basal decubit pneumonia and bronchopneumonia in the study group compared to 21 patients in the control group. Also, the hemorrhagic transformation was higher in the control group (Diagram no. 2).

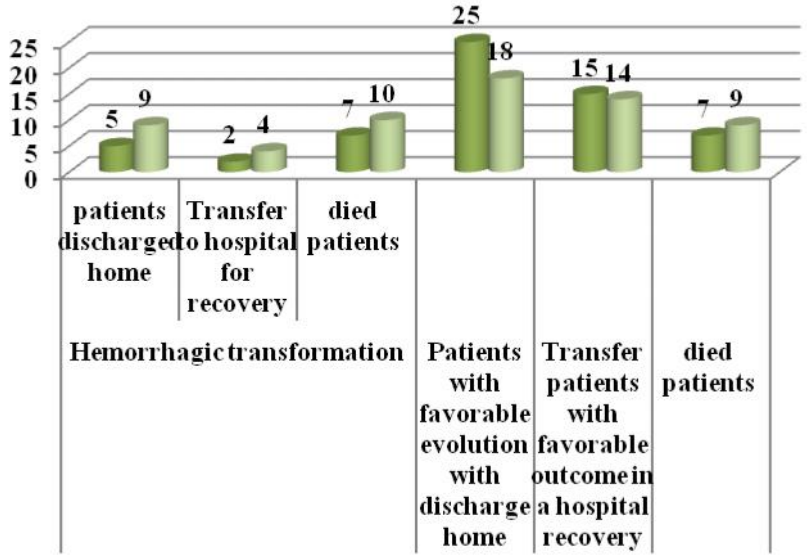


Diagram no. 2 Distribution of patients in both analyzed groups according to neurological status at discharge

Of those with hemorrhagic transformation, 20 patients of the total group, due to the favorable neurological development, measured by NIHSS score of 8.29 ± 5.88 on average in the study group compared with 6.5 ± 3.53 in the control group, 14 was discharged at home with treatment and neurologic control recommendation at one month and 6 patients were transferred to the neurological rehabilitation unit, with significant difference between groups.

The patients whose neurologic status reflected by NIHSS score ranging in the interval 0-10 allowed the discharge at home of 25 patients in the study group compared to 18 patients in the control group without statistically significant differences (Table no. 5).

Modified Rankin scale, Barthel index and Glasgow scale represent the whole range of functions from death and severe disability to full

recovery. NIHSS measures neuronal deficit and not the functional outcome. As used here, it has ensured that full recovery also means neurological recovery regardless the function.

A NIHSS score ranging from 1 to 21 pointed out the transfer of 15 patients from the study group and 14 patients from the control group in the neurological recovery clinic.

The mortality rate in the study group was of 22.95%, significantly lower than in the group of non-thrombolysed patients (25%).

CONCLUSIONS

One benefit of the intravenous treatment with rt-PA in patients with acute cerebral ischemic stroke was demonstrated when it was set up within three hours from the onset of symptoms. This demonstrates the evolution of NIHSS score at 24 hours post-thrombolysis.

Compared with no-trombolysis patients, approximately 77% of the patients treated with rt-PA had a favorable evolution with neurological status recovery (with at least 4 points) and minimal neurological disabilities.

In conclusion, despite a high incidence of intra-cerebral hemorrhage (22.95%) an improvement in clinical outcomes was recorded at 24 hours in patients treated with intravenous rt-PA within three hours from the acute ischemic stroke.

The limiting factor in this study is the limited casuistry regarding the thrombolysis of patients with acute ischemic stroke, since it applies only since March 2012 in the Emergency Clinical Hospital from Oradea. For more eloquent statistical results, further studies on a larger group of patients would be required.

REFERENCES

1. Altman DG: Practical statistics for medical research. London : Chapman & Hall 1991
2. American Heart Association: 2002 Heart and Stroke Facts Statistical Update. Dallas, American Heart Association, 2001.
3. Brott TG, Haley EC Jr, Levy DE, et al. Urgent therapy for stroke. I. Pilot study of tissue plasminogen activator administered within 90 minutes. Stroke 1992;23:632-640
4. Caplan LR, Wityk RJ, Glass TA, Tapia J, Pazdera L, Chang HM, et al. New England Medical Center posterior circulation registry. Ann Neurol2004;56:389.
5. Feigin VL (2005). "Stroke epidemiology in the developing world". Lancet **365** (9478): 2160–1.
6. Gulli G, Khan S, Markus HS. Vertebrobasilar stenosis predicts high early recurrent stroke risk in posterior circulation stroke and TIA. Stroke2009;40:2732-7.

7. Gulli G, Marquardt L, Rothwell PM, Markus HS. Stroke risk after posterior circulation stroke/transient ischemic attack and its relationship to site of vertebrobasilar stenosis: Pooled data analysis from prospective studies. Stroke2013;44:598-604.
8. Haley EC Jr, Levy DE, Brott TG, et al. Urgent therapy for stroke. II. Pilot study of tissue plasminogen activator administered 91-180 minutes from onset. Stroke 1992;23:641-645
9. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ: Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367:1747-1757.
10. O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, Bowler JV,Ballard C, DeCarli C, Gorelick PB, Rockwood K, Burns A, Gauthier S, DeKosky ST:Vascular cognitive impairment. Lancet Neurol 2003;2:89-98.
11. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, Redgrave JN, Bull LM, Welch SJ, Cuthbertson FC, Binney LE, Gutnikov SA, Anslow P, Banning AP, Mant D, Mehta Z: Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet 2005;366:1773-1783.
12. Sacco RL: Newer risk factors for stroke. *Neurology* 2001; 57(Suppl 2):S31-S34.
13. *Savitz SI, Caplan LR. Vertebrobasilar disease. N Engl J Med2005;352:2618.*
14. Williams G.R., Incidence and characteristics of total stroke in the United States. *BMC Neurol* (2001).