Neurologic Deterioration After Intravenous Thrombolysis Among Stroke Patients in Assiut University Hospitals

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Abstract:

Background: Cerebrovascular Disease is categorized in the ICD-11 as Acute focal neurological impairment due to focal infarction at one or more locations in the brain or retina, also known as a stroke. The risk of early neurological decline (END) after recanalization therapy is a major concern.

Aim and Objectives: To investigate the prevalence of neurological deterioration in individuals with acute ischemic stroke who have received thrombolytic therapy.

Subjects and Methods: This prospective study was conducted at the Neurology Department Stroke Unit, Assiut University Hospitals, Assiut, Egypt, and included all acute ischemic stroke individuals stated in the duration from 1/1/2021 to 31/12/2021

Result: The survival rate was (93%), 69% of patients showed significant improvement in NIHSS and mRS at 24h, and progressive improvement within 7 days of follow-up, 27% showed no difference in NIHSS or mRS at 24h, 3 days, 7 days of follow-up, and 4% showed deterioration at follow-up points without significant changes in NIHSS & mRS. Also, 68% showed a significant reduction in mRS from baseline to one month of follow-up.

Conclusion: Early neurological deterioration was prevalent among cases with acute ischemic stroke after successful recanalization, with an incidence rate of 10.1%.

Keywords: Early Neurological Deterioration, Recanalization Treatment, Acute Ischemic Stroke.

Introduction:

Ischemic stroke of the brain (defined as acute focal neurological impairment due to focal infarction at single or multiple locations of the brain or retina) is one type of cerebrovascular disease included in the ICD-11. There are a few different kinds of strokes, the most common of which are acute infarction (proven by signs lasting for more than twenty-four hours or by neuroimaging or another technique in the clinically relevant area of the brain), intracerebral and subarachnoid hemorrhage), as well as stroke of unknown [1].

After ischemic heart disease (16.2%), stroke was 2nd biggest reason for death worldwide (at 11.6% of all fatalities). After newborn diseases (7.3%) and ischemic heart disease (7.2%), stroke was 3rd most outstanding reason for death and disability worldwide in 2019 (5.7%) of total Disability-Adjusted Life Years (DALYs) [2].

The goal of emergency treatment for Acute Ischemic Stroke (AIS) is to restore blood flow as quickly as possible, and this is

accomplished by using intravenous tissue plasminogen activator (IV tPA) for thrombolysis, endovascular thrombectomy, or both. Premature reperfusion has been shown to cause the death of around 1.9 million neurons each minute, making time of the essence. At three months, the probability of long-term impairment is significantly reduced for every fifteen-minute reduction in onset-to-treatment time (according to the World Health Organization, WHO) [3, 4].

Significant advancements in AIS management have been made during the past 25 years. The medical standard therapy for AIS is intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA). Improved clinical outcomes & survival rates have been linked to early recanalization of occluded blood arteries in AIS cases with rt-PA administration or endovascular revascularization [3].

The purpose of this research is to investigate the frequency of early neurological deterioration in individuals with acute ischemic stroke who received intravenous thrombolysis in Assiut University hospitals.

Patients and Methods

The current prospective research was conducted at the Neurology Department Stroke Unit, Assiut University Hospitals, Assiut, Egypt & included all acute ischemic stroke cases admitted from 1/1/2021 to 31/12/2021.

Inclusion Criteria: cases with acute ischemic stroke included inside the therapeutic time window (0-4.5h) and received IV thrombolysis[5], aged over 18 years, and accepting all study requirements.

Exclusion Criteria: Patients with any exclusion criteria for IV thrombolysis[6], Patients with hemorrhagic stroke, Patients < 18 years, and those who refused to participate in the study.

Methodology

All participants underwent: Complete neurological history and examination, Lab investigations (Basic laboratory investigations were done for all patients to detect any contraindication for IV rt-PA), Radiologic assessment (Non-contrast CT brain (model: Siemens go.up32 slice) was done to every patient on admission to exclude hemorrhagic stroke, and ASPECT score was assessed accordingly then 24h later follow up NCCT brain was done, and Some patients had additional MRI Brain (model: Philips Acheiva 1.5 T)), Echocardiogram if needed, Temperature and Oxygen saturation measurement at admission, after 24 hours and if deterioration occurred.

After a good selection of patients according to inclusion and exclusion criteria, meticulous assessment was done, and patients received the rt-PA therapy.

Tools

1. National Institute of Health Stroke Scale (NIHSS) [7]: at the onset of admission, directly, 24h, 72h, and 1 week after thrombolysis.
2. Modified Rankin Scale (mRS) [8]**:** a scale for neurologic disability ranging (0-6) after 1 week and 1 month.

We used the improvement according to NIHSS as a decrease in score of 4 or more, unless the case had no improvement or a stationary course.

According to NIHSS, deterioration increased the score by 4 or more.

Administration of IV rt-PA

The following was done to every patient receiving rtPa: The cases were transported to the Stroke Unit & an intravenous infusion of rt-PA was started. 0.9 mg/kg, with a ten percent bolus administered in one minute and the remaining dosage administered for one hour, with a maximum dose of 90 mg. The

neurological evaluation (NIHSS score) was repeated every 15 minutes during infusion, every thirty minutes in the following six hours, and every hour until 24 hours; blood pressure monitoring was performed every fifteen minutes in the first two hours of therapy and every thirty minutes after that.

Ethical Committee

The research protocol was approved by the Assiut Medical Ethical Review Board (IRB no. 17101758), informed written permission was collected from all participants or the subjects' families, and confidentiality was maintained throughout the research.

Statistical Analysis

For all statistical computations, version 22 of the SPSS (statistical application for the social sciences; SPSS Inc., Chicago, Illinois, USA) program was utilized. The data were statistically represented using mean, standard deviation, median, and range, where the data were not normally distributed. Additionally, frequencies (number of instances) and relative frequencies (percentages) were used when applicable. The Student t-test and ANOVA tests were applied to evaluate quantitative variables to determine if the data were distributed regularly. If not, the Mann-Whitney U test & Kruskal-Wallis test were employed. Quantitative-dependent data was compared over time utilizing the Friedman test. We used the Chi-square ($\chi 2$) test to compare categorical data. The exact test was employed for anticipated frequencies under five. The odds ratio (OR) with 95% CI was used to analyze risk variables for early neurological deterioration among cases. All two-tailed P-values are significant at 0.05.

Results

Table 1: Clinical outcome of the studied patients within 7 days (n = 100)

Variable name	Baseline	After 24 hours	After 3 days	After 7 days	P value
NIHSS					
• **Improved (n=69)**	11.23±3.62	4.46±3.19*	4.14±4.81**	3.21±4.64***	**<0.001**
• **Deteriorated (n=4)**	13.50±4.66	15.00±4.83	18.00±4.36	18.00±5.66	0.180
• **Stationary (n=27)**	14.56±4.28	14.48±4.48	14.63±5.21	14.13±5.91	0.414
mRS					
• **Improved (n=69)**	3.86±0.83	1.91±1.09*	1.59±1.39**	1.29±1.40***	**<0.001**
• **Deteriorated (n=4)**	4.25±0.96	4.50±1.00	5.25±0.50	5.50±0.58	0.067
• **Stationary (n=27)**	4.37±0.69	4.41±0.69	4.44±0.75	4.29±0.86	0.572

NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin scale.
* Statistically significant difference between baseline and after 24 hours
** Statistically significant difference between after 24 hours and 3 days.
*** Statistically significant difference between 3 days and after 7 days.

This table showed that sixty-nine percent (69%) of patients showed significant improvement in NIHSS and mRS at 24h and progressive improvement within 7 days of follow-up **(P < 0.001),** (27%) showed no difference in NIHSS or mRS at 24h, 3days, 7 days of follow-up, and (4%) showed deterioration at follow-up points without significant changes in NIHSS & mRS. Also, the improved group showed a significant difference in NIHSS and mRS between baseline and after 24h and 3 days, and between 3 days and 7 days (deterioration was defined according to the change in NIHSS)

Table 2: Follow-up of the studied cases for one month (n = 100)

Variable name	Baseline	After 7 days	After 1 month	P value
mRS				
• **Improved (n=68)**	3.81 ± 0.82	1.25 ± 0.15	0.87 ± 0.16	**<0.001***
• **Deteriorated (n=14)**	4.36 ± 0.75	4.86 ± 0.38	5.79 ± 0.43	**<0.001***
• **Stationary (n=18)**	4.50 ± 0.62	4.50 ± 0.62	4.50 ± 0.62	1

mRS: modified Rankin scale.

This table showed that mRS" of the studied patients during 7 days of follow-up among improved cases. Sixty-eight percent (68%) of patients showed a significant reduction in mRS from baseline to one month of follow-up (P<0.001), and deteriorated cases clinically (14%) showed a significant increase in mRS and NIHSS from baseline to after one month of follow-up time (P>0.05). While (18%) still had stationery courses with no significant changes in mRS from baseline until one month of follow-up.

Table 3: Incidence of early neurological deterioration after successful recanalization. (n = 69)

	Baseline	After 24 hours	After 3 days	After 7 days	P value
NIHSS					
• **No (n=62)**	10.77±3.32	4.23±0.40*	2.85±0.35**	2.00±0.32***	**<0.001***
• **Yes (n=7)**	15.29±3.95	6.57±1.09*	15.57±1.41**	15.50±1.29	------
mRS					
• **No (n=62)**	3.77±0.79	1.82±1.08*	1.24±0.91**	0.97±0.12***	**<0.001***
• **Yes (n=7)**	4.57±0.79	2.71±0.95*	4.71±0.48	4.67±0.52	-----

** Statistically significant difference between after 24 hours and 3 days.

*** Statistically significant difference between 3 days and after 7 days.

This table showed that Sixty-nine patients had significant improvement immediately and 24h after thrombolysis with a considerable reduction in both NIHSS and mRS from baseline to 24h, sixty-two of them (89.9%) had substantial progressive improvement in NIHSS and mRS up to 7 days. Seven (10.1%) deteriorated again at 72h (3rd day) with a significant increase in NIHSS between 24h and 3 follow-up days.

Discussion

Stroke has risen rapidly as a significant global health problem [9].

Significant advancements in AIS management have been made during the past 25 years. The medical standard therapy for AIS is intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA). Recanalization of blocked blood arteries early in AIS individuals with rt-PA administration or endovascular revascularization has been related to improved clinical outcomes & survival rates [3]. Even after successful recanalization, some patients have shown substantial neurological deterioration, leading to extended hospitalization and a very poor prognosis, according to certain research [10].

The study included 100 cases suffering from acute ischemic stroke; their mean age was 60.64 ± 11.43 years & ranged from 25 to 88 years old. The chance of having a stroke doubles every ten years beyond age

55, and aging is the strongest risk factor that can't be changed. People over the age of 65 account for almost 75% of all stroke cases [11]. In line with the present research, Feigin et al. and Benjamin et al. stated that most strokes occur in people >65 years [12,13].

In our study, we found that the incidence of early improvement within 24h after rtPA was 69%, and this was in line with the study of Andrei V. Alexandrov, who studied 60 patients with a proximal MCA occlusion recanalization during the first 2 hours after TPA bolus was complete in 18 patients (30%) and partial in 29 patients (48%). No recanalization was found in 13 patients (22%) [14]

Also, we discovered that 62 individuals (62 percent) of all those studied continued to improve after 24 hours until a one-week follow-up. This was consistent with the findings of Marta Rubiera, who discovered that among 84 individuals who were recanalized, 53 (63 percent) exhibited sustained neurological improvement within the initial twenty-four hours, ten (12 percent) did not improve, and twenty-one (25 percent) patients deteriorated after improvement [15]

Our study classified END into 2 categories: Those who deteriorated immediately after rtPA (4%) of all studied patients and those who deteriorated after clinically successful recanalization treatment (10.1%) of 69 patients.

According to the follow-up imaging, brain edema, ischemia progression, & symptomatic hemorrhage were identified as the mechanisms of neurological deterioration [16]; increasing NIHSS score by ≥ 4 points or death within 24 hours of IV thrombolysis is the standard definition of END in most studies [17].

Our study comes in agreement with the overall incidence of END, which was defined by previous literature that approximately 5.8 to 34.9% of individuals with acute ischemic stroke might encounter END [18,19]. The percentage of END was variable between studies: Marta Rubiera found (25%) of patients experienced deterioration after improvement [17]. The incidence of END was 5.8 percent in a study by Simonsen et al. of 569 participants who had reperfusion therapy (END is referred to a rise of 4 points or more in total NIHSS within 24 h) [19], In 2022 the Chinese study of Che et al. reported that 81 (7.32%) of cases with AIS developed END (END was defined as an increase of NIHSS ≥ 4 points or death within 24 hours after intravenous thrombolysis) [19], but our study was not in line with : Bathia et al. studied 114 patients had END (END was defined as a ≥ 3 point increase in the NIHSS during the first 72 hours of hospitalization [20], Lee and lee, reported that among the studied 516 patients with acute ischemic stroke 19% developed END (END was defined as a ≥ 2 point increase in the NIHSS during the first 72 hours of hospitalization) [21] and the recent Egyptian study of Helal et al. in 2019 who reported that the incidence rate of END after AIS was 16.7% (definition of END was increase in the NIHSS by two or more points or stroke related death between admission and day 3) [22] , The difference in prevalence of END can be attributed to the lack of a unified definition of END (i.e., different stroke scales and time frames used to assess deterioration), There are variations in the cases of stroke patients, the diagnostic criteria utilized for END, and the time frame of evaluations following acute stroke. The vast variances observed in the studies may be due to factors such as the development of specialist stroke units for the treatment of AIS & the introduction of new stroke management procedures (intravenous thrombolysis and mechanical thrombectomy) [22]. According to late outcomes within 7 days to 1 month, our study was in line with the study of Eldeeb et

al., which found that 56% of the patients had Significant changes in mRS and NIHSS at 24 h, upon discharge and 3 months and 6 months after tPA administration, Mortality was encountered in 18% of all patients [23], a meta-analysis included 12 trials (7012 patients) showed mRS of 0–2 at the final follow-up in 46·3% of the patients [24]. Also, several studies showed approximately similar results as well [25,26,27].

According to END successful recanalization treatment we found that 7 cases out of 69 cases had END after successful recanalization treatment (10.1%), this finding was better than the study of Zhang et al. who reported that about 34.2% of studied patients had END (END was defined as the same in the current study) [28], also better than the incidence of END which reported by the recent study of Zhong et al. who reported that END occurred in 21 (14.2%) patients (END was defined as an NIHSS score increase ≥4 points, or death, from baseline to 24 h after EVT) [29].

The low percentage could be because we only considered those who were successfully recanalized.

Our results may shed light on previously unknown causes of stroke and have significant clinical consequences for stroke sufferers.

Study Limitations are shown regarding time constraints and a lack of prior research studies.

Conclusion

Early neurological deterioration among cases with acute ischemic stroke after successful recanalization is incident, and also late deterioration.

So, early assessment and management of medical complications are essential to prevent poor functional outcomes.

References:

1. Feigin VL, Roth GA, Naghavi M. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. 2016 Sep;15(9):913-24.
2. Feigin V, Stark B, Johnson C; GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2021 Oct;20(10):795-820.
3. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015 Jan 1;372:11-20.
4. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015 Mar 12;372(11):1019-30.
5. Jauch EC, Saver J, Adams Jr H, et al.; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Mar;44(3):870-947.
6. Martins S, Pontes-Neto O, Alves C, et al. Brazilian Stroke Network. Past, present, and future of stroke in middle-income countries: the Brazilian experience. Int J Stroke. 2013 Apr; 8:106-11.
7. NIH Stroke Scale. National Institutes of Neurological Disorders and Stroke [Internet]. Bethesda: National Institutes of Health; [cited 2022 Jun 10]. Available from: https://www.stroke.nih.gov/documents/

NIH_Stroke_Scale_508C.pdf. Revised 2003 Oct 1.
8. Van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988 May-Jun;19(5):604-7.
9. Katan M, Luft A. Global burden of stroke. Semin Neurol. 2018 Apr;38(2):208-11.
10. Thiebaut AM, Gauberti M, Ali C, et al. The role of plasminogen activators in stroke treatment: fibrinolysis and beyond. Lancet Neurol. 2018 Dec 1;17(12):1121-32.
11. Yousufuddin M, Young N. Aging and ischemic stroke. Aging (Albany, NY). 2019 May 10;11(9):2542.
12. Feigin VL, Lawes CM, Bennett DA. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol. 2003 Jan;2(1):43-53.
13. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation. 2017 Mar 7;135(10)
14. Alexandrov AV, Grotta JC. Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator. Neurology. 2002 Sep 24;59(6):862-7. doi: 10.1212/wnl. 59.6.862.
15. Rubiera M, Alvarez-Sabín J, Ribo M, et al. Predictors of early arterial reocclusion after tissue plasminogen activator-induced recanalization in acute ischemic stroke. Stroke. 2005 Jul;36(7):1452-6. doi: 10.1161/01.str.0000170711.43405.81.
16. Kim J-M, Moon J, Ahn S-W. The etiologies of early neurological deterioration after thrombolysis and risk factors of ischemia progression. J Stroke Cerebrovasc Dis. 2016 Feb;25(2):383-8.
17. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008 Sep 25;359(13):1317-29. doi: 10.1056/NEJMoa0804656.
18. Huang Z-X, Huang Y, Zeng J. Admission glucose levels may increase the risk for early neurological deterioration in females with acute ischemic stroke. Front Neurol. 2020; 11:548892.
19. Simonsen CZ, Schmitz ML, Madsen MH, et al. Early neurological deterioration after thrombolysis: Clinical and imaging predictors. Int J Stroke. 2016 Oct;11(7):776-82. doi: 10.1177/1747493016650454.
20. Bhatia K, Mohanty S, Tripathi B. Predictors of early neurological deterioration in patients with acute ischaemic stroke with special reference to blood urea nitrogen (BUN)/creatinine ratio & urine specific gravity. Indian J Med Res. 2015 Mar;141(3):299.
21. Lee S-J, Lee D-G. Distribution of atherosclerotic stenosis determining early neurologic deterioration in acute ischemic stroke. PLoS One. 2017 Sep 28;12(9).
22. Helal sam, Aref Ha, Nassef Am. Early Neurological Deterioration in Acute Ischemic Stroke: Potential Predictors, Causes and Relation to Infarct Growth. Ain Shams Med J. 2019 Oct;70(10, 11 & 12):747-58.
23. Eldeeb H, Elsalamawy D, Elabd A. Predictors of the functional outcome after thrombolysis in an Egyptian patients' sample. Egypt J Neurol Psychiatr Neurosurg. 2021 Jan;57(1):1-12.
24. Wardlaw JM, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet. 2012 Jun 30;379(9834):2364-72.

25. Latchaw RE, Alberts MJ, Lev MH, et al. Recommendations for imaging of acute ischemic stroke: a scientific statement from the American Heart Association. Stroke. 2009 Nov;40(11):364 6-78.
26. Sandercock P, Wardlaw J, Lindley R, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 hours of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomized controlled trial. Lancet. 2012 Jun 30; 379:2352-63.
27. Salam K, Ummer K, Kumar VP. Intravenous thrombolysis for acute ischemic stroke: the Malabar experience 2003 to 2008. J Clin Neurosci. 2009 Oct;16(10):1276-8.
28. Zhang Y-B, Su Y-Y, He Y-B. Early neurological deterioration after recanalization treatment in patients with acute ischemic stroke: a retrospective study. Chin Med J (Engl). 2018 Jan 20;131(2):137-43.
29. Zhong X, Tong X, Sun X. Early neurological deterioration despite recanalization in basilar artery occlusion treated by endovascular therapy. Front Neurol. 2020; 11:592003.