

TREATMENT OUTCOMES OF ISCHEMIC STROKE WITH AND WITHOUT ADMINISTRATION OF THROMBOLYTIC THERAPY: A COMPARATIVE STUDY.

Varahabhatla Vamsi ¹, Vinisha Tekwani ¹, Vedula Ushakiranmayi ², Marina Sikorskaa³,

ABSTRACT

Introduction: Intravenous thrombolytic therapy at the cerebral circulation within the first 3 hours of ischemic stroke onset offers substantial net benefits for virtually all patients with potentially disabling deficits.

Aim: Evaluate the course of the disease in patients with ischemic stroke with a clinical improvement of the neurological deficit during the 3-hour window period in the groups of patients who received and did not receive intravenous thrombolysis.

Methods: A descriptive, retrospective study was performed, in which we reviewed demographical, clinical, tomographical, procedural records of the patients at 6th Municipal Clinical Hospital, Zaporozhye from 2010-2017. A total of 78 case histories were analyzed, 12 were patients with Intravenous thrombolytic therapy and 66 with traditional therapy. The results of the treatment were assessed on the basis of NIHSS scale and the Modified Rankin scale after 90 days after treatment. The statistical data was processed using STATISTICA® 7.0.

Results: In the group of patients with Intravenous thrombolytic therapy, none of the patients showed clinical worsening. In the 2nd group, 21 patients showed an increase in neurologic deficit in the first 3-5 days after hospitalization. The NIHSS score in the 1st group, when deciding on Intravenous thrombolytic therapy and at discharge for 20 days, was $6 \pm 3,8$ and $0,5 \pm 0,2$, respectively. In the 2nd group; $6 \pm 2,9$ and $4 \pm 1,1$. According to the modified Rankine scale, after 3 months in the first group, the index was $0,5 \pm 0,1$ (≤ 1 in 8 patients); in the second group $1 \pm 0,3$.

Conclusions: Intravenous thrombolysis in patients with spontaneous early regression of neurological

INTRODUCTION

Ischemic stroke is a condition that occurs due to lack of sufficient blood supply to brain. Ischemic stroke around the world remains an important medical and social problem due to the high incidence of disability rates¹. The main causative factor of Ischemic stroke is the cerebral artery occlusion even though it may vary in populations². It is estimated that 15 million people suffer from stroke every year, of which 1,2 million cases are registered in Europe, as updated by World Health Organization. The Ministry of Health of Ukraine, in their annual reports estimated that approximately 100 000 to 120 000 people admit in the emergency unit with a new or recurrent stroke each year³. Ischemic stroke mainly manifests in older age (60 or more years), and its risk increases with age. Early Treatment is a important factor during reperfusion therapy in ischemic stroke⁵. There has been many substantial changes in the treatment of ischemic stroke after revealing the efficacy of thrombolytic therapy based on results of many researches⁶. Modern methods of treatment and, in particular, Thrombolytic therapy (TLT) are aimed at restoring blood flow in the effected vessel during the first hours of the disease, which helps to prevent the development of irreversible damage to the brain substance or to reduce its volume, and, therefore, to minimize the degree of residual neurological deficit. Post-stroke disability takes first place among its causes and is 3,2 per 10 000 population. Up to 20% of patients return to work, about 80% remain disabled, and 25% of them need outside help⁷. Systemic intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (r-tPA) is the most effective method for treating ischemic stroke during the first 4,5

¹ Student of 5th year, School of Medicine, Zaporozhye State Medical University.

² Resident Doctor, Health University Dr. NTR, Vijayawada, India

³ Associate Teacher, Neurology Department, 6^o Hospital Municipal Municipal, State Medical University de Zaporozhye, Zaporozhye, Ucraina.

Keywords: Stroke, thrombolytic therapy, Depression, Quality of Life.

Received for publication:
May, 12 2018

Accepted for publication:
July, 14 2018

Cite as:
Rev Cient Cienc Med
2018;21(1):30-39

hours after onset of symptoms. The European Cooperative Acute Stroke, "extended the 3 hour time window period for the TLT administration for acute ischemic stroke to 4,5 hours⁸". Hacke W. et al, in their randomized, double-blind, placebo-controlled trial of 620 patients, reported the positive results of the use of intravenous thrombolysis with the recombinant tissue plasminogen activator for acute hemispheric stroke, indicating the complications of r-tPA in patients with ineligibility⁹.

High efficiency of the method makes it reasonable and necessary to increase the number of patients in whom it can be administered. A large number of contraindications significantly limit the number of patients administered with TLT.

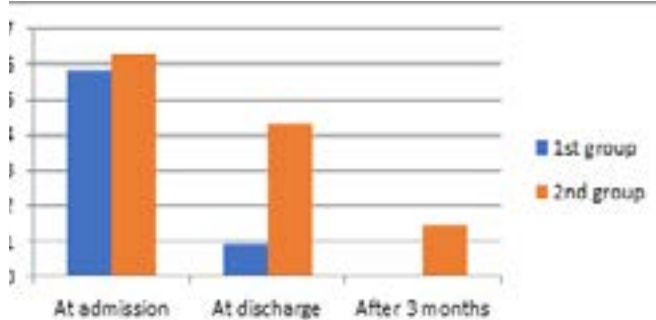
MATERIALS AND METHODS

This descriptive, randomized, retrospective study was approved by the local ethics committee of Zaporozhye State Medical University in the period from 2010 to 2017. We analyzed 78 case histories of patients with acute hemispheric ischemic stroke treated in the Department of acute cerebral circulation disorders of the 6th city clinical hospital in Zaporozhye. Treatment with thrombolysis was received by 12 patients (group 1) and standard therapy without TLT - 66 patients (group 2). The inclusion criterion was a clinical improvement of 1-2 points on the stroke scale of the National Institutes of Health Stroke Scale (NIHSS) in the first 3 hours after the onset of the disease. The tissue activator of plasminogen (Actilyse[®]) was administered at a rate of 0,9 mg / kg (not more than 90 mg), 10% solution was administered for 1 minute bolus, for 60 minutes. The results of the treatment were assessed on the NIHSS scale and on the modified Rankine scale at discharge and 90 days after the stroke. Ischemic stroke was verified by CT examination (repeated) in 7 patients in the first group and in 43 patients in the second group. In the first group, all patients entered the clinic within 2-3 hours from the onset of the disease. The demographic and tomographic indicators were also evaluated. The statistical data was processed using STATISTICA 7.0, with the standard programs.

RESULTS

In the first group, all patients entered the clinic within 2-3 hours from the onset of the disease. On the scale of NIHSS patients had from 3 to 8 points (an average of 5,85) as shown in Fig1. All patients in the neurological status had paresis of varying degrees of severity, and 4 patients had motor aphasia. All patients noted some improvement in the condition until they entered the clinic as an increase in the volume of active movements in one or two extremities (an average of 1-2 points on the NIHSS scale) and one patient noted improvement in speech. Due to the fact that the improvement of the condition was not rapid, and in no case there was no complete regression of neurologi

Figure 1. Represents severity of ischemic stroke in the first 3 months (using the NIHSS scale).



cal symptoms, a decision was made to conduct TLT. According to the CT scan, no signs of the formation of the focus were observed. The time from the onset of the disease to admission to the clinic was 105 minutes on average. The time from admission to the clinic before the start of treatment is 50-70 minutes.

At discharge, the mean score on the NIHSS scale in this group was 0,93 points and the level of functional independence was assessed according to the modified Rankine scale as in Fig. 2, finally, in this group of patients it made 0,5 points (while 7 patients - 0 points).

At admission, the total score in the second group was 6,32, the course of the disease was marked by significant polymorphism: in 9 patients (13,6%) the neurologic deficit completely regressed during 2-6 days, 36 (54,5%) patients showed no worsening neurological deficit, positive dynamics, and to the extract on the NIHSS scale did not exceed 2,5 points, and the level of functional independence averaged 1,3 points on the Rankine scale. In addition, 21 patients (31,8%) had an increase in neurologic symptoms on average by 4,1 points on the NIHSS scale over the course of 5 days compared to the admission status. Subsequently, the regression of neurologic symptoms was noted and to the NIHSS discharge these patients had an average of 8,1 points, and according to the modified Rankine scale 1,8 points.

The total score in the second group of patients on the

Figure 2. Disability and functional independence of patients in the first 3 months (with modified Rankine scale).

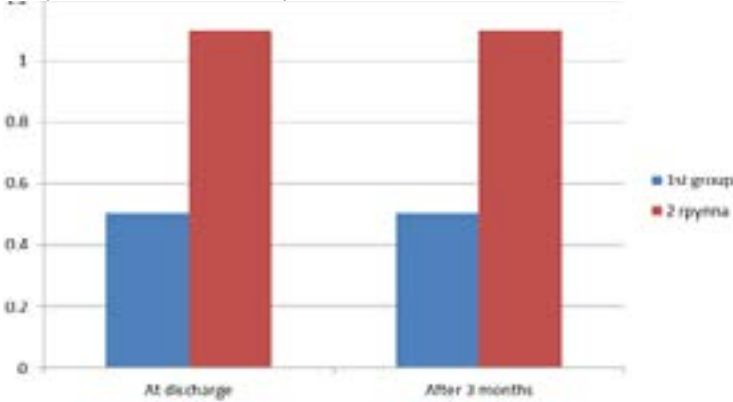
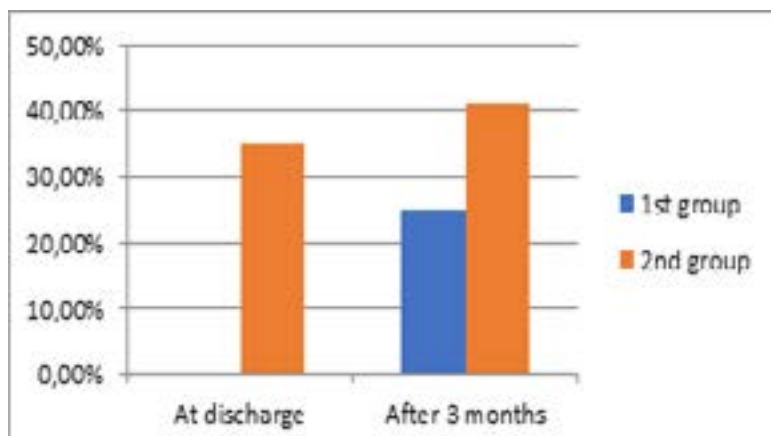


Figure 3 Depressive disorders in the first 3 months of the disease (using the DASS scale).



NIHSS scale was 4,3; and on the Rankin score 1,1. Evaluation of results in treatment on day 90 from the onset of the disease was a significant complication, as patients were usually at home. 8 patients of the first group and 22 of the second group were examined in the clinic, information from the remaining patients or their relatives was obtained as a result of a telephone interview, which reduces the reliability of the results obtained. In the first group of patients, there were no lethal outcomes of the disease. On the NIHSS scale, the mean score was 0 (patients had 0-1 points), Rankin score 0,5; with 8 patients less than 1 point.

In the second group, the death of one patient was noted (repeated ischemic stroke 2,5 months after the first one was transferred). The total score for NIHSS decreased to 1,75 points due to recovery of motor and aphasic disorders, and on the Rankin scale 1,0 point. In addition, we analyzed the depressive disorders that occurred in patients within 3 months after a stroke. As you know, post-stroke depression will significantly slow down the process of recovery, worsening the quality of rehabilitation of patients. The presence of depression is determined using the DASS scale as shown in Fig 3. At discharge, patients in the first group showed an absence of depression. In the second group, 43 patients (65,2%) had no depression (0-9 DASS scores), a mild (10-13) degree of disorders in 13 patients (19,7%) and moderate (14-20 points) depressive disorders in 10 patients (15,1%).

After 3 months, signs of mild depression in DASS were noted in 3 patients of group 1 (25,0%). In the second group, there was a decrease in the number of patients without depressive disorders to 39 people (59,0%), an increase in patients with mild depressive disorders from 13 to 18 patients (27,3%), and 9 patients showed a moderate degree of depression (13,7%). It was also noted that depressive disorders were predominantly observed in persons with focal neurological symptomatology, which, apparently, reflected the quality of life of patients and, as a consequence, increased depressive disorders.

DISCUSSION

In our study, in the first and the second group, there were no dynamics from the moment of discharge and 3 months after the development of the disease. Believing that the process of restoring functions would continue on its own. Patients of the first group easily recovered from motor and aphasic disturbances during their stay in the hospital, they practically did not then engage in a speech therapist and rehabilitator session. In the second group, patients underwent a course of rehabilitation, both in the hospital (Department of Neurorehabilitation) and outpatient (at rehabilitation clinics or individually with rehabilitation specialists), which is confirmed by the NIHSS indices, however, mostly pre-retirement and retirement patients noted that the help of relatives was necessary, because they are afraid to leave the house themselves, prepare food, wash clothes and bathe. In our opinion, it is mainly due to psychological problems. First, it ensures frequent visits to children and grandchildren, increased attention of relatives, and secondly, facilitates the quality of life in these patients.

We found that the dynamics of depressive disorders was found to be very interesting. In the first group of patients, by the end of 3 months, the number of violations reached 25% due to the appearance of many disorders (at discharge). It can be assumed that finding a home (all patients did not work), the isolation in the pastime, decreased social communication with friends contributed to the appearance of depressive syndrome. In the second group there is an increase in the total number of patients with depression from 34,8% to 41,0%, with a decrease in the number of patients without signs of depression and with moderate severity, and the number of patients with mild depressive disorders (from 19,8% to 27,3 %). These causes can be considered characteristic to the first group, but the presence of a motor deficit and a higher degree of functional dependence are additional.

Marten G et al in their study mentioned that in acute ischemic stroke treatment can be started within 3 or 4,5 hours of symptom onset with intravenous (IV) (r-tPA) over without using it¹⁰.

Kim JT et al in their study stated the initiation of thrombolysis within the first (golden hour) of stroke, associated with regression of their symptoms in patients with acute ischemic stroke¹¹.

Emberson J et al with 6756 patients and 9 randomized clinical trials mentioned that Alteplase is effective in treatment of acute ischaemic stroke, especially in older patients as well as in patients with recurrent strokes. The author postulated the beneficial effects of Alteplase usage with 4.5 hours of stroke onset. They also compared the results with

and without the administration of Alteplase and stated the positive outcome of its administration¹².

Logallo N et al with 1100 patients conducted a randomized blinded endpoint trial stating Tenecteplase is a new thrombolytic agent with some pharmacological benefits compared to Alteplase but further clinical trials are necessary for proving the benefits and safety usage of Tenecteplase over Alteplase¹³.

Breuer et al in their study stated that there were no specific benefits found after thrombolytic therapy in patients who underwent MRI screening and in patients without MRI screening¹⁴.

Tsivgoulis et al in their meta-analysis showed that use of high-frequency ultrasound can achieve complete recanalization of arteries when compared to rt-PA alone¹⁵.

Sandercock et al in their study on 3035 participants, stated the results of the third International stroke trial (IST-3), administered IV alteplase within 6 hours of stroke onset, improving the functioning in patients¹⁶.

Anderson et al conducted the ENCHANTED study, to compare the dosage of alteplase with standard dosage with that of lower dosage of its administration. They hypothesized that lower dosage of alteplase could possibly reduce the risk of intracerebral hemorrhage and improve recovery¹⁷.

Rothwell P, in his 2016 round up review mentioned different studies on stroke and its management in a clinical setting. He discussed about ATACH-2 trial and INTERACT-2 trial which focused on moderately reducing the systolic blood pressure, which increased the safety, lowering the disability in acute stroke patients. A high systolic of 180mm/hg was reduced using IV nicardipine, to an average of 140mm/hg¹⁸.

Sandercock P and Ricci in their systematic review clearly confirm that 'time is brain as the priority for recognizing these patients and fast track transportation to the hospital during the golden window period, followed by clinical and

radiological investigations and prompt TLT. These could reduce the neurological deficits and increase the quality of life².

Moussaddy et al in their systematic review, discussed the future considerations on stroke therapy. They described clot imaging, Angio-suite imaging and external thrombi-retrievers which describe the thrombus composition, playing a potential role in putting the clinical diagnosis and initiating urgent treatment protocols. The introduction of pre-ambulatory treatments have been emphasized in their literature, which could possibly serve as modern mobile stroke units equipped with a CT scanner and thrombolytic agents¹⁹.

It is interesting that the patients of the first group noted that the fact of carrying out the most modern and expensive method of treatment of ischemic stroke, which inspired them with confidence in the positive result of therapy and recovery. After a comparative analysis of the results of treatment of patients, it can be noted that the severity of the neurologic deficit in the NIHSS scale is more pronounced and rapid in patients of group 1 (Figure 1), however, in the second group there is a persistent positive dynamic (from 6,32 to 1,45 points), which can be explained by the fact that all patients had mild disease form and the effectiveness of rehabilitation measures.

Conclusions: Both in the first and in the second group the older people were more susceptible to depression.

The results suggest that the dynamics of the degree of neurological deficit and functional independence of patients is more pronounced in the group of patients where the treatment of ischemic hemispheric stroke was performed with the use of thrombolytic therapy, and, consequently, intravenous thrombolysis in patients with spontaneous early regress of neurological deficit is expedient, and failure is not always justified.

REFERENCES

1. Bivard A, Levi C, Krishnamurthy V, et al. **Perfusion computed tomography to assist decision making for stroke thrombolysis.** *Brain.* 2015 July 1;138(7): 1919-31.
2. Sandercock P, Ricci S. **Controversies in Trombolysis.** *Curr Neurol Neurosci Rep.* 2017 Jun 30;17(8):60. Doi: 10.1007/s11910-017-0767-5. PubMed PMID: 28667504; PubMed Central PMCID: PMC5493717
3. O.O. Filipets, V.M. Pashkovsky. **Stroke burden in ukraine: analysis of the official stroke statistics and overview of population-based epidemiological studies.** *Clin. and experim. Pathol.* 2014;13(3 Suppl 49):189-93.
4. Royal college of physicians, National clinical Guideline for stroke prepared by intercollegiate stroke working party. 2016; 5th Edition. Available from: <https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-%281%29.aspx>
5. Stroke, Available from: <http://www.strokecenter.org/patients/about-stroke/what-is-a-stroke/>.
6. Luciana C, Joseph T, Marc F. Acute Ischemic Stroke Therapy Overview. In *stroke compendium of Clinical Research* page 541-558. February 3, 2017.
7. Bernhard N, Christoph K, Guido S et al. **Ischaemic stroke: a thrombo-inflammatory disease.** *J Physiol.* 2011 Sep 1; 589(Pt 17): 4115-23.
8. Milija D. Mijajlovic. **Thrombolytic or endovascular therapy for acute ischemic stroke: Time is brain.** *J Neurosci Rural Pract.* 2014 Jan-Mar; 5(1): 3-5.
9. Hacke W, Kaste M, Fieschi C et al. **Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke.** The European Cooperative Acute Stroke Study (ECASS), *JAMA.* 1995 Oct 4; 274(13):1017-25.
10. Maarten G, Lansberg, Martin J, et al. **Antithrombotic and Thrombolytic Therapy for Ischemic Stroke, Antithrombotic Therapy and Prevention of Thrombosis,** 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Chest. 2012 Feb; 141(2 Suppl): e601S-e36S.
11. Kim JT; Fonarow GC; Smith EE, et al. **Treatment With Tissue Plasminogen Activator in the Golden Hour and the Shape of the 4.5-Hour Time-Benefit Curve in the National United States Get With The Guidelines-Stroke Population.** 2017; 135(2):128-139.
12. Emberson J; Lees KR; Lyden P, et al. **Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomized trials.** *Lancet.* 2014;

384(9958):1929-35.

13. Logallo N, Novotny V, Assmus J, et al. **Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomized, open-label, blinded endpoint trial.** *Lancet Neurol.* 2017; 16(10):781-8.

14. Breuer L., Schellinger P.D., Huttner H.B., et al. **Feasibility and safety of magnetic resonance imaging-based thrombolysis in patients with stroke on awakening: Initial single-centre experience.** *Int J Stroke.* 2010;5: 68–73

15. Tsivgoulis G., Eggers J., Ribo M., et al. **Safety and efficacy of ultrasound-enhanced thrombolysis: A comprehensive review and meta-analysis of randomized and nonrandomized studies.** *Stroke.* 2010;41: 280–287.

16. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, et al. **The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomized controlled trial.** *Lancet.* 2012;379(9834):2352–2363.

17. Anderson CS, Robinson T, Lindley RI et al. **Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke.** *NEJM.* 2016; 374(24):2313–2323.

18. Rothwell PM. **Stroke research in 2016: when more medicine is better, and when it isn't.** *Lancet Neurol.* 2017;16(1):2–3.

19. Moussaddy A, Demchuk A.M, Hill M.D. Invited review. **Thrombolytic therapies for ischemic stroke: Triumphs and future challenges.** *Neuropharmacology.* 2018 May. 134 (Part B):272-9.