The effectiveness of thrombolytic therapy in the acute phase of ischemic stroke based on the experience of the rural community of the Lublin Province in eastern Poland

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Abstract

Background: Intravenous thrombolysis - recombinant tissue plasminogen activator is currently popular among the recommended treatments for fresh ischemic stroke, mainly within 4 – 5 hours of the first symptoms. Still too many patients are delayed or not eligible for causal treatment because of a time out. Despite the growing public awareness associated with brain vascular diseases, there are still environments where it seems inadequate. This mainly applies to rural areas. Evaluation of the effectiveness of thrombolytic therapy in the acute phase of ischemic stroke on the background of differences related to the time of measurement. The aim of the study was to assess the effectiveness of thrombolytic therapy in the acute phase of ischemic stroke based on the experience of the rural community of the Lublin Province in eastern Poland.

Methods: The diagnostic survey method with the survey technique was used. A standardized research tool was used - the National Institute of Health Stroke Scale (NIHSS). The study involved 81 patients of the Department of Neurology - Stroke Unit of the Provincial Specialist Hospital in Lublin, reporting their place of residence in rural areas.

Results: The biggest difference in patients treated with alteplase was observed in measurements between day 1 and 10 (Z = 3.951, p <0.001), where the average NIHSS score on the first day it brought M = 10.36, and on the 10th day M = 4.04. A slight difference in NIHSS scores was observed in patients who did not receive thrombolytic therapy. The largest difference was observed between day 1 and 10 (Z = 5.408 p <0.001), where the average NIHSS score on day 1 was M = 9.08 and on 10. M = 5.21.

Conclusions: Among patients who received thrombolytic therapy there was a faster improvement in neurological status compared to patients who did not receive such treatment.

Key words: thrombolytic therapy; ischemic stroke; rural community; NIHSS scale

Introduction

Thrombolytic treatment with a recombinant tissue plasminogen activator (rt – PA) has been in use for acute ischemic stroke for several years. In randomized international clinical trials, it has been shown that this method is effective and safe, provided that the drug administration procedures are followed, contraindications are taken into account, and the 3 – 4.5 – hour time window regime is respected (1-4). The effectiveness of this method has been confirmed both in the treatment of strokes caused by cerebrovascular thrombosis, lacunar strokes and strokes caused by arterial emboli (5). A recombinant tissue plasminogen activator is used at a dose of 0.9 mg / kg of body weight to a maximum of 90 mg / kg of body weight, with 10% of the dose is administered in a bolus within 1 – 2 min, the remaining 90%, in a continuous one – hour infusion (6).

In the NINDS (National Institute of Neurological Disorders and Stroke) clinical trial, it has been demonstrated that in patients treated up to 3 hours, the therapy reduces the absolute risk of disability or death after 3 months by 13%, and the beneficial effect persists up to one year after the stroke (7). The ECASS 3 (European Cooperative Acute Stroke Study) study, however, proved that in patients treated for 3 – 4.5 hours, an additional 7% chance for a favorable prognosis was found as 0 – 1 in the modified Rankin scale (8).

A recently published IST – 3 (Third International Stroke Trial) trial found that the thrombolysis applied up to 6 hours after the onset of symptoms improves the prognosis in some patients. Patients treated with thrombolysis more often regained a total health condition. This applies mainly to older patients, in a severe neurological status and to patients fully efficient prior to stroke (9). The reduction of the absolute risk of death or disability after thrombolysis during the 6 – month follow – up was 3% and was statistically significant. These results were confirmed by a combined meta –
analysis of clinical trials in which rt – PA was used within 6 hours from the onset of symptoms (10). The chance of achieving full efficiency (0 – 1 points in the modified Rankin scale) equaled to even 6% more after thrombolysis. The results of the IST – 3 trial and the meta – analysis mentioned above justify the admission of rt – PA application up to 6 hours after the first symptoms of stroke. In addition, the IST – 3 study confirmed that the benefits of rt – PA therapy are those gained by patients who are above 80 years old, with clinically severe (≥ 20 NIHSS points) and a small neurological syndrome (≤ 5 NIHSS points) (9).

Before the treatment is implemented, the exact time of the occurrence of the first symptoms of stroke should be determined, e.g. on the basis of an interview with the patient or close relatives. If the precise hour of onset of stroke symptoms cannot be indicated, the beginning of the stroke is considered to be the last moment when the patient was seen without symptoms.

Stroke is the main cause of disability in adults. Rapid treatment plays a very important role in preventing the effects of previous brain stroke. Knowing, identifying and modifying risk factors also plays a high role here. Patients with suspected stroke should be transported to the stroke ward, and often patients living in rural areas first go to intermediate hospitals, which also extends the time to diagnose the problem and provide appropriate assistance. If a patient qualifies, he should receive causal treatment, i.e. intravenous administration of recombinant tissue plasminogen activator (rt-PA; intravenous thrombolysis). Still too many patients are delayed or not eligible for causal treatment because of a time out. Despite the growing public awareness associated with brain vascular diseases, there are still environments where it seems inadequate. This mainly applies to rural areas. Evaluation of the effectiveness of thrombolytic therapy in the acute phase of ischemic stroke on the background of differences related to the time of measurement (11-15).

The aim of the study was to assess the effectiveness of thrombolytic therapy in the acute phase of ischemic stroke based on the experience of the rural community of the Lublin Province in eastern Poland.

Materials and Methods

Research material

The research was carried out in eastern Poland in the Lublin Province. The examination involved 81 patients, hospitalized in the Department of Neurology – the Subdivision of Stroke Treatment of the Province Specialist Hospital in Lublin, reporting their place of residence in a rural area. The collection of research material utilised the diagnostic survey method, with the use of the survey technique. The following criteria for qualifying patients for the study were established:

- hospitalization due to ischemic stroke,
- age above 18 years,
- rural area, notified as a place of residence,
- written consent of the patient,
- physiological breath without support,
- consciousness preserved.

Methods

In order to implement the selected research technique, a tool was used - The National Institute of Health Stroke Scale (NIHSS). This tool enabled a schematic and quantitative understanding of the intensity of the neurological deficit based on elements of the neurological examination. In quantitative (point) assessment, the scale gives comparative possibilities for changes in the patient’s condition spread out over time. When examining a patient using this scale, the following are assessed:

1a. level of consciousness
1b. answer to the question about the month and age,
1c. carrying out orders
2. eye mobility,
3. field of view,
4. facial nerve palsy,
5. muscular strength of the upper limbs,
6. muscular strength of the lower limbs,
7. presence of ataxia,
8. sensory disturbance,
9. aphasia
10. dysarthria,
11. responding to external stimuli.
The NIHSS scale is also used to predict the patient’s functioning after a stroke and for this reason it is used as a measure of final results in clinical trials. It was found that the values of 16 points in the acute period of stroke correlate with a high probability of death or high post-stroke disability, while a score of 6 points correlates with good long-term treatment results. Other studies confirm a similar relationship - the lower the NIHSS value in the acute period of stroke, the greater the chance of the patient’s independence after the disease (16).

The condition of each patient was verified three times: on the first, seventh and tenth day of hospitalization. Group of 28 patients underwent a thrombolytic treatment (intravenous administration of alteplase), while 53 of them, due to existing contraindications, did not receive such a treatment. The most frequent contraindication was their presence in the hospital ward beyond the so – called therapeutic window.

**Ethical aspects**

The study was anonymous and voluntary. All respondents met the inclusion criteria and gave their written consent to participate in it. The Bioethical Commission of the Medical University of Lublin (Poland) approved the study in accordance with the requirements of the Helsinki Declaration (KE decision number - 0254/91/2015).

**Statistical analysis**

The empirical data collected was statistically analyzed. Values of measurable parameters were included by mean (M), median (Me), minimum values (Min) and maximum (Max), lower (Q1) and upper quartile (Q3) and standard deviation (SD), and for non – measurable by means of cardinality (N) and interest (%). The Shapiro-Wilk test of normality was used to check the normality of the distribution of variables. The Mann – Whitney nonparametric test was used to assess the differences between the two groups, and in the case of comparison of two subsequent measurements (dependent tests) the Wilcoxon pairs order test. The relationships between selected variables were assessed using Pearson’s correlation (after removal of outliers). A level of significance of p <0.05 indicating the existence of statistically significant differences or dependencies was adopted. Statistical analyzes were performed in the Statistica 9.1 program (StatSoft, Poland).

**Results**

**Analysis of differences in the NIHSS scale of the entire study group on the first, seventh and tenth day**

In the assessment of neurological status of all the examined patients, statistically significant differences were found in each measurement. Between the first and seventh day, the scoring differences were $Z = 6.385, p <0.001$. Between the seventh and tenth day the differences were $Z = 4.094, p <0.001$. Between the first and the tenth day the difference was $Z = 6.653, p <0.001$. After examining the whole control group, it can be concluded that the number of NIHSS points decreased significantly, which indicates an improvement in neurological status of patients. The statistical analysis is presented in Table 1.

<table>
<thead>
<tr>
<th>Day</th>
<th>M</th>
<th>Me</th>
<th>Min.</th>
<th>Max.</th>
<th>Q1</th>
<th>Q3</th>
<th>SD</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.52</td>
<td>8.00</td>
<td>1.00</td>
<td>24.00</td>
<td>5.00</td>
<td>14.00</td>
<td>5.80</td>
<td>1. and 7. day $Z=6.385, p&lt;0.001$</td>
</tr>
<tr>
<td>7</td>
<td>5.41</td>
<td>3.00</td>
<td>0.00</td>
<td>21.00</td>
<td>2.00</td>
<td>8.00</td>
<td>5.22</td>
<td>7. and 10. day $Z=4.094, p&lt;0.001$</td>
</tr>
<tr>
<td>10</td>
<td>4.80</td>
<td>3.00</td>
<td>0.00</td>
<td>21.00</td>
<td>1.00</td>
<td>7.00</td>
<td>4.97</td>
<td>1. and 10. day $Z=6.653, p&lt;0.001$</td>
</tr>
</tbody>
</table>

**Assessment of the differences in the neurological status according to the NIHSS scale with division into thrombolytic treatment (with the participation of rt - PA, alteplase) and without thrombolytic treatment**

Evaluation of neurological status of patients after the thrombolytic treatment (involving rt – PA) indicated the existence of statistically significant differences between the individual measurements. Between the first and seventh day the difference in the NIHSS score was $Z = 3.904, p <0.001$. In addition, there was a difference between the seventh and tenth day at the level of $Z = 2.314, p = 0.021$. The biggest difference was shown between the first and the tenth day $Z = 3.951, p <0.001$. In connection with the above, it should be clearly stated that the obtained NIHSS scale values have...
decreased significantly – neurological status of patients has significantly improved. The detailed statistical analysis is presented in Table 2.

Table 2. Differences in the NIHSS scale among 28 patients treated with thrombolysis

<table>
<thead>
<tr>
<th>Day</th>
<th>M</th>
<th>Me</th>
<th>Min.</th>
<th>Max.</th>
<th>Q1</th>
<th>Q3</th>
<th>SD</th>
<th>Differences</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>10.36</td>
<td>8.00</td>
<td>5.00</td>
<td>22.00</td>
<td>7.00</td>
<td>14.50</td>
<td>4.83</td>
<td>1. 17. day</td>
<td>3.904</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7.</td>
<td>4.75</td>
<td>2.00</td>
<td>0.00</td>
<td>19.00</td>
<td>0.00</td>
<td>9.00</td>
<td>5.71</td>
<td>7. 10. day</td>
<td>2.314</td>
<td>0.021</td>
</tr>
<tr>
<td>10.</td>
<td>4.04</td>
<td>1.50</td>
<td>0.00</td>
<td>18.00</td>
<td>0.00</td>
<td>7.00</td>
<td>5.41</td>
<td>1. 10. day</td>
<td>3.951</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Among patients who did not receive the thrombolytic therapy due to contraindications, an improvement in neurological status was also noted, however, of much less significance. Between the first and seventh day the difference in the NIHSS score was Z = 5.009, p <0.001. An important difference was also recorded between the seventh and the tenth day (Z = 3.523, p = 0.001). The biggest difference was observed between the first and tenth day Z = 5.408 p <0.001. It should be noted that the decrease in the NIHSS scale values were accompanied by an improved neurological status. The detailed statistical analysis is presented in Table 3.

Table 3. Differences in the NIHSS scale among 53 patients not treated with thrombolysis

<table>
<thead>
<tr>
<th>Day</th>
<th>M</th>
<th>Me</th>
<th>Min.</th>
<th>Max.</th>
<th>Q1</th>
<th>Q3</th>
<th>SD</th>
<th>Differences</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>9.08</td>
<td>7.00</td>
<td>1.00</td>
<td>24.00</td>
<td>4.00</td>
<td>14.00</td>
<td>6.24</td>
<td>1. 17. day</td>
<td>5.009</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7.</td>
<td>5.75</td>
<td>4.00</td>
<td>0.00</td>
<td>21.00</td>
<td>2.00</td>
<td>8.00</td>
<td>4.96</td>
<td>7. 10. day</td>
<td>3.523</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10.</td>
<td>5.21</td>
<td>4.00</td>
<td>0.00</td>
<td>21.00</td>
<td>2.00</td>
<td>7.00</td>
<td>4.72</td>
<td>1. 10. day</td>
<td>5.408</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Assessment of the difference in NIHSS between days in subsequent measurements divided into thrombolytic and non-thrombolytic treatment

Further, the differences in the NIHSS scale values were compared between patients with the thrombolytic therapy implemented and the ones without such a treatment. The results of the study indicate the existence of statistically significant differences (days 1 – 7) between the group treated with thrombolysis and non – thrombolysis (Z = 2.856, p = 0.004). In the group of patients treated with thrombolysis, there was a greater decrease in the NIHSS index (M = – 5.61, Me = – 6.00) than in the group of patients not subjected to the thrombolytic therapy (M = – 3.32, Me = – 3.00). In addition, statistically significant differences in the size of the NIHSS change between the first and tenth day were observed (Z = 3.064, p = 0.002). In the group of patients treated with thrombolysis, there was also a greater decrease in the NIHSS index (M = – 6.32, Me = – 7.00) than in the group of patients treated with non – thrombolysis (M = – 3.87, Me = – 3.00). The difference in the NIHSS scale values obtained during the measurement between the seventh and tenth day was not statistically significant (Table 4).

Table 4. Analysis of the difference in NIHSS change between the days in subsequent measurements

<table>
<thead>
<tr>
<th>NIHSS change (day)</th>
<th>Group</th>
<th>M</th>
<th>Me</th>
<th>Min.</th>
<th>Max.</th>
<th>Q1</th>
<th>Q3</th>
<th>SD</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. – 7.</td>
<td>thrombolytic treatment</td>
<td>– 5.61</td>
<td>– 6.00</td>
<td>– 18.00</td>
<td>12.00</td>
<td>– 7.00</td>
<td>– 4.00</td>
<td>5.12</td>
<td>Z = – 2.856, p = 0.004</td>
</tr>
<tr>
<td></td>
<td>non – thrombolytic treatment</td>
<td>– 3.32</td>
<td>– 3.00</td>
<td>– 13.00</td>
<td>8.00</td>
<td>– 6.00</td>
<td>– 1.00</td>
<td>3.86</td>
<td></td>
</tr>
<tr>
<td>1. – 10.</td>
<td>thrombolytic treatment</td>
<td>– 6.32</td>
<td>– 7.00</td>
<td>– 18.00</td>
<td>11.00</td>
<td>– 8.00</td>
<td>– 4.50</td>
<td>5.46</td>
<td>Z = – 3.064, p = 0.002</td>
</tr>
<tr>
<td></td>
<td>non – thrombolytic treatment</td>
<td>– 3.87</td>
<td>– 3.00</td>
<td>– 15.00</td>
<td>5.00</td>
<td>– 6.00</td>
<td>– 1.00</td>
<td>3.98</td>
<td></td>
</tr>
<tr>
<td>7. – 10.</td>
<td>thrombolytic treatment</td>
<td>– 0.71</td>
<td>0.00</td>
<td>– 4.00</td>
<td>2.00</td>
<td>– 1.50</td>
<td>0.00</td>
<td>1.46</td>
<td>Z = – 0.134, p = 0.894</td>
</tr>
<tr>
<td></td>
<td>non – thrombolytic treatment</td>
<td>– 0.55</td>
<td>0.00</td>
<td>– 6.00</td>
<td>1.00</td>
<td>– 1.00</td>
<td>0.00</td>
<td>1.10</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

Currently, thrombolytic treatment seems to be one of the most effective methods of treatment of acute ischemic stroke. It allows to achieve a significant improvement in the condition of patients and their daily functioning, enabling a more independent and active life after a stroke. The very first attempts to use rt – PA in patients with acute ischemic stroke have shown that decongesting a closed cerebral vessel is possible. In a pilot NINDS trial in which various doses of rt – PA (0.35 – 1.08 mg / kg of body weight) were administered to 74 patients in the acute phase of ischemic stroke, the likelihood of recanalisation of the vessel was not significantly affected by the administered dose. However, the probability of intracranial bleeding associated with the therapy significantly increases above the dose of 0.95 mg / kg of body weight. The examination also found a significant improvement in neurological status in 30% of patients having undergone the therapy.

In order to define the factors determining the efficacy and safety of thrombolytic therapy, a meta – analysis of data from ECASS I and II, NINDS and ATLANTIS trials was carried out (17). An observational study / registry of SITS – MOST patients became an important source of information on the safety and efficacy of a thrombolytic therapy. The significance of the arguments was guaranteed by a very large total number of patients from 285 centers maintaining the register. The results of the assessment of the treatment undertaken in the first 3 hours were unambiguously positive – they proved the safety and effectiveness of the therapy and its advantage over not implementing the therapy (18). Evaluation of the data from the same period relating to the treatment implemented in the time span of 3 – 4.5 hours confirmed the safety of the method (18). Case studies of 23942 patients, whose number significantly increased after the publication of the ECASS III study results in 2008, and among whom 2376 patients were treated within the time span of 3 – 4.5 hours from the onset of stroke, showed slightly fewer benefits, perhaps, than within the first 3 hours, but clearly indicated the possibilities of benefits for patients who "did not fit" in a 3 – hour therapeutic window (19).

In the self – assessment of neurological status of patients, the whole group (81 patients) was characterized by the presence of statistically significant differences in each measurement. The decrease in the number of NIHSS points means that neurological status of patients has been gradually improved. The examined patients were divided into 2 groups: the first group constituted patients treated thrombolytically with alteplase, and the other group included patients who were not treated with thrombolysis. Among patients treated with alteplase a significant improvement in the condition of patients was observed or their status deteriorated gradually. In the NINDS trial, the percentage of cured and fully independent patients constituted mere 39%, in the meta – analysis of all randomized controlled trials – 49%, whereas in the SITSMOST register results published in 2007 – 54% (20,21).

The largest meta – analysis of clinical trial results so far (NINDS, ECASS I, ECASS II, ECASS III, ATLANTIS, EPITHET, IST – 3, 6756 patients) confirmed not only the absolute benefit of thrombolytic treatment used in the first 3 hours of stroke, but also the benefit of the later treatment, undertaken 4.5 – 6 hours from the beginning of the incident. Between the third and the sixth month, this benefit involved 2% more risk of death of intracranial bleeding, which, however, was compensated for less disability in 10% treated within the first 3 hours and in 5% treated within 3 – 4.5 hours (22).

In 2012, IST – 3 published results and the meta – analysis of all clinical trials with the use of thrombolysis gave the basis for the possibility of extending the use of the therapy. They showed that a treatment for up to 6 hours after having been affected by a stroke reduced the risk of disability in the 6 – month observation, without increasing mortality during that time, although it slightly increased the number of deaths and intracranial hemorrhages in the first week. However, it was not demonstrated that the treatment between 4.5 – 6 hours was better than the lack of it (9).

It is believed that there is a group of patients, still unidentified, that may benefit from such a therapy. At the same time, it was confirmed that intravenous thrombolysis was beneficial for patients the age of 80 and they were able to benefit even more than patients within younger age groups. In addition, an improvement in health after rt – PA treatment was observed in patients with a small deficit (NIHSS≤5) and severe strokes (NIHSS≥25).
Limitations of the study

The research cited is not free of restrictions. We are aware of the fact that for such a popular disease unit there is a small group of patients.

Clinical implications/future directions

It seems that the possibilities of extending the qualifying indications for the thrombolytic intravenous therapy in cerebral infarction have reached their limits. Therefore, it is necessary to continue the research on shortening the time which elapses between the occurrence of stroke symptoms and patients' request for help and to accelerate in-hospital procedures until the thrombolytic therapy has been implemented.

Conclusions

1. Patients treated with alteplase were characterized by significant statistical differences between individual measurements.
2. In the group of patients treated with thrombolysis, there was a greater decrease in the NIHSS index than in the group of patients not treated with alteplase.
3. Among patients who received the thrombolytic therapy, an improvement in their neurological status was faster than among patients who did not receive such a treatment.

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Ethical Committee Statement: The study was anonymous and voluntary. All respondents met the inclusion criteria and gave their written consent to participate in it. The Bioethical Commission of the Medical University of Lublin (Poland) approved the study in accordance with the requirements of the Helsinki Declaration (KE decision number - 0254/91/2015).

Informed Consent Statement: Informed consent was obtained from all study participants.

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