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Assessment of the Functional Status of Patients with Ischaemic Stroke Receiving Thrombolytic Treatment

Ocena stanu funkcjonalnego chorych po udarze niedokrwiennym mózgu leczonych trombolitycznie

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Abstract

Introduction. Intravenous thrombolysis is a gold standard in the treatment of acute ischaemic stroke. It causes reperfusion in the region of ischaemia and as a result it has a positive effect on functional outcomes of patients. The sooner this treatment is introduced the higher efficacy can be expected.
Aim. The study objective was to assess the functional status of patients with ischaemic stroke, undergoing thrombolytic treatment and the incidence of thrombolysis complications.
Material and Methods. Retrospective studies were conducted on a group of 109 patients hospitalised due to ischaemic cerebral stroke and qualified for thrombolytic treatment. The functional status was assessed with the use of the modified Rankin Scale and National Institutes of Health Stroke Scales on admission and discharge day. The study group included 55 males and 54 females (respectively: 50.5% and 49.5% of the total study population). The subject age was between 32 and 96 years, with the mean age of 69.8.
Results. The average time between the onset of symptoms and initiation of thrombolytic treatment was 182 minutes. The National Institutes of Health Stroke Scale at the moment of qualification for treatment was 10.11 points, and the Rankin Scale was 2.88 points. On the day of discharge, the values were 5.81 and 2.05, respectively. A statistically significant ($p<0.0001$) improvement in the functional status was observed in the group of patients who had no intra cerebral haemorrhage after thrombolysis. The most common complication of thrombolytic treatment was haemorrhagic transformation of the ischaemic stroke focus — 27 cases (24.77%). Death occurred in 9 subjects (8.26% of total), including 6 cases in males (10.91% of males) and was related to haemorrhagic transformation of the ischaemic stroke focus ($p=0.000$).
Conclusions. The implemented treatment of stroke resulted in improvement of the functional status. The most frequent complication was haemorrhagic conversion of stroke. **(JNNN 2020;9(1):12–19)**
Key Words: stroke, thrombolysis, functional status

Streszczenie

Wstęp. Dożylna tromboliza stanowi złoty standard w leczeniu ostrego udaru niedokrwiennego mózgu, powoduje reperfuzję w obszarze niedokrwienia i w efekcie wpływa korzystnie na wyniki funkcjonalne pacjentów, przy czym skuteczność leczenia jest tym większa, im szybciej zostanie ono wdrożone.
Cel. Celem pracy była ocena stanu funkcjonalnego pacjentów z udarem niedokrwiennym mózgu poddanych leczeniu trombolitycznemu oraz częstości występowania powikłań po trombolizie.
Materiał i metody. Badania retrospektywne przeprowadzono w grupie 109 chorych hospitalizowanych z powodu udaru niedokrwiennego mózgu i zakwalifikowanych do leczenia trombolitycznego. Stan funkcjonalny oceniano z zastosowaniem skali Rankin i Skali Udarów Narodowego Instytutu Zdrowia w dniu przyjęcia i w dniu wypisu ze szpitala. W badanej grupie było 55 mężczyzn (50,5% ogółu badanych). Wiek chorych mieścił się w granicach od 32 do 96 lat, średnia wieku wynosiła 69,8.
Wyniki. Średni czas od pojawienia się pierwszych objawów do rozpoczęcia leczenia trombolitycznego wynosił 182 minuty. Punktacja w Skali Udarów Narodowego Instytutu Zdrowia w chwili kwalifikacji do leczenia wynosiła

10,11 pkt, w skali Rankin 2,88 pkt. W dniu wypisu wartości te wynosiły odpowiednio 5,81 i 2,05 pkt. Wykazano istotną statystycznie (p<0,0001) poprawę stanu funkcjonalnego w grupie chorych, u których nie doszło do krwawienia śródmózgowego po zastosowaniu trombolizy. Najczęściej występującym powikłaniem leczenia trombolitycznego było ukrwotocznienie ogniska udarowego — 27 (24,77%) przypadków. Zgon wystąpił u 9 chorych (8,26% ogółu), w tym u 6 mężczyzn (10,91% mężczyzn) i był związany z ukrwotocznieniem ogniska udarowego (p=0,000).
Wnioski. Wdrożone leczenie udaru przyniosło poprawę stanu funkcjonalnego. Najczęściej występującym powikłaniem było ukrwotocznienie udaru mózgu. **(PNN 2020;9(1):12–19)**
Słowa kluczowe: udar mózgu, stan funkcjonalny, tromboliza

Introduction

Ischaemic stroke is an important social and economic problem due to high incidence and high disability and mortality rate. In Poland, the incidence of stroke is constantly growing, and currently accounts 90 thousands per year, while in the 2nd half of the 20th century there were about 60/70 thousand of new cases per year [1].

Stroke is the main cause of adult disability in Poland; therefore, prompt diagnosis and implementation of adequate treatment is of a key importance. Since 1996, when FDA (Food and Drug Administration) approved alteplase (recombinant tissue plasminogen activator, rt-PA) for thrombolytic treatment of ischaemic stroke, intravenous thrombolysis has been a gold standard in the treatment of acute stroke [2]. In Poland, alteplase has been registered for the treatment of stroke since 2003. Results of randomised studies have shown that the use of this kind of treatment, within 4.5 hours of the occurrence of stroke symptoms causes reperfusion in the region of ischaemia and as a result it has a positive effect on functional outcomes of patients, wherein treatment efficacy is the higher, the sooner it is introduced [3,4]. Currently, two treatments are recommended for an acute phase of ischaemic stroke: intravenous thrombolytic therapy and mechanical thrombectomy involving mechanical removal of thrombus from the cerebral vessel [5–7].

Thrombolytic treatment, despite its numerous benefits, involves a risk of adverse effects and complications, mostly haemorrhagic, which primarily stem from prolonged period of bleeding. The main complication of thrombolytic treatment is intracranial bleeding, which mainly includes haemorrhagic transformation of the ischaemic focus and intracerebral haemorrhage. Symptomatic intracranial bleeding was reported in 1.7–8.0% of treated patients [8–12]. Studies of Lokeskrawee T. et al. [13] conducted on a group of 1172 patients showed 21.2% cases of intracranial haemorrhage after thrombolysis, including 13.1% asymptomatic haemorrhage and 8.1% fully symptomatic intracerebral haemorrhage. Serious systemic (extracranial) haemorrhages were reported in 0.4–1.5% of patients [10,11]. Haemorrhagic complications typically include bleeding from impaired blood vessels (e.g. at the site of injection, biopsy, after catheterisation, injuries), less frequently bleeding from the respiratory pathways (e.g. epistaxis, haemoptysis), from oral mucosa and from upper and lower parts of the gastrointestinal tract, as well as from the urogenital system in females [9,14]. Angiooedema of tongue, lips, face or neck was reported in 1–5% patients receiving intravenous rt-PA [15,16]. In the majority of cases, the symptoms were not intense and resolved quickly. A significant correlation between such reaction and concurrent use of angiotensin-converting enzyme inhibitors was revealed.

The study objective is to assess the functional status of patients with ischaemic stroke undergoing thrombolytic treatment and the incidence of treatment complications.

Material and Methods

Retrospective studies were conducted in a group of 109 patients, including 55 males and 54 females (respectively: 50.5% and 49.5% of the whole study population) hospitalised in 2017–2018 in the Stroke Department of the Provincial Specialist Hospital in Słupsk due to ischaemic stroke, who were qualified for thrombolytic treatment. The patients age was between 32 and 96 years, with the mean age of 69.8 and median 70 years. The assessment of the functional status was based on a modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS) [17]. The functional status was assessed twice: on admission and discharge from the Stroke Department. In the mRS the patient may receive from 0 to 5 points. 0 means no symptoms and 5 means severe disability. In the NIHSS, the range of points is 0 to 42, and similarly to the Rankin scale, the fewer points, the lower neurological deficits. The analysis accounted for the patient age, sex, stroke risk factors and comorbidities, time between the onset of symptoms and treatment implementation, incidence of haemorrhagic transformation and other complications. The studies and publication of results were approved by the Management Board of the Provincial Specialist Hospital in Słupsk and Local Ethical Committee (KB-9/20).

Statistical analysis was performed with the use of Statistica software, version 13.3). The results of the conducted studies were considered statistically significant when $p<0.05$. A Shapiro–Wilk test was used to determine the distribution of the study variables. A non-parametric Mann–Whitney U test was used to compare a quantitative trait without normal distribution between independent groups. In order to assess changes in the functional status in time, a Wilcoxon signed-rank test was conducted for comparisons of two dependent variables. Pearson's χ^2 test was used to assess significance of differences in dependent variables expressed in an ordinal and nominal scale.

Results

Characteristics of the Study Group

In the study group, 76 subjects (69.72% of total) had ischaemic stroke for the first time in their life, including 35 women, which is 64.81% of all study females and 41 males — 74.54% of all study males. Right-sided stroke occurred in 50 study subjects (45.9%), and left-sided stroke occurred in 55 subjects (50.5%).

The most common comorbidity was arterial hypertension, which occurred in 96 patients (88.07% of total) and was significantly more frequent in males than in females (p=0.0356). Diabetes occurred in 41 patients (37.67% of total). Atrial fibrillation was diagnosed in 32 subjects (29.36%), and coronary heart disease occurred in 26 study subjects (23.85% of total subjects) (Table 1).

Complications of Thrombolytic Treatment

The most common complication of thrombolytic treatment was haemorrhagic transformation of the ischaemic focus — 27 cases, which is 24.77% of the total study subjects. In females, there were 12 cases of haemorrhagic transformation (22.22% of study females), and in males there were 15 cases (27.27% of study males). Death occurred in 9 subjects (8.26% of total), including 6 males (10.91% of males) and 3 females (5.56% of females) and was related to haemorrhagic transformation (p=0.000). The second most common complication was the occurrence of subcutaneous haematomas in 19 subjects (17.43% of total), including 13 females (24.07% of females) and 6 males (10.91% of males). Bleeding from the urinary tract occurred in 18 subjects (16.67% of total), including 6 females (11.11% of females) and 12 males (21.82% of males). No significant correlation was observed between sex and the incidence of complications following thrombolytic treatment. Age was statistically significant regarding such complications as tract urinary bleeding (p=0.032) and death (p=0.017) (Table 2).

A statistically significant correlation was reported between haemorrhagic transformation of ischemic stroke and the occurrence of diabetes (p=0.001). In patients with a neoplastic disease, gastrointestinal bleeding was reported significantly more frequently (p=0.015). The occurrence of ecchymoses was significantly correlated with the presence of diabetes (p=0.002) and obesity (p=0.034). The occurrence of patient death was statistically significantly correlated with the occurrence of diabetes (p=0.009) and atrial fibrillation (p=0.010) (Table 3).

Table 1. Incidence of comorbidities and other modifiable risk factors

Incidence of co-morbidities /risk factors	Female N=54 (100%)		Male N=55 (100%)		Total N=109 (100%)		M vs F (p<0.05)*
	N	%	N	%	N	%	
Arterial hypertension	44	81.48	52	94.55	96	88.07	0.0356
Diabetes	20	37.04	21	38.18	41	37.61	0.9029
Atrial fibrillation	12	22.22	20	36.36	32	29.36	0.1069
Coronary heart disease	10	18.52	16	29.09	26	23.85	0.1988
Thyroid disease	13	24.07	2	3.64	15	13.76	0.0017
Cancers	3	5.56	10	18.18	13	11.93	0.0424
Urinary tract infection	7	12.96	6	10.91	13	11.93	0.7436
Gout	7	12.96	9	16.36	16	14.68	0.6198
Alcohol dependence syndrome	2	3.7	5	9.09	7	642	0.2554
Obesity	8	14.81	9	16.36	17	15.60	0.8256
Smoking	10	18.52	5	9.09	15	13.76	0.1560

*χ^2 — chi-square test

Table 2. Incidence of complications of thrombolytic treatment

Complications of thrombolytic treatment	Female N=54 (100%)		Male N=55 (100%)		Total N=109 (100%)		M vs F (p<0.05)*	Age (p<0.05)**
	N	%	N	%	N	%		
Haemorrhagic transformation of the ischaemic focus	12	22.22	15	27.27	27	24.77	0.546	0.221
Subcutaneous haematomas	13	24.07	6	10.91	19	17.43	0.071	0.052
Bleeding from the urinary tract	6	11.11	12	21.82	18	16.67	0.124	0.032
Psychomotor hyperactivity after rtPa administration	7	12.96	3	5.45	10	9.17	0.178	0.307
Death	3	5.56	6	10.91	9	8.26	0.314	0.017
Gastrointestinal bleeding	0	0.00	5	9.09	5	4.59	0.173	0.342
Allergic reaction	3	5.56	1	1.82	4	3.67	0.304	0.911

*χ^2 — chi-square test, **Mann–Whitney U test

Table 3. Presentation of thrombolysis complications with regard to concurrent diseases

Thrombolysis complications	AH	DM	AF	CHD	ADS	Ob.	Sm.	Ca	G
Haemorrhagic transformation of the ischaemic focus	0.408	0.001	0.136	0.773	0.118	0.633	0.081	0.227	0.222
Subcutaneous haematomas	0.328	0.002	0.817	0.755	0.823	0.034	0.241	0.837	0.881
Bleeding from the urinary tract	0.896	0.724	0.028	0.109	0.224	0.907	0.226	0.416	0.229
Gastrointestinal bleeding	0.707	0.123	0.192	0.856	0.839	0.800	0664	0.015	0.643
Death	0.253	0.009	0.010	0.132	0.416	0.701	0.214	0.324	0.197
Allergic reaction	0.411	0.115	0.355	0.956	0.593	0.381	0.415	0.453	0.397

χ^2 — chi-square test, AH — Arterial hypertension, DM — diabetes, AF — Atrial fibrillation, CHD — Coronary heart disease, ADS — Alcohol dependence syndrome, Ob. — Obesity, Sm. — Smoking, Ca — Cancers, G — Gout

The time-lapse between the onset of symptoms and implementation of thrombolytic treatment varied between 65 and 270 minutes; the mean time was 182 minutes and median time was 180. The most frequently occurring value was 120 minutes. In the group of patients with haemorrhagic transformation of the ischaemic stroke, the average value of this parameter was 185 minutes, and it patients with no haemorrhagic transformation of stroke, the value was 180 minutes. There was no significant correlation between the time-point of treatment implementation and the haemorrhagic transformation of the stroke (p=0.539). Duration of patient hospitalisation varied from 2 to 42 days, with a mean value of 11.11 days and median 8.5 days. The most frequent value was 8 days. The analysis of the material gathered showed a statistically significant correlation between haemorrhagic transformation of ischaemic stroke and duration of hospitalisation (p=0.001). The mean duration of hospitalisation among subjects with no haemorrhagic conversion was 10 days, and among subjects with haemorrhagic transformation the mean duration of hospitalisation was 14.5 days. A statistically significant correlation was reported between haemorrhagic transformation of ischaemic stroke and the number of deaths in the study group (p=0.000) (Table 4).

Table 4. Correlation of death and stroke multiplicity with haemorrhagic transformation of ischaemic stroke

Feature	Criterion	Total N (% totality)	Parenchimal haemorrhage		(p<0.05)*
			Yes (N (% totality))	No (N (% totality))	
Death	Yes	9 (8.26)	8 (7.34)	1 (0.92)	0.000
	No	100 (91.74)	19 (17.43)	81 (74.31)	
Number of stroke	=1	76 (69.72)	17 (15.6)	59 (54.13)	0.377
	≥2	33 (30.28)	10 (9.17)	23 (21.10)	

*χ^2 — chi-square test

Assessment of Patient Functional Status

The mean score in the mRS scale was 2.88 in the first assessment and 2.05 in the second assessment. A comparison of the functional status scores on the day of admission and on the day of discharge showed a statistically significant difference between these two measurements (Wilcoxon signed-rank test p<0.0001) (Figure 1).

The patients with haemorrhagic transformation of stroke on the admission day had a significantly worse mRS score than the patients who did not have this complication (p=0.011). The median mRS score was 4 and 3 points, respectively. On the day of discharge from hospital, the scores were 4 points and 1 point (median), respectively. The values showed statistically significant differences (p<0.0001) (Figure 2). The degree of improvement in the functional status assessed with mRS and expressed as a difference between the scores on the admission and discharge days showed no statistically significant difference between the groups of subjects with and without haemorrhagic transformation, and the values were 0 and 1 point, respectively (p=0.074).

Our results have revealed that patients had significant improvement in their functional status also in the NIHSS score. The mean score in the first assessment was 10.11 points and in the second assessment 5.81 points. A comparison of the functional status scores on the day of admission and on the day of discharge of the patient showed a statistically significant difference between these two measurements (Wilcoxon signed-rank test p=0.000) (Figure 3).

The median NIHSS score on the admission day was 7 points in the group of subjects without haemorrhagic transformation of stroke and 14 points in the group of subjects with this complication. The difference between the values of these measurements was statistically significant. The median values of the functional status assessment in the NIHSS score on the day of discharge from the Stroke Department were 2 points in the group of subjects without haemorrhagic transformation of ischaemic stroke and 11 points in the group with haemorrhagic transformation

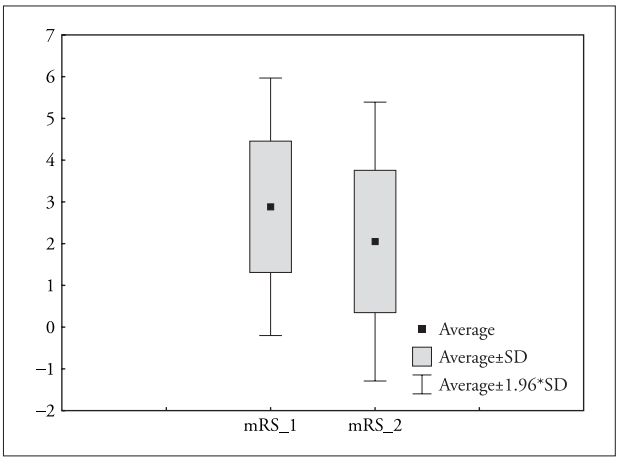

Figure 1. Results of two measurements of the functional status in mRS

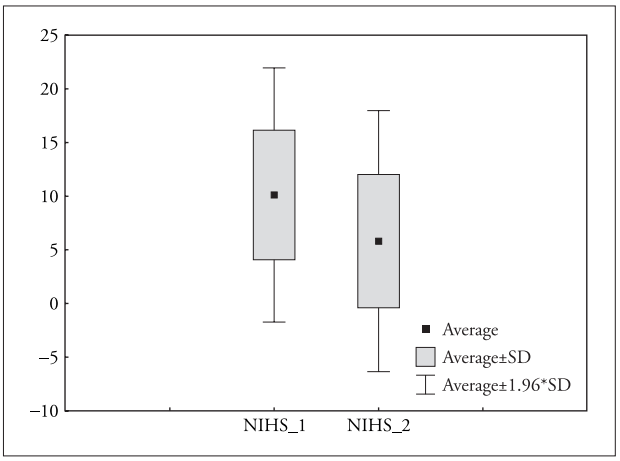

Figure 3. Results of two measurements of patient functional status in the NIHSS scale

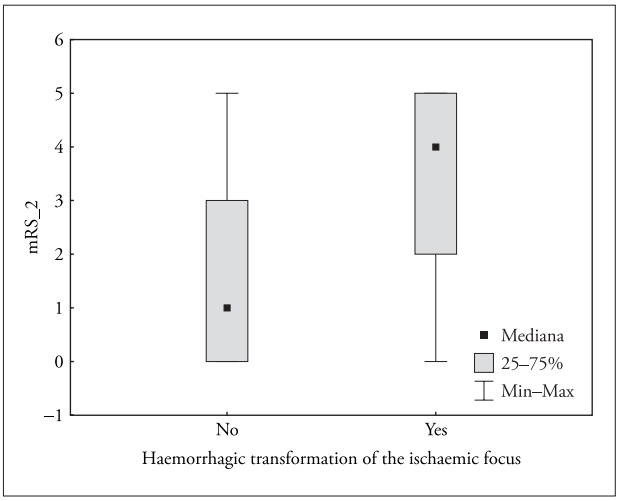

Figure 2. Functional status in the mRS scale on the discharge day depending on the occurrence of haemorrhagic transformation of the ischaemic focus

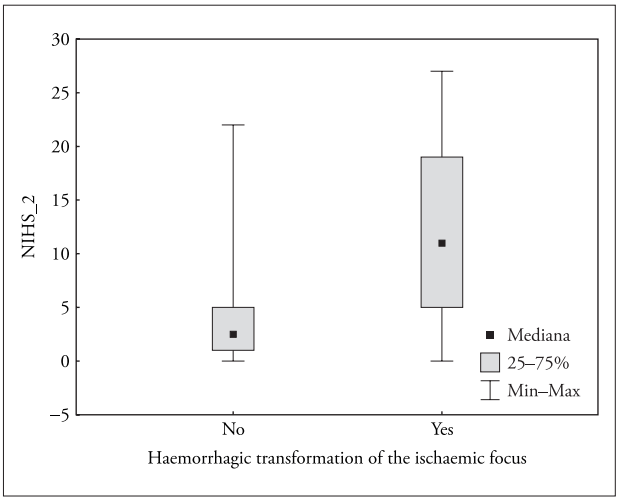

Figure 4. Functional status in the NIHSS scale on the discharge day depending on the occurrence of haemorrhagic transformation of the ischaemic focus

($p<0.0001$) (Figure 4). The degree of improvement in the functional status assessed by NIHSS on the day of discharge from hospital revealed statistically significant difference between the group with and without haemorrhagic transformation of ischaemic stroke (0 and 4 points, respectively; $p<0.0001$).

Discussion

According to the report of the Health Care Institute the incidence of stroke increases with age and is doubled after 55 years of age [18]. Stroke is more common among men, but in the group aged over 70th there are more women. The presented studies were conducted in the group of 109 patients with a history of ischaemic stroke receiving thrombolytic treatment. The study group comprised 54 females (49.54%) and 55 males (50.46%). The mean age was 69.8 years and the median was 70 years. In studies by Gurański et al., [19] the mean age of patients receiving thrombolytic treatment was 53 years. Similarly, in studies by Rosińczuk et al., [20] the largest age group (30% of study subjects) was between 52 and 59 years. However, studies by the other authors prove that stroke and implemented thrombolytic therapy refer primarily to subjects over 65 years of age [8,13,20–23].

The main factors predisposing to ischaemic stroke include: arterial hypertension, atrial fibrillation, diabetes, ischaemic heart disease [19]. Also obesity, smoking cigarettes or alcohol abuse involve a risk of ischaemic stroke. These modifiable factors are frequently associated with the other risk factors [18]. With regard to the presented study results, most patients had arterial hypertension. Every third patient had diabetes and atrial fibrillation, and every fourth patient suffered from the ischaemic heart disease. The study group also included smokers, subjects diagnosed with mental and behavioural disorders due to use of alcohol and subjects with obesity. However, no correlation was observed between the occurrence of these conditions or risk factors and complications during thrombolytic treatment. Only diabetic patients demonstrated a higher frequency of haemorrhagic transformation of stroke and death in comparison with other patients. Atrial fibrillation was also associated with a higher risk of death in the study group.

The time-lapse from the onset of symptoms to administration of alteplase was slightly longer in the study group than the values achieved in multicentre studies and other similar published studies, where it ranged between 130 and 140 minutes [24–28]. In the presented studies, the mean time from the onset of stroke symptoms to introduction of thrombolytic treatment was 182 minutes (range from 65 to 270 minutes). The cause of the difference may be attributed to the logistic transport solutions and work organisation at hospital emergency departments, including efficacy of hospital procedures. The results similar to ours were presented by Lokeskrawee T et al. [13]. In this study, the mean time from the onset of symptoms to the implementation of thrombolytic treatment was 175 minutes in the group of subjects with intracerebral haemorrhage and 168 minutes in the group of subjects without haemorrhagic transformation of stroke. The presented studies showed no significant effect of the time of treatment implementation on haemorrhagic transformation of stroke. However, haemorrhagic transformation of stroke had a significant effect on duration of hospitalisation.

In the presented study, the most common complication of thrombolytic treatment was haemorrhagic transformation of the stroke focus and it occurred in 24.77% of the study group. Sex and age of the patients were non-significant for the occurrence of this complication. Based on the analysis of the material gathered it was shown that diabetic patients significantly more frequently suffered from haemorrhagic transformation. There was also a significant correlation between haemorrhagic transformation of stroke and death, which occurred in 9 patients, i.e. 8.3% of the study group, including only one case without intracerebral haemorrhage as a complication of thrombolysis. Wawrzyńczyk M. et al. [28] in their retrospective study on a group of 70 patients receiving thrombolytic treatment, revealed that hospital mortality in the study group was 11.4%, and intracerebral haemorrhage caused by thrombolysis occurred in 21.1% of subjects. Similar results were presented by Lokeskrawee T. et al. [13]. In a group of 1172 patients there were 21.2% cases of intracerebral haemorrhage after thrombolysis, including 13.1% asymptomatic haemorrhage and 8.1% fully symptomatic intracerebral haemorrhage.

The degree of neurological deficit has a significant effect on the course of thrombolytic treatment, a risk of haemorrhagic complications and prognosis. In the study group, the average NIHSS score on admission to the department was 10.11 points, and in the mRS scale — 2.88 points. These results were comparable with the extent of neurological deficit in other studies [19,20, 28,29].

The mean level of improvement in the functional status according to the NIHSS score was 4.3 points (difference of two measurements — on the day of admission to and discharge from hospital), and according to the mRS scale, the difference was on average 0.83 point to the benefit of the patient. A statistically significant improvement in the functional status was shown with regard to the NIHSS score measurement. However, a change in the functional status measured in the mRS scale was not statistically significant. This results from

the range of point scales, and as a consequence, from their sensitivity. In the mRS scale, the range of points is small, i.e. from 0 to 5, while the NIHSS scale has a range from 0 to 42, which ensures higher sensitivity of the latter scale. A similar therapeutic outcome was shown in the studies by Gurański et al., [19] where improvement in the patient functional status after thrombolytic treatment was on average 4 points in the NIHSS scale. Similarly, Wawrzyńczyk et al. and Rosińczuk et al. showed significant improvement in the functional status assessed with NIHSS scale in two measurements before introduction of the thrombolytic treatment and 24 hours after treatment [20,28].

The analysis of our results revealed statistically significant correlation between haemorrhagic transformation of stroke and the functional status. The patients with haemorrhagic transformation of stroke had significantly lower scores in the functional status on the day of admission to the department than the patients without haemorrhagic transformation of stroke. Similarly, the assessment of the functional status on the day of discharge of patients with intracerebral haemorrhage after thrombolytic treatment did not reveal improvement in the functional status. For the purpose of further follow-up, it would be justified to prolong studies to at least 90 days of the occurrence of stroke.

Conclusions

1. The thrombolytic treatment of ischemic stroke brought about a significant improvement in the functional state of the patients in the studied group.
2. Haemorrhagic transformation of the ischaemic focus was the most common complication of thrombolytic therapy.
3. Haemorrhagic transformation of the ischaemic focus significantly correlated with a higher percentage of deaths in the studied group and no improvement in their functional status.

Implications for Nursing Practice

The results of the conducted studies confirm the efficacy and safety of thrombolytic treatment in ischaemic stroke. Nursing staff are directly involved in thrombolytic therapy and in current assessment of the patient's functional status and minimizing the risk of thrombolytic therapy complications. Of note is a longer time from the onset of symptoms to treatment initiation than in other authors of studies presented in this paper. The difference is 40–52 minutes. Since time is of key importance for qualification for this kind of treatment, the reason for such a big difference should be investigated. The reasons may be related to several issues: knowledge of the community with regard to recognising first symptoms of stroke and important 4,5 hours of therapeutic window to thrombolysis initiation; pre-hospital assistance and immediate transport to a stroke department, as well as in-hospital procedure, which, if improperly managed, may cause a significant delay in the implementation of treatment of specific stroke. Therefore, extensive education is invaluable, not only with regard to educating the society on recognising first symptoms and the importance of time for introducing advanced treatment methods, but also with regard to permanent education of paramedics and other workers of the health care sector. Public education is a very important task for nursing staff.

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