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Dynamics of the Parameters of Platelet Hemostasis in Patients with Ischemic Stroke after Systemic Thrombolytic Therapy

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Abstract

Were examined 89 patients with ischemic stroke (IS) (mean age 58.54 (55.05, 64.73)), 42 of them with systemic thrombolytic therapy (TLT) (mean age 64.26)60.58; 68,06)) and 47 patients with IS without TLT (54,52 (47,48, 60,83)). In the subgroup of moderate severity (from 7 to 14 points in NIHSS) included 13 patients after TLT, of severe severity (more than 15 points for NIHSS) included 29 patients after TLT. The determination of platelet hemostasis was carried out by the method of Born and O'Brien with the determination of aggregation, sizes of platelet aggregates for adrenaline, adenosine diphosphate (ADP), ristomycin, spontaneous aggregation and fibrinogen concentrations on days 1, 7 and 14. Clinical evaluation of the severity of the condition was carried out according to the NIHSS scale. Specific features of changes in platelet hemostasis in inducers (adrenaline, ristomycin, ADP) in patients with IS after TLT at 1, 7 and 14 days in comparison with the indices of patients without TLT and their relationship with the dynamics of neurologic deficit, which allow to clarify the features of the vascular flow process, its forecast.

Keywords: Systemic thrombolytic therapy; Hemostasis; Prognosis; Ischemic stroke; Adrenaline

Introduction

At present, the main cause of death and disability in developed countries are cardiovascular diseases. The frequency of strokes in the world increases and acquires a critical epidemiological situation with a tendency towards rejuvenation. The development of additional prognostic criteria for the course of ischemic stroke after systemic thrombolytic therapy will allow selecting appropriate therapy and thereby reducing the percentage of unfavorable outcomes.

Methods and Materials

In the Regional Vascular Center of the City Clinical Hospital No. 1 named after. N.I. Pirogov were examined 89 patients with ischemic stroke (mean age 58.54 (55.05, 64.73)), of whom 42 patients with TLT (mean age 64.26 (60.58, 68.06)) and 47 patients with non-TLT (54,52 (47,48, 60,83)) [1]. In the subgroup of moderate severity (from 7 to 14 points in NIHSS) with TLT included 13 patients, severe severity (more than 15 points for NIHSS) 29 patients entered. Determination of platelet hemostasis was carried out with the determination of aggregation, sizes of aggregates of platelets on adrenaline, ADP, ristomycin, spontaneous aggregation on days 1.7 and 14. Clinical evaluation of the severity of the condition was carried out according to the NIHSS. Statistical processing of the research data was carried out using the software Statistical 10, Microsoft Excel. A descriptive statistic of continuous quantitative data is presented as a median (Me) for an abnormal distribution, and values of 25% of the lower and 75% of the upper quartiles (via a semicolon). Analytical statistics were performed using the Wilcoxon/Mann-Whitney (mw) rank/mark sum criterion for quantitative data with a distribution different from the normal and the Spearman rank correlation coefficient. Differences were considered significant at $p<0.05$.

Results and Discussion

In 42 patients with ischemic stroke after systemic TLT, the recovery dynamics was significantly ($p_{mw}<0.05$) higher than in patients without TLT-6 (4;7) scores in patients with TLT and 3 (2,4) on the NIHSS score in patients without TLT. Patients at both medium and severe on the NIHSS scale after TLT showed the greatest recovery by the fourteenth day (7 (5.46, 8.12) scores in patients of moderate severity, and 6 (5.32, 7.22) scores in patients with severe disease) compared with patients who did not undergo TLT (3 (2;3) scores in patients with moderate severity, and 3.5 (2;5) scores in severe patients), which can be related to the result conducted systemic TLT; lysis of the thrombus, restoration of perfusion and, as a consequence, reduction of the lesion focus.

At the first stage, the parameters of platelet aggregation for ristomycin were studied. There was a significant decrease in platelet aggregation to ristomycin in patients after TLT, which were within the normal range (50%-70%) to 14 days of observation, which was not observed in patients without TLT (1^{st} day: with TLT - 58.03 (55, 5, 61.23)%, without TLT - 72.85 (57.6, 86.1)% $p<0.001$; 7^{th} day: with TLT - 58.9 (57.42, 61.45)%, without TLT - 73.88 (61.8, 83.1)% $p<0.00001$; 14^{th} day: with TLT - 57.27 (48.67, 60.12)%, without TLT - 74, 48 (69.19, 78.8)% $p<0.000001$). The revealed changes in platelet aggregation to ristomycin in patients after TLT are important for predicting the course of the vascular process and possible complications [2].

These changes in platelet aggregation to ristomycin can be considered as additional markers of endothelial dysfunction and evaluation of the efficacy of systemic thrombolytic therapy and are associated with early thrombus lysis, restoration of perfusion, a decrease in the degree of hypoxia, as a consequence, a decrease in the

volume of circulating free radicals and the degree of damage to the endothelium. Ristomycin binds to von Willebrand factor, which, by interacting with the glycoprotein receptors Ib and IIb/IIIa on the platelet membranes, causes their aggregation. The von Willebrand factor is synthesized by endothelial cells, which release it both into the bloodstream and into the subendothelial space.

The revealed peculiarities of the dynamics of the platelet aggregation parameters for ristomycin in patients after TLT indicate a correction of vascular endothelial function after systemic thrombolysis. In 85% (n=11) patients, after TLT of moderate severity, normal indices of induced platelet aggregation on adrenaline prevailed (on the 1-st day - Me-50.25% (47.13, 51.86), on the 7th day - Me-48, 42 (48,01, 48,57)% and on the 14th day - Me-50,12% (49,09, 50,51)) and in patients without TLT tended to increase (in 1 day was Me-52, 8% (47.5, 64.65), on the 7th day - Me-62.85% (60.0, 64.7) and on the 14th day - Me-65.5.12% (63.27; 69,4). The indices of spontaneous platelet aggregation did not have clear differences in patients after TLT and without TLT and remained within the normal range throughout the monitoring stage, which could be evidence (on the 1st day of Me-0.10% (0.0; 0.75), on the 7th day - Me-0.30% (0.26, 0.33) and on the 14th day - Me-0,31% (0,29, 0,35)) and in patients without TLT (on Day 1 Me-0,03% (0,0; 0,02), on the 7th day - Me-0, 27% (0,0; 0,34) and on the 14th day - Me-1,42% (0,44, 1,45).

It can be assumed that the revealed features of platelet link in patients after systemic thrombolysis are caused by early restoration hemodynamics and microcirculation as well as the delivery of metabolic substrates in zone penumbra that promotes rapid activation of autoregulatory mechanisms, structural and functional processes, improvement of endothelium activity with stimulation of prostacyclin synthesis, transformation of proaggregant prostaglandin H2 into antiplatelet prostaglandin I2, reduction of thromboxane A2 formation. In support of this assumption, the normal platelet aggregation rates for ristomycin (ristocycline) found in patients receiving TLT and significantly elevated figures of this parameter in patients without TLT during the entire follow-up period may support this assumption [3].

The mechanism of platelet aggregation for adrenaline is based on the interaction factor of adrenaline with α2-adrenoreceptors of platelets, which causes inhibition of adenylate cyclase. Probably, this mechanism is associated with the ability of adenylate cyclase to change the permeability of the cell membrane for Ca^{2+} ions. Secondary aggregation during the induction of the process with adrenaline occurs as a result of the release reaction and production of thromboxane A2. Thromboxane A2, in turn, is synthesized by activated platelets. It also activates new platelets and their aggregation. Aggregation of platelets is achieved by increasing the expression level of the GP IIb/IIIa glycoprotein complex on cell membranes. A significant decrease in platelet aggregation rates for adrenaline in patients after TLT is probably due to the effect of systemic TLT on microcirculation and, as a consequence, on endotheliocytes. Vessel endotheliocytes produce a variety of substances with antiplatelet properties and one of them is nitric oxide (NO), which reduces the circulation of free radicals, while NO is consumed to bind free radicals, with a decrease in vasodilating and antiaggregant functions (1-3).

This is confirmed by previous studies the study of microcirculation by laser Doppler flowmetry: in patients in the acute period of ischemic stroke after thrombolytic therapy, there was an increase in blood flow to the microcirculatory bed with the activation of myogenic activity of muscular-containing arterioles. Thus, these mechanisms may indicate a sufficient safety of the regulation of the hemodynamic system and hemostasis (including the morphofunctional properties of platelets) in patients with IS and to a greater extent in patient with IS after systemic TLT [4-6].

The platelet aggregation rates for ristomycin in patients with moderate severity after TLT decreased to normal values (pw<0.05) and were within the normal range (50-70%) until the end of the follow-up period (61.94% at 1 day (58.18, 67.62), on the 7th day - 56.08% (53.73, 60.61) and on the 14th day- 53.63% (40.43, 71.0)), and in patients of moderate severity TLT is higher than normal (79.07% (57.3, 104.86) for 1 day, 74.52% for the 7th day (59.3, 94.64), and for 78 days - 78.68% (74, 43, 90.08), (Figure 1).

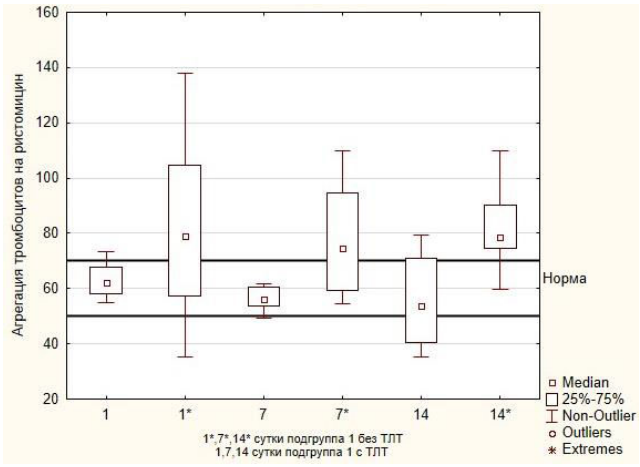

Figure 1: Dynamics of platelet aggregation rates on ristomycin (%) in patients with moderate severity (from 7 to 14 points in NIHSS) with TLT (n-13) and without TLT (n-10) at 1, 7 and 14 days.

These changes in platelet aggregation to ristomycin in patients with moderate severity after TLT (normalization to 14 days of observation) compared with patients who did not undergo TLT can be regarded as restoration of the regulatory function of the endothelium after systemic TLT. Parameters of platelet aggregation on ADP in patients with moderate severity after TLT tended to be reliably reduced by the end of the observation period and from the seventh day were significantly lower than the normal (50%-60%) - 1 day - 49.69% (49.2; 51.2), on the 7th day - 37.91% (36.47; 39,91), on the 14 th day - 34,85% (30,49; 43.29). Patients without TLT were within normal limits until the fourteenth day - 1 day - 57.15% (53.55; 58.0), on the 7th day - 47.5% (43.27; 51,85), on the 14th day - Me-54,47% (49,66; 58,61) (Figure 2). These changes are explained by the activation of platelets ADP, thrombin, thromboxane A2, and other pro-aggregating factors (3) [7-9].

Through the receptors of platelets associated with G-protein, GPIIbIIIa-dependent platelet aggregation is additionally activated. The conglomerate of platelets is constantly increasing at the expense of release of new portions of ADP from the intact platelets involved in the process. This process could continue to spread through the bloodstream if it were not limited to prostaglandin I2.

In response to the release of ADP from platelet aggregation and platelet factor 3, which stimulates the "internal pathway" for the formation of thrombin, an arachidonic cascade is included in intact endotheliocytes and platelets, producing prostaglandin H2, which is

transformed into prostaglandin I2, which prevents further aggregation of platelets, and limits the size aggregate of platelets.

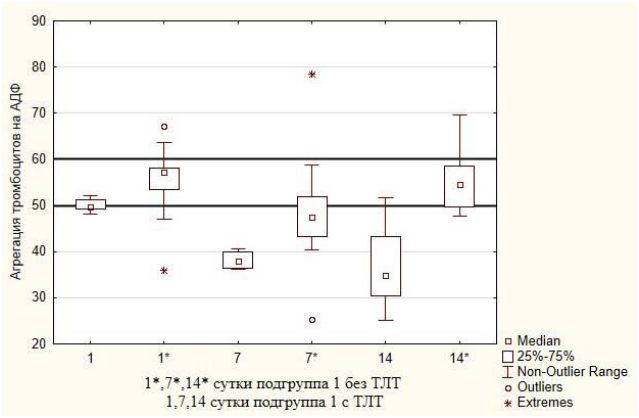

Figure 2: Dynamics of platelet aggregation on ADP (%) in patients of moderate severity (from 7 to 14 points in NIHSS) with TLT (n-13) and without TLT (n-10) on 1, 7 and 14 days.

Carrying out systemic TLT helps to improve the function of endotheliocytes and platelets, as a result of which the concentration of prostaglandin I2 increases, which leads to a significant decrease in platelet aggregation rates on ADP in patients after TLT. In 29 patients after severe thyroidal hypertension (more than 14 on the NIHSS scale) significant ($p<0.05$) decrease in indices of induced platelet aggregation by adrenaline (1.5 - 2 times) below the norm. In one day, -25.61 (23.16; 27,37), on the 7th day - Me-24,3 (23,83; 25.4), day 14 - Me-20.02 (18.94; 21.05). In patients without TLT (n=37), platelet aggregation rates for adrenaline were also below the norm (45-55) to 14 days of observation: on day 1, 26.5 (24; 28.2), on the 7th day - Me-32.35 (29.0; 39.65) and on the 14th day - Me-29.66 (27.5; 31,5), but they did not reach the level of decline in patients after TLT (Figure 3). Probably, these changes in patients after TLT are associated with increased production of platelets and a vascular wall of antiplatelet agents (1-3).

In contrast to patients of moderate severity with a smaller lesion of brain tissue, in this case, in the mechanism of aggregation, NO plays a lesser role, since in patients with a severe degree of large lesion, a much higher degree of hypoxia and a concentration of free radicals, with NO to a greater extent is spent on the binding of free radicals. The platelet aggregation rates for ristomycin in patients after severe TLT were within the normal range (50-70%) until the end of the observation period, as well as in patients with moderate severity after TLT (1st day -54.11 (51.16, 56,98)%, on the 7th day - Me-58.9 (55.19, 60.31)%, on the 14th day - Me-59.63 (58.98, 62.5)%), and in patients with severe degree without TLT above the norm (1 day -76.3 (67.75, 90.65)%, for the 7th day - Me-79.25 (74.59, 84.38)%, for the 14th day - Me-68, 25 (65.51, 73.13)%) (Figure 4) [10].

Thus, normal platelet aggregation rates in patients with severe disease (more than 14 NIHSS scores) per ristomycin can be considered as favorable prognostic criteria for outcomes of ischemic stroke. Parameters of platelet aggregation on ADP in patients with severe disease severity (more than 14 points) after TLT were significantly lower than normal (50-60%) - 1 day 44.1 (37.47; 47.04)%, for the 7th day - Me-43.18 (37.0; 51.2)%, for the 14th day -46.02 (43.33; 47.87)%.

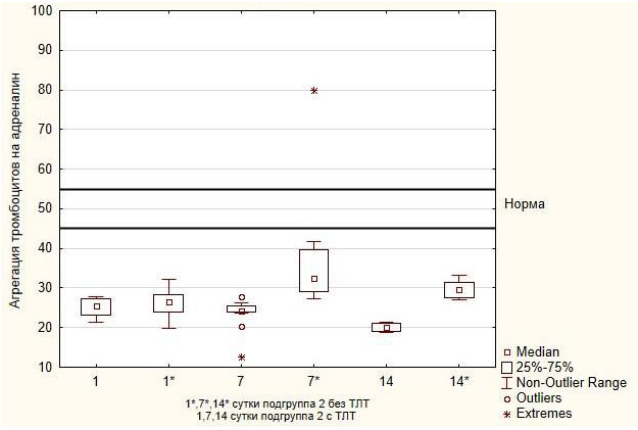

Figure 3: The dynamics of platelet aggregation to adrenalin (%) in severe patients (more than 14 points on the NIHSS) TLT (n-29) and without TLT (n-37) at 1, 7 and 14 days.

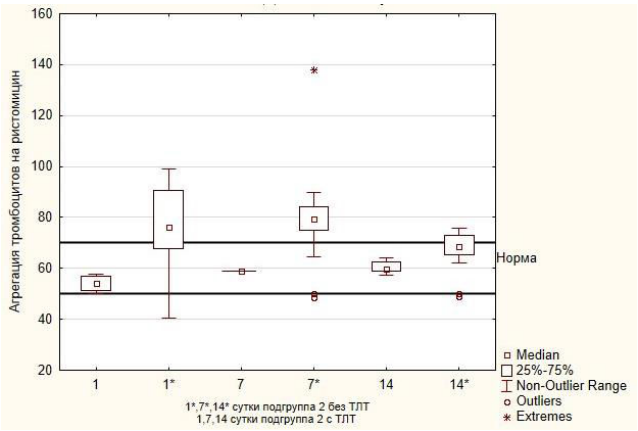

Figure 4: Dynamics of platelet aggregation rates for ristomycin (%) in patients with severe degree (more than 14 NIHSS scores) with TLT (n-29) and without TLT (n-37) at 1, 7 and 14 days.

In patients without TLT of severe severity (more than 14 points), platelet aggregation rates for ADP were below the norm up to 7 days, but had a tendency to increase in indices at the fourteenth day - 1 day -44.9 (33.66; 48,51)%, on the 7th day - 48,72 (43,18; 52.67)%, for the 14th day - Me-48.54 (40.48; 54,98)% (Figure 5). Dynamics of platelet aggregation rates on ADP in patients with TLT and without severe TLT (over 14 points) had a certain tendency with a tendency to decrease especially in patients after TLT (1-3).

The peculiarities of the dynamics of spontaneous platelet aggregation in patients with severe degree (more than 14 NIHSS scores) after TLT were revealed, which was manifested by an increase in spontaneous platelet aggregation by 7 days, followed by a decrease by 14 days. In most patients with TLT, spontaneous aggregation at day 1 was not recorded or was within the normal range, at day 7 - Me-0.62 (0.57; 0.63)% and on the 14th day - Me-0.31 (0.26; 0.32)%. In patients without TLT also spontaneous aggregation was not registered or within the normal range, on day 7 - Me-0.51 (0.2; 0.92)% and on the 14th day

- Me-1.43 (1.51; 1.66)% (Figure 6). In patients without TLT, the increase in spontaneous aggregation on day 7 was maintained until day 14 of the observation.

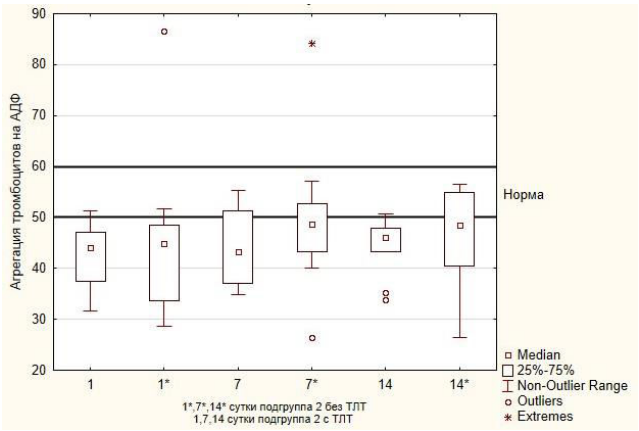

Figure 5: Dynamics of platelet aggregation rates for ADP (%) in patients with severe severity (more than 14 NIHSS scores) with TLT (n-29) and without TLT (n-37) at 1, 7 and 14 days.

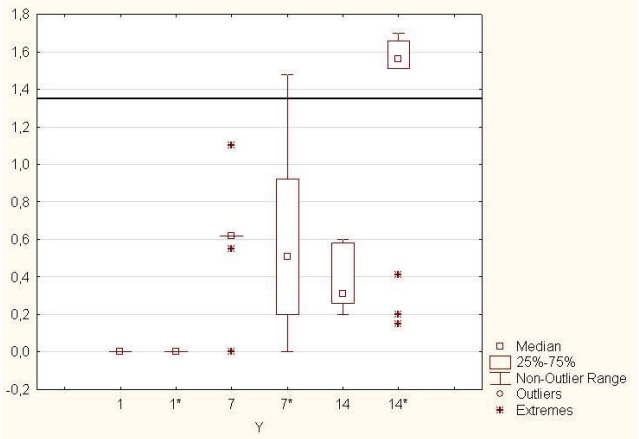

Figure 6: Dynamics of spontaneous aggregation rates (%) in patients with severe degree (more than 14 NIHSS scores) with TLT (n-29) and without TLT (n-37) at 1, 7 and 14 days.

The results of monitoring spontaneous aggregation parameters can be considered as additional markers of the severity of the course of the vascular process in patients without TLT. Among patients with severe degree after TLT (more than 14 points for NIHSS), 13 patients were observed whose recovery was significantly lower than the rest (NIHHS-2 (1,72, 2,01) points). In patients after TLT, high rates of spontaneous platelet aggregation (1 day 3,72 (3,56, 3,87)%, on day 7- 2,33 (0,66, 2,39)% and on day 14- 1.62 (1.47, 1.79)% at a rate of 1.25%), which tended to be reliably reduced to the fourteenth day of observation. And in patients without TLT, the increase in spontaneous platelet aggregation was maintained until the end of the follow-up period-1 day -3,80 (0,28; 1.87)%, on day 7 - 3.73 (0.39; 3.51)% and on the 14th day - 3.68 (3.39; 3,64)% (Figure 7).

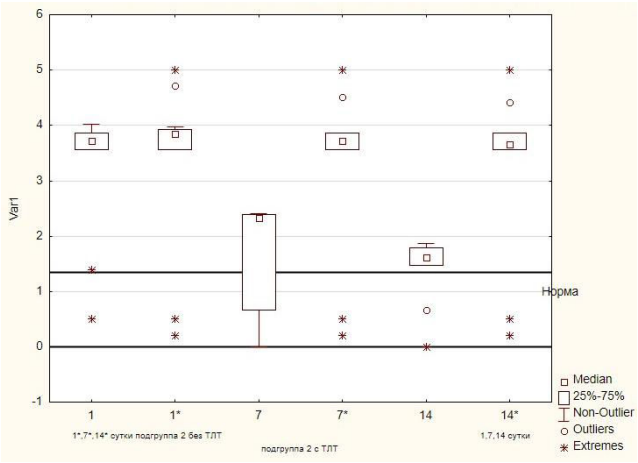

Figure 7: Dynamics of spontaneous aggregation in patients with TLT (n-13) with the lowest degree of recovery and without TLT at 1, 7 and 14 days of severe severity (more than 14 points according to NIHSS).

Conclusion

The dynamics of spontaneous aggregation rates correlated with the regression of clinical symptoms in patients after TLT (from 18 to 16 points in NIHSS) with a practical lack of regression in patients without TLT. Thus, the obtained data on changes in hemostasis on inducers (adrenaline, ADP, ristomycin) in dynamics in patients with ischemic stroke after systemic thrombolytic therapy are marker characteristics of severity (from 7 and over 14 points on the NIHSS scale), and prognosis of the course of the disease after thrombolytic therapy.

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