https://doi.org/10.30629/2618-6667-2020-18-4-16-25
УДК 616.89; 615.832.9; 615.851

Thrombodynamics Method in Assessing Coagulation Parameters During Psychopharmacotherapy of Endogenous Mental Disorders

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RESEARCH

Summary

Background: it has currently been shown that one of the main links in the pathogenesis of endogenous mental disorders is neuroinflammation (NI). It is also known that chronic NI is accompanied by a violation of the permeability of the blood-brain barrier and the activation of platelets, that generate procoagulant microparticles, which leads to disruption of the hemostasis system, causing an increase in blood clotting in patients. **The objective** of the study was to analyze the dynamics of the procoagulant activity of the blood of patients with endogenous mental disorders before and after psychopharmacotherapy. **Patients and methods.** The study included 185 female patients aged 16 to 64, who were admitted to the FSBSI "Mental Health Research Centre" clinic due to exacerbation/attack/phase of endogenous mental illness. In accordance with ICD-10, the following diagnoses were established: schizophrenia with attack-like/ progressive attack-like/continuous course type (F20.00-2), affective disorder (F31.1-5; F32.0-3; F33.0-3), schizotypal disorder with affective reactions and phases (F21.3-4). Thrombodynamics test (TD) was performed on a T-2 thrombodynamics recorder according to the manufacturer's instructions (HemaCore LLC, Moscow, Russia). All the patients received pharmacotherapy. **Results:** there was a significant decrease in the procoagulant activity of spontaneous clots in the blood plasma of female patients after psychopharmacological treatment. The obtained data on the positive dynamics of changes in the values of TD test's indicators in the majority of the examined female patients suggest that a decrease in the coagulation activity of the patients' blood as a result of treatment may be associated with the anti-inflammatory effect of antipsychotics and antidepressants. **Conclusion:** for the first time it was shown that during psychopharmacotherapy in most patients with endogenous mental diseases, there is a positive dynamics of changes in the values of the main parameters of the TD test. The results of TD tests can be the basis for monitoring response to therapy.

Keywords: endogenous mental disorders; thrombodynamics; hypercoagulation with spontaneous clots; antidepressants; antipsychotics.

For citation: Karpova N.S., Brusov O.S., Oleichik I.V., Faktor M.I., Levchenko N.S., Sizov S.V., Nikolaeva E.R. Thrombodynamics Method in Assessing Coagulation Parameters During Psychopharmacotherapy of Endogenous Mental Disorders. *Psychiatry (Moscow) (Psikhiatriya)*. 2020;18(4):16–25. https://doi.org/10.30629/2618-6667-2020-18-4-16-25

There is no conflict of interest

INTRODUCTION

It is well known that patients with endogenous mental disorders develop neuroinflammation (NI) and, as a consequence, systemic inflammation (SI) forms, which significantly affects the condition of patients, which made it possible to formulate a neuroinflammatory hypothesis of schizophrenia [1]. NI is closely related to disorders of the hemostasis system, a biological system, that provides both the fluid state of the blood and thrombus formation in case of damage to the walls of blood vessels.

It is also known that in chronic HI, there is an activation of platelets and a violation of the permeability of the blood-brain barrier, which leads to disruption of the hemostasis system, causing an increase in blood clotting in patients. Procoagulant microparticles, generated by platelets, can penetrate the brain [2]. This increases the risk of thrombotic events, which is determined on the basis of thrombodynamic parameters of blood plasma coagulation in patients with schizophrenia [3].

Our early studies showed, that patients with endogenous mental disorders have increased blood clotting (hypercoagulation), accompanied by the generation of spontaneous clots formed from procoagulant microparticles [2–4]. This phenomenon is the basis for the formation of microthrombi in small vessels of the brain. Cerebral microthrom-

bosis can form ischemic zones, which cause the development of destruction and death of neurons and neuroglia in these zones and increase the risk of thrombus formation, detected using the thrombodynamics test [3].

It can be assumed, that one of the mechanisms of the development of cognitive disorders in patients is changes in the brain parenchyma, caused by spontaneous clots, generated by platelets due to systemic inflammation. This makes the task of reducing the procoagulant blood activity in endogenous mental disorders urgent. It is known that a number of antidepressants [5] and antipsychotics [6] have pronounced anti-inflammatory effects *in vitro* (in tissue cultures) and *in vivo* (in laboratory animals).

The aim of the work is to study the dynamics of the procoagulant activity of the blood in patients with endogenous mental disorders before and after psychopharmacotherapy.

PATIENTS AND METHODS

The study included 185 female patients aged 16 to 64 years (median age [Q1; Q3] — 25 years [20; 33]), who were admitted for treatment at the clinic of the FSBSI Mental Health Research Centre (Head of the Department of Endogenous Mental Disorders and Affective States, prof. A.N. Barkhatova) in a state of exacerbation of the disease.

Criteria for inclusion in this study: diagnosis of schizophrenia with attack-like/attack-like/continuous course (F20.0 0–2), affective or mood disorder (F31.1–5; F32.0–3; F33.0–3), schizotypal disorder with affective reactions/phases (F21.3–4).

Non-inclusion criteria: organic diseases of the central nervous system; somatic diseases in the acute stage; a history of substance abuse.

PATIENT GROUPS

The patients were divided into 3 groups. Group 1 made up 104 female patients aged 16 to 57 years, the median age [Q1; Q3] — 29 years [22.3; 37.0]) with a diagnosis of attack-like/attack-like progressive/continuous schizophrenia. Group 2 consisted of 37 female patients aged 16 to 64 years (median age [Q1; Q3] — 21 years [18.0; 25.8]) with a diagnosis of affective disorder. Group 3 included 44 female patients aged 16 to 41 years (median age [Q1; Q3] — 20.5 years [18.0; 25.0]) with a diagnosis of schizotypal disorder with affective disturbances. All female patients received complex psychopharmacotherapy, adequate to the psychopathological picture of the state.

The study complied with the 1964 Declaration of Helsinki on Medical Ethics, revised in 2013, and was conducted with the rights, interests and dignity of the participants in mind. The research plan was approved by the Local Ethics Committee of the FSBSI "MHRC". All the subjects gave written informed consent to participate in the study.

The study used the method for determining the parameters of thrombodynamics using the Thrombodynamics Test (TD), clinical, clinical-psychopathological, and statistical methods.

In all patients, the next day after admission to the hospital and upon discharge after psychopharmacotherapy, in the morning, venous blood was taken from the cubital vein into a Vacuette type vacutainer (Austria), containing 3.2% sodium citrate solution. The ratio of the volume of anticoagulant to blood was 1:9. Fresh blood was centrifuged for 15 minutes at 1600 g. The platelet-depleted plasma was collected and centrifuged for 5 minutes at 10,000 g. A contact clotting inhibitor was added to the resulting platelet-free plasma. The values of the reference ranges for the TD parameters were determined by HemaCore in a large sample (about 600 people) of mentally and somatically healthy donors.

The Thrombodynamics test was intended to investigate in vitro the spatio-temporal dynamics of blood coagulation initiated by a localized coagulation activator. The test was performed in a thin plasma layer without stirring. To carry it out, blood plasma samples were placed in the channels of the measuring cuvette. Then a special insert (activator) was introduced into the channels of the cuvette, on the end of which a coating with a coagulation activator (tissue factor) was applied. As soon as the blood plasma comes into contact with the activator, the clotting process begins, i.e. from the tissue factor localized at the end of the insert, a fibrin clot begins to grow into the plasma volume, as on the damaged vessel wall *in vivo*. The process of occurrence and growth of a fibrin clot is recorded by a digital video camera in diffused light. Based on the data obtained, using special software, the numerical parameters of the spatio-temporal dynamics of fibrin clot growth are calculated: the time of delay in clot growth (Tlag, min), The initial, stationary and nonlinearity-corrected clot growth rate (Vi, Vst and V, μm/min, respectively), clot size after 30 minutes of thrombodynamics test (CS, μm), clot density (D, arb. units), time of occurrence of spontaneous thrombus formation (Tsp, min) in the entire volume of the cuvette. The TD test was carried out according to the manufacturer's instructions on reagent kits from HemaCore (HemaCore LTD, Moscow, Russia) [7].

Statistical method statistica, version 8 (Statsoft, USA) and MedCalc, version 17.4.1 (Belgium) were used for statistical analysis of the data. To calculate the statistical estimates of the values

of the TD parameters, we used the criteria of the normal distribution of the Kolmogorov–Smirnov data (Kolmogorov–Smirnov test, sample size greater than 50) and Shapiro–Wilk test (Shapiro–Wilk test, sample size less than 50). When comparing indicators with the norm, the T-test (One-sample T-test) for indicators with a normal distribution and a nonparametric signed test of the sum of ranks (One-sample Signed RS test) for indicators with a distribution other than normal were used. To assess the differences in thrombodynamic parameters among 3 groups of patients, corrections were made for multiple comparisons. The Kruskal–Wallis ANOVA test was used to compare the differences. When comparing indicators before and after treatment, the paired Wilcoxon test (paired samples) was used. When processing statistical data, the significance level was chosen $p = 0.05$.

RESULTS AND DISCUSSION

The female patients of the study groups underwent blood sampling at admission and at discharge for a second TD test, the results of which make it possible to trace the dynamics of the values of coagulation parameters. *Figure 1* shows the frames obtained at the 30th minute of the thrombodynamics test in a female patient diagnosed with bipolar disorder before and after treatment. It can be seen that after the treatment, the thickness of the clot growing from the activator became smaller, and the number of spontaneous clots decreased sharply. This may be due to a decrease in the severity of neuroinflammation during psychopharmacotherapy.

Statistical analysis of TD parameters before treatment showed that in all three groups of patients the Tlag and D parameters did not statistically significantly differ from the norm. The Tsp parameter was statistically significantly below normal values in groups 1 and 3, and did not differ statistically significantly from the norm in group 2. This is consistent with the fact that affective disorder is more favorable than schizophrenia, reflecting the different contributions of neuroinflammation to the pathogenesis of these disorders. The rest of the parameters are statistically significantly higher than the norm in all three groups of patients, which indicates increased blood plasma coagulation (hypercoagulation with spontaneous clots) in patients with endogenous mental illnesses. A statistically significant decrease in the time for the appearance of spontaneous clots compared with the norm (Tsp > 30 min) in groups 1 and 3 indicates the presence in the blood of patients of a large number of procoagulant platelet microparticles, from which early spontaneous clots are formed. Comparison of the values of TD parameters between groups of patients was carried out using the Kruskal–Wallis ANOVA criterion ($p = 0.05$). There were no statistically significant differences between the groups of patients. *Table 1* shows the results of statistical analysis of TD parameters before treatment. The TD test performed on the blood plasma of patients after treatment showed that in all three groups the parameters D, Tlag, and Tsp did not differ statistically significantly from the normal values. The rest of the parameters are statistically significantly higher than the norm, as before treatment. It was also shown that there were no statistically significant differences between the groups of patients. The results of statistical analysis of the values of TD parameters after treatment are presented in *Table 2*.

Despite the fact that 4 out of 7 TD parameters in all three groups are statistically significantly higher than the norm, both before and after treatment, the analysis of the values of statistical estimates of the parameters showed that as a result of treatment, a positive dynamics of TD values was observed in majority of patients. The values of the Tsp parameter in group 2 increased after treatment, although both before and after treatment this parameter did not differ statistically significantly ($p = 0.05$) from the norm. Before treatment, the median Tsp was 24.60 minutes, after treatment — 31.30 minutes. Normally, the Tsp value is greater than 30 minutes. To assess the reliability of changes in the values of TD parameters before and after treatment, these parameters were compared in groups 1–3. The comparison was carried out by the paired Wilcoxon test ($p = 0.05$). The data obtained are shown in *Table 3*.

In group 1, the values of the Vi and D parameters decreased statistically significantly, the Tsp values increased after treatment. In group 3, the values of

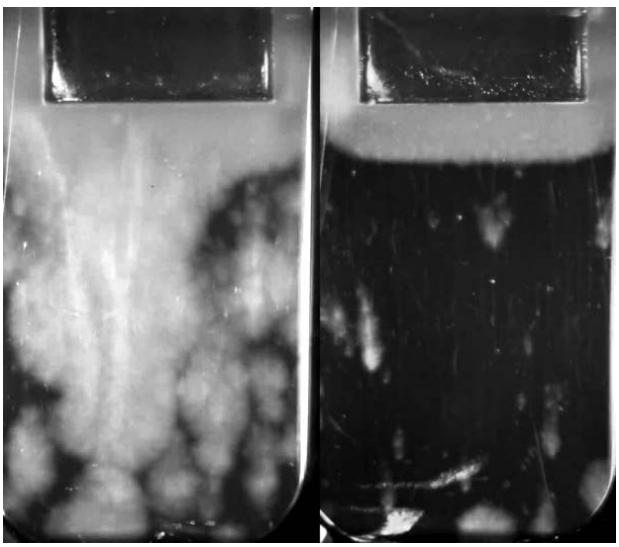

Fig. 1. Frames of the TD test at the 30th minute before (left) and after (right) treatment

Table 1. Descriptive statistics of thrombodynamic parameters in compared groups of patients before treatment

Parameter TD	Reference interval	Group 1			Group 2			Group 3			Kruskal–Wallis ANOVA p-level
		Me [Q1; Q3]	95% CI Me	One-sample t-test/ Signed RS test p-level	Me [Q1; Q3]	95% CI Me	One-sample t-test/ Signed RS test p-level	Me [Q1; Q3]	95% CI Me	One-sample t-test/ Signed RS test p-level	
Tlag, min	0.6–1.5	1.10 [0.90; 1.40]	1.04–1.10	0.1050	1.10 [0.90; 1.15]	0.90–1.10	0.6041	1.10 [1.00;1.40]	1.10–1.40	0.1351	0.15
Vi, μm/min	38–56	58.20 [54.48; 62.35]	56.83–59.50	< 0.0001***	55.50 [52.50; 60.90]	53.63–58.65	< 0.0001***	56.50 [52.85; 60.28]	54.46–59.38	< 0.0001***	0.14
Vst, μm/min	20–29	32.80 [30.05; 39.10]	30.90–34.72	< 0.0001***	30.80 [28.70; 35.40]	29.46–34.83	< 0.0001***	33.75 [29.85; 39.45]	31.28–36.16	< 0.0001***	0.23
V, μm/min	20–29	39.35 [31.00; 53.40]	35.03–44.07	< 0.0001***	36.40 [30.05; 49.80]	31.63–45.41	< 0.0001***	39.45 [31.80; 50.25]	34.22–45.58	< 0.0001***	0.53
CS, μm	800–1200	1250 [1178; 1367]	1215–1307	< 0.0001***	1235 [1143; 1290]	1165–1273	< 0.0001***	1237 [1170; 1352]	1190–1325	< 0.0001***	0.42
D, c.u.	15,000–32,000	24,892 [22,609; 28,338]	24,363–25,890	0.0781#	22,495 [20,464; 25,997]	21,642–24,726	0.7620	24,945 [21,521; 26,886]	23,169–25,891	0.1289	0.09#
Tsp, min	> 30	22.70 [13.65; 33.80]	19.66–26.29	0.0001***	24.60 [16.65; 35.25]	18.27–32.26	0.0711#	21.65 [17.45; 34.95]	19.09–28.5	0.0102*	0.81

* $p < 0.05$; *** $p < 0.001$; # statistical significance at the trend level ($0.05 < p < 0.1$).

MMA. ISSN1683-8319 (print)'. journalpsychiatry.com DOI 10.30629/2618-6667-2020-18-4-16-25

Table 2. Descriptive statistics of thrombodynamic parameters in compared groups of patients after treatment

Parameter TD	Reference interval	Group 1			Group 2			Group 3			Kruskal–Wallis ANOVA p-level
		Me [Q1; Q3]	95% CI Me	One-sample t-test/Signed RS test p-level	Me [Q1; Q3]	95% CI Me	One-sample t-test/Signed RS test p-level	Me [Q1; Q3]	95% CI Me	One-sample t-test/Signed RS test p-level	
Tlag, min	0.6–1.5	1.10 [0.90;1.40]	1.10-1.24	0.8334	1.10 [1.00;1.40]	1.06-1.24	0.3994	1.10 [0.90;1.40]	1.10-1.10	0.5117	0.85
Vi, μm/min	38–56	54.50 [50.23; 59.18]	52.91–56.40	< 0.0001***	55.40 [51.30; 58.85]	52.90–57.90	< 0.0001***	53.55 [50.10; 58.60]	51.60–56.55	< 0.0001***	0.61
Vst, μm/min	20–29	31.85 [29.90; 35.40]	30.81–33.37	< 0.0001***	30.75 [27.70; 32.60]	28.08–32.03	< 0.0001***	29.20 [26.75; 33.20]	27.24–32.39	< 0.0001***	0.06#
V, μm/min	20–29	33.90 [30.20; 45.35]	32.21–37.23	< 0.0001***	32.30 [29.70; 49.15]	30.60–39.32	< 0.0001***	32.00 [27.48; 47.60]	29.08–39.07	< 0.0001***	0.61
CS, μm	800–1200	1219 [1125; 1329]	1176–1268	< 0.0001***	1206 [1139; 1304]	1144–1288	< 0.0001***	1131 [1071; 1278]	1086–1234	0.0001***	0.21
D, c.u.	15,000–32,000	23,759 [20,624; 27,144]	21,970–25,206	0.7231	23,298 [20,508; 25,166]	21,532–24,259	0.6457	22,760 [20,791; 26,561]	21,778–25,691	0.7615	0.84
Tsp, min	> 30	26.00 [18.50; 38.60]	22.84–33.22	0.3383	31.30 [20.65; 40.65]	22.54–38.96	0.6572	26.90 [18.35; 35.20]	21.52–31.53	0.5071	0.49

*** $p < 0.001$.

MIA' ISSN2618-6667 (online)' journalpsychiatry.com DOI 10.30629/2618-6667-2020-18-4-16-25

Table 3. Statistical analysis of paired comparisons of the TD parameters in groups of patients before and after treatment

TD parameters before treatment	TD parameters after treatment	Wilcoxon test (paired samples) (p-levels)		
		Group 1	Group 2	Group 3
Tlag_1	Tlag_2	0.38	0.053#	0.44
Vi_1	Vi_2	0.0001***	0.15	0.0063**
Vst_1	Vst_2	0.37	0.45	0.087#
V_1	V_2	0.052#	0.26	0.16
CS_1	CS_2	0.051#	0.95	0.02*
D_1	D_2	0.03*	0.4	0.17
Tsp_1	Tsp_2	0.008**	0.25	0.49

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; # statistical significance at the trend level ($0.05 < p < 0.1$).

Vi and CS parameters significantly decreased after treatment. Thus, as a result of treatment, there is a statistically significant improvement in the values of the main parameters of TD. This is clearly seen in the comparative dot plots of the parameters of the TD test of female patients before and after treatment (*Fig. 2–4*).

In group 2, there were no statistically significant differences in TD parameters before and after treatment. However, as shown above, the Tsp index did not statistically significantly differ from the normal value before treatment; the values of the other TD parameters in this group were closer to the normal values, than in other groups before treatment. This is clearly seen in *Fig. 5* for parameters Vst and V.

To quantify changes in thrombodynamics parameters that statistically significantly differed from the norm before treatment in all groups (Vi, Vst, V, CS), and the Tsp indicator, which was statistically significantly different from the normal values before treatment, in groups 1 and 3, the difference between the values of the indicators was calculated after treatment and before treatment.

Since the values of the parameters Vi, Vst, V, and CS were statistically significantly higher than the norm, the negative values of the calculated differences corresponded to the positive dynamics of the values of the residuals after treatment, and vice versa. For the parameter Tsp, on the contrary, positive values of the differences corresponded to positive dynamics. The analysis of the obtained results showed that in most of the patients, as a result of treatment, there was a positive dynamics in the values of TD parameters, i.e. the shift of the parameter values was in the direction of improve-

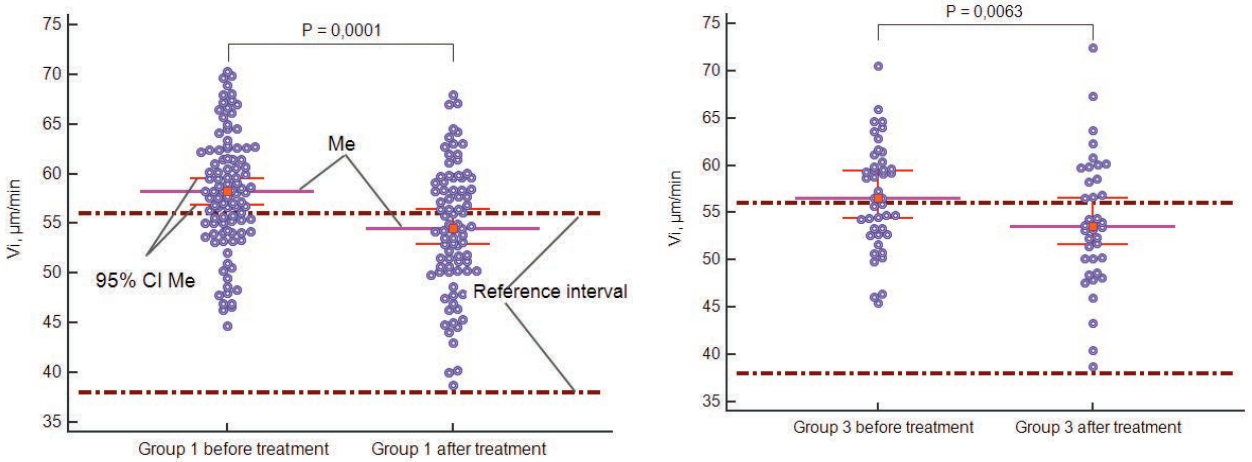

Fig. 2. Dot plot comparison of variable Vi in patient group 1 (on theleft) and group 3 (on the right) before and after treatment

ment. However, in some patients there was a negative dynamics in the values of TD parameters after treatment (see Tables 1 and 2), which may indicate a deterioration in the parameters of the hemostasis system. *Table 4* shows data on the dynamics of the values of TD parameters and the significance of the differences between positive and negative dynamics in all the groups.

The table shows that for all TD indicators in all groups (except for CS group 2), negative dynamics was observed less often than positive dynamics of parameter values as a result of psychopharmacotherapy. *Figure 6* shows a histogram of changes in CS values in group 3. It can be seen that in half of the female patients with positive dynamics the CS value decreased by more than 100 units, which is 10% of the average value of the norm.

Such dynamics of the values of plasma hemostasis parameters may indicate a decrease in the blood coagulation activity in most patients with endogenous mental diseases during treatment. An increase in the value of the Tsp parameter (time of appearance of spontaneous clots) may indicate a decrease in the procoagulant activity of platelet microparticles, i.e. a decrease in platelet activation during treatment. Thus, according to the results of the TD test, antiaggregatory corrective therapy can be prescribed. Modern neuroimaging studies indicate that an atrophic decrease in the volume of various areas of the brain, leading to the development of cognitive decline, is observed not only in neurodegenerative diseases, but also in endogenous mental disorders, which confirms the participation of neurodegenerative processes in the pathogenesis of these diseases. Positron emission computed tomography, using a specific ligand, showed that it is the activated microglia that is responsible for the processes of neurodegeneration in schizophrenia [8, 9]. This is also supported by the fact, that inhibitors of microglia activation (Celecoxib, Minocycline) have antipsychotic effect [10, 11]. Currently, there is evidence that a num-

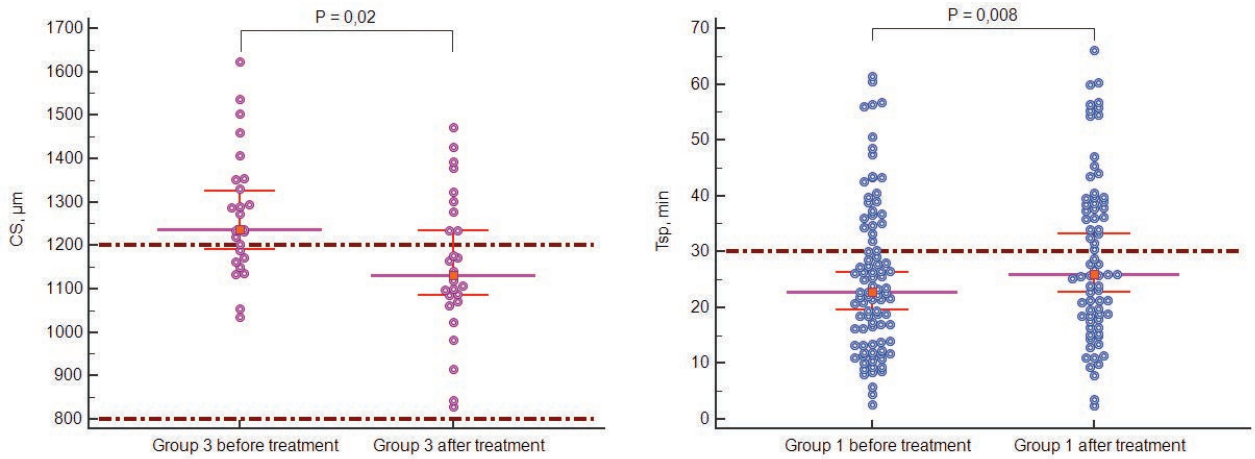

Fig. 3. Dot plot comparison of variable CS in patient group 3 (on theleft) and of variable T spin patient group 1 (on the right) before and after treatment.

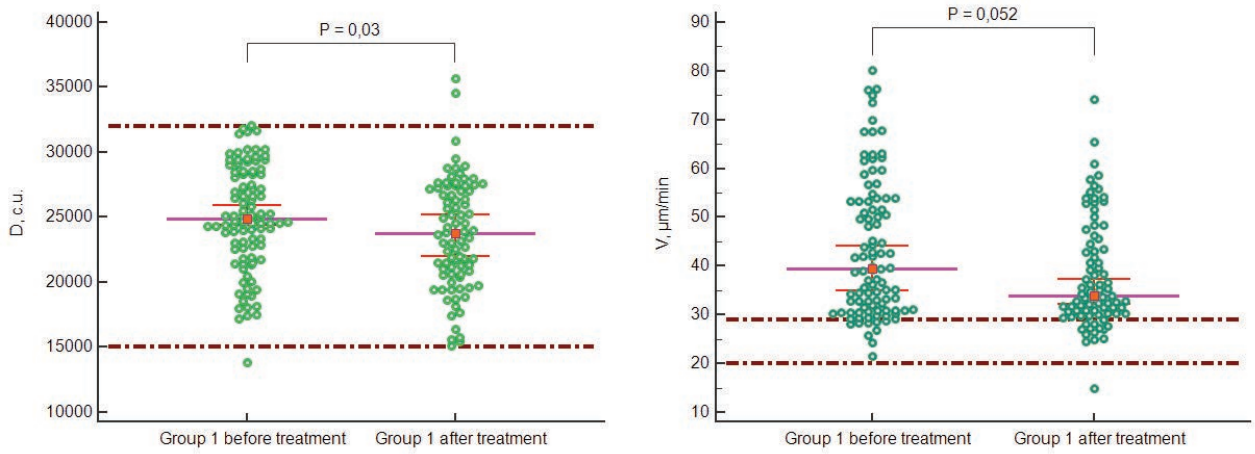

Fig. 4. Dot plot comparison of variable D (on theleft) and V (on the right) in patients of group 1 before and after treatment

Table 4. Table of the dynamics of TD values after psychopharmacotherapy

Parameter TD	Group 1			Group 2			Group 3		
	Positive dynamic *n*[1]/%	Negative dynamic *n*/%	Difference test p-level	Positive dynamic *n*/%	Negative dynamic *n*/%	Difference test p-level	Positive dynamic *n*/%	Negative dynamic *n*/%	Difference test p-level
Vi	52/67	26/33	0.0056**	19/61	12/39	0.2419	28/74	10/26	0.0111*
Vst	24/62	15/38	0.1526	8/62	5/38	0.4170	14/70	6/30	0.1141
V	50/64	28/36	0.0198*	19/61	12/39	0.2419	25/64	14/36	0.1008
CS	21/62	13/38	0.1826	7/50	7/50	1.0000	14/78	4/22	0.0541#
Tsp	40/61	26/39	0.0852#	15/65	8/35	0.1832	15/60	10/40	0.3370

[1]*n* – the number of patients with this dynamic; * $p < 0.05$; ** $p < 0.01$.

ber of antipsychotic drugs have anti-inflammatory activity capable of in vitro suppressing the activation of microglia in cultures of these cells [12].

The obtained data on the positive dynamics of the values of TD tests in the majority of the examined female patients as a result of treatment suggest, that a decrease in the blood plasma clotting activity of patients may be associated with the anti-inflammatory effect of antipsychotics and antidepressants. We have previously shown that in patients with endogenous mental disorder a state of exacerbation/attack, platelet activation is observed, accompanied by the generation of procoagulant spontaneous clots [3]. The treatment of these patients is accompanied by a change in the values of the thrombodynamic parameters towards the norm. Our studies have shown for the first time that when patients are treated with antidepressants and antipsychotics in general, the generation of spontaneous clots is reduced. This is of great practical importance, since hypercoagulation with spontaneous clots in patients with endogenous mental disorders can exacerbate the course of chronic diseases, such as atherosclerosis, hypertension, diabetes, autoimmune disorders, thrombophilia, post-stroke, post-infarction states, rheumatism, arthritis, arthrosis vascular dementia and others, in pathogenesis of which, a significant contribution is made by systemic inflammation) [13].

CONCLUSION

This study showed for the first time that as a result of psychopharmacotherapy in women suffering from endogenous mental disorders, the TD parameters shifted towards the norm. In the group of schizophrenic patients with attack-like/attack-like progressive/continuous course type (group 1) three parameters of seven parameters changed statistically significantly ($p = 0.05$) and two parameters were statistically significant at the trend level. In the group of patients with schizotypal disorder with affective fluctuations

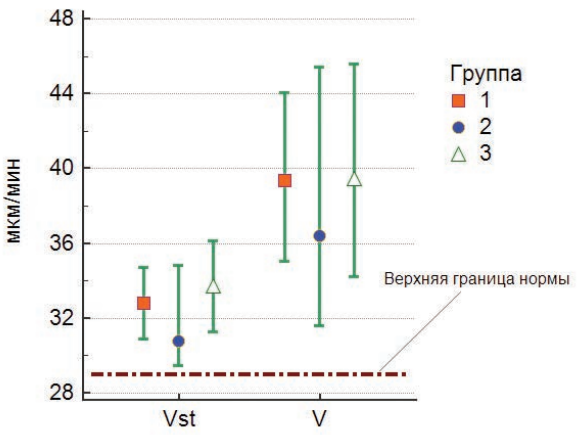

Fig. 5. 95% CI median parameters Vst and V before treatment in groups 1–3

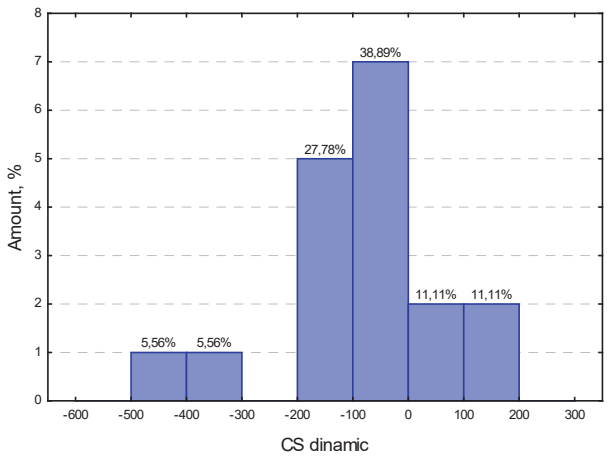

Fig. 6. Histogram of the change in CS values in group 3 after treatment

(group 3), out of seven parameters, two parameters changed statistically significantly (p = 0.05) and one parameter at the trend level. In all groups of patients, the time of the onset of spontaneous clot formation (Tsp, min) ceased to differ statistically significantly (p = 0.05) from the normal value of this indicator. In the majority of patients with endogenous mental disorders, a positive dynamics of the TD test parameters was observed, and in groups 1 and 3 the differences in the positive and negative dynamics of some of the TD parameters were statistically significant at a significance level of 0.05, or at the trend level. It can be assumed, that the results obtained, indicate a decrease in the procoagulant activity of the patients' blood. This is possibly due to the anti-inflammatory properties of antipsychotics and antidepressants. Thus, impairment of the hemostasis system of patients may be a potential target of therapy. To develop a personalized regimen of protoagulant therapy for each patient, it is necessary to search for markers of hemostasis impairment, on the basis of which the treatment regimen will be developed. The analysis of the dynamic of the TD parameters in the course of treatment can be used to correct the initially developed therapy.

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Received 09.07.2020	Revised 06.08.2020	Accepted for publication 03.09.2020