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The effectiveness of thiotriazoline in the complex treatment of patients with post-Covid syndrome

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Key words:

Thiotriazolin tablets, post-Covid syndrome, metabolitotropic effect, antiplatelet effect, anticoagulant effect.

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The purpose of the work is to evaluate the complex therapeutic effect of thiotriazoline (anticoagulant, antiplatelet, metabolithotropic, endothelial protective activity) in patients with post-Covid syndrome in comparison with basic therapy.

Materials and methods. The studies involved 30 patients aged 30 to 60 years with post-Covid syndrome: 15 received basic therapy (antibiotics, anticoagulants, acetylsalicylic acid), and 15 patients, against the background of basic therapy, received thiotriazoline in the form of tablets of 200 mg twice a day. within 30 days. The criterion for inclusion in the study is a positive PCR test for COVID-19; if the PCR test is negative, the presence of IgM COVID-19 or IgG COVID-19 (with radiologically confirmed pneumonia). The level of lung damage is up to 45%. The patients had the following concomitant pathologies: diabetes mellitus in the compensation stage, arterial hypertension, coronary heart disease without heart failure. The results of the study were calculated using Statistica for Windows 13 (StatSoft Inc., ÿ JPZ804I382130ARCN10-J), SPSS 16.0 ÿ Microsoft Office Excel 2003.

Results. The inclusion of thiotriazoline in the complex basic therapy of post-Covid syndrome led to a significant increase in the effectiveness of basic endothelioprotective, anticoagulant and antiplatelet therapy and contributed to the prevention of thrombus formation. The administration of thiotriazoline led to a significant improvement in general clinical parameters in patients with post-covid syndrome: complaints of palpitations disappeared, blood pressure stabilized (without additional correction with antihypertensive drugs), weakness and increased fatigue disappeared. Saturation in 14 (93.4%) patients increased to 97–98%. In the control group, only 7 (46.7%) of 15 patients had saturation at the level of 97–98%.

Conclusions. The introduction of thiotriazoline into the complex basic therapy of post-Covid syndrome in the form of tablets of 200 mg twice a day for 30 days leads to a significant increase in the basic endothelial-protective, antiplatelet and anticoagulant therapy and helps prevent thrombus formation while improving the condition of the myocardium and vascular endothelium.

Key words:

Thiotriazoline tablets, post-covid syndrome, metabolitotropic antiplatelet effect, anticoagulant effect.

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Effectiveness of thiotriazoline during complex treatment of patients with post-covid syndrome

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The purpose of the work is to evaluate the complex therapeutic effect of thiotriazoline (anticoagulant, antiaggregant, metabolitotropic, endothelioprotective effects) in patients with post-covid syndrome compared to basic therapy.

Materials and methods. 30 patients aged 30 to 60 with post-covid syndrome took part in the study: 15 people received basic therapy (antibiotics, anticoagulants, acetylsalicylic acid), 15 patients on the background of basic therapy received thiotriazoline in the form of tablets of 200 mg twice a day for 30 days . Criteria for involvement in the study: positive PCR test for COVID-19; if the PCR test is negative, the presence of IgM COVID-19 or IgG COVID-19 (with radiologically confirmed pneumonia). The level of lung damage is up to 45%. The patients had the following concomitant pathologies: diabetes in the compensation stage, arterial hypertension, coronary heart disease without heart failure. The results of the study were calculated using Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J), SPSS 16.0, and Microsoft Office Excel 2003.

The results. The inclusion of thiotriazoline in the complex basic therapy of the post-covid syndrome led to a probable increase in the effectiveness of the basic endothelioprotective, anticoagulant and antiaggregation therapy and contributed to the prevention of thrombus formation.

The appointment of thiotriazoline improved general clinical indicators in patients with post-covid syndrome: complaints of palpitations disappeared, blood pressure stabilized (without additional correction with hypotensive drugs), weakness and increased fatigue disappeared. Saturation in 14 (93.4%) patients increased to 97–98%. In the control group, only 7 (46.7%) of 15 patients had saturation at the level of 97–98%.

Conclusions. Addition of thiotriazoline in the form of tablets of 200 mg twice a day for 30 days to the complex basic therapy of post-covid syndrome leads to a probable strengthening of the basic endothelioprotective, antiaggregation and anticoagulant therapy, contributes to the prevention of thrombus formation against the background of improving the condition of the myocardium and vascular endothelium.

Thiotriazolin effectiveness in complex treatment of patients with post-COVID syndrome

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Key words: Thiotriazolin, tablets, post COVID syndrome, metabolitotropic effect, antiplatelet effect, anticoagulant effect.

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The aim of this work is to evaluate the complex therapeutic effect of Thiotriazolin (anticoagulant, antiplatelet, metabolitotropic, endothelioprotective activity) in patients with post-COVID syndrome in comparison with basic therapy.

Materials and methods. The studies involved 30 patients aged between 30 to 60 years with post-COVID syndrome. Of these, 15 persons received basic therapy (antibiotics, anticoagulants, acetylsalicylic acid), and other 15 patients received Thiotriazolin in the form of 200 mg tablets twice a day for 30 days against the background of basic therapy. Inclusion criteria were a positive PCR test for COVID-19; if the PCR test was negative, then the patients were enrolled based on the presence of IgM COVID-19 or IgG COVID-19 (with X-ray confirmed pneumonia). The rate of lung damage is up to 45 %. The patients had the following comorbidities: diabetes mellitus in the stage of compensation, arterial hypertension, ischemic heart disease without heart failure. The results of the study were calculated using the standard statistical package Statistica for Windows 13 (StatSoft Inc., ÿ JPZ804I382130ARCN10-J), ÿs well as SPSS 16.0, Microsoft Office Excel 2003.

Results. The inclusion of Thiotriazolin in the complex basic therapy of post-COVID syndrome led to a significant increase in the effectiveness of basic endothelioprotective, anticoagulant and antiaggregatory therapy and contributed to the prevention of throm bus formation. The administration of Thiotriazolin led to a significant improvement in general clinical parameters in patients with post-COVID syndrome – complaints of tachycardia disappeared, blood pressure was stabilized (without additional correction with antihypertensive drugs), weakness and increased fatigue disappeared. Saturation in 14 (93.4 %) patients increased to 97–98 %. In the control group only 7 (46.7 %) of 15 patients had oxygen saturation at 97–98 % level.

Conclusions. The introduction of the drug Thiotriazolin in the form of 200 mg tablets twice a day for 30 days into the complex basic therapy of post-COVID syndrome leads to a significant increase in the basic endothelioprotective, antiaggregatory and anticoagulant therapy and contributes to the prevention of thrombus formation against the background of improving the state of the myocardium and vascular endothelium.

Coronavirus disease is associated with severe inflammatory process, as well as cytokine storm [1–4]. Scientists are paying more and more attention to the role of autoimmune mechanisms in the pathogenesis of COVID-19, especially when studying the mechanisms of development of complications of this pathology, the most dangerous of which is acute respiratory distress syndrome, which develops in 15–33% of patients [5–7].

It is believed that one of the main links in its pathogenesis is a cascade of cytokine reactions (hypercytokinemia - IL1ÿ, IL-2, IL-6, IL-7, IL-8, IL-17 IFNÿ, G-CSF, MCP1, TNFÿ, etc.), which is conventionally called a “cytokine storm,” which occurs in the patient’s body due to excessive activity of neutrophils and their ability to form extracellular neutrophil traps (NETs). This leads to a logical question about the role of eicosanoids in the pathogenesis of COVID-19, which act as mediators of the inflammatory response.

and are inextricably linked with the signaling cascades that Some are realized by cytokines and other signaling molecules [4,8–13]. It is assumed that eicosanoids, especially prostaglandin E2, perform one of the leading functions in the development of autoimmune and inflammatory-destructive processes in COVID-19 [5,7,14–18].

Inflammation during viral infection leads to oxidative stress, secondary mitochondrial dysfunction, energy deficiency and lactic acidosis in the cell. This leads to damage to cell membranes and cellular organelles by ROS from free radicals and peroxidation products, which, in turn, leads to dysfunction and cell death such as apoptosis or even necrosis [7,9,12,19–22].

All this theoretically substantiates the prospects of using thiotriazolin in the complex therapy of post-Covid syndrome, which has a metabolitotropic (positive effect on energy, carbohydrate, protein metabolism), immunomodulatory, anti-inflammatory, antioxidant,

anti-ischemic, cardioprotective and hepatoprotective activities. The effectiveness of thiotriazoline
these types of activities have been proven both in preclinical,
both at the clinical stages of research and under
has been confirmed by more than 20 years of use in healthcare in post-Soviet countries.

The main pharmacological effect of thiotriazoline is antioxidant. Thiotriazoline reactivates the antioxidant enzymes glutathione peroxidase and superoxide dismutase, the latter is involved in protecting proteins from oxidative modification. Thiotriazolin helps to increase the level of reduced glutathione, which regulates the Red/Oxi mechanisms of expression of genes responsible for the synthesis of enzymes in

including those regulating pro-inflammatory cascades – lipoxygenase and cyclooxygenase. Thiotriazolin can directly participate in the regulation of transcriptional activity, prevents the development of imbalance of the thiosulfide system during ROS overproduction, providing functions such as cell signal transmission through the receptor ionoform complex, preserving the activity of proteins, enzymes, transcription factors and the integrity of cell membranes [23–25].

There is evidence that thiotriazoline exhibits immunomodulatory activity, increasing the level of interferon, as well as increasing the number of T-lymphocytes. Numerous studies have established that thiotriazoline exhibits anti-inflammatory activity, preventing the irreversible inactivation of the transcription factor NF-Kappa B and inhibits the expression of proinflammatory cytokines - IL-1b, IL-6, TNF-a, as well as C-reactive protein, inducible nitric oxide synthase – iNOS [25–28].

Thiotriazolin stabilizes the membranes of basophils, mast cells and eosinophils, and increases the phagocytic activity of macrophages. Considering the data that convincingly prove the negative role of ROS,

cytotoxic intermediates of nitric oxide and oxidative stress in the mechanisms of inflammation, pain and edema, inclusion of thiotriazoline in the treatment complex has a predictable potentiation of the effect of basic therapy. In addition, given a number of serious side effects of basic non-steroidal anti-inflammatory and analgesic non-narcotic drugs

ical drugs associated with disruption of fine links in the metabolism of cardiomyocytes, endothelial cells, hepatocytes, etc., the appointment of antioxidants, including thiotriazoline, in the complex therapy of diseases, can increase the safety of the proposed drug treatment.

The very interesting effects of thiotriazolin include its endothelial protective effect, which is of great importance in the complex therapy of COVID-19, since endothelial dysfunction inevitably develops with this pathology [10]. As a result of experimental and clinical studies, it was established that thiotriazoline, due to its antioxidant properties, normalizes the nitrooxide system in diseases of the cardiovascular system [27].

It is known that COVID-19 leads to complications and disrupts blood clotting and thrombus formation. Thiotriazolin exhibits fibrinolytic and antiplatelet properties [26,28], which justifies its use in the complex treatment of patients with post-Covid syndrome.

Considering the cardiovascular complications caused by exposure to both coronavirus, and drugs used for treatment of COVID-19, the data on the cardioprotective effect of thiotriazoline, which were obtained in a number of preclinical and clinical studies, and also confirmed by the experience of its use in cardiology, are relevant [23,24,26]. Thiotriazolin reduces mortality, improves ECG parameters, and reduces the area of necrosis in experimental myocardial infarction. The drug enhances ATP synthesis, normalizes the mitochondrial respiratory chain and increases the utilization of glucose, free fatty acids, glycogen in cells, limits unproductive glycolysis and prevents the development of lactic acidosis in cardiomyocytes, normalizes the work of Krebs cycle enzymes, and in conditions of myocardial ischemia activates the compensatory malate-aspartate shunt energy (more productive and safe than glycolysis) [26,27]. In terms of the strength of its cardioprotective action, thiotriazoline is superior to such well-known cardioprotectors as mildronate, L-carnitine, trimetazidine (preductal), riboxin, cytoflavin, yantovit, mitomin, coenzyme Q10, ATP-long.

In clinical studies on more than 1000 patients (including the elderly), it was shown positive effect of thiotriazoline on the condition cardiohemodynamics in ischemic heart disease [26]. Thiotriazoline noticeably decreased the total peripheral vascular resistance and significantly increased the volume of cardiac output with a progressive decrease in myocardial energy consumption. In the group of patients receiving thiotriazoline, exercise tolerance increased ke, which was accompanied by a noticeable increase in the value inotropic reserve of the myocardium [24,26,28].

Thiotriazoline also increased the effectiveness of basic antihypertensive and antianginal therapy. When thiotriazoline was prescribed to patients with acute coronary syndrome, there was a significant decrease in mortality associated with a decrease in the number of ventricular arrhythmias and a more rapid recovery of myocardial function. A course of use (8 weeks) of thiotriazoline at a daily dose of 600 mg for the treatment of coronary artery disease and stable angina pectoris class II–III has been shown to be well tolerated and safe [27]. Clinical studies have shown that thiotriazoline reduces the cardiotoxicity of doxorubicin and other cytostatics (ECG and biochemical studies).

Recent data also indicate the neurotoxic effect of SARS-CoV-2, in particular it manifests itself in the form of acute respiratory distress syndrome due to toxic damage to the brain stem, which leads to disruption of the cardiorespiratory center and respiratory arrest. Preclinical studies have established the neuroprotective activity of thiotriazoline in acute cerebrovascular accidents [26,27]. Yes, application

Thiotriazoline led to a decrease in mortality, an increase in the density of neurons in the sensorimotor zone of the cerebral cortex, inhibition of neuroapoptosis, an increase in ATP and ADP in brain tissue and inhibition of oxidative stress. Also, the administration of thiotriazoline led to a decrease in neurological symptoms after modeling stroke.

The clinical use of thiotriazoline has been shown to be highly effective in the treatment of vascular pathology of the eye – transudative forms of central chorioretinal dystrophies [26]. It has been shown that when thiotriazoline is included in the complex treatment of children with functional pathology of the central nervous system, improvement is achieved in a shorter time and gives good long-term results. Cephalosporin antibiotics used in the treatment of COVID-19 lead to a deficiency of GABA and other neurotransmitters, which increases the convulsive readiness of the brain, and also leads to depression, anxiety, and nightmares [25].

It has been established that thiotriazoline increases the anticonvulsant activity of the base drug carbamazepine and the antianxiety activity of glycine and noofen when prescribed to children and adolescents. Combining thiotriazoline with glycine increases the resistance of neurons to hypoxia by inhibiting the hyperexcitability of NMDA glutamate receptors (potentiating the Red/Oxi mechanism), as well as by enhancing the GABAergic properties of glycine and increasing the concentration of GABA in the brain [27]. The combination of thiotriazoline and glycine increases the resistance of neurons to hypoxia by enhancing the functioning of compensatory mechanisms of ATP production (GABA shunt).

Drug therapy for COVID-19 is aggressive, causes serious adverse reactions from the liver and has a number of contraindications (patients with liver failure, previous hepatitis, elderly patients). At the end of the 1980s. installed

high hepatoprotective activity of thiotriazoline. It has been shown that thiotriazoline leads to normalization of the activity of ALT and AST, LDH, a decrease in the thymol test, increases protein levels and reduces the activity of oxidative stress [23,25,26]. Thiotriazolin modulates the processes of biotransformation of xenobiotics, increases the activity of the liver detoxification system, and increases the resistance of hepatocytes. It has been shown that the use of thiotriazoline in the treatment of patients with alcoholic liver disease is accompanied by positive dynamics in the clinical and biochemical activity of the disease: regression of clinical symptoms, a significant decrease in the severity of cytolytic syndrome, and improvement in the protein-synthetic function of the liver [26]. Inclusion of thiotriazolin with piracetam in complex therapy of patients with subcompensated liver cirrhosis leads to a significant reduction in the symptoms of hepatic encephalopathy, improving the quality of life of patients. The inclusion of thiotriazoline in treatment regimens for patients with liver cirrhosis gives a good therapeutic effect, including normalization of markers of fibrotic processes within 6 months [23,26].

Thus, the domestic drug thiotriazoline has immunomodulatory and anti-inflammatory properties. therapeutic, antioxidant, cardioprotective and hepatoprotective properties, has a thoroughly studied safety profile and extensive experience in clinical practice, which justifies its use in the treatment (as part of combination therapy) of patients with post-Covid syndrome. All this actualizes clinical studies of thiotriazoline for use in complex

therapy for post-Covid syndrome.

Goal of the work

Evaluation of the complex therapeutic effect of thiotriazoline (anticoagulant, antiplatelet, endothelial protective action) in patients with post-Covid syndrome in comparison with basic therapy.

Materials and research methods

The studies were conducted at the University Clinic of Zaporozhye State Medical University. The studies involved 30 patients aged 30 to 60 years with post-Covid syndrome: 15 received basic therapy (antibiotics, anticoagulants, acetylsalicylic acid), and 15 patients, against the background of basic therapy, additionally received thiotriazoline in the form of tablets of 200 mg twice a day. day for 30 days. The inclusion criterion for the study was a positive PCR test for COVID-19; if the PCR test is negative, the presence of IgM COVID-19 or IgG COVID-19 (with radiologically confirmed pneumonia). The presence of pneumonia was confirmed using a computer or x-ray examination of the chest organs. The level of lung damage was up to 45%. Patients had the following concomitant pathologies: diabetes mellitus in the compensation stage, arterial hypertension, ischemic heart disease without heart failure. The following biochemical parameters were studied: C-reactive protein - by immunoturbodimetric method (set produced by Cormay, biochemical analyzer ACCENT-200, Poland); D-dimer – by enzyme immunoassay (kit produced by Vector-Best, enzyme immunoassay analyzer Immunochem-2200, USA); ferritin – immunochemiluminescent method (kit manufactured by Siemens, Immulate 1000 analyzer, UK); endothelial NO synthase (eNOS) – by enzyme immunoassay (kit produced by Cloud-Clone Corporation, USA; enzyme immunoassay analyzer Immunochem-2200, USA).

The international normalized ratio (INR) was also determined using the coagulometer method (kit manufactured by Dragon, Austria, device – coagulometer CoagChrom 3003, Poland).

In parallel with biochemical studies, platelet aggregation was determined to assess their hemostatic function. The aggregation activity of platelets was studied using the turbidimetric method (optical aggregometry) on a Solar AP 2110 aggregometer (Republic of Belarus).

The level of platelet aggregation activity was studied when the aggregation inducer ADP (5.0 ÿM) was added. Material for research: platelet-rich citrate plasma. Two weeks before the study, medications that affect platelet aggregation were stopped. Whole blood was collected into a plastic tube with 3.2% (0.109 M) or 3.8% (0.129 M) sodium citrate in a ratio of 9:1 or into vacuum blood collection systems with 3.2% (0.109 M) sodium citrate. Immediately after blood collection, the tube was carefully moved by inverting at least 5 times without foaming. Within 45 minutes, the tube was delivered to the laboratory and centrifuged. Centrifugation of a whole blood sample was carried out at room temperature (18–25 °C) for 5–7 minutes at 1000 rpm. After centrifugation was completed, 1 ml of TTP was immediately collected into a clean plastic tube for further study. Platelet-poor plasma (PPP) is used as a blank sample (reference point). To obtain platelet-poor plasma, a whole blood sample was centrifuged at room temperature (18–25 °C) for 15 minutes at 3000 rpm.

After centrifugation was completed, 1 ml of BTP was collected into a clean plastic tube. Blood was collected only into vacuum systems or plastic tubes with 3.8% sodium citrate. Before analysis, a preliminary count of cells in plasma was carried out on hematology analyzer or microscopic method, according to the results obtained, platelet-rich plasma was diluted with platelet-poor plasma (from the same patient) so that the final number of platelets in the mixture was 200–300 × 109 / l.

An ADP solution with a concentration of 5.0 ÿM was used as an aggregation activator. To prepare the working solution, 4.7 mg of ADP was added to 20 ml of physiological solution, then 1 ml of the resulting solution was added to 9 ml of physiological solution. The results obtained were measured by the percentage of light absorption.

The study results were calculated using Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J), SPSS 16.0, Microsoft Office Excel 2003. Normality of distribution was assessed using the Shapiro–Wilk test. Data are presented as mean values. Reliability of differences

between the mean values was determined using the Student's test (in the case of normal distribution). IN
in the case of a distribution different from normal,
or analysis of ordinal variables, the Mann–Whitney U test was used. To compare independent variables in more than two samples, we used analysis of variance (ANOVA) for a normal distribution or the Kruskal–Wallis test for a non-normal distribution. For all types

analysis, differences p < 0.05 (95%) were considered statistically significant.

results

Upon admission, all patients complained of severe weakness, increased fatigue, palpitations, and increased body temperature from 37.2 °C to 38.3 °C. The level of lung damage is up to 45%. Absent

Table 1. Subjective state of patients upon admission and 1 month after treatment (n)

Complaints/indicators	Upon admission and before treatment, n = 30	Group 1 – basic therapy (control) after treatment, n = 15	Group 2 – basic therapy + thiotriazoline (after treatment), n = 15
Weakness	28	11	2
Body temperature from 37.2 °C to 38.3 °C	28	-	-
Lack of sense of smell and taste	9	5	1
Shortness of	13	7	1
breath Cough	10	4	-
Palpitations	28	11	2
Arrhythmia Diarrhea	-	-	-
	3	1	-
Abdominal pain	3	1	-
Increased fatigue Saturation at 98–99%	28	10	1
	-	7	14

Loss of smell and taste was recorded in 32% of patients, cough – in 35%, shortness of breath – in 42%, diarrhea and abdominal pain – in 12% (Table 1). Patients also reported fluctuations in blood pressure, especially those with concomitant hypertension. Fluctuations occurred despite the constant use of specific therapy (Ca++ channel blockers, ACE inhibitors, sartans, beta-blockers). After treatment, in the group of patients taking thiotriazoline, complaints of palpitations disappeared, blood pressure stabilized (without additional correction with antihypertensive drugs), weakness and fatigue disappeared. Saturation in 14 (93.4%) patients increased to 97–98%. In the control group, only 7 (46.7%) of 15 patients had saturation at this level *(Table* 1).

In the course of biochemical and coagulometric studies, it was established that in patients with post-Covid syndrome upon admission to the clinic, a derivation of eNOS expression was observed against the background of an increase in the concentration of ferritin and C-reactive protein according to towards relatively healthy patients.
In patients with post-Covid syndrome, after a course of basic therapy (antibiotics, anticoagulants, acetylsalicylic acid), an increased concentration of C-reactive protein and ferritin was noted (Table 2) *against* the background of a reduced INR and eNOS concentration in the blood plasma compared to a group of relatively healthy people . However, in this group, a decrease in C-reactive protein was recorded compared to the values before treatment *(Table* 3). When studying the D-dimer content, no statistically significant changes were established (reference values are up to 285 DDU).

The inclusion of thiotriazoline in basic therapy (for 1 month) *(Table* 2) led to normalization of the INR (significant increase relative to
indicators upon admission and before the start of treatment by 93.6% and in relation to the basic therapy group - by 68.5%) and an increase in the content of eNOS (a significant increase relative to the indicators upon admission and before the start of treatment by 92.5%, in relation to group of basic therapy – by 76%), decrease in D-dimer

Table 2. Biochemical parameters of blood plasma, concentration of eNOS and INR of patients with post-Covid syndrome (30 days from the start of treatment)

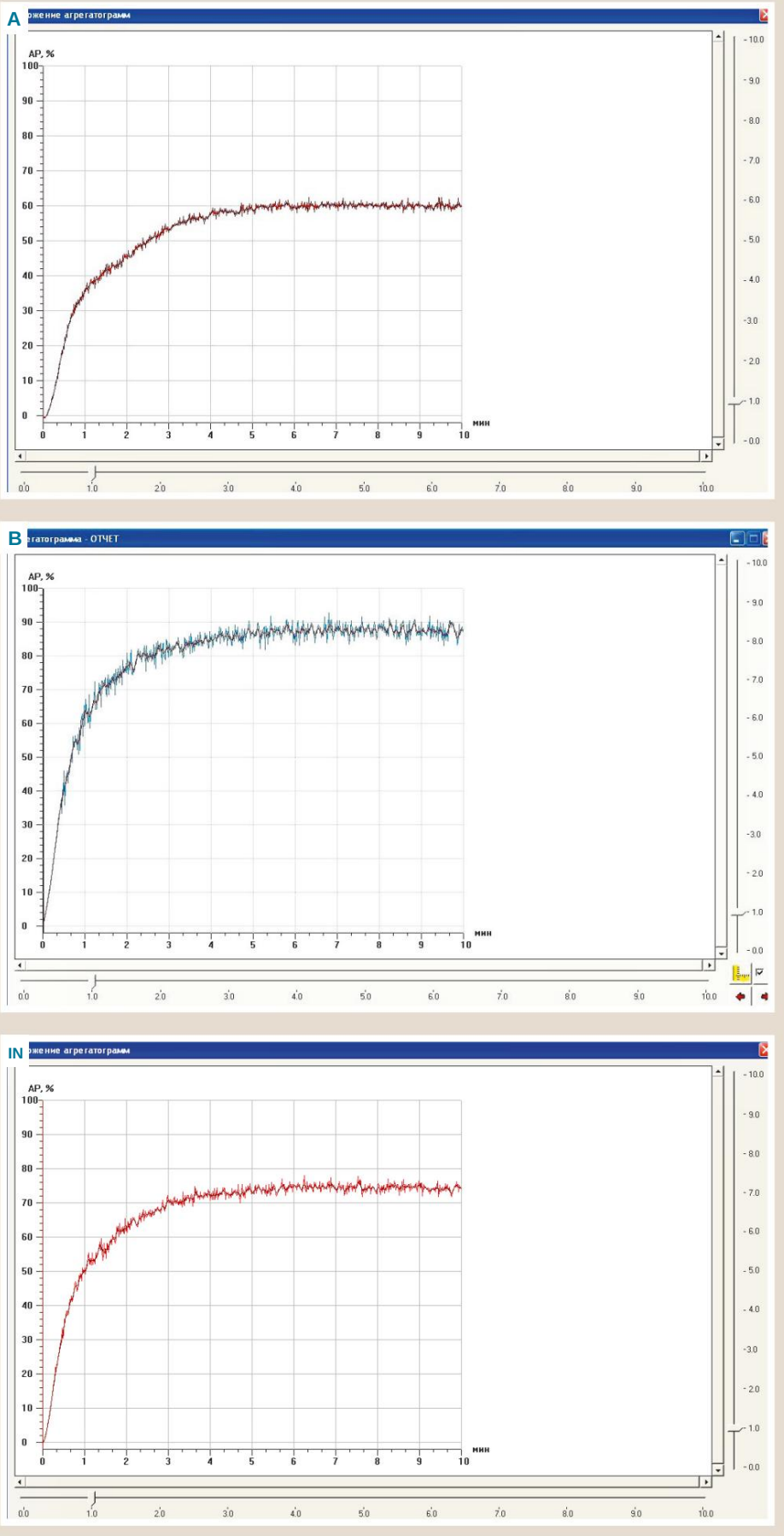
Groups of patients	C-reactive protein, mg/l	Ferritin, ng/ml	D-dimer, DDU MNO		eNOS, pg/ml
Relatively healthy, n = 15 On admission and	21.2 ± 2.6	451.0 ± 11.2	187.8 ± 7.4	0.47 ± 0.051	57,8 ± 4,3
before treatment, n = 30 Post-Covid syndrome + basic therapy,					26,7 ± 7,2
n = 15	15,7 ± 1,81	411,0 ± 7,8	157,8 ± 11,8	0,54 ± 0,048	29,2 ± 5,7
Post-Covid syndrome + basic therapy + thiotriazoline, n = 15	11,3 ± 2,51	400,0 ± 10,91	132,4 ± 8,2*1	0,91 ± 0,03*1	51,4 ± 6,1*1

1: p < 0.05 in relation to patients on admission; *: p < 0.05 in relation to patients with post-Covid syndrome and basic therapy.

Table 3. Hemostasiogram of patients with post-Covid syndrome (30 days from the start of treatment), (%)

Patient groups Relatively	Platelet aggregation with ADP, %	Speed at 30 seconds, %	Platelet count, 109 /l
healthy (n = 15) Post-Covid syndrome + basic	60.0 ± 10.4	70.0 ± 15.2	311,0 ± 31,4
therapy (n = 15) Post-Covid syndrome + basic therapy + thiotriazoline (n	99,2 ± 6,3	157,3 ± 9,4	377,0 ± 52,4
= 15)	71,1 ± 5,3*	79,3 ± 8,7*	359,0 ± 48,3

*: p<0.05 in relation to patients with post-Covid syndrome and basic therapy.



Rice. 1. Platelet aggregation activity.

A. Relatively healthy patients. Aggregation response in the reference interval. Irreversible aggregation, light transmission percentage 60%.

B. Patients with post-Covid syndrome during treatment with basic therapy. Aggregation response in the reference interval. Irreversible aggregation, light transmission percentage 93%.

B. Patients with post-Covid syndrome during treatment with basic therapy and thiotriazoline. Aggregation response in the reference interval. Irreversible aggregation, light transmission percentage 75%.

(a significant increase relative to the indicators upon admission and before the start of treatment by 29.5%, in relation to the basic therapy group - by 16.1%). INR (international normalized ratio) is one of the tests for prothrombin. It is used to determine the state of the patient's blood coagulation system. This protein is a precursor to the protein thrombin and stimulates the formation of a blood clot. A decrease in eNOS levels is a sign of endothelial dysfunction. D-dimer is the most specific marker of degradation of fibrin clots of any location, in other words, a marker of the intensity and nature of thrombus formation processes. An increase in the concentration of D-dimer clearly and unambiguously indicates the activation of fibrinolysis, which is necessarily preceded by excessive formation of insoluble fibrin, i.e., a blood clot. The values of C-reactive protein and ferritin did not differ statistically from similar values in the control group of patients.

When determining platelet aggregation activity in patients with post-Covid syndrome during treatment with basic therapy, compared with healthy patients, an increase in platelet aggregation activity was noted. The percentage of light absorption averaged 99.4% versus 60.0% in relatively healthy patients *(Table* 3, *Fig. 1A,* B). In parallel, an increase in speed was observed at 30 seconds while maintaining a normal platelet count (380.0 × 109 /l ± 54.8). The indicators of relatively healthy patients did not differ from the reference values (platelet aggregation – 50–80%, speed at 30 seconds – 58–114%, platelet count – 260–600 × 109 / l). The introduction of thiotriazoline into basic therapy (for 1 month) *(Table* 2, *Fig. 1B)* led to a decrease in platelet aggregation activity by 28.3%, aggregation rate at 30 seconds - 95.3%. It is worth noting that the indicators of patients in this group, according to *Table* 3, decreased to the indicators

relatively healthy patients.

Discussion

As a result of a number of studies, data have been obtained on the protective effect of thiotriazolin on the vascular endothelium [29,30], which is of great importance in COVID-19, since endothelial dysfunction inevitably develops with this pathology. It has been noted that the formation of endothelial dysfunction in COVID-19 occurs more quickly in elderly patients taking ACE inhibitors [9,10,11]. Endothelial dysfunction is a predictor of such serious diseases as stroke and myocardial infarction.

It is well known that NO is an unstable, short-lived radical, for the stabilization and further transport of which mechanisms such as interaction with thiol-containing low-molecular compounds (glutathione, cysteine, methionine) and the reproduction of stable S-nitrozole complexes are provided. Under conditions of deficiency of thiol compounds in COVID-19, NO transport is disrupted, as it is attacked by ROS such as superoc

sidradical and hydroxyl radical with transformation into a cytotoxic product - peroxynitrite [26,27,29]. In this case, an increase in the formation of endothelial dysfunction is observed.

Preclinical reports and dissertation studies of thiotriazoline have shown that it increases the bioavailability of NO by increasing the level of SH compounds, as well as independently forming nitrosothiol complexes with NO [24,29]. All this protects NO from interactions with reactive oxygen species and its conversion into cytotoxic proinflammatory peroxynitrite. Thiotriazoline increases the density of endothelial cells, the density of proliferating endothelial cells, and increases the expression of vasculoendothelial factor (VEGF) and endothelial nitric oxide synthase (eNOS). Clinical studies have shown that combining

thiotriazoline and arginine leads to increased endothelial lyoprotective effect and has a protective effect on the synthesis and transport of NO, its bioavailability [25–27,29–31].

Data were obtained on the anticoagulant effect of thiotriazoline. It is known that COVID-19 leads to complications and disrupts blood clotting and thrombus formation. Thiotriazolin exhibits anticoagulant, antiplatelet and fibrinolytic properties. Data have been obtained that during myocardial ischemia, thiotriazolin in platelets significantly increases the activity of glutathione peroxidase, reduces the accumulation of products of oxidative modification of lipids, which probably leads to a decrease in the blood level of thromboxanes involved in thrombus formation. The influence of thiotriazoline on ROS-dependence cannot be excluded

known mechanisms of tissue plasminogen expression [23–30].

Thus, the introduction of the drug Tiotriazolin in the form of tablets (200 mg twice a day for 30 days) into the complex basic therapy of post-Covid syndrome led to a significant increase in the basic endothelial-protective and anticoagulant therapy and contributed to the prevention of thrombus formation while improving the condition of the myocardium and vascular endothelium.

conclusions

1. The inclusion of the drug Thiotriazolin in the form of tablets (200 mg twice a day) for 30 days in the complex basic therapy of post-Covid syndrome led to a significant increase in the effectiveness of basic anticoagulant and antiplatelet activity and contributed to the prevention of thrombus formation. The introduction of thiotriazoline into basic therapy led to a decrease in platelet aggregation activity and aggregation rate to the levels of relatively healthy patients.

2. The administration of thiotriazoline led to a significant increase in the expression of eNOS (a significant increase relative to the indicators at admission by 92.5%, relative to the basic therapy group - by 76%), which indicated the endothelial protective activity of the drug.

3. Thiotriazolin significantly reduced the level of D-dimer in the blood of patients (a significant increase relative to the indicators at admission and before the start of treatment by 29.5%, relative to the basic therapy group - by 16.1%) (a biochemical marker of thrombus formation), and also normalized the INR, which reflects the state of the blood coagulation system. All this indicated the pronounced antiplatelet and fibrinolytic effects of thiotriazolin, as well as its ability to reduce the risks of heart attacks and strokes in post-Covid syndrome.

4. The administration of thiotriazoline led to a significant improvement in general clinical parameters in patients with post-Covid syndrome: complaints of palpitations disappeared, blood pressure stabilized (without additional correction with antihypertensive drugs), weakness and increased fatigue disappeared. Saturation in 14 (93.4%) patients increased to 98–99%. In the control group, only 7 (46.7%) of 15 patients had saturation at 98%.

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