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Effectiveness Of Antiplatelet Therapy In Patients With Thrombophilia Gene Mutations

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ABSTRACT

In mild coronavirus infection, the significance of genetic mutations predisposing to thrombophilia was not confirmed. However, in moderate and severe cases, an un-favorable genotype of the MTHFR 677 C>T (rs1801133) gene and the MTR 5p15.31 66 A>G (rs1801394) gene was significantly more common. The high-risk homozygous mutation of thrombophilia genes was observed only in patients with severe COVID-19, with the predominant genotype being the mutant G/G genotype of the MTR 5p15.31 66 A>G (rs1801394) gene in 23 cases (67.65%). In severe coronavirus infection with a homozygous mutation, the effectiveness of antiplatelet therapy was observed in 3-4 months

KEYWORDS: Coronavirus Infection, Genetic Mutations, Thrombophilia Genes, Covid-19, Platelet Activity, Antiplatelet Therapy.

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INTRODUCTION

According to modern interpretations, thrombophilia is a pathological condition of the blood characterized by a temporary or permanent thrombotic risk, leading to the development of thrombosis [6].

Thrombogenic risk factors can be either permanent (genetic) or transient (de-veloping over a certain period). If timely measures are not taken, these can result in thrombosis-related complications. To date, more than 100 secondary thrombo-genic risk factors have been identified [11].

Hypercoagulation caused by exogenous factors (such as infections, medica-tions, diet, etc.) or endogenous factors (such as immune or hormonal changes, an-tiphospholipid syndrome, autoimmune diseases, oncological conditions, etc.) is primarily of a transient nature. In contrast, thrombophilia caused by defects in the genetic apparatus results in a lifelong increased risk of thrombosis formation. In the presence of hypercoagulation, prolonged immobilization, frequent venipunc-tures, long-term catheter placement, infections, or oncological diseases significant-ly increase the risk of thrombosis development several times over [5].

Patients with an unfavorable genotype of thrombophilia genes who develop is-chemic heart disease tend to have significantly higher systolic and diastolic blood pressure compared to those without mutations, and their treatment duration is relatively longer. In addition, standard antiplatelet therapy has reduced effective-ness in patients with hemostasis disorders resulting from thrombophilia gene mu-tations [2].

Genetic testing is being increasingly integrated into medical research. GWAS (Genome-Wide Association Studies) is a method for identifying genetic variations linked to human diseases. It involves breaking down the genome into hundreds or thousands of nucleotides and determining their specific sequence associated with particular diseases [14].

Methylated folates enter the bloodstream as 5-methyltetrahydrofolate and are transported into cells via endocytosis with the help of specific folate receptors. Inside the cell, 5-methyltetrahydrofolate serves as the primary source of both me-thyl groups and tetrahydrofolate. Homozygosity for the 677T allele results in a sharp increase in homocysteine levels, which becomes more pronounced when fo-late levels in the blood are low [16].

Unlike natural folates, folic acid is difficult to convert into 5-methyltetrahydrofolate because 80% of folic acid is processed and utilized in the liver via the portal vein before being available for metabolism [12].

During transsulfuration, cystathionine-β-synthase catalyzes the conversion of homocysteine and serine into cystathionine, which is then hydrolyzed by cysta-thionase into cysteine and α-ketobutyrate. These two reactions require vitamin B6 as a cofactor. Excess cysteine is further oxidized into taurine and inorganic sul-fates, which are excreted from the body via urine [4].

Homocysteine damages the endothelial layer of blood vessels and activates the coagulation process. The endothelium serves as a barrier between the blood vessel wall and circulating blood, producing vasoactive substances, mediators, and their inhibitors. As a result, in hyperhomocysteinemia, the synthesis of nitric oxide, a key factor in vasodilation and endothelial protection, decreases [8].

Oxidative stress and endothelial dysfunction caused by elevated homocysteine levels lead to a decrease in prostacyclin (PGI2), a vasoactive compound, and an increase in thromboxane A2. Both substances are synthesized from arachidonic acid under the influence of cyclooxygenase (COX). Thromboxane enhances plate-let aggregation, promoting clot formation and severe vasoconstriction. Prostacy-clin, primarily synthesized in the vascular endothelium, has the opposite effect, causing vascular smooth muscle relaxation, inhibition of platelet aggregation, and stimulation of fibrinolysis [3].

Studies indicate that homocysteine activates elastase, leading to elastin degra-dation, which makes the endothelium fragile and prone to damage. This contrib-utes to the deposition of calcium, cholesterol, and lipids, deforming the blood ves-sel walls. Homocysteine also reduces the production of endothelin-1, a 21-amino acid peptide synthesized by endothelial cells. Endothelin-1 binds to specific transmembrane receptors on smooth muscle cells, stimulating their proliferation and acting as a potent vasoconstrictor. Normally, endothelial cells prevent blood cell adhesion to the vascular surface, exhibiting antithrombotic and fibrinolytic properties. However, endothelial injury caused by hyperhomocysteinemia in-creases platelet aggregation [3, 18].

During severe infections, the blood coagulation system is activated as a protec-tive mechanism to prevent the spread of microorganisms. In severe cases, acute generalized inflammatory reactions lead to widespread endothelial injury, causing coagulation system dysregulation and loss of control over endogenous anticoagu-lant mechanisms. This results in the development of acute disseminated throm-boinflammatory injury (DTII) syndrome, leading to ischemia of vital organs and tissues. Sepsis-induced coagulopathy is considered an intermediate stage between infection-induced coagulation activation and acute DTII syndrome [17].

Autopsy studies have shown that COVID-19 causes diffuse edema, microangi-opathic, hemorrhagic, and thrombotic changes in lung tissue. Extensive alveolar damage and the presence of a large number of CD4+ lymphocytes around small thrombotic vessels were observed in the lungs of COVID-19 patients [13].

The increase in inflammatory cytokines in COVID-19 triggers a cytokine storm, which damages vascular endothelium and stimulates tissue thromboplastin ex-pression, thereby activating the coagulation system [7].

The endothelium not only regulates hemostasis but also maintains vascular in-tegrity. Disruption of endothelial integrity leads to systemic circulation disorders, vasoconstriction, microcirculatory dysfunction, and ischemia of damaged organs [9]. Additionally, activation and increase of neutrophilic leukocytes further pro-mote coagulation activation and thrombosis formation. Leukocytes play a key role in immunothrombosis, with monocytes and neutrophils producing cytokines that activate platelets and coagulation hemostasis [15].

Damaged endothelial cells and monocytes produce tissue thromboplastin (TT), which activates the extrinsic coagulation pathway [1]. Hyperinflammatory reac-tions cause tissue injury, endothelial barrier disruption, and uncontrollable coagu-lation activation [10].

GENERAL CLINICAL DESCRIPTION

Clinical examinations were conducted at Zangiota Infectious Diseases Hospital No. 2 in 2021. The scientific study involved 400 patients, including 100 with mild cases, 150 with moderate cases, and 150 with severe cases of coronavirus infection (CI). All patients were tested for CI virus markers using enzyme-linked immuno-sorbent assay (ELISA) and polymerase chain reaction (PCR) methods. To deter-mine the extent of lung damage, patients underwent multi-slice computed tomog-raphy (MSCT).
For diagnosis, the study followed the diagnostic criteria outlined in the 8th edi-tion of the “Temporary Guidelines for the Treatment of Patients with Coronavirus Infection.” The severity of CI was assessed based on clinical signs (fever, respira-tory rate, heart rate), blood oxygen saturation levels, laboratory indicators, and changes observed in chest CT scans. Additionally, patients’ complaints (cough, fever, excessive sweating, shortness of breath, general weakness, headache, etc.) and medical history (contact with COVID-19 patients, duration of illness, comor-bidities, etc.) were taken into account.

Patients who tested negative for COVID-19 virus markers in ELISA (IFA) and PCR tests were excluded from the study. Additionally, patients with coagulation disorders, hypertension, oncological diseases, diabetes mellitus, liver cirrhosis, prolonged steroid use, or systemic connective tissue diseases were not included in the main study groups.

RESEARCH METHODS

One of the most important laboratory diagnostic methods in clinical practice is complete blood analysis. In this study, the complete blood count (CBC) was per-formed using the Sysmex XN-550 6-diff (Japan) automatic hematology analyzer.

Coagulation hemostasis was examined in several stages using the Sysmex CA 660 (Japan) automatic coagulometer. The Sysmex CA 660 is an automatic coag-ulometer used for in vitro detection of hemostasis system pathologies, minimizing human error during analysis.

In this clinical study, the presence of thrombophilia genes MTHFR A1298C (rs1801131), MTHFR C677T (rs1801133), MTRR A66G (rs1801394), and MTR A2756G (rs1805087) was analyzed in coronavirus infection. The alleles and geno-types of these thrombophilia-related genes were identified using venous blood samples, amplified with a DT-Lite 48 DNA amplifier (OOO "NPO DNA-Technology", Russia) and reagents from "NPO DNA-Technology" (Russia). The analysis was performed using real-time polymerase chain reaction (PCR).

To detect the genes in the examined material, the polymerase chain reaction (PCR) method was applied. PCR allows for nucleotide sequence analysis of genet-ic material (DNA) and helps determine genetic predisposition to thrombophilia in patients. Statistical data processing was performed using a Pentium IV computer with a statistical analysis software package. The calculations included mean (M), stand-ard deviation (σ), and relative frequency (m). The statistical significance of the measured values was assessed using Student's t-test, with a p-value of <0.05 con-sidered statistically significant. In such cases, clinical and laboratory research data were processed following statistical analysis guidelines.

Statistical processing of genetic data was performed using the Statistica 6.1 software (StatSoft, USA). The χ^2 (chi-square) test was applied to evaluate geno-type frequency distribution according to Hardy-Weinberg equilibrium.

To confirm the association between alleles/genotypes and disease susceptibility, the relative risk (RR) and odds ratio (OR) were calculated with a 95% confidence interval (95% CI).

To determine the correlation between disease development and the presence of an unfavorable genotype, binary logistic regression was applied, considering Wald's χ^2 test. A p-value < 0.05 was considered statistically significant.

RESULTS

The effectiveness of antiplatelet and anticoagulant therapy was assessed in 18 patients with identified thrombophilia gene mutations. All patients received Pi-gasprin 75/75 mg once daily (per os) for 3–6 months.

In Group 2, consisting of 23 patients with thrombophilia gene mutations, the prescribed dose of Pigasprin did not lead to a reduction in platelet adhesion to normal levels within 10 days: Before treatment: 75.4 ± 6.2%, Day 5 of treatment: 69.3 ± 7.1%, Day 10: 61.8 ± 6.4%, After 1 month: 53.4 ± 5.3% (P<0.01), After 2 months: 43.1 ± 4.4% *** (P<0.001)***, After 3 months: 35.2 ± 3.2%*, After 4 months: 30.7 ± 3.0%*, After 5 months: 28.8 ± 2.6%*, After 6 months: 22.4 ± 2.1%* (Figure 1)

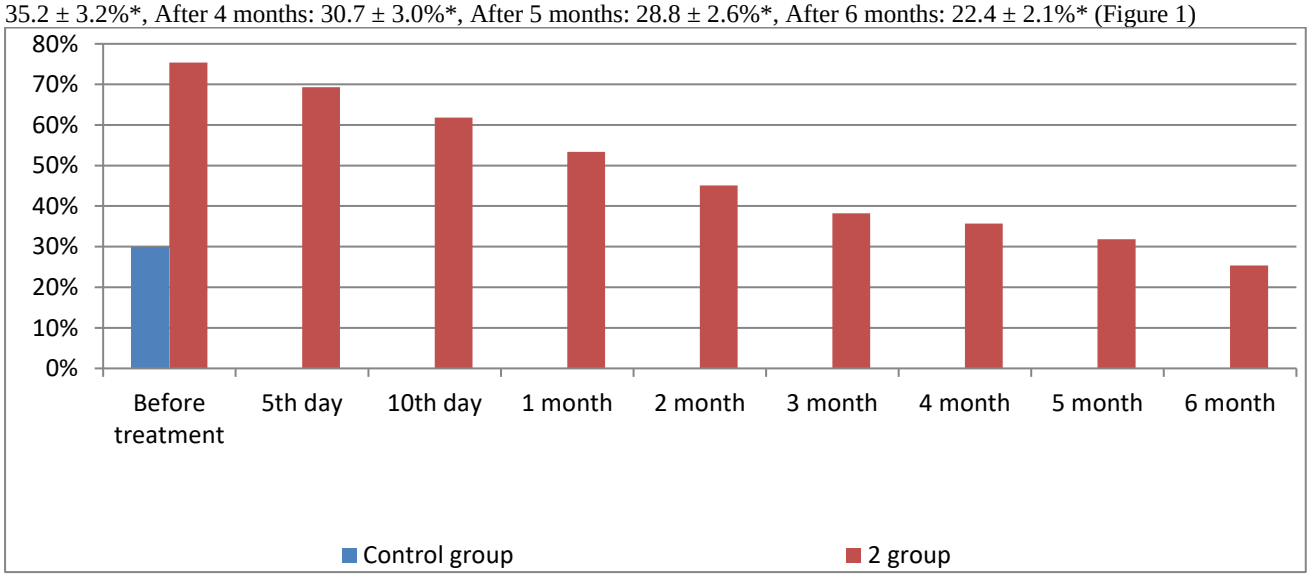

Fig.1. Platelet Adhesion During Antiplatelet Therapy in Group 2 Patients with Thrombophilia Gene Mutations

Platelet adhesion normalized only after 3 months of Pigasprin therapy. In pa-tients with thrombophilia gene mutations, long-term Pigasprin therapy (at least 3–6 months) is necessary to achieve and maintain normal platelet adhesion levels and prevent hypercoagulability-related complications.

In Group 3, consisting of 31 patients with severe COVID-19 (KI) and identified thrombophilia gene mutations, the effectiveness of Pigasprin was observed only after 4 months of therapy.

In patients with severe COVID-19 and heterozygous mutations in three throm-bophilia genes, platelet adhesion was 82.2 ± 5.6% before treatment. By day 5 of therapy, this value decreased to 78.4 ± 6.8%, and by day 10, it reached 69.5 ± 5.8%. One month after treatment, platelet adhesion was 56.7 ± 5.1%, at two months 49.8 ± 4.2%, at three months 40.9 ± 3.6%, at four months 36.6 ± 3.2%, at five months 32.2 ± 2.9%, and by six months, it further decreased to 28.8 ± 2.5% (Figure 2).

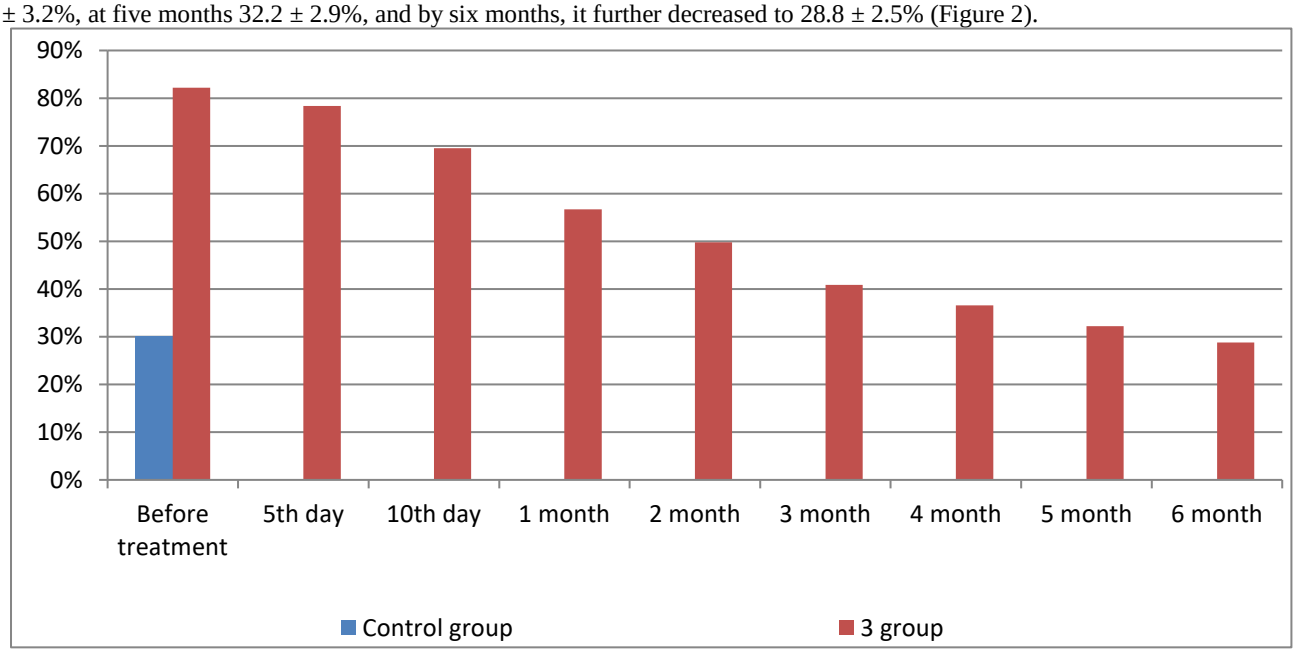

Fig. 2. Platelet Adhesion During Antiplatelet Therapy in Group 3 Patients with Mutations in Three Thrombophilia Genes.

In patients from Group 3 with homozygous mutations, platelet adhesion was 90.2 ± 6.1%* before treatment. Only by the fourth month of combination therapy with Pigasprin 80 did platelet adhesion normalize. On day 5 of antiplatelet thera-py, platelet adhesion decreased to 86.5 ± 7.2%, and by day 10, it reached 79.7 ± 5.9%. After one month, platelet adhesion was 63.9 ± 5.9%, at two months 56.4 ± 4.6%, at three months 51.2 ± 5.9% **, at four months 44.8 ± 3.4%, at five months 40.8 ± 3.2%, and by six months, it further decreased to 36.6 ± 3.2% (Figure 3).

In severe COVID-19 patients with heterozygous mutations, platelet adhesion normalized only after 4 months of Pigasprin therapy. For patients with homozygous mutations, platelet adhesion took even longer—approximately 6 months—to reach normal levels. Antiplatelet therapy should be extended for at least 4–6 months in severe COVID-19 patients with thrombophilia gene mutations to ensure effective correc-tion of platelet hyperfunction and prevent thrombosis.

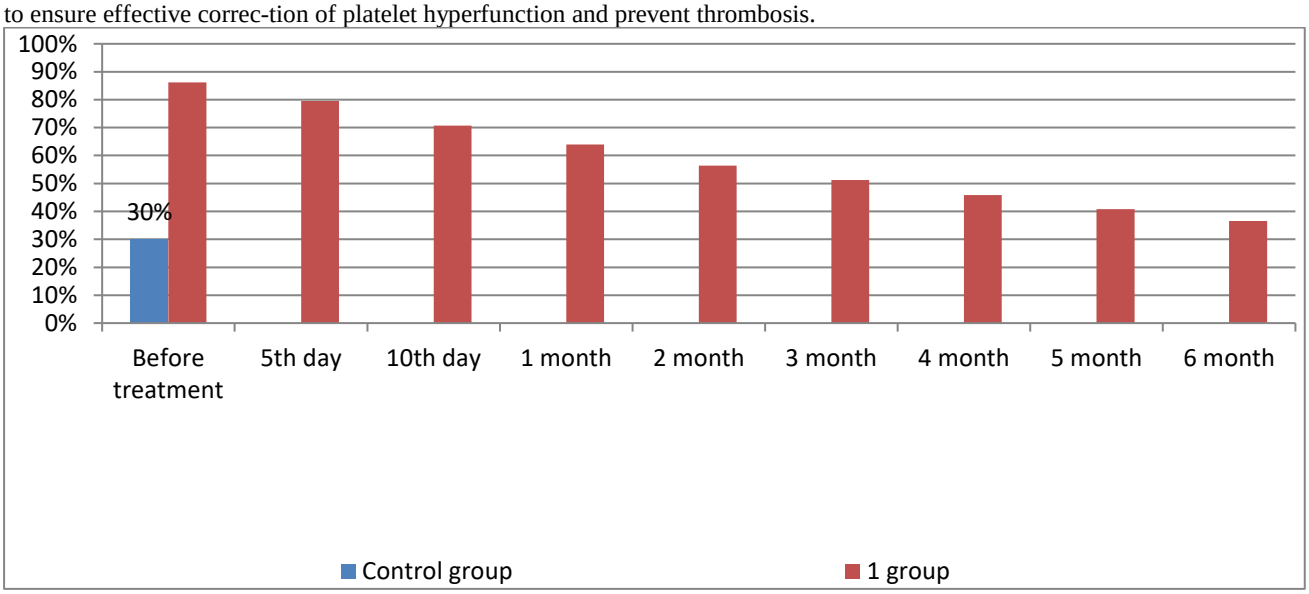

Fig. 3. Platelet Adhesion Under Antiplatelet Therapy in Group 3 Patients with Identified Homozygous Thrombophilia Gene Mutations.

The comparative effectiveness of antiplatelet therapy when Pigasprin was rec-ommended for patients in Groups 2 and 3 with moderate and severe CI and identi-fied thrombophilia gene mutations is presented in Figure 4.

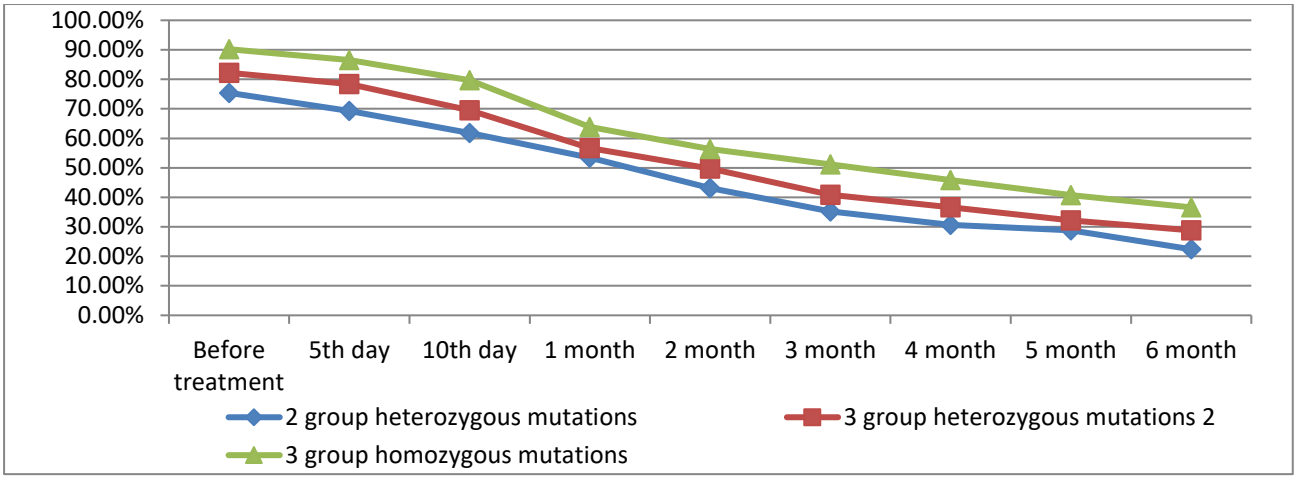

Fig.4. The Effect of Antiplatelet Therapy on Platelet Adhesion in Patients with Identified Thrombophilia Gene Mutations

As seen in Figure 4, platelet adhesion impairment is associated with the severity of the disease and the degree of genetic mutations. In cases of moderate and severe CI with heterozygous mutations, antiplatelet therapy proved effective by the third month. However, discontinuation of therapy led to a rapid recurrence of hyperco-agulation, which is why treatment was continued for up to six months. In cases of severe CI with homozygous mutations, the effectiveness of antiplatelet therapy was observed only by the fifth month.

In Group 2, patients with moderate-to-severe CI and heterozygous mutations in thrombophilia genes exhibited the following changes in spontaneous aggregation degree (SAD) after treatment with Pigasprin for platelet hyperfunction: before treatment: 11.1 ± 0.9%*, day 5: 9.0 ± 0.8%*, day 10: 7.9 ± 0.6%*^, 1 month: 5.5 ± 0.4%*^^^, 2 months: 4.0 ± 0.3%*^^^, 3 months: 2.5 ± 0.2%*^^^, 4 months: **1.8 ± 0.2%*^^^, 5 months: **1.3 ± 0.1%^^^, 6 months: 0.8 ± 0.1%^^^. These findings suggest that Pigasprin treatment effectively reduced platelet hyperfunction over time, with significant improvements observed as early as the first month and reaching near-normal levels after six months.

The adenosine diphosphate-induced aggregation degree (ADF IAD) at 5 µg/mL in Group 2 (patients with moderate-to-severe CI and heterozygous mutations in thrombophilia genes) showed the following changes under Pigasprin treatment: be-fore treatment: 87 ± 7.5%*, day 5: 80 ± 6.2%*, day 10: 74 ± 5.8%*, 1 month: 62 ± 5.2%^^, 2 months: 56 ± 4.3%*^^^, 3 months: 48 ± 4.1%^^^, 4 months: 41 ± 3.6%^^^, 5 months: 32 ± 3.1%^^^, 6 months: 28 ± 2.1%^^^. These results indi-cate that ADFIAD gradually decreased over time with Pigasprin therapy, achiev-ing significant reduction by the third month and approaching near-normal levels after six months.

The adenosine diphosphate-induced aggregation degree (ADF IAD) at 2.5 µg/mL in Group 2 (patients with moderate-to-severe CI and heterozygous muta-tions in thrombophilia genes) showed the following changes under Pigasprin treatment: before treatment: 70 ± 5.1%*, day 5: 65 ± 5.0%*, day 10: 61 ± 4.8%*, 1 month: 52 ± 4.2%*^^, 2 months: 41 ± 3.6%*^^^, 3 months: 30 ± 2.8%^^^, 4 months: 24 ± 2.2%^^^, 5 months: 20 ± 1.8%^^^, 6 months: 17 ± 1.1%^^^. These findings indicate that ADF IAD at 2.5 µg/mL gradually decreased over time with Pigasprin therapy, achieving a significant reduction by the third month and reaching near-normal levels after six months.

TABLE 1. PLATELET AGGREGATION INDICATORS IN GROUP 2 PA-TIENTS WITH HETEROZYGOUS THROMBOPHILIA MUTATIONS TREAT-ED WITH PIGASPIN

Treatment Duration	SAD, %	5 µg/mL ADP-IAD, %	2.5 µg/mL ADP-IAD, %	MAT, U
Control Group	1,2 ± 0,1	44±3,9	26±2,1	32±2,8
Before Treatment	11,1±0,9 ***	87±7,5 ***	70±5,1 ***	73±6,5 ***
Day 5	9,0±0,8 ***	80±6,2 ***	65±5,0 ***	66±5,4 ***
Day 10	7,9±0,6 ***^	74±5,8 ***	61±4,8 ***	59±5,0 ***
1 month	5,5±0,4 ***^^^	62±5,2 **^^	52±4,2 ***^^	48±3,9 **^^
2 month	4,0±0,3 ***^^^	56±4,3 *^^^	41±3,6 ***^^^	42±3,1 *^^^
3 month	2,5±0,2 ***^^^	48±4,1 ^^^	30±2,8 ^^^	36±2,8 ^^^
4 month	1,8 ± 0,2 *^^^	41±3,6 ^^^	24±2,2 ^^^	30±2,6 ^^^

5 month	1,3 ± 0,1 ^^^	32±3,1 ^^^	20±1,8 ^^^	26±2,1 ^^^
6 month	0,8 ± 0,1 ^^^	28±2,1 ^^^	17±1,1 ^^^	20±1,8 ^^^

Notes: Statistical Significance: * - Significant difference compared to the control group (*p < 0.05; p < 0.01; *p < 0.001). - ^ - Significant difference compared to baseline (^p < 0.05; ^^p < 0.01; ^^^p < 0.001).

Before therapy, MAT was 73 ± 6.5 SB*. During the treatment of KI, the follow-ing changes were observed: day 5: 66 ± 5.4 SB*, day 10: 59 ± 5.0 SB*, after 1 month: 48 ± 3.9 SB^^, after 2 months: 42 ± 3.1 SB^^^*, after 3 months: 36 ± 2.8 SB^^^, after 4 months: 30 ± 2.6 SB^^^, after 5 months: 26 ± 2.1 SB^^^, after 6 months: 20 ± 1.8 SB^^^. These results indicate a gradual decrease in platelet ag-gregation and stabilization of the hemostasis system, with significant effectiveness observed between 3 and 4 months and a steady state achieved by 6 months.

In the control group, the following indicators were recorded: Spontaneous Ag-gregation Degree (SAD): 1.2 ± 0.1%, 5 µg/mL ADP-Induced Aggregation (AD-FIAD): 44 ± 3.9%, 2.5 µg/mL ADP-Induced Aggregation (ADFIAD): 26 ± 2.1%, Maximum Aggregation Threshold (MAT): 32 ± 2.8 SB. These values serve as a baseline reference, highlighting the differences in platelet function between the con-trol group and patients undergoing Pigaspin therapy for KI.

In Group 3 (patients with severe KI and heterozygous mutations in three genes), Pigaspin therapy led to the following changes in Spontaneous Aggregation Degree (SAD): before treatment: 18.2 ± 1.5%*, day 5: 16.0 ± 1.3%*, day 10: 14.5 ± 1.2%*, 1 month: 10.2 ± 0.8%*^^^, 2 months: 5.9 ± 0.4%*^^^, 3 months: 3.6 ± 0.2%*^^^, 4 months: 2.2 ± 0.2%*^^^, 5 months: 1.4 ± 0.1%^^^, 6 months: 1.1 ± 0.1%^^^. This indicates a steady and significant decrease in platelet hyperfunc-tion, reflecting the effectiveness of Pigaspin therapy in normalizing hemostatic pa-rameters over six months.

In Group 3 (patients with severe KI and heterozygous mutations in three genes), the degree of ADP-induced platelet aggregation (5 µg/mL ADP-IAD) changed as follows during Pigaspin therapy: before treatment: 92 ± 8.8%*, day 5: 86 ± 6.9%*, day 10: 80 ± 6.4%*, 1 month: 69 ± 5.5%^, 2 months: 60 ± 5.1%^^, 3 months: 54 ± 4.3%^^, 4 months: 44 ± 3.8%^^^, 5 months: 40 ± 3.8%^^^, 6 months: 36 ± 2.9%^^^. This data demonstrates a consistent decline in platelet aggregation over time, suggesting a progressive improvement in platelet function and reduced hy-peractivity due to Pigaspin therapy.

In Group 3 (patients with severe KI and heterozygous mutations in three genes), the degree of ADP-induced platelet aggregation (2.5 µg/mL ADP-IAD) changed as follows during Pigaspin therapy: before treatment: 78 ± 6.7%*, day 5: 72 ± 5.5%*, day 10: 66 ± 5.2%*, 1 month: 59 ± 4.5%*^, 2 months: 50 ± 4.3%*^^, 3 months: 41 ± 3.6%^^^, 4 months: 30 ± 2.7%^^^, 5 months: 24 ± 2.1%^^^, 6 months: 20 ± 1.6%^^^. This gradual reduction in ADP-IAD suggests that Pigaspin therapy effectively mitigates platelet hyperactivity over time, contributing to improved hemostatic balance in patients with severe KI and thrombophilia-related genetic mutations.

In Group 3 (patients with severe KI and heterozygous mutations in three genes), the mean aggregation time (MAT) showed the following changes during Pigaspin therapy: before treatment: 81 ± 7.3 SHB*, day 5: 75 ± 6.6 SHB*, day 10: 70 ± 5.9 SHB*, 1 month: 62 ± 3.9 SHB*^, 2 months: 54 ± 4.7 SHB^^, 3 months: 42 ± 3.6 SHB^^^*, 4 months: 35 ± 3.3 SHB^^^, 5 months: 30 ± 2.8 SHB^^^, 6 months: 26 ± 1.9 SHB^^^. This gradual decrease in MAT indicates a significant reduction in platelet hyperactivity over time, confirming the long-term effectiveness of Pi-gaspin therapy in improving hemostatic function in patients with severe KI and thrombophilia-related genetic mutations (Table 2).

TABLE 2. PLATELET AGGREGATION INDICATORS IN GROUP 3 PA-TIENTS WITH HETEROZYGOUS MUTATIONS TREATED WITH PIGASPIN

Treatment Duration	SAD, %	5 µg/mL ADP-IAD, %	2.5 µg/mL ADP-IAD, %	MAT, U
Control Group	1,2 ± 0,1	44±3,9	26±2,1	32±2,8
Before Treatment	18,2±1,5 *	92±8,8 *	78±6,7 *	81±7,3 *
Day 5	16,0±1,3 *	86±6,9 *	72±5,5 *	75±6,6 *
Day 10	14,5±1,2 *	80±6,4 *	66±5,2 *	70±5,9 *
1 month	10,2±0,8 *^^^	69±5,5 ^	59±4,5 *^	62±3,9 *^
2 month	5,9±0,4 *^^^	60±5,1 *^^	50±4,3 *^^	54±4,7 ^^
3 month	3,6±0,2 *^^^	54±4,3 ^^	41±3,6 ^^^	42±3,6 *^^^
4 month	2,2±0,2 *^^^	44±3,8 ^^^	30±2,7 ^^^	35 ±3,3 ^^^
5 month	1,4±0,1 ^^^	40±3,8 ^^^	24±2,1 ^^^	30 ±2,8 ^^^

6 month	1,1±0,1 ^^^	36±2,9 ^^^	20±1,6 ^^^	26±1,9 ^^^

Notes: Statistical Significance: * - Significant difference compared to the control group (*p < 0.05; p < 0.01; *p < 0.001). - ^ - Significant difference compared to baseline (^p < 0.05; ^^p < 0.01; ^^^p < 0.001).

The table clearly shows that in patients with severe KI and mutations in three thrombophilia genes, anti-aggregant therapy led to normalization of aggregation indicators by the 4th month.

In Group 3, where patients had severe KI with homozygous mutations, platelet aggregation normalized only by the 5th month of anti-aggregant therapy. Howev-er, when the therapy was discontinued, an increase in platelet aggregation was ob-served, indicating the persistent risk of hyperaggregation.

Therefore, long-term anti-aggregant therapy is recommended to maintain normal hemostatic function and prevent excessive platelet activation (Table 3).

TABLE 3. PLATELET AGGREGATION INDICATORS IN GROUP 3 PA-TIENTS WITH HOMOZYGOUS MUTATIONS TREATED WITH PIGASPIN

Treatment Duration	SAD, %	5 µg/mL ADP-IAD, %	2.5 µg/mL ADP-IAD, %	MAT, U
Control Group	1,2±0,1	44±3,9	26±2,1	32±2,8
Before Treatment	22,8±1,8 ***	98 ± 8,6 ***	80 ± 7,1 ***	86 ± 7,8 ***
Day 5	20,0 ± 1,8 ***	90 ± 8,2 ***	75±6,8 ***	81±7,8 ***
Day 10	18,5 ± 1,7 ***	85 ± 7,3 ***	71±5,9 ***	76±6,6 ***
1 month	12,4±1,1 ***^^^	73 ± 6,5 ***^	60 ± 5,7 ***^	69±5,8 ***
2 month	7,5±0,6 ***^^^	66 ± 5,9 **^^	53 ± 4,5 ***^^	61±5,5 ***^
3 month	5,1±0,4 ***^^^	59 ± 4,7 *^^^	44 ± 4,2 ***^^^	54±4,4 ***^^^
4 month	3,4 ± 0,3 ***^^^	50 ± 4,5 ^^^	35 ± 3,1 *^^^	42±3,9 *^^^
5 month	2,1 ± 0,2 ***^^^	44 ± 4,1 ^^^	26 ± 2,4 ^^^	34 ± 3,1 ^^^
6 month	1,2 ± 0,1 ^^^	39 ± 3,3 ^^^	22 ± 2,1 ^^^	29 ±2,2 ^^^

Notes: Statistical Significance: * - Significant difference compared to the control group (*p < 0.05; p < 0.01; *p < 0.001). - ^ - Significant difference compared to baseline (^p < 0.05; ^^p < 0.01; ^^^p < 0.001).

The study of D-dimer levels to assess the effectiveness of anti-aggregant therapy showed the following trends in Group 2 patients with heterozygous mutations in thrombophilia genes: baseline D-dimer: 420 ± 35 ng/mL, day 5: 401 ± 34 ng/mL, day 10: 352 ± 28 ng/mL, month 1: 269 ± 21 ng/mL, month 2: 195 ± 16 ng/mL, month 3: 148 ± 13 ng/mL, month 4: 126 ± 11 ng/mL, month 5: 82 ± 6 ng/mL, month 6: 75 ± 8 ng/mL. This data (illustrated in Figure 5) demonstrates a progres-sive reduction in D-dimer levels, indicating effective suppression of thrombotic ac-tivity and successful platelet aggregation control with anti-aggregant therapy.

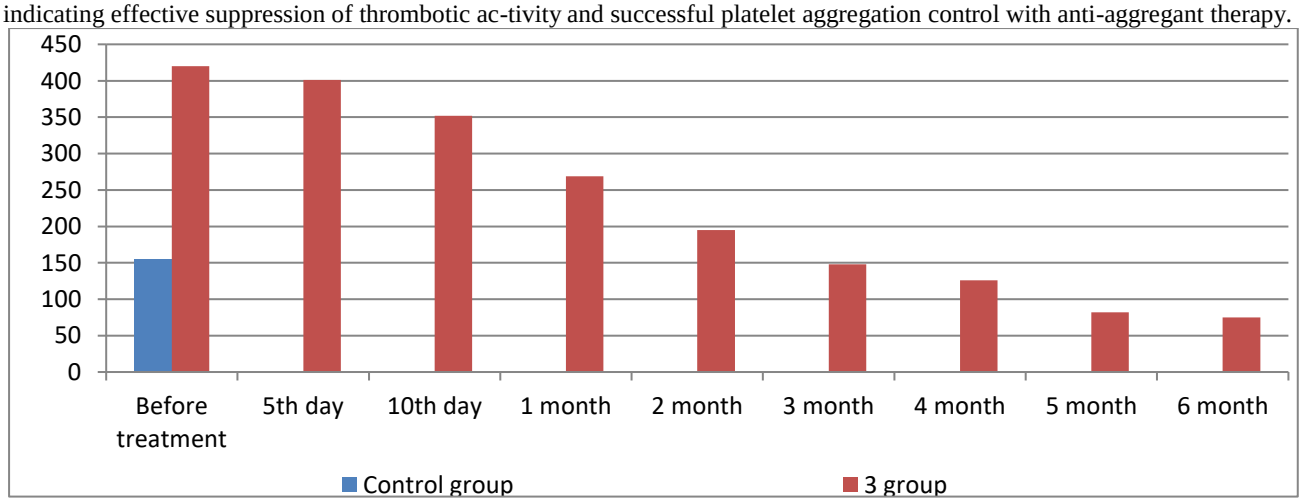

Fig. 5. D-dimer levels in moderate-to-severe COVID-19 patients with thrombo-philia gene mutation undergoing antiplatelet therapy.

In Group 3 patients with severe COVID-19 and confirmed heterozygous muta-tions in three thrombophilia genes, D-dimer levels were measured at different stag-es of antiplatelet therapy: before treatment: 480 ± 45 ng/mL, day 5 of therapy: 463 ± 40 ng/mL, day 10: 414 ± 36 ng/mL, after 1 month: 360 ± 29 ng/mL*, after 2 months 285 ± 22 ng/mL, after 3 months: 207 ± 19 ng/mL*, after 4 months: 166 ± 14 ng/mL*, after 5 months: 134 ± 12 ng/mL*, after 6 months: 108 ± 9 ng/mL* (Figure 6) indicate statistically significant reductions in D-dimer levels over time.

In Group 3 patients with severe COVID-19 and confirmed homozygous throm-bophilia mutation, D-dimer levels were measured at different stages of antiplatelet therapy: before treatment: 684 ± 58 ng/mL, day 5 of therapy: 609 ± 55 ng/mL, day 10: 553 ± 49 ng/mL, after 1 month: 526 ± 58 ng/mL, after 2 months: 496 ± 42 ng/mL*, after 3 months: 453 ± 42 ng/mL, after 4 months: 377 ± 28 ng/mL*, after 5 months: 291 ± 23 ng/mL*, after 6 months: 219 ± 10 ng/mL* (Figure 7) indicate statistical significance in the reduction of D-dimer levels over time.

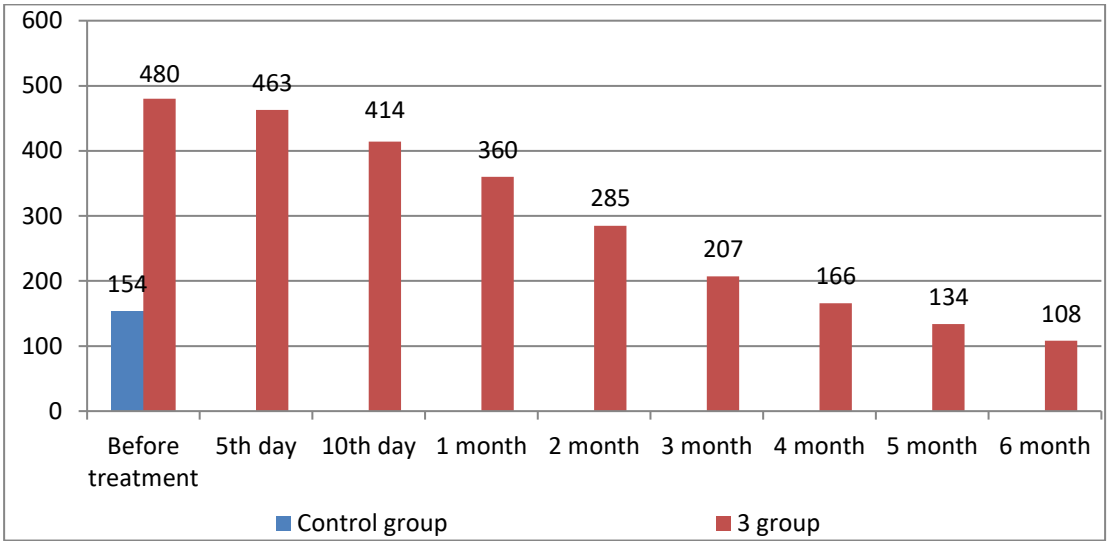

Fig. 6. D-dimer levels in severe COVID-19 patients with thrombophilia gene muta-tion undergoing antiplatelet therapy.

In conclusion, platelet adhesion and aggregation properties were increased in COVID-19, and these indicators rose sharply when an unfavorable thrombophilia genotype was detected. In patients with moderate COVID-19 treated with Pi-gasprin, platelet adhesion and aggregation normalized by 3-4 months, while in se-vere cases, treatment effectiveness was observed at 4-5 months. However, after discontinuation of the drug, hemostatic indicators shifted back towards hyperco-agulation, indicating the need for continued therapy.

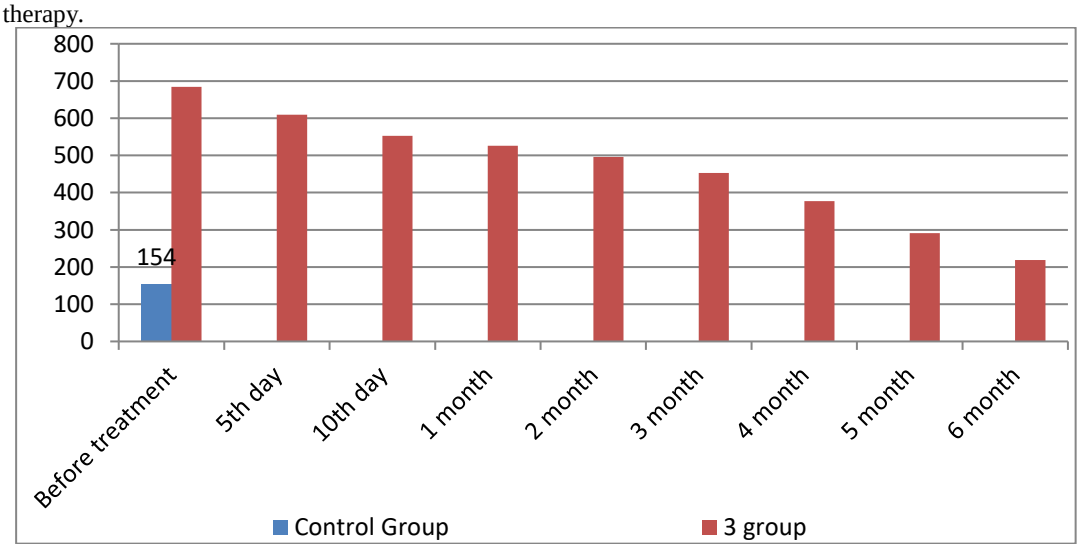

Fig.7. D-dimer levels in severe COVID-19 patients with thrombophilia gene muta-tion undergoing antiplatelet therapy.

CONCLUSIONS

1. In mild coronavirus infection, the significance of genetic mutations predispos-ing to thrombophilia was not confirmed. However, in moderate and severe cases, an unfavorable genotype of the MTHFR 677 C>T (rs1801133) gene and the MTR 5p15.31 66 A>G (rs1801394) gene was significantly more common.
2. The high-risk homozygous mutation of thrombophilia genes was observed only in patients with severe COVID-19, with the predominant genotype being the mutant G/G genotype of the MTR 5p15.31 66 A>G (rs1801394) gene in 23 cases (67.65%).
3. In coronavirus infection, patients without a genetic predisposition to thrombophilia had normal homocysteine levels. However, when a heterozygous genotype of thrombophilia genes was detected, homocysteine levels increased by 3.0-4.4 times, and in the presence of a homozygous mutation, the levels increased by 5.6 times.

4. In coronavirus infection, when an unfavorable genotype of thrombophilia genes was identified, platelet adhesion activity increased sharply by 2.3-2.6 times, and aggregation activity increased by 1.9-2.5 times.
5. In moderate and severe cases of coronavirus infection, D-dimer levels increased by 1.27 times, while in the presence of an unfavorable thrombophilia genotype, this indicator increased by 2.73-4.44 times.
6. Impairment of platelet adhesion and aggregation properties depended on the severity of the disease and the degree of genetic alteration. When an unfavorable heterozygous genotype was identified in moderate and severe cases of coronavirus infection, the effectiveness of antiplatelet therapy (75 mg of acetylsalicylic acid and 75 mg of clopidogrel combination) was observed in 2-3 months. In severe coronavirus infection with a homozygous mutation, the effectiveness of antiplatelet therapy was observed in 3-4 months.

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