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Evaluation Of The Efficacy Of Antiaggregant Therapy In Covid-19

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ABSTRACT

In patients with mild coronavirus infection, platelet activity and coagulation he-mostasis did not show significant changes. However, in moderate and severe cas-es, platelet aggregation and adhesion activity increased. When platelet aggregation and adhesion activity increased, treatment with a combination of acetylsalicylic ac-id and 75 mg of clopidogrel, compared to standard therapy, provided the most ef-fective correction of hemostatic changes.

KEYWORDS: Coronavirus Infection, Platelet Activity, Coagulation Hemostasis, Platelet Aggrega-tion, Platelet Adhesion, Acetylsalicylic Acid, Clopidogrel.

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INTRODUCTION

Coronavirus infection (COVID-19) is a new infectious disease that spread rapidly worldwide and is characterized by severe complications. In December 2019, an epidemic of an unknown infection was observed in Wuhan, leading to the development of pneumonia in many patients, which created an emergency situation in China's healthcare system [17]. The China Centers for Disease Control and Prevention studied the samples taken from patients' throat swabs and confirmed that the disease was caused by a new type of beta-coronavirus [12]. The new virus was named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus) [13].

Coronaviruses are widespread in nature, and most do not cause significant harm to human health. Only in 25% of cases do they lead to various types of colds. Due to mutations, coronaviruses occasionally cause epidemics in humans [2].

When SARS-CoV-2 patients are in poorly ventilated and enclosed spaces, the virus tends to accumulate, increasing the likelihood of transmission. Currently, transmission of SARS-CoV-2 from animals to humans is considered to be low [7].

Patients with asymptomatic infection or those who have recovered from COVID-19 but still have detectable virus in their feces are considered sources of infection. SARS-CoV-2 RNA has also been identified in wastewater, though the virus's ability to survive in the external environment has not yet been fully determined [11].

ACE2 is part of the surfactant composition, and type II alveocytes produce it from blood plasma components. The SARS-CoV-2 spike proteins bind to it, ACE2 levels decrease, leading to the breakdown of protective barriers and allowing the virus to penetrate. Experimental studies have shown that increasing ACE2 expression allows more viral attachment, leading to a reduction in ACE2 levels. Up to three viruses may attach to a single ACE2 molecule. The intensity of the disease's spread varies across European and Asian populations because the amounts of ACE2 and TMPRSS2 differ [1].

Because ACE2 receptors are also present in the gastrointestinal tract, the intestines become a target for SARS-CoV-2. The gastrointestinal disturbances, including diarrhea, caused by coronavirus infection are linked to the direct impact of the virus as well as tissue and organ damage due to immune reactions [3].

The spread of the coronavirus in the body leads to a hyperimmune reaction—referred to as the "cytokine storm"—which results in the production of numerous inflammatory cytokines, including C-reactive protein, ferritin, lactate dehydrogenase, D-dimer, interleukins 1-beta, 6, and 2, tumor necrosis factor, and chemokines [15]. The "cytokine storm" exacerbates the damage, causing the blood vessel endothelium to lose its anticoagulant properties [18].

The development of hypercoagulation in COVID-19 results in numerous complications and is observed in severe cases of the infection. The activation of hemostasis and the formation of fibrin clots are adaptive mechanisms aimed at limiting inflammation. However, the cytokine storm and macrophage activation syndrome lead to hyperinflammation, causing the hemostatic system to malfunction [5]. Macrophage activation syndrome is a cascade of inflammatory responses that leads to sepsis and thrombosis, contributing to high mortality [6].

According to epidemiological data, older individuals (65 years and older), patients with cardiovascular diseases, hypertension, diabetes, obesity, malignancies, chronic lung, liver, and kidney diseases, and those with immunodeficiencies are at higher risk for severe complications [14]. Specifically, in patients with liver cirrhosis, not only is the course of COVID-19 more severe, but it also exacerbates the underlying chronic liver disease [16].

COVID-19 is a systemic disease that progresses with hyperimmune inflammation, an imbalance in the renin-angiotensin-aldosterone system, endothelial dysfunction, and severe vasculopathy (thrombotic microangiopathy and coagulopathy) [8].

Although the coronavirus infection primarily affects the respiratory system, recent data shows that COVID-19 is a systemic disease affecting the respiratory, cardiovascular, gastrointestinal, urinary, neurological, hematologic, and immune systems [9]. This worsens the patient's condition and increases mortality [10]. The mortality rate in COVID-19 infection is generally between 0.5-3% [4].

GENERAL CLINICAL DESCRIPTION

Clinical examinations were conducted at Zangiota Infectious Diseases Hospital No. 2 in 2021. The scientific study involved 120 patients of coronavirus infection (CI). All patients were tested for CI virus markers using immunochromatographic analysis (Snibe, China) and polymerase chain reaction (PCR) methods (DNA technology). To determine the extent of lung damage, patients underwent multi-slice computed tomography.

For diagnosis, the study followed the diagnostic criteria outlined in the 8th edition of the "Temporary Guidelines for the Treatment of Patients with Coronavirus Infection." The severity of CI was assessed based on clinical signs (fever, respiratory 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, comorbidities, etc.) were taken into account.

Patients were divided into four groups:
Group 1 (n=30): Did not receive any antiplatelet therapy.
Group 2 (n=30): Received Acetylsalicylic acid (ASA) 81 mg, orally once daily for 10 days.
Group 3 (n=30): Received Clopidogrel 75 mg, orally once daily for 10 days.
Group 4 (n=30): Received Pigasprin 75/75 mg, orally once daily for 10 days.
Acetylsalicylic Acid (ASA) 81 mg, manufacturer: KEM Pharma LLC (USA), LNK International, Inc. Excipients: Iron oxide, cellulose, colloidal silicon dioxide, starch, etc. ASA is a round, yellow enteric-coated tablet. After absorption, ASA is hydrolyzed to salicylic acid and reaches peak plasma concentration within 1 hour. ASA irreversibly inhibits cyclooxygenase-1 (COX-1), thereby reducing the production of thromboxane A2, a key inducer of platelet aggregation. ASA inhibits platelet aggregation by blocking COX-1, preventing thromboxane A2 synthesis.

Clopidogrel 75 mg. Clopidogrel's active metabolite inhibits platelet aggregation by selectively blocking P2Y12 receptors, preventing ADP from binding. This inhibits the activation of the glycoprotein IIb/IIIa complex, preventing platelet aggregation for the lifespan of platelets (7-10 days). After stopping clopidogrel, ADP-induced platelet aggregation restores within 3–7 days. 50% of clopidogrel is absorbed, reaching peak plasma concentration in 45 minutes. Clopidogrel inhibits platelet aggregation by blocking P2Y12 receptors, preventing ADP-mediated activation.

Pigasprin, Acetylsalicylic Acid 75 mg and Clopidogrel 75 mg. Pigasprin (India, Medeor Life Care LLP, Ratnamani Healthcare Pvt). Form: Pink gelatin capsule. Both ASA and clopidogrel are widely used as antiplatelet agents in clinical practice.

Platelet activity was measured before treatment, on day 5 of treatment, on day 10 of treatment, one month after treatment.

A control group was also established, consisting of 20 healthy individuals matched by age and gender. Patients selected for the scientific study voluntarily agreed to participate.

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 performed 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 coagulometer 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 genotypes 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 genetic material (DNA or RNA) 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), standard 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 considered 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).

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

A study was conducted to assess the effectiveness of treating increased platelet adhesion and aggregation in patients with moderate COVID-19 infection.

Von Willebrand factor (vWF), a key component of vascular-platelet hemostasis, was evaluated in each treatment group. Von Willebrand Factor (vWF) in Group 1 (No antiplatelet therapy) Baseline vWF: 155 ± 11%*, Day 5: 142 ± 11%*, Day 10: 135 ± 11%, 1 month: 108 ± 9%^^, Control group: 96 ± 7% (*Statistical significance: *-P<0.05; **-P<0.01; ***-P<0.001 compared to the control group).

In Group 2 (ASA 81 mg daily for 10 days) Baseline vWF: 158 ± 13%*, Day 5: 133 ± 11%, Day 10: 118 ± 8%*^, 1 month: 82 ± 6.8%^^^. The addition of ASA resulted in a significant reduction in vWF levels within 10 days, reaching normal levels within a month.

In Group 3 (Clopidogrel 75 mg daily for 10 days) Baseline vWF: 159 ± 12.8%*, Day 5: 136 ± 11.5%, Day 10: 116 ± 7%*^, 1 month: 85 ± 7%^^^. The inclusion of Clopidogrel improved vWF levels significantly in moderate COVID-19 cases, leading to normalization within one month (*^: Significant difference compared to pre-treatment values: ^-P<0.05; ^^-P<0.01; ^^^-P<0.001) (Fig. 1)

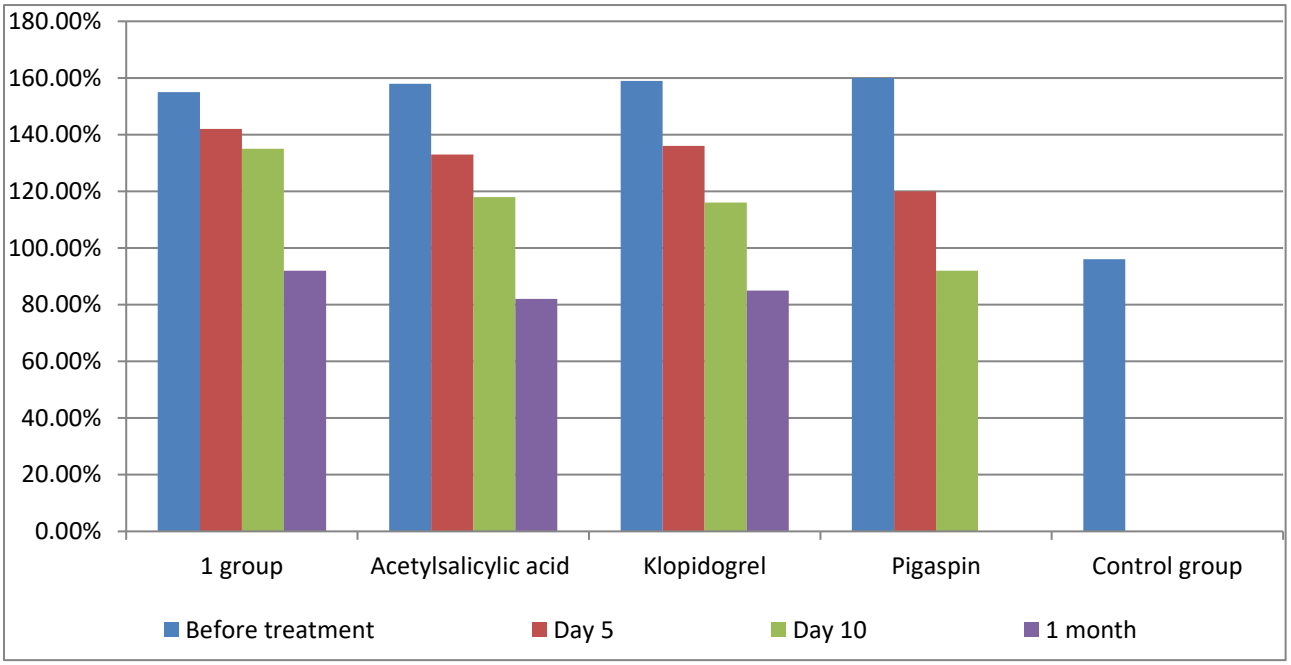

Fig. 1. Effect of Pigasprin on vWF Levels

These findings indicate that Pigasprin, Acetylsalicylic Acid, and Clopidogrel effectively reduce platelet hyperactivity, with Clopidogrel and ASA showing strong antiplatelet effects in COVID-19 patients. Combination therapy for COVID-19 patients normalized vWF levels within one month.

As seen in Figure 1, the inclusion of Pigasprin (a dual-component drug) in the treatment regimen significantly reduced von Willebrand Factor (vWF) levels to normal ranges. Before treatment: 160 ± 14%*, Day 5: 120 ± 10%*^, Day 10: 92 ± 8%^^^. This indicates that Pigasprin significantly reduces vWF levels within 10 days, normalizing by the end of therapy.

Studies on platelet aggregation in Group 1 (no antiplatelet therapy) revealed: Spontaneous Aggregation Degree (SAD) Before treatment: 3.1 ± 0.3%*, Day 5: 3.0 ± 0.3%*, Day 10: 2.9 ± 0.3%*, 1 month: 1.5 ± 0.1%^^^. Adenosine Diphosphate (ADP)-Induced Aggregation Degree (IAD) (5 µg/mL) Before treatment: 72 ± 5.5%*, Day 5: 70 ± 5.2%*, Day 10: 67 ± 5.8%, 1 month: 47 ± 3.8%^^^

Adenosine Diphosphate (ADP)-IAD (2.5 µg/mL) Before treatment: 48 ± 3.1%*, Day 5: 46 ± 4.0%*, Day 10: 44 ± 4.1%*, 1 month: 32 ± 2.8%^^^.

Maximum Aggregation Rate (MAR, in Shear Units - SU) Before treatment: 49 ± 4.5 SU, Day 5: 47 ± 4.1 SU, Day 10: 45 ± 4.0 SU, 1 month: 35 ± 3.2 SU^.

In the control group (healthy individuals), the baseline values were: SAD: 1.2 ± 0.1%, ADP-IAD (5 µg/mL): 44 ± 3.9%, ADP-Induced Aggregation (2.5 µg/mL): 26 ± 2.1%, MAR: 32 ± 2.8 SU (Table 1).

TABLE 1. PLATELET AGGREGATION INDICATORS

Platelet Aggregation Indicators	Control Group	Before Treatment	During Treatment		
			5th day	10th day	1 month
SAD, %	1,2±0,1	3,1±0,3 ***	3,0±0,3***	2,9±0,3***	1,5±0,1^^^
5 µg/ml ADP - IAD, %	44±3,9	72±5,5 ***	70±5,2 ***	67±5,8 **	47±3,8 ^^^
2.5 µg/ml ADP - IAD, %	26±2,1	48±3,1 ***	46±4,0 ***	44±4,1 ***	32±2,8 ^^^
Maximum Aggregation Rate, AU	32±2,8	49±4,5 **	47±4,1 **	45±4,0 *	35±3,2 ^

Note: * - significant difference compared to the control group (*-P<0.05; **-P<0.01; ***-P<0.001); ^ - significant difference compared to pre-treatment values (^-P<0.05; ^^-P<0.01; ^^^ - P<0.001)

In Group 2, the use of Acetylsalicylic Acid led to a relative improvement in these indicators. From Table 2, it is evident that before treatment, the Spontaneous Aggregation Degree (SAD) was 3.2 ± 0.3%, *but on the 5th day of treatment, it decreased to 2.7 ± 0.2%*, on the 10th day to 2.3 ± 0.2%^, and after 1 month, it reached 1.0 ± 0.05%^^^.

TABLE 2. PLATELET AGGREGATION INDICATORS IN CI PATIENTS TREATED WITH ACETYLSALICYLIC ACID

Platelet Aggregation Indicators	Control Group	Before Treatment	During Treatment		
			5th day	10th day	1 month
SAD, %	1,2±0,1	3.2±0.3 ***	2.7±0.2 ***	2,3±0,2***^	1,0±0,05 ^^^
5 µg/ml ADP - IAD, %	44±3,9	73±5.5 ***	65±4.8 **	56±4,1 *^	35±3,2 ^^^
2.5 µg/ml ADP - IAD, %	26±2,1	49±3.6 ***	40±3.5***	35±2,8 *^^	22±1,9^^^
Maximum Aggregation Rate, AU	32±2,8	50±4.6 ***	45±3.4 **	39±3,0 ^	28±2,2 ^^^

Note: * - significant difference compared to the control group (*-P<0.05; **-P<0.01; ***-P<0.001); ^ - significant difference compared to pre-treatment values (^-P<0.05; ^^-P<0.01; ^^^ - P<0.001).

Similarly, the 5 µg/ml ADP - IAD value was 73 ± 5.5%* before treatment, but during therapy, it dropped to 65 ± 4.8% on the 5th day, 56 ± 4.1%*^ on the 10th day, and 35 ± 3.2%^^^ after 1 month.

For 2.5 µg/ml ADP - IAD, the pre-treatment value was 49 ± 3.6%, *but it decreased to 40 ± 3.5%* on the 5th day, 30 ± 2.8%*^^ on the 10th day, and 22 ± 1.9%^^^ after 1 month.

The Maximum Aggregation Rate (MAR) was 50 ± 4.6 AU before therapy. Under CI treatment, it decreased to 45 ± 3.4 AU on the 5th day, 39 ± 3.0 AU^ on the 10th day, and 28 ± 2.2 AU^^^ after 1 month.

The use of Clopidogrel resulted in similar changes in platelet aggregation indicators as treatment with acetylsalicylic acid (Table 3).

TABLE 3. PLATELET AGGREGATION INDICATORS IN CI PATIENTS TREATED WITH CLOPIDOGREL

Platelet Aggregation Indicators	Control Group	Before Treat-ment	During Treatment		
			5th day	10th day	1 month
SAD, %	,2±0,1	.1 ±0.3 ***	.6 ± 0.3 ***	,2±0,2 ***^	,0±0,1 ^^^
5 µg/ml ADP - IAD, %	4±3,9	2±6.1 ***	4±4.8 **	6±4,0 *^c	3±3,9 ^^^
2.5 µg/ml ADP - IAD, %	6±2,1	8±3.9 ***	8±3.4 **	4±2,5 *^^	3±1,6 ^^^
Maximum Aggregation Rate, AU	2±2,8	0±4.9 **	2±3.6 *	6±2,7 ^	7±2,3 ^^^

Note: * - significant difference compared to the control group (*-P<0.05; **-P<0.01; ***-P<0.001); ^ - significant difference compared to pre-treatment values (^-P<0.05; ^^-P<0.01; ^^^ - P<0.001).

As seen in Table 3, before treatment with Clopidogrel, the spontaneous aggregation degree (SAD) was 3.1 ± 0.3%. *By the 5th day of treatment, SAD decreased to 2.6 ± 0.3%*, by the 10th day to 2.2 ± 0.2%*^, and after 1 month, it reached 1.0 ± 0.1%^^^. The 5 µg/mL ADP-induced aggregation degree (IAD) was 72 ± 6.1%* before treatment. On the 5th day, it dropped to 64 ± 4.8%, on the 10th day to 56 ± 4.0%*^, and after 1 month, it reached 33 ± 3.9%^^^.

The 2.5 µg/mL ADP-IAD was 48 ± 3.9%* before treatment. On the 5th day, it decreased to 38 ± 3.4%, by the 10th day to 34 ± 2.5%*^^, and after 1 month, it reached 23 ± 1.6%^^^.

The maximum aggregation rate (MAR) was 50 ± 4.9 units (U) before therapy. On the 5th day, it dropped to 42 ± 3.6 U, on the 10th day to 36 ± 2.7 U^, and after 1 month, it reached 27 ± 2.3 U^^^ (Table 4).

TABLE 4. PLATELET AGGREGATION PARAMETERS IN CI PATIENTS TREATED WITH PIGASPIN

Platelet Aggregation Indicators	Control Group	Before Treat-ment	During Treatment	
			5th day	10th day
SAD), %	1,2 ± 0,1	3,2 ± 0,3 ***	2,4 ± 0,2 ***^	1,5±0,2 ^^^
5 µg/mL ADP-IAD, %	44 ± 3,9	73 ± 6,6 ***	57 ± 4,0 *^	46±2,9 ^^^
2.5 µg/mL ADP-IAD, %	26 ± 2,1	49±4,0 ***	36±2,8 **^	28±1,9 ^^^
Maximum Aggregation Rate (MAR), U	32 ± 2,8	50 ± 3,5 ***	41 ±2,8 *^	34 ±2,1 ^^^

Note: * - statistically significant difference compared to the control group (*p<0.05; **p<0.01; ***p<0.001); ^ - statistically significant difference compared to pre-treatment values (^p<0.05; ^^p<0.01; ^^^p<0.001).

The acquired platelet hyperfunction, characterized by increased platelet aggregation activity, was most effectively corrected using Pigaspin treatment, leading to significant hemostasiological improvements.

No Antiplatelet Therapy (Group 1) – Platelet adhesion decreased slowly and remained above normal levels until 1 month.

Aspirin (Group 2) and Clopidogrel (Group 3) – Both significantly reduced platelet adhesion by Day 5 and achieved near-normal levels by 1 month.

Combination Therapy (Group 4) – Showed the fastest and most effective reduction in platelet adhesion, reaching near-normal values by Day 10.

Clinical Implication – Antiplatelet therapy, especially Aspirin + Clopidogrel combination, is highly effective in reducing

excessive platelet adhesion in COVID-19 patients, potentially lowering thrombotic risks.
Pigasprin has been confirmed as the most effective antiplatelet agent in managing platelet hyperfunction in COVID-19, ensuring rapid and stable normalization of hemostasis.

CONCLUSIONS

1. In patients with mild coronavirus infection, platelet activity did not change significantly. However, in moderate and severe cases, platelet aggregation properties increased by 39-54%, and adhesion activity increased by 60-98%.
2. In patients with mild COVID-19, coagulation hemostasis parameters did not show significant changes. However, in moderate and severe cases, activated partial thromboplastin time (APTT) was reduced by 26-40%, thrombin time (TT) was reduced by 22.3-45.2%, and fibrinogen levels increased by 37.4-58.6%. While D-dimer levels remained normal in Group 1, they increased by 1-fold in Group 2 and by more than 2-fold in Group 3.
3. When platelet aggregation and adhesion activity increased, treatment with a combination of acetylsalicylic acid and 75 mg of clopidogrel, compared to standard therapy, provided the most effective correction of hemostatic changes. This led to the normalization of platelet adhesion and aggregation properties as early as the fifth day of treatment.

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