https://doi.org/10.23873/2074-0506-2024-16-3-328-336

Dynamics of hemostasis system parameters in assessing the risk of complications in the patients with acute myocardial infarction receiving antiplatelet therapy

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Abstract

Background. *Current treatment of patients with myocardial infarction is based on the strategy of early invasive coronary intervention in combination with dual antiplatelet therapy - with acetylsalicylic acid and a P2Y12 blocker of platelet adenosine diphosphate receptors. In patients with thrombosis of the infarct-related artery, the phenomenon of "slow/no reflow" (slowing of blood flow due to distal embolization of the artery), inhibitors of glycoprotein IIb/IIIa platelet receptors are administered as additional disaggregant therapy. In patients undergoing standard antiplatelet therapy in combination with glycoprotein IIb/IIIa inhibitors, there is a risk of hemorrhagic complications, therefore, monitoring of hemostasis parameters is necessary. Currently, there are no standard approaches to monitor the antiplatelet therapy.*

Objective. *To study the dynamics of hemostatic system parameters in patients with acute myocardial infarction during antiplatelet therapy.*

Material and methods. *We assessed platelet aggregation with 10 µmol of* adenosine phosphate *as an inducer in patients with ST-segment elevation myocardial infarction with different options of standard antiplatelet therapy in combination with GP IIb/IIIa inhibitors. Group 1 included 20 patients on dual antiplatelet therapy (clopidogrel 75 mg + acetylsalicylic acid 100 mg) + GP IIb/IIIa inhibitor (tirofiban). Group 2 included 15 patients on dual antiplatelet therapy (ticagrelor 180 mg + acetylsalicylic acid 100 mg) + GP IIb/IIIa inhibitor.*

Results. *While on antiplatelet therapy the patients in both groups 1 and 2 demonstrated a decrease in platelet aggregation ability under the impact of adenosine phosphate, relative to the norm: 38 (21;43) % and 14 (11;15) %, respectively, the norm being 79 (73;84)% ($p<0.05$). Meantime, no thrombotic events in the form of stent thrombosis were noted, which indicated antiplatelet therapy efficacy. In an intragroup comparison, the decrease in the platelet aggregation ability was most pronounced in group 2 ($p<0.05$). By the 7th day of myocardial infarction, the platelet aggregation had continued to decrease to 26 (17;43)% in group 1, to 10 (7;11)% in group 2. The most pronounced effect of antiplatelet therapy was observed in group 2 ($p<0.05$), which was manifested by a statistically significant decrease in platelet aggregation ability under the impact of 10 µmol of adenosine phosphate.*

Conclusions. *While studying the hemostasis system changes over time in patients with myocardial infarction receiving antiplatelet therapy, we have found that making the platelet aggregation ability assessment with 10 µmol of adenosine phosphate as an inducer is possible to identify the effect of medications. However, further studies including larger patient groups are needed to determine the target values of platelet aggregation with 10 µmol of adenosine phosphate and assess the therapy efficacy.*

Keywords: acute coronary syndrome, antiplatelet therapy, glycoprotein IIb/IIIa platelet receptor inhibitors, hemostasis

Conflict of interests Authors declare no conflict of interest

Financing The study was performed without external funding

For citation: Gvindzhiliya TR, Kuzmina IM, Klychnikova EV, Tazina EV, Kochetova AA, Muradyan NA, et al. Dynamics of hemostasis system parameters in assessing the risk of complications in the patients with acute myocardial infarction receiving antiplatelet therapy. *Transplantologiya. The Russian Journal of Transplantation.* 2024;16(3):328–336. (In Russ.). https://doi.org/10.23873/2074-0506-2024-16-3-328-336

ACS, acute coronary syndrome
ADP, adenosine phosphate
APTT, activated partial thromboplastin time
CHD, coronary heart disease
CVD, cardiovascular disease
DAPT, dual antiplatelet therapy
ECG, electrocardiogram
EchoCG, echocardiogram
EF, ejection fraction
FG, fibrinogen
GP, glycoprotein
GP IIb/IIIa inhibitors, glycoprotein IIb/IIIa inhibitors of platelet receptors
INR, international normalized ratio
MI, myocardial infarction
NSTEMI, non-ST segment elevation myocardial infarction
PCI, percutaneous coronary intervention
PT Quick, Quick prothrombin time test
PT, prothrombin time
STEMI, ST segment elevation myocardial infarction
TT, thrombin time
UA, unstable angina

Introduction

Cardiovascular disease remains the leading cause of death worldwide, with almost half of these deaths attributable to myocardial infarction (MI) [1]. One of the manifestations of coronary heart disease (CHD) is acute coronary syndrome (ACS), which includes the following

clinical forms: unstable angina (UA), ST segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI).

Along with percutaneous coronary intervention (PCI) in the early stages of the disease, pharmacological treatment of MI affects survival and reduces the incidence of recurrent ischemic events. To reduce the risk of thrombotic complications in patients with ACS, a standard dual antiplatelet therapy (DAPT), being one of the main kinds of drug therapy, is administered [2]. Antiplatelet agents can be classified according to their mechanism of action as follows:

1. Platelet aggregation inhibitors. Acetylsalicylic acid irreversibly inhibits the activity of the cyclooxygenase enzyme in the prostaglandin synthesis pathway (PGH2). This prostaglandin is a precursor to thromboxane A2 (TXA2) and PGI2. Aspirin is a mandatory component of dual antiplatelet therapy for ACS [3].

2. Oral thienopyridines, such as clopidogrel, ticagrelor, prasugrel, are inhibitors of adenosine platelet receptors P2Y12 [4], further reducing the risk of thrombotic events in patients. Clopidogrel is widely used in clinical practice, but has some disadvantages: a slow onset of action in the acute phase and the inability to achieve adequate platelet inhibition in a significant proportion of patients due to individual variability in drug response associated with cytochrome P450 activity. Ticagrelor is a reversible and long-acting antagonist of the P2Y12 adenosine diphosphate receptor [5]. It provides a faster onset of action and greater platelet inhibition than clopidogrel.

And it is known: DAPT, including a P2Y12 receptor inhibitor in combination with acetylsalicylic acid, is recommended by current guidelines as an effective therapy against ACS, which significantly reduces platelet reactivity and prevents ischemic events [6].

3. Inhibitors of platelet glycoprotein IIb/IIIa receptors (GP IIb/IIIa inhibitors) such as abciximab, eptifibatide, tirofiban.

One of the indications for prescribing GP IIb/IIIa inhibitors is the phenomenon of delayed and(or) coronary blood no-reflow (slow/no-reflow). This phenomenon is one of the complications of endovascular interventions (distal embolization with thrombotic masses and fragments of atherosclerotic plaque), affecting the prognosis. Diagnosis of the "slow/no-reflow" phenomenon is made intraoperatively and is defined as a slowdown or complete absence of blood flow according to the TIMI Coronary Grade Flow score [7]. GP IIb/IIIa receptor inhibitors are also administered for massive intracoronary thrombosis [8].

On the surface of each platelet, there are from 50,000 to 80,000 type IIb/IIIa glycoprotein (GP) complexes, which are inactive under normal conditions, but are activated when the platelet configuration changes. Activated type IIb/IIIa GP complexes serve as receptors for the formation of fibrinogen bridges between platelets and, as a result, prevent further platelet aggregation [9].

Tirofiban is a synthetic derivative of tyrosine by its chemical structure [10]. Tirofiban is a selective GP IIb/IIIa receptor inhibitor with a rapid onset of action and a short half-life (2–4 hours). Its effect is quickly reversible after the therapy discontinuation. Numerous studies have also shown the anti-inflammatory effect of tirofiban. [11].

Recently, some efforts have been made to identify patients with high platelet reactivity and a high risk of bleeding during treatment, using laboratory tests of hemostasis.

The objective was to study the dynamics of the hemostasis system parameters in patients with acute myocardial infarction when using various antiplatelet therapy regimens.

Material and methods

The study included 35 patients with STEMI receiving different options of standard antiplatelet therapy in combination with GP IIb/IIIa inhibitors. Patients of group 1 received DAPT (clopidogrel 75 mg + acetylsalicylic acid 100 mg) + GP IIb/IIIa inhibitor (tirofiban) (n=20 patients). Group 2 included patients who received DAPT (ticagrelor 180 mg + acetylsalicylic acid 100 mg) + GP IIb/IIIa inhibitor (tirofiban) (n=15 patients). All patients underwent primary PCI, electrocardiogram (ECG), echocardiography (assessment of lesion area and ejection fraction - EF) were recorded upon admission and over time.

Table 1 shows the characteristics of the patients included in the study. The mean age of patients was 56 years. The mean ejection fraction was 40±5%. All patients had an ECG pattern of ST segment elevation, large-focal myocardial infarction and multiple vessel coronary lesions. Meanwhile, the patients of group 1 were admitted at the hospital at a later stage from the onset of the disease. There were no statistically significant differences between the compared groups in demographic and clinical characteristics presented in the Table.

Table 1. Characteristics of patients included in the study

Patient characteristics	1st group (n=20)	2nd group (n=15)
Demographic characteristics (m/f)	m. 85% (n=17) f. 15% (n=3)	m. 80% (n=12) f. 20% (n=3)
ECG pattern (ST segment elevation)	Yes	Yes
"Pain-to-door" time	207 ±10 min	160±10 min
"Pain-to-balloon" time	58±10 min	77±10 min
Depth of myocardial damage	macrofocal	macrofocal
Extent of coronary artery damage	Multiple-vessel lesion	Multiple-vessel lesion
Ejection fraction	40±5%	4 2 ±5%

The parameters of the hemostatic system status, namely the activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalized ratio (INR), prothrombin according to Quick (PT), thrombin time (TT), fibrinogen (FG) and D-dimer levels were studied using the automatic "ACLTOP-700" coagulometer, Instrumentation Laboratory (USA) with the respective reagents. Platelet aggregation was assessed using a Chrono-Log 490 aggregometer manufactured by Chrono-Log (USA). 10 μmol of adenosine phosphate (ADP) was used as an induction of platelet activation. The tests were performed on the 1st, 3^{rd}, and 7^{th} days of treatment.

Statistical analysis was made using Statistica 10.0 software. Descriptive statistics are presented in the form of medians (Me), interquartile ranges (Q_1;Q_3), maximum (max) and minimum (min) values. Comparative statistics were performed using nonparametric tests; quantitative variables were compared using Fisher's exact test, continuous unrelated samples were compared using the Mann–Whitney test (cr. M–W). The statistical significance of differences was set at $p<0.05$.

Results and discussion

Various studies have reported that tirofiban has significant effects in preventing thrombosis, inhibiting platelet aggregation and suppressing the inflammatory response [7, 12]. A number of studies have demonstrated the combined effect of DAPT with tirofiban in clinical practice [13]. In the present study, we compared the effect of tirofiban in combination with clopidogrel + acetylsalicylic acid (group 1) and ticagrelor + acetylsalicylic acid (group 2) on changes in laboratory parameters of hemostasis in patients with ACS.

At the hospital stage (7–9 days of MI) 25% of patients of group 1 showed a dynamic decrease of the affected area and an increase in EF. Meantime, in group 2, an improvement in the contractility of the left ventricular myocardium was noted in 53%, and a decrease of the affected area was observed in 47% of patients (Fig. 1).

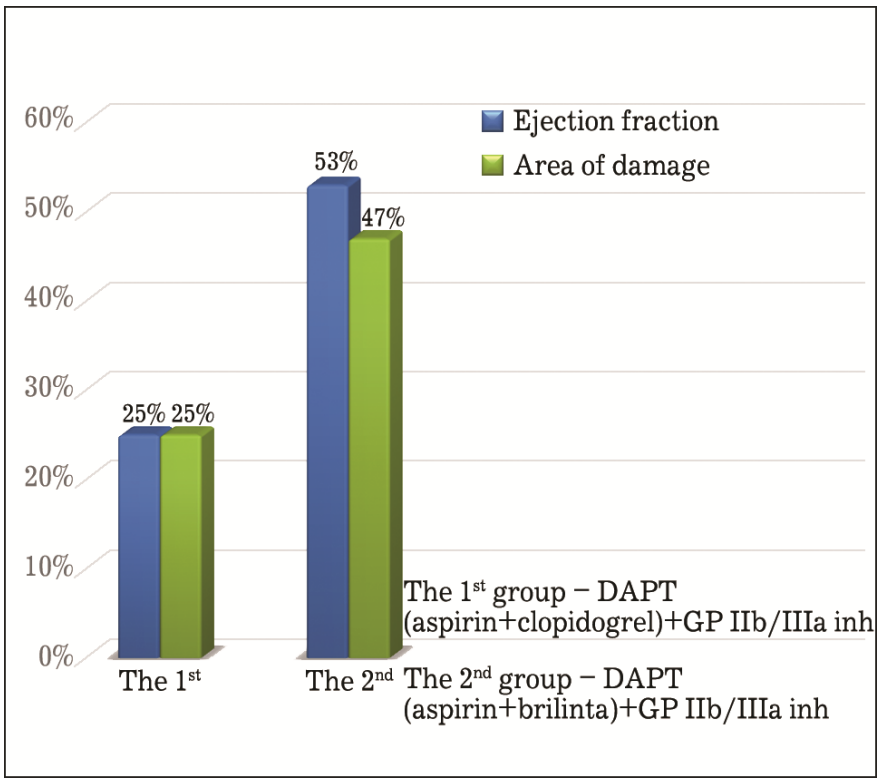

Fig. 1. Results obtained from echocardiography data

Upon admission, the level of D-dimer in patients differed from normal values, both in group 1: 0.60 (0.35;1.16) μg/mL, and in group 2: 0.40 (0.32;1.56) μg/mL ($p<0.05$) while the norm was 0.17 (0.17;0.23) μg/mL (Table 2). APTT in these groups was statistically significantly decreased relative to the normal one, to 22.5 (21.8;23.4) sec. and 24.6 (23.1;25.3) sec, respectively, while the norm was 27.1 (26.5;28.2) sec. ($p<0.05$), which indicated the activation of the procoagulant system and the fibrinolysis system in patients upon admission.

Table 2. Laboratory parameters of the hemostatic system in patients with acute coronary syndrome before and after dual antiplatelet therapy

Parameter	Norm	Day			
		Before tirofiban therapy	1st	3rd	7th
Clopidogrel + tirofiban					
APTT, sec	27.1 (26.5;28.2)	22.5 (21.8;23.4)*	28.8 (26.9;31.2)*,•	30.0 (29.3;32.0)*,•	31.3 (29.9;33.3)*,•
D-dimer, µg/mL	0.17 (0.17;0.23)	0.60 (0.35;1, 16)*	—	0.49 (0.41;0.70)*	—
FG, g/L	2.36 (2.09;2.88)	—	3.15 (2.60;4.23)*	4.53 (3.79;5.13)*	4.60 (4.35;4.95)*
Platelet aggregation, %, 10 µmol of ADP	79 (73;84)	—	**38 (21;43)***	—	**26 (17;43)***
Ticagrelor + tirofiban					
APTT, sec	27.1 (26.5;28.2)	24.6 (23.1;25.3)*	28.0 (26.4;28.4)	30.0 (29.0;32.0)*	29.0 (26.3;32.8)
D-dimer, µg/mL	0.17 (0.17;0.23)	0.40 (0.32;1.56)*	—	0.70 (0.48;0.90)*	—
FG, g/L	2.36 (2.09;2.88)	—	3.30 (2.70;4.10)*	4.29 (3.86;4.30)*	5.00 (4.34;5.70)*
Platelet aggregation, %, 10 µmol of ADP	79 (73;84)	—	**14 (11;15)*,▲**	—	**10(7;11)*,▲**

Notes: * p<0.05 relative to the norm; • p<0.008 relative to the "before tirofiban/before PCI" time-point (intragroup comparison at four points); ▲ p<0.05 relative to Group 1, "Clopidogrel + tirofiban" (intergroup comparison).

When adding DAPT to patients both in group 1 and in group 2, the aggregation ability of platelets statistically significantly decreased in response to the impact of 10 µmol of ADF, showing 38 (21;43)% and 14 (11;15) %, respectively, relative to the norm of 79 (73;84)% (p<0.05), which reflected the effect of antiplatelet therapy. The high efficacy of DAPT is confirmed by the study results [14], which showed that tirofiban in combination with ticagrelor can prevent thrombosis and improve coronary blood flow in patients after PCI, as well as by the study [15], which revealed the ability of clopidogrel in combination with tirofiban

quickly inhibit the platelet aggregation, improve myocardial reperfusion, and reduce the incidence of complications.

We should also note that an intragroup comparison demonstrated a more pronounced decrease in platelet aggregation ability in group 2 ($p<0.05$). By the 7th day of therapy for MI, the platelet aggregation continued to decrease to 26 (17;43)% in group 1, to 10 (7;11)% in group 2. The most pronounced effect of antiplatelet therapy was observed in group 2 ($p<0.05$). These results suggest that ticagrelor makes the greatest contribution to the reduction in platelet aggregation ability. These data are in good agreement with the study [16], in which ticagrelor provided a more potent platelet inhibition than clopidogrel, suggesting that ticagrelor may have a greater antiplatelet efficacy.

A number of authors have indicated that patients with ACS who received DAPT with a PG IIb/IIIa inhibitor had a higher number of hemorrhagic complications than patients who did not receive a PG IIb/IIIa inhibitor [17]. In our study, no major bleeding was reported in the two groups. However, a hematoma was observed at the puncture site of the right radial artery in 20% of patients (n=3) in the 2nd group, and in 5% of patients (n=1) in the 1st group

In the study [18], which compared DAPT with clopidogrel or ticagrelor in patients with ACS, there were no significant differences in the overall incidence of “major” bleeding.

The results of studies [17–19] showed that the risk of any bleeding and major bleeding was increased in patients receiving a combination therapy, which indicates the need to monitor hemostasis during antiplatelet therapy.

Conclusion

When studying the dynamics of the hemostatic system parameters in patients with myocardial infarction during antiplatelet therapy, we

found that the assessment of platelet aggregation ability with 10 μmol of adenosine phosphate as an inducer, was possible to use for identifying the effect of drugs. A more significant laboratory effect was revealed when the PG IIb/IIIa receptor inhibitor, tirofiban, was added to a dual antiplatelet therapy regimen that included ticagrelor. However, further studies are needed in a larger patient series to determine the target platelet aggregation values with 10 μmol of adenosine phosphate to assess the therapy efficacy.

Based on the study results we may conclude the following:

1. In patients with myocardial infarction, when using dual antiplatelet therapy, both in combination of clopidogrel + tirofiban and ticagrelor + tirofiban, there was a statistically significant decrease in platelet aggregation ability relative to the norm ($p<0.05$) on the 1st and 7th days from the moment of hospital admission, with using adenosine phosphate (concentration 10 μmol) as an inducer.

2. The platelet aggregation ability using 10 μmol of adenosine phosphate as an inducer decreased more significantly with the combination of ticagrelor + tirofiban than with the combination of clopidogrel + tirofiban on days 1 and 7, to 14 (11;15)% and 38 (21;43)% and to 10 (7;11)% and 26 (17;43)%, respectively.

3. In patients with myocardial infarction when using dual antiplatelet therapy, either in combination of clopidogrel + tirofiban or in combination of ticagrelor + tirofiban, no statistically significant differences in activated partial thromboplastin time, fibrinogen, or D-dimer were seen.

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10%, laboratory investigations according to the study design, data interpretation

The article was received on February 14, 2024;
approved after reviewing on May 15, 2024;
accepted for publication on June 26, 2024