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ROLE OF PREHOSPITAL ADMINISTRATION OF CLOPIDOGREL TREATMENT IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION WITH ST SEGMENT ELEVATION WITH PRIMARY CORONARY ANGIOPLASTY *

ULOGA PREHOSPITALNOG DAVANJA KLOPIDOGRELA U LEČENJU BOLESNIKA SA AKUTNIM INFARKTOM MIOKARDA PRIMARNOM KORONARNOM ANGIOPLASTIKOM *

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Key words
AIM, STEMI, pPCI, dual antiplatelet therapy, ADP receptor, VASP method.

Ključne reči
AIM, STEMI, pPCI, dvojna antiagregaciona terapija, ADP receptor, VASP metoda.

Abstract

Introduction/Aim. Acute myocardial infarction is a common emergency disease with potentially poor prognosis. Acute myocardial infarction with ST-segment elevation is defined as myocardial cell death due to complete interruption of coronary circulation. The cause of a sudden interruption of coronary circulation is usually fissure, rupture or ulceration of atherosclerotic plaques. The consequence of rupture or fissure is a disturbance of blood flow through the coronary artery with the development of heart failure. The platelet activation and aggregation via the ADP receptor plays a major role in the pathogenesis of arterial thrombosis. Dual antiplatelet therapy (aspirin and clopidogrel) is a mandatory therapy after the primary percutaneous coronary intervention in patients with acute myocardial infarction with ST-segment elevation. Nowadays, it is accepted that the primary percutaneous coronary intervention is the best choice of the reperfusion therapy in clinical and / or ECG findings of progressive myocardial necrosis within 12 hours of the onset of symptoms. The aim of the research was to compare the degree of inhibition of the platelet aggregation measured by VASP method after clopidogrel loading dose of 600 mg given immediately after the diagnosis of STEMI and prior to transport to the Emergency Room / cardiac catheterization room (Group I) in relation to the administration of drugs after an admission to the Emergency Room / cardiac catheterization room immediately before the primary percutaneous coronary intervention (group II). **Methods**. This is a prospective study of the Clinic of Cardiology, Clinical Center of Serbia. The study included patients with acute myocardial infarction with ST-segment elevation treated with intracoronary stenting. The evaluation of the effect of clopidogrel on platelet analyzed before primary percutaneous coronary intervention (prime or basal pattern) and 2 h after primary percutaneous coronary intervention using flow cytometry determination of ADP (P2Y12) receptor platelet reactivity (the first pattern - the aim of the study). The patients whose ADP receptor reactivity was > 50% measured 2 h after the primary percutaneous coronary intervention were identified as non-responders (unsatisfactory antiplatelet effect of clopidogrel). **Results**. The study included 73 patients with acute myocardial infarction with ST-segment elevation (STEMI) out of which 32 patients belonged to the group I (those who were given

a dose of clopidogrel 600 mg immediately after the diagnosis of acute myocardial infarction with ST-segment elevation and prior to the transport to the Emergency Room / cardiac catheterization room) and 41 patients belonged to the group II (those who received clopidogrel after an admission to the Emergency Room / cardiac catheterization room immediately before primary percutaneous coronary intervention). In the study population of 73 patients in the zero-basal sample immediately prior to the percutaneous coronary intervention, there were 40 patients with ADPrr <50% (satisfactory antiplatelet effect of clopidogrel). In the group I (32 patients) the average time interval between the administration of clopidogrel to taking a zero sample in the cardiac catheterization room immediately before the intervention was 81 ± 59 min. (20 min. - 185 min). In the group II (41 patients) was 46 ± 39 min. (5 min. - 220 min), p = 0.0051. There was a statistically significant difference between the average time interval to taking a zero sample between these two groups because the patients in the group I received the drug on average half an hour earlier (p = 0.0051). Within the group I, 18 patients (52.9%) had satisfactory antiplatelet effect of clopidogrel, and in the group II 22 (56.4%) patients. There were no statistically significant differences in the number of patients with ADPrr <50% (satisfactory antiplatelet effect of clopidogrel) between the two groups (52.9% vs 56.4%, p = 0.8253). Measurement of the inhibition of platelet aggregation in a sample 2 hours after the intervention showed that 48 (65.8%) patients achieved a good response to clopidogrel, i.e. 24 (70.6%) patients in the Group I and 24 (61.5%) patients in the group II (p = 0.1413). Based on these results, there was no difference in the frequency of responders between the two groups of patients even in a sample taken 2 hours after the intervention, but there was a trend of a better response in the group I (70.6% vs 61.5%, p = 0.1413) . **Conclusion**. The timing of the loading dose of clopidogrel in patients with acute myocardial infarction with ST-segment elevation does not affect significantly the inhibition ADPrr measured 2 hours after the primary percutaneous coronary intervention.

INTRODUCTION.

Acute myocardial infarction is a common emergency disease with potentially poor prognosis. Acute myocardial infarction with ST-segment elevation (STEMI) is defined as myocardial cell death due to complete interruption of coronary circulation.

The cause of a sudden interruption of coronary circulation is usually fissure, rupture or ulceration of atherosclerotic plaques. The consequence of the rupture or fissure is a disturbance of blood flow through the coronary artery with the development of a heart attack.

The endothelium has a central place in the regulation of the blood vessel response to different substances and irritating, and its rupture caused the loss of its protective role. One of the most important roles of the endothelium is the prevention of platelet aggregation and thrombus formation. The platelet activation and aggregation via the ADP receptor plays a major role in the pathogenesis of arterial thrombosis.(1) An ADP receptor is a receptor on the surface of platelets through which act antiplatelet drugs from the group of thienopyridine by directly binding to it and irreversibly inhibiting it, which finally leads to antiaggregatory effect.

Thienopyridines irreversibly inhibit the P2Y12 receptor and thus inhibit ADP-induced inhibition of the phosphorylation of VASP.

Dual antiplatelet therapy consisting of aspirin and clopidogrel is required after the primary PCI in the patients with acute myocardial infarction with ST-segment elevation, with the aim of reducing the frequency of repeated ischemic events especially stent thrombosis.(2,3) The beneficial effects of clopidogrel administration on the incidence of repeated ischemic events in the patients with acute coronary syndrome have been confirmed in many clinical studies.(4)

The aim of treatment of acute myocardial infarction is an early introduction of reperfusion: pharmacological thrombolytic drugs or mechanical primary percutaneous coronary intervention (pPCI).

Nowadays it is accepted that the pPCI is the best choice of reperfusion therapy in clinical and / or ECG findings of progressive myocardial necrosis within 12 hours after the onset of symptoms.(5)

The primary PCI is angioplasty, which is done without a prior or concomitant thrombolytic therapy, is the best treatment option today.(6)

The primary PCI is effective in saving infarction and maintenance of coronary blood flow, while significantly reducing the complications of bleeding which gives thrombolytic therapy because it gives a better infarct artery reperfusion (TIMI 3), shortens hospital stay, prevent new cases of re-infarction, reduces the incidence of accompanying cardiac insufficiency, reduces the number of patients with post-infarction angina, reduces the number of patients with stroke in acute myocardial reduces the number of re-hospitalizations and improves short-term survival.(7)

The aim of the research was to compare the degree of inhibition of platelet aggregation measured by VASP method after clopidogrel loading dose of 600 mg given immediately after the diagnosis of STEMI and prior to the transport to the Emergency Room (ER) / cardiac catheterization room (Group I) in relation to the administration of drugs after an admission to the ER / cardiac catheterization room immediately before the primary PCI (group II).

METHODS

This is a prospective study of the Clinic of Cardiology, Clinical Center of Serbia. The study included the patients with acute myocardial infarction with ST-segment elevation treated with intracoronary stenting.

The study protocol was in accordance with the Declaration of Helsinki.

All patients had given a written informed consent prior to the inclusion.

The inclusion criteria: all patients with acute myocardial infarction with ST-segment elevation pPCI treated at the Clinic of Cardiology Clinical Center of Serbia.

The exclusion criteria: the patients who had not given their consent for the inclusion in the study.

The Group I patients who received 300 mg of aspirin and 600 mg of clopidogrel before the transport to the ER / cardiac catheterization room immediately after the diagnosis of STEMI by the emergency medical service or the relevant Clinical Center .

The Group II patients who received this therapy after the admission to the ER / cardiac catheterization room.

An evaluation of the effect of clopidogrel on the platelet analyzed before the PCI (prime or basal pattern) and 2 h after the PCI using flow cytometry determination of ADP (P2Y12) receptor platelet reactivity (the first pattern - the goal of the study).

The patients whose ADP receptor reactivity > 50% was measured 2 h after the PCI were identified as non-responders (unsatisfactory antiplatelet effect of clopidogrel).

The descriptive statistics methods used in the research study are as follows: measures of central tendency (mean and median), measures of variability (standard deviation and variation interval) and relative numbers. Moreover, the analytical statistics methods were also used - Student's test, chi square test, Fisher test and rank sum test. The data were analyzed in the statistical program GraphPad Instat and Prism v3.10 5.0.

RESULTS

The study included 73 consecutive patients with acute myocardial infarction with ST-segment elevation (STEMI) treated with the primary PCI during 2008 in the cardiac catheterization room of the Clinical Center of Serbia.

The clinical features of these patients are shown in the Table 1.

Out of the 73 patients, 32 patients belonged to the group I (given a dose of clopidogrel 600 mg immediately after the diagnosis of STEMI and prior to the transport to the ER / cardiac catheterization room), and 41 patients belonged to the group II (those who had received clopidogrel after an admission to the ER/ cardiac catheterization room immediately before the primary PCI).

In a population dominated men, with the expected frequency of risk factors for coronary heart disease. A half of the patients in both groups was clinically presented previous angina pectoris. A tenth of the patients catch the disease before the intervention myocardial infarction, none of the patients in the study population had previous surgical revascularization. No statistically significant differences between the two groups on the basis of clinical features.

Tabela 1. *Clinical features of the tested population*

	Group I	**Group II**	**P**
Number of patients	32	41	
Age, years (range)	(60,41±10,56) 39-79	(59,51±10,91) 43-81	0.8597
Men	24 (75%)	28 (68,29%)	0.6079
Women	8 (25%)	13 (31,71%)	0.6079
Hypertension	19 (59,37%)	24 (58,54%)	0.9424
Diabetes mellitus	4 (12,5%)	10 (24,39%)	0,2424
Former or current smoker	19 (59,37%)	23 (56,1%)	0,7786
Hypercholesterolemia	11 (34,37%)	13 (31,71%)	0,8098
Family history of coronary heart disease	20 (62,5%)	26 (63,41%)	0,9360
Multivessel coronary disease	9 (28,12%)	8 (19,51%)	0,4161
Angina pectoris	14 (43,75%)	20 (48,78%)	0,6690
No ischemia	18 (56,25%)	21 (51,22%)	0,6690
Previous myocardial infarction	3 (9,37%)	3 (7,32%)	0,9360
Previous by-pass	0 (0%)	0 (0%)	NA
Previous PTCA	3 (9,37%)	8 (19,51%)	0,3275

These are mean values ± SD or the number and percentage of patients

Basic angiographic characteristics of treated coronary arteries constrictions are presented in the Table 2. Constrictions were usually localized in the studied population both groups' anterior descending branch of the left and in the right coronary artery with a relatively even distribution of localization in all segments of the coronary tree, except for the distal where the narrowing frequency is small but numerically more pronounced in group I.

Tabela 2. *Angiographic features of the treated coronary constricions*

Group	**I**	**II**	**P**
LAD	20 (44,44%)	22 (44,9%)	0,4483
Cx	5 (11,12%)	7 (14,29%)	0,8684
RCA	20 (44,44%)	20 (40,81%)	0,2425
Proximal	17 (37,78%)	23 (46,94%)	0,8001
Middle	22 (48,89%)	23 (46,94%)	0,2700
Distal	6 (13,33%)	3 (6,12%)	0,1404

Values are the number and percentage of lesions.

Percutaneous coronary intervention was performed with the use of the standard method and in accordance with the international recommendations, by the placement of a stent access via the femoral artery.

Procedural characteristics are shown in the Table 3. The population was dominated by the embedded BMS stents while there were drug-eluting stents in quite a small number with a significant trend towards more frequent application of these stents in the group 2. Concerning the glycoprotein IIb / IIIa inhibitor, tirofiban (agrastat) was exclusively used and it was administered in approximately one quarter of the patients in both groups.

Tabela 3. *Procedural parameters*

	Group I	Group II	P
Total number of implanted stents	41	47	
Diameter stent (mm) (range)	(3,34±0,43) 2,50-4,50	(3,16±0,44) 2,00-4,00	0,0560
Stent Length (mm) (range)	(22,66±5,42) 12,00-30,00	(21,21±5,17) 12,00-30,00	0,2044
BMS stent	40(97,56%)	41(87,23%)	0,0793
Drug-eluting stent	1(2,44%)	6(12,77%)	0,0793
Tirofiban (Aggrastat)	11(26,83%)	11(23,40%)	0,4857
Balloon predilatation	35(85,37%)	34(72,34%)	0,1385

These are mean values ± SD ora number of lesions

In the group I (32 patients) the average time interval between the administration of clopidogrel to taking a zero sample in the cardiac catheterization room immediately before the intervention was 81 ± 59 min. (20 min. - 185 min). In the group II (41 patients) was 46 ± 39 min. (5 min. - 220 min), p = 0.0051.

There was a statistically significant difference between the average time interval to taking a zero sample between these two groups because the patients in the group I received the drug on average half an hour earlier (p = 0.0051).

In the study population of 73 patients in the zero-basal sample immediately prior to percutaneous coronary intervention, there were 40 patients with ADPrr <50% (satisfactory antiplatelet effect of clopidogrel). In the group I, 18 patients (52.9%) had satisfactory antiplatelet effect of clopidogrel, and in the group II 22 (56.4%) patients. There were no statistically significant differences in the number of patients with ADPrr <50% (satisfactory antiplatelet effect of clopidogrel) between the two groups (52.9% vs 56.4%, p = 0.8253).

Measurement of the inhibition of platelet aggregation in sample 2 hours after the intervention showed that 48 (65.8%) patients achieved a good response to clopidogrel, i.e. 24 (70.6%) patients in the group I and 24 (61.5%) patients in the group II (p = 0.1413).

Based on these results, there was no difference in the frequency of responders between the two groups of patients even in a sample taken 2 hours after the intervention, but there was a trend of a better response in the group I (70.6% vs 61.5%, p = 0.1413) .

The group I included 8 non-responders (poor inhibition ADPrr 2 hours after the intervention) and the group II had 17 non-responders. From the eight non-responders in the group I seven patients were with clopidogrel 75 mg. Although non-responders, treatment was not increased to 150 mg of clopidogrel. One patient was changed the therapy from 75 mg of clopidogrel to ticlopidine, 250 mg of the 2x1. In the group II, 16 patients were on clopidogrel 75mg and one patient after the intervention took clopidogrel 75mg, but because of his resistance to that drug it was changed to ticlopidine 250 mg 2x1 and then to prasugrel. All patients were after the intervention under the supervision of their competent cardiologist.

The main adverse cardiac and cerebrovascular events (MACCE) are defined as: death (cardiac and non-cardiac), re-infarction, stroke, repeat revascularization of the target (target) lesion (TLR) either by percutaneous coronary intervention or bypass surgery, a proven stent thrombosis and major bleeding by TIMI classification. MACCE were assessed during the hospitalization, the follow-up period and cumulatively.

A total of 73 patients were treated and the average duration of clinical follow-up was 206 ± 166 days. All patients were followed for 30 days.

The main adverse cardiac and cerebrovascular events (MACCE) in the course of the patients' follow-up (30 days) are shown in the Table 4 and were similar in both groups (9.37% vs 14.64%).

In the follow-up period of 30 days there were 3 (9.37%) adverse events (MACCE) registered in the group I and 6 (14.64%) in the group II. One (2.44%) of the treated patients died during the follow-up. It was the female patient from the group II, which was by the VASP method a non-responder. Five days upon leaving the hospital, she got a myocardial re-infarction and died. We have been unable to get the medical records, so we do not know whether there was any of stent thrombosis or not. One (3 .13%) patient in the Group I and 3 (7.32%) patients in the group II had reinfarction. It is the patient from the group I with myocardial reinfarction. Three days after the intervention he got stent thrombosis. He is the responder by the VASP and he received dual antiplatelet therapy - clopidogrel 75 mg and aspirin 100 mg. Stent thrombosis was treated with the repeated PCI (TLR).

In the group II myocardial re-infarction was present in 3 patients. One of the patients with myocardial reinfarction got a stent thrombosis 4 days after the PCI. Stent thrombosis was treated with the repeated PCI (TLR). By the VASP method he was a responder. The recommended therapy was clopidogrel 75 mg and aspirin 300 mg in the first three months, and then turned to ticlopidine 250 mg 2x1. Another patient in the group II had a myocardial reinfarction 13 days after the primary PCI. She underwent a coronary stent implantation proximal to the primary lesion (TVR). By the VASP method she is a responder. The recommended treatment by then had included clopidogrel 75 mg and aspirin 100 mg. Afterwards she received ticlopidine 250 mg 2x1.

The third already mentioned patient died. The most common adverse event in the 30 days' follow-up period was the repeated revascularization of the target lesinon. One patient from the group I (TLR-3.13%) and one patient from the group II (TLR- 2.44%) demanded the re-PTCA target lesion. Another two patients in the group II, in addition to the aforementioned one (TLR), had a re-intervention in the second lesion in the target blood vessel (TVR 7.32%). Therefore, the overall incidence of the re-intervention in the target court in both groups is (3.13% vs. 7.32% P = 0.6263). One of the two patients, who had re-intervention in the second lesion in the target blood vessel (TVR), had a successful angioplasty with the stent implantation BM 28 days after the primary PCI. The female patient with reinfarction, who has already been mentioned, was implanted the stent across the lesion of the target vessel 13 days after the primary PCI. One patient from the Group I had revascularization in the other blood

vessel during the 30 days' follow-up period. Eight days after the intervention, he got myocardial infarction on the second PCI blood vessel and the BM 1 stent was implanted.

The patient was by the VASP method a responder. The recommended therapy after the primary PCI included clopidogrel 75 mg and aspirin 100 mg and was afterwards turned to ticlodix 250 mg 2x1. During the monitoring period, the patient was asymptomatic. In the group I, two patients had a little bleeding. One of the patients was a responder even by the VASP method. The second one was a non responder by the VASP method. In the group II, six patients had a little bleeding. Among them, two patients achieved a satisfactory inhibition ADPrr by the VASP method. Four patients were non-responders by the VASP method. In our study, there was no occurrence of cerebral infarction during the follow-up.

Cumulative analysis of adverse events (MACCE) during the hospitalization and the 30 days' follow-up period showed that there were some of the adverse events in 9 patients (12.32%) - 3 (9.37%) patients in the group I and 6 (14 64%) patients in the group II. One female patient (2.44%) died, in the group I one patient had a reinfarction (3.13%) and 3 (7.32%) patients in the group II. Re-target lesion revascularization (TLR) had one (3.13%) patient in the group I and one (2.44%) patient in the group II. Stent thrombosis had one (3.13%) patient in the group I and one (2.44%) in the group II.

***Tabela 4**. Adverse events in the 30 days follow-up period*

	Group I	Group II	P
Number of patients	32	41	
Death	0 (0)	1(2,44)	1,0000
Reinfarction	1(3,13)	3(7,32)	0.6263
Myocardial infarction in another artery	1(3,13)	0 (0)	0,4384
Stroke	0 (0)	0 (0)	NA
Re-target lesion revascularization (TLR)	1(3,13)	1(2,44)	1,0000
PTCA	1(3,13)	1(2,44)	1,0000
CABG	0 (0)	0 (0)	NA
Repeat revascularization of the target vessel (TVR)	1(3,13)	3(7,32)	0.6263
Repeat revascularization of the second vessel	1 (3,13)	0 (0)	0,4384
PTCA	1(3,13)	0 (0)	0,4384
CABG	0 (0)	0 (0)	NA
Stent thrombosis	1(3,13)	1(2,44)	1,0000
Minor bleeding	2(6,25)	6(14,63)	0.4526
Major bleeding	0 (0)	0 (0)	NA
Cumulative events during the 30 days' follow-up (MACCE)	3(9,37)	6(14,64)	0.7224

* MACCE = major adverse cardiac and cerebrovascular events defined as death (cardiac and non-cardiac), re-infarction, stroke, repeat revascularization of the target (target) lesion (TLR) either by percutaneous coronary intervention or bypass surgery, demonstrated thrombosis stent and major bleeding by TIMI classification.

Values are the number and percentage of patients. CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.

According to the results, during the 30 days' follow-up, there was no statistically significant difference (9.37% vs 14.64% P = 0.7224) in the group I and the group II as far as the major adverse cardiac and cerebrovascular events (MACCE) are concerned.

DISCUSSION

A damage to the endothelium increased a platelet reactivity during the stent implantation as a foreign body leads to the platelet activation and initiation of coagulation cascade. That is the reason why today is insisted upon a dual antiplatelet therapy before, during and one year after the PCI (aspirin and thienopyridine), and in the case of the PCI in acute coronary syndromes and application GPIIbIIIa antagonists (abciximab).[12]

In one randomized trial [16] was compared the pre-hospital 600 mg or 900 mg vs. peri-interventional 300 mg undergoing the primary coronary angioplasty clopidogrel in the patients with ST- elevation myocardial infarction. They studied 168 patients with STEMI referred from the territorial emergency medical services for the primary coronary angioplasty. The patients were randomized to the following arms at first medical contact: clopidogrel 900 mg; 600 mg or no pre-treatment. The latter group of the patients received a standard loading dose of 300 mg of clopidogrel just prior to the primary PCI.

The primary endpoint of the study was the comparison of the rate of Thrombolysis in Myocardial Infarction Perfusion Grade 3 (TMPG 3, open microvasculature) between the patients randomized to pre-hospital loading dose (600 or 900 mg clopidogrel) and those randomized to no pre-treatment (300 mg).(17) The key secondary endpoint was the platelet inhibition assessed as Verify-Now Platelet Reaction Units immediately prior to PCI [18].

In the present study, althought heaverage clopidogrel load to balloon time was twofold that of the ARMYDA-6 MI, they could not find any difference in terms of myocardial perfusion and platelet reactivity. Vavuranakis et al. (19) found a significant inverse correlation between platelet reactivity and myocardial blush in the patients with STEMI and very long first-medical-contact-to-balloon times (4.5±3.0h).

In the other trial [19] was compared a loading dose of 600 mg clopidogrel given in the prehospital phase versus clopidogrel administered after the diagnostic angiogram in the patients with STEMI scheduled for the primary PCI. The primary efficacy endpoint was the TIMI 2/3 patency of the infarct-related artery in the diagnostic angiography immediately prior to PCI. They randomized 337 patients to pre-hospital (n=166) loading dose versus standard therapy (n=171). The time interval between initiation of clopidogrel therapy and diagnostic angiography was 47 min. TIMI 2/3 patency before PCI was not different between the groups (49.3 vs. 45.1%, P=0.5). Early inhibition of the platelet ADP-receptor with a high loading dose of 600 mg clopidogrel given in the pre-hospital phase in the patients with STEMI scheduled for primary PCI is safe, did not increase pre-PCI patency of the

infarct vessel, but was associated with a trend towards a reduction in clinical events.

The clopidogrel tablets of 75 mg per day cause a certain degree of platelet aggregation for 2 hours after an oral administration, but the maximum inhibition is achieved after 3-7 days.[8] A larger loading dose of clopidogrel 600 mg results in earlier and more strongly aggregation-inhibiting platelets.[1]

The question is whether, in patients with acute coronary syndrome, especially myocardial infarction with ST-segment elevation who were indicated an urgent coronary angiography and possible percutaneous coronary intervention should be given clopidogrel as early as possible, i.e. immediately after the diagnosis or acceptable and safe to be given the drug after the transport to the cardiac catheterization room before the start of the intervention.[12] Therefore, we have designed a study that would compare the degree of platelet inhibition before and after percutaneous intervention in these two patient populations.

The results of our study showed that the timing of the loading dose of clopidogrel in the patients with STEMI does not affect significantly the inhibition ADPrr measured 2 hours after the primary PCI, although there was a trend of a better response in the patients who had received the drug before they were transported to the cardiac catheterization room.

In order to support this strategy with the adequate scientific evidence there were presented various laboratory tests to measure the platelet aggregation and thus prove the existence of optimal antithrombotic status.[10]

Tests of the platelet function in vitro are widely used in research and the study of the mechanism of action of platelets ensures the implementation of antiplatelet therapy. Comparing the results of these tests with clinical outcomes, their results are used as a guide to the therapy, but there are still challenging goals. The ideal test for the assessment of platelet function had to be fast, easy to use, inexpensive and a reliable indicator of clinical response to the specific antiplatelet therapy.

The key question is whether the tests for the assessment of platelet function could indicate risk patients according to the degree of inhibition of platelet aggregation as a response to antiplatelet agense.[13]

In a prospective study in the patients with STEMI treated with the primary angioplasty, we used flow cytometry (VASP analysis) and studies showed no clinically significant difference in the degree of inhibition of platelet loading dose of clopidogrel between the two study groups of patients (the group I took clopidogrel immediately after the dg by the emergency medical service or the relevant Clinical Center; and the group II patients received this therapy after the admission to the ER / cardiac catheterization room).

Results of ARMYDA-5 studies are somewhat controversial because there is no relationship between the clinical outcomes and a high platelet reactivity during the PCI and during the „critical" 2 hours after the PCI.[14,15] One reason may be a sample size too small to detect differences in the clinical outcomes (which leads to a relatively small number of adverse events), so there could not have been seen the difference between the clinical results and a high platelet reactivity.

There is then a question what is the real clinical significance of determination of the platelet reactivity in the patients referred for the PCI. In our study, the P2Y12 reactivity is in relation to the time of taking clopidogrel different in two groups. Although the platelet reactivity is higher in the the group who took clopidogrel in the cardiac catheterization room, there is a concern about the early stent thrombosis, so larger studies are needed that would deal with.

However, the relatively small number of patients involved can be a limitation of the study to make a definitive judgment about the importance of an early drug administration.

Another possible explanation is that the laboratory tests (VASP) having been used so far are not fully adequate in terms of their ability to identify high-risk patients for the occurrence of major adverse cardiac and cerebrovascular events in the patients with acute coronary syndrome.

On the basis of this and all previous available studies it can be concluded that it does not support the use of tests for the assessment of platelet function in routine clinical practice in the patient population addressed in the elective or the primary PCI.

CONCLUSION

The timing of the loading dose of clopidogrel in patients with acute myocardial infarction with ST-segment elevation does not affect significantly the inhibition ADPrr measured 2 hours after the primary percutaneous coronary intervention. Since there is a trend of a better response in the patients who received the drug earlier, before the transport to the cardiac catheterization room, a greater study particularly in the patients with a longer transport to the cardiac catheterization room to confirm the superiority of this strategy is necessary.

The test to assess the platelet function was carried out in order to discover whether a high platelet reactivity could be used as a prognostic marker in clinical practice.

However, based on the results of this study, the routine use of tests for the assessment of the platelet function in daily clinical practice in a population of patients with acute myocardial infarction with ST-segment elevation treated with the primary percutaneous coronary intervention is not supported.

Sažetak

Uvod/Cilj. Akutni infarkt miokarda je česta urgentna bolest sa potencijalno lošom prognozom. Akutni infarkt miokarda sa elevacijom ST segmenta definiše se kao smrt ćelija miokarda usled potpunog prekida koronarne cirkulacije. Uzrok naglog prekida koronarne cirkulacije najčešće je fisura, ruptura ili ulceracija aterosklerotične pločice. Posledica rupture ili fisure je prekid cirkulacije kroz koronarnu arteriju sa razvojem infarkta. Aktivacija i agregacija trombocita preko ADP receptora igra glavnu uloga u patogenezi arterijalne tromboze. Dvostruka antiagregaciona terapija (aspirin i klopidogrel) je obavezna terapija nakon primarne perkutane koronarne intervencije kod bolesnika sa akutnim infarktom miokarda i elevacijom ST segmenta. Danas je prihvaćeno mišljenje da je primarna perkutana koronarna intervencija najbolji izbor reperfuzione terapije pri klinički i/ili EKG nalazu napredujuće nekroze miokarda unutar 12 sati od početka simptoma. Cilj istraživanja je poređenje stepena inhibicije agregacije trombocita mereno VASP metodom nakon udarne doze klopidogrela od 600 mg datog neposredno po postavljanju dijagnoze akutnog infarkta miokarda sa elevacijom ST segmenta, a pre transporta u Urgentni centar/salu za kateterizacije srca (grupa I) u odnosu na davanje leka nakon prijema u Urgentni centar/salu za kateterizacije neposredno pre primarne perkutane koronarne intervencije (grupa II). **Metode.** Ovo je prospektivna studija Instituta za kardiovaskularne bolesti Kliničkog centra Srbije. Studija je obuhvatila bolesnike sa akutnim infarktom miokarda sa elevacijom ST segmenta lečene intrakoronarnim stentom. Procena antiagregacijskog efekta klopidogrela analizirala se pre primarne perkutane koronarne intervencije (nulti ili bazalni uzorak) i 2h nakon primarne perkutane koronarne intervencije metodom protočne citometrije određivanjem ADP (P2Y12) receptorske reaktivnosti trombocita (prvi uzorak- cilj studije). Bolesnici čija je ADP receptorska reaktivnost >50% merena 2h posle primarne perkutane koronarne intervencije su označeni kao non responderi (nezadovoljavajući antiagregacijski efekat klopidogrela). **Rezultati.** Studija je obuhvatila 73 bolesnika sa akutnim infarktom miokarda i elevacijom ST segmenta od čega su 32 bolesnika pripadala grupi I (dat klopidogrel u dozi od 600 mg neposredno po postavljanju dijagnoze akutnog infarkta miokarda sa elevacijom ST segmenta, a pre transporta u Urgentni centar/salu za kateterizacije srca) i 41 bolesnik je pripadao grupi II (oni koji su dobili klopidogrel nakon prijema u Urgentni centar/salu za kateterizacije neposredno pre primarne perkutane koronarne intervencije). U ispitivanoj populaciji od 73 bolesnika u nultom-bazalnom uzorku neposredno pre perkutane koronarne intervencije bilo je 40 bolesnika sa ADPrr < 50 % (zadovoljavajući antiagregacijski efekat klopidogrela). U grupi I (32 bolesnika) prosečan vremenski interval od davanja klopidogrela do uzimanja nultog uzorka u sali za kateterizacije srca neposredno pre intervencije iznosio je 81±59 min. (20 min. – 185 min). U grupi II (41 bolesnik) iznosio je 46±39 min. (5 min. – 220 min), p= 0.0051. Postoji statistički značajna razlika između prosečnog vremenskog intervala do uzimanja nultog uzorka između ove dve grupe, jer su bolesnici u grupi I dobili lek u proseku pola sata ranije (p= 0.0051). U grupi I 18 bolesnika (52,9%) je imalo zadovoljavajući antiagregacijski efekat klopidogrela, a u grupi II 22 (56,4%) bolesnika. Nije bilo statistički značajne razlike u broju bolesnika sa ADPrr < 50 % (zadovoljavajući antiagregacijski efekat klopidogrela) između dve grupe bolesnika (52,9% vs 56,4% p=0,8253). Merenje inhibicije agregacije trombocita u uzorku 2 sata nakon intervencije pokazalo je da 48 (65,8%) bolesnika postiglo dobar odgovor na klopidogrel i to 24 (70,6%) bolesnika u grupi I i 24 (61,5%) bolesnika u grupi II (p=0,1413). Na osnovu ovih rezultata nije bilo razlike u učestalosti respondera između 2 grupe bolesnika ni u uzorku uzetom nakon 2 sata od intervencije, ali je postojao trend ka boljem odgovoru u grupi I (70,6% vs 61,5% p=0,1413). **Zaključak**. Vreme davanja udarne doze klopidogrela u bolesnika sa akutnim infarktom mikarda sa elevacijom ST segmenta ne utiče statistički značajno na inhibiciju ADPrr merenu 2 sata nakon primarne perkutane koronarne intervencije.

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