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ORIGINAL RESEARCH

Effectiveness of Different P_2Y_{12} Inhibitors on Coronary Flow in Patients with ST-Elevation Myocardial Infarction

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ABSTRACT

Background: ST-segment elevation myocardial infarction (STEMI) is a clinical syndrome with high mortality. The main purpose of STEMI treatment is to achieve optimal revascularization for tissue perfusion. Besides the innovations in revascularization strategies, developments in antithrombotic therapy resulted in a significant reduction in STEMI-related mortality. Reperfusion can be demonstrated by resolution of ST-segment elevation (STR), TIMI frame count (TFC), and myocardial blush grade (MBG). Aim of the study: In our study, we investigated the effects of P_2Y_{12} inhibitors clopidogrel, prasugrel, and ticagrelor on reperfusion parameters such as TFC, MBG, and STR, after primary percutaneous coronary intervention (pPCI) in STEMI. **Material and Methods:** The study was a retrospective analysis of STEMI patients who underwent successful pPCI. A total of 120 patients were included in the study as 3 equal groups according to the type of P_2Y_{12} inhibitor administered in loading dose in the acute phase, and reperfusion parameters were compared between the groups. **Results:** There was no statistically significant difference between the groups in terms of baseline demographic, clinical, and angiographic parameters. Evaluation of reperfusion parameters indicated that STR, MBG, angina relief after pPCI and corrected TFC (cTFC) were significantly different between the groups ($p < 0.05$). In post-hoc analysis, the percentage of change in STR, MBG, angina relief after pPCI, and cTFC was significantly higher in the prasugrel group ($p < 0.017$). **Conclusion:** In STEMI patients undergoing pPCI, the analysis of tissue level reperfusion parameters indicates a superior effect of prasugrel compared with other P_2Y_{12} inhibitors used to achieve reperfusion.

Keywords: P_2Y_{12} inhibitors, ST segment resolution, TIMI frame count, myocardial blush grade

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INTRODUCTION

Worldwide, ischemic heart disease, and especially ST-segment elevation myocardial infarction (STEMI), is the most common cause of death.[1] Mortality in STEMI patients is associated with many factors such as advanced age, Killip class, delay in reperfusion therapy, presence and functionality of emergency medical system-based STEMI networks, treatment strategy, history of myocardial infarction (MI), diabetes mellitus, renal failure, number of diseased coronary arteries, and left ventricular ejection fraction (LVEF).[2] In accordance with the developments in treatment regimens and interventional techniques, there is a significant decrease in mortality caused by ischemic heart diseases, and especially by STEMI.[3,4] In STEMI patients, it is essential to revascularize the infarct-related artery (IRA) as soon as possible by primary percutaneous coronary intervention (pPCI).[2] In some patients, although coronary revascularization has been achieved, the distal blood flow may be slow or absent due to absence of reperfusion at a tissue level. This condition is associated with increased mortality.[5] Tissue-level reperfusion can be shown electrocardiographically by resolution of ST segment elevation (STR) and angiographically by parameters such as TIMI frame count (TFC) and myocardial blush grade (MBG).[6–8] Antithrombotic therapy is one of the most important therapeutic steps in the management of STEMI patients. Different P_2Y_{12} inhibitors can be used in addition to aspirin for antithrombotic therapy for up to 12 months in patients undergoing pPCI.[2] Clopidogrel, prasugrel, and ticagrelor are P_2Y_{12} inhibitors frequently used in STEMI, providing significant benefits on mortality and morbidity rates.[2] However, the effect of these agents on the tissue-level reperfusion parameters is ambiguous. In our study, we investigated the effects of different P_2Y_{12} inhibitors on reperfusion parameters after pPCI in STEMI patients.

METHODS

The study was a retrospective analysis of 120 consecutive STEMI patients who underwent successful primary PCI, defined as post-procedural TIMI 3 flow in the IRA, with a residual stenosis less than 20% and absence of clear dissection, thrombus, or perforation in the revascularized vessel.

One hundred and twenty patients who were admitted in the emergency department and diagnosed with STEMI were included in the study. All patients fulfilled the ECG criteria of STEMI,[9] and received P_2Y_{12} loading before the pPCI. The study population was divided into three equal groups according to the type of P_2Y_{12} inhibitors administrated in loading dose in the emergency department before pPCI: group I consisted of 40 patients who received 600 mg of clopidogrel; group II consisted of 40 patients who received 60 mg of prasugrel; and group III included 40 patients who received 180 mg of ticagrelor.

Ethics committee approval was obtained from Ondokuz Mayıs University Faculty of Medicine Clinical Research Ethics Committee for the study with the decision numbered OMU KAEK 2017/414. All study procedures were in accordance with the principles stipulated in the Declaration of Helsinki.

As exclusion criteria for the study, we mention the presence of coronary anomalies, vasculitis, cardiogenic shock before revascularization, thrombolytic therapy within the previous 2 weeks, previous angioplasty of the IRA, prior CABG, pPCI failure (<3 TIMI flow in the IRA), re-intervention for stent thrombosis, no stent implantation to the IRA, median diameter of the IRA less than 2 mm, the need for thrombus aspiration, the use of IIb III3a glycoprotein inhibitors, contraindication of dual antiplatelet therapy, requirement of PCI for bifurcation lesions, intravascular ultrasound (IVUS)-guided procedures or oral anticoagulant treatment. We also excluded patients with His bundle block, temporary or permanent ventricular pacing, and atrial fibrillation.

All patients' age, gender, body weight, height, cardiovascular risk factors, medications, compliance to treatment, and other systemic diseases were recorded. All patients' full blood cell count and basic biochemical blood tests results, 12-lead electrocardiogram (ECG), transthoracic echocardiography (TTE) reports, and coronary angiography images were obtained from the local medical database.

Twelve-lead ECG was performed for all patients using an E70 12-channel ECG device (Biolight Meditech, Guangdong, China.) before and at least two hours after pPCI. Transthoracic echocardiography was performed by an experienced echocardiography specialist the next day after pPCI. A Vivid E9 (GE Vingmed Ultrasound, Horten, Norway) echocardiography device and an M5S (1.5–4.5 MHz) ultrasound probe were used for the echocardiographic measurements. Ejection fraction (EF) was calculated with the modified Simpson's method using apical 4-chamber and 2-chamber images.

In all patients, pPCI was performed using femoral or radial access. All patients were administered 70–100 U/kg intravenous bolus unfractionated heparin at the beginning of the procedure. Coronary angiography was performed

with a Philips Allura Xper FD20 angiography equipment, with the recordings taken at a rate of 30 frames/sec.

Pain relief was defined as more than 50% reduction of angina pectoris severity rated up to 1–10 compared to the pre-procedure pain score. The ratio of ST segment elevation one hour after pPCI to ST segment level before the procedure was defined as STR.[6] Pain relief and STR were evaluated 2 hours after pPCI. STR >70% was accepted as the clinical reperfusion criterion. Successful PCI was performed in the IRA with implantation of an appropriately sized coronary stent, and procedural results were confirmed to be optimal by a cardiologist who was blinded to the study. After the procedure, TFC was calculated from the image recordings by two cardiologists who were blinded to the allocated drug. TFC was defined as the number of frames required for the contrast dye to first opacify a standard distal landmark. The distal landmarks were defined as follows: for the left anterior descending artery (LAD) – the closest point to the apex, for the circumflex artery (CX) – the last point in the longest branch containing the lesion, and for the right coronary artery (RCA) – the first branch arising from the posterior lateral extension of the RCA after the origin of the posterior descending artery. Correction was applied for the LAD because it is longer than other major epicardial coronary arteries. For this reason, corrected TFC (cTFC) was calculated by dividing the LADs' TIMI frame counts by 1.7 to normalize for their longer lengths in accordance with standard methods.[8] The degree of myocardial blushing was evaluated according to the contrast intensity in angiography images, as followes:[10]

- MBG 0: no contrast blushing, no contrast in microvascular tissue;
- MBG I: minimal contrast blushing, no slow entry and exit of contrast into the microvascular space, opacities remain in the tissue fed by the coronary which includes the responsible lesion, and these opacities are still visible in the myocardium after the next contrast ejection or about 30 seconds;
- MBG II: moderate contrasting, moderate opacities only after 3 cardiac cycles;
- MBG III: contrast blushing evaluated as the normal region.

Study data were computerized using SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL). Descriptive statistics were expressed as mean ± standard deviation (minimum-maximum), frequency distribution, and percentage. Pearson's Chi-squared test was used to evaluate categorical variables. The distribution normality of the variables was examined using visual (histogram and probability graphs) and analytic methods (Shapiro-Wilk Test). For the normally distributed variables one-way ANOVA tests were utilized to detect significant differences between groups. When there was a significant difference between the groups, post-hoc Bonferroni correction was performed to determine the source of difference. When a significant difference was found, Tukey's test was used for pairwise post-hoc comparisons. A p value <0.05 was considered statistically significant in all analyses except for post-hoc comparisons in which p <0.017 was statistically significant.

RESULTS

Baseline clinical characteristics and risk factors were well-balanced between the three study groups, and no statistical differences were recorded in terms of age, gender, smoking status presence of hypertension (HT), diabetes mellitus (DM), or hyperlipidemia (Table 1). There was no statistically significant difference between the study groups in terms of systolic and diastolic blood pressure, heart rate, KILLIP class, and post-pPCI EF (Table 2).

There was no difference between the basic angiographic parameters and stent size among the patient groups included in the study (Table 3). In addition, the pain-to-balloon (PBT) and door-to-balloon times (DBT) were similar in all groups.

Evaluation of reperfusion parameters detected STR in 90.0% of the patients in group II, 65.0% of patients in group III, and 60.0% of patients in group I. Inter-group assessment showed a statistically significant difference of STR between the study groups (p = 0.006). The percentage of those with STR in group II was significantly higher than in group I (p <0.001) and in group III (p <0.001) (Table 4).

There was a statistically significant difference between the groups in terms of cTFC value, which was 22.9 ± 11.4 in group I, 19.6 ± 10.8 in group II, and 25.9 ± 22.7 in group III (p = 0.031). Post-hoc binary comparison demonstrated that patients in group II had significantly lower cTFC values than patients in group III (p = 0.007) (Table 4).

Evaluation of MBG across the three groups revealed the presence of MBG 3 in 55% of patients from group I, in all patients from group II, and in 77.5% of patients from group III. The percentage of patients with MBG 3 in group II was significantly higher than in group III (p = 0.006) and group I (p <0.001), respectively. In addition, MBG degree in group III was superior to the one recorded in group I (p = 0.033) (Table 4).

TABLE 1. Basic demographic characteristics of the patients included in the study

Variables	Group I (n = 40)	Group II (n = 40)	Group III (n = 40)	p value
Age, years	63.4 ± 14.3	57.8 ± 9.1	58.1 ± 11.6	0.1
Gender, female, n (%)	32 (80)	34 (85)	33 (82.5)	0.8
DM, n (%)	8 (20.0)	7 (17.5)	9 (22.5)	0.8
HT, n (%)	27 (67.5)	21 (52.5)	21 (52.5)	0.2
Hyperlipidemia, n (%)	17 (42.5)	11 (27.5)	12 (30.0)	0.3
Smoking, n (%)	31 (77.5)	34 (85.0)	33 (82.5)	0.6
Previous MI, n (%)	4 (10.0)	2 (5.0)	2 (5.0)	0.5
SBP, mmHg	119.8 ± 25.0	114.2 ± 13.1	119.2 ± 13.1	0.6
DBP, mmHg	74.5 ± 13.1	70.8 ± 12.5	73.2 ± 13.5	0.5
Heart rate, beats/min	73.6 ± 16.4	72.9 ± 12.1	73.8 ± 14.1	0.9
KILLIP class, n (%)				
I	31 (77.5)	31 (77.5)	32 (80.0)	0.7
II	7 (17.5)	8 (20.0)	8 (20.0)	0.5
III	2 (5.0)	1 (2.5)	0	0.8
EF, %	43.8 ± 8.3	44.5 ± 8.8	44.4 ± 9.3	0.8

Data are given as mean ± SD, median (interquantile range) or n (%).
DBP – diastolic blood pressure; DM – diabetus mellitus; EF – ejection fraction; HT – hypertension; MI – myocardial infarction; SBP – systolic blood pressure

STR, MBG, angina relief after pPCI, and cTFC were significantly different between the groups ($p < 0.05$). In post-hoc analyses, the percentages of the change in STR, MBG, angina relief after pPCI, and cTFC were significantly higher in the prasugrel group ($p < 0.017$). At the same time, post-hoc analysis showed a significant difference between group II and other groups in respect to STR, MBG, and angina relief parameters ($p < 0.017$), but with no significant difference between group I and group III ($p > 0.017$) (Table 4).

DISCUSSIONS

P_2Y_{12} inhibitors are used in addition to aspirin for their antithrombotic effect, which provides significant benefits on mortality in STEMI.[2] We aimed to evaluate the effect of different P_2Y_{12} inhibitors concurrently on reperfusion parameters. Our study revealed that STEMI patients who recieved prasugrel loading dose before pPCI had better myocardial perfusion.

TABLE 2. Basic laboratory parameters of the patients included in the study

Variables	Group I (n = 40)	Group II (n = 40)	Group III (n = 40)	p value
Hemoglobin, g/dL	14.2 ± 2.5	14.2 ± 2.0	14.6 ± 1.8	0.6
Hematocrit, %	40.1 ± 5.8	41.8 ± 5.5	42.7 ± 4.9	0.09
White blood cells, 103/uL	11.7 ± 3.1	11.5 ± 3.5	11.6 ± 4.0	0.9
Platelets, 103/uL	264.8 ± 96.1	251.3 ± 71.8	238.4 ± 67.3	0.5
Creatinine, mg/dL	1.01 ± 0.58	0.90 ± 0.23	1.11 ± 1.33	0.4
Total cholesterol, mg/dL	180.4 ± 42.8	173.3 ± 43.0	173.8 ± 35.2	0.6
Triglycerides, mg/dL	151.6 ± 71.3	156.4 ± 67.6	172.1 ± 103.5	0.8
HDL, mg/dL	38.5 ± 10.3	39.0 ± 11.9	40.9 ± 14.2	0.8
LDL, mg/dL	111.5 ± 38.0	104.0 ± 36.8	97.7 ± 33.1	0.2
CRP, mg/L	23.9 ± 32.8	20.4 ± 39.5	25.5 ± 36.7	0.5
Initial troponin I, ng/mL	11.4 ± 16.4	5.7 ± 12.7	10.0 ± 16.6	0.05
Peak troponin I, ng/mL	42.0 ± 15.9	41.4 ± 15.4	39.6 ± 16.0	0.5

Data are given as mean ± SD, median (interquantile range) or n (%).
CRP – C reactive protein; HDL – high-density lipoprotein; LDL – low-density lipoprotein

TABLE 3. Basic angiographic parameters of the patients included in the study

Variables	Group I (n = 40)	Group II (n = 40)	Group III (n = 40)	p value
Pain-to-balloon time, min	324.8 ± 233.5	252.8 ± 124.3	296.2 ± 150.4	0.2
Door-to-balloon time, min	50.2 ± 12.0	45.4 ± 12.0	50.9 ± 16.2	0.1
Infarct-related artery, n (%)				
LAD	22 (55.0)	20 (50.0)	27 (67.5)	0.4
CX	5 (12.5)	4 (10.0)	5 (12.5)	0.2
RCA	13 (32.5)	16 (40.0)	8 (20.0)	0.3
Predilatation, n (%)	29 (72.5)	33 (82.5)	32 (80.0)	0.5
Stent diameter, mm	2.8 ± 0.3	2.9 ± 0.3	2.8 ± 0.4	0.6
Stent length, mm	23.8 ± 7.9	25.0 ± 8.8	22.9 ± 7.7	0.6
Postdilatation, n (%)	20 (51.3)	27 (67.5)	18 (45.0)	0.1

Data are given as mean ± SD, median (interquantile range) or n (%).
LAD – left anterior descending artery; CX – circumflex artery; RCA – right coronary artery

The main purpose of pPCI is to provide optimal coronary blood flow in the IRA, as documented by the presence of TIMI 3 flow, and hence myocardial perfusion. However, despite developing technical possibilities, in some patients this result still cannot be reached. Although TIMI 3 coronary flow is considered to be a good indicator of myocardial perfusion, other clinical indicators of reperfusion, such as STR, cTFC, and MBG, remain also valid indicators of optimal results.[6,10–12] It has been demonstrated with SPECT imaging analysis that STR is associated with the extent of infarction and therefore with mortality after acute coronary syndromes.[8] In the subgroup analysis of the ATLANTIC study, it was emphasized that a low STR is associated with major cardiovascular events and can be considered as a clinical marker for reperfusion.[11] In our study, positive results were obtained in all groups in terms of STR and angina relief, with the group receiving prasugrel showing superior results. In concordance with previous studies, no difference was observed in terms of STR between the groups receiving ticagrelor and clopidogrel.[13]

Myocardial blush grade is the angiographic indicator of myocardial tissue perfusion beyond epicardial coronary blood flow.[10] In a study conducted in 2003, it was stated that MBG was an independent determinant of recovery of left ventricular function in patients with acute coronary syndromes who underwent PCI.[14] In addition,

TABLE 3. Distribution of reperfusion parameters of the patients

Variables	Group I (n = 40)	Group II (n = 40)	Group III (n = 40)	p value
STR, n (%)	24 (60.0)	36 (90.0)[ab]	26 (65.0)	0.006*
Angina relief after pPCI	26 (65.0)	37 (92.5)[ab]	33 (82.5)	0.008*
TIMI flow grade, n (%)				
1	1 (2.5)	0	0	0.2
2	3 (7.5)	1 (2.5)	5 (12.5)	0.5
3	36 (90.0)	39 (97.5)	35 (87.5)	0.6
cTFC, frame/sec	22.9 ± 11.4	19.6 ± 10.8[ab]	25.9 ± 22.7	0.03*
Myocardial blush grade, n (%)				
2	18 (45.0)	0[ab]	16 (22.5)	<0.001*
3	22 (55.0)	40 (100)[ab]	21 (77.5)	0.002*

Data are given as mean ± SD, median (interquantile range) or n (%).
cTFC – corrected TIMI frame count; pPCI – primary percutaneous coronary intervention; STR – resolution of ST segment elevation
* One way analysis of variance ($p < 0.05$ is considered significant)
[a] The post-hoc analysis revealed a difference between group II and group I ($p < 0.017$)
[b] The post-hoc analysis revealed a difference between group II and group III ($p < 0.017$)

it has also been demonstrated that there is a correlation between infarct size and MBG, and low-grade MBG is associated with increased mortality in the long term.[15] In a study published in 2007, Kaya *et al.* investigated the prognostic significance of TIMI flow and MBG measurements in patients with acute coronary syndromes. They found that MBG was a good predictor of mortality during a five-year follow-up.[16] Also in a subgroup analysis of the HORIZONS-AMI study in which 2,367 patients were analyzed, it was reported that MBG was an important predictor of long-term prognosis.[17] In a subgroup analysis of the COCTAIL II study, the effect of different P_2Y_{12} inhibitors on reperfusion parameters was compared. In this study, the frequency of MBG III was significantly higher in the prasugrel group compared with clopidogrel and ticagrelor.[18] The percentage of those who had MBG III in the prasugrel group was significantly higher than the other groups also in our study. According to this result, considering the predictive efficacy of MBG on long-term mortality, it may be appropriate to carry out extensive research to assess long-term mortality in patients receiving prasugrel.

One of the most common methods used to measure myocardial perfusion is the TIMI frame count.[15] A low TFC has been identified as a predictor of myocardial recovery in patients with acute coronary syndromes.[6] Studies have demonstrated a relationship between TFC and left ventricular function, cardiac arrhythmias, mortality, length of hospital stay, and long-term prognosis.[12] In a study comparing STEMI patients who recieved ticagrelor or prasugrel in terms of cTFC values, no statistical difference was found, although a trend was identified in favor of ticagrelor.13 In the subgroup analysis of the COCTAIL II study mentioned above, the effect of P_2Y_{12} inhibitors on the final TIMI flow, TFC, and STR was also investigated and no difference was found between the groups.[18] In our study, the best TFC value was found in the prasugrel group. In addition, in the prasugrel group, cTFC was statistically different compared to the ticagrelor group, while it was similar to the clopidogrel group (19.6 ± 10.8 vs. 25.9 ± 22.7, $p = 0.007$; 22.9 ± 1 1.4, $p = 0.123$). These differences may be related to the pharmacological features of the molecules, but it is obvious that more extensive studies are needed to reach more valuable data.

The active metabolites of clopidogrel and prasugrel, which are members of the thienopridin group, irreversibly antagonize the P_2Y_{12} receptor.[19,20] Ticagrelor antagonizes the P_2Y_{12} receptor in a reversible and non-competitive way.[21,22] In a study conducted by Hae-Sun *et al.* in 2015, serum ADP levels and platelet activations of patients receiving prasugrel or ticagrelor were compared. A stronger, faster, and longer inhibition was detected in the prasugrel group.[23] In addition, unlike other P_2Y_{12} inhibitors, prasugrel requires only one hydrolysis in order to transform into its active metabolite. These properties indicate that prasugrel can transform into its active metabolite more quickly.[24] However, in another study, platelet inhibition levels after two hours were not statistically different in patients with STEMI who received prasugrel or ticagrelor. Despite this, in other studies, a trend was found in favor of prasugrel.[25] In this context, the positive results recorded in terms of reperfusion parameters in patients receiving prasugrel may be related to the early and strong onset of the drugs' efficacy. A more comprehensive, randomized controlled, long-term follow-up study should follow in order to demonstrate this hypothesis.

STUDY LIMITATIONS

Our study has several limitations. First of all, the platelet inhibition levels of the P_2Y_{12} groups were not evaluated. This makes it difficult to assess the relationship between the results of the study and platelet function. At the same time, only clinical, electrocardiographic, and angiographic methods were used to evaluate myocardial perfusion, while more advanced imaging methods, such as SPECT, MRI, or PET, could provide more objective results. Finally, short-term side effects – especially bleeding – were not evaluated in our study.

CONCLUSIONS

P_2Y_{12} inhibitors used in STEMI patients differ in terms of their effectiveness on tissue perfusion. Our study investigated the effect of different P_2Y_{12} inhibitors on reperfusion parameters. In STEMI patients undergoing pPCI, analysis of tissue level reperfusion parameters indicates a superior effect of prasugrel compared with other P_2Y_{12} inhibitors to achieve reperfusion.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest..

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