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The effect of early dual antiplatelet timing on the microvascular resistance and ventricular function in primary percutaneous coronary intervention

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Abstract

Although dual antiplatelet therapy (DAPT) has been shown to improve index of microcirculatory resistance (IMR), the importance of the early DAPT administration on IMR and left ventricular function has not been clearly defined. In this study, we aimed to assess whether early DAPT administration affect IMR, epicardial flow, and left ventricular function in ST-segment elevation myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI).

This was a prospective non-randomized study on STEMI receiving primary PCI in a tertiary hospital. All subjects received loading dose DAPT (Aspirin + Clopidogrel) before primary PCI. Patients were then divided into 2 groups, the first group consists of patients receiving DAPT time ≤2 hours and the second group consists of those with DAPT time >2 hours. The primary endpoint of this study was IMR, a microvasculature function index measured quantitatively by pressure-/temperature-tipped guidewire after balloon dilatation. The secondary endpoint was the mean difference of global longitudinal strain (GLS) change at 6 months follow-up, TIMI flow before, and after PCI between the 2 groups.

There were 40 subjects qualified for the study, 20 subjects in each group. There was no significant difference in IMR (50.90 [34.66] vs 58.06 [45.56], $P = .579$) between the 2 groups. Early administration of DAPT improved ventricular function at 6 months, reflected by statistically significant greater improvement in terms of ΔGLS (–3.48 [2.61] vs –1.23 [2.87], $P = .013$) and Δejection fraction (10.65% [8.74] vs –0.75% [12.83], $P = .002$) in the DAPT time ≤2 hours group compared with DAPT time >2 hours group. TIMI flow before PCI ($P = .653$) and TIMI flow after PCI ($P = .205$) were similar in the 2 groups.

Early DAPT administration ≤2 hours may improve left ventricular function, but not IMR and TIMI flow.

Abbreviations: ceCMR = contrast-enhanced cardiac magnetic resonance imaging, DAPT = dual antiplatelet therapy, EF = ejection fraction, GLS = global longitudinal strain, IMR = index of microcirculatory resistance, MVO = microvascular obstruction, PCI = percutaneous coronary intervention, PPCI = primary percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction.

Keywords: aspirin, clopidogrel, dual-antiplatelet therapy, global longitudinal strain, microcirculation

1. Introduction

Myocardial infarction (MI) is one of the leading cause of mortality worldwide.[1] In the United States alone, there are about 600,000 new cases and 320,000 recurrent cases each year.[2] Central to the mechanism are activation and aggregation of platelets to the ruptured/eroded atherosclerotic plaque in the coronary vessels.[3] Early administration of dual antiplatelet (DAPT) which consists of aspirin and a P_2Y_{12} inhibitor, is essential to suppress the thrombi progression and is recommended by the guidelines.[4–7] Prehospital administration of DAPT in ST-segment elevation myocardial infarction (STEMI) is associated with higher survival.[8] Hence, the timing of DAPT administration has become increasingly important.

In STEMI patients, administration of DAPT is followed by reperfusion therapy, preferable through primary percutaneous coronary intervention (PCI). Although PCI may result in recovery of epicardial flow when performed early, the reperfusion at myocardial level is not achieved in almost one-third of the cases. Termed no reflow phenomenon or microvascular obstruction (MVO), this condition is caused by persistent disruption of microcirculation.[9] Studies have shown that MVO is associated with infarct size, impaired ventricular function, major adverse cardiovascular events, and mortality.[9–13] Global longitudinal

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strain (GLS) has been shown to be able to reflect myocardial impairment, even at early stage in patients with MVO.[12] Currently, the gold standard to assess coronary MVO is contrast-enhanced cardiac magnetic resonance imaging (ceCMR), but its use is limited because of safety reasons, duration, and cost.[14] Index of microcirculatory resistance (IMR), a novel pressure-/temperature-tipped guidewire-based quantitative measure of coronary microvasculature function, is an alternative that has shown to be reliable. Previous study showed that increase in IMR correlate with the increase of MVO measured by ceCMR.[14–16]

Although DAPT has been shown to improve IMR,[17] the importance of the early DAPT administration on IMR and left ventricular function has not been clearly defined. In this study, we aimed to assess whether early DAPT (Aspirin + Clopidogrel) administration affect IMR, epicardial flow, and left ventricular function (measured by GLS) in STEMI patients undergoing PCI.

2. Methods

This was a prospective non-randomized study in STEMI patients receiving primary PCI in a tertiary hospital, between January 2014 and November 2014. All subjects received loading dose DAPT (aspirin + clopidogrel) before primary PCI. Patients with cardiogenic shock, atrial fibrillation, history of previous MI, bundle branch block, use of permanent/temporary pacemaker, ventilator dependent, or having other procedure within 6 months were excluded. Patients were then divided into 2 groups, the first group consisted of patients receiving DAPT time $\leq$2 hours after symptom onset and the second group consisted of those with DAPT time >2 hours after symptom onset. DAPT time was defined as time from pain onset to the DAPT administration. The 2 hours cut-off point was based on the time needed for clopidogrel to reach the peak antiplatelet effect. Written informed consents were obtained from all participants before the procedure. This study was performed in compliance with the guidelines for good clinical practice and the Declaration of Helsinki and was approved by the institutional ethical review board of National Cardiovascular Center Harapan Kita, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

The primary endpoint of this study was IMR, a microvasculature function index measured quantitatively by pressure/temperature-tipped guidewire. Following balloon dilatation and successful stenting of the culprit lesion, a pressure wire (Radi Medical Systems, Uppsala, Sweden) was then calibrated outside the body, and advanced to the distal two-thirds of the culprit vessel to measure IMR. Three milliliters of room-temperature saline were then injected along the culprit vessel for 3 times at rest, the resting transit times, were then recorded. The maximal hyperemia was then induced by administering 140 μg/kg/min of intravenous adenosine through a central venous catheter. Afterwards, another 3 mL of room temperature saline were again injected along the culprit vessel, and the hyperemic transit times were recorded. The IMR in this study was defined as distal coronary pressure divided by flow during the peak hyperemia and was calculated by dividing the mean distal coronary pressure by the inverse of hyperemic transit time. The IMR measurement method followed the methods of previous study conducted by Fearon et al.[18]

The secondary endpoint was the mean difference of ΔGLS at 6 months follow-up, ΔEjection Fraction (EF) at 6 months follow-up, TIMI flow before, and after PCI between the 2 groups. Global left ventricle longitudinal strain (GLS) was calculated using the automated functional imaging (AFI) technique, a modality based on 2D longitudinal strain imaging. Longitudinal strain in % is defined as the physiological change in length of the region of interest from end-diastole to end-systole. During this period, strain in the longitudinal direction is a negative value as the length of the region of interest decreases. Longitudinal strain can be calculated using the following formula: longitudinal strain (%) = $[L\ (\text{end-systole}) - L\ (\text{end-diastole})]/L\ (\text{end-diastole}) \times 100\%$; where L is the length of the region of interest.[19] All patients underwent echocardiography examination in 24 hours, 3 and 6 months following primary percutaneous coronary intervention (PPCI). LV improvement was defined as a negative value difference GLS on follow-up minus GLS in 24 hours after PPCI.

Shapiro Wilk test was used to measure the mean change on follow-up. An independent *t* test was used to compare the mean difference between the 2 groups of DAPT time for parametric variables. Mann–Whitney *U* test was used to compare difference between the groups with non-parametric variables. *P*-values are 2 tailed and set at 0.05. Data were managed and analyzed using IBM SPSS Statistics 23.

3. Results

There were 53 consecutive patients with STEMI that underwent PPCI, 6 patients were excluded because of unsuccessful IMR measurement (n = 3), unclear echocardiography (n = 3). There were 47 observed patients that fulfilled inclusion and exclusion criteria. There were 7 patients that were lost to follow-up, and 40 patients completed the follow-up. There are 20 patients with DAPT time $\leq$2 hours and 20 patients with DAPT time >2 hours. The characteristics of the subjects were similar, with the exception of dyslipidemia and pain onset to PCI. We arrived at the pain onset cutoff point of >4.5 hours by receiver operating characteristic (ROC) curve test. The baseline characteristics for each group are presented in Table 1. There was no significant difference in IMR (50.90 [34.66] vs 58.06 [45.56], $P = .579$) between the 2 groups. ΔGLS was greater in the DAPT time $\leq$2 hours group compared with DAPT time >2 hours group (–3.48 [2.61] vs –1.23 [2.87], $P = .013$). ΔEF was better in the DAPT time $\leq$2 hours group compared with DAPT time >2 hours group (10.65% [8.74] vs –0.75% [12.83], $P = .002$). There is no significant difference in TIMI flow before PCI ($P = .653$) and TIMI flow after PCI ($P = .205$) between the 2 groups. Table 2 shows bivariate test analysis of the variables.

4. Discussion

DAPT time $\leq$2 hours was associated with improved 6 months GLS and EF, but similar IMR and TIMI flow compared with DAPT time >2 hours. Clopidogrel action to improve coronary microvascular function has been described in Willoughby et al[20] study, in which clopidogrel 75 mg daily resulted in the increase of reactive hyperemic index by 20 ± 10% in 1 week and 21 ± 9% in 3 months compared with the control group.

The prevalence of dyslipidemia was higher in the DAPT time $\leq$2 hours group. Moreover, the longer pain onset (>4.5 hours) are more common in the DAPT group $\leq$2 hours. Longer pain onset translates to a longer ischemic time, an increased thrombus composition, and a greater transmural necrosis.[21,22] Furthermore, a delay in mechanical reperfusion is associated with greater microvascular injury.[23] Hence, the longer pain onset is a potential confounder in this study. Nevertheless, such finding

Table 1

Baseline characteristics.

Variable	DAPT time ≤2 hours (n = 20)	DAPT time >2 hours (n = 20)	*P*-value	All population (n = 40)
Demographic				
Age, mean [SD]	53.9 [9]	54.8 [9.2]	.745	54.38 [9.07]
Gender			.106	
Male, n (%)	20 (100)	16 (80)		36 (90)
Female, n (%)	0 (0)	4 (20)		4 (10)
BMI, mean [SD]	24.52 [4.5]	25.00 [4.75]	.660	24.76 [3.32]
Cardiovascular risk				
Hypertension, n (%)	8 (40)	9 (45)	.749	17 (42.5)
Diabetes mellitus, n (%)	7 (35)	3 (15)	.144	10 (25)
Dyslipidemia, n (%)	11 (55)	3 (15)	.019*	14 (35)
Smoking, n (%)			.343	31 (77.5)
Current	9 (45)	12 (60)		21 (52.5)
Previous	7 (35)	3 (15)		10 (25)
Pain onset to PCI, mean [SD]			.001*	5.92 [2.95]
>4.5 hour, n (%)	14 (70)	3 (15)		17 (42.5)
<4.5 hour, n (%)	6 (30)	17 (85)		23 (57.5)
Culprit lesion				
Right coronary artery	5 (25)	4 (20)	1	9 (22.5)
Left anterior Descending	14 (70)	13 (65)	.736	27 (67.5)
Left circumflex	1 (5)	3 (15)	.605	4 (10)

BMI = body mass index, DAPT = dual antiplatelet therapy, PCI = percutaneous coronary intervention, SD = standard deviation, TIMI = Thrombolysis in myocardial infarction.

strengthen the importance of DAPT time ≤2 hours that despite having a higher risk, the improvement of ventricular function as expressed by ΔGLS was still in favor of DAPT time ≤2 hours. These results support the current recommendation, which states that DAPT should be given as soon as possible in MI patient.[4–7]

DAPT time did not influence the IMR, TIMI flow before PCI, and TIMI flow after PCI between the 2 groups. This might be due to a longer pain onset to PCI time, hence, the pain to balloon time, in the DAPT ≤2 hours group. The longer pain to balloon time allows a more extensive thrombus progression. Hence, a worse microvascular obstruction is expected in these subjects, despite early DAPT. The effect of early DAPT on TIMI flow is as expected. CIPAMI and ATLANTIC have demonstrated that early DAPT treatment has no significant effect on TIMI flow. Early therapy in these studies were defined as administration of $P2Y_{12}$ inhibitor, clopidogrel in CIPAMI and Ticagerol in ATLANTIC, before the PCI, with the median time of pretreatment to PCI of 47 minutes (CIPAMI) and 48 minutes (ATLANTIC).[22,24] The non-significant results may be due to short pretreatment time, which has not passed the maximum inhibitory time of 120 minutes in clopidogrel and 30 minutes to 4 hours in ticagrelol.[25,26] In contrast, MACE study showed that clopidogrel pretreatment affects TIMI flow before PCI and clinical outcome, however, this was conducted in stable coronary artery disease.[20] Besides earlier therapy, a sustained DAPT regiment as recommended by the guideline is of utmost importance, a study showed that DAPT cessation was associated with higher cardiac death, MI, and stent thrombosis in both low and high risk for atherothrombosis.[27]

Table 2

Bivariate analysis of DAPT time effect on IMR, GLS, and TIMI flow.

Variable	DAPT time ≤2 hours (n = 20)	DAPT Time >2 hours (n = 20)	*P*-value
IMR, mean [SD]	50.90 [34.66]	58.06 [45.46]	.579
ΔGLS, mean [SD]	−3.48 [2.61]	−1.23 [2.87]	.013*
ΔEF (%), mean [SD]	10.65 [8.74]	−0.75 [12.83]	.002*
TIMI flow pre, n (%)			.653
0	16 (80)	17 (85)	
1	1 (5)	1 (5)	
2	1 (5)	1 (5)	
3	2 (10)	1 (5)	
TIMI flow post, n (%)			.205
0	1 (5)	0 (0)	
1	0 (0)	1 (5)	
2	3 (15)	7 (35)	
3	16 (80)	12 (60)	

DAPT = dual antiplatelet therapy, EF = ejection fraction, GLS = global longitudinal strain, IMR = index of microcirculatory resistance, SD = standard deviation, TIMI = thrombolysis in myocardial infarction.
* Indicates $P < .05$.

Limitations of this study include the small sample size. Additionally, we attempted to perform linear regression (multivariate analysis) for the ΔGLS at 6 months, however, the model did not pass the normality assumption, possibly due to the small sample size. This study used clopidogrel, hence, the result cannot be generalized to different type of antiplatelets (prasugrel, ticagrelol, etc). Also this study only involved a small number of female patients.

5. Conclusion

Early DAPT administration ≤2 hours may improve left ventricular function which is reflected by the improved GLS compared with >2 hours DAPT time group. IMR and TIMI flow were similar in both DAPT time groups. This finding needs to be verified by studies with larger sample size before drawing a definite conclusion.

Author contributions

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