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Short Communication

The Effects of Dual Antiplatelet Post Percutaneous Coronary Intervention on Percentage of Aggregation In Myocardial Infarction Patients with Diabetes Mellitus and Non Diabetes Mellitus

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ABSTRACT

To analyze the differences in the effect of dual antiplatelet post PCI on the percentage of aggregation in myocardial infarction patients with DM and non DM. Percentage of aggregation were analyzed using light transmission aggregometry (LTA) before loading dose, after PCI, and after maintenance dose of dual antiplatelet (aspirin 100mg and clopidogrel 75mg). Total 22 patients were participated in this study divided into 10 and 12 patients in diabetic and non diabetic group. Percentage of aggregation after taking dual antiplatelet maintenace dose decrease significantly in both group (p=0.006 in diabetic group and p=0.002 in non diabetic group). Mean reduction of percentage of aggregation in diabetic group (3.30±2.91%) is less than non diabetic group (6.83±5.97%). Statistical analysis shows that the mean reduction of percentage of aggregation between two groups were not significantly different (p>0.05). Mean percentage of aggregation after dual antiplatelet maintenance dose was higher in diabetic group and mean reduction of percentage of aggregation was higher in non diabetic group, although statistically in both group it is not significantly different.

Keyword: Myocardial infarction, Diabetes Mellitus, Dual antiplatelet, Aspirin and Clopidogrel, Percentage of aggregation

INTRODUCTION

Myocardial infarction is an irreversible death or necrosis of the heart muscle due to a lack of oxygen supply (Zafari *et al,* 2016). The cause of myocardial infarction is the presence of either total (STEMI) or partial (NSTEMI) blood vessel occlusion (PERKI, 2015). Revascularization of percutaneous coronary intervention (PCI) is one of the management of myocardial infarction. The installation of stent either DES or BMS may cause thrombotic complications such as stent thrombosis and restenosis (O'Gara *et al*., 2013; Amsterdam *et al*, 2014). Diabetes mellitus (DM) is one of the risk factor of myocardial infarction and can lead to platelet hyperreactivity. Increases platelet aggregation in diabetic patients caused by several factors such as metabolic abnormalities (hyperglycemia and hyperlipidemia, insulin resistance, and oxidative stress (Schneider *et al*, 2009; Kakouros *et al*., 2011). The therapy given after installation of stent is dual antiplatelet (aspirin 100 mg and clopidogrel 75 mg).

In patients with DM there can be an increased in platelet turnover, the short-lived aspirin appears unabled to acetylated new platelets which are released from megakaryosit (MKs) during 24h dosing interval, thus resulting in a progressive increase in TXA_2 (Rocca *et al*., 2013). Similarly, in DM patients treated with clopidogrel, impaired platelet $P2Y_{12}$ blockade is largely attributed to marked reduction (lower than non diabetic) in the pharmacokinetic profile of clopidogrel's active metabolite (drug exposure) and attributed to much lesser degree to altered functional status of the $P2Y_{12}$ signaling pathway (drug response) (Angiolillo *et al*., 2014). Reccurent ischemic that occurs in patients myocardial infarction with DM post PCI allegedly due to increase in platelet activity (O'Gara *et al*., 2013; Amsterdam *et al*., 2014). Therefore, it is necessary to conduct a study related to differences in the effect of dual antiplatelet post PCI on the percentage of aggregation in myocardial infarction patients with DM and non DM.

Table I. Baseline characteristic of patients

Patient characteristics	Diabetic group		Non diabetic group		p
	n	Percentage (%)	n	Percentage (%)	
Total patient	10	54.54	12	45.46	
Age (31-70 years)		52.1 ± 9.61		55.42 ± 7.77	0.381
Gender					
Male	8	80	9	75	0.781
Female	2	20	3	25	
Smoking					
Yes	8	80	8	66.7	0.892
No	2	20	4	33.3	
Risk Factor					
Hypertension	7	70	5	41.7	0.184
Dyslipidemia	2	20	1	8.3	0.427

MATERIAL AND METHODS

We conducted a prospective observational study from November 2016 to March 2017 at Cardiology Department of Dr.Soetomo Teaching Hospital Surabaya. The inclusion criteria were as follow: 1) patients aged>18 years who were diagnosed with myocardial infarction with diabetic and non diabetic, 2) patients who did the installation of stent either DES or BMS, and 3) patients who received dual antiplatelet therapy (Aspirin 100mg and Clopidogrel 75mg) after PCI. Exclusion criteria were patients with thrombotic disorder, history use of NSAID, anticoagulant, thrombolytics, GP IIb/IIIa inhibitor, and steroid 1 week before the study. Blood samples for measurement of platelet aggregation were collected from patients before loading dose, after PCI, and after maintenance dose of dual antiplatelet Aspirin 100mg and Clopidogrel 75mg (patients were followed approximately one week to get the blood sample).

Before starting the study, we explained the study methods, effects, and therapy of dual antiplatelet to the patients. A standard medical history (drugs that are routinely used to avoid interaction, and comorbidities), clinical, and laboratory data (blood glucose, platelet count) were collected from patient information and based on medical records. Percentage of aggregation were measured with Light Transmission Aggregometry (LTA) method. This study was approved by Ethics Committee of the Dr.Soetomo Teaching Hospital Surabaya.

Analysis data using SPSS ver. 20 started with normality test with Saphiro Wilk test. A comparative hypothesis test was performed to determined the differences of percentage of aggregation before loading dose (t=0), after PCI (t=1) and after maintenance dose dual antiplatelet (t=2) in diabetic and non diabetic group with paired sample T-test and Wilcoxon test and the differences in the effect of percentage of aggregation between diabetic and non diabetic group with independent T-test and Mann-Whitney test. The test resulted significant statistically if probability (p) <0.05 with a confindence interval 95%.

RESULTS AND DISCUSSION

Table I showed the baseline characteristic of patients. The majority of myocardial infarction patients were male with mean age 52.1±9.61 years old and 55.42±7.77 years old in diabetic and non diabetic group respectively. Almost all of patients in both group have a history of smoking, 80% in diabetic and 66.7% in non diabetic. The most common risk factor in this study is hypertension. After homogenity test, it was found that the patient's initial characteristics were similiar in both diabetic and non diabetic groups.

In this research used two kind of agonists Adenoisne Diphosphate and Arachodonic Acid (ADP and AA), which is

Table II. Mean percentage of aggregation

	Mean percentage of aggregation (%)				p*
	DM		Non DM		
	ADP	AA	ADP	AA	
t=0	20.70 ± 13.98	0.50 ± 0.85	14.92 ± 10.77	1.00 ± 1.41	0.355
t=1	22.70 ± 10.91	1.00 ± 0.94	22.67 ± 10.15	1.42 ± 2.27	0.994
t=2	19.40 ± 12.05	1.10 ± 0.99	15.83 ± 10.36	0.92 ± 1.16	0.464
Δt0-t1	2.00 ± 8.25	0.50 ± 0.97	7.75 ± 5.51	0.42 ± 2.54	0.059
Δt1-t2	3.30 ± 2.91	0.10 ± 0.74	6.83 ± 5.97	0.50 ± 2.81	0.103

*p value from percentage of aggregation with agonist ADP

related to the mechanism of action of antiplatelet (aspirin and clopidogrel). Aspirin works by inhibiting COX-1 enzymes thus preventing the conversion of arachidonic acid into prostaglandin which then lowers the synthesis of TXA_2 (Patrono *et al.*, 2012). Clopidogrel works by preventing the bonding between ADP and $P2Y_{12}$ receptor in the surface of platelet membrane (Jiang *et al*, 2015). From the data obtained (Table II), mean percentage of aggregation with agonist AA indicates a very low value (0-1%). This is because patients have previously had a history of antiplatelet use, so the addition of agonists AA was not able to increase the synthesis of TXA2 which would induce the platelet aggregation. In contrast to ADP agonists that directly induce platelet aggregation, history of antiplatelet use did not affect the value of percentage of aggregation (Cattaneo, 2009).

Table II showed mean percentage of aggregation in diabetic and non diabetic group. Measurement at t=0 aim to see the effect of antiplatelet used previously by patients. From the data obtain in table II, it appears that the percentage of aggregation with agonists ADP at t=0 higher in diabetic group than in non-diabetic group (20.70±13.98 vs 14.92±10.77, p=0.355). Although the value of percentage of aggregation higher in diabetic group, it still considered respond favorably in both groups because the cut-off point resistance with agonists ADP was percentage of aggregation > 50% (Angiolillo *et al.*, 2007).

The measurement at t=1 aims to see an increase in percentage of aggregation after stent installation. In table II showed that there is an increase in the percentage of aggregation at t=1 in both diabetic and non diabetic groups. This is consistent with patophysiology theory that states the installation of stents can cause adhesion, activation, and platelet aggregation caused by damage to the endothelium (Luscher *et al.*, 2007). And the measurement at t=2 aims to see the effect of dual antiplatelet (aspirin 100mg and clopidogrel 75 mg) post PCI.

Table II also showed that percentage of aggregation after dual antiplatelet therapy higher in diabetic than non diabetic group (19.40±12.05 vs 15.83±10.36, p=0.464). Also in this study, as shown in table 2, difference of aggregation after dual antiplatelet therapy administration (Δt1-t2) is higher in non diabetic group than in diabetic group (3.30±2.91 vs 6.83±5.97, p=0.103). As mentioned in another research, diabetes mellitus can lead to platelet hyperreactivity (increased adhesion, activation, aggregation, and platelet turnover) (Ferreiro *et al.*, 2011; Schuette *et al.*, 2015). Thus, some researcher or clinician sometimes increase the maintenance dose of dual antiplatelet (Angiolillo *et al.,* 2007; DiChiara *et al.*, 2007), or used triple antiplatelet as maintenance dose after PCI (Lee *et al.*, 2005). In this study we assess the effect of dual antiplatelet therapy by measure the percentage of aggregation before loading dose, after PCI, and after maintenance dose of dual antiplatelet in diabetic and non diabetic group. Our findings demonstrate the higher value of percentage of aggregation in diabetic group than non diabetic group either before loading dose and after maintenance dose of dual antiplatelet. The high value of percentage of aggregation in diabetic group may be due to a several factors, such as comorbidities (hypertension and dyslipidemia)

or poor blood glucose control. However in our study, we did not observe any correlation between that factors. Limitations of this study is the low number of patients enrolled and the stability of the sample which is only 4 hours. A further limitation is percentage of aggregation was not measured at acute phase. This was because patients were already receiving either aspirin or clopidogrel prior the study. Further studies are warranted to define the effect of dual antiplatelet therapy on percentage of aggregation in acute myocardial infarct patients with diabetes. Overall, it appears that in diabetic group, mean percentage of aggregation is higher than non diabetic group and the difference of percentage of aggregation after dual antiplatelet therapy appears to higher in non diabetic group.

CONCLUSION

In summary, we have examined the effect of dual antiplatelet therapy post PCI in myocardial infarct patient with diabetic and non diabettic by measure the percentage of aggregation. The mean percentage aggregation after maintenance dose of dual antiplatelet is higher in diabetic than non diabetic group, although statistically in both group it is not significantly different, highlighting the need to further investigation with more number of patients.

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