ACETOSAL RESISTANCE IN CORONARY ARTERY DISEASE BETWEEN AND WITHIN TYPE 2 DIABETES MELLITUS PATIENTS

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ABSTRAK


Kata kunci: Resistensi acetosal, diabetes melitus tipe 2, penyakit jantung koroner

ABSTRACT

Acetosal reduces the odds of an arterial thrombotic event in high risk patients. However, 10%-20% of patients with an arterial thrombotic event who are treated with acetosal have a recurrent arterial thrombotic event during long-term follow up. Acetosal resistance has been described in some patient populations such as those with an acute coronary syndrome, ischemic stroke, and percutaneous coronary intervention with drug-eluting stent, stent re-stenosis, and Type 2 Diabetes Mellitus. Patients were divided into two groups of ten patients each, 10 patients Coronary Artery Diseases with Type 2 Diabetes Mellitus and 10 patients non-Type 2 Diabetes Mellitus. The sampling of this cross sectional study was conducted at department of Cardiology Dr. Soetomo Hospital Surabaya during July-August 2014. Data from 20 patients were analyzed after exclusion due to protocol violations. All subjects were on Asetosal 100 mg/day. Four (40%) patients with Type 2 Diabetes Mellitus were acetosal non-responders, acetosal resistance was observed in 3 (30%) of nondiabetic patients (p=1.000). In conclusion, no difference has been found on acetosal resistance in coronary artery disease patients with or without Type 2 Diabetes Mellitus. (FMI 2015;51:137-141)

Keywords: Asetosal Resistance, Type 2 Diabetes Mellitus, Coronary Artery Disease

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INTRODUCTION

Cardiovascular disease, particularly coronary artery disease resulting from accelerated atherosclerosis, is the leading cause of morbidity and mortality in patients with diabetes mellitus (DM). Patients with diabetes mellitus presenting with acute coronary syndrome have a higher risk of cardiovascular complications and recurrent ischemic events when compared to non-diabetic counterparts (Ferreiro et al 2011).

Different mechanisms including endothelial dysfunction, platelet hyperactivity, and abnormalities in coagulation and fibrinolysis have been implicated for this increased atherothrombotic risk. Platelets play an important role in atherogenesis and its thrombotic complications in diabetic patients with acute coronary syndrome. Hence, potent platelet inhibition is of paramount importance in order to optimize outcomes of diabetic patients with acute coronary syndrome (Balasubramaniam et al 2012).

Platelet aggregation and activation mediated by various agonists play fundamental roles in the development of ischemia in patients with coronary artery diseases (CAD) and in thromboischemic complications after percutaneous coronary intervention (PCI). Activated platelets mediate vessel wall inflammation, and generat-
ion of thrombin and platelet–platelet aggregates mechanically obstruct vessels (Mosorjakova et al 2007).

Acetylsalicylic acid (ASA) therapy is a mainstay of drug treatment in atherosclerosis, resulting in a significant reduction of CV morbidity and mortality (Cieslicka et al 2013). However, it has been estimated that 8-45% of patients may experience thromboembolic events despite acetosal therapy. In vascular patients with symptomatic disease it failed in 75 % of cases. It is suggested that 70% to 75% of non-fatal and 80% to 85% of fatal events are not prevented by these drug (Mirkhel et al 2006).

RESULTS

The demographic data of the patients enrolled in the study are reported in Table 1. No significant differences in any of the demographic parameters were evident between two groups. Among 20 consecutive patients suffering from coronary artery disease, 4 (40%) patients with Type 2 Diabetes Mellitus were acetosal non-responders and had ARU (Aspirin Reaction Unit) more than 550, acetosal resistance was observed in 3 (30%) of non-diabetic patients (p=1.000). This suggests that diabetes mellitus made no different effect to acetosal resistance.

MATERIALS AND METHODS

This study is an analytic observational study with cross sectional design. Selection of study subjects performed consecutive sampling in which every patient who met the study criteria were included in the study until a certain time. Study population were patients attending Outpatient Heart Disease Unit Dr. Soetomo Hospital suffering from coronary artery disease (CAD) with or without type 2 diabetes, aged > 21 years, receiving aspirin therapy 100 mg daily for 7 days, aspirin was taken at least 24 hours prior to sampling.

Patients with history of gastrointestinal disorders, platelet count < 100,000/ul, use of NSAIDs, anticoagulants, antiplatelet agents other than aspirin for 10 days before the study as well as drugs that can affect platelet aggregation, complications due to diabetes (gangrene, DM nephropathy), creatinine > 2 mg/dl, heart failure were all excluded from the study. On completion of each dose, the platelet acetosal response was determined using VerifyNow, with the degree of platelet aggregation assessed based on the measurement of light transmittance using a specific algorithm to express the result in aspirin reaction units (ARU) in all patients.

Blood was collected in the morning hours. Acetosal assay cassettes were used with arachidonic acid as the agonist. Measurements were performed in whole blood collected to vacuum tubes containing 3.2% sodium citrate. Persistent platelet activation despite ASA treatment was defined as ≥ 550 ARU. Distributions of variables were assessed for normality using Shapiro-Wilk test. To determine difference in aspirin resistance between CAD patients with and without diabetes Type 2 we used chi square test. If the chi square test requirements are not met, an alternative test extract Fisher was done.

DISCUSSION

In this study, the normality test against ARU value by using the Shapiro-Wilk test, the test is chosen because the number of patients < 20, the results obtained from the test group ARU value distribution of CAD patients with Type 2 DM and CAD without Type 2 DM is not normal. Therefore test measurements different ARU value to both groups continued using the Mann-Whitney Test. The results of the statistical test p value = 0.344, this indicates that there is no significant difference between the two groups on the value of ARU. In addition, this study also performed different tests on the number of patients who develop resistance acetosal using Chi-Square, but the test results using the chi-square method cannot be done because there are 2 cells that do not meet expectations, as well as the number of samples ≤ 20, so that different test forwarded using Fisher’s Exact test. Based on using the Fisher Exact test showed no statistically significant difference in the two groups (p = 1.000). Of the two different tests that are done, get the same result, there is no significant difference between the two groups of the acetosal resistance. This can be caused by many things, including comorbidities, age, body mass index (BMI), smoking, and genetic (Saad et al 2012).

The results of this study, the average age in the group with Type 2 DM was 57 years, 2 ± 11.2 years, while in the CAD group without diabetes was 53.4 ± 9.8 years. A number of 583 patients who received a dose of 75-325 mg daily showed an increase in the value of ARU > 550 occurs at age > 75 years (p = 0.007), whereas at age < 75 years, the influence of age on acetosal resistance can be caused by increased micro vascular disturbances in the elderly, which will impact on the decrease in the amount of nitric oxide synthesis, and impaired platelet response to vasoactive substances, but it can also be due to increase in platelet reactivity, and increased platelet turnover (Gremmel et al 2010, Mari et al 2008).
Tabel 1. Demographic data of the patients enrolled

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Samples ACD (n=20)</th>
<th>With Type 2 DM (n=10)</th>
<th>Non Type 2 DM (n=10)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>57.2 ± 11.5</td>
<td>53.4 ± 9.8</td>
<td>0.603</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>Male</td>
<td>5 (50%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>5 (50%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>24.9 ± 2.6</td>
<td>24.6 ± 1.0</td>
<td>0.081</td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td>8 (80%)</td>
<td>9 (90%)</td>
<td>0.270</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>6 (60%)</td>
<td>6 (60%)</td>
<td>0.158</td>
</tr>
<tr>
<td>Hyperlipidemia &gt; 1 disease</td>
<td></td>
<td>5 (50%)</td>
<td>5 (50%)</td>
<td>#</td>
</tr>
<tr>
<td>Risk Factor</td>
<td></td>
<td>Smoking</td>
<td>2 (20%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statin</td>
<td>7 (70%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACEI</td>
<td>7 (70%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ARB</td>
<td>3 (30%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CCB</td>
<td>4 (40%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nitrat</td>
<td>7 (70%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β-blocker</td>
<td>9 (90%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diuretic</td>
<td>3 (30%)</td>
<td>1 (10%)</td>
</tr>
</tbody>
</table>

P value* comparing between type 2 DM and without type 2 diabetes, is considered significant when the p value < 0.0

* # no statistical analysis

In both groups of this study, hypertension and dyslipidemia is still the most dominant risk factor. High plasma glucose levels will lead to increased levels of reactive oxygen species (ROS) and the formation of Advanced Glycosilation End Product (AGE Product) on the vascular endothelium, causing endothelial damage. Endothelial damage will cause inflammation in blood vessels accompanied by the synthesis of nitric oxide barriers causing vasoconstriction (Hamm et al 2008).

Acetosal resistance occurs more frequently in women with a statistical results of 34.4% vs 17.3% (p = 0.001). Another study showed that women tend to develop higher resistance to acetosal than men (23.4% vs 7.8%; p = 0.01). This could be due to women who are estrogen producer which provide protection against atherosclerosis, besides women are also more prone to interference of the vasodilating response to acetylcholine. But in this study, female patients who develop resistance was found to be lower than male patients (3 patients vs 4 patients) (Gum et al 2001).

In this study, a group of CAD without Type 2 diabetes who develop acetosal resistance acetosal are patients who smoke. While in the CAD group with Type 2 diabetes patients who smoke do not develop acetosal resistance. This shows that smoking affects acetosal resistance. In acute conditions, smoking increases platelet thrombus formation in the arterial wall. Inhibition of platelet COX by acetosal can be insufficient in preventing acute conditions which increase platelet thrombus formation after smoking.
Increased platelet thrombus formation is due to increased aggregation response to thrombin. Increased acute platelet thrombus formation after smoking may be associated with increased levels of epinephrine resulting in increased platelet aggregation although given acetosal therapy (Maree et al 2005).

Therapy was given to both groups in accordance with the guidelines for CAD, including the provision of β-blockers, statins, ACEI (Gibbons et al 2003). In both groups, some patients with CAD accompanied given combination of antidiabetic drugs (OAD) with insulin, insulin function such as for inhibiting platelet aggregation which is protection against thrombus formation and release of vasoactive mediators and chemotactic mitogenic agents which contributes to the pathophysiology of thrombosis and atherosclerosis. Acetosal resistance occurs at 4.7% of OAD group, while 8.6% in the insulin group, there was no statistically significant difference in the OAD and insulin administration on the incidence acetosal resistance among groups of patients receiving OAD with the group of patients who received insulin (p = 0.359) (Ariturk et al 2012).

Acetosal resistance can also be caused by many things, including genetic variation and individuals, while studies that support the response of individual variation acetosal on Heredity and Performed type Intervention (HAPI) Heart study, the response measurement acetosal of the 745 patients, including 400 men and 345 women using the TAT (Platelet aggregation test) at a dose of 81 mg acetosal a day after patients take acetosal for 14 days. The results obtained, as many as 21% of patients develop resistance to acetosal, 30% acetosal resistance in women, while in men as much as 16% fewer barriers platelet aggregation in women than by men (49.9 ± 30.9 vs. 57.5 ± 42.5, p = 0.005) (Saad et al 2012).

In addition, resistance acetosal can also be due to genetic polymorphism. Genetic polymorphisms in conjunction with resistance acetosal mostly caused by several factors, or can also be caused by other hemostatic genetic variation (polymorphism such as blood coagulation and fibrinolytic factors). A series of single nucleotide polymorphisms (SNPs) in the genes of prostaglandin endoperoxide synthase 1 (PTGS1) includes A842G, C22T [R8W], G128A [Q41Q], C644A [G213G], and C714A [L237M] associated with the response to acetosal (Maree et al 2005).

At the level of platelets, acetosal translocation to the cytoplasm in Multidrug Resistance is influenced by the presence of protein-4 (MRP-4), an increase of MRP-4 will lower the intracellular availability of acetosal. This increase is individual and influenced by some diseases, one of which DM. Dipyridamole inhibits MRP-4, it explains why the effects will increase acetosal after administration of dipyridamole. MRP-4 are generally elevated in patients after revascularization using coronary artery bypass grafting which is also an increase in the production of TXA2 during therapy in these patients (Bultas 2013).

CONCLUSION
There was no different acetosal resistance in coronary artery disease with and without Type 2 Diabetes Mellitus patients from 20 patients which were divided into two groups of ten patients each, 10 patients Coronary Artery Diseases with Type 2 Diabetes Mellitus and 10 patients non-Type 2 Diabetes Mellitus.

REFERENCES
dependency in the initial phase of antiplatelet therapy with clopidogrel. J Thromb Haemost 8, 37-42