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Effect of aspirin resistance with dyslipidemia against VerifyNOW® measurement in Bethesda hospital Yogyakarta

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Original Article

ABSTRACT

Background: Aspirin is first line drug of choice to prevent ischemic stroke. However, some cases are found occuring of aspirin resistance.
Objective: This study was to examine the effect of dyslipidemia on the risk of antiplatelet resistance with VerifyNOW® at Bethesda Hospital Yogyakart
Method: This research was observational analysis using a nested case-control study design. The subjects were ischemic stroke patients who underwent tests of platelet function by VerifyNOW® (Accumetrics, San Diego, CA, USA). The Case group was ischemic stroke patients who has history of aspirin resistance. The control group was ischemic stroke patients who response on aspirin therapy. Both groups were analyzed and compared to the state of dyslipidemia.
Results: Bivariate analysis on the incidence of aspirin resistance indicate that dyslipidemia had OR = 0.979 (95% CI; 0.378 to 2.531), p = 0.572. Hypercholesterolemia had OR = 0,909 (CI 95%; 0,377-2,190) p = 0,500; hypertrigliceride had OR = 0,838 (CI 95%; 0,331-2,119) p = 0,409; abnormal HDL had OR = 1,468 (CI 95% 0,564-3,817) p = 0,238; abnormal LDL had OR = 0,937 (CI 95% 0,374-2,345) p = 0,500. Patient factors such as age >55 years (p = 0.168) and female gender (p = 0.226) showed a non-significant results.
Conclusion: Ischemic stroke patients at Bethesda Hospital Yogyakarta who had dyslipidemia were not evident to have a greater risk of aspirin resistance than ischemic stroke patients who did not undergo dyslipidemia.

Latar Belakang.
Aspirin merupakan obat pilihan pertama pada pencegahan sekunder stroke iskemik. Namun, pada beberapa kasus ditemukan resistensi aspirin.
Tujuan
Untuk mengkaji pengaruh dislipidemia terhadap risiko resistensi antiplatelet menggunakan alat VerifyNOW® (Accumetrics, San Diego, CA,USA) *di Rumah Sakit Bethesda Yogyakarta.*
Metode
Jenis penelitian ini adalah observasional analitik dengan menggunakan rancangan penelitian nested case control. *Subyeknya adalah pasien stroke iskemik yang menjalani tes fungsi platelet dengan alat VerifyNOW®.*

Kelompok kasus adalah pasien stroke iskemik yang mengalami resistensi aspirin. Kelompok kontrol adalah pasien stroke iskemik yang respon pada terapi aspirin. Kedua kelompok diteliti serta dibandingkan pada keadaan dislipidemia.

Hasil
Analisis bivariat faktor prediktor terhadap kejadian resistensi aspirin menunjukkan bahwa dislipidemia memiliki OR = 0,979 (CI 95%; 0,378-2,531), p=0,572. Hiperkolesterolemia mempunyai OR = 0,909 (CI 95%; 0,377-2,190) dan p=0,500; hipertrigliserida OR = 0,838 (CI 95%; 0,331-2,119) dan p=0,409; HDL abnormal OR = 1,468 (CI 95% 0,564-3,817) dan p=0,238; LDL abnormal OR = 0,937 (CI 95% 0,374-2,345) dan p=0,500. Faktor pasien yaitu umur > 55 tahun (p=0,168) dan jenis kelamin perempuan (p=0,226) menunjukkan hasil yang tidak bermakna.

Simpulan
Pasien stroke iskemik di Rumah sakit Bethesda Yogyakarta yang mengalami dislipidemia tidak terbukti mempunyai risiko lebih besar mengalami resistensi aspirin dibandingkan pasien stroke iskemik yang tidak mengalami dislipidemia.

INTRODUCTION

World Health Organization (WHO) states that stroke is the second leading cause of death in the world after ischemic heart disease.[1] In Indonesia, based on the data base Hospital, the incidence of stroke is 63.52 per 100,000 population in the age group over 65 years.[2]

According to the American Heart Association (AHA), incidence of stroke and/or transient ischemic attack (TIA) by whatever reason will increase the occurrence of subsequent stroke.[3] Secondary prevention of ischemic stroke/TIA can be implemented by the administration of antiplatelet drugs. A meta-analysis conducted by Antithrombotic Trialists' Colaboration showed that antiplatelet therapy decreases 25% occurrence of vascular diseases in serious patients having suffered from high risk of coronary heart disease and ischemic stroke.[4]

The use of antiplatelet therapy especially aspirin is still rarely practiced. In several cases the incidence of thromboembolic was found that in various patients during aspirin therapy in progress. This indicates that these patients do not response to aspirin and commonly called aspirin-resistant. Aspirin resistance is associated with increased risk of occurrence of ischemic stroke and coronary heart disease in patients.[5]

The comorbid factors in ischemic stroke patients may have an impact on aspirin resistance. Dyslipidemia is a frequently appeared comorbid in ischemic stroke patients. High levels of total cholesterol, triglycerides, and LDL (Lipid Density Lipoprotein) cause the appearance of plaques in blood vessels.[6]

Aspirin resistance is one of the causes of treatment failure. Moreover, in patients with ischemic stroke were strongly influenced by antiplatelet therapy. The low response to aspirin as antiplatelet is at risk of an increase in platelet aggregation and causes recurrent strokes.[7] Examination of response to aspirin therapy can be practiced, one of the approaches usage of VerifyNOW® (Accumetrics, San Diego, CA, USA).[5] This test is very useful to determine the recurrent stroke prevention therapy that is appropriate for ischemic stroke patients.

Prevention of ischemic stroke secondary to Bethesda Hospital in Yogyakarta according guideline is to use aspirin as antiplatelet.[8] Studies on aspects affecting the aspirin resistance is needed to prevent recurrent ischemic stroke. The purpose of this study was to assess the effect on the risk of dyslipidemia antiplatelet resistance using VerifyNOW® at Bethesda Hospital in Yogyakarta.

METHODS

This research was an analytic observational study design using nested case control study to assess the effect of dyslipidemia against the risk of antiplatelet resistance, which was measured using a VerifyNOW® at Bethesda Hospital in Yogyakarta. The used research material was cohort data where ischemic stroke patients were treated with aspirin and test of VerifyNOW® platelet function was conducted at Bethesda Hospital in Yogyakarta.

The study began after having obtained ethical clearance from the committee of ethical research at the Faculty of Medicine, University of Gadjah Mada and got permission from the authority of Bethesda Hospital in Yogyakarta. Data were taken to the subject of ischemic stroke patients treated with aspirin and conducted tests

of platelet function VerifyNOW® at Bethesda Hospital in Yogyakarta. Subjects were divided into group of study case and control. The case group consisted of subjects who are resistant to aspirin and the control group consisted of subjects who are responsive to aspirin.

Aspirin resistance was indicated by the value of aspirin reaction units (ARU) ≥550. Responsive to aspirin was indicated by the value ARU <550. Analysis of data was conducted using data processing software. Categorical variables were presented in the form of frequency and percentage, whereas numeric variables were presented in the form of mean and standard deviation (SD) in the table and narrative. Data were tested based on the characteristics of case and control groups. The T test was used for numerical data while for categorical data chi square was used. Bivariate analysis was used to test the hypothesis with the tested variables, namely the state of dyslipidemia on the incidence of aspirin resistance.

RESULTS

Subjects in this study were stroke patients with an average age of 63.37 ± 11.39 years. Among people 45 (40.9%) and 65 men (59.1%) were female and male subjects respectively. Most subjects received anticoagulant therapy. Patients with anticoagulant therapy as many as 14 (12.7%) and the 96 (87.3%) did not use anticoagulant therapy at the time of platelet function tests. Therapy with antiplatelet also varied, some are administered aspirin alone (68.2%) and some are received combination with other antiplatelet (31.8%).

Subject to the resistant group was mean age of 63.31 ± 12.71 years and subject to the responsive group was 63.38 ± 10.95 years. This indicated that the proportions were not significantly different between resistant and responsive group (p> 0.05).

Characteristics of the subjects by gender data showed aspirin-resistant group consisted of 14 (46.7%) women and 16 (53.3%) men. Responsive to aspirin group consisted of 31 (38.8%) women and 49 (61.2%) men. The proportion of incidence of aspirin resistance was greater in the group of women than men, but this did not show a statistically significant difference (p> 0.05).

Subjects who received anticoagulant therapy was also compared between groups of resistant and responsive. It was executed to see the characteristics of each group. The same approach was done on the subject of antiplatelet therapy with aspirin alone and a combination of aspirin with other antiplatelet. The proportion of each different group but did not demonstrate significant difference (p> 0.05).

Results of laboratory tests were also considered for basic assessment of subject characteristics. Laboratory tests were performed when the subject experienced ischemic incidence. Data from laboratory test was represented in the form of quantitative data. This data are shown the mean and standard deviation (SD). Later, the data were tested using the Mann-Whitney test. Data from laboratory tests are presented in Table 1.

Table 1 Characteristics of the basic subjects in the resistant and responsive group

Characteristic	Resistant Aspirin	Responsive Aspirin	p
	n=30(%)	n=80(%)	
Age	63,31±12,71	63,38±10,95	0,484
Female gender	14(46,7)	31 (38,8)	0,226
BSA (mg/dL)	161,13±81,53	157,88±96,05	0,483
Cholesterol (mg/dL)	195,81±63,27	195,54±47,22	0,491
Triglycerides (mg/dL)	124,58±77,91	156,97±119,05	0,097
HDL (mg/dL)	59,25±50,40	45,32±21,53	0,345
LDL (mg/dL)	117,8±53,63	127,12±44,17	0,192

*Significant if p<0,05

BSA: Blood Sugar at the time that ; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein.

In this study the relationship of independent variables (dyslipidemia) and the dependent variable (response to aspirin) were analyzed by chi square at significant level α = 0.05 while to see how big the occurrence of outcomes that may occur in the population can be observed from the OR and CI value at 95% . The relationship between dyslipidemia in ischemic stroke patients with incidence of aspirin resistance is shown in Table 2.

Table 2 Correlation between dyslipidemia and aspirin resistance

Status	Resistant n=30(%)	Responsive n=80(%)	OR	CI	p
Dyslipidemia	22(73,3)	59(73,8)	0,979	0,378-2,531	0,155
Hyper cholesterol	12(42,9)	33(45,2)	0,909	0,377-2,190	0,500
Hyper triglyceride	9(32,1)	26(36,1)	0,838	0,331-2,119	0,409
HDL abnormal	13(56,5)	31(47,0)	1,468	0,564-3,817	0,238
LDL abnormal	110(37,0)	27(38,6)	0,937	0,374-2,345	0,500

*significant if p<0,05

Table 2 shows that the proportion of dyslipidemia in resistant group was 73.3% and responsive group73.8%. Its OR value was 0.979 (95% CI, 0.378 to 2.531). It is not statistically significant (p = 0.155). Based on bivariate analysis, it can be seen that dyslipidemia is not statistically proven risk factors incidence of aspirin resistance. Table 2 also shows the proportion of hypercholesterolemia, hypertriglyceride, abnormal HDL, and LDL abnormal in groups of resistant and responsive. In each of these group did not show statistically significant values (p> 0.05). Under these conditions, the state of hypercholesterolemia, hypertriglyceride, abnormal HDL and LDL abnormal does not prove to be a risk factor for the incidence of aspirin resistance.

DISCUSSION

The status of Dyslipidemia according to the operational definition of research is the existence of abnormal levels of at least one among the levels of total cholesterol, triglycerides, HDL and LDL. Dyslipidemia state predictor factors included in the incidence of aspirin resistance. High levels of cholesterol, triglycerides, and LDL can support the occurrence of plaque. The plaque can potentially cause a blockage in the blood vessels. In addition, the attachment of plaque on the walls of the blood vessels will increase the occurrence of platelet aggregation.[6] It is based on hyperlipidemic condition that favors the occurrence of endothelial dysfunction in the blood vessels, causing an increase in platelet reactivity and the occurrence of thrombosis.[9]

Platelets in hyperlipidemic patients are very active to form a thrombus. This will exacerbate the platelet response to aspirin therapy, subsequently which induces the occurrence of aspirin resistance.[10] Research conducted by Friend et al, it was mentioned that aspirin resistant patients have average levels of LDL and higher amount of total cholesterol than responsive patients.[11] However, it is possible to the emergence of aspirin resistance due to other factors.

Ischemic stroke in a population of patients at Bethesda Hospital in Yogyakarta, the status of dyslipidemia does not have effect. This is because of dyslipidemia is not the only factor of the incidence of platelets resistance, possibly there are some other factors that have stronger influence on the incidence of aspirin resistance in comparison with dyslipidemia.

However, there is weakness of this study. Some of the factors such as polymorphism, accelerated platelet regeneration, obesity, and smoking were not studied, which could affect the study results. Further study on risk factors for aspirin resistance is to determine the incidence of recurrent strokes so that the therapy can be avoided.

CONCLUSIONS

Ischemic stroke patients who had dyslipidemia at Bethesda Hospital in Yogyakarta were not proven to have a greater risk of aspirin resistance compared to patients with ischemic stroke who had not been experienced with dyslipidemia.

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