ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 13, Issue 12, 2020

Online - 2455-3891
Print - 0974-2441

Research Article

THE VASCULAR RISK FACTORS ASSOCIATED WITH ANTIPLATELET RESISTANCE IN ISCHEMIC STROKE PATIENTS

RIZALDY TASLIM PINZON, BULAN MARCHELLIA WIJAYA

Department of Neurology Bethesda Hospital, Faculty of Medicine Duta Wacana Christian University, Yogyakarta, Indonesia.
Email: drpinzon17@gmail.com

Received: 02 June 2020, Revised and Accepted: 20 October 2020

ABSTRACT

Objectives: This research is to measure the prevalence rate of antiplatelet resistance in ischemic stroke patients and measure the vascular risk factors associated with antiplatelet resistance in patients with ischemic stroke.

Methods and Subjects: This was a cross-sectional study with the number of respondents in this study amounted to 155 patients who all had ischemic stroke disease at Bethesda Hospital in Yogyakarta Indonesia used stroke registry to complete the data of the risk factors. VerifyNow method is used to measure the responsiveness of antiplatelet therapy.

Results: Among the 155 patients with ischemic stroke, 45 were women (29%), 110 were men (71%), and the elderly (age more than 60 years old) in 81 patients. In total 155 patients with ischemic stroke, 106 of them have hypertensive, with diabetes are 19 patients, dyslipidemia is 90 patients, and ischemic heart disease in 13 patients. The prevalence of antiplatelet resistance in risk factors, for age more than 60 years, is 21 patients (25%, RR=1.06, *p=0.96), in diabetes is 7 patients (36%, RR=1.17, **p=0.74), dyslipidemia is 19 patients (21%, RR=0.68, ***p=0.24), and ischemic heart disease is four patients (30%). Among 127 patients, 22% (28 patients) had aspirin resistance, while from 42 patients, 26.2% (11 patients) were resistant to clopidogrel.

Conclusion: Antiplatelet resistance is common in ischemic stroke patients. One of five patients treated with antiplatelet showed non-responsiveness. Vascular risk factors do not increase the risk of antiplatelet resistance in ischemic stroke patients.

Keywords: Antiplatelet, Resistance, Ischemic stroke, Hypertension, Dyslipidemia, Diabetes.

 DOI: http://dx.doi.org/10.22159/ajpcr.2020.v13i12.38591

INTRODUCTION

Stroke is defined as an acute focal or global neurological deficit lasting longer than 24 h or leading to death. Stroke is a major cause of mortality and morbidity globally. Stroke is classified in hemorrhagic or ischemic depending on the pathological process responsible. About 87% of all strokes are ischemic strokes [1]. Ischemic stroke is an acute brain infarction or injury resulting from reduced blood supply in areas of the brain [2]. According to the Global Burden of Disease Study in 2017, stoke was found to be the 2nd leading cause of death worldwide having mortality rates of 11.02% per 100,000 population. Ischemic stroke showed mortality rates of 16% per 100,000 population worldwide [3].

A set of etiologies and risk factors influence the development of ischemic stroke. The most common risk in ischemic stroke is age, hypertension, diabetes, and dyslipidemia [4]. Those risk factors can trigger ischemic stroke incidents. Several sociodemographic characteristics are considered the risk factors of chronic kidney disease which includes sex, in which the prevalence is higher among men compared to women (74% vs. 26%), age >60 years old are 30%. Risk factors like hypertension take 63% cause ischemic stroke, 21% in diabetes mellitus, and 7% in dyslipidemia [5].

Start treatment in patients with ischemic stroke has to be as quickly as possible [6]. Antiplatelet therapy (combination aspirin and clopidogrel) as soon as possible after the even within 24 h can lower the risk for recurrent stroke and functional disability with dual therapy [6-8]. The combination of clopidogrel and aspirin as an antiplatelet theraphy is more often used in almost all ischemic stroke patients than other drugs [9]. However, the combination of antiplatelet therapy will not be essential when there is resistance to the drug administered. Resistance antiplatelet in patients with ischemic stroke impacts on therapeutic costs and therapeutic response [10]. The previous review showed that the prevalence of antiplatelet resistance ranges from 22 to 44% [11]. This study about antiplatelet resistance risk factor in ischemic stroke in Indonesia is very limited. This study aimed to measure the role of vascular risk factors in increasing the risk of antiplatelet resistance. Thus, if the hypertension has a role increasing antiplatelet resistance in sichemic stroke patients, it can be prevent.

METHODS

This study was conducted using a cross-sectional design. The subjects included patients with ischemic stroke at Bethesda, Yogyakarta. The study was conducted in 2019 from stroke registry data. The inclusion criteria include patients aged over 18 years old who were clinically and radiological (with computed tomography or magnetic resonance imaging) diagnosed with ischemic stroke at Bethesda either first or recurrent events. The data were obtained retrospectively through patients' medical records that had gotten ethical approval previously.

The sample size was calculated using a sample size formula for a cross-sectional study with 95% confidence and a 5% error where it resulted in a minimum sample size of 97 subjects. The total of this study used 155 patients with ischemic stroke disease. Secondary data were collected from patients who met inclusion by recording their medical records. The measurement of antiplatelet resistance using standardizes VerifyNow method.

RESULTS

This study used total data of 155 patients with ischemic stroke disease. Among all, there were 110 (71%) male and 45 (29%) female patients. A total of 155 patients were measure with standardized criteria such as age, sex, hypertension, diabetes, and dyslipidemia. Antiplatelet

resistance in this study performed in aspirin and clopidogrel test using standardized VerifyNow method. Aspirin resistance test is performed in 127 patients and clopidogrel test 42 patients. The result aspirin resistance presents in 22% and clopidogrel resistance presents in 26.2%.

Of a total of 155 patients, 81 (52%) of them were elderly (age >60 years old), while the remaining 74 patients aged below 60 years old. Among 81 elderly patients, 21 were resistant (25%). Among those 155 patients, their history of other illnesses that were associated with increased resistance of antiplatelet was also recorded. Medical records patients showed the other diseases from patients (hypertension, diabetes, and dyslipidemia). It was noted with a total of 155 patients that 19 (12%) of them were diabetes, with 7 (36%) of patients with diabetes showed resistance with antiplatelet therapy. Dyslipidemia found in 90 (58%) patients, with 19 (21%) of them showed resistance with antiplatelet therapy. Hypertension is known to increase the risk factors of antiplatelet resistance in patients with ischemic stroke. The result showed among 155 patients with ischemic stroke that 106 (68%) of them were patient hypertensive. The test resistance in hypertension patients is 39 (26.4%) patients. The results are presented in Table 1.

DISCUSSION

A total of 155 patients with ischemic stroke were included in the analyses and were characterized based on their age, sex, and history of illnesses (hypertension, diabetes, and dyslipidemia). In general, the study participants consisted of more male than female patients who were 110 (71%) and 45 (29%) patients, respectively. It was found higher in males than females this might be due to the increased stress levels in males and protective estrogen effects in females [7]. Most patients with age more than 60 years old were 81 patients (52%). This result has a corelation to the study by Spurthi *et al*. Regarding the risk factors, hypertension had the highest percentage of 68%, which was followed by dyslipidemia in 58%, and diabetes mellitus in 19%. Hypertension had a high-risk factor for ischemic stroke that relates to atherosclerotic disease that can lead to ischemic stroke. It is similar to dyslipidemia or hyperlipidemia who increases the risk factor to atherosclerosis [12]. In patients with diabetes mellitus, macroangiopathy accelerates forming an atherosclerotic in a coronary artery, carotid artery, cerebral artery, and peripheral artery [13].

Test resistance in this study used to VerifyNow method. This method used a venous blood sample with a tube containing 3.2% sodium citrate. The VerifyNow system mimics light transmittance aggregometry because it is a turbidimetric based optical detection system that measures platelet-induced aggregation. In aspirin resistance, the VerifyNow system contains fibrinogen-coated microparticles and is designed to measure platelet function based on the ability of activated platelets to bind fibrinogen. The VerifyNow P2y12 assay measures clopidogrel resistance because clopidogrel specifically inhibits the P2y12 receptor [14]. A total of 127 patients tested for aspirin resistance, 22% of whom were aspirin resistance with 20 are males, 8 are female (Fig. 1). Clopidogrel resistance test is performed in 42 patients with a result of resistance in male six and female five patients with a percentage of 26.2% (Fig. 2).

The high result of resistance antiplatelet (aspirin and clopidogrel) can increase the risk of severe stroke and large infarct volume [15]. In other preception, aspirin resistance is more prone to increased clinical severity stroke during the acute phase, early neurological deterioration, and recurrent ischemic lesions during the follow-up period [16]. Clopidogrel resistance is associated with early neurological deterioration and increased recurrence of ischemic events [17]. Resistance antiplatelet in patients with ischemic stroke has been an interest in many studies due to the effect of efficiency of therapy. Jain K, et al study mention that clopidogrel has better stability than other antiplatelet. Clopidogrel was stable in human plasma at least in 24 h, this is more than others antiplatelet [18].

Another study about resistance antiplatelet, in Sadeghi *et al.* resistance aspirin in coronary artery disease (CAD), was 75.3% [10]. Jung *et al.* study showed 14% of patients with CAD and ischemic cerebrovascular disease was resistant antiplatelet [14]. Yi *et al*. had 426 patients with acute minor ischemic stroke, was found 24.4% aspirin resistance, and 35.9% resistance clopidogrel [19]. Samir *et al*. found 64.6% patients with inadequate response to clopidogrel (15.4% resistance and 49.2% semi-responders) and 4.6% patients with inadequate response to aspirin (3.1% resistance and 1.5% semi-responder) [20]. In this study, the result is quite similar with other study before. According to a higher

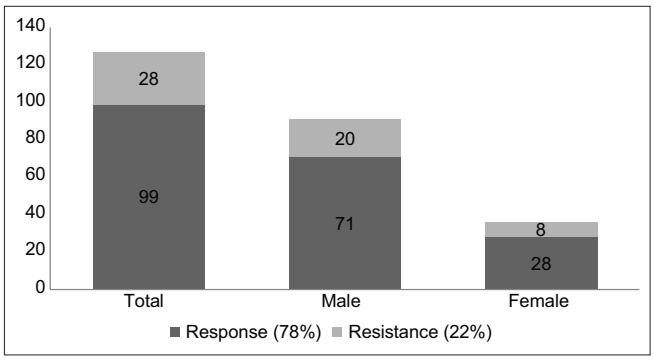

Fig. 1: Aspirin resistance

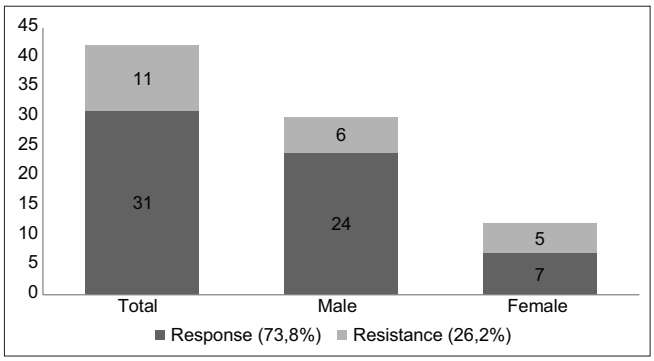

Fig. 2: Clopidogrel resistance

Table 1: Risk factors of antiplatelet resistance

Variables	Criteria	Antiplatelet		p-value	RR (95% CI)	Total
		Resistance	Response			Freq (n=155)
Older age	≥60 years	21	60	0.96	1.06 (0.61–1.83)	81
	<60 years	18	56			64
Hypertension	Yes	28	78	0.74	1.17 (0.64–2.61)	106
	No	11	38			49
Diabetes mellitus	Yes	7	12	0.32	1.56 (0.80–3.303)	19
	No	32	104			136
Dyslipidemia	Yes	19	71	0.24	0.68 (0.4–17.02)	90
	No	20	45			65

result of antiplatelet, resistance had the probable reason for a response aspirin that may be due to polymorphism in cyclooxygenase (COX) 1 and 2 genes and other metabolites of arachidonic acid [21].

The higher result of antiplatelet resistance gives interest in many studies. Aspirin resistance in many studies showed the high result, inpatient with ischemic stroke aspirin resistance is associated significantly with the degree of severity of acute stroke in aspirin resistance group with a median of National Institutes of Health Stroke Scale (NIHSS) score of 11 compared to responsive aspirin group, which had median NIHSS score of 4 (*p<0.001) [16]. Aspirin is an effective antiplatelet agent, by irreversibly inhibiting platelet COX-1 enzyme, thus preventing the production of thromboxane A2 (TxA2) [22]. Clopidogrel results in the upregulation of $P2Y_{12}$ – independent pathways with thrombin, TxA2, collagen, and $P2Y_1$ receptor-mediated platelet aggregation [23]. The key for resistance antiplatelet is several pharmacokinetic and pharmacodynamic factors, including reduced bioavailability genetic polymorphisms, activation of alternate platelet-stimulation pathways, accelerated platelet turnover, and factors associated with antiplatelet-resistant state [11].

The result prevalence resistance in other risk factors such as hypertension was 26.4%. The patient with diabetes mellitus was 36% resistance to antiplatelet therapy. Resistance in a patient with dyslipidemia was 21%. As the result, the presentation of various diseases was high; however, there is no significantly due to the p-value (>0.05). However, hypertension is known in many studies that can increase the risk of antiplatelet resistance. The mechanism of antiplatelet such as aspirin and clopidogrel activate platelets through COX-1 or P2Y12 independent pathways. However, the COX-2 enzyme is inducible under certain conditions, such as inflammation and atherosclerosis, and can continue to provide TxA2 to platelets. Patients with hypertension also received more β- blockers and angiotensin-converting enzyme inhibitor medications and calcium channel blockers that investigated can affect antiplatelet activity [24]. In other word, that pathway might affect the antiplatelet drug and cause the resistance. The patient diabetes mellitus in other studies also can increase resistance antiplatelet. In another study, insulin-treated patients with type 2 diabetes have greater adenosine diphosphate-induced platelet aggregation compared with non-insulin treated diabetic patients who take antiplatelet treatment [25]. Other studies explain that another mechanism of unresponsive antiplatelet treatment is increased availability of circulating platelet that is not exposed to antiplatelet medication in the bloodstream [23].

This study has large enough subjects for the analysis. A computerized stroke registry is used to take data from patients. The method in this study used the standardized statistical method. However, this study has a limitation from the cross-sectional study. The risk factors in patients are not all measured. In this study, the patients had no follow-up period for clinical outcomes. Thus, the implication for practice must consider the resistance as one of the causes of the recurrence of ischemic events. This study suggests that modifiable risk factors that can affect antiplatelet resistance need treatment. There is an option for patients with resistance antiplatelet such as add doses the treatment, add cilostazol, or add omega-3. The implications for research for further studies with more subjects and more risk factors should be studied.

CONCLUSION

From the analysis, antiplatelet resistance is common in ischemic stroke patients. One of five patients treated with antiplatelet showed non-responsiveness. Vascular risk factors do not increase the risk of antiplatelet resistance in ischemic stroke patients.

AUTHORS' CONTRIBUTIONS

This work was compiled in collaboration with all authors.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHORS FUNDING

Nil.

REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Raja D, *et al*. Heart disease and stroke statistics-2017 update: A report from the American heart association. Am Heart Assoc 2017;135:229-445.
2. Power WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al*. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American stroke association. Stroke 2018;49:46-110.
3. Centers for Disease Control and Prevention. Global Burden Compare: Global Stroke Disease. Atlanta, Georgia, United States: Centers for Disease Control and Prevention; 2017. Available from: https://www.vizhub.healthdata.org/gbd-compare. [Last assessed 2019 Oct 24].
4. Putaala J, Yesilot N, Waje-Andreassen U, Janne P, Sofia V, Katiuscia N, *et al*. Demographic and geographic vascular risk factor differences in European young adults with ischemic stroke: The 15 cities young stroke study. Stroke 2012;43:2624-30.
5. Hossain AM, Ahmed NU, Rahman M, Islam MR, Sadhya G, Faridpur KF. Analysis of sociodemographic and clinical factors associated with hospitalized stroke patients of Bangladesh. Faridpur Med Coll J 2011;6:19-23.
6. Kameshwar P, Reed S, Qiukui H, Gordon G, Martin O, Lyubov L. Dual antiplatelet therapy with aspirin and clopidogrel for acute high risk transient ischaemic attack and minor ischaemic stroke: A clinical practice guideline. BMJ 2018;363:k5130.
7. Spurthi T, Gowthami B, Khyathi D, Vinod G. Risk elements and drug utilization in stroke patient. Int J Pharm Pharm Sci 2016;10:290-2.
8. Venkateswaramurthy N, Krishnaveni K, Freeda RM, Kumar RS. Assessment of potential drug-drug interaction in stroke patients. Int J Pharm Pharm Sci 2016;8:221-4.
9. Wagle L, Thomas A, Shrestha S. Drug utilisation study of stroke and other patients admitted to general ward of neurology unit at quaternary care private hospital. Int J Curr Pharm Res 2017;9:23.
10. Sadeghi M, Emami A, Ziyaei N, Majid Y, Allahyar G, Azam S. Aspirin resistance and ischemic heart disease on Iranian experience. Adv Biomed Res 2012;1:33.
11. Topcuoglu MA, Arsava EM, Hakan A. Antiplatelet resistance in stroke. Expert Rev Neurother 2011;11:251-63.
12. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. Circ Res2017;120:472-95.
13. Brain Edema: Ismail Setyopranoto. Patients with Acute Ischemic Stroke. Vol. 8. Indonesia: Gadjah Mada University Faculty of Medicine Publishing; 2012.
14. Jung KH, Kyung LH, Kyunja H, Kyung KH. Prevalence and risk factors for aspirin and clopidogrel resistance in patients with coronary artery disease or ischemic cerebrovascular disease. Ann Clin Lab Sci 2009;39:289-94.
15. Oh MS, Yu KH, Lee JH, Jung S, Kim C, Jang Min UK. Aspirin resistance is associated with increased stroke severity and infarct volume. Neurology 2016;86:1808-17.
16. Zheng AS, Churilov L, Colley RE, Christine G, Stephen MD, Bernard Y. Association of aspirin resistance with increased stroke severity and infarct size. JAMA Neurol 2013;70:208-13.
17. Yi X, Lin J, Zhou Q, Wu L, Cheng W, Wang C. Clopidogrel resistance increases the rate of recurrent stroke and other vascular events in Chinese population. J Stroke Cerebrovasc Dis 2016;25:1222-8.
18. Jain K, Deore D. Bioanalytical method development and validation for estimation of clopidogrel bisulfate in human plasma by RP-HPLC. Int J Appl Pharm 2016;8:28-33.
19. Yi X, Wang C, Liu P, Fu C, Lin J, Chen Y. Antiplatelet drug resistance is associated with early neurological deterioration in acute minor ischemic stroke in the Chinese population. J Neurol 2016;263:1612-9.
20. Samir P, Agrawal CS, Vandang A, Amrita S, Manorama B. Aspirin and clopidogrel resistance in indian patients with ischemic stroke and its associations with gene polymorphisms: A pilot study. Ann Indian Acad Neurol 2019;22:147-52.
21. Kasoktasis G, Pipinos II, Lynch TG. Current evidence and clinical implication of aspirin resistance. J Vasc Surg 2009;50:1500-10.
22. Beste O, Azra MT, Tomris O, Oguz C. Aspirin resistance in hypertensive patients. J Clin Hypertens 2010;12:714-20.
23. Hedegaard SS, Hvas AM, Grove EL, Jens R, Bianca R, Giovanni D, *et al*. Optical platelet aggregation versus thromboxane metabolites in healthy individuals and patients with stable coronary artery

disease after low-dose aspirin administration. Thromb Res 2009;124:96-100.

24. Ibrahim AF, Fatma CN, Mehmet E, Nilgun T, Ahmet AF, Ozgur S, *et al.* Hypertension as a risk factor for aspirin and clopidogrel resistance in patients with stable coronary artery disease. Clin Appl Thromb Hemost 2014;20:749-54.
25. Angiolillo DJ, Bernardo E, Ramirez C, Costa MA, Sabate M, Jimenez QP, *et al.* Insulin therapy is associated with platelet dysfunction in patients with Type 2 diabetes mellitus on dual oral antiplatelet treatment. J Am Coll Cardiol 2006;48:298-304.