

Research Article

The Relations of Aspirin Resistance and Hypertension in Patients with Recurrent Ischemic Stroke

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ABSTRACT

Aspirin is an antiplatelet agent that is often used in patients with ischemic stroke. However, patients known to develop resistance to aspirin are about 15 -25%. Resistance occurs due to hypertension allegedly suffered by patients which causes an increase in blood viscosity and platelet aggregation, and thus it reduces the effectiveness of aspirin antiplatelet. In addition to hypertension, antihypertensive drugs such as Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARBs) can also lead to aspirin resistance through increased platelet aggregation. In the study, we investigated the effect of hypertension and the use of antihypertensive against aspirin resistance in patients with recurrent ischemic stroke. The study was performed using a descriptive method with a nested case-control study design. The study compared groups of patients with recurrent ischemic stroke who were aspirin resistance and who were non resistance based on the results of VerifyNow Aspirin System in the form of the value of aspirin reaction units (ARU). Patients were classified into groups aspirin resistant subjects if the ARU value was ≥ 550 and were grouped into groups of control if the ARU value was < 550 . Then a search through medical records and registers of each stroke patient was done. The results were then analyzed by using bivariate and multivariate analyzes. A total of 86 patients with recurrent ischemic stroke had *verifynow test checkup*. Seventy eight patients met the inclusion criteria and 20.5% of them were patients with aspirin resistance. Results of bivariate analysis showed hypertension and anti-hypertensive use in patients had no effect on aspirin resistance. Although ACEI group did not significantly affect the incidence of aspirin resistance recurrent ischemic stroke patients, but the use of ACEI more at risk of aspirin resistance than recurrent ischemic stroke patients who did not use aspirin. In conclusion, Hypertension and anti-hypertensive do not have any effect on the incidence of aspirin resistance in patients with recurrent ischemic stroke.

Key Words: Hypertension, anti-hypertensive, recurrent ischemic stroke, aspirin resistance, VerifyNow Aspirin System

INTRODUCTION

Stroke is a cerebrovascular disease that occurs suddenly and causes neurological damage. In the United States, Stroke becomes the fourth killer disease and it was reported that 800,000 people suffered a stroke each year and approximately 185,000 patients a recurrent stroke patients. Recurrent stroke risk of death is higher because of the disability of the brain that has been injured by the first stroke (Silva *et al.*, 2012). Ischemic stroke is the most type of stroke that people suffered. There was 88% with recurrent ischemic stroke incidence rate occurred in a high rate (Mohan *et al.*, 2009).

Aspirin is an antiplatelet agent that is most widely used in patients with ischemic stroke. Aspirin has a good effectiveness in the singular or in combination (Sacco *et al.*, 2006). Although huge benefit, 15-25% of patients reported experiencing resistance to aspirin (Alberts, 2010).

Hypertension is a factor that can lead to aspirin resistance in patients with recurrent ischemic stroke because it causes an increase in shear stress and platelet activation. Both erythrocyte interaction and platelet are known to affect antiplatelet effects of aspirin. A study (Macchi *et al.*, 2004) showed that hypertension significantly affect resistance to aspirin ($P = 0.03$). Hypertension ($p < 0.001$; OR = 2.460; CI = 1.059 to 2.875) affects 56.6% of patients who experience recurrent ischemic stroke. From research conducted in 450 ischemic stroke patients who develop resistance to aspirin, it was found that as much as 56.6% of ischemic stroke patients had a history of hypertension. Hypertension has a significant ($p < 0.001$; OR = 2.460; CI = 1.059 to 2.875) effect on aspirin-resistant cases that occur (Sharma *et al.*, 2013).

Antihypertensive drugs are widely used in patients with recurrent ischemic stroke with hypertension. This disease has an influence on the incidence of aspirin resistance that

Table 1: The predictors factors of mortality outcome at hospitals for ischemic stroke patients with atrial fibrillation.

Variables	Die (n=68)	Survive (n=72)	OR	95% CI	p
Age					
≥65 years old	39 (57)	44 (61)	0,8	0,4-1,6	0,651
<65 years old	29 (43)	28 (39)			
Gender					
Male	36 (53)	43 (60)	0,7	0,3-1,4	0,419
Female	32 (47)	29 (40)			
Smoking	20 (29)	16 (22)	1,4	0,6-3,1	0,331
Not Smoking	48 (71)	56 (78)			
Take aspirin	15 (22)	27 (38)	0,4	0,2-0,9	0,046
Not Taking aspirin	53 (78)	45 (62)			
Take Clopidogrel	11 (16)	19 (26)	0,5	0,2-1,2	0,141
Not Taking Clopidogrel	57 (84)	53 (74)			
Degree of Awareness					
≤ 7 (low)	19 (28)	5 (7)	5,1	1,8-14,8	0,001
>7 (high)	49 (72)	67 (93)			
Anticoagulation Control (TTR)					
<60% (poor)					
≥60% (good)	56 (82)	50 (69)	2,05	0,9-4,5	0,075
	12 (18)	22 (31)			
CHADS2 Scores					
6	1 (1,5)	2 (3)	0,9	0,06-12,5	0,938
5	10 (15)	7 (10)	2,5	1,5-11,05	0,200
4	26 (38)	29 (40)	1,6	0,4-5,4	0,438
3	26 (38)	25 (35)	1,8	0,5-6,3	0,311
2	5 (7,5)	9 (12)			

Table 2: The predictor factors of the mortality outcome at hospitals for the ischemic stroke patients with atrial fibrillation according to concomitant diseases.

Variable	Died (n=68)	Live (n=72)	OR	95% CI	p
Dislipidemia	10 (15)	13 (18)	0,7	0,3-1,9	0,593
Not Dislipidemia	58 (85)	59 (82)			
Coronary Heart Disease	9 (13)	15 (21)	0,5	0,2-1,4	0,233
Not Coronary Heart Disease	59 (87)	57 (79)			
DM	30 (44)	19 (26)	2,2	1,08-4,4	0,028
Not DM	38 (56)	53 (74)			
Hypertension	58 (85)	60 (83)	1,1	0,4-2,8	0,750
Normotensive	10 (15)	12 (17)			
CHF	17 (25)	27 (38)	0,5	0,2-1,1	0,111
Not CHF	51 (75)	45 (63)			
Sepsis	28 (41)	6 (8)	7,7	2,9-20,2	0,000
Not Sepsis	40 (59)	66 (92)			

occurs. ACEI (angiotensin converting enzyme inhibitor) and ARB (angiotensin receptor blocker) is a widely used class of antihypertensive significant and shows the effect on the incidence of aspirin resistance in patients with stroke ($p = 0.02$). While the use of CCB (calcium channel blocker) showed no significant effect on aspirin resistance occurred ($p = 0.52$) (Seok *et al.*, 2008).

Aspirin resistance in patients with recurrent ischemic stroke can be determined through testing platelet function by using a light source to detect the amount of platelet aggregation using VerifyNow Aspirin System (Saraf *et al.*, 2009). Patients were grouped into aspirin resistance when results ARU (aspirin reaction units) ≥ 550 (Kim *et al.*,

2009). In Indonesia, the cause of aspirin resistance that occurs in patients with recurrent ischemic stroke is not known certainly the cause of aspirin resistance that occurs in patients with recurrent ischemic stroke. Based on the above result, we investigated the relationship of aspirin resistance and hypertension in patients with recurrent ischemic stroke.

METHODS

This research is an analytical study using *nested case control study* design. The study compared the case of recurrent ischemic stroke patients that aspirin resistance with aspirin non-resistance. Research subjects were

Table 3: The multivariate analysis of mortality predictor at hospitals for ischemic stroke patients with atrial fibrillation

Variable	OR	95% CI	p
Sepsis	6,721	2,3-19,1	0,000
Coronary Heart Disease	0,754	0,2-2,2	0,611
Diabetes melitus	1,632	0,6-3,9	0,273
Heart Failure	0,527	0,2-1,2	0,159
Take aspirin	0,374	0,1-0,9	0,032
Take Clopidogrel	0,436	0,1-1,2	0,120
Degree of Awareness	3,371	0,9-11,6	0,054
Anticoagulation Control	1,651	0,6-4,3	0,316
CHADS2 5 Scores	2,571	0,5-11,0	0,204

recurrent ischemic stroke patients in a hospital in Yogyakarta Indonesia who do *VerifyNow* test of 1 February 2012 until 31 March 2013 that met the inclusion and exclusion criteria. Inclusion criteria included patients with recurrent ischemic stroke, during aspirin treatment, and above 18 years of age. Exclusion criteria included cancer patient, patient with a combination of several antiplatelet drugs, incomplete medical record. The study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Gadjah Mada Indonesia (Ref :KE/FK/268/EC March 22, 2013).

Based on *VerifyNow* test, the value of aspirin resistance unit (ARU) ≥ 550 showed the presence of aspirin resistance in patients with recurrent ischemic stroke. Aspirin resistant patient group were compared with non-resistant patients aspirin by searching medical records and stroke registers for the history of disease, the treatment and the results of laboratory examination of patients. The data was then analyzed statistically. Categorical data analysis was done using chi square and logistic regression tests. Whereas, numeric data was analyzed with Mann Whitney and linier regression tests. Subsequently, relationship between aspirin resistance and hypertension in patients with recurrent ischemic stroke was conducted using a bivariate analysis. The analysis was then continued with a multivariate analysis with the logistic regression method.

RESULT AND DISCUSSION

Development of research in clinical pharmacy is very important for pharmacists to play a prominent role in generating the new knowledge used to guide patient pharmacotherapy (Parker et al., 2013). In Indonesia, research in clinical pharmacy become interesting in the last decade (Indrianto et al., 2012; Rumi et al., 2014; Rahmadina et al., 2015; Purnami et al., 2015; Vilaplana et al., 2012; Rahmawati et al., 2008; Suprapti et al., 2014). This study involved 64 patients who met the inclusion criteria. They were then grouped into the control group that was the non-aspirin resistance group and the subject group that was the aspirin resistance group. Based on the result, about 18.8% of patients experiencing a recurrent ischemic stroke had aspirin resistance. The clinical characteristics was then traced from the obtained data. The result showed that ARB had an impact on aspirin resistance that occurs in patients with recurrent ischemic stroke as it is shown in

Table 1. The ARB increased synthesis of prostglandin as opposed to aspirin. Aspirin inhibits prostaglandin synthesis. Decreasing of prostaglandins will affect the enzyme inhibition of COX-1 and COX-2. Aspirin inhibits not only irreversibly prostaglandin synthesis but also platelet COX TXA2 through acetylation ultimately platelet aggregation.

ARBs works by blocking the AT1 receptor activating phospholipase A2 and increasing COX-2. AT1 is located in the muscle cells and mediate the production of PGE2, TXA2 and cell proliferation. The function of AT2 receptor is not yet clear, but suspected AT2 receptor is associated with increased COX-2. The highest use of ARBs was often reported if compared with other antihypertensives. Average age of patients is estimated to affect prescribing antihypertensive. Besides medical history and medications used by patients with recurrent ischemic stroke, the effect of the results of laboratory tests are shown in Table 2.

LDL is an influential factor in the incidence of aspirin resistance because LDL causes an increase in platelet formation. LDL levels in patients with aspirin resistance was lower than this in non-resistant patients. Increased regulation of the expression of COX-2 may be one of the causes of resistance in patients with normal LDL levels (Friend et al., 2003).

A study conducted by Seok et al. (2008) showed that low LDL levels ($p = 0.02$) significantly affect the incidence of aspirin resistance. This study used *VerifyNow* aspirin system and thromboxane B2 to determine resistance of aspirin. From both of the tests, it was found that the average result of LDL levels which influence resistance by the *VerifyNow* aspirin and thromboxane B2 were 78.8 ± 25.5 and 91.0 ± 23.7 , respectively. On the other hand, the value of the *VerifyNow* test and thromboxane in the non aspirin resistance were 99.5 ± 26.8 and 97.5 ± 27.5 , respectively. This results indicate that low LDL levels affect the incidence of aspirin resistance in patients with recurrent ischemic stroke.

Low HDL level was predicted to inhibit LDL oxidation and platelet activation (Coma-Canella et al., 2005). Besides HDL, high triglycerides also correlated to low levels of LDL in patients. Platelets which are formed from hyperlipidemic patients have a high thrombogenic. Other factors such as high regulation in the expression of COX-2 is also a cause of low platelet response to aspirin.

Therefore, patients who have these conditions should be given aspirin in higher doses, combination with other antiplatelet or treatment to lower total cholesterol concentration (Friend et al., 2003).

The results of the bivariate analysis showed that the factors have a significance value ($p < 0.25$). Then, it was followed by multivariate analysis using logistic regression for patient characteristics and linear regression for the results of laboratory examination of patients. From Table 3 it can be seen that there are no characteristics that influence the incidence of aspirin resistance in patients with recurrent ischemic stroke. Different results can be seen in the results of linear regression analysis of laboratory results. From Table 4 it can be seen that LDL is a laboratory value that most influence on the incidence of aspirin resistance with the resulting equation, $y = 1.468$ to 0.003 (LDL levels). This equation is used to predict the status of aspirin resistance recurrent ischemic stroke patients ($y =$ status aspirin resistance). If the result of this equation shows the calculation with a value of 1, it can be concluded recurrent ischemic stroke patients develop resistance to aspirin. Conversely if the value is 2, it indicates the non recurrent ischemic stroke patients resistant to aspirin.

CONCLUSION

Hypertension and antihypertensive drugs do not affect the incidence of aspirin resistance that occurs in patients with recurrent ischemic stroke.

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