

The Role of Anticoagulation Control on the Mortality Rate in Warfarin Treated Ischemic Stroke Patients with Atrial Fibrillation.

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ABSTRACT

Stroke in atrial fibrillation patients can increase mortality risk which is a consequence of thromboembolic events. Thromboprophylaxis can be attained using anticoagulant such as warfarin. However, its administration must be controlled continuously to minimize the bleeding. Anticoagulation control could be done by observing the International Normalized Ratio (INRs) with the target of 1.5 up to 2.0. An effective control of anticoagulation is expected to lower the mortality rate. In the study, we investigated the factors affecting the quality of anticoagulation control on warfarin-treated ischemic stroke patients with atrial fibrillation, and its effect on the clinical outcome i.e. mortality rate. The study was conducted by using the case control method, in which the patients with the primary diagnosis of ischemic stroke and the secondary diagnosis of atrial fibrillation receiving warfarin therapy (n = 140). The percentage of the anticoagulation control was evaluated using INRs to categorize good and poor anticoagulation controls. Based on the multivariate analysis on the 140 subjects, it was found that the variables which were statistically related to the mortality rate in the hospital were incidence of sepsis (one of comorbidity) (OR = 6,721; 95% CI = 2,3-19,1; p = 0,000) and the use of aspirin along with warfarin (OR = 0,374; 95% CI = 1,1-0,9; p = 0,032). However, the anticoagulation control on the warfarin therapy did not significantly affect the mortality rate at the hospital for ischemic stroke patients with atrial fibrillation (OR = 0,316; 95% CI = 0,6-4,3; p = 1,651). In conclusion, incidence of sepsis and the use of aspirin along with warfarin are two factors affecting to the mortality, however, poor anticoagulation control was not related to the mortality rate at the hospital for ischemic stroke patients with atrial fibrillation using warfarin.

Keywords: Warfarin, INR (International Normalized Ratio), anticoagulation control, mortality, ischemic stroke, atrial fibrillation.

INTRODUCTION

Stroke is most serious long-term risk related to atrial fibrillation. Stroke is a main cause of many serious disabilities. The rate of stroke incidencies in Indonesia has risen sharply. Indonesia is a country with the largest number of stroke patients in Asia, and the fourth in the world after India, China, and United State¹. It is estimated that there are about 800 up to 1000 stroke cases occur each year. Based on the household survey, the stroke mortality is around 37,3 per 100,000 people. Furthermore, stroke is also the third death cause after the malignancy and cardiovascular diseases.

Atrial fibrillation affects 1-1,5% of the population in developed countries. Clinically, the significance of atrial fibrillation on the elevation of stroke risk is five times larger. Stroke in patient with atrial fibrillation tends to be more severe with a higher recurrence, reaching 6.9% compared to 4.7% in stroke patients without atrial fibrillation. This stroke usually tends to be more severe and can increase the risk of morbidity, mortality, and poor

functional outcome. Most of the morbidity and mortality of stroke patients with atrial fibrillation are the consequences of the thromboembolic events, that cause the thromboembolic prevention become an important component in the management of ischemic stroke patients with atrial fibrillation².

The development and research of thromboprophylactic agents continue around the world, both in basic and clinical/applied research. Thromboprophylaxis could be attained with antithrombotic drugs, either by interfering the coagulation pathways (anticoagulants), or by inhibiting the platelet aggregation (antiplatelet). Anticoagulant is more effective for patients with atrial fibrillation in comparison to the antiplatelet, especially for those with a high-risk³. Warfarin is an effective anticoagulant that can reduce the risk of stroke by 64%⁴. The research by Currie *et al*⁵ reported that the mortality risk of ischemic stroke patients with atrial fibrillation using warfarin was lower than the patients using warfarin.

The warfarin therapy must reach a blood dilution rate on a certain level. Its administration must be controlled continuously to maximize the protection over stroke and minimize the bleeding complication. If the target of blood dilution level could not be achieved, so the therapy will not be effective. Otherwise, if the blood dilution level is too low, so the bleeding may occur⁶. The control of blood dilution level or anticoagulation control can be done through the International Normalized Ratio (INR) test. The INR value would be influenced by certain factors such as age, comorbidities, other medications, genetics, and diet⁴. The research by Hylek *et al*⁶ indicated that the ischemic stroke patients with atrial fibrillation treated with warfarin therapy with the INR score of 2,0 or more have a lower mortality rate of 30 days in comparison to those treated with warfarin with the INR score less than 2,0 (6% vs 16%). The research by Gallagher *et al*⁷ using the Time in Therapeutic Range (TTR) to assess the relation of anticoagulation control with the mortality rate, reported that mortality was lower by 81% in the group of good anticoagulation control than the poor one.

A similar study has never been conducted in Indonesia. The present study is conducted by using the method of case control through the search of the patients' medical records to evaluate the effect of the anticoagulation control on the mortality rate at a hospital for ischemic stroke patients with atrial fibrillation treated with warfarin.

METHODS

Subject and Research Design

The present study was categorized as an observational research with case control method using secondary data through medical record of patients. In the case-control design, a group of cases (ischemic stroke patients with atrial fibrillation treated with warfarin who experiencing death) compared to control group (ischemic stroke patients with atrial fibrillation treated with warfarin who does not experiencing death). Then retrospectively, the risk factors that might explain why the case had the effect (death) were observed.

The subjects were selected regarding to inclusion and exclusion criteria. The inclusion criteria for participation in the study were ischemic stroke patients with atrial fibrillation taking warfarin at a hospital in Yogyakarta with a minimum of 2 times INR checks during hospitalization and over 18 years old. The exclusion criteria referred to the medical records that could not be read and unclear, and to the patients who did not have any laboratory data examination of INR. The variables evaluated for their effect on the clinical outcome in the study were age, sex, smoking status, use aspirin along with warfarin, use clopidogrel along with warfarin, level of awareness, CHADS2 scores and concomitant diseases (dyslipidemia, coronary heart disease, diabetes mellitus, chronic heart failure, sepsis). This study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Gadjah Mada, Indonesia (Ref : KE/FK/311/EC).

Fraction of INRs in Range

The patient's anticoagulation control refers to the assessment of anticoagulation intensity in the patients who can be maintained within their therapeutic range determined by measuring the Time in Therapeutic Range (TTR). One of the methods that can be used to calculate TTR is a fraction of INRs. The method is done by calculating the number of laboratory tests for INR value which were right on target (1.5-2.0), and divide them with the number of the total tests. If the score is < 60%, so it can be stated that the patient's anticoagulation control is suboptimal/poor. However, if the score is ≥ 60%, so it can be declared that the patients' anticoagulation control is optimal/good. This method is the simplest way to calculate Time in Therapeutic Range.

Statistical Analysis

The analysis of the factors affecting the mortality was conducted using a bivariate analysis. The analysis was then continued with a multivariate analysis with the logistic regression method to evaluate the significant and independent factors related to the mortality rate in warfarin-treated ischemic stroke patients with atrial fibrillation.

RESULT

A total of 140 ischemic stroke patients with atrial fibrillation treated with warfarin and fulfilling both the inclusion and exclusion criteria, have been selected in the study. Among all patients, 68 subjects died in the hospital (subjects with risk factors) while the other 72 subjects survived. The factors influencing the mortality in the ischemic stroke patients with atrial fibrillation receiving the warfarin therapy could be observed by using a bivariate analysis including all variables of risk factors. These variables or factors are age, sex, smoking status, use aspirin along with warfarin, use clopidogrel along with warfarin, level of awareness, CHADS2 scores and concomitant diseases (dyslipidemia, coronary heart disease, diabetes mellitus, chronic heart failure, sepsis). The results of bivariate analysis are shown in Table 1 and 2. Based on a bivariate analysis, we selected the variables or factors affecting the mortality during hospitalization in warfarin-treated ischemic stroke patients with atrial fibrillation. There were nine variables included and analysed further using multivariate analysis. These mortality-affecting factors were anticoagulation control, level of patient awareness, CHADS2 score, use aspirin along with warfarin, use clopidogrel along with warfarin and concomitant disease i.e. coronary heart disease, congestive heart failure (CHF), sepsis, and diabetes mellitus. These factors were then evaluated with a multivariate analysis with the logistic regression method for evaluate the significant and independent relationship to the mortality of stroke patients with atrial fibrillation at hospitals. The results of the multivariate analysis are shown in Table 3. Based on the multivariate analysis, the variables statistically related to the mortality rate in the hospital were incidence of sepsis (one of comorbidity) (OR = 6,721; 95% CI = 2,3-19,1; p = 0,000) and the use of aspirin along with warfarin (OR = 0,374; 95% CI = 1,1-0,9; p = 0,032). The result of this analysis also showed that

Table 1: The mortality-affecting variables in ischemic stroke patients with atrial fibrillation in the hospital

Variables	Died (n=68)	Alive (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)	56 (82)	50 (69)	2,05	0,9-4,5	0,075
60% (good)	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. Analysis of mortality-affecting concomitant diseases in ischemic stroke patients with atrial fibrillation in the hospital.

Variable	Died (n=68)	Alive (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)			

the anticoagulation control on the warfarin use did not significantly affect the mortality rate in ischemic stroke patients with atrial fibrillation in the hospital (OR = 1,651; 95% CI = 0,6-4,3; p =0,316). The control of anticoagulation in the patients was based on the assessment of the effectiveness of anticoagulation intensity within their therapeutic range. This assessment was done using the fraction of INRs in range methods. The method is done by calculating the number of INR value in the target range (1.5-2.0), and is divided with the number of the total tests taken during hospitalization. If the score is < 60%, so it means that the anticoagulation control in the patient is suboptimal or poor. However, if the score is 60%, so it means that the anticoagulation control in the patient is optimal/good⁸.

DISCUSSION

Stroke is most common cause of long-term disability and death in the world. Stroke is a type of cerebrovascular disease occurring suddenly and can cause neurologic damage and death. This damage was caused by total or partial blockages on cerebral vessels (lack of blood flow) and hemorrhagic. Most stroke incidences are ischemic (85-90%) that is related to alteration of blood supply to the brain^{9,10,11}. The rest one is hemorrhagic resulted from rupture of blood vessels and can cause the bleeding. Nevertheless, the bleeding can also occur in the area of ischemia. There are some risk factors for ischemic stroke such as age, gender, race, heredity, ethnic. Besides, some predisposing factors for ischemic stroke are diabetes

mellitus, hypertension, smoking status, hyperlipidemia, physical inactivity, stress¹⁰⁻¹³. The use of warfarin, an anticoagulant agent, in stroke patient with atrial fibrillation is choice to reduce the stroke risk^{9,11}. In the study, after bivariate analysis nine mortality-affecting factors were included for further analysis (multivariate analysis). These factors were anticoagulation control, level of patient awareness, CHADS2 score, use aspirin along with warfarin, use clopidogrel along with warfarin and concomitant diseases i.e. coronary heart disease, congestive heart failure (CHF), sepsis, and diabetes mellitus. In multivariate analysis, the variables related the mortality rate in the hospital were only incidence of sepsis (one of comorbidity) and the use of aspirin along with warfarin. According to the research of Gallagher *et al*⁷ on 27,458 subjects, the good anticoagulation control could lower the mortality rate by 81% in the ischemic stroke patients with atrial fibrillation under warfarin therapy.

However, in the present research, most of the patients who died or patients who have been out of the hospital had poor anticoagulation control. This result is inline with a restrospective study by Melamed *et al*⁴ on 906 patients, in which about two third of the patients with atrial fibrillation treated with warfarin had poor anticoagulation control. Unsimilar results with the previous studies is related to the INR value of warfarin use of each subject was also affected by age, gender, other medications, genetics and diet^{14,15}. The INR score greater than 3 is associated with higher rate of bleeding that causes death. Whereas the INR score below 2 is related to low clot formation from the blood. Therefore, these factors can influence the result indirectly. Effect of diet on each patient can indirectly affect the results because the diet can affects the INR value. This is caused by the consumption of supplements or foods containing vitamin K. The vitamin K has an opposite mechanism with warfarin. Foods with high vitamin K inhibit the effect of warfarin. Patients should keep the amount of vitamin K intake to 70-140 mcg/ day in their diet. Foods with high vitamin K include green vegetables, beef liver, and green tea.

The genetic also can influence the INR score so that may indirectly affect the results. This is caused by the cytochrome enzyme P450, subtype 2C9 (CYP2C9) involved in drug metabolism and the vitamin K epoxide reductase 1 (VKORC1) involved in the activation of vitamin K¹⁶. In the study of Aithal *et al*¹⁷, individuals with polymorphisms in the CYP2C9 gene experienced much more bleeding due to decrease of warfarin metabolism. The bleeding in warfarin use is generally illustrated with the INR value that is over the target. Therefore, the patients with polymorphisms in the CYP2C9 gene tend to have high INR value. According to a study conducted by Takahashi *et al*¹⁸, CYP2C9 gene

Table 3: Multivariate analysis of the variables related to the mortality of stroke patients with atrial fibrillation at hospitals.

Variable	OR	95% CI	p
Sepsis	6,721	2,3-19,1	0,000
Coronary Disease	Heart 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

polymorphism was rarely found in the Japanese population in comparison to the population of Caucasian and African-Americans. Whereas VKORC1 that causes the activation of vitamin K has a greater frequency in the population of Japan (89.1%) in comparison to this of Caucasian (42.2%) and African-Americans (8.6%). The result of the multivariate analysis showed that sepsis was significantly related to incidence of death in the hospital. Subjects with sepsis had a greater mortality risk by 6.7 times in comparison to the subjects with no sepsis. According to Sinta & Sutarni¹⁹, sepsis on stroke patient contributed 3.68% of patient mortality during hospitalization. Sepsis in patients with ischemic stroke were mostly related to respiratory and urinary infection. In general, stroke patients are hospitalized for a long time and they have limited activities. Consequently, they can get infection during hospitalization. Multi organ failure on the sepsis is a main cause of the high mortality rate. In the study, the use of aspirin along with warfarin was significantly related to death incidence in the ischemic stroke patients with atrial fibrillation in the hospital even though the OR score was less than 2. The combination is used for the 42 subjects in this study. The combination of aspirin and warfarin was commonly used. In a cohort study with 118.606 subjects, around 15,5% of subjects got the combination of aspirin and warfarin. The combination of aspirin and warfarin is associated with the increase of bleeding incidence of 1,6% each year. Some studies reported that the administration of aspirin along with warfarin increased the incidence of bleeding that in turn can cause death²⁰. However, the majority of subjects in the present study was a group of moderate to high-risk category (based on the characteristics of CHADS2 score) for having recurrent stroke. According to Shireman *et al*²¹, the combination of warfarin and aspirin for secondary stroke prevention is needed for patients with coronary artery disease. This drug combination is also used in patients with mechanical heart valves or occasionally in patients with high risk of stroke repetition. In contrast, the combination of clopidogrel along with warfarin did not have a significant relationship with incidence of death in the ischemic stroke patients with atrial fibrillation in the hospital. The use of aspirin exhibited a higher risk of bleeding in comparison to this of clopidogrel. In addition, there was a risk of resistance that could result in the failure of anti-trombotic therapy for patients receiving the aspirin therapy^{20,22}. Those factors become causes of the high incidence of death on the use of aspirin with warfarin (15 subjects) compared to the use of clopidogrel with warfarin (11 subjects). The variable of the level of awareness had a significant relationship with

incidence of death in the hospital, however variable of CHADS2 score 5 did not. The subjects with a low level of awareness had a higher mortality risk by 3.3 times in comparison to the subjects with a high level of awareness. The subjects with the CHADS2 score 5 had a higher risk of death by 2.5 times in comparison to the subjects with the CHADS2 score 2.

CONCLUSION

In the study, variables related to the mortality of ischemic stroke patients with atrial fibrillation were only incidence of sepsis (one of comorbidity) and the use of aspirin along with warfarin. Poor anticoagulation control was not related to the mortality rate on warfarin-treated ischemic stroke patients with atrial fibrillation.

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