TIME IN THERAPEUTIC RANGE (TTR) IN ATRIAL FIBRILLATION WITH WARFARIN THERAPY IN SEMARANG, INDONESIA

by Pipin Ardhianto

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Della Dafina Sekarsari[1], Mochamad Ali Sobirin[2], Erwin Kresnoadi[3], Pipin Ardhianto[2*]

[1]Undergraduate Program, Faculty of Medicine, Diponegoro Univeristy, Semarang, Indonesia
[2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Diponegoro Univeristy, Semarang, Indonesia
[3]Department of Anesthesiology, Faculty of Medicine, Diponegoro Univeristy, Semarang, Indonesia
* Corresponding Author : E-mail : pipin.ardhianto@gmail.com

ABSTRACT

Background: Atrial fibrillation is one of the factors forming thromboembolism. Thromboembolism can be prevented by warfarin. A side effect of warfarin is increasing the occurrence of bleeding, this therapy requires an evaluation of its usage. These evaluations can be seen in the Time in Therapeutic Range (TTR) patients. TTR is the duration in which the International Normalized Ratio (INR) patients in referral value are 2.0-3.0. TTR > 70% can prevent bleeding in FA patients with warfarin therapy. **Aim:** To determine TTR in patients receiving warfarin with atrial fibrillation. **Methods:** This study was descriptive with a cross-sectional design for six months at Dr. Kariadi Hospital Semarang. TTR was calculated using Rosendaal's Methods after collecting three INRs and patients' demographics. **Results:** Total subject was 111 patients with an average age of 52,63 and the TTR average is 53,75. TTR in this study was divided into two groups, that groups were poor TTR (TTR < 70%) with 82 patients (73.88%) and good TTR (≥70%) with 29 patients (26.12%). **Conclusions:** The average TTR in FA patients with warfarin therapy was 53,75%.
Keywords: Atrial Fibrillation, Warfarin, Time in Therapeutic Range, International Normalized Ratio

INTRODUCTION

Atrial fibrillation (FA) is one of the most frequent types of arrhythmia and its prevalence is increasing in the world.[1] FA affects more than 886,000 new people each year in Europe. More than 1 million people suffer from FA in every country such as France, Germany, Italy, and the United Kingdom.[2] Atrial fibrillation is related to increased risk of stroke, myocardium infarction, heart failure, dementia, chronic kidney disease, and even increased mortality.[3,4] FA is a risk factor in the appearance of a thromboembolic[5] and increases six times the risk of stroke over than a sinus rhythm because FA has the Virchow triage criteria needed for the formation of a thrombus: static blood, endothelial dysfunction, and increasing blood clot activity.[6] Embolism can flow through the blood to various parts of the body and it can block the flow of blood to the lungs, brain, intestines, spleen, or kidney. If embolism blocks the flow to the brain can cause a stroke.[7]

Warfarin is antagonistic vitamin K oral which is effective in preventing the risk of systemic stroke and embolism.[8] Warfarin is the world's most widely used anticoagulant, and at least 1% of all people in the United Kingdom use warfarin. That is because of its ubiquity and price.[9] Warfarin action is to inhibit vitamin K epoxide reductase enzymes that catalyze *γ-carboxylation vitamin K-dependent factors* (II, VII, IX, dan X). Research shows that warfarin therapy reduces the risk of stroke by 66%.[10]

Warfarin has limits that can increase the risk of bleeding, reported intracranial bleeding by 0.3%-0.6% per year in patients with warfarin therapy, this risk increases in patients with higher the international normalized ratio (INR).[10] INR is a patients' prothrombin time compared with the normal prothrombin in the laboratory.[11] Warfarin therapy needed regular monitoring to ensure that the therapeutic anticoagulation met their INR target, a 2.0-3.3.[11] Warfarin therapy needed regular supervision to ensure that the therapeutic anticoagulation met their INR target, a 2.0-3.3.[12] This monitoring by evaluation of TTR patents. . TTR > 70% percent can guarantee admissible stroke risk prevention, but such percentages are rarely reached even in large trials.[13] his research is to determine the TTR of atrial fibrillation patients who were received warfarin therapy at Dr. Kariadi Semarang hospital.

METHOD

The study was a descriptive study conducted at Dr. Kariadi Semarang Hospital. The subjects of this study were atrial fibrillation patients given warfarin at Dr. Kariadi from January 2019 to April 2020. The data collection method was using a total sample. The data were obtained from patients' medical records. The study already has research permits

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issued by the Health Research Ethics Committee Faculty of Medicine Diponegoro University. Inclusions criteria were patients with atrial fibrillation administered by warfarin from January 2019 to January 2020. The results of the INR laboratory were calculated using Roosendaal's formula to determine TTR patients by comparing the number of INR days on target (2.0-3.0) and a total of days.

RESULTS

This study involved 111 patients with 61 male patients (54.95%) and 50 female patients (45.05%). The average age of the subject of this study is 52.63 years, the youngest was 24 years and the oldest was 82 years. The study of characteristics of patients were shown in table 1. The educational status is distinguished into two groups that undergraduate and post-graduate. The undergraduate consists of elementary, middle school, and high school. The postgraduate consists of a diploma, degree, and higher.
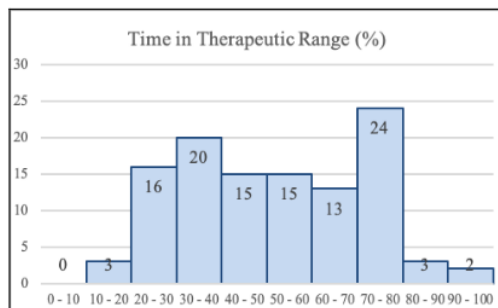

Figure 1. The Result of Time in Therapeutic Range

Study of TTR were shown in figure 1. The average TTR was 53.75%. The lowest TTR is 12.15% and the highest TTR is 100%. TTR in this study was classified into two groups - poor TTR (TTR < 70%) and good TTR (≥70%). There were 29 patients (26.12%) in good TTR groups and 82 (73.88%) were in poor TTR groups.

Table 1. The Characteristics of Patients

Characteristic	Frequency (%)
Gender	
Male	61 (54,95)
Female	55 (45,05)
Age	
≥65	20 (18,02)
<65	91 (81,98)
Educational Status	
Undergraduate	21 (18,92)
Postgraduate	90 (81,08)
Marital Status	
Single	12 (10,81)
Married	99 (89,19)

Table 2. Comparisons of study subjects TTR according gender, age, educational status and marital status

	TTR		P
	Good control	Poor control	
Gender			
Male	20 (32,79%)	41 (67,21%)	0,684
Female	14 (28%)	36 (72%)	
Age			
≥65	1 (5%)	19(95%)	**0,018**
<65	28 (30,77%)	63 (69,23%)	
Educational Status			
Undergraduate	3 (14,29%)	18 (85,71%)	**0,093**
Postgraduate	26 (28,89%)	64 (71,11%)	
Marital Status			
Single	8 (66,67%)	4 (33,33%)	**0,170**
Married	21 (21,21%)	78 (78,79%)	

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Comparisons of study subjects TTR according to gender, age, educational status, and marital status were shown in table 2. Analysis showed there were no differences between gender, educational, and marital status (0.684, 0.093, and 0.170). There was a significant difference between TTR and age group, the rate of poor control is 95% in patients with age ≥65 years old despite in a patient with age <65 years old the rate decrease to <70%. To evaluate the independent effects of each variable as a predictor of poor control, we performed a multivariate logistic regression. We identified only age ≥65 years old as significant predictors of poor control (OR = 2.134; 95% CI, 1.077, 0.074).

DISCUSSION

Warfarin is a vitamin K antagonist that has an effective deterrent to thromboembolism. Warfarin has a narrow therapeutic window that makes its effectiveness and safety dependent on patient presentation. Poor control of anticoagulant use may increase the risk the blood platelets. That is safe if TTR> 70%. [14] TTR is an accumulation of days in which INR patients match the value of referrals to prevent thromboembolism in FA patients.[14] INR is a time ratio of prothrombin to prothrombin control with a referral value of 2.0-3.0.[15] Three laboratory results from INR patients were measured using the Roosendaal formula to create a TTR score in percent.

Based on the results of our study, the lowest TTR was 12.5%, and the highest was 100%. The TTR average in this study is 53.75%, our study shows that the TTR average is distant from secure TTR references (≥ 70%). In our study, 29 people (26.12%) were in good TTR groups, and 82 (73.88%). Our average TTR result (53.75%) is lower than the research performed by Gateman et al. in Canada (58.05%)[16] and Farsad et al. in Iran (54.9 ± 11.9%)[14]. The good TTR group (26.12%) is lower than the research conducted by Gateman et al. (29.33%),[16] Farsad et al. (37.3%),[14] and Cotte et al. in four European countries (France, (47.8%), Germany (44.2%), Italy (46.1%) and the United Kingdom (65.4%)).[17]

The difference in TTR values in this study and other studies is because the Windows therapy and the way warfarin works are affected by patient characteristics, patient health conditions, diet, and other drug interactions.[18] The patient's age significantly affects TTR value in this study, group patients with age < 65 years compared to patients ≥ 65 years (30.37% over 5%). According to Marcatto and et al. in Sao Paulo shows that TTR is affected by age because of differences in the level of drug compliance. This level of drug compliance is due to differences in educational background, knowledge of diseases and administered drugs, the severity of the disease, and socioeconomic condition.[19] According to Abohelaika et al. in Britain, the high rate of TTR in patients with more than 65 years of the group caused by the level of adherence to drugs, and fitness at the age < 65 is better than ≥ 65-year-olds.[20] According to Golchin et al. in Ohio, show the age 65-year-olds are taking more drugs or polypharmaceuticals. Polypharmaceutical is a term that takes five or more drugs. These are due to chronic levels of disease, the severity of the disease, and complications of the disease.[21] A study by farsad et al. shows more combinations of drugs fewer good TTR groups, so more drugs affect TTR values.[14] According to Leiss et al. patients 65 years old consume more drugs that cause the difficulty of controlling INR because of the easy interaction of warfarin with other drugs.[22] INR is affected by diets, changes in pharmaceutical formulations, intestines and bowel function, comorbid or chronic diseases, such drugs as antibiotics and nonsteroidal antiinflammatory, and herbs[16] Warfarin will be tied up with 99% plasma albumin and will be metabolized in the liver by cyp2c9, cyp1a2, and cyp3a4. Medicines such as salicylate and phenytoin would disrupt the warfarin ties with plasma albumin. Other drugs interfere with warfarin metabolism by affecting the work of p450 cytochrome in the liver.[23,24] Drugs that can impede the work of p450 cytokine are antibiotics (metronidazole, cotrimoxazole, tripmetropin-sulfamethoxazole, and ciprofloxacin) and anti arithmetic drugs like amidoran. A drug that can induce p450 cytochrome to promote the metabolism of warfarin is rifampin.[24] According to Izzo there are reported links between warfarin and herbs such as cranberry, chamomile, klebet seeds, ginger, green tea, and ginseng[25] that herbs block vitamin k activity and suppress the development of blood clotting.[26]

There are several limitations to our study. First, the data are restricted to one hospital in Dr. Kariadi Semarang Hospital, so data of patient FA who gets

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warfarin therapy at other hospitals can't be taken as the subject of research. Research time constraints also cause research subjects to drop a lot. The study merely analyzes the patient's demographic data with TTR patients. Second, the study was conducted during pandemic Covid-19, so patients may not have regular checkups at the hospital for the absence of newer data. In the future, multi-center research is needed to identify more generalized risk factors and acquire more accurate data.

CONCLUSION

The average of TTR patient FA with warfarin therapy at Dr. Career hospital is 53.75%. Based on this study, the use of warfarin in FA patients should be more controlled, thereby preventing the risk of bleeding and the formation of thrombus. Future studies are needed to evaluate factors that may affect TTR in patients who use warfarin as an anticoagulant.

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