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Evaluation of Warfarin Use in Cardiac Clinic Outpatients

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Abstract

The use of warfarin was monitored using the International Normalized Ratio (INR) value. This study aims to determine the relationship between the patient's demographic variables and INR, as well as the therapy result and differences in their INR value. A cross-sectional study was used with retrospective observational data collected by tracing secondary information of medical records from outpatients with heart disease on warfarin therapy at Dr. Hasan Sadikin hospital Bandung between 2016 to 2020. Subsequently, the difference in patients' INR value was analyzed with the Mann-Whitney test based on dosage. At the same time, the relationship between demographic variables and INR was examined using the Chi-square test and Spearman correlation. The INR examination results in 192 subjects showed 124 patients (64.6%) reached the target with an average value of 2.37 ± 0.21 and a warfarin dose of 19.31 ± 6.25 mg weekly, while 68 (35.4%) had an average of 1.82 ± 0.73 and a dose of 20.24 ± 6.24 mg weekly. Subsequently, the difference test with Mann Whitney ($p = 0.004$) showed a variation in the INR value based on the warfarin dose. The Spearman correlation analysis results indicated a relationship between BMI ($p = 0.009$), daily (0.010), and weekly dose (0.008) on the INR value with the correlation coefficient of 0.188; 0.186; and 0.192; indicating a negative association with very weak correlation strength. This study showed that a majority of patients reached the INR value of 2-3, and the demographic variables associated with this ratio were BMI and warfarin dose. The decision to increase and decrease the warfarin dose is determined by INR value and BMI.

Keywords: warfarin, dose, INR, outpatients

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Introduction

World Health Organization (WHO) stated that about 17.9 million deaths occurred globally due to heart disease in 2016. This condition occurs due to impaired function and blood vessels and consists of coronary and rheumatic heart disorder, cerebrovascular disease, and other conditions.[1] According to Riskesdas data, the 2018 prevalence of heart disease in Indonesia was 1.5%.[2]

Consequently, anticoagulants are drugs that prevent the blood clotting process by inhibiting fibrin formation. One of the most common anticoagulants is warfarin, which is widely used to treat or prevent thromboembolism-related diseases, including stroke, heart attack, embolism, atrial fibrillation, and deep vein thrombosis. This drug is still widely used even after six decades.[3,4]

Warfarin has a narrow therapeutic index, which indicates that a slight dose difference causes a significant alteration in response. Therefore, administration of a large dose increases the bleeding risk, while a small quantity will cause failure in the treatment or prevention of thromboembolism. Since drug doses vary widely between patients and must be individualized, dosage adjustment is necessary and would lead to variations in its use. This variability is due to age, gender, ethnicity, anticoagulant indication, vitamin intake, body weight, albumin levels, and drugs consumed.[3] Anticoagulant status during warfarin use was monitored with INR, where the most common target value was between 2 to 3. Also, patient INR values are examined every 4 to 6 weeks for dose adjustment until it is stabilized.[5,6]

In Lithuania, a study on warfarin showed the INR value for patients with atrial fibrillation was out of the target range by more than half (57.3%), where approximately 40% of cases occur because the subjects do not evaluate and adjust the dose.[7] Patient knowledge of warfarin therapy is still low, although the level of adherence is high.[8] Our study showed, most warfarin therapy has not reached the therapeutic INR range of 2 to 3.[9] Also, a study by Megawati et al., 2019 evaluating this drug use showed that only 27% of patients achieved the target range.[10] Consequently, INR monitoring can improve its stability within the therapeutic range and prevent serious complications.[11]

Based on the background described above, an evaluation of warfarin use in heart disease patients at Dr. Hasan Sadikin Hospital was conducted to determine the drug use profile, effectiveness, and if the administered therapy dose has reached the target therapeutic INR value of 2 to 3. Dispensation of safe and effective warfarin doses improves the therapy's success and patient's life quality and avoids side effects of bleeding.

Methods

Study Design

This is a cross-sectional study with retrospective observational data collected by searching secondary information in medical records from outpatients with heart disease at Dr. Hasan Sadikin Hospital between January 2016 and December 2020. The obtained data included gender, age, height, weight, disease diagnosis, warfarin dose, duration of warfarin use, comorbidities, other drugs used concurrently, and INR values. Subsequently, the information was processed and analyzed statistically. This study has been approved by the Ethics Commission of Universitas Padjadjaran, Bandung, Indonesia (No. 28/UN6. KEP/EC/2021).

Study Subject

The study subjects included all medical records from heart disease outpatients who used oral warfarin anticoagulants in Dr. Hasan Sadikin

Hospital between January 2016 to December 2020. Also, patients were required to have used this drug for a minimum of one month and have measured the INR value at least once. The exclusion criteria were incomplete and untraceable medical record data.

Statistical Analysis

Descriptive analyses were used to represent subjects' demographic data, including gender, age, Body Mass Index (BMI), warfarin indication, and amount of it. The Mann-Whitney test was used to compare differences in INR values based on daily warfarin doses. Meanwhile, Chi-Square and Spearman methods were used to determine the relationship between the parameters. The analysis was performed using SPSS software with a p-value <0.05 for significant results.

Table 1. Characteristics of Respondent

Characteristics	N	(%)
Gender		
Male	92	47.9
Female	100	52.1
Age (Year)		
15-24	5	2.6
25-34	10	5.2
35-44	32	16.7
45-54	54	28.1
55-64	55	28.6
65-74	28	14.6
>75	8	4.2
BMI		
Under weight (<18.5)	12	6.3
Normal (18.5-24.9)	128	66.7
Pre-Obesity (25.0-29.9)	39	20.3
Obesity (>30)	13	6.8
Warfarin Indicator		
AF	100	52.1
CAD	2	12.0
DVT	1	0.5
RHD	68	35.4
Number of Drugs		
<5	102	53.1
>5	90	46.9

Table 2. The Use of Warfarin Dose

Warfarin (mg/week)	N	(%)
7 mg	1	0.5
12 mg	14	7.3
14 mg	22	11.5
16 mg	29	15.1
18 mg	27	14.1
20 mg	30	15.6
21 mg	14	7.3
23 mg	13	6.8
25 mg	8	4.2
27 mg	13	6.8
29 mg	9	4.7
31 mg	4	2.1
33 mg	4	2.1
36 mg	2	1.0
45 mg	1	0.5
50 mg	1	0.5

Table 3. Comparison of Warfarin Dose in Patients with Reached and Unreached INR Value

INR Achievement	Number of Patients	INR Value (mean ± SD)	Warfarin Dose (mg/weeks) (mean ± SD)	P value
Target INR Achieved	124	2.37 ± 0.21	19.31 ± 6.25	
Target INR Unachieved	68	1.82 ± 0.73	20.24 ± 6.24	0.282
Total		22	11.5	

Results and Discussion

In this study, 192 medical records were obtained from patients who had and are currently using warfarin anticoagulant therapy. Furthermore, the respondents' treatments were monitored with INR examination. The results included data on respondent characteristics, patient INR values, warfarin dose, and the relationship between respondent characteristics and INR.

Characteristics of Respondents

Based on the data, the average age was 53 years, and 52.1% of the patients were female. Most patients who received warfarin were diagnosed with Atrial Fibrillation (AF) (52.1%) and Rheumatic Heart Disease (RHD) (35.4%), while a total of 53.1% received less than five other drugs. Moreover, the warfarin dose in each individual varies because it is usually adjusted with the patient's condition and INR value. (Table 1) Furthermore, the majority of patients were given 20 mg of weekly warfarin dosage (15.6%). (Table 2)

Reached and Unreached INR Values in Patients

Warfarin therapy was monitored using INR values for dose adjustment. This process was conducted daily or at intervals of the initial treatment. In this study, patients had a monthly INR check, where the recommended target for most warfarin indications is between 2 to 3 but varies per individual condition. About 124 patients (64.6%) had achieved the target INR (mean: 2.37 ± 0.21). The warfarin dose is considered to affect the INR value. Hence the amount administered to the patients is usually adjusted. Comparative analysis of the drug quantity in the group of patients with reached and unreached INR values with Mann-Whitney ($p < 0.05$) provided insignificant results ($p = 0.282$); hence there was no difference in warfarin dose between the two groups. (Table 3)

Patients who achieve the target INR use daily and weekly doses are maintained until the INR value was checked in the next month. If the INR value was still ideal, the amount was continued. The daily and weekly doses should be changed if the result was below or above the ideal INR value. Patients who did not reach the target INR, the dose of warfarin should be adjusted for one month and then re-evaluated by looking at the INR value.

Data Analysis of The Relationship Between Respondents Characteristics and INR

The respondents' characteristics related to the patient's INR value are BMI ($p = 0.009$) and warfarin dose ($p < 0.05$) are presented in Table 4.

Several studies on the evaluation of warfarin use monitored through INR values have been conducted. A report by Mansur et al., 2012, 80% of AF patients aged >65 years have

Table 4. Relationship Between Characteristics of Respondents and INR

Characteristic of Respondents	INR P value
Gender[a]	0.563
Drug Interaction[a]	0.738
Comorbid[a]	0.744
Age[b]	0.914
BMI[b]	0.009*
Warfarin Dose[b]	
- Daily Dose	0.010*
- Weekly Dose	0.008*

[a]Variables were analyzed by Chi-square method; [b]Variables were analyzed by Spearman method
*p<0.05: there is a significant relationship

achieved the INR target of 2 to 3 with warfarin dose of 2 to 5 mg/day.[12] Another study showed that most patients (N= 124 patients; 64.6%) reached the target, while 54 patients (62.79%) failed.[13] Therefore, dose adjustments with good enough patient adherence to warfarin consumption were conducted based on the INR value for those who reached the target.

The success of warfarin therapy can also be achieved with the role of pharmacists. Our previous study showed that counseling from the professionals significantly influences the patient's knowledge and perception of the treatment.[14] Furthermore, education and comprehensive counseling on this therapy, including risks, benefits, and drug and food interactions, are considered essential components to achieving warfarin therapy success.

Low patient knowledge about warfarin and medical personnel education is why some individuals did not reach the INR target,[15] where limited knowledge of the drug's indications is associated with non-adherence to the therapy.[16] In this study, there was no difference in the daily dose of warfarin in the group of patients with reached and unreached INR. The result is in line with the study by Furdiyanti et al., 2014, which gave insignificant findings.[13] Therefore, the patient's response to warfarin therapy may vary. However, the same dose is administered because the treatment is influenced by factors such as age, gender, comorbidities, adherence, and changes in diet or alcohol consumption.[17]

This study showed a significant difference in INR values based on warfarin dose (p=0.004). Consequently, patients with different amounts provided therapeutic results in the form of varying INR values due to clinical, non-clinical, and genetic factors.[18] Warfarin dose-response is unpredictable in every patient. Therefore, monitoring the INR daily during the initiation phase, weekly after reaching the desired target, and monthly after the value is stable is recommended.[19]

Warfarin dose-response is influenced by age, BMI, nutritional status, comorbid disease, drug interactions, pharmacogenetics, and ethnicity.[20] Therefore, monitoring the drug with INR is an essential factor affecting warfarin therapy's suitability.[21] The factors associated with INR values in this study included BMI (p = 0.009), daily (p = 0.010), and a weekly dose of warfarin (0.008). However, other respondent characteristics, such as gender,

drug interactions, comorbidities, and age, were not associated with INR ($p > 0.05$).

BMI is thought to affect the weekly dose of warfarin, but the results are insignificant. Hence the effect of this factor on determining the drug dose requirements is still unclear.[22] According to Mueller et al., 2014, patients with high BMI require a high Total Weekly Dose (TWD) of warfarin to maintain a stable therapeutic INR. The results of this study indicate that there is a relationship between BMI and INR ($p = 0.009$) with a correlation coefficient of –0.188 (very weak).[23] Also, a study by Ogunsua et al., 2015 showed that obesity class II (BMI 35-39.9 kg/m^2) and III (>40 kg/m^2) significantly increased the risk of major bleeding compared to patients with normal weight. In addition, obese patients on this therapy took longer to reach the therapeutic INR time than the non-obese. Moreover, the risk of bleeding increased in patients with a high INR value greater than 3.[24]

The INR value in warfarin therapy is influenced by its dose, where the risk of bleeding and thromboembolism increases and decreases with the dose, respectively.[3] However, warfarin dose-response to INR value varies for each individual; hence regularly adjusting the dose to the patient is necessary. The results of Spearman analysis showed a significant relationship between the daily ($p = 0.010$; $\rho = -0.186$) and weekly dose ($p = 0.008$; $\rho = -0.192$) with INR value.

A study by Khairunnisa et al., 2013.[25] showed a significant relationship between dose and INR in ischemic stroke patients with atrial fibrillation. According to Mansur et al., 2012, elderly patients with chronic atrial fibrillation also showed a relationship between these two factors with a p-value and correlation of 0.012 and 0.22, respectively.[12]

Also, genetic polymorphism is a factor that influences warfarin therapy, where the genes that affect the response to this treatment, including CYP2C9 and VKORC1. CYP2C9 plays a role in the drug's metabolism, which is associated with slower warfarin metabolism and a longer time to reach a stable INR value. At the same time, VKORC1 is the site gene for encoding VKORs related to the drug's sensitivity.[20,26] However, the analysis of the relationship between genetic polymorphisms and INR was not performed in this study because there was no genetic data in the patient's medical record, although genetics is a factor that affects the determination of the warfarin dose and patient's INR value.

This study's limitations include the location, which was restricted. Hence further investigations are expected to add this factor to obtain a larger patient number. In addition, only medical record data was used without considering other factors that influence the response to warfarin therapy, such as food interactions, genetic polymorphisms, and smoking habits.

Conclusion

Most patients have reached the target INR value of 2 to 3, and factors that affect the INR value are BMI and warfarin dose.

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Conflict of Interest

The authors declared no conflict of interest in the manuscript

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