Original Article

Simplified Warfarin Dosing Formula to Guide the Initiating Dose in Thai Patients

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Background: Warfarin-related bleeding occurred most commonly during the first three months of therapy, possibly due to an initiating overdose of warfarin. Previous small study reported that 3-mg initiating dose of warfarin appeared to be safe in Thai patients.

Objective: To compare the performance of simplified warfarin dosing formula and 3-mg initiating dose to predict actual warfarin dose that achieved therapeutic range of target international normalized ratio (INR).

Materials and Methods: The present study was a retrospective study including 640 patients who had been receiving warfarin with target INR of 2.0 to 3.0. The actual warfarin dose was defined as warfarin dose that resulted in INR of 2.0 to 3.0 for at least two consecutive follow-ups after initiation. The simplified warfarin dosing formula was 3.2 – (0.03×age(years)) + (0.02×body weight(kg)) (10% dose reduction if presence of heart failure (HF) and/or stroke). The optimal dosage was defined as difference from actual dose as being within 20%.

Results: Mean age was 65±13 years. The mean actual dose of warfarin was 2.8±1.2 mg. The warfarin dosing formula resulted in optimal dosing in 41% and overdosing in 21% of cases, whereas 3-mg initiating dose resulted in optimal dosing in 39% and overdosing in 43% of patients. In patients with HF and/or stroke, using formula resulted in overdosing in 23% of cases, whereas 3-mg initiating dose led to overdosing in 53% of patients.

Conclusion: A simplified warfarin dosing formula appeared to be safer than 3-mg initiating dose. Overdosing after using warfarin formula was less prevalent than using 3-mg initiating dose particularly in patients with HF and/or stroke.

Keywords: Warfarin, Algorithms, Atrial fibrillation, Anticoagulant

J Med Assoc Thai 2019;102(9):957-61
Website: http://www.jmatonline.com
Received 15 May 2019 | Revised 4 Jul 2019 | Accepted 11 Jul 2019

Warfarin, an oral vitamin K antagonist, has been the mainstay therapy for the prevention of stroke and systemic thromboembolism in patients with atrial fibrillation (AF). Although warfarin is highly effective for stroke prevention in AF, it is associated with significant risk of bleeding complications[1]. Warfarin has a very narrow therapeutic range with an international normalized ratio (INR) within 2.0 to 3.0, which would provide adequate protection from stroke with a low risk of bleeding complications. If the INR was above 3.5 to 4.0, the risk of major bleeding increased, reflecting over-anticoagulation[2,3]. A supratherapeutic INR in the first 90 days of warfarin use was also associated with a 3-fold increase risk of bleeding[3]. This highlights the importance of the early phase of warfarin therapy to avoid over-anticoagulation of warfarin. Due to the fact that many factors can influence the dose requirement of warfarin between individuals, the initiation of warfarin therapy can be a challenge in clinical practice[4].

Several investigators have developed and tested clinical-guided and genotype-guided algorithms to guide dose selection, particularly for initial therapy[5]. The mean daily dose of warfarin in an Asian population was reported to be 3 mg, which was lower than the 5 mg dosage reported in Caucasians[6,7]. The difference was attributable to the dissimilarities in genotypes between Asians and Caucasians. Sarapakdi et al have developed a genotype-guided algorithm

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How to cite this article: Pongbangli N, Phrommintikul A, Wongcharoen W. Simplified Warfarin Dosing Formula to Guide the Initiating Dose in Thai Patients. J Med Assoc Thai 2019;102:957-61.

to guide warfarin dosing in the Thai population[8]. The independent predicting factors included age, body weight, cytochrome P450 2C9 (CYP2C9) genotype, and vitamin K epoxide reductase complex 1 (VKORC1) haplotype. However, the genotype data are not widely available, which limits the use of this genotype-guided algorithm in real-world practice. Bearing this in mind, the authors modified the algorithm based on the common genotypes of the Thai population using only age and body weight. The authors sought to compare the performance of the simplified warfarin dosing formula and a fixed 3-mg dose to predict the appropriate initiating dose of warfarin in the Thai population.

Materials and Methods

The present study was a retrospective cohort study in which 640 patients were enrolled (15 years or older) who had been receiving warfarin with the target INR of 2.0 to 3.0 at the outpatient clinic, Maharaj Nakorn Chiang Mai Hospital. Patients were excluded if an INR 2.0 to 3.0 had not been achieved for at least two consecutive follow-ups during the first year of warfarin therapy, and those who had incomplete data. The medical records of patients that met the inclusion criteria were reviewed. Baseline characteristics including age, body weight, co-morbidities, medications, actual warfarin dose, and INR levels were collected. The study protocol was approved by the Medical Ethics Committee of Faculty of Medicine, Chiang Mai University.

The simplified warfarin dosing formula used in the present study was derived using the Sarapakdi et al algorithm. The Sarapakidi et al algorithm was developed using genotypes, age, and body weight as followed: dose (mg/day) = 2.075 – 0.028 × (age) + 0.022 × (weight) + 1.173 × (CYP2C9*3) + 1.788 × VKORC1-AB + 3.705 × VKORC1-BB, (input age in years; weight in kg; input 0 for CYP2C9*1/*3, 1 for CYP2C9*1/*1; input 1 for VKORC1-AB, 0 for otherwise; input 1 for VKORC1-BB, 0 for other)[8].

The most common genotypes in the Thai population are VKORC1-AA and CYP2C9*1/*1[8]. Therefore, the authors modified the Sarapakidi et al algorithm by replacing VKORC1-AA and CYP2C9*1/*1 in the algorithm. The present study simplified warfarin dosing formula (mg/day) was 3.2 – (0.03×age (years)) + (0.02×body weight (kg)). Calculated dose was reduced by 10% if there was history of heart failure (HF) and/or stroke.

The actual warfarin dose was defined as the warfarin dose that resulted in an INR 2.0 to 3.0 for at least two consecutive follow-ups after the warfarin initiation. The optimal dosage was defined as the difference from actual dose being within 20%. The underdosing of warfarin was defined as the predicted dose being more than 20% lower than the actual dose. The overdosing of warfarin was defined as the predicted dose being more than 20% higher than the actual dose.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median and interquartile range. Categorical variables were displayed as percentages. Differences between continuous variables were assessed using an unpaired 2-tailed t-test for normally distributed continuous variables and the Mann-Whitney test for skewed variables. Proportions were compared using a chi-square test or Fisher's exact test when appropriate. The level of agreement between predicted dose and actual dose was demonstrated using a Bland-Altman plot. All statistical significances were set at p-value less than 0.05 and all statistical analyses were carried out using SPSS 17.0 (SPSS Inc., USA).

Results

Six hundred forty patients receiving warfarin with the target INR of 2.0 to 3.0 were included in the present study. Mean age was 65±13 years. Mean body weight was 59±15 kg. Non-valvular AF was presented in 69% of patients. The baseline characteristics of the studied population are shown in Table 1. The mean actual dose of warfarin in the total population was 2.8±1.2 mg/day. Interestingly, the authors demonstrated that patients with a history of HF and/or ischemic stroke had a lower mean actual dose than those without (2.5±1.2 mg/day versus 2.9±1.3 mg/day, respectively, p=0.001).

The simplified warfarin dosing formula resulted in optimal dosing in 41% and overdosing in 21% of cases, whereas a 3-mg initiating dose resulted in optimal dosing in 39% and overdosing in 43% of patients. In patients with HF and/or stroke, using the simplified warfarin dosing formula resulted in overdosing in 23% of patients, whereas a 3-mg initiating dose led to overdosing in 53% of patients (Table 2). The level of agreement between the calculated dose from the simplified warfarin dosing formula and the actual warfarin dose is shown in Figure 1. The dispersion value between the calculated dose and actual dose was –0.43 (–1.63 to 0.76) mg/day. The disagreement was more apparent in patients requiring a higher dose of warfarin.

Discussion

Despite the availability of non-vitamin K oral anticoagulants, warfarin is still a commonly used oral anticoagulant for prevention of stroke and systemic thromboembolism in patients with AF in developing countries. In addition, warfarin remains the recommended oral anticoagulant therapy in patients with rheumatic mitral stenosis, those with mechanical heart valve replacement, and AF patients with severe renal impairment. The bleeding complications of warfarin are mainly due to the narrow therapeutic index of warfarin and inter- and intra-individual variability in the dose response of warfarin[9]. It has been shown that warfarin-related bleeding occurs more frequently in the early phase of warfarin therapy[3]. Therefore, the appropriate initiating dose of warfarin is essential to avoid over-anticoagulation, which in turn, increases the risk of bleeding[10,11].

Table 1. Baseline characteristics of studied population

Baseline characteristics	Total (n=640) n (%)
Age (years), Mean±SD	65.0±13.5
Age ≥75 years	178 (27.8)
Male	178 (43.4)
Body weight (kg), Mean±SD	59.2±15.0
Hemoglobin (gm/dl), Mean±SD	12.1±2.0
Creatinine (mg/dl), Mean±SD	1.2±0.8
Albumin (mg/dl), Mean±SD	3.8±0.5
Non-valvular AF	444 (69.4)
Rheumatic valve disease	149 (23.3)
Valve replacement	47 (7.3)
Diabetes mellitus	115 (18.0)
Hypertension	301 (47.0)
Chronic kidney disease	96 (15.0)
Cirrhosis	5 (0.8)
Heart failure	103 (16.1)
History of ischemic stroke	109 (17.0)
History of hemorrhagic stroke	1 (0.2)
Concomitant antiplatelet	19 (3.0)
Use of amiodarone	9 (1.4)

AF=atrial fibrillation; SD=standard deviation

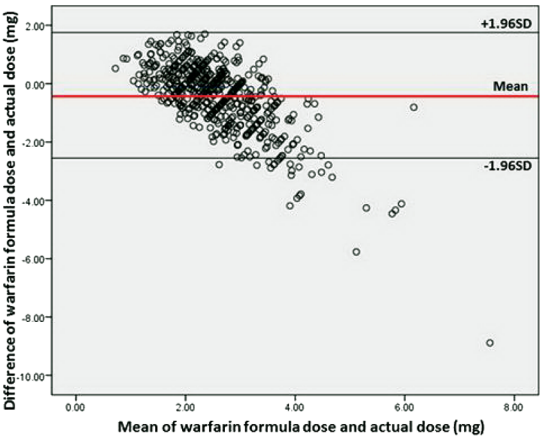

Figure 1. Bland-Altman plot showing level of agreement between warfarin formula dose and actual warfarin dose.

Previous studies have shown that genetic variation affect warfarin response and dosage requirement to a larger extent than clinical factors[12]. The genetic polymorphisms of CYP2C9 and VKORC1 genotypes on the pharmacokinetics and pharmacodynamics of warfarin play an important role in predicting the maintenance dose of warfarin. The genetic differences between ethnic groups resulting in different mean doses of warfarin have been described[13]. The VKORC1 haplotype A is associated with low-dose warfarin requirement and haplotype B is associated with high-dose warfarin requirement. Haplotype A is found more frequently in Asian populations than in other ethnic groups. As a result, patients from an Asian population require lower warfarin doses than other ethnic populations.

Table 2. The comparative performance between simplified warfarin dosing formula and fixed 3-mg dose strategy to predict optimal dose of warfarin

	Simplified warfarin dosing formula		Fixed 3-mg dose	
	Total population (n=640)	Heart failure/stroke (n=196)	Total population (n=640)	Heart failure/stroke (n=196)
Underdosing	38%	38%	18%	12%
Optimal dosing	41%	39%	39%	35%
Overdosing	21%	23%	43%	53%

Sarapakdi et al have developed a genotype-guided algorithm to guide warfarin dosing in the Thai population based on age, body weight, CYP2C9 genotype, and VKORC1 haplotype. The investigators found that those variables in the algorithm contributed to 60.6% of the variability in warfarin dose[8]. Nevertheless, the genetic data is not widely available, which limits the use of the genotype-guided algorithm in clinical practice. In addition, whether genotype-guided dosing improves anticoagulation control when compared to a clinical algorithm remains controversial[14].

The common dosing strategy for initiating warfarin therapy is the standard fixed-dose method[15]. The mean daily dose of warfarin in Asians has been reported to be 3 mg. A previous small study demonstrated that a 3-mg warfarin initiating dose appeared to be safe in the Thai population[6]. However, a fixed 3-mg dose strategy may result in over-anticoagulation in certain patients, such as elderly patients or those with extremely low body weight. The actual performance between a fixed 3-mg dose and use of the clinical algorithm to guide the initiating dose of warfarin has never been studied in a Thai population. The prevalence of CYP2C9*1/*1 genotype and VKORC1 haplotype AA ranges from 95% to 99% and 57% to 63%, respectively, in Thai population[8,16]. Based on these common genotypes in Thai population, the authors developed a clinical algorithm derived from the Sarapakdi et al genotype-guided algorithm using only age and body weight[8].

In the present study, the authors compared the performance of a simplified warfarin dosing formula and a fixed 3-mg dose strategy in predicting the optimal dose of warfarin. The authors demonstrated that the simplified warfarin dosing formula could predict the optimal dose in 40% of patients, which was comparable to the results from the fixed 3-mg dose strategy. Nevertheless, the authors found that the simplified warfarin dosing formula was associated with a lower risk of warfarin overdosing when compared to the fixed 3-mg dose strategy (21% versus 43%). With regards to the present study, the use of the simplified warfarin dosing formula to guide the initiating dose of warfarin appeared to be a safer approach than the fixed dose strategy in the Thai population.

A previous study demonstrated that patients with left ventricular systolic dysfunction required lower doses of warfarin[17]. The present study's findings gave weight to the results of the study as the mean actual dose of warfarin was lower in patients with HF than those without. The use of the simplified warfarin dosing formula with a 10% dose reduction in patients with HF led to a much lower risk of warfarin overdosing, compared to the fixed 3-mg dose strategy (23% versus 53%).

The present study had several limitations. First, the performance of the simplified warfarin dosing formula was tested in a population residing in a northern part of Thailand. The validity of the present study warfarin dosing formula in other population is unknown. Furthermore, the simplified warfarin dosing formula cannot be applied in patients that need a target INR other than 2.0 to 3.0.

Conclusion

A simplified warfarin dosing formula appeared to be safer than the conventional 3-mg initiating dose. Overdosing from simplified warfarin dosing formula was less prevalent than it was in the cases given the 3-mg initiating dose particularly in patients with HF and/or stroke.

What is already known on this topic?

The initiation of warfarin therapy can be a challenge in clinical practice, due to very narrow therapeutic range with INR 2.0 to 3.0 for stroke prevention in AF. The 3-mg initiating dose of warfarin appeared to be safe in a Thai population.

What this study adds?

A simplified warfarin dosing formula appeared to be safer than 3-mg initiating dose.

Ethics approval and consent to participate

Simplified warfarin dosing formula to guide initiation dose in Thai patients was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University and registered to http://www.clinicaltrials.in.th/ which submission number TCTR20180612002. The investigations were carried out in accordance with the Declaration of Helsinki.

Acknowledgement

This study was supported by grants from the Faculty of Medicine Endowment Fund for medical research, Chiang Mai University, Thailand. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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