Original article

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CLINICAL FACTOR RELATED TO INTERNATIONAL NORMALIZED RATIO CHANGES IN WARFARIN USERS WHO UNDERWENT HEART VALVE REPLACEMENT AT WARFARIN CLINIC OF PHRAMONGKUTKLAO HOSPITAL

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ABSTRACT

Warfarin is oral anticoagulant that has been used for prevention of systemic thromboembolism in valve replacement patients. There are many factors that can change the international normalized ratio (INR) in warfarin users. This study aimed to determine the influence of factors that related to the target range of INR among warfarin users who underwent heart valve replacement. This study is a retrospective study. The data were collected in patients who underwent valve replacement in warfarin clinic, Phramongkutklao Hospital, Thailand from January 2007 to December 2015. Demographic data including gender, age, type of prosthetic valve, co-morbidities, other medications used with warfarin, herbs or dietary supplements used with warfarin, laboratory data, warfarin initial dosing regimen and INR value were collected. The demographic data and the risk factors were analyzed via descriptive statistics and Fisher's exact test consecutively by using R-program. One hundred and nineteen patients were included. Sixty-four cases were male (53.78%) and mean (±SD) age was 55.09±14.78 years old. The mean (±SD) of body weight was 61.48±13.97 kilograms. Of those, 96 cases (80.67%) had mechanical valve replacement. Only sixteen of warfarin users (13.45%) had INR values with in target range. The results of the present study showed that drug interaction was one of the important factors that was associated with out-of-range INR target (OR 10.17, 95%CI 0.59-175.77) (p=0.051). Drug interaction including drug-drug, drug-herbs and drug-dietary supplement interaction were concerned in patients who received warfarin underwent heart valve replacement.

Keywords: warfarin, factors, prosthetic valve, international normalized ratio (INR)

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Introduction

Warfarin is oral anticoagulants in vitamin K antagonist group that has been used for prevention of systemic or cerebral thromboembolism including deep vein thrombosis (DVT), pulmonary embolism (PE) and atrial fibrillation (AF). Therefore, treatment and prevention of systemic thromboembolism in heart valve replacement including mechanical and tissue valves.[1] The international normalized ratio (INR) is the therapeutic and toxicity monitoring parameters among patients who taking warfarin. The target INR is within 2.5-3.5 for mechanical heart valve replacement and 2.0-3.0 for tissue valve replacement.[2] The pharmacokinetic properties of warfarin are complicated that completely absorbed almost 100 percent and metabolized by the cytochrome P450 enzyme via CYP1A2, CYP2C9 and CYP3A4.[1,3] Those enzymes are involved by certain medications which act as enzyme inducer or inhibitor. There are cause of drug-drug or drug-herb interactions and drug-dietary supplements. Nevertheless, the action of warfarin is affected by many known factors such as initial doses, genetic polymorphisms, food containing high vitamin K, comorbid conditions such as heart failure, hyperthyroidism, hypothyroidism, liver disease, hypoalbuminemia, smoking and alcohol consumption.[4-6] Therefore, patients having these factors could alter the INR values. The out of target INR values results in bleeding or thromboembolic events. Data from the previous studies in the other countries indicated that factors affecting to INR change were an initial dose, heart failure, hyper or hypothyroidism, interaction with many medication or herbs.

In present study, we aimed to determine the affecting clinical factors of INR changing in warfarin users who underwent heart valve replacement at the warfarin clinic. The benefit of this study might be a guidance for awareness and monitoring in warfarin users who underwent heart valve replacement.

Materials and methods

The present study was a retrospective study at Phramongkutklao Hospital, a 1,200-bed tertiary care hospital, Bangkok, Thailand from January 2007 to December 2015. The patients' data from an electronic medical record database and pharmacist's notes in warfarin clinic. Ethic approval was obtained from the Ethic Committee of Phramongkutklao College of Medicine, Thailand with a waiver for informed consent (Issued No. S048h/58).

Definitions

The target range of INR is 2.5-3.5 for mechanical valve replacement in mitral position and aortic position with condition (e.g. AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions or an older generation mechanical AVR (such as ball-in-cage) and 2.0-3.0 for tissue valve and mechanical valve replacement in aortic replacement position without condition according to the guideline for management of oral anticoagulant for valvular heart disease.[2]

Drug or herb interaction with warfarin is drugs or herb that interact with warfarin which can increase or decrease the activity of warfarin.[7] In this study, determine significant between warfarin and drugs or herbs interaction by Drug – Drug interaction facts and literatures had been recorded. Of medications, antibiotics (e.g. co-trimoxazole, metronidazole, macrolides and fluoroquinolones), antifungals (e.g. fluconazole, miconazole), rifampicin, antiplatelet agents (e.g. acetylsalicylic acid, clopidogrel, ticlopidine) amiodarone, anti-inflammatory agents including selective cyclooxygenase-2 inhibitors, and acetaminophen were reported as drug interaction with warfarin. For herbal products or dietary supplements such as Gingko biloba, dong quai, ginseng, garlic, fish oil and vitamin E significantly interact with warfarin. We gathered data about interaction from outpatient charts that there were recorded by pharmacist.

Participants

Eligible patients were recorded by ICD10 related to prosthetic heart valve (Z95.2). The inclusion criteria in this study consisted of 1) age of 18 years or older 2) being diagnosed with underwent heart valve replacement, and 3) being initiated warfarin at Phramongkutklao Hospital in study period. Exclusion criteria were patients transferred to the other hospital and whose follow-up information could not be obtained, patients with incomplete medical record data and pregnancy and lactation were also excluded.

Data collection

Patients'data including gender, age, type of prosthetic valve, co-morbidities, other medication used with warfarin, albumin level, AST level, ALT level, thyroid function test, warfarin initial dosing regimen were collected. The herbs or dietary supplements used that can interact with warfarin were collected from warfarin data form by pharmacist. The primary outcome is the out-of-range INR target, the therapeutic and toxicity monitoring parameters among patients taking warfarin that target INR were 2.5-3.5 for mechanical valve replacement and 2.0-3.0 for tissue valve replacement according to the guideline for management of oral anticoagulant for valvular heart disease.[2]

Statistical analysis

Descriptive statistics were used for analyzing the data via R-program version 3.5.1. All variables were analyzed using descriptive statistics to determine percentage of demographic data (e.g. gender, age, type of prosthetic valve, co-morbidities, social history). Chi-square or Fisher's exact test, as appropriate, was used to determine the correlation between the categorical factors. The risk factors were analyzed by Chi-square or Fisher's exact test and logistic regression analysis. All significant variables in the univariate analysis as a p-value < 0.1 were further tested by the multivariate logistic regression. The dependent variable was out-of-range INR target, whereas the independent variables previously described included gender, type of prosthetic valve, smoking, alcohol comsumption, hepatic disease thyroid disease, non-compliance and drug interaction.[8] Statistical significant level for all tests was set at a type I error of 5%.

Results

A total of 119 patients were collected during the study period. Sixty-four cases were male (53.78%) and mean (±SD) age was 55.09±14.78 years old. The mean (±SD) of body weight was 61.48±13.97 kilograms. Most of the cases had mechanical valve replacement was 80.67 percent. Position of valve replacement were mitral valve (65.55%), aortic valve (20.17%), mitral valve with aortic valve (10.08%), and others (4.20%), respectively.

For the social history, twelve cases were smoking and seventeen cases were alcohol consumption. The top five rank of comorbidity were atrial fibrillation (36.97%), hypertension (36.13%), dyslipidemia (19.33%), diabetes mellitus (10.92%), and ischemic stroke (5.04%), respectively (Table 1). More than half of patients (103 cases) receiving warfarin had INR values out of target range and minority (16 cases) had reaching within their target of INR.

Focusing on the lists of drug interaction, amiodarone, lipid-lowering drugs and doxycycline were used to study patients taking warfarin. Moreover, Panax ginseng (chainease gingseng), Ginkgo biloba (ginkgo), Allium sativum (garlic), Andrographis paniculata (Echinacea) and Curcuma longa (Echinacea) were mostly used in participants taking warfarin.

According to the results above, drug interaction was the only factor that nearly correlated with out-of-range INR target from univariate analysis whereas the other factors including gender, type of valve replacement, smoking, alcohol consumption, hepatic disease, thyroid disease, non-compliance and high vitamin K intake were not associated with INR value. (Table 2).

Table 1 Demographic and clinical characteristics of 119 patients who received warfarin underwent heart valve replacement

Characteristics	Value
Gender	
Male	64 (53.78)
Female	55 (46.22)
Age (Mean ± SD, year)	55.09 ± 14.78
Weight (Mean ± SD, kilogram)	61.48 ± 13.97
Type of valve, no (%)	
Mechanical valve	96 (80.67)
Tissue valve	22 (18.49)
Not reported	1 (0.84)
Valve position, no (%)	
Mitral valve	78 (65.55)
Aortic valve	24 (20.17)
Mitral valve with aortic valve	12 (10.08)
Others*	5 (4.20)
INR in target range, no (%)	
Yes	16 (13.45)
No	103 (86.55)
INR values (Mean ± SD)	
Mechanical vale	2.50 ± 1.45
Tissue valve	2.36 ± 1.15
Herbs or dietary supplements used, no (%)	
Used	14 (11.76)
Not reported	105 (88.24)
Social History, no (%)	
Smoking	12 (10.08)
Alcohol consumption	17 (14.29)
Co-morbidities, no (%)	
Atrial fibrillation	44 (36.97)
Hypertension	43 (36.13)
Dyslipidemia	23 (19.33)
Diabetes mellitus	13 (10.92)
Ischemic stroke	6 (5.04)
Others**	24 (20.17)

Others* = tricuspid valve replacement or tricuspid valve with mitral valve replacement

Others** = heart failure, chronic kidney disease, hepatic disease, coronary artery disease, rheumatoid arthritis, thyroid disorder, gout

Table 2 Factors effect to out-of-range INR target in patients who received warfarin underwent heart valve replacement (n=119)

Factors	Univariate analysis	
	Odd ratio (95%CI)	*p*-value
Age > 60 years	1.65 (0.57-4.81)	0.356
Male	1.19 (0.42-3.42)	0.744
Mechanical valve replacement	2.27 (0.70-7.39)	0.164
Underlying diseases		
Chronic kidney disease	0.60 (0.06-5.79)	0.521
Heart failure	0.28 (0.05-1.69)	0.184
Hepatic disease	0.30 (0.03-3.48)	0.354
Thyroid disease	0.61 (0.06-5.79)	0.521
Cancer	0.30 (0.03-3.48)	0.354
Smoking	1.79 (0.22-14.92)	1.000
Alcohol consumptions	2.76 (0.34-22.38)	0.463
Non compliance	2.17 (0.26-17.80)	0.690
Drug interaction	10.17 (0.59-175.77)	0.051
High vitamin K intake	0.61 (0.06-5.79)	0.521

Discussion

Warfarin has been used for treatment and prevention of systemic thromboembolism and cardioembolism.[1] The important limitation for warfarin used that pharmacokinetic were complicated. The several studies were report about many factors affect to warfarin.[1] Old age, body weight, genetic polymorphisms, co-morbidities (including chronic kidney disease, heart failure, liver disease or cancer) are patient's factors influencing to warfarin. Therefore, other factors are vitamin K consumption, drug-drug interaction, drug – herb interaction and drug – dietary supplement interaction.[9] The target INR range for most indications of warfarin therapy is 2.0–3.0 or 2.5–3.5. 2) The number of patients achieved INR target were less than prior report.[8,10] The reason was most of participants were elderly patients and there were received polypharmacy. In addition, the physician considered to set the INR target lower than 2.0 in some patients because there are high risk of bleeding. The genetic of Thai people, as CYP2C9 and vitamin K 2,3 epoxide reductase complex subunit 1 (VKORC1) trend to increase bleeding tendency.[11,12]

In this study, gender did not affect the achieving INR target value which was concordant to other studies.[8] Hepatic disease and thyroid disorder did not show statistical significant that contrast to previous report due to a few patients with these comorbidities.[13] Previous studies provided the effect of thyroid dysfunction that hypothyroidism effect to decreased INR value by decreasing metabolism of clotting factors and hyperthyroidism affected to increased INR value by increasing metabolism of clotting factors.[14,15] Liver disease is well documented to increase response to warfarin because it could decrease metabolism of warfarin.[16] Unfortunately, liver function test were not complete reported in our study.

Drug interaction is the nearly one factor affected out-of-range INR target. As almost patients with drug interaction between warfarin and other medications or herbs did not achieve INR target value. Warfarin interacts with many prescription and herbal and natural products. Many drugs affect the

absorption, metabolism, increasing or decreasing its levels and activity of warfarin. Absorption of warfarin is inhibited by some medications such as cholestyramine or sucralfate.[17] Warfarin undergoes approximately 60% oxidative metabolism, primarily by 4 cytochrome P450 (CYP450) isoforms, CYP1A2, CYP2C9, CYP3A4, and to a lesser extent, CYP2C19. Warfarin is inhibited by medications that induced CYP450 such as rifampicin (CYP3A4), phenytoin (CYP2C9) and carbamazepine (CYP2C9) to decreased INR. In addition, warfarin also interacts with other medications that enhance anticoagulation effect, including amiodarone, gemfibrozil, metronidazole, and azole-antifungals to increased INR.[17]

In recent years, people are becoming more knowledgeable regarding how to use vitamins and dietary supplements. The results from this study showed two-third of patients with drug interaction found dietary supplements or herbs-drug interaction. The most commonly found herbs-drug interaction which increased INR were ginseng, Ginkgo biloba, garlic and ginger while green tea and chlorophyll extract reduced INR value. There are dietary supplements or herbs well known like as a previous study in Asian country found the traditional Chinese herbs (American ginseng, dong quai, licorice, safflower, etc.) had potential interactions between these herbs and warfarin, a drug that is especially susceptible to herb-drug interactions due to its narrow or wide therapeutic range.[18]

One-third of patients with interaction were found drug interactions caused prolong INR values were amiodarone, doxycycline, fibrate and statins. The most of all, mechanism of drug interaction are pharmacokinetic interaction.[17] For example, amiodarone can increase INR values because it is potent enzyme inhibitors of CYP1A2, CYP2C9 and CYP3A4.[14] Others interaction decreased INR were phytonadione and phenytion. The results of the interaction between warfarin and medications or herbs affected INR concordant to previous studies.[13,19] The degree of drug interaction is expected to have an association with the achieving of INR target value, in the previous studies found that coadministered of nonsteroidal anti-inflammatory drugs (NSAIDs) had OR 3.16 (95%CI 1.17-8.54) for INR increased 20 and low INR values were observed during the concomitant use of warfarin and rifampicin (30%-50%).[21]

The clinical outcome was not collected because of the limitation of retrospective study. The pharmacist should concern about the drug-drug interaction, drug-herb and drug-dietary supplement interaction while patient were taking warfarin. Patient adherence, other medication or some condition uses from over the counter drug (OTC) or self-medication were also affected to INR values.

Conclusion

In conclusion, the present study showed that the interaction was important factor that nearly significant affecting out-of-range INR target including drug – drug and drug-dietary supplement interaction. However, other factors e.g. diseases or some condition were concerned. Thus, the healthcare professionals have to carefully monitor INR values in individual cases warfarin with risk factors use in order to make more safety and better efficacy.

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References

1. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133 (6 Suppl):160S-98S.
2. Ozkan J. ESC Clinical Practice Guidelines on the Management of Valvular Heart Disease-2017 Update. Eur Heart J. 2017;38:2697-8.

3. Holford NHG. Clinical Pharmacokinetics and Pharmacodynamics of Warfarin: understanding the dose-effect relationship. Clin Pharmacokinet. 1986;11(6):483-504.
4. Suwanawiboon B, Kongtim P, Chinthammitr Y, Ruchutrakool T, Wanachiwanawin W. The efficacy of 3-mg warfarin initiating dose in adult Thai patients, who required long-term anticoagulant therapy. J Med Assoc Thai. 2011;94(2 Suppl 1):S225-31.
5. Uygungul E, Ayrik C, Narci H, Erdogan S, Toker I, Demir F, et al. Determining risk factors of bleeding in patients on warfarin treatment. Adv Hematol. 2014;2014:369084.
6. Wigle P, Hein B, Bloomfield HE, Tubb M, Doherty M. Updated guidelines on outpatient anticoagulation. Am Fam Physician. 2013;87(8):556-66.
7. Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug-drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. Can Med Assoc J. 2007; 177(4):347-51.
8. Abdel-Aziz MI, Ali MA, Hassan AK, Elfaham TH. Factors influencing warfarin response in hospitalized patients. Saudi Pharm J. 2015;23:642-9.
9. Al-Momany NH, Makahleh ZM, Al-Omari NA, Al-Sarayreh HA, Momani RO. Analysis of factors that interrupt with INR control in the first anticoagulation clinic monitoring Jordanian patients. Clin Appl Thromb Hemost. 2019;25: 1076029619870252.
10. Bal U, Aydinalp A, Yilmaz K, Ozcalik E, Hasirci S, Atar I, et al. The effects of a low international normalized ratio on thromboembolic and bleeding complications in patients with mechanical mitral valve replacement. J Cardiothorac Surg. 2014;9:79.
11. Gaikwad T, Ghosh K, Shetty S. VKORC1 and CYP2C9 genotype distribution in Asian countries. Thromb Res. 2014;134:537-44.
12. Wattanachai N, Kaewmoongkun S, Pussadhamma B, Makarawate P, Wongvipaporn C, Kiatchoosakun S, et al. The impact of non-genetic and genetic factors on a stable warfarin dose in Thai patients. Eur J Clin Pharmacol. 2017;73(8):973-80.
13. Hirsh J, Dalen JE, Anderson DR, Poller L, Bussey H, Ansell J, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest. 2001;119(1 Suppl):8S-21S.
14. Holm J, Lindh JD, Andersson ML, Mannheimer B. The effect of amiodarone on warfarin anticoagulation: a register-based nationwide cohort study involving the Swedish population. J Thromb Haemost. 2017;15:446-53.
15. Busenbark LA, Cushnie SA. Effect of Graves' disease and methimazole on warfarin anticoagulation. Ann Pharmacother. 2006;40(6):1200-3.
16. Self TH, Owens RE, Sakaan SA, Wallace JL, Sands CW, Howard-Thompson A. Effect of diseases on response to vitamin K antagonists. Curr Med Res Opin. 2016;32(4):613-20.
17. Bungard TJ, Yakiwchuk E, Foisy M, Brocklebank C. Drug interactions involving warfarin: Practice tool and practical management tips. Can Pharm J. 2011;144(1):21-5.
18. Chua YT, Ang XL, Zhong XM, Khoo KS. Interaction between warfarin and Chinese herbal medicines. Singapore Med J. 2015;56(1):11-8.
19. Juurlink DN. Drug interactions with warfarin: what clinicians need to know. Can Med Assoc J. 2007;177(4):369-71.
20. Choi KH, Kim AJ, Son IJ, Kim KH, Kim KB, Ahn H, et al. Risk factors of drug interaction between warfarin and nonsteroidal anti-inflammatory drugs in practical setting. J Korean Med Sci. 2010;25(3):337-341.
21. Wada K, Kojima E, Takada M, Shibakawa M. Interaction of Warfarin and Rifampicin on Medical Report. Jpn J Pharm Health Care Sci. 2002;28(1):85-90.