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Effect of Patient-Specific Factors on Warfarin Dose in a Sample of Iraqi Patients

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Abstract: To explore the impact of different patient-specific factors on the daily warfarin maintenance dose. This is a cross sectional study which was conducted on 80 Iraqi patients of Arab ethnicity. The ethical approval of this study was obtained from the Medical College / Al-Nahrain University and conducted in accordance with the Declaration of Helsinki. After sample addition, tubes were transferred to the laboratory for PT&INR measuring. Demographics of gender, age, weight, and height, Body mass index (BMI) was calculated via weight and height as well as date of warfarin initiation, and indication, additional medical problems and concurrent medications were also recorded. Warfarin dose was not significantly correlated with gender and height, while it was significant with age but negatively correlated so as the age increased the dose decreased, and warfarin dose was highly significant with weight and body mass index and positively correlated so as the body weight increase warfarin dose increase. The target INR is highly not significant with dose. Simple linear regression equation showed a significant effect of age, height, weight, and BMI on daily warfarin maintenance dose with a no significant effect of gender. This study found that there is an impact of patient-specific factors on the daily warfarin maintenance dose. However, their effects were variable from one parameter to another.

Keywords: Warfarin, demographic, patient-specific, age, BMI.

INTRODUCTION

Warfarin is a widely used oral anticoagulant given for the prevention heart valves [1]. The wide inter- individual variation in drug response, and narrow therapeutic range with the risk of haemorrhage, all make warfarin a challenging drug to use clinically. Warfarin dose requirements, with the stability of anticoagulation and risk of hemorrhage are affected by environmental factors such as vitamin K intake, concomitant disease, age, gender, concomitant medication, and genetic factors [2].

Warfarin consist of two racemic isomers an (R)- and (S)- enantiomers. They differ in their plasma concentrations, antithrombotic potency and in the enzymes responsible for their metabolism, the S-form is 3–5 times more active than the R-form in the inhibitory effect on the target enzymeVKORC1and accounts for 60% to 70% of warfarin's anticoagulant activity Both enantiomers are metabolized by cytochrome *P*450's . S - warfarin is metabolized almost exclusively by CYP2C9, whereas CYP1A2, CYP2C19 and CYP3A4 are responsible for the metabolism of the *R*-enantiomer [3, 4]. Warfarin blocks the γ-carboxylation of glutamic acid residues in clotting factors II, VII, IX and X as well as endogenous anticoagulant proteins C&S. This interference results in coagulation factor molecules that are biologically inactive [5] .Warfarin do this by inhibiting vitamin K epoxide reductase component 1 (VKORC1), thus preventing the reductive metabolism of inactive vitamin K epoxide to its active hydroquinone form and thus exert its anticoagulant effect [6].

The effectiveness and safety of Warfarin therapy is critically dependent on maintaining the prothrombin time expressed as INR, (which is a ratio of the time required for the patient's blood to coagulate relative to a standardized coagulation time), within the desired therapeutic range [7]. Target INR usually2.5 except for mechanical heart valves in mitral position when target is (3.0 - 3.5) [8] .

Initiation of Warfarin therapy in patients is complex in which, initially a standard dose is prescribed and then adjusted based on observed response. But, stabilizing therapy may take weeks to months. Even after stabilization, INR is maintained in target range only 40-60% of the time [9, 10]. As a result, during the remaining un-protected time periods, especially during initiation of therapy, patients may be at an increased risk of haemorrhagic or thromboembolic complications [10] .

Stable warfarin dose to achieve a target INR of 2–3 can range from 1–20 mg/ day. The process to define the appropriate dose can take weeks to months [11]. This large variability in warfarin dose may be explained, by gender, nutritional status, concomitant medications, alcohol consumption, liver disease, hyperthyroidism, diarrhea, fever, chronic heart failure and more recently, ethnicity [12].

AIM OF THE STUDY

To explore the impact of different patient-specific factors like age, gender, weight, height, BMI and disease on the daily warfarin maintenance dose Patients, materials and methods.

This is a cross sectional study which was conducted on 80 Iraqi patients of Arab ethnicity. The participants were recruited from Ibn AL-Bitar Specialized Center for cardiac surgery in Baghdad. All the patients have been receiving continuous warfarin therapy for ≥ three months due to thromboembolic disorders including deep venous thrombosis, surgical cardiac valve replacement and those at risk of stroke. The exclusion criteria of the study were elevated prothrombin time (PT), Smoking &drinking alcohol, Renal failure, Hepatic failure, Pregnant women, advanced physiological age, terminal illness. Medication that effect the pharmacokinetic or dynamic of warfarin (eg. enzyme inducer or inhibitor). Food and herbs that interact with warfarin and effect PT level. The ethical approval of this study was obtained from the Medical College / Al-Nahrain University and conducted in accordance with the Declaration of Helsinki .Written informed consent was obtained from each patient. Venous blood sample was collected Greatest care was used during and after sample collection to avoid agitation to the sample. A volume of 2.5 ml was transferred to a sample tubes that contains 0.5 ml sodium citrate (1/10 volume sodium citrate). After sample addition, tubes were transferred to the laboratory for PT&INR measuring. Demographics of gender, age, weight, and height, Body mass index (BMI) was calculated via weight and height as well as date of warfarin initiation, and indication, additional medical problems and concurrent medications were also recorded.

Statistical analysis

All the variables are presented as mean and standard deviation (SD).The clinical factors were evaluated by t-test and ANOVA. Correlation between warfarin dose and the height, weight age, BMI, analyzed using Pearson correlation coefficient .Simple linear regression was performed to model the relationships of warfarin dose with patient-specific variables measured and used to develop a warfarin dosing algorithm. A P-value of≤0.05 was considered to be statistically significant. All Statistical analysis was performed using SPSS 17.0 software.

RESULTS

Characteristics of the study patients

A total of 80 patients were enrolled in this study .The mean age of all the patients involved in this study was (47.65 ± 10.12) years. The mean body mass index (BMI) of all patients was (26.09 ± 2.33) Kg/m², including 41 male (51.25%) and 39 female (48.75%).According to the underlying diseases, 51(63.75%) had hypertension, 11 (13.75%) had diabetes mellitus and 18 (22.5%) had no other disease. The average warfarin dose was4.29±1.69 mg per day and stable INR averaged 2.2 ± 0.82The demographic data of the patients were summarized in table-1.

Table-1: demographic characteristics of study patients

Variable		Value
Number		80
Gender	Male	41 (51.25%)
	Female	39 (48.75%)
Age (Years)		47.65 ± 10.12
Weight(kg)		74.33 ± 9.88
Height(cm)		168.68 ± 9.48
Body mass index(kg/m^2)		26.09 ± 2.33
Average of INR		2.315 ± 0.823
Warfarin dose(mg/day)		4.29 ± 1.69
Primary reason for anticoagulation	Stroke	6 (7.5%)
	CVR	70(87.5%)
	DVT	4(5%)
History of concomitant disease	hypertension	51(63.75%)
	Diabetes mellitus	11 (13.75%)
	Non	18 (22.5%)

Classification of patients according to Gender

The Men required higher daily doses of warfarin than women because the mean of the height and the body weight for the men is higher than the women table 2.

Classification of patients according to Age

Patients younger than 60 years required higher daily warfarin dosages than older patients table-3.

Table-2: Anthropometric data of study patients

Gender	Patients		Dose(mg) Mean ± SD	Weight(kg) Mean ± SD	Height(cm) Mean ± SD
	No.	%			
Male	41	51.25%	4.32 ± 2.01	78.05 ± 5.72	176.49 ± 4.27
Female	39	48.75%	4.26 ± 1.31	68.95 ± 6.51	160.23 ± 4.76

Note: No: number of patients

Table-3: Doses mean according to age

Age(year)	Dose(mg) Mean± SD
Patients younger than 60	4.45 ± 1.71
Patients older than 60	3.6 ± 1.47

Classification of patients according to the primary reason for anticoagulation therapy

About 87.5% of patients were on warfarin therapy due to heart valve replacement (n=70) while 7.5% (n=6) were complaining from stroke and bn 5% (n=4) were complaining from DVT (figure 1). The average INR of the patients was 2.32 ± 0.82.

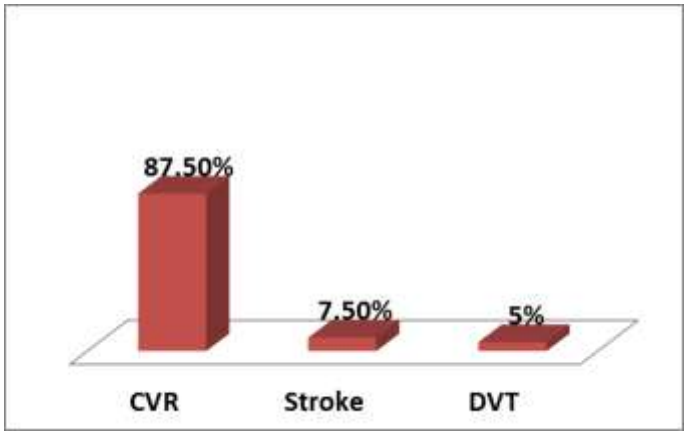

Fig-1: Distribution of patients by the type of disease

Classification of patients according to BMI

The sample was classified according to the classification of WHO and it was found that 24% of the patients were normal weight and 67.5% were overweight while on 30% were classified as obese (figure 2).the average body mass index was 26.09 ± 2.33kg/m^2.

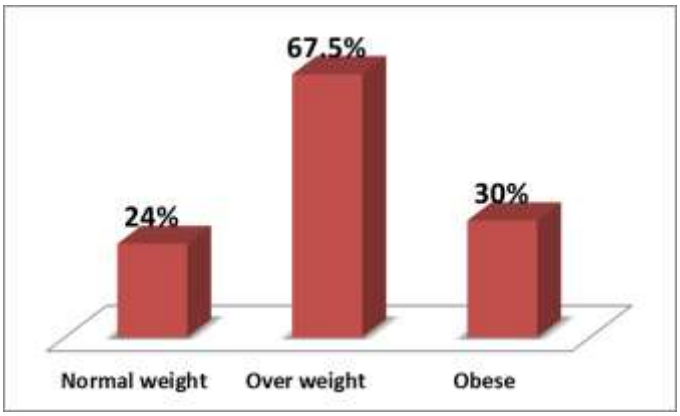

Fig-2: Distribution of patients by body mass index

t- Test for the effect of patient-specific variable

To test the mean effect for variables on warfarin dose and the following results appeared based on the present study data.

As the age increase the dose of drugs decrease as appears in our study patients because of an impaired metabolism and slower renal elimination rate of the drug and reduced synthesis of clotting factors (table 4 and 5).

Table-4: t-test value for patient specific variable

Variables	t-test	p-value
Gender	-0.161	0.873
Age (Years)	41.981**	0.000
Weight(kg)	67.268**	0.000
Height(cm)	159.116**	0.000
Body mass index(kg/m^2)	100.202**	0.000

Note:**; highly significant

Table-5: t-test for the difference between warfarin dose according to age

Age	No.	Warfarin dose Mean ± SD	t-test	p-value	Test for Difference
More than 60	15	3.6±1.466	9.509	0.000	t=1.949
Less than 60	65	4.446 ±1.712	20.94	0.000	P=0.063

Correlation of patient -specific variables with dose

Pearson correlation coefficient was used and the following results appeared based on the present study data (table 6).

In the above table the value of Pearson correlation coefficient revealed that warfarin dose was not significantly correlated with gender and height, while it was significant with age but negatively correlated so as the age increased the dose decreased, and warfarin dose was highly significant with weight and body mass index and positively correlated so as the body weight increase warfarin dose increase. The target INR is highly not significant with dose.

Table-6: correlation-value of patients-specific variables with dose

Variables	r	p-value
Gender	0.018	0.874
Height(cm)	0.165	0.144
Age (Years)	-0.212*	0.049
Weight(kg)	0.546**	0.000
Body mass index(kg/m^2)	0.538**	0.000
Target INR 2-3.5	0.048	0.647

**highly significant; *significant

Simple Linear Regression for patient-specific variables with dose

Linear regression analysis was performed to estimate the relative contributions of (age, gender, weight, height, body mass index) to dose (table 7). From the simple linear regression equation in the table the physician can predict warfarin dose based on:

a) Age: the significant equation demonstrate that the increase in age by one year require dose reduction by 0.035mg and R^2=4.5% present the percentage that age variable will explain from the changes occurring to warfarin dose .
b) Gender: not significant equation in dose, that R^2 =0.0% meaning that gender variable will not explain any changes occurring to warfarin dose.
c) Height: not significant equation in dose, and R^2 =2.7% meaning that height variable will explain only 2.7 % from the changes occurring to warfarin dose.
d) Weight: the significant equation demonstrate that the increase in weight by one kilogram require increase in dose by 0.093mg and R^2=29.8 % present the percentage that weight variable will explain from the changes occurring to warfarin dose.
e) Body mass index: the significant equation demonstrate that the increase in BMI by 1kg/m^2 will increase the dose by0.39 mg one kilogram require increase in dose by 0.093mg and R^2=28.9 % present the percentage that BMI variable will explain from the changes occurring to warfarin dose.

Table-7: Simple Liner Regression equations for predicting warfarin daily dose

Variables	Simple regression	p-value	R^2
Age(year)	Dose = 5.973-0.035 (age)	0.049	4.5%
Gender	Dose = 4.196+0.061 (gender)	0.874	0.000
Height (cm)	Dose = - 0.680+0.029 (height)	0.144	2.7%
Weight(kg)	Dose = - 2.658 +0.093 (weight)	0.000	29.8%
Body mass index (kg/m^2)	Dose= - 5.909+0.39 (BMI)	0.000	28.9%

DISCUSSION

This study was designed to analyze the influence of patient- specific factors on warfarin dose in Iraqi patients .our study included patients with target INR2-3.5 the correlation coefficient of 0.048 indicated that the target INR had a low influence on warfarin dose in our study group.

The present study demonstrated significant positive correlations between warfarin dose and each of body mass index(r=0.538),the regression analysis quantified positive association that is statistically significant .It is probably that the variation in warfarin-dose requirements are attributable to body size, higher daily warfarin doses were prescribed to heavier and taller patients. These results are also consistence with the finding by [13]. Other study found that height has a greater predictive value of warfarin dose than does body weight or BMI [7].

A very weak correlation existed between gender and warfarin dose (r=0.018) although not statistically significant ,Men required higher daily doses of warfarin (78.05± 5.72) than women (68.95 ± 6.51)This can be explained by anthropometric variations between men and women, as men had higher weight and were taller in comparison with women. This finding is similar with previous studies reporting lower doses for women compared to men [12, 14].

Significant correlations between warfarin dose and body height and weight have been presented by other studies as well [15, 16]. Patient's body weight and height indirectly reflect the warfarin distribution level within the human body, which theoretically is the volume of fluid in which drug must be dissolved to produce the required plasma concentration. Warfarin is an acidic drug, so its characteristic feature is binding especially to plasma albumin, with concomitant low absorption by tissues [17].

In previous studies [7, 12, 18, 19] warfarin dose was decreased as the age increased which agrees with the present study that warfarin dose is inversely proportion with age (r= - 0.212), decreasing by approximately 0.035mg per 1 year between the ages of 30to 65 years .In our study group Patients younger than 60 years needed higher daily warfarin doses (4.45 mg± 1.71) than older patients (3.6 mg± 1.47), These results are also in consistence with the finding by [16]. This is a result of an impaired metabolism of medications in the elderly [20], a slower renal elimination rate of warfarin metabolites, which have anticoagulant effect and altered synthesis of clotting factors. Impaired vitamin K absorption and a slower rate of oxidized vitamin K reduction in the elderly result in decreased synthesis of coagulation factors [21].

It was found that 63.75% of the patients involved in this study have hypertension which was higher than that reported in Korean patients study 24.8% [13], and Indian patient study19.3% [22], and chines patients 54% [23] and 13.75% of the patients were diabetic which was also higher than other studies [13, 22].The primary reason for warfarin therapy in this study was due to heart valve replacement because the study patients from Ibn AL-Bitar Specialized Center for cardiac surgery this was in consistence with the finding by [22, 24, 25].

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