فراوانی دو واریانت ژن VKORC1 و ارتباط آن با مقدار دوزِ مورد نیاز وارفارین در بیماران ایرانی تعویض دریچه‌های قلب

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چکیده. وارفارین متداول‌ترین داروی ضدانعقادی مورد تجویز برای درمان و پیشگیری از ترومبوآمبولی است. نیاز به دوزهای متفاوت وارفارین در افراد مختلف وابسته به عوامل ژنتیکی و محیطی است. در این مطالعه فراوانی دو پلی‌مورفیسم ژنتیکی مهم ژن زیرواحد ۱ کمپلکس‌ویتامین K اپوکسیدردوکتاز (*VKORC1*) ((1173 C>T(rs9934438 و (3730 G>A (rs7294) و ارتباط آن با میزان دوزِ مورد نیاز وارفارین در بیماران با دریچه های قلبی تعویض شده در استان آذربایجان غربی ارزیابی گردید. بدین منظور، ۱۸۵ بیمار که حداقل به مدت۲ ماه نسبت نرمال شده بین المللی(INR) پایدار داشتند، مورد مطالعه قرار گرفتند. برای تعیین ژنوتیپ بیماران از تکنیک واکنش زنجیره ای پلیمراز- چند شکلیِ طول قطعه محدودشونده (PCR-RFLP) استفاده شد. بررسی تفاوت دوز بین گروه‌های ژنوتیپی با آنالیز واریانس یک طرفه و آزمونِ Tukey's post-hoc صورت گرفت. فراوانی الل مینور(T) در افراد مورد مطالعه برای C>T 1173، ٪ ۵۴ و آلل مینور A برای G>A 3730 ٪ ۵۳/۷ بود. بیمارانی که حامل الل مینور T 1173 و الل اصلی G 3730 بودند به طور معنی‌داری به میزان متوسط دوز روزانه پایین‌تری از وارفارین نیاز داشتند ($P < 0.001$). این مطالعه نشان می‌دهد که در بیمارانی که دریچه‌ی قلب آنها تعویض شده است، در نظر گرفتن پلی-مورفیسم‌های موجود در ساختار قطعه ژنیِ *VKORC1*، در تجویز دوز مناسب وارفارین بویژه در مرحله شروع درمان مفید است و این نیز، به نوبه خود، عوارض ناشی از مصرف میزان نامناسب وارفارین را کاهش خواهد داد.

واژه‌های کلیدی. چند شکلی طول قطعه محدود شونده، دوز دارو، شخصی سازی درمان، واکنش زنجیره ای پلیمراز

Frequency of two *VKORC1* gene variants and its correlation with warfarin maintenance dose

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Abstract. Warfarin is a commonly-prescribed anticoagulant used to treat and prevent thromboembolic events. The requirement for varying doses of warfarin depends on genetic and environmental components. In this study, the frequency of two single-nucleotide polymorphic variants of the vitamin K epoxide reductase complex subunit 1 (*VKORC1*) gene (1173 C>T (rs9934438) and 3730 G>A (rs7294)) and its correlation with warfarin maintenance doses were investigated in patients with heart valve replacement from West Azarbayejan, Iran. Blood samples were obtained from 185 patients; their genomic DNA was extracted and samples were genotyped by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) assay. To assess if the blood warfarin level is different among genotypes, we used a one-way analysis of variance (ANOVA) followed by a Tukey's post-hoc comparison. The minor allele frequency was determined to be 54% for 1173T and 53.7% for 3730A. Patients who carried the G allele at position 3730 and T allele at position 1173 required a significantly lower daily mean warfarin dosage (P <0.001). Consideration of the *VKORC1* gene polymorphism, especially at the initial stages of the therapy, can be helpful in pre-treatment dosing of warfarin, which, in turn, reduces the adverse effects resulting from inappropriate drug prescription.

Keywords. drug dose, personalised treatment, polymerase chain reaction, restriction fragment length polymorphism

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INTRODUCTION

Warfarin is one of the most widely prescribed anticoagulants in modern medicine. However its application could cause adverse effects due to its narrow therapeutic range (Zhang *et al.*, 2016). Owing to interindividual variations, it is difficult to predict the anticoagulating efficiency of warfarin in response to a stable dose, especially at the initial stages of its use (Sconce *et al*., 2006). *VKORC1* gene encodes the vitamin K epoxide reductase (VKOR), which is a key enzyme in vitamin K cycle and the molecular motivator of warfarin.

Warfarin impairs the synthesis of functional coagulation factors by inhibiting VKOR (Oldenburg *et al*., 2007). Mutations and polymorphism in *VKORC1* lead to various phenotypic symptoms, including warfarin resistance or sensitivity and a rare bleeding disorder called vitamin K-dependent clotting factor deficiency type 2 (VKCFD2) (Rost *et al*., 2004). D'Andrea *et al.* (2005) described two common variants in *VKORC1* gene, 1173C>T in the intron and 3730 G> A in the 3'UTR region of the gene. These variants are in linkage disequilibrium with -1639 G>A and have been shown to be associated with warfarin dose requirements (Bodin *et al*., 2005). Different allelic frequencies have been observed for 1173C>T and 3730 G>A variants of *VKORC1* in the investigated ethnic groups worldwide (Salehifar *et al*., 2012).

Iran is a home to diverse ethnic groups who historically colonized in different parts of the country. While interbreeding has been common among these ethnics, many of them could still be discriminated phenotypically. Nevertheless, there are only limited data on the genetic polymorphism of warfarin metabolism in Iranians based on the studies on a small number of patients (Poopak *et al*., 2015). This study aimed to assess the allelic and genotypic frequencies of the two *VKORC1* variants and evaluate their correlation with warfarin maintenance doses among patients mostly with heart valve replacement from Iran.

MATERIALS AND METHODS

Subject and criteria

This study was performed between February 2016 and March 2017 on a total of 185 patients with heart valve replacement (112 females and 73 males) aged 25-86 in heart replacement patients of West-Azarbayejan, Iran. Patients who received warfarin maintenance doses less than 1.5 mg/day were considered as warfarin-sensitive. Patients with more than 7.5 mg/day warfarin were considered to be warfarin-resistant.

Patients with an intermediate dosage of warfarin (1.5 to 7.5 mg/day) were considered to be the control group. Patients who had stable doses and the international normalized ratios (INRs) in the range of 2.5-3.5 within the last 2 months were included in the study. The excluded subjects were patients who suffered from cancer, liver and kidney diseases. Questionnaires were prepared to evaluate demographic factors such as age, weight and ethnicity. The study was approved by the Scientific and Ethical Committee of Urmia University of Medical Sciences (Ir.umsu.rec.1394.282).

Genotyping of *VKORC1* variants

A volume of 2ml of the peripheral blood obtained from each patient was transferred to EDTA-containing tubes in order to prevent clotting, and stored at -20°C prior to the experiment. Genomic DNA was extracted from individual blood samples by employing DNA extraction mini-kit (YTA Company, Iran) according to the manufacturer's instructions.

To detect polymorphism in *VKORC1* gene, a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis was carried out according to D'Andrea *et al.* (2005) and Li *et al.* (2006). PCR reactions were performed at a final volume of 25µl, containing 1µl of each of the forward and reverse primers which were ordered from NEB company, 0.2µl dNTPs, 2.5µl PCR buffer, 17µl double-distilled H_2O and 3µl of the sample DNA.

Amplification protocol consisted of an initial DNA denaturation for 5 minutes at 94ºC, 30 cycles of DNA denaturation for 30s at 94ºC, primer annealing for 30s at 59ºC, and DNA extension for 30s at 72ºC, followed by a final extension at 72°C for 5 minutes. The PCR products were digested with 1 unit of each of the restriction enzymes in a final volume of 30 µl in an appropriate 10X Tango buffer at a temperature of 37°C for at least 5 hours. *HinfI* (NEB) restriction endonuclease was used for *VKORC1* 1173C>T, while *SsiI* (Fermentas MBI) was applied to digest *VKORC1* 3730 G>A. The digestion products were analyzed by electrophoresis on 2% Agarose gel.

Table 1. Genotype frequency of *VKORC1* genetic polymorphisms in the present study (n=185)

Categorical Variables	Categories	n	%
Genotype 1173	CC	38	20.5
	CT	94	50.8
	TT	53	28.6
Genotype 3730	AA	66	35.7
	GA	67	36.2
	GG	52	28.1

Statistical analysis

The genotypic distribution of the single nucleotide polymorphism (SNP) was evaluated and checked against the Hardy-Weinberg equilibrium (HWE) using the Chi-square goodness-of-fit test with a degrees of freedom (*df*) of one. To analyze the differences in warfarin dosage among the three genotypes, a one-way analysis of variance (ANOVA) test was applied, followed by a Tukey's post-hoc test.

The Boxplot analysis was performed to display the dispersion and skewness of the genotyping data graphically. Multiple linear regressions, used to find the *VKORC1* genotypes, were coded as 1 for the wild-type, 2 for heterozygous and 3 for homozygous. Statistical analysis was conducted following the insertion of the data into the IBM SPSS version 21 (IBM SPSS Inc., Chicago, IL). The statistical level of significance was set at $P < 0.05$.

RESULTS AND DISCUSSION

Digestion with *HinfI* restriction enzyme resulted in the production of two fragments of 353 and 8bp in length from a 361bp amplicon in patients with the wild-type (CC) genotype. In patients with the mutant genotype of TT, the amplicons were digested into 3 fragments of 310, 43 and 8bp, and in patients with heterozygote CT genotype, four segments of 353, 310, 48 and 8bp in length were produced. The genotype frequencies of 1173 C>T were 20.5%, 50.8% and 28.6% for CC, CT and TT genotypes, respectively (Table 1).

For the 3730 G>A (rs7294) variant, **226**bp DNA fragment was amplified. After using the *SsiI* restriction enzyme, the presence of the mutant allele A was indicated by loss of the *SsiI* site, and a single band of **226**bp was observed. Patients with wild GG genotype produced **195** and **31**bp fragments. In heterozygous patients with GA genotype, the amplicons were digested into 3 fragments of **226, 195 and 31bp**. The genotype frequencies of the 3730 G>A variant were 28.1%, 36.2% and 35.7% for GG, GA and AA genotypes, respectively (Table 1). The minor allele frequency was determined to be 54% for 1173T and 53.7% for 3730A. No significant deviation of the variants from Hardy-Weinberg equilibrium was noticed ($P > 0.05$).

Comparison of warfarin daily maintenance doses among the genotypic groups showed that daily mean dose of warfarin in 1173 CC patients was 7.65 ± 1.87mg, which is significantly higher than those for 1173 CT (4.07 ± 1.44 mg) and 1173 TT patients (2.16 ± 1.31 mg) ($P < 0.001$). The daily mean dose of warfarin in 3730 GG patients was 3.52 ± 2.28 mg, which is significantly lower than those for 3730 GA (4.35 ± 2.13 mg) and 3730 AA patients (4.75 ± 2.70mg) ($P < 0.015$).

Distribution of the warfarin doses within the varying genotypes are illustrated in Table 2. Genotypic pattern was significantly different among the warfarin dosage groups for *VKORC1* 1173 C>T ($P < 0.001$) but not for 3730 G>A (Fig. 1).

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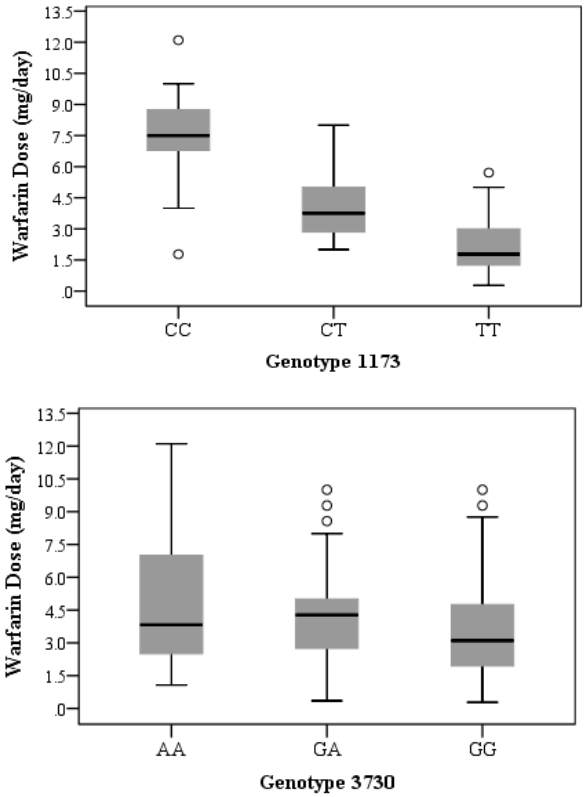


Fig. 1. Box plot of daily warfarin dosage (mg/d) against the *VKORC1* 1173 C>T and 3730 G>A variants. Vertical lines at the ends of boxes indicate the minimum and maximum values. (see Table 1 for details).

Table 2. Results of the one-way ANOVA analysis showing the relationship between genetic variants and warfarin requirements dose (n=185). Data with different alphabetic letters are significantly different (Tukey's HSD pairwise comparisons).

SNP	Categories	Mean ± SD	Median (IQR)	$F_{(2,184)}$	P-value
1173C>T	CC	[a]7.65 ± 1.87	7.50 (2.10)	135.44	<0.001
	CT	[b]4.07 ± 1.44	3.75 (2.15)		
	TT	[c]2.16 ± 1.31	1.78 (1.75)		
3730G>A	AA	[a]4.75 ± 2.70	3.83 (4.63)	4.30	0.015
	GA	[ab]4.35 ± 2.13	4.28 (2.50)		
	GG	[b]3.52 ± 2.28	3.10 (3.01)		

Final regression model results of warfarin dose requirement showed the significant effect of age, body mass index, hypertension and *VKORC1* 1173 C>T SNP on warfarin dose (P<0.001) (Table 3). The negative impact of age was significant on warfarin dose (β=-0.017, P=0.019). Body mass index positively correlated with warfarin dose requirement (β=-0.013, P=0.038). Hypertensive patients had a higher warfarin dose requirement (β=0.161, P=0.028). Azari ethnic patients required a lower dose of warfarin (β=-0.017, P=0.042). The examination of the *VKORC1* 1173 C>T polymorphism effect indicates that patients with CC (β=1.211, P<0.001) and CT genotypes (β=0.511, P<0.001) have higher warfarin dose requirement compared to TT genotype (Table 3).

Final regression model results of warfarin dose requirement for *VKORC1* 3730 G>A showed hypertension (β=0.169, P<0.04) and diabetes (β=0.376, P<0.006) were positively associated with warfarin dose requirements, while age (β=-0.018, P<0.001), ethnicity (β=-0.239, P<0.031) and *VKORC1* 3730 G>A polymorphism had negative correlations with warfarin dose requirements. Patients with AA (β=-0.34, P<0.001) and GA (β=-0.239, P=0.017) of *VKORC1* 3730 G>A had lower warfarin dose requirement compared with AA genotype (Table 4).

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Table 3. Final backward regression model of warfarin dose requirements affected by significant demographic and clinical variables and *VKORC1* 1173 C>T.

Variables	Categories	Beta	Std. error	CI 95%	P-value
Intercept		1.57	0.21	(1.14 , 1.99)	<0.001
Age		-0.017	0.003	(-0.02 , -0.01)	0.019
BMI*		0.013	0.006	(0.01 , 0.03)	0.038
Hypertension	Positive	0.161	0.072	(0.02 , 0.31)	0.028
	negative	0	.	.	.
Ethnicity	Azaris	-0.171	0.085	(-0.34 , -0.02)	0.042
	others	0	.	.	.
VKORC1 1173 C>T	CC	1.211	0.101	(1.01 , 1.41)	<0.001
	CT	0.511	0.077	(0.36 , 0.66)	<0.001
	TT	0	.	.	.

CI: Confidence Interval.
Square root transformation was done on warfarin dose value.
R^2 for model equal 59%.
Regression equation: SQRT (Dose) = 1.57 – 0.02 (age) + 0.01 (BMI) + 0.16 (hypertensive) - 0.17 (ethnic=Turks) + 1.21 (genotype-1173 =CC) + 0.51 (genotype-1173 =CT).
*BMI: Body Mass Index

Table 4. Final backward regression model of warfarin requirements affected by main demographic and clinical variables and *VKORC1* 3730 G>A.

Variable	Category	Beta	Std. error	CI 95%	P-value
Intercept		2.88	0.20	(2.49 , 3.27)	<0.001
Age		-0.018	0.003	(-0.02 , -0.01)	<0.001
Diabetics	Positive	0.376	0.126	(0.11 , 0.64)	0.006
	Negative	0	.	.	.
Hypertension	Positive	0.169	0.063	(0.02 , 0.36)	0.040
	Negative	0	.	.	.
Ethnicity	Azaris	-0.239	0.110	(-0.46 , -0.02)	0.031
	Others	0	.	.	.
VKORC1 3730 G>A	AA	0.242	0.100	(0.05 , 0.44)	0.016
	GA	0.239	0.099	(0.04 , 0.44)	0.017
	GG	0	.	.	.

CI: Confidence Interval.
Square root transformation was done on warfarin dose value.
R^2 for model equals 22%.
Regression equation: SQRT (Dose) = 2.88 – 0.02 (age) + 0.38 (diabetic) + 0.17 (hypertensive) - 0.24 (ethnic=Turks) + 0.24 (genotype-3730=AA) + 0.24 (genotype-3730=GA).
*BMI: Body Mass Index

Gamma-carboxylation of the coagulation factors (II, VII, IX and X) by vitamin K is essential in the initiation and regulation of blood coagulation. During the carboxylation, the vitamin K epoxide reductase enzyme reduces vitamin K to vitamin K 2,3-epoxide for recycling of vitamin K (Tie & Stafford, 2016). Warfarin inhibits vitamin K epoxide reductase and subsequently, the synthesis of coagulation factors by reducing the regeneration of vitamin K (Shen *et al.*, 2017).

Warfarin is an anticoagulant with narrow therapeutic index (Tamargo *et al*., 2015). High warfarin doses can cause the risk of potential lethal bleeding, whereas its low doses could make the patients not benefit from the therapeutic effect of this drug (Shoeb & Fang, 2013). Therefore, it is necessary to improve the protocols for warfarin therapy. One of the main pathways in the development of pharmacogenetics is the identification of genes and alleles that influence the response of individuals to the drugs (Wolf *et al*., 2000).

In addition to some of the mutations in the *VKORC1* gene, polymorphism has already been identified to be associated with the average warfarin dose requirement (Li *et al.*, 2006).

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D'Andrea *et al*. (2005) found that patients with CC genotype of the 1173 C>T variant required a higher dose of warfarin. In other words, the presence of the T allele in the 1173 *VKORC1* causes warfarin-sensitivity. They detected no alternative splicing caused by 1173 C>T SNP in *VKORC1* mRNA. In a case-control study by Reitsma *et al.* (2005), 110 warfarin-treated patients with bleeding and 220 controls patients without bleeding were evaluated. The results showed that, in order to achieve the same INR, patients who carried at least one T allele required lower doses of warfarin and had an increased risk of bleeding compared with the CC genotype patients at *VKORC1* 1173 C>T.

Salehifar *et al*. (2012) investigated the warfarin requirements of 29 patients with *VKORC1* 1173 C>T variant in Mazandaran Province, Iran. Twenty-six patients (84%) had TT genotype, whereas 2 patients (6.9%) had CT and one (3.4%) TT genotypes. According to their results, the required mean dose of warfarin in the patients with CT genotype was lower than that for the other two genotypes, but their INR was higher. Therefore, it was concluded that the heterozygote CT genotype increased the response to warfarin and reduced the maintenance dose requirements. Similar results were obtained by Kosaki *et al*. (2006) where 31 patients with 1173 C>T variant in intron 1 of their *VKORC1* gene were evaluated. Among them, 26 patients (84%) were homozygous TT, while 5 (16%) were heterozygous CT.

Our results show that, regardless of the existence of other variables, to keep INR stable, patients with 1173 T allele would require minor doses of warfarin and were mainly considered to be warfarin-sensitive. In a study conducted by Yuan *et al*. (2005), the 3730 G> A variant was spotted in the 3'UTR region of *VKORC1* gene in a number of Chinese patients. The 3730 G>A SNP was in linkage disequilibrium with -1639 G> A and 1173 C> T. The 3730 G allele was associated with the 1639 A and 1173 T alleles. In the study of Salehifar *et al.* (2012), it was demonstrated that 28 out of 29 patients (96.5%) had *VKORC1* 3730 GG genotype and only one patient (3.5%) was GA, and while GA genotype had higher warfarin dose requirement than GG genotype, the average warfarin dose in two genotypes did not differ significantly. Kosaki *et al*. (2006) figured it out that all the patients with TT genotype in the *VKORC1* 1173 C>T region had GG genotype in *VKORC1* 3730 G>A, and the patients with TC genotype in 1173 C>T had GA genotype in 3730 G> A. In other words, a complete linkage disequilibrium between 1173 C>T and 3730 G>A variants was observed.

In the study of D'Andrea *et al*. (2005) it was concluded that individuals with the 3730 AA genotype required a higher mean dose of warfarin in comparison with the GG or GA genotype carriers. This study investigated the allelic and genotypic frequencies of *VKORC1* patients from Northwestern Iran undergoing warfarin treatment and the effect of these genotypes on the required dose of warfarin. Our findings confirm the results obtained by earlier investigations state that genotyping of the patients for *VKORC1* gene polymorphism in the initial stages of warfarin therapy would be beneficial and could prevent the drug side-effects while increasing the medication efficiency.

CONCLUSION

In conclusion, the results of the present study showed that prescribing an appropriate dosing regimen of warfarin in accordance with the patient's pharmacogenetic data is beneficial. This study demonstrated that patients with *VKORC1* 1173T and 3730G variant alleles required a lower dose of warfarin and were mainly considered to be warfarin sensitive. Since the prevalence of these variants is high in the study population, it is important to consider this fact before prescribing warfarin.

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