Development and comparison of warfarin dosing algorithms in stroke patients

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Development and comparison of warfarin dosing algorithms in stroke patients

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ABSTRACT

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The genes for cytochrome P450 2C9 (*CYP2C9*) and vitamin k epoxide reductase complex subunit 1 (*VKORC1*) have been identified and studied as important genetic determinants of warfarin dosing. We developed warfarin algorithm for Korean patients with stroke and compared the accuracy of warfarin dose prediction algorithms based on the pharmacogenetics.

A total of 95 patients on stable maintenance dose of warfarin were enrolled. Warfarin dosing algorithm was developed using multiple linear regression analysis. The performance of all the algorithms was characterized with coefficient of determination, determined by linear regression, and the mean of percent deviation predicted doses from the actual dose. In addition, we compared the performance of the algorithms using percentage of predicted dose falling within ±20% of clinically observed dose and dividing the patients into a low-dose group (≤3mg/day), an intermediate-dose group (3-7mg/day), and a high-dose group (≥7mg/day).

A newly developed algorithm included the variables of age, body weight, and *CYP2C9* and *VKORC1* genotype. Our algorithm accounted for 46.5% of variation in stable warfarin doses. The predicted doses using algorithms derived from Anderson and this study showed the best

correlation with the actual maintenance doses. Our algorithm performed best in predicting dose within 20% of actual dose and intermediate-dose.

Our warfarin dosing algorithm may be useful for Korean patients with stroke.

Key words: *CYP2C9*, Korean, stroke, *VKORC1*, warfarin

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I. INTRODUCTION

Warfarin, the most commonly used oral anticoagulant in the world, is indicated for the prevention and treatment of thromboembolic events in patients with deep vein thrombosis, pulmonary embolism, atrial fibrillation and prosthetic heart valves. It is administered as a racemic mixture of the R- and S-enantiomers of warfarin. S-warfarin is more active isomer and has a higher rate of therapeutic effect. These enantiomers are extensively metabolized by various cytochrome P450 enzymes. R-warfarin is mainly metabolized by cytochrome P450 1A2 (CYP1A2), CYP2C19 and CYP3A4, while S-warfarin is predominantly metabolized by CYP2C9.[1] Both enantiomers affect the coagulation cascade by inhibiting the activity of vitamin K epoxide reductase complex 1 (VKORC1) and thus interfering with the activation of clotting

factors II, VII, IX and X.[2,3] However, despite its considerable benefit, warfarin is less frequently prescribed than it should be,[4] which is a result of a relatively high adverse event rate and the difficulty in managing the therapy.[5-7] Common adverse drug events (ADEs) arising from warfarin treatment include major and minor bleeding and hemorrhagic stroke.[8] ADEs are also frequently due to insufficient therapy: ischemic stroke and venous thromboembolism.[9] Warfarin, has narrow therapeutic index, shows not only large inter-individual variations in dose response but also intra-individual variation. Because patients' clinical characteristics such as age, gender, body weight, concurrent medications, diet, co-morbidities and patient compliance level have shown to have large influence in warfarin dosing,[10] frequently monitoring of its effect, as measured by the international normalized ratio (INR), is warranted.

CYP2C9 and *VKORC1* have been identified as important genetic determinants of warfarin dosing and have been studied. The most common *CYP2C9* genotype among all ethnic is *CYP2C9*1*, found in about 80% of Caucasians[11] and 93% of Korean.[12] Lindh et al[13] demonstrated that carriers of *CYP2C9*2* and *CYP2C9*3* alleles require less warfarin dose than carriers of wild type *CYP2C9*1* genotype. Different allelic frequency was also observed with the most common

single nucleotide polymorphisms (SNPs) in the *VKORC1* gene, 1173C>T (rs9934438). Around 35% of Caucasian carry CC genotype, while only about 15% carry the TT genotype. However, most of the Korean showed TT genotype, but less than 1% carry CC genotype.[14] Carriers of 1173CT and 1173CC genotype need 44% and 97% more warfarin dose than carriers of 1173TT genotype.[15] The clinical algorithms for determining warfarin dose containing clinical characteristics and pharmacogenetics information of the patients have been developed for more proper warfarin dose prediction. These algorithms are not intended to replace INR monitoring, but to increase the accuracy and reduce trial and error approach in warfarin dosing. According to International Warfarin Pharmacogenetics Consortium (IWPC) study,[16] the algorithms using clinical and genetic information increase the accuracy in dose prediction than a fixed-dose approach or algorithms derived from clinical information. In addition, those are useful especially in the patients who may be administered more or less than appropriate dose.[16]

Personalized dosing and INR monitoring is required, because response to warfarin is different according to indication and the state of the disease. Studies of warfarin dose assessment so far have looked at mainly targeted at valvular heart disease. Among the leading causes of death in Korea,

stroke is occupied in the second place. In order to prevent recurrence of this stroke, warfarin has been widely used. However, there were few studies about comparison of predictive power of warfarin dosing control based on pharmacogenetics. Therefore, this study reviewed prescribed dose and actual INR response in patients with stroke and compared the accuracy of 10 warfarin dose prediction algorithms based on the pharmacogenetics. In addition, warfarin dosing algorithm for Korean patients with stroke was developed to improve the quality of care for stroke patients.

II. MATERIALS AND METHODS

1. Study subjects

A total of 111 patients undergoing warfarin treatment for prevention and treatment of stroke and requesting genotyping of *CYP2C9* and *VKORC1* were recruited retrospectively at the neurology clinic at the Severance Hospital, Seoul, Korea. All study participants were enrolled between January 2009 and August 2014. Patients included were adults, whose warfarin dose requirement had remained constant for at least 3 previous clinic visits over a minimum period of 3 months, and with an INR of the prothrombin time within the range of 1.5 to 3.0.[17] Sixteen patients were excluded from the study according to enrolment criteria. This study was

approved by the Institutional Review Board of the Yonsei University Severance Hospital, Seoul, Korea. Written informed consent for genetic analysis was obtained from the patients.

2. Demographic and clinical data collection

Data were collected from patients' medical records. These data included demographic characteristics, comorbidities, the stable therapeutic dose of warfarin, the INR achieved with a stable warfarin dose, the use of concomitant medications, and the genotype of *CYP2C9* and *VKORC1*. The interacting drugs, which were defined based on previously published literature, were also reviewed.[18,19]

3. Genotyping

Genomic DNA was extracted from EDTA whole blood samples with QIAamp DNA extraction kit (Qiagen, Hilden, Germany). For determination of the *CYP2C9* genotype, the *CYP2C9*3* (1075A>C; rs1057910) SNP is selected. For *VKORC1* genotypes, the *VKORC1* 1173C>T (rs 9934438) SNP is determined. PCR and direct sequencing were performed using primers designed in Primer3 software (http://Frodo.wi.mit.edu/cgi-bin/primer3/primer3). Purified PCR products were obtained using a QIAquick Gel Extraction Kit (Qiagen, Düsseldorf, Germany) and were sequenced using a Big Dye Terminator Cycle

Sequencing Ready Reaction Kit (AppliedBiosystems, Foster City, CA, USA). Sequences were analyzed using an ABI 3500dx system (Applied Biosystems). To detect any sequence variations, the sequences were compared to the reference sequences using Sequencher software (Gene Codes, Ann Arbor, MI, USA).

4. Dosing algorithms

A literature search was performed from Pubmed database, with the search terms warfarin, algorithm, polymorphism, *CYP2C9* and *VKORC1*, to select warfarin dosing algorithms. Algorithms were included based on the following criteria; 1) Equations to predict maintenance warfarin dose. 2) Only two SNPs consisting of *VKORC1* 1173G>T (or *VKORC1* -1639G>A and 2255C>T) and *CYP2C9*2* and/or **3*. 3) Published in English.

Nine algorithms were selected from the literature that met our inclusion criteria. These are referred to as Sconce et al,[20] Anderson et al,[21] Gage et al,[22] Wu et al,[23] IWPC,[16] Wadelius et al,[24] Huang et al,[25] Ohno et al,[26] and Cho et al[27] throughout this manuscript. The aforementioned algorithms included adult patients with atrial fibrillation, venous thromboembolic diseases, recent orthopedic surgery, valvular disease, and stroke.

5. Data analysis

Stepwise multiple regression analysis was performed to develop new warfarin dosing algorithm and the results of univariate analysis were used to choice predictors for multivariate analysis. Comparison of warfarin doses between the different genotypes was performed using the Mann Whitney U-test. Predictive accuracy was assessed by comparing the dose predicted by the ten algorithms to actual dose which the patient was taking. Predicted dose was calculated using published equations, except Gage's calculated by input on the website http://www.warfarindosing.org. A best fit trendline and correlation coefficient were determined by linear regression. In addition, the mean of percent deviation of predicted dose from the actual dose was used to evaluate the predictive accuracy of each algorithm. In addition, we compared the performance of the algorithms using percentage of predicted dose falling within ±20% of clinically observed dose [28] and dividing the patients into a low-dose group (≤3mg/day), an intermediate-dose group (3-7mg/day), and a high-dose group (≥ 7mg/day).[16] All statistical tests were performed with a p-value < 0.05 significance. All analyses were performed using the Statistical Package for Social Science (SPSS18.0 SPSS science, Chicago, IL, USA).

III. RESULTS

1. Characteristics of the study groups

The characteristics of all 95 patients are listed in Table 1. This study included 95 patients with a mean age 64 years (SD, ±13.2) ranging from 27 to 88 years, including 62 males (65%). The mean body weight was 65.1kg (SD, ±10.5) and the mean BSA was 1.7 (SD, ±0.2). The mean stable warfarin dose was 3.75 mg/day (SD, ±1.43). Concurrent diseases associated with these patients included atrial fibrillation (62 patients, 65.3%), hypertension (47 patients, 49.5%), diabetes mellitus (25 patients, 26.3%), heart diseases including coronary arterial occlusive disease (13 patients, 13.7%), heart failure (6 patients, 6.3%), and cardiac valvular disease (9 patients, 9.5%). A total of 41 (43.2%) patients were receiving comedications that could affect the anticoagulation effect of warfarin, including amiodarone, aspirin, antiplatelet drugs, statins, thyroid hormone, and verapamil.

Table 1. Characteristics of the study population

Variables	n=95		
Men (%)	62/33	(65%/35%)	
Mean age (SD) (range) years	63.7	(13.2)	(27-88)
Body weight (SD) (range) kg	65.1	(10.5)	(44-90)
Mean BSA (SD) (range) m^2	1.7	(0.2)	(1.3-2.1)
Smoking patients (%)	23/95	(24.2%)	
Concurrent disease (%)			
Atrial fibrillation	62/95	(65.3%)	
Cancer	1/95	(1.1%)	
Cardiac valvular disease	9/95	(9.5%)	
CHF*/Cardiomyopathy	6/95	(6.3%)	
CAOD†	13/95	(13.7%)	
Diabetes mellitus	25/95	(26.3%)	
Hypertension	47/95	(49.5%)	
Hyperthyroidism	2/95	(2.1%)	
Hypothyroidism	1/95	(1.1%)	
Comedications			
Amiodarone	3/95	(3.2%)	
Aspirin	35/95	(36.8%)	
Antiplatelet drug	12/95	(12.6%)	
Statins	73/95	(76.8%)	
Thyroid hormone	1/95	(1.1%)	
Verapamil	24/95	(25.3%)	

*CHF: Congestive heart failure

†CAOD: Coronary arterial occlusive disease

2. Effects of genotype on stable dose of warfarin

Table 2 showed the daily warfarin dose of different genotypes. For *CYP2C9*, 91 patients (95.8%) were identified to be homozygous for *CYP2C9*1,* and 4 patients (4.2%) were heterozygous for *CYP2C9*3*. The frequency of the *VKORC1* 1173TT genotype was 83.2% and that of 1173CT genotype was 16.8%. In our study, no patients with homozygous *CYP2C9*3/*3* and *VKORC1* 1173CC genotypes were identified. The stable warfarin doses for patients with *VKORC1* CT genotype (4.6 ± 1.9 mg/day) were significantly higher than that of TT type (3.6 ± 1.2 mg/day). However, the difference in the stable warfarin doses between patients with homozygous for *CYP2C9*1* (3.8 ± 1.4 mg/day) and heterozygous for *CYP2C9*3* (2.6 ± 0.5 mg/day) was not significant.

Table 2. Effects of *VKORC1* 1173C>T and *CYP2C9* genotypes on warfarin stable dose

Genotype	n	warfarin dose (mg/day)	*p*-value
VKORC1 1173			
CC	0		
CT	16	4.6 ± 1.9	< 0.05
TT	79	3.6 ± 1.2	
*CYP2C9*3*			
*1/*1	91	3.8 ± 1.4	0.073
*1/*3	4	2.6 ± 0.5	
*3/*3	0		

3. Establishment of Dosing Algorithm

For multiple linear regression analysis, 4 variables including age, bodyweight, *CYP2C9*3* and *VKORC1* 1173 genotypes were selected (R^2=0.465, Table 3). We established the warfarin dosing formula with following equation: maintenance dose = exp {1.896 - 0.016(age) + 0.005(body weight) – 0.275(*CYP2C9* genotype) + 0.318(*VKORC1* genotype)}. It was coded as 1 in the case of the presence of the *CYP2C9* variant, or the presence of the *VKORC1* 1173 C allele.

Table 3. Contribution of individual variables to the algorithm

Variables	R (R^2_{adj})	Slope (beta)	Standard Error	p-value
All	0.699 (0.465)			
Age	0.606 (0.360)	-0.016	0.002	< 0.001
Body weight	0.002 (0.004)	0.005	0.003	0.074
CYP2C9 genotypes	0.015 (0.012)	-0.275	0.14	0.053
VKORC1 1173 genotypes	0.076 (0.097)	0.318	0.076	< 0.001

R^2_{adj}: R^2 adjusted.

4. Comparison of Dosing Algorithms

A comparison of the ten algorithms for determining warfarin maintenance dosing is shown in Table 4. Most algorithms that evaluated, including the dosing algorithm derived from this study, had a good correlation. However, the algorithms by Gage et al,[22] Wu et al,[23] and Huang et al[25] showed poor correlation. Algorithms from this study, Sconce et al,[20] Anderson et al,[21] and Ohno et al[26] produce similar accuracy with mean deviation ranging from -10.8 to 3.9. These algorithms were selected based on their correlation coefficient (r > 0.6) and the mean deviation from the actual dose (mean deviation about 10%) for further analysis. The does which was predicted by using the algorithm from this study was more accurate in telling whether it falls within ± 20% of clinically observed dose (Table 5), while other algorithms show

similar accuracy among them and less accuracy to the algorithm above. Algorithms by Sconce et al,[20] and Ohno et al[26] tend to underestimate in about 40% of cases. In addition, the accuracy of this study was better than others for patients who need intermediate-dose group (Table 6). For patients who need less than 3 mg/day, algorithm by Ohno was well performed. However, for patients who required more than 7 mg/day, all algorithms performed poorly, with underestimation for all patients.

Table 4. Comparison of the warfarin dosing algorithms

Algorithm	R	R^2 (R^2_{adj})	Mean Deviation %	Regression Equation
This study	0.684	0.468 (0.462)	2.8	y = 1.034x + 0.028
Gage et al	0.55	0.303 (0.295)	-3.6	y = 0.686x + 1.516
Sconce et al	0.613	0.376 (0.370)	-10.3	y = 0.952x + 0.753
Wu et al	0.398	0.159 (0.150)	46.9	y = 0.673x + 0.430
Anderson et al	0.68	0.463 (0.457)	3.9	y = 1.589x - 1.875
Ohno et al	0.676	0.458 (0.452)	-10.8	y = 1.648x - 1.293
Huang et al	0.464	0.215 (0.207)	-17.1	y = 0.958x + 1.042
Wadelius et al	0.621	0.386 (0.379)	49.9	y = 1.082x - 1.743
IWPC	0.673	0.453 (0.447)	-20.2	y = 1.421x - 0.198
Cho et al	0.642	0.412 (0.406)	-54.9	y = 0.080x + 1.212

R^2_{adj}: R^2 adjusted.

Table 5. Percentage of patients with an ideal, underestimated, or overestimated dose of warfarin as estimated by each algorithm

Algorithm	Ideal dose (%)	Underestimation (%)	Overestimation (%)
This study	53.7	21.1	25.3
Anderson et al	48.4	21.1	30.5
Sconce et al	45.3	40	14.7
Ohno et al	44.2	43.2	12.6

Ideal dose: predicted dose falling within ±20% of clinically observed dose

Table 6. Sensitivity analysis with low-, intermediate-, and high- dose patient groups

Algorithm	Subgroups based on the warfarin dose		
	≤ 3 mg/d (n = 47)	> 3, < 7 mg/d (n = 45)	≥ 7 mg/d (n = 3)
This study	44.7	64.4	0
Anderson et al	40.4	60	0
Sconce et al	51.1	42.2	0
Ohno et al	61.7	28.9	0

IV. DISCUSSION

Warfarin, the first human anticoagulant, is the most commonly prescribed oral anticoagulant in the world. Warfarin exerts its anticoagulant effect by inhibiting the activity of *VKORC1* and thus interfering with the activation of vitamin K-dependent clotting factors II, VII, IX and X.[2,3] Warfarin is underutilized for stroke prevention. The Agency for Healthcare Policy and Research noted that physicians avoid to prescribe warfarin, because they are not familiar with techniques for administrating the drug safely and fear bleeding complication.[29] Warfarin therapy is challenging, since warfarin has narrow therapeutic index. In addition, it shows not only large inter-individual variations in dose response but also intra-individual variation. Because patients' clinical characteristics such as age, gender, body weight, concurrent medications, diet, co-morbidities and patient compliance level largely influence in warfarin dosing,[10] frequently monitoring of its effect, as measured by the

INR, is warranted.

Since *CYP2C9* and *VKORC1* have been identified and studied as important genetic determinants of warfarin dosing. Two prospective studies[21,30] on genotype-guided warfarin dosing predicted more accurately, resulted in reduction of dosing changes, minor bleeding complication, and time to reach in the therapeutic range. Although numerous warfarin dosing algorithms have been developed, their indications for warfarin usage were heterogeneous. Until now, there is no consensus among pharmacogenetic-guided dosing algorithms.

We developed an algorithm to provide a practical formula for Korean patients with stroke. The warfarin dosing algorithm reported in this study was developed on a homogeneous population and single disease indication for stroke, since warfarin have been underused for prevention of stroke[29] and there are few studies about warfarin dosing algorithm focused on stroke patients. Because the distribution of warfarin dose was skewed, we created dosing algorithm for log transformation of doses, as evidenced by a mean percent deviation that was lower than that for both the raw doses and square root of doses. We analyzed whether ten selected dosing algorithms, including the algorithm derived from this study, could accurately predict warfarin dose in the study population. Algorithm from

this study demonstrated good correlation with actual dose, with coefficient of determination (R^2) of 0.465. Algorithm derived from this study is consisted with four factors; age, body weight, and genotypes of *CYP2C9* and *VKORC1*. While reduced incorporated factors are convenient for physicians to use, this algorithm performed better than Gage et al,[22] Wu et al,[23] and IWPC.[16] Approximately 11% of the variance in warfarin dosing can be explained by genotypes. Because allele frequencies of *VKORC1* and *CYP2C9* were different from race, the R^2 values of these genes differ among studies.

Anderson et al,[21] Ohno et al,[26] and Sconce et al[20] also showed good linear relationship with actual dose and predicted dose. However, the R^2 indicate only the linearity of the association, the mean deviation from actual dose is a better measure of the algorithms performance. Although those three algorithms showed a good correlation with the actual dose in our study population, a better prediction of dosage was achieved by our model.

The algorithm devised by Cho et al[27] was the latest warfarin dosing algorithm for Korean patients with atrial fibrillation and the best model for prediction of daily maintenance dose from the validation study. This algorithm showed a good relationship between the actual dose and the

predicted warfarin dose in our study population as reported in the previous study. However, this algorithm was the worst performing algorithm by means of the mean deviation. The mean age, the strongest predictor of warfarin dose, was slightly older in cohort of Cho et al., although its significance is unclear. Because these two algorithms developed for two different single disease indication; atrial fibrillation and stroke, these patients may be differently influenced by environmental factors such as coadministered drugs and comorbidities. Atrial fibrillation was indeed the most common indication of warfarin usage in this study. Beside heart problems that are shown in the table.1, other sources of cardioembolism including patent foramen ovale and left atrial thrombus were identified. Likewise with reports from western countries,[31] cervicocephalic artery dissections were common causes of stroke in young patients under 45. Cho et al[27] reported that statins influence with the daily dose of warfarin. Simvastatin, fluvastatin, and lovasatin potentiate warfarin's effect.[19,32] In our study, most patients were taking statins which do not affect the warfarin's effect such as atorvastatin, pitavastatin, and rosuvastatin. There is no correlation between daily dose of warfarin and statin status regardless of types of statins.

The algorithm derived from this study was less predictable among

patients who required high doses of warfarin (≥7 mg/day). As this study was a small retrospective analysis with only a few patients requiring high doses, the results may have been skewed because of the individual patients. About 3% of the patient could have complications due to underdose. Of the three outliers, two patients were *VKORC1* CT genotype. The other was TT type and he was taking antituberculosis drugs. Rifampin decreases INR increase via induction of hepatic metabolism of warfarin.[19,33] Removal of these three data points improve the correlation coefficient for our algorithm (R^2=0.55). However, the sample size was too small to make conclusion about efficacy of the dosing algorithms in this population.

In this study, we found 0 and 4% prevalence of *CYP2C9*2* and *CYP2C9*3*, respectively, which compares with the report of Cho et al., who also found no *CYP2C9*2* and an 8.5% prevalence of *3. For *VKORC1*, we found 83.2%, 17.8% and 0% prevalence of *VKORC1* TT, CT, CC genotype, respectively, which compares with the report of Cho et al., who found 75.4%, 23.1% and 1.5%, respectively. Our data showed that the *CYP2C9* and *VKORC* SNPs for Korean were in Hardy-Weinberg equilibrium.

Our study has several limitations. First, we did not have sufficient data

to include potentially important factors such as vitamin K intake or compliance of administration even if we educated the patients when starting warfarin. However, the percentage of variability in warfarin dosing from our study is similar to that in other compared models, so the effect of these variables is probably small. Second, because we investigated only one *VKORC1* SNPs, requiring us to impute missing genotype for evaluation some models. Therefore, we substituted missing genotype based on linkage disequilibrium, which is generally reliable.[34] However, it may cause an error that would lead to decrease of the accuracy of our model. Third, only 4% of the study population was younger than 40 year of age; so, it may need additional models for stroke patients with younger age, as age is important factor of prediction.

In order to improve dosing algorithms further, additional study will be necessary to find new genes and SNPs contained with these genes that influence warfarin pharmacokinetics and pharmacodynamics. Although the incorporation of additional variables could improve predictive algorithm, the gains may be modest and probably do not justify the cost effectiveness and improvement of clinical outcome. In addition, studies about clinical utility of these pharmacogenetic-guided algorithms should be evaluated.

V. CONCLUSION

In conclusion, we developed warfarin dose prediction algorithm for patients with stroke and it explained 47% of the variation in the daily maintenance warfarin dose. Further studies to elucidate clinical utility of genotype-guided dosing and find the additional genetic association are necessary.

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ABSTRACT(IN KOREAN)

뇌졸중 환자의 와파린 용량 예측을 위한 알고리즘의 개발과 기존 알고리즘과의 비교

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조 선 미

와파린 용량 결정에 중요한 역할을 하는 유전자인 cytochrome P450 2C9 (*CYP2C9*)와 vitamin k epoxide reductase complex subunit 1 (*VKORC1*)이 발견된 이후로 이에 관하여 많은 연구가 진행되었다. 본 연구에서는 한국인 뇌졸중 환자군으로부터 와파린 용량을 예측하는 알고리즘을 도출하고, 기존의 약물유적학적 방법을 이용한 알고리즘과의 수행능을 평가하였다.

안정적인 유지 용량을 복용하는 95명의 환자를 대상으로 하였다. 와파린 용량 예측 알고리즘은 다중 선형 회귀 분석을 이용하여 구하였다. 알고리즘의 평가는 선형 회귀로부터 도출한 결정 계수, 실제용량과 예측용량의 퍼센트 편차의 평균(mean of percent deviation)을 사용하였다. 이에 더해, 실제 용량의 ±20%를 이상적인 용량으로 정하여 이에 도달하는 백분율과 각기 다른 용량에서의 예측의 정확성을 비교하였다.

나이, 몸무게, *CYP2C9* 와 *VKORC1* 유전자형을 변수로 하는 알고리즘을 개발하였고 이는 와파린 용량의 약 47%의 설명력을 가졌다. Anderson 등의 연구와 본 연구에서 도출된 알고리즘의 예측 용량은 실제 용량과 가장 좋은 연관성을 보였다. 또한, 본 연구에서 도출된 알고리즘은 이상적 용량예측과 와파린 중간 용량군에서의 예측에 가장 우수하였다.

본 연구에서 개발된 와파린 용량 예측은 한국인 뇌졸중

환자에서 유용할 것으로 생각한다.

핵심되는 말: 뇌졸중, 와파린, 한국인, *CYP2C9* 유전자, *VKORC1* 유전자