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Full Length Article

Comparison of the Performance of the Warfarin Pharmacogenetics Algorithms in Patients with Surgery of Heart Valve Replacement and Heart Valvuloplasty

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ABSTRACT

A large number of warfarin pharmacogenetics algorithms have been published. Our research was aimed to evaluate the performance of the selected pharmacogenetic algorithms in patients with surgery of heart valve replacement and heart valvuloplasty during the phase of initial and stable anticoagulation treatment.

10 pharmacogenetic algorithms were selected by searching PubMed. We compared the performance of the selected algorithms in a cohort of 193 patients during the phase of initial and stable anticoagulation therapy. Predicted dose was compared to therapeutic dose by using a predicted dose percentage that falls within 20% threshold of the actual dose (percentage within 20%) and mean absolute error (MAE).

The average warfarin dose for patients was 3.05 ± 1.23 mg/day for initial treatment and 3.45 ± 1.18 mg/day for stable treatment. The percentages of the predicted dose within 20% of the therapeutic dose were 44.0 ± 8.8% and 44.6 ± 9.7% for the initial and stable phases, respectively. The MAEs of the selected algorithms were 0.85 ± 0.18 mg/day and 0.93 ± 0.19 mg/day, respectively. All algorithms had better performance in the ideal group than in the low dose and high dose groups. The only exception is the Wadelius et al. algorithm, which had better performance in the high dose group.

The algorithms had similar performance except for the Wadelius et al. and Miao et al. algorithms, which had poor accuracy in our study cohort. The Gage et al. algorithm had better performance in both phases of initial and stable treatment. Algorithms had relatively higher accuracy in the >50 years group of patients on the stable phase.

1. Introduction

Warfarin, the most common oral anticoagulants, is widely prescribed for the prevention of thromboembolism disorders such as deep vein thrombosis, stroke, and pulmonary embolism. Though a life-long medication for patients with the heart valve replacement surgery, warfarin has a narrow therapeutic index [1], which leads to the increased risk of adverse events like bleeding for overdose and thrombosis for insufficient treatment [2]. It is important for patients to get appropriate prescriptions of warfarin, especially for patients in the early phase of post-surgery who had surgery for heart valve replacement and heart valvuloplasty (HV). The risk for thromboembolism disorders can be decreased by shortening the time to reach the therapeutic INR (International Normalized Ratio) [3].

The metabolism of warfarin differs among individuals as a result of the single nucleotide polymorphisms (SNPs) in genes of cytochrome P450 (CYP) 2C9 and vitamin K epoxide reductase (VKORC1) [4–6]. Clinical factors such as race, age, gender, body weight, diet and concomitant medication also have relevance to the diversity of the warfain dose requirements [7–9].

A number of algorithms [10–19] were derived by the incorporation of gene factors and clinical factors. Theses algorithms were established to make warfarin prescriptions more accurate for individual patients. The algorithms were also aimed to shorten the time needed to reach the therapeutic INR and keep the anticoagulation treatment safe. The performance of some algorithms has been validated by several researches [20,21]. However, there is little data of verifications conducted in the cohort of patients undertaking mechanical heart valve replacement. Most of the algorithms in published papers were derived from patients in the steady state of anticoagulation. Sensitivity to warfarin

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increases in the patients after heart valve surgery [22–24], and a progressive decrease in sensitivity to warfarin has been discovered in these patients [25]. The performance of the algorithms is needed to be validated in periods of initial and stable anticoagulation treatment. The performance of warfarin dosing algorithms might be influenced by specific factors of derivation population, such as age and races. Since chronic heart failure has a high prevalence in patients undertaking heart surgery, it might also be the factors that contributed to the performance variation.

In the study, we aimed to validate the performance of the established pharmacogenetics-based algorithms by a cohort of patients undertaking heart valve surgery during the period of initial and stable periods of anticoagulation therapy. Accuracy of pharmacogenetics-based algorithms was also evaluated in subgroups divided by dose range, heart function and age.

2. Patients and Methods

2.1. Study Design

The genotyping of CYP2C9*3 (1075G > T, rs1057910) and VKORC1 (1639G > A, rs9923231) was accomplished after the recruitment of the patients. Warfarin was prescribed the day after the surgery. The INR was aimed to control in the range of 1.8-2.5 and was measured every day for the initial anticoagulation therapy. The initial dose of wafarin was defined as the constant dose prescribed to obtain 3 consecutive therapeutic INRs at least 5 days after the anticoagulation therapy started.

Follow-up data were collected by the anticoagulation clinic of the Drum Tower Hospital Affiliated to Nanjing University Medical School. Stable anticoagulation was indicated by patient received same dose of warfarin that led to 3 consecutive INR tests separated by at least 1 week within target range from 1 year after the surgery.

2.2. Patients

A total of 212 Han-Chinese patients were registered consecutively from the Affiliated Drum Tower Hospital of Nanjing University from July 2012 to December 2012 for the prospective study. Patients were recruited by criteria as follows: (1) Be admitted to hospital for heart valve surgery and would need to receive warfarin for anticoagulation therapy after the surgery; (2) The patients had to be at least 18 years old;(3) Patients had the willingness to participate in the study and the ability to provide written informed consent; (4) Able to followed the schedule for anticoagulation visit and had adherence of warfarin prescription. All of these patients started warfarin therapy the day after their surgeries. Patients were excluded by criteria as follows: (1) Contraindications of anticoagulation or holding warfarin during the following-up period; (2) Patients with abnormal liver function or renal impairment that may influence the accuracy of the study; (3) Pregnancy or lactating; (4) Patients with abnormal function of coagulation due to liver disease, antiphospholipid antibody; (5) Poorly cognitive of informed consent or lack of compliance of prescription for warfarin and INR test; (6) Abuse of alcohol or irregular diet.The protocol of this study was approved by the Ethics Review Board of the Affiliated Drum Tower Hospital of Nanjing University. The protocol was admitted for the fulfillment of the Declaration of Helsinki. Patients were recruited with written informed consent.

2.3. Data Collection

The demographic data of the patients, including gender, age, height, and weight, were collected by regular interviews. The data of the INR and warfarin doses were collected by a pharmacist during the treatment in hospital and in the anticoagulation clinic for discharged patients during the follow up.

2.4. Genotyping

Polymorphisms of CYP2C9*3 (1075G > T, rs1057910) and VKORC1 (1639G > A, rs9923231) were detected by using DNA microarrays. Whole blood obtained from the forearm vein was collected after the patients registered for the study before surgery. Genomic DNA was extracted by a DNA Blood mini kit (Baio Technology Co, Ltd, Shanghai, China), as described by the product. Gene sequences were amplified by PCR. Mutant alleles were detected by using genotyping microarray (Baio Technology Co, Ltd, Shanghai, China).

2.5. Follow-up

A one more year long follow-up was accomplished by the Anticoagulation Clinic of the hospital at least once every 3 months after the patients were discharged, and the INRs of the patients were monitored during the phase of follow-up. The dosage of warfarin was adjusted to keep the therapeutic INR within the range of 1.8-2.5. During the follow-up period, medication, dietary habits, and other information were also collected.

2.6. Selection and Comparison of Algorithms

We searched for articles reporting pharmacogenetics algorithms for warfarin dosing through PubMed. MeSH terms were used as follows: 'warfarin,' 'pharmacogenetics,' 'CYP2C9,' and 'VKORC1.' The selected algorithms needed to include clinical and genetic (CYP2C9 and VKORC1 only) variables. We selected algorithms derived from mixed race, Caucasians, Asians (especially East Asian) and Han-Chinese to compare the influence of population to the performance. We chose the algorithm of Kim et al., which incorporate chronic heart function and derived from patients undertaking heart valve replacement, to evaluate contribution of heart function. Since we only tested SNPs of CYP2C9 and VKORC1, the algorithms with genetic variables other than CYP2C9 and VKORC1 were excluded. Algorithms with a sample size less than 100 patients were also excluded.

To compare the performance of the algorithms, the MAE (mean absolute error) and percentage of patients whose predicted warfarin dose fell within 20% of the actual therapeutic dose in both initial and stable phases were considered in accordance to other studies [10]. The MAE was defined as the mean absolute difference between the predictive dose and actual therapeutic dose. The percentage of patients whose predictive warfarin dose was below (underestimation), above (overestimation) and within (ideal dose) the 20% of actual therapeutic dose was calculated to evaluate the accuracy of the algorithms. The predicted warfarin doses of the patients were calculated by using the algorithms established by each study and the collected data of the patients. The genotype of VKORC1 1639G > A was used if the algorithm contained VKORC1 polymorphism other than VKORC1 1639G > A, but in a strong linkage disequilibrium with it [26]. The performance of the algorithms was also evaluated in subgroups: (1) a low dose group (1.88 mg/day), an ideal dose group (1.88–4.38 mg/day), and a high dose group (4.38 mg/day) [15,27,28], (2) Patients with chronic heart failure (CHF) and without CHF, and (3) patients older than 50 (≥50) and younger than 50 (<50).

2.7. Statistical Analysis

The frequency distribution, percentage distribution, mean, and standard deviation were calculated as descriptive statistics. The Hardy-Weinberg equilibrium was used to evaluate the distribution of each genotype by using a chi-square test. Comparison between two groups was conducted by a t-test for continuous variables. Analysis of the statistics was completed by the Statistical Package for Social Science (SPSS ver. 18.0, SPSS Science, Chicago, IL, USA). A p-value of <0.5 was considered statistically significant.