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Original Article

CYP2C9 and VKORC1 genotype-guided individualized warfarin therapy in Chinese patients with acute pulmonary thromboembolism: a randomized controlled clinical study

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Abstract: To investigate efficacy and safety of genotype-guided individualized anticoagulant therapy with warfarin for acute pulmonary thromboembolism (APTE) patients in Han Chinese. Patients enrolled were randomly divided into genotype-guided group and control group. The genotype of VKORC1 and CYP2C9 for all the patients was analyzed using PCR and biochip technology. The warfarin dosages in genotype-guided group on 1-3 days were determined by dosing algorithm on platform (http://www.warfarindosing.org), while the dosage in control group was 3 mg/24 h. From the 4th day, dosages were modulated according to international normalized ratio (INR) and clinical conditions. Therapy lasted for 12 weeks. Record INR values frequently. The average time to reach INR target range 2-3 (T_t) in genotype-guided group was significantly shorter compared with control group ($P < 0.001$). The average time to reach stable warfarin dosage (T_s) in genotype-guided group was significantly less than that of control group ($P < 0.001$). The percentage of patients reaching stable warfarin dose within 3 weeks (67.8%) was higher in genotyping-guided group than that in control group ($P < 0.001$). However, during weeks 4 to 12, it showed no significant difference except for week 5. Occurrence rate of INR > 4 and bleeding events showed no statistical difference. INR fluctuation (f_{INR}) at initial therapy was more apparent in control group than that in genotype-guided group.CYP2C9 and VKORC1 genotype-guided method could be more efficient than normal dosing method. The data here supplied evidence for supporting the individual therapy of warfarin in clinic for Han Chinese.

Keywords: Genotype-guided, warfarin, CYP2C9, VKORC1, individualized anticoagulant therapy, pulmonary embolism

Introduction

Pulmonary embolism (PE), being subset of venous thromboembolism (VTE)-the third leading cause of cardiovascular-associated death, is a common disease being high disability rate and mortality [1]. It is usually caused by blockage of pulmonary artery or its branches due to embolic obstruction related to exogenous or endogenous substances [2]. Overall, thrombolytic therapy and anticoagulation therapy are the two main methods for PE, in which anticoagulation therapy is the mainstream treatment [3]. Warfarin is an oral anticoagulant applied for preventing and treating for kinds of thromboembolic events in clinic. Due to its evident proven efficacy, low cost, and abundant clinical experience, warfarin is the most common anticoagulant agent and widely considered as the mainstay of anticoagulant therapy [4]. There are millions of patients over the world relying on warfarin therapy, and about 2 million people started on warfarin annually in the United States alone [5].

However, with a narrow therapeutic window, any inappropriate adjustment during the therapy would possibly lead to adverse events (AE), such as insufficient or excessive anticoagulation events. Embolism or stroke may happen if under-anticoagulant exists, and bleeding events are often associated with over-anticoagu-

Table 1. Exclusion criteria for this study

Exclusion criteria
Age < 18 years
Used to accept warfarin therapy
Has any contraindications for anticoagulation
With serious infection
Abnormal liver function with ransaminase 2 times greater than normal values
Abnormal kidney function with serum creatinine > 120 mmol/L
Hyperthyroidism with TSH < 0.1 mIU/L
Congestive heart-failure (CHF) exists
Patients with cancer
Accept aspirin, amiodarone, or rifampicin et al treatments which could influence the pharmacokinetics or pharmacodynamics of warfarin
Poor adherence
Could not complete the whole study or fail to follow up

lant, all of which could be fatal, thus sometimes monitoring is necessary. Currently, the common index to evaluate the efficacy of warfarin is international normalized ratio (INR). According to this biomarker for bleeding events [4], the warfarin dosage could be modulated in order to ensure the efficacy and safety.

Increasing studies have indicated that dose-response relationship of warfarin is highly variable, both interindividually and interethnically [6-8]. The polymorphisms of both metabolic enzyme CYP2C9 and target gene VKORC1 (Vitamin K epoxide reductase subunit 1) of warfarin in combination with ages and body-surface area have been reported to be able to explain about 50% of warfarin variability [9]. Up to 47% and 2-27% of the warfarin variation could be explained by VKORC1 and CYP2C9 genotype polymorphisms, respectively [4, 10]. CYP2C9*1 (wild type) is the best common type in all the populations, with a percentage of 80% in Caucasians, and 95% in Han population, while CYP2C9*2 changes evidently in ethnics, with 10-15% in Caucasians, and basicly 0% in Chinese [11]. It is also demonstrated that *2 and *3 type have a reduced catabolic ability of warfarin, and patients carrying such variants needs a comparatively decreased dosage for therapy and a comparative long period to reach a stable warfarin dosage [12]. When come to VKORC1-1639 G > A, the distribution tendencies of VKORC1-1639 alleys are opposite in Caucasians and Chinese: in Caucasians, GG genotype occupies about 36%, and AA genotype about 15%, while separately 1% and 83% for GG and AA genotype in Chinese [11]. A previous meta analysis [13] showed that Caucasian patients carrying one A alley will decrease the warfarin dosage by 25%, and two A alleys by 50%, while in Asian patients, carrying one A alley will decrease it by 14% and two A alleys by 38% [13]. Other researches have demonstrated that carrying A alley implies a higher bleeding risk, with incidence rate 4.9% for AA genotype, 2.3% for GA genotype, and 0.47% for GG genotype [14]. What's more, it should be noted that Chinese population is multi-national, and this situation will plus additional efficacy and safety variation in China.

Several warfarin dosing algorithms based on genotype and clinical characteristics have been applied to the individualized anticoagulant therapy [15-18]. It should be noticed that these studies confirmed superiority of genotype-guided warfarin anticoagulant therapy in certain aspects, mostly based on mixed races population [19-21], while studies on Han Chinese population are more less [22]. The difference of gene polymorphism between Chinese and white race is apparent, and fundamentally, the average warfarin maintenance dose for Chinese population is lower than that of western population [23]. In order to aid to apply warfarin therapy and improve symptoms for patients in China, the efficacy and safety of individualized warfarin anticoagulant therapy through genotype-guided method in Han Chinese population calls for an urgent confirmation.

Therefore, the comparison between genotype-guided warfarin therapy and normal warfarin therapy for patients with PE in Han Chinese

Table 2. Demographic information for patients who completed the whole study

	Number	Gender	Age	Height	Height	Body surface area
Control	123	63/60	68 ± 12	165.8 ± 8.2	67.2 ± 10.9	1.09 ± 0.14
Genotype-guided group	115	57/58	69 ± 12	166.2 ± 8.5	67.1 ± 11.3	1.09 ± 0.14
test values		x^2=0.065	t=-0.229	t=-0.372	t=0.05	t=0.014
P		0.799	0.819	0.710	0.960	0.989

Table 3. Genotyping information for patients in genotype-guided group and control group

	Genotype-guided group (N=115)	Control group (N=123)
CYP2C9 (n/%)		
*1*1	99/86.09%	104/84.55%
*1*3	16/13.91%	16/13.01%
*3*3	0/0%	3/2.44%
VKORC1 (n/%)		
AA	93/80.87%	104/84.5%
GA	22/19.13%	19/15.45%
GG	0/0	0/0

population may not only provide a meaningful way for PE therapy in Han Chinese, but also provide the evidence for the efficacy and safety of genotype-guided individualized warfarin therapy in Chinese population.

Materials and methods

Patients

The patients with acute pulmonary-thromboembolism (APTE) that scheduled for anticoagulant therapy were recruited in this study. All the patients were hospitalized in the Emergency Medicine Department of Tianjin Medical University during July 2014 to December 2015. The patients were diagnosed according to the Chinese expert consensus on the diagnosis and management of acute pulmonary embolism (Supplementary 1). The exclusion criterion was described in **Table 1**. Detailed demographic information of investigated population was summarized in **Table 2**. The study was conducted in accordance with Declaration of Helsinkiand. All the procedures were approved by the Ethics Committee of hospital. Each subject provided with written informed consent before participation.

Study design and methods

The study is a randomized, single-blinded controlled trial. The patients were randomly assigned to either the genotype-guided group or control group. The genotyping information and basal INR value for all the patients were determined before the start of therapy.

Genotyping process was performed as follows: A venous blood sample was taken from every subject. Patients' DNA was extracted by commercial blood DNA extraction kits (Bai'AOCO. Ltd., Shanghai, China) and then amplified through PCR technology. The genotyping information was obtained from biochip (BE 2.0) through hybridization (by e-Hyb automated hybridization instrument, BR-526-24) of the amplified products with the commercial kits for CYP2C9 and VKORC1.

With the individual genotyping information, the warfarin dosages for the genotype-guided group patients on day 1-3 were calculated from the algorithm on website http://www.warfarindosing.org, supported by International Warfarin Pharmacogenetics Consortium (IWPC) and Gage [4]. While the initial loading dosage for the control group patients was set at 3 mg/24 h on the first 3 days, which is complying with the dosing regimen principle for Chinese population. After the first 3 days, the dosage for the two groups were all modulated according to personal INR values and the clinical requirements. The baseline INR value for each subject should be determined on the first day.

All patients were followed up for 12 weeks, with INR measured on day 0 (one day before the trial started), day 1, 4, 6, 8, 15, 22, 28, 56, 70, and 84. If the clinical needs exist, some patients could have additional clinic visits and INR measurements. During this period, the outcome measures related to the efficacy and safety should be recorded.

Outcome measures

Besides daily warfarin dosage for each subject, several outcome measures were used to record and evaluate the efficacy of warfarin. Firstly, T_f,

Table 4. Outcome measures in genotype-guided group and control group

	Genotype-guided group (n=115)	Control group (n=123)	Test values	*P* value
T_f (days)	10.10 ± 2.91	12.56 ± 3.05	t=6.368	< 0.001
Maintainance time range (days)	6~17	8~17		
T_s (days)	20.87 ± 4.51	23.86 ± 5.99	t=4.332	< 0.001
Maintainance time range (days)	15~35	12~48		
The number or percentage of patients with stable warfarin dosage in each week mainly from the 3rd week to 12th week (n/%)				
1-2 weeks	0/0	1/0.8	x^2=0.939	0.333
3 weeks	78/67.8	47/38.2	x^2=20.903	< 0.001
4 weeks	105/91.3	104/84.6	x^2=2.532	0.112
5 weeks	115/100	117/95.1	x^2=5.755	0.016
6 weeks	115/100	121/98.4	x^2=1.886	0.170
7-12 weeks	115/100	123/100	---	---

Note: T_f means the time to reach the target INR range ($2 \leq INR \leq 3$) for the first time; Ts means the time to reach stable warfarin dosage (at which the measured INR values maintained in the range of 2-3 for at least 3 times (≥ 7 days), continuously.

means the time to reach the target INR range for the first time (2 ≤ 2mea3). Secondly, T_s, means the time to reach a stable warfarin dosage (at which the measured INR values maintained in the range of 2-3 for at least 3 times (≥ 7 days), continuously. Thirdly, the percentage of patients in the two groups who have reached maintenance warfarin dosage in each week from 3rd week to 12th week, separately. The baseline INR values for the two groups were also determined. The secondary outcome measure is the incidence of INR > 4 and adverse events (AE), such as gum bleeding, skin petechia and other bleeding events. Finally, we have also spared attention to the INF fluctuation (f_{INR}) for the two groups at the initial therapy.

Statistical analysis

All analyses were carried out with the SPSS software (version 19.0). Apply the nonparametric Kolmogorov-Smirnov test method to verify normal distribution. The data which followed the normal distribution was expressed as Mean ± SD. Two-sample-independent t test was used to compare between the two groups. A nominal two tailed $P < 0.05$ was considered as statistically significant.

Results

Demographic information for patients

Overall, 264 patients were enrolled in this study and 238 patients completed the whole study. The demographic information of patients was summarized in **Table 2**, and the parameters such as gender, age, height, weight, body surface area were compared between the two groups, however, there existed no statistical difference.

Genotyping information for patients

The genotype distribution of CYP2C9 and VKORCl was shown in **Table 3**. In the genotype-guided group, the majority of patients were individuals with CYP2C9*1*1 genotype, accounting for 86.09% (n=99), the minority patients were individuals with CYP2C9*l*3 genotype, accounting for 13.91% (n=16), and there was no CYP2C9*3*3 genotype in all the patients. VKORCl AA genotype was identified in 80.87% of the patients (n=93), VKORCl GA genotype was identified in 19.13% (n=22), and there was no VKORCl GG genotype in the whole patients. In addition, in the control group, the percentage of CYP2C9*1*1 was 84.55% (n=104), 13.01% for CYP2C9*l*3 (n=16), and 2.44% for CYP2C9*3*3 patients (n=3), while the percentage of VKORCl AA was 84.5% (n=104), 15.45% (n=19) for VKORCl GA, and there were no patients with VKORCl GG genotype in this group.

Outcome measures in the in genotype-guided group and control group

During the 12-week follow up period, T_f, T_s and the percentage of patients reaching the stable warfarin dosagein each week from the 3rd week to the 12th week were summarized in **Table 4**.

Table 5. Incidence rate of adverse events in genotype-guided group (n=115) and control group (n=123)

	Genotype-guided group (n/%)	Control group (n/%)
INR > 4	14 (12.2%)	18 (14.6%)
Gum bleeding	2 (1.7%)	4 (3.3%)
Skin petechia	3 (2.6%)	8 (6.5%)
Blood in stool	0 (0%)	2 (1.6%)
Hematuria	3 (2.6%)	4 (3.3%)
Summary	22 (19.1%)	36 (29.3%)

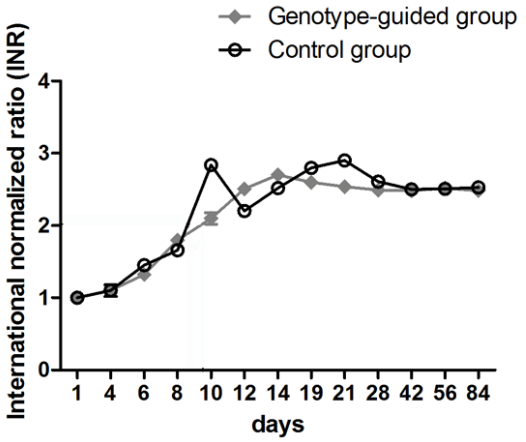

Figure 1. The curve of INR value during the 12-week follow-up periods in genotype-guided group (n=115) and control group (n=123).

The mean T_f of genotype-guided group was 10.10 ± 2.91 days, with during time being 6-17 days. T_f showed a significant difference in comparison with control group (12.56 ± 3.05 days, 8-17 days, $P < 0.001$). The mean T_s for the patients in genotype-guided group was 20.87 ± 4.51 days, with during time being 15-35 days, which had a significant difference compared with control group (23.86 ± 5.99 days, 12-48 days, $P < 0.001$). The percentage of patients who reach the stable warfarin dosage for genotyping-guided group in the 3rd week was 67.8%, 38.2% for control group. Thus, there existed significantly difference while it was compared ($P < 0.001$). What is more, the percentage was 100% in genotyping-guided group and 95.1% in control group in the 5fh week with P value of 0.016. Except for the 3rd and 5th week, there was no significant difference in this percentage between the two groups from the 4th week to 12th week ($P > 0.05$).

Side effect and INR fluctuation

As described previously, the adverse events, especially bleeding events were carefully monitored. The results indicated that the incidence of adverse events in the genotype-group (19.1%) was lower than that in control group (29.3%), with no significant difference (x^2= 2.813, P=0.094) (**Table 5**).

The fluctuation in INR during the 12 weeks for the two groups was separately shown in **Figure 1**. The average baseline INR values for genotype-guided group and control group were 1.0106 ± 0.05891 and 1.0024 ± 0.07518, respectively, which showed no significant difference (t=-0.929, P=0.354). As shown in **Figure 1**, T_f and T_s of the genotype-guided group was shorter than that of the control group. The fluctuation difference of INR between the two groups was more apparent at the initial therapy stage than that at the later stage, which basically no difference between the two groups.

Discussion

There are several studies aimed to prove whether genotype-method has superiority over the normal method in warfarin study. Pirmohamed et al has shown that patients had a reduced time to reach the target INR and the stable warfarin dosage in the United Kingdom and Sweden [9]. A study carried by Wang M also has demonstrated that patients with rheumatic heart disease in Han Chinese had a deceased time to maintain a stable dosage with genotype-guided therapy after valve replacement [24]. In our study, T_f and T_s in the genotype-guided group was shorter than that in the control group with significant difference ($P < 0.0001$). The results in Han Chinese with acute pulmonary-thromboembolism (APTE) were basically complied with previous data. In the 3rd week of the follow-up period, the percentage of patients who reach the stable warfarin dosage in the 3rd week was higher in the genotyping-guided group (67.8%) than that in control group (38.2%) with significant difference ($P < 0.001$). The results have confirmed the efficacy of genotype-guided regimen by reducing T_f and T_s in Han Chinese patients with APTE.

In clinical practice, it usually needs several weeks to reach the therapeutic INR, while it will be much longer for patients carrying variant

alleys like CYP2C9 *2 and *3 which could increase the risk of adverse events [12]. Variant alleles of VKORC1-1639 also lead to different incidence ratios of bleeding risk, 4.9% for AA genotype, 2.3% for AG genotype, 0.47% for GG genotype [14]. With reducing the time needed to achieve target INR and stable warfarin dosage (T_f and T_s), the genotype-guided therapy could possibly reduce the ADR incidence at the same time, though we have not found a significant difference in adverse events between the two groups in our study.

The incidence of INR ≥ 4 is treated as a surrogate biomarker for adverse events [4]. We learned a conclusion from the research conducted by Pirmohamed et. that the incidence rate of INR ≥ 4 in the genotype-guided warfarin therapy was comparatively lower than control group [9], in contrary, the results of another study carried by Anderson stated that the incidence rate for INR values out of the target range in genotype-guided group was not lower than that of control group [25]. It is interesting that when Anderson's result was analyzed through genetic subtypes grouping, the incidence in the subgroup with variant alleys was lower than that of control group [25]. In our study, the incidence rates for INR > 4 in genotype-guided group and control group were comparable, and there was no significant difference in the incidence of the bleeding events between the two groups. This may attribute to the small number cases who carried the variant alleys. The analysis according to the genetic subtype grouping in our study could be implemented in the future.

We have also investigated the fluctuation of the average INR values (f_{INR}) for the two groups during the whole period (**Figure 1**). It is noticeable that the difference of f_{INR} between the two groups was evident at the initial stage but basically maintained at the platform level in latter stage. At the initial stage, the f_{INR} of the genotype-guided group was smaller than that of the control group. This characteristic may attribute to the different treatments for patients: the genotype-guided group was treated by the genotype-guided method on the first 3 days, while the control group accepted the loading dosage of 3 mg/24 h. At the latter stage, the warfarin dosages for all the patients were modulated according to their individual INR values and clinical experience, thus the fluctuations of the two groups are nearly the same. The comparatively small fluctuation at the initial range in the genotype-guided group may imply a more evident and steady efficacy, which at the same time possibly reduce the adverse event incidence [4].

During more than 60 years of applying warfarin in clinical practice, we have accumulated abundant clinical evidence on its efficacy, safety, and genomics, but it seems not enough on the genotye-guided therapy for patients, especially for Han Chinese. Several literatures stated that genotype testing should be completed before warfarin therapy, then the warfarin dosage could be set according to the genotype polymorphism and other effecting factors [4], while some other literatures and clinical practice indicated that although commercial technology of gene testing was available, genotype testing was not recommended. Thus further researches in more diseases, more districts and more populations will help to accelerate the validation process for genotype-guided therapy method.

Conclusions

Above all, we could conclude that the genotype-guided method had an active role in reducing the time to reach the target INR value and stable warfarin dosage in individualized warfarin therapy for Han Chinese patients with acute pulmonary embolism. The genotype-guided method had a certain clinical values in guiding the anticoagulation therapy at the initial stage. Our study could be supplied as an evidence for supporting the genotype-guided therapy of warfarin being more efficient, and help to expand warfarin therapy in China. Because of the low patients' number and no consideration on the effect of smoking and diet states, the value of our study was limited. A more detailed study which considering more effect factors such as age, weight, height, smoking state, comorbidity etc. should be conducted for further analysis.

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Disclosure of conflict of interest

None.

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