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Correlation between demographic factors and warfarin stable dosage in population of Western China.

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Abstract

Objective: To investigate the correlation between warfarin stable dosage and demographic factors in patients undergoing valve replacement in Western China and then guide individualized anticoagulant therapy.

Methods: From MCCT database of low intensity anticoagulation therapy for Chinese population with heart valve replacement, a total of 236 patients who underwent valve replacement in the Han population were selected as the objects, the demographic factors including age, height, weight, body surface area, body mass index and clinical factors were observed and the correlation was compared between above indexes and warfarin stable dosage followed by obtainment of individual anticoagulation equation.

Results: There was no difference in warfarin stable dosage and INR value between the male and the female (p>0.05), atrial fibrillation, pulmonary embolism and heart function were the main influencing factors of warfarin stable dose variation, and there was correlation between the factor of age, height, weight as well as body surface area and stable warfarin stable dose (P<0.05), multivariate linear regression analysis showed that demographic factors could explain 7.1% of warfarin stable dose variation.

Conclusion: There is correlation between warfarin stable dosage and demographic factors in patients undergoing valve replacement in Western China and the effects of demographic factors on warfarin should be taken into consideration in the case of warfarin therapy.

Keywords: Western China, Warfarin, Demography, Multivariate linear regression analysis.

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Introduction

Valvular heart disease is a disease of the heart that is caused by one or several valves in the heart valve, or (or) closed. The main causes are rheumatic, degenerative, congenital, traumatic, and so on. In general, surgical treatment should be performed as early as possible in patients with severe heart valve disease. At present, valve replacement is the most important method for the treatment of valvular heart disease. Patients with mechanical valve replacement need to take warfarin anticoagulation therapy, while patients with biological valve replacement usually need 3-6 months of anticoagulant therapy, such as biological valve replacement in patients with giant left atrium, postoperative atrial fibrillation and other risk factors for thrombosis also need lifelong anticoagulation therapy. With the improvement of valve replacement technique and perioperative management, surgical complications and mortality have decreased significantly. However, the complications caused by inappropriate anticoagulation therapy have become more prominent. As reported, hemorrhage and thrombus after valve replacement makes up 75% of the total complications. Among them, hemorrhage is the most common and serious complication of anticoagulant therapy in China, and the annual cost of treatment of anticoagulant complications are up to 100 million Yuan. Therefore, it is important to optimize the current anticoagulant therapy to reduce the complications, improve the survival rate, and reduce the economic burden of the country and the family.

Current universal International Normalized Ratio (INR) can only reflect the activity of coagulation factors II, VI, K, X, but cannot reflect the total coagulation activity. Therefore, the use of INR to monitor the initial anticoagulation and low intensity anticoagulation is not accurate enough. It was reported that the dose of Warfarin was closely related to demographic factors. But at present, there are still relatively few reports about the correlation between the demographic factors and the dosage of warfarin. Chinese Han population has a wide distribution, mainly living in the Northeast Plain and the eastern coastal areas. Among them, the incidence of rheumatic heart disease in eastern coastal areas is higher, and the number of patients is very large. In this study, the subjects of the Han nationality in East China were studied. With great individual difference, warfarin is one of the commonly used oral anticoagulants after cardiac valve replacement. National multi center database was combined to study the relationship between the stable dose of warfarin and the demographic factors of Han population in eastern coastal areas.

Materials and Methods

All operations were performed under hypothermic cardiopulmonary bypass, in which 96 cases were performed mitral valve replacement, 108 cases were performed double valve replacement and 2 cases were performed with mitral valve replacement with aortic valve replacement. The preset value of INR is set as 1.5-2.5 and multicenter follow-up data was used. At the same time, in this study, the subjects were followed up for 6-12 months. PT-INR values were reviewed weekly in the first month after surgery, and it was reexamined two weeks after surgery. Since the third month, the PT-INR value was reviewed every month, and the dosage was about 1/8-1/4 tablet. The INR value was measured once a week after adjusting warfarin dose. Three months after operation, when the INR value reached the anticoagulant standard (1.5-2.5) after two consecutive reviews, no dose adjustment was needed. It was seemed to achieve a stable state of anticoagulation; the stable warfarin dose was recorded.

The International Sensitivity Index (ISI) values of the reagents used in the multi center monitoring INR value was corrected with the international certified INR standard, which is consistent with the valency of warfarin with no statistical difference. Main observation index: Atrial fibrillation, embolism, cardiac function (NYHA grading), hypertension, diabetes and other preoperative clinical indicators; Age, sex, height, weight, Body Surface Area (BSA), Body Mass Index (BMI) and other demographic factors and daily warfarin dose after valve replacement (Warfarin stable dose), PT-INR and anticoagulant related hemorrhage, embolism and other complications was also monitored.

Statistical analysis

The comparison of the demographic factors between groups was performed by F test, and the comparison of the demographic factors among the groups was analysed by one-way ANOVA. Comparison between groups using F test, Spearman linear correlation analysis was used to analyse the correlation between two variables. Multivariate regression analysis of the relationship between demographic factors and warfarin stabilizer, $p<0.05$ was statistically significant, and SPSS 13 software was used for statistical analysis.

Results

General information of the research object

There were 86 males and 150 females with an average age of 43.99 ± 12.27 y old, an average height of 161.02 ± 8.42 cm, and an average body weight of 55.94 ± 11 09 kg (Table 1).

Correlation between preoperative clinical factors and anticoagulation indexes

As shown in Tables 2-4, in the preoperative patients with atrial fibrillation, the stable dose of Warfarin was lower than that in patients without atrial fibrillation ($p<0.01$). The value of INR was higher than that of the patients with the history of preoperative embolization and the stable dose of warfarin was lower than that of the patients without history of embolization. Warfarin levels were higher in patients with preoperative cardiac function (I and II) than that in patients with cardiac function (III and IV).

Table 1. General information.

General information	n=236
Gender	
Male	86 (36.4%)
Female	150 (63.6%)
Age (y)	43.99 ± 12.27
Height (cm)	160.02 ± 8.42
Weight (kg)	55.94 ± 11.09
Mitral diseases	
Mitral regurgitation	66 (28.0%)
Mitral stenosis	50 (21.2%)
Mitral stenosis with regurgitation	96 (40.7%)
Aortic valve disease	
Aortic regurgitation	138 (58.5%)
Aortic valve stenosis	4 (1.7%)
Aortic valve stenosis with regurgitation	40 (16.9%)
Cardiac function (I and II)	96 (40.7%)
Cardiac function (III and IV)	140 (59.3%)
Ejection fraction (%)	55.55 ± 9.28
Left atrial diameter (mm)	51.70 ± 13.68
Left ventricular internal diastolic (mm)	53.50 ± 12.63
Complication	
Atrial fibrillation	130 (55.1%)
Embolization	14 (5.9%)
History of hypertension	4 (1.7%)
History of diabetes mellitus	2 (0.8%)

Table 2. Preoperative clinical factors and anticoagulation indexes.

Clinical factors	Atrial fibrillation (Yes) n=130	Atrial fibrillation (No) n=106	P
Stable dose (mg/d)	2.60 ± 1.24	2.93 ± 0.91	0.007

INR	1.88 ± 0.35	1.79 ± 0.32	0.046

Table 3. Preoperative clinical factors and anticoagulation indexes.

Clinical factors	Embolism (Yes) n=14	Embolism (No) n=222	P
Stable dose (mg/d)	2.34 ± 1.17	3.07 ± 0.41	0.007
INR	1.92 ± 0.33	1.63 ± 0.21	0.035

Table 4. Preoperative clinical factors and anticoagulation indexes.

Clinical factors	Cardiac function (I-II) n=96	Cardiac function (III-IV) n=140	P
Stable dose (mg/d)	3.04 ± 1.17	2.55 ± 0.98	0.02
INR	1.78 ± 0.34	1.87 ± 0.30	0.03
Note: cardiac function grading refers to NYHA standard			

Correlation between sex and anticoagulation index

Table 5 shows that there was no significant difference in the stable dose of warfarin and the INR level between different genders.

Table 5. Comparison of anticoagulant indexes in different gender groups.

Clinical factors	Male n=86	Female n=150	P
Stable dose (mg/d)	1.8 ± 0.93	2.67 ± 0.86	0.328
INR	1.84 ± 0.33	1.78 ± 0.31	0.159

Correlation between age and anticoagulation index

Table 6 shows that there is a statistically significant difference in the stable dose of warfarin and INR between the three age groups (p<0.05).

Table 6. Correlation between age and anticoagulation index.

Clinical factors	16-40 (y) n=90	41-60 (y) n=128	61-75 (y) n=18	P
Stable dose (mg/d)	2.86 ± 0.90	2.75 ± 1.23	2.31 ± 0.67	0.015
INR	1.85 ± 0.35	1.83 ± 0.32	1.88 ± 0.36	0.011

Study on the individual medication equation of warfarin stable dose and demographic factors

(1) Multiple linear regression analysis: Taking Indose as the dependent variable, age, height, weight, BSA, BMI was taken as independent variables. Finally, the multiple linear regression analysis models were established. 4 variables were included in the equation. Equation of linear regression: Y (mg/d)=log (0.092-0.005 × Age+0.008 × Height+0.001 × Weight-0.008 × BMI), F=4.430, P=0.002, R^2=0.071. That is, demographic factors may account for 7.1% of warfarin dose differences. (Note: the absolute value of the standard deviation of the equation is <3).

(2) Stepwise regression analysis: Taking "Indose" as the dependent variable, the average age was 43.99 ± 12.27 y old, the height was 161.02 ± 8.42 cm, the weight was 55.94 ± 11.09 kg, and the BSA was 1.67 ± 0.18 m. The multivariate stepwise regression analysis model is obtained. Finally, 2 equations are obtained. Regression equation 1: Y (mg/d)=antilog (-0.573+0.009 × Height), r=0.198, r=0.039, F=9.534, P=0.002. That is, demographic factors may account for 3.9% of warfarin dose differences. Regression equation 2: Y (mg/d)=antilog (-0.391+0.01 × Height-0.005 × Age), r=0.258, r=0.067, F=8.324, P=0.000. That is, demographic factors may account for 6.7% of warfarin dose differences. (Note: the absolute value of the standard deviation of the two equation is <3).

Compared with the control group, the warfarin stable dose and INR value were higher in the male group than in the female group, but there was no statistical difference between the two groups, which indicated that gender may not be an important factor in warfarin dose differences. It was reported that [1] because estrogen and estrogen can activate nuclear receptors, which will regulate the transcriptional expression of drug metabolizing enzymes and further effects the expression of genes related to drug metabolism in liver. This will lead to differences in drug metabolism. The stable does of Warfarin was significantly higher than that of male patients. Therefore, it is necessary to consider the influence of gender difference on drug metabolism in the clinical application of warfarin. Comparison of anticoagulant indexes in different age groups revealed that in 16-40 y old group, 41-60 y old group and older than 60 y old group, the warfarin stable dose was 2.86 ± 0.90 mg/d, 2.75 ± 1.23 mg/d, 2.31 ± 0.67 mg/d, respectively. The stable does of warfarin decreased with age increased. Because the data do not conform to the normal distribution, the non-parametric Friedman test has statistical difference (P<0.05). In the preoperative patients with atrial fibrillation, the stable dose of Warfarin was lower than that in patients without atrial fibrillation (p<0.01). The value of INR was higher than that of the patients with the history of preoperative embolization and the stable dose of warfarin was lower than that of the patients without history of embolization. Warfarin levels were higher in patients with preoperative cardiac function (I and II) than that in patients with cardiac function (III and IV). What's more, we also found that there was no significant difference in the stable dose of warfarin and the INR level between different genders and there is a statistically significant difference in the stable dose of warfarin and INR between the three age groups (p<0.05). At present, elderly patients with anticoagulant regimens are not uniform [2-5], as reported that the main risk of anticoagulant therapy for Chinese people is bleeding rather than blocking. It is suggested that the standard of anticoagulation should be 1.5-2.0, which can reduce the risk of bleeding [6]. While some studies believe that to ensure safe and effective anticoagulant therapy, stable and reasonable low intensity anticoagulation that INR value is generally controlled at 1.65-2.5, and it did not increase the incidence of bleeding and thromboembolism in elderly patients. At present, for elderly patients, the effect of anticoagulation is more stable in the narrow range of INR. By measuring the INR value and adjusting the dosage of warfarin, we can get a better anticoagulant effect.

In our study, multiple linear regression analysis: Taking Indose as the dependent variable, age, height, weight, BSA, BMI were taken as independent variables. Finally, the multiple linear regression analysis models were established. 4 variables were included in the equation. Equation of linear regression: Y (mg/d)=antilog (-0.092-0.005 × Age+0.008 × Height+0.001 × Weight-0.008 × BMI), F=4.430, P=0.002, R^2=0.071, i.e. demographic factors may account for 7.1% of warfarin dose differences. (Note: the absolute value of the standard deviation of the equation is <3). Moreover, stepwise regression analysis: Taking “Indose” as the dependent variable, the average age was 43.99 ± 12.27 y old, the height was 161.02 ± 8.42 cm, the weight was 55.94 ± 11.09 kg, and the BSA was 1.67 ± 0.18 m. The multivariate stepwise regression analysis model is obtained. Finally, 2 equations are obtained. Regression equation 1: Y (mg/d)=antilog (-0.573+0.009 × height), r=0.198, r=0.039, F=9.534, P=0.002. That is, demographic factors may account for 3.9% of warfarin dose differences. Regression equation 2: Y (mg/d)=antilog (-0.391+0.01 × Height-0.005 × Age), r=0.258, r=0.067, F=8.324, P=0.000. That is, demographic factors may account for 6.7% of warfarin dose differences. (Note: the absolute value of the standard deviation of the two equation is <3).

The age, sex, BMI and target INR (2 and 3) were used to study the drug delivery model by Martina et al. [7]. They found that 12.6% of warfarin individual differences can be explained. Xu et al. [8] found in 852 patients in the Guangdong area that age and body surface area were the only factors explaining the difference of warfarin dose between 6.3% and 11.4%, while the combined age and body surface area of the factor of two can explain the difference of warfarin dose of about 17.9%.The results of this study indicate that demographic factors had little effect on warfarin stable dose, and this may be due to differences in the quality of the population of the Han population in the eastern coastal areas of China. In addition, different geographical populations, such as eating habits, environmental factors may also lead to such differences. At present, demographic factors had little effect on warfarin stable dose, because a large proportion of dose differences are caused by other factors.

Although there was a correlation between the demographic factors and the dose of warfarin, but it could not fully explain the individual difference of warfarin dose. Some genetic factors may be an important reason for the difference of individual dose and the difference among individuals. Therefore, we will conduct an in-depth study of some important genetic factors to combine genetic and non-genetic factors to obtain the equation of individual medication model of warfarin, to guide the clinical medication accurately and effectively.

To sum up, we believe that there is a correlation between the demographic factors and the stable dose of warfarin in the east coast of the Han population in the patients undergoing valve replacement.

Discussion

Warfarin is one of the most commonly used oral anticoagulant drugs after valve replacement, but the treatment window is narrow, the difference is very large, and the dosage is difficult to grasp. Hemorrhage and blood coagulation are the main complications after operation. Current studies have shown that warfarin dose is associated with demographic factors [9-12]. The results of this study show that in patients with preoperative atrial fibrillation, the stable dose of warfarin was 2.60 ± 1.24 mg/d and the INR was 1.88 ± 0.35. In patients without preoperative atrial fibrillation, the stable does of warfarin was 2.93 ± 0.91 mg/d and the INR was 1.79 ± 0.32; a comparison between two groups shows that the stable dose of warfarin in patients with preoperative atrial fibrillation was lower than that without atrial fibrillation. The difference was statistically significant (P<0.05). The stable does of warfarin in patients with preoperative embolization was 2.34 ± 1.17 mg/d and the INR value was 1.92 ± 0.33. In patients without preoperative embolization, the stable dose of Warfarin was 3.07 ± 0.41 mg/d and the INR value was 1.63 ± 0.21, the stable dose of warfarin was lower than that in patients without embolization. The difference was statistically significant (P<0.05). INR value: the embolization group was higher than that without embolization group. The difference was statistically significant (P<0.05). In patients with atrial fibrillation or embolism mitral stenosis was commonly seen, and mitral valve replacement surgery was needed. The upper limit of the control range of INR after operation was 2.0-2.5. While in patients without history of atrial fibrillation, the lower limit of INR control range was 1.5-2.0. The INR value of the former is higher than that of the latter. Atrial fibrillation and embolization in patients with valvular heart disease were more likely to be associated with impaired cardiac function. Cardiac dysfunction can lead to liver congestion and liver dysfunction [12]. Such patients will reduce the demand for warfarin. In addition, some patients with atrial fibrillation and embolization were treated with radiofrequency catheter ablation. What's more, the amiodarone was used in combination with warfarin, by which the Warfarin dose and INR may also be affected. It is also possible that the stable dose of warfarin in patients with atrial fibrillation and embolization was lower than that in the patients without complications, but the INR value was higher than that in the non-atrial fibrillation group. In the following study, we will discuss the effect of amiodarone on warfarin dose. The heart function (I and II) of patients with better postoperative warfarin stable does was 3.04 ± 1.17 mg/d, which significantly higher than that of the patients with heart function (III and IV) (2.55 ± 0.98 mg/d), the difference between the two groups was statistically significant (P<0.05), which indicated that the difference of cardiac function before operation was correlated with the dose of warfarin. Congestive heart failure and congestive heart failure may be associated with abnormal liver function and liver function (including cardiogenic liver damage), which will lead to reduced synthesis of coagulation factors and strengthened efficiency of warfarin. So, the dose of warfarin was lower than that of patients with better cardiac function.

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