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Original Article

Effect of amiodarone on warfarin anticoagulation in patients after cardiac valve operation

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Abstract: Objective: To investigate the effect of amiodarone on warfarin anticoagulation in patients after cardiac valve operation. Methods: 200 patients, who underwent cardiac valve surgery in our hospital from August 2012 to August 2014, were retrospectively analyzed and divided into experiment group (100 cases) and control group (100 cases). The patients in control group were treated with warfarin alone after heart valve replacement; and patients in experiment group were treated with combined amiodarone on the treatment basis of control group. We compared the cumulative dose of warfarin in the first 5 days after operation, the time difference of INR entering into therapeutic window (1 week after surgery and the first entry), as well as the anticoagulation effect in 1 month after surgery between the two groups. Result: The cumulative dose of warfarin in the first 5 days after surgery in experiment group was lower than that of control group, the use of amiodarone did not affect the time of INR entering into therapeutic window (1 week after the surgery or first entry). The platelet count and APTT value of experimental group was significantly better than that of control group (palette count: (141 ± 40) 10^9/L *vs.* (131 ± 46) 10^9/L; APTT: (26 ± 4) *vs.* (20 ± 5)), the difference was statistically significant (P<0.05). The fibrin (3.11 ± 0.96) mg/dl, whole blood viscosity (4.08 ± 0.34) MPa-s, whole blood low shear viscosity (15.87 ± 4.49) MPa-s, blood cell volume (38.22 ± 5.27%) and plasma viscosity (1.35 ± 0.27) MPa-s of experiment group were lower than those of the control group (fibrin original: (4.53 ± 1.19) mg/dl; Whole blood viscosity: (5.86 ± 0.41) MPa-s; whole blood low shear viscosity: (19.26 ± 4.81) MPa-s; blood cell volume: (45.81 ± 5.09%); plasma viscosity: (2.16 ± 0.34) MPa-s), the difference was statistically significant (P<0.05). The incidence of complications in control group was 12.0%, which was significantly higher than 4.0% of the experiment group. Conclusion: Amiodarone combined with Warfarin anticoagulant therapy after cardiac valve surgery can reduce the dose of warfarin and the incidence of complications, thus it has important clinical significance.

Keywords: Warfarin, amiodarone, heart valve surgery, anticoagulant effect

Introduction

Valvular heart disease (VHD) is a common heart disease in China, and rheumatic fever induced valvular lesion is the most common one. Valvular heart disease refers to the lesions on mitral valve, tricuspid valve, aortic valve or pulmonary artery valve, which affects the blood circulation and causes abnormal cardiac function and eventually lead to single or combined aortic valve lesions; the main causes of the lesion include rheumatic fever, mucoid degeneration, degenerative changes, congenital malformation, avascular necrosis, infection or trauma lesions [1]. With the aging population to intensify, senile valvular disease becomes more and more common. Cardiac valve replacement is the main method for the treatment of valvular disease; the replacement materials mainly are artificial mechanical heart valve made from synthetic material and bioprosthetic valve made from biological tissues [2]. Biological valve, with central blood flow, has good hemodynamic characteristics and low incidence of thrombosis; there is no need for lifetime anticoagulation, however, its service life doesn't quite satisfactory, and most patients may need surgery again. Mechanical valve, with high endurance and long service time, has been widely used in clinical application; however, the biggest problem with mechanical valve is lifelong anticoagulation and the possibility of

Table 1. Comparison of baseline data between the two groups

Group	Gender		Age	Disease types			
	Male	Female	(Years old)	Mitral stenosis	Mitral regurgitation	Aortic valve stenosis	Aortic valve insufficiency
The experimental group (n=100)	55	45	46.9 ± 12.9	42	36	12	10
The control group (n=100)	54	46	45.9 ± 13.9	43	34	14	9
T value	0.012		0.021	0.014			
P value	>0.05		>0.05	>0.05			

Table 2. Effect of amiodarone on cumulative dose of warfarin in first 5 days after operation

Therapeutic window	Therapeutic window	Partial regression coefficient	SE	Beta	P
INR1.8~2.5	Whole	-1.321	0.688	-0.016	0.065
	Enter	-0.686	0.751	-0.062	0.377
	Did not enter	-1.671	1.146	-0.149	0.158

inducing thrombosis or bleeding that affects the patients' work and quality of life [3]. Most patients with valvular heart disease are accompanied with atrial fibrillation or arrhythmias after heart valve surgery; amiodarone therapy was often used in the perioperative period to achieve a better therapeutic effect. There are studies show that amiodarone enhances anticoagulation effect of warfarin by prolonging the prothrombin time; the prolong effect could occurred early at 3~4 d after treatment or late at 3 weeks after treatment, this synergy can be sustained for several weeks or months, and the maintenance dose of warfarin can be reduced by 1/3~1/2 [4]. Based on the research of anticoagulant effect of warfarin performed in 200 patients underwent cardiac valve surgery from August 2012 to August 2014, this study investigated the effect of amiodarone on anticoagulation effect of warfarin to guide the postoperative anticoagulation for VHD patients.

Material and methods

General information

We retrospectively studied 200 patients underwent heart valvular surgery in our hospital from August 2012 to August 2014 in this study. All patients were divided into experiment group (n=100) and control group (n=100); the experiment group consisted of 55 males and 45 females, aged 23-79 years old, the average age was 46.9 ± 12.9 years old; among them, there were 42 cases of mitral stenosis, 36 cases of mitral regurgitation, 12 cases of aortic valve stenosis, and 10 cases of aortic valve insufficiency. The control group consisted of 54 males and 46 females, aged 24-78 years old, the average age was 45.9 ± 13.9 years old; among them, there were 43 cases of mitral stenosis, 34 cases of mitral regurgitation, 14 cases of aortic valve stenosis, and 9 cases of aortic valve insufficiency. Patients in experiment group were treated with combined warfarin and amiodarone while the patients in control group were treated with warfarin alone. There was no significant difference in age, sex, disease type and other basic data between the two groups (P>0.05), see **Table 1**.

Methods

Heart valve replacement was performed in all patients, and warfarin was administrated postoperatively with first oral dose of 5.0 mg (produced by OrionCorporation, Registration Certificate No. H20110108). International normalized ratio (INR) value and the dose of warfarin and amiodarone (Hangzhou Senofi-Pharmaceutical Co., Ltd, H19993254) ect. were recorded daily. Cumulative dose of warfarin in the first 5 days after cardiac valve surgery was assessed. The time of INR entering into treatment window for the first time and in one week after surgery was observed and recorded in both groups. At the same time, the anti-coagulation effect of amiodarone in 1 month after operation was observed and recorded.

Statistical methods

SPSS 19.0 statistical software was used for statistical analysis. Measurement data were expressed by mean ± standard deviation ($\bar{x}$ ±

Table 3. The correlation between amiodarone and INR entering into therapeutic window 1 week after operation

Therapeutic window	Correlation	Relative risk	95% CI	P
INR1.8~2.5	0.113	1.118	0.557-2.278	0.785

Table 4. Correlation between amiodarone and INR first entering into therapeutic window after surgery

Therapeutic window	Correlation	Relative risk	SE	P
INR1.8~2.5	0.228	1.275	0.158	0.179

Table 5. Comparison of platelet count and coagulation function in two groups of patients after operation

Group	Platelet count (10^9/L)	APTT value (S)
The experimental group (n=100)	131 ± 46	20 ± 5
The control group (n=100)	141 ± 40	26 ± 4
T value	4.726	5.074
P value	<0.05	<0.05

S) and examined by t test. The count data was expressed by number and percentage and examined by χ^2. The correlation between warfarin and the cumulative dose of amiodarone, the time of INR entering into the therapeutic window were analyzed by Logistic and Cox regression analysis. *P*<0.05 was considered with statistical significance.

Results

Effect of amiodarone on cumulative dose of warfarin in first 5 days after operation

The application of amiodarone didn't significantly influent the cumulative dose of warfarin in the first 5 days after surgery (P>0.05), see in **Table 2**. However, the cumulative dose of warfarin in the first 5 days after operation in experiment group was lower than that in control group.

Effect of amiodarone on INR entering into therapeutic window within 1 week after surgery

1 week after operation, patients in experiment group who did not reach, entered or exceed the therapeutic window were 5 cases (5%), 80 cases (80%) and 15 cases (15%) respectively; patients in control group who did not reach, entered or exceed the therapeutic window were 9 cases (9%), 79 cases (79%) and 12 cases (12%) respectively. The difference between the two groups had no statistical significance (P>0.05). The results showed that amiodarone was not associated with INR entering into therapeutic window in 1 week after surgery, see in the **Table 3**.

Correlation between amiodarone and INR first entering into therapeutic window postoperatively

For patients with target INR of 1.8-2.5, the time difference of INR first entering into therapeutic window between experiment group and control group had no statistical significant (P>0.05). Correlation results showed that the application of amiodarone wouldn't affect the time of entering into therapeutic window in patients after heart valve surgery, see in **Table 4**.

Comparison of postoperative platelet count and blood coagulation function in patients of two groups

The platelet count (141 ± 40) 10^9/L and coagulation function APTT value (26 ± 4) in patients of experiment group was significantly better than that of the control group ((131 ± 46) 10^9/L and APTT (20 ± 5)), the difference between two groups was statistically significant (P<0.05), see in the **Table 5**.

Comparison of postoperative hemodynamic parameters between the two groups

See from **Table 6**, fibrin (3.11 ± 0.96) mg/dl, whole blood viscosity (4.08 ± 0.34) MPa.s, whole blood low shear viscosity (15.87 ± 4.49) MPa.s, blood cell volume (38.22 ± 5.27)% and plasma viscosity (1.35 ± 0.27) MPa.s in patients of experiment group were lower than those of control group (fibrin (4.53 ± 1.19) mg/dl, whole blood viscosity (5.86 ± 0.41) MPa.s, whole blood low shear viscosity (19.26 ± 4.81) MPa.s, blood cell volume (45.81 ± 5.09)%, plasma viscosity (2.16 ± 0.34) MPa.s), the difference was statistically significant (P<0.05).

Comparison of complication incidence between patients of two groups

See from the **Table 7**, the complication incidence (4.0%) in experiment group was signifi-

Table 6. Comparison of hemodynamic parameters between the two groups

Group	Fibrous protein (mg/dl)	High blood viscosity (mpa·s)	Whole blood low shear viscosity (mpa·s)	Hematocrit (%)	Plasma viscosity (mpa·s)
The experimental group	3.11 ± 0.96	4.08 ± 0.34	15.87 ± 4.49	38.22 ± 5.27	1.35±0.27
The control group	4.53 ± 1.19	5.86 ± 0.41	19.26 ± 4.81	45.81 ± 5.09	2.16±0.34
T value	5.41	8.50	4.00	6.04	6.87
P value	P<0.05	P<0.05	P<0.05	P<0.05	P<0.05

Table 7. The incidence of complications in two groups of patients

	Cutaneous purpura	Nasal bleeding	Hemorrhage of digestive tract	Conjunctival hemorrhage	Cerebral hemorrhage	Incidence rate
The experimental group (n=100)	1	1	1	1	1	4.0
The control group (n=100)	2	3	3	2	2	12.0
χ^2	4.289	5.276	5.276	4.289	4.289	5.198
P	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

cantly lower than that in control group (12.0%), which had statistical significance (P<0.05).

Discussion

Heart valve insufficiency, especially the insufficiency of the atrioventricular valve or the concomitant stenosis, is usually caused by the burden on multiple structures of the heart, such as the leaf, the tendon, the papillary muscle and the valve annulus [5]. The current treatment includes value repair, artificial mechanical valve replacement, and biological valve replacement etc. With the development in the technologies of cardiac surgery, valve repair has become one of the main methods for the treatment of VHD. Compared with artificial mechanical valve replacement, valve repair has no need of anticoagulation, avoiding the complications caused by anticoagulation drugs such as Warfarin; the favorable forming effect of mechanical valve replacement is good for the cardiac function recovery [6]. Although the anticoagulant time of biological valve replacement surgery is shorter, the short service life is the main obstacle that limits its wide application [7]. For children with heart valve insufficiency, since the disc ring is small and at the development stage, the patients shall have a second valve replacement after they grow up [8]. Patients with ischemic valvular disease, degenerative valvular disease, rheumatic valvular disease without severe calcification, and female patients at childbearing age, as well as patients with anticoagulant taboo are particularly suitable for valvuloplasty [9]. Patients must take oral anticoagulant drugs after heart valve surgery, and the common domestic drug is Warfarin. But the anticoagulant effect of Warfarin can be influenced by genetic polymorphisms, combined medication, diet, age, and pathologic or physiologic conditions [10]. The anti-coagulant effect of Warfarin differs a lot in different patients, and the dosage is not easy to control [11]. At the same time, the patients might have embolization if the anti-coagulation effect of warfarin is insufficient, otherwise, excessive bleeding might happen while over-anticoagulation [12]. Fortunately, amiodarone can avoid these disadvantages of warfarin and maximize the anticoagulant effect of warfarin; moreover, amiodarone can also stabilize the dosage of warfarin to reduce the occurrence of adverse reactions in patients [13].

Warfarin is the derivatives of coumarin, the chemical structure is 3-(a-phenyl acetone)-4-hydroxyl coumarin. Warfarin has no anticoagulant function in tubes, which means, it doesn't participate in anticoagulant process in vitro; it mainly inhibits the synthesis of vitamin K-dependent coagulation factors II, VII, IX and X in the liver microsomes, however, the process is slow and the maximum effect was achieved within 3-5 days [14]. Vitamin K can promote the carboxylation of n-terminal glutamate on vitamin K-dependent coagulation factor II, VII, IX and X to transit into γ-carboxyl glutamic acid; carboxylation can promote vitamin K-dependent coagulation factors to combined onto the sur-

face of phospholipids, thus to accelerate the blood coagulation [15, 16]. The γ-carboxylation needs the involvement of reduced form of vitamin K [17, 18]. The use of warfarin also has great impact on the underlying diseases in elderly patients, for example: the blood glucose will be increased in patients with diabetes, as well as the blood pressure will be increased in patients with hypertension; so, warfarin is quite difficult to achieve the best effect during its application [19, 20]. The incidence of adverse reactions is also very high. The results of this study also illustrated this point of view, the incidence of complications in warfarin group was 12.0%, which was significantly higher than the 4.0% of amiodarone combined group. In the mean while, the dose of warfarin was stably controlled at about 24.8 mg/d after amiodarone was combined used, which was significantly lower than that of the pure oral administration of warfarin; amiodarone is more favorable for reducing the dose of warfarin and maximize its anticoagulant effect [21, 22]. Amiodarone is a strong inhibitor in the metabolism and clearance of R and S - the two isomers of warfarin. Amiodarone and its active metabolite of desethylamiodarone inhibit the metabolism of warfarin (S, R), especially S, by inhibiting the activity of CYP2C9 and CYP1A2 [23, 24], thus to increase the concentration of blood S-warfarin [25, 26]. By increasing the concentration of warfarin, Amiodarone enhances the anticoagulant effect of warfarin and reduces the complications. The results of this study showed that amiodarone can improve the anticoagulant effect of warfarin, and reduce cumulative dose of warfarin, which is the difference from other studies and the advantage of this study.

In conclusion, adding amiodarone to warfarin anticoagulant treatment in patients after cardiac valve operation can reduce the cumulative dose of warfarin and the complications, which have important clinical significance.

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Disclosure of conflict of interest

None.

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