The Heart Surgery Forum #2015-520
18 (2), 2015 [Epub April 2015]
doi: 10.1532/hsf.1241

Online address: http://journal.hsforum.com

# Clinical Observation of Postoperative Warfarin Anticoagulation in 300 Patients Undergoing Mitral Valve Replacement with a Carbomedics Mechanical Valve

**Lianhe Wu, MM**[1,2,4] Qing Chang, MD[2] Tianyi Wang, MM[3] Zhengsheng Zhang, MM[1] Yanmeng Lou, MM[2,4]

[1] Department of Cardiovascular Surgery , The First People's Hospital of Jining City, Jining; [2]Department of Cardiovascular Surgery, The Affiliated Hospital of Qingdao University; [3]Department of Cardiovascular Surgery , Qingdao Municipal Hospital; [4]Department of Cardiovascular Surgery , Qingdao University, Qingdao, China

## ABSTRACT

**Objective:** The objective of this study was to evaluate the safety and efficacy of low-intensity warfarin treatment in Chinese patients after mitral valve replacement as well as the rationality of the INR standards of the hospital (The First People's Hospital of Jining City).

**Methods:** We retrospectively analyzed 270 cases in our hospital from January 2009 to December 2013; 239 patients completed the 5-year follow-up. There were 192 male and 78 female subjects, age 32-65 years old with a mean age 51.51 ± 12.12 years old. All eligible candidates received a Carbomedics artificial mechanical valve replacement and were anticoagulated under this hospital's current guidelines for postoperative anticoagulant therapy mitral valve replacement (INR 1.8-2.5). We analyzed the patient's regularly recorded prothrombin times (PTs) and the occurrence of anticoagulation-related complications, such as bleeding, thrombosis, and embolism.

**Results:** A follow-up for 239 of 300 patients was performed for 3-60 months. Within this group, one patient died from cerebral hemorrhage, there was 1 case of subcutaneous bleeding, 1 case of epistaxis, 12 cases of gingival bleeding, in 15 menstrual quantity increased, and in 1 case we found cerebral infarction.

**Conclusion:** In conclusion, low-intensity anticoagulation after mitral Carbomedics valve replacement is therapeutically effective and safe. There is room to improve the anticoagulation standard currently used, perhaps at a slightly lower level than this standard suggests. From our research we can formulate individualized treatment plans and effectively reduce the occurrence of complications.

## INTRODUCTION

As a major postoperative anticoagulant for valvular heart disease, warfarin has been widely used, and its effect on preventing thrombosis formation and the incidence of circulation embolism has been widely confirmed by clinical validation [Xie 2010]. Due to the differences in geographic region, race/ethnicity, and dietary habits in different regions, the requirements for anticoagulation intensity are different, and greater differences appear especially when compared with international anticoagulation standards [Gan 2003]. For patients in the Jining area, there are no specific standards for what anticoagulation intensity is effective while maximally reducing the risk of complications. This paper aims to explore the use of the anticoagulation standard, i.e. international normalized ratio (INR) in a range of 1.8-2.5, for the patients from Jining who underwent mitral valve surgery to implant a mechanical valve in our hospital. Whether this anticoagulation standard is safe and effective was evaluated by monitoring complications.

*Received February 25, 2015; received in revised form March 3, 2015; accepted March 20, 2015.*

*Correspondence: Qing Chang, Department of Cardiovascular Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China; +8618661809208 (e-mail: changqing20671@126.com).*

## MATERIALS AND METHODS

From December 2009 to December 2013, the clinical data of 270 patients who underwent mitral valve surgery to implant a mechanical valve in our hospital were collected. There were 192 male subjects and 78 female subjects age 32 to 65 years with a mean age of 51.51 ± 12.12 years. Patients had no preoperative hemorrhagic diseases. There were 240 subjects with rheumatic heart diseases, 60 subjects with degenerative diseases, 48 subjects with atrial fibrillation, 18 subjects underwent concomitant coronary artery bypass grafting at the same time, 101 subjects underwent concomitant tricuspid annuloplasty at the same time, and 25 subjects underwent left atrial thrombus resection.

### *Surgical Approach*

The cardiopulmonary bypass was established by cannulating the ascending aorta, the superior vena cava, and the inferior vena cava. After cardioplegic arrest, surgery was performed under direct vision. The surgical route was through the right atrium-atrial septum route. Carbomedics mechanical mitral valves were implanted in patients.

### *Postoperative Anticoagulation*

After patients returned to the intensive care unit, the pericardial and retrosternal drainages were closely monitored. Postoperative hemorrhage (drainage) and measured activated clotting time (ACT) were used to determine the amounts of protamine for neurolizing heparin, plasma and cryoprecipitate for supplementing coagulation factor, and hemostatic drugs including Dicynone and vitamin K1. If the volume of pericardial and retrosternal drainages was less than 30 mL six hours after surgery, unfractionated heparin was given at a

dose of 0.5 mg/kg by intravenous bolus every six hours (q6h) to prevent coagulation. After postoperative extubation, the administration of unfractionated heparin was stopped, and warfarin was administered orally with a first dose of 2.5 mg and a maintenance dose of 2.5 mg/day. After the second day of warfarin administration, prothrombin time (PT) and INR were measured every day. The warfarin dose was adjusted based on the result. If the INR value was less than 1.2, one more warfarin tablet (2.5 mg) was administered orally. If the INR value was between 1.2 and 1.5, an additional 1/2 warfarin tablet (1.25 mg) was administered orally. If the INR value was between 1.5 and 1.8, an additional 1/4 warfarin tablet (0.625 mg) was administered orally. When the INR value was between 1.8 and 2.5, the dose of warfarin was not adjusted. When the INR value was greater than 2.5, the oral dose of warfarin was reduced by 1/4 tablet (0.625 mg). When INR value was greater than 3.0, the administration of warfarin was stopped, until the INR value was less than 3.0, and the original dose was reduced by 1/4 tablet. When INR value was greater than 5.0, 10 mg vitamin K1 was given by intramuscular injection. If the INR value was less than 3.0 at the reexamination on the next day, the oral dose of warfarin was reduced by 1/2 tablet. When patients were discharged, their INR values were stabilized within a range of 1.8-2.5. The INR value was measured every three days during the first two weeks after discharge, every five days in the third and the fourth weeks, every week in the second month, every two weeks after three months, and every two months after six months, respectively. The INR values of most patients were reexamined in the outpatient clinic of our hospital, and the anticoagulant therapy using warfarin was guided by cardiac surgeons at our hospital. Few patients telephoned the cardiac surgeons at our hospital after they were reexamined at local secondary (or higher level) hospitals. If the INR value was higher than 2.5 or lower than 1.8, they would come to our hospital for reexamination.

### *Follow-Up*

Postoperative follow-up was conducted to check if embolization or hemorrhagic complications occurred. For the patients who experienced hemorrhage, the following were recorded: the hemorrhage site; whether there were large fluctuations in the INR values before hemorrhage; the last INR value before hemorrhage; the measured INR value after hemorrhage; whether any medications were taken before hemorrhage (such as aspirin and other nonsteroidal anti-inflammatory drugs); whether the dietary pattern was regular before hemorrhage; and whether any special foods were taken. For embolization patients, the following were recorded: embolic location; clinical manifestations; diagnostic evidence; the hospital determining the diagnosis; therapeutic efficacy; whether there were large fluctuations in the INR values before hemorrhage; the last INR value before embolization; the measured INR value after embolization; and whether other medications or large amounts of foods rich in vitamin K1 were taken before embolization. For the patients who died later, the following were recorded: the time of death; the place of death; the cause of death; the clinical manifestations before death; whether the patient was diagnosed by a doctor; diagnostic evidence; and the diagnosing hospital grade.

### *Statistical Analysis*

The statistical analysis of related data was carried out by SPSS 13.0 statistical software. Statistical description of quantitative data was expressed in $x \pm s$, statistical description of categorical data was expressed in percentage and relative ratio, and chi-square test was used for statistical inference. $P < .05$ meant that the difference was considered statistically significant.

## RESULTS

All patients were followed up for five years, 25 subjects were lost to follow-up, three subject died; the follow-up rate was 88.5% (239/270 patients). This is the main weaknesses of our study. Because China is a rapid developing country, many people moved to other cities, and changed their phone numbers and addresses, so we could not reach these patients.

One subject underwent infusion therapy due to shortness of breath and chest tightness in a local hospital, and died after the worsening of symptoms. The local hospital made a diagnosis of acute heart failure as the cause of death. One subject died of cerebral hemorrhage during hospital stay at the department of neurology of our hospital. One subject suddenly died at home with an unknown cause of death. Postoperative gastrointestinal hemorrhage occurred in three subjects who were hospitalized in the department of gastroenterology of our hospital and were discharged after recovery. Menorrhagia was found in 20 subjects. During the postoperative period, subcutaneous hemorrhage occurred in eight subjects, five of whom recovered after reducing the dose of warfarin, and three patients with an INR greater than 5.0 recovered after intramuscular injection of vitamin K. Gingival hemorrhage was found in three subjects who recovered after the dose of oral warfarin was reduced. Cerebral infarction occurred in one subject. A total of 37 subjects had hemorrhagic complications, and one subject had embolic complications. The INR values of the patients with hemorrhagic complications were all above 3.0. No apparent changes were found in the medication and dietary habits of the 37 subjects who had excessive anticoagulation, and the incidence of hemorrhage was 13.7%

Incidence of Complications of Anticoagulation among 239 Subjects with Different INR Levels

| Anticoagulation intensity (INR) | Subjects, n | Average INR | Hemorrhage, n (%) | Embolization, n (%) |
|---|---|---|---|---|
| <1.8 | 10 | 1.48 ± 0.52 | 0 (0) | 1 (10.0)* |
| 1.8-2.5 | 172 | 2.32 ± 1.08 | 4 (2.33)* | 0 |
| 2.5-3.5 | 45 | 3.05 ± 0.88 | 13 (28.89)* | 0 |
| >3.5 | 12 | 3.85 ± 0.54 | 10 (83.33)* | 0 |

*Indicates significant difference ($P < .05$).

(37/270). For the subject with cerebral infarction, the measured INR two months before embolization was 1.30, and no large amounts of foods rich in vitamin K1 or drugs were taken before embolization. The incidence of embolic complications was 0.37% (1/270).

The incidences of hemorrhagic and embolic complications among the different anticoagulation intensities are shown in the Table, and the differences were statistically significant ($P < .05$).

## DISCUSSION

Because of their durability, mechanical valves have been widely used in clinical practice. However, the poor histocompatibility of their materials can easily lead to thrombosis. Additionally, many patients require lifelong anticoagulation therapy due to hemodynamic changes, increasing number of damaged blood cells, and other factors after mechanical valve implantation. Currently, warfarin is the most widely used anticoagulant agent [Sun 2004], and hemorrhage, thrombosis, as well as thromboembolism are common complications of warfarin [Fihn 1993; Jafri 2004]. The complications caused by inappropriate anticoagulation intensity account for 75% of long-term postoperative complications, and therefore, it is particularly important to choose an appropriate intensity of anticoagulation [Emery 2008]. Currently, there isn't one uniform standard for anticoagulation in China, and the international data are used as a reference. Nevertheless, because of differences in race/ethnicity, physical fitness, dietary pattern, drug metabolism, and other factors, anticoagulation standards are quite different [Zhu 2007]. In China, the oral dose of warfarin for patients with mechanical heart valve replacements is generally lower than that of foreign patients [Chen 2000]. Therefore, for a population in a given area, there is clinical significance in exploring the anticoagulation standards of warfarin.

In this paper, the postoperative anticoagulation standard, i.e. INR in a range of 1.8-2.5, recommended in some regions of China was adopted for the patients undergoing mitral valve replacement. INR values may be expanded for patients with atrial fibrillation and pulmonary embolism, patients with a high risk of atrial fibrillation and pulmonary embolism, and those in a hypercoagulable state with a high risk of deep vein thrombosis. The international studies tend to control the INR for patients with hypercoagulability to be between 2.0 and 3.0 [Gebauer 2003]. In the studies of Chinese researchers, the low intensity warfarin anticoagulation is safer for patients with valve replacement [Wang 2010; Wang 2014]. Among the reports of the incidence of postoperative complications, Ma et al reported that the incidence rates for hemorrhage and thrombosis were 7.8% and 0.98%, respectively, when INR range was between 1.5 and 2.0 [Ma 2012]. The incidence rates for hemorrhage and thrombosis in the study by He et al were 10.4% and 0.4%, respectively [He 2010]. In this paper, the anticoagulation intensity in the Jining area was investigated, with an incidence rate of hemorrhage due to excessive anticoagulation of 12.3%, and an incidence rate of embolic complications due to insufficient anticoagulation of 0.3%. Individualized drug dosage was adopted and the guidance for anticoagulation therapy in patients was strengthened. Periodic reexamination provided assurance for the long-term survival and improvements in the quality of life among the patients taking warfarin orally after heart valve replacement surgery. In the clinical data collected in this study, the majority of patients with complications did not perform periodic reexaminations suggested by doctors.

In this paper, the investigation found that the disease history was not significantly changed by the medication or dietary pattern before hemorrhage in the majority of patients with hemorrhage. The majority of patients in our study area were in poor economic conditions, had limited educational attainment, and did not have comprehensive knowledge about anticoagulation with warfarin. The incidence of complications in patients could be effectively reduced by maintaining an appropriate intensity of anticoagulation, while strengthening the patients' education on anticoagulation knowledge, improving compliance, and developing anticoagulant therapy by doctors and patients together. In this study, hemorrhage was the most common and the most important complication of the anticoagulant therapy with warfarin, and the incidence was significantly higher than that in the similar studies by foreign researchers [Shrestha 2009]. This may be related to cultural differences, patient compliance, and the development of medical technology. The important risk factors for the incidence of hemorrhage include excessive anticoagulation, taking foods that can affect the metabolism of warfarin, and drug combinations [Wang 2011]. The anticoagulant standard currently used in our hospital should be safe and effective for the patients in the Jining area. For this group of patients, the incidence rates of hemorrhage and embolic complications were 13.7% (37/270) and 0.3%, respectively. The incidence rate of hemorrhage was slightly higher than those reported for other regions in China, while the incidence rate of embolic complications was lower than those in the similar domestic reports. Hence there should be room to improve the anticoagulation standard currently used by our hospital. Perhaps the intensity of anticoagulation should be a bit lower than this standard (INR 1.8-2.5), but this needs further study and much bigger sample size follow up to confirm it.

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