Original Article

Anticoagulant Therapy after Prosthetic Valve Replacement –Optimal PT-INR in Japanese Patients–

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Values of the international normalized ratio of prothrombin time (PT-INR) were analyzed at the time when anticoagulant-related complications developed in patients undergoing prosthetic valve replacement so as to evaluate the optimal therapeutic range in PT-INR value in Japanese patients.

A total of 102 patients with a prosthetic heart valve who have been followed up at our department during the past 25 years were enrolled in this study. PT-INRs were determined regularly in these patients for the period between October 1996 and March 1999.

Although no thromboembolic complications occurred during the period of this study, hemorrhagic complications developed in 26 (25.5%) patients. Three (2.9%) patients suffered from life threatening bleeding, such as cerebral bleeding and gastrointestinal bleeding and were defined as the major hemorrhagic group. Another 23 (22.5%) patients had minor bleeding complications such as nasal, gingival or subcutaneous bleeding and were defined as the minor hemorrhagic group. Mean PT-INR values were 3.8±2.0 and 3.2±1.0 at the onset of the complications in major and minor hemorrhagic groups, respectively, and there was no significant difference between the two groups. However, mean PT-INR values in the minor bleeding group differed significantly from that in a patient group with no hemorrhagic complications (N=76).

Among the cases with bleeding complications, only 19% of the patients belonged to the range below 2.5 of PT-INR value and 54% of the patients were included in the range from 2.5 to 3.5 ($p<0.05$).

In conclusion, the optimal therapeutic range between 2.5 and 3.5 in PT-INR recommended by the American Heart Association for patients with a prosthetic heart value in Western countries may be too high in Japanese patients. PT-INR below 2.5 is considered to be safe to prevent hemorrhagic complications. (Ann Thorac Cardiovasc Surg 2002; 8: 83–7)

Key words: prosthetic valve replacement, anticoagulant therapy, warfarin, PT-INR

Introduction

Anticoagulant therapy after valve replacement using a mechanical valve is indispensable for prevention of thromboembolism. On the other hand, hemorrhagic complications due to overdosing of anticoagulants deteriorate the quality of life (QOL) of the patients.

Therefore the blood coagulation test must be periodically performed to keep an optimal therapeutic range of the anticoagulant therapy.

In Japan, the thrombotest is preferably used as an indicator for determination of the optimum dose of warfarin. However, using the prothrombin time-international normalized ratio (PT-INR) has been proposed in recent years.[1] The guideline of the American Heart Association (AHA) in 1992 set the optimal clinical range of warfarin

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for patients with artificial valve replacement at 2.5-3.5 in terms of the PT-INR value, and further recommended that slightly lower PT-INR values of 2.0-3.0 should be used for the management of the patients with a high risk of bleeding.[2] However, this clinical range for Europeans and Americans has been emperically questioned as being excessively high for Japanese people. To make a guideline for the clinical range suitable for Asians including Japanese in the future, we studied whether the therapeutic range recommended by the AHA is appropriate for preventing complications in Japanese patients.

Patients and Methods

A total of 102 patients who underwent valve replacement using a mechanical valve at the Showa University hospital since 1973 and who have been followed up at the outpatient clinic of our department were enrolled in this study. They composed of 33 cases (18 men and 15 women) with aortic valve replacement (AVR group), 56 cases (18 men and 38 women) with mitral valve replacement (MVR group) and 13 cases (3 men and 10 women) with double valve replacement (DVR group). The operation was performed 119.6±62.5 months ago, ranging from 9 to 318 months ago. Mean age at operation was 60.5±12.0 years, ranging from 23 to 82 years. Twenty six St. Jude Medical valves (SJM valve, 21-29 mm, St. Jude Medical, St. Paul, MN, USA) , 20 CarboMedics valves (CM valve, 19-29 mm, Sulzer Carbomedics, Lane Austin, TX, USA) and 1 other prosthetic valve had been used in the aortic position, and 46 SJM valves (25-31 mm), 18 CM valves (25-29 mm) and 3 others in the mitral position. Atrial fibrillation as a complication was associated in 6 cases (18.2%) with AVR, 31 cases (55.4%) with MVR and 9 cases (69.2%) with DVR. The dose of warfarin (Eisai Co., Tokyo, Japan) was controlled at the discretion of the physicians in charge of the ambulatory patients while using PT-INR of 2.5-3.5 as the target value according to the guideline of the AHA. Combined use of anti-platelet drugs, 1-3 of aspirin, dipyridamol and ticlopidine, was performed in almost all cases. The PT-INR within 2 weeks before and after the development of complications was regarded as the drug-related PT-INR at the onset of complications in order to analyze the relationship between hemorrhagic complications, thromboembolism and PT-INR over 2 years and 5 months from October 1996 to March 1999. The PT-INR was measured 1,846 times in total, an average of 7.7±2.3 times/year per patient.

Table 1. Cases of hemorrhagic complications and PT-INR

Complication	No. of patients	PT-INR
Thromboembolism	0	–
Major bleeding	3 (2.9%)	3.8±2.0
Cerebral	2	
GI tract	1	
Minor bleeding	23 (22.5%)	3.2±1.0
Nasal	7	
Gingival	10	
Subcutaneous	6	
No complications	76	2.1±0.5

Statistical analysis

Continuous variables are expressed as a mean±standard deviation. Differences between groups were assessed by student t test or chi square contingency analysis. P values<0.05 was considered statistically significant.

Results

During the period of investigation, the PT-INR fluctuated from 0.8 to 6.4 with an average of 1.9±0.6 in the AVR group, from 0.9 to 8.4 in the MVR group with an average of 2.2±0.9 and from 1.0 to 4.8 in the DVR group with an average of 2.1±0.9, there being no difference between the groups. When examined for all the cases, it fluctuated from 0.8 to 8.4, averaging 2.1±0.8. Although, no cases showed thromboembolism, hemorrhagic complications occurred in 26 (25.5%) out of 102 cases (Table 1). In the major bleeding group in which hemorrhagic complications occured which caused a deterioration of a patients' life prognosis or QOL, there were 2 cases of cerebral hemorrhage and 1 case of gastrointestinal bleeding, a total of 3 cases (2.9%). In the minor bleeding group in which such bleeding had no influence on QOL, there were epistaxis in 7 cases, gingival hemorrhage in 10 cases, and subcutaneous hemorrhage in 6 cases, a total of 23 cases (22.5%). Hemorrhagic complications occurred in 8 (22.4%) out of 33 AVR cases, 16 (28.6%) in 56 MVR cases and 2 (15.4%) out of 13 DVR cases. Atrial fibrillation was found in 11 (42%) out of 26 complication cases, with 1 (12.5%) out of 8 AVR cases, 8 (50%) out of 16 MVR cases and 2 (100%) out of 2 DVR cases. The PT-INR at the development of hemorrhagic complications in 26 cases ranged from 1.7 to 6.6. It was 3.8±2.0 in the major bleeding group and 3.2±1.0 in the minor bleeding group. The mean PT-INR was 2.1±0.5 in 76 cases in the

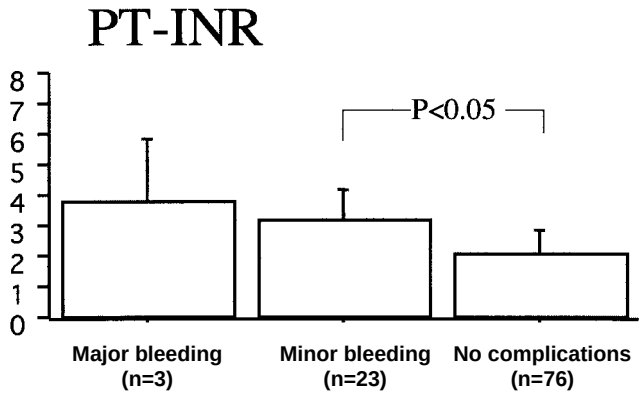

Fig. 1. Average PT-INR at the time when hemorrhagic complications developed.

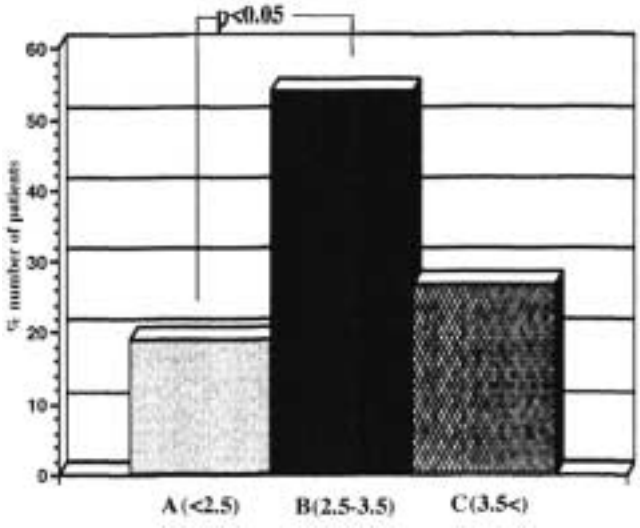

Fig. 2. On the PT-INR distribution in the cases of hemorrhagic complications.

no complication group (Fig. 1). A significant difference was found only between the minor bleeding group and no complication group ($p<0.05$).

The hemorrhagic complication cases were redistributed into the PT-INR<2.5 group (group A), 2.5-3.5 group (group B) and >3.5 group (group C) on the basis of the optimal clinical range of PT-INR (2.5-3.5) proposed by the AHA's guideline (Fig. 2). Of them, 5 cases (19%) were included in group A, 14 cases (54%) in group B and 7 cases (27%) in group C.

The number of cases in group C with an evident poor control with anti-coagulation therapy showed no significant difference from the other groups. However, the number of cases included in group B was significantly higher compared with group A ($p<0.05$).

Discussion

The thrombotest most commonly used in Japan is so designed as to have less measurement error. It is said that coagulation time can be easily assessed with this test.[3] Bovine brain thrombotest reagent for mesurement has long been standardized as a product.[4] In Japan, thrombotest value expressed as per cent is generally used for managing the patients undergoing anticoagulant therapy. But, thrombotest has several drawbacks.[7] The actual clinical therapeutic range in thrombotest is much wider compared with the clinical range set by prothrombin time[5,6] and it is difficult to assess the absolute anticoagulant effect when the thrombotest shows less than 5%.[7] Therefore, the use of PT-INR has been recently proposed instead of thromotest and prothrombin time (expressed as second or %) as an indicator for anti-coagulation therapy after valve replacement. Two kinds of thromboplastin reagent used for measurement of prothrombin time are available; rabbit brain thromboplastin with low sensitivity is widely used in the United States and human brain thromboplastin with high sensitivity used mainly in Britain. Thus, thromboplastin reagent prepared from the human brain reacts more sharply to the decrease in the vitamin K-dependent coagulation factors than that of the rabbit brain, and there arise differences in judgement of anticoagulant effects, which may result in different doses of warfarin.[8,9] As such, a proposal has been put forward that the standardizing of the laboratory data of data and interchangeability of results in anti-coagulation therapy should be established by correcting by ISI (international sensitivity index), titer of thromboplastin reagents available on the market and indicating by INR=[PT (second) of patient's plasma/PT (second) of normal plasma]^{ISI}. Another advantage of the PT-INR measurement is that inexpensive reagents can be used compared with the thrombotest. However, some measurement errors of the PT-INR arising from measuring technique, sample preparation, and varied quality of measuring instruments or control sample are problems that still remain to be resolved.[10]

The optimal PT-INR has been argued in Japan, and most of those reports gave a warning that the international standard value of 2.5-3.5 adopted in Europe and America is too high as the clinical therapeutic range for Japanese and that a clinical range of our own should be established. There have been various reports such as the optimal clinical range should be set at 1.6-2.8 and that 2.0-3.0 is desirable for the high-risk cases for thromboem-

bolism.[11–14)]

Most of our patients underwent valve replacement 10 years ago, and the doses of drugs administered are almost stable. Nevertheless, the PT-INR fluctuated widely between 0.8 and 8.4, showing the difficulty in controlling the doses of warfarin. During the study period of about two years and a half, hemorrhagic complications were found in about 25% of the patients. At the development of complications, the PT-INR was more than 1.7, averaging 3.2±1.1. More than half of the patients at the development of complications showed the PT-INR 2.5 or more, and only 19% were within the range of 1.5-2.5. PT-INR 2.5 may be taken as the upper limit for preventing hemorrhagic complications. The designs, implanted position and number of artificial valves as well as parameters for the cardiac function such as left ventricular ejection fraction, left atrial diameter and atrial fibrillation were added to the variables to analyze. Regarding hemorrhagic complications, needless to say, there was no evident associated between them and these variables.

Recently the design of artificial valves has been improved, and the incidence of thromboembolism is low so long as an optimal range of anticoagulations is maintained. Our study has made it clear that the risk of hemorrhagic complications due to warfarin is rather high. But, antiplatelet drugs were used in combination in all of our cases, therefore, we might have to clarify the relationship between the combined use of these drugs and development of hemorrhagic complications hereafter.

Suppression of platelet functions in the process of a thrombus being formed after valve replacement is desirable, and there are many reports that show the combined use of anti-platelet drugs to be effective for preventing thromboembolism in clinical cases.[15–20)] Also in our series a combined use of anti-platelet agents may be a reason why occurrence of thromboembolism has been prevented so far. However, as to the question of which antiplatelet drug is more effective, including the question of doses and side-effects (prolongation of bleeding time), not enough study has been carried out yet.[21)]

It is well known that the anticoagulant effect of warfarin is enhanced by pharmacodynamic mechanisms, technological factors and so forth. There are many drugs (i.e., sulfinpyrazone, cimetidine, amiodaron) that inhibit the metabolic clearance of warfarin, thereby increasing the warfarin concentration. Poor fat absorption, hepatic dysfunction, fever and hyperthyroidism impair the synthesis/consumption balance of vitamin K-dependent coagulation factors. Cepharospolines enhance warfarin effect by inhibiting circulatory interchange of vitamin K without affecting the plasma level of warfarin. Anabolic steroids, clofibrate, isoniazid, tamoxifen, phenytoin and acetoaminophen also increase the anticoagulant effect of warfarin due to an unknown mechanism.[22)] Poor compliance of patients for drug intake and poor communication between patients and physicians are other factors affecting the anticoagulant effect of warfarin. Strict guidance to patients on the management of drugs and daily life is essential.

Conclusion

1) During the study period of 2.5 years, hemorrhagic complications were noted in 26 (25.5%) of 102 patients with a prosthetic heart valve; major bleeding in 3 patients (2.9%) and minor bleeding in 23 (22.5%).
2) The PT-INR was 2.1±0.6 in the cases without hemorrhagic complications, 3.8±2.0 in the patients associated with major bleeding, and 3.2±1.0 in patients with minor bleeding. There was significant difference in PT-INR between the minor bleeding group and no complication group.
3) More than 80% of the patients with hemorrhagic complications showed the PT-INR 2.5 or more.
4) The optimal therapeutic range between 2.5 and 3.5 in PT-INR recommended by American Heart Association for the patients with a prosthetic heart valve in Western countries may be too high in Japanese patients.
5) PT-INR below 2.5 is considered to be safe for preventing hemorrhagic complications.

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