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Relationship between the Occurrence of Thromboembolism and INR Measurement Interval in Low Intensity Anticoagulation after Aortic Mechanical Valve Replacement

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Background: We investigated changes in the International Normalized Ratio (INR) and its measurement interval in patients with thromboembolic events who were treated by low intensity anticoagulation therapy after isolated mechanical aortic valve replacement. ***Materials and Methods:*** Seventy-seven patients who underwent surgery from June 1990 to September 2006 were enrolled in the study and observed until August 2008. The patients were followed up at 4～8 week intervals and their warfarin (Coumadin)® dosage was adjusted aiming for a target range of INR 1.5～2.5. The rate of thromboembolic events was obtained. Changes in the mean INR and INR measurement interval were comparatively analyzed between the normal group (event free group, N=52) who had no anticoagulation-related complications and the thromboembolic group (N=10). Hospital records were reviewed retrospectively. ***Results:*** The observation period was 666.75 patient-years. Thromboembolic events occurred in 10 patients. The linearized occurrence rate of thromboembolism was 1.50%/patient-years. Actuarial thromboembolism-free rates were 97.10±2.02% at 5 years, 84.30±5.22% at 10 years, and 67.44±12.14% at 15 years. The percentages of INR within the target range and mean INR were not statistically significantly different for the normal and thromboembolic groups. However, the mean INR during the segmented period just before the events showed a significantly lower level in the thromboembolic group (during a 4 month period: normal group, 1.86±0.14 vs. thromboembolic group, 1.50±0.28, $p < 0.001$). The mean intervals of INR measurement during the whole observation period showed no significant differences between groups, but in the segmented period just before the events, the interval was significantly longer in thromboembolic group (during a 6 month period: normal group, 49.04±9.47 days vs. thromboembolic group, 65.89±44.88 days, $p < 0.01$). ***Conclusion:*** To prevent the occurrence of thromboembolic events in patients who receive isolated aortic valve replacement and low intensity anticoagulation therapy, we suggest that it would be safe to maintain an INR level above 1.8 and to measure the INR at least every 7～8 weeks.

Key words: 1. Mechanical heart valve
2. Thromboembolism
3. Anticoagulation
4. INR measurement interval

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INTRODUCTION

Although experience of anticoagulation treatment after mechanical prosthetic valve replacement has accumulated, the proper level of anticoagulation remains controversial. Over-dosage of Coumadin, which is an oral anticoagulant, can result in bleeding and under-dosage can bring on the complication of a thromboembolic event, so it is very important for patients and doctors to try to maintain an adequate INR level (International Normalized Ratio), which is a value used for making dosage decisions. Determining an adequate anticoagulation level and maintaining the compliance of patients are important. A higher INR could reduce the tendency toward thromboembolic events but increase the tendency toward bleeding, so it is better to maintain the INR as low as possible, while staying within the range that lowers thromboembolic events.

The American College of Chest Physicians (ACCP) have suggested a standard level of INR to be 2.5 (2.0 to 3.0) for patients who have bi-leaflet mechanical prosthetic valves in normal sinus rhythm [1]. However, there have been a number of studies about the adequate level of INR, and also trials to determine the proper anticoagulation treatment (level of anticoagulation) [2-5]. There are ethnic differences in response to anticoagulation therapy, so a lower INR has been suggested for Asian than for Westerners [6-9]. The authors have also reported an adequacy of INR ranging from 1.5 to 2.5 [10]. In order to prevent thromboembolic events, the good compliance of patients is essential [4]. In this study, the patients lived near the hospital, so we checked the patient's INR at intervals of 4 to 8 weeks. We reviewed the relationship between thromboembolic events and the mean INR and INR measurement interval in patients who had undergone mechanical prosthetic aortic valve replacements and maintained the level of INR from 1.5 to 2.5.

MATERIALS AND METHODS

We reviewed patient records up to August 2008 and obtained the rate of thromboembolic events of the 77 patients who had undergone surgeries from June 1990 until September 2006. We analyzed the mean INR and the INR measurement interval between the normal group (N=52) which had no complications related to oral anticoagulation treatment and the group (N=10) with thromboembolic events.

We measured the INR whenever patients visited the hospital with at intervals of 4 to 8 weeks. When the INR was out of the range of the target or varied widely, we shortened the INR measurement interval.

We titrated the dosage of oral warfarin sodium (Coumadin®) according to the INR, and did not use antiplatelet agents. We reviewed the medical records retrospectively.

We regarded a thromboembolic event as an end point. We judged symptoms and signs as a thromboembolic event if they were consistent with the ischemia or infarction of a major organ even without a definite diagnosis of thromboembolism. We analyzed the thromboembolism incidence and its long-term results. Furthermore, we compared and analyzed the mean INR and the INR measurement interval between the normal group (N=52) without complications related to anticoagulation therapy and the thromboembolism event group (N=10).

We calculated the mean INR during the four months just before the thromboembolic events in order to determine the changes in the INR right before thromboembolic complications. The reason we calculated the mean INR over the course of four months was to obtain the results of INR at least twice during that period. We calculated the mean INR measurement interval during the six months right before the thromboembolic events so as to determine the relationship of the complication and the INR measurement interval. We calculated the INR measurement interval during the six months in order to obtain the INR measurement interval at least twice.

We present the cumulative variables as mean and standard deviation, and the linearized occurrence rate as %/patient-year. We used Kaplan-Meier analysis for the long-term results of thromboembolism and distinguished the differences between the groups with the Student's t-test. We regarded the value of $p < 0.05$ as significant.

RESULTS

The median age at surgery was 53 years old (16 to 72).

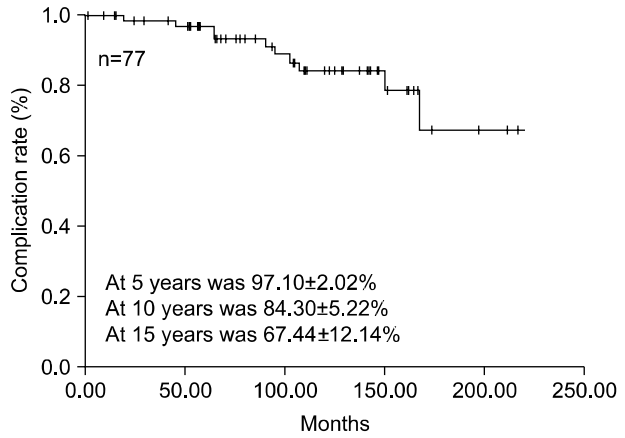

Fig. 1. Actuarial freedom rate from thromboembolism.

Table 1. Comparison of percentages within target range (INR 1.5～2.5)

	EF (N=52)	TE (N=10)	p-value
Percentages within target range (%)	59.12±11.80	58.11±13.21	p=0.40
Mean INR during the observed period	1.857±0.135	1.798±0.111	p=0.367
Mean INR during the segmented 4-month period before the event	1.857±0.135	1.504±0.279	p＜0.001

N=Number of patients; INR=International normalized ratio; EF=Event free (normal) group; TE=Thromboembolic group.

We applied various valves to the patients according to regional characteristics. The valves were of 6 types: St. Jude, Carbomedics, ATS, SORIN, ON-X, and ATS-AP. We did not perform an analysis according to valve type because of the small sample size.

During the follow-up period of 666.75 pt-yr, there were 10 cases of thromboembolism, which means a 1.50%/pt-yr linearized occurrence rate. According to Kaplan-Meier analysis, the actuarial freedom rates from thromboembolism were 97.10±2.02% at 5 years, 84.30±5.22% at 10 years, and 67.44±12.14% at 15 years (Fig. 1).

We compared the rate of target maintenance between the thromboembolism event group (N=10) and the normal group (N=52) without complications related to anticoagulation. The INR of all patients varied within the range of 0.9 to 11.97. We targeted an INR range from 1.5 to 2.5. There was no significant difference in the mean maintenance rate between the normal group (N=52) and the thromboembolic event group (N=10), which was 59.12±11.80%, 58.11±13.21% in each group, respectively (p=0.40) (Table 1).

Table 2. Comparison of the interval of INR measurement between groups

	EF (N=52)	TE (N=10)	p-value
Mean interval during the observed period (day)	49.04±9.48	45.12±14.30	p=0.14
Interval during the segmented 6-month period before the event (day)	49.04±9.47	65.89±44.88	p＜0.01

N=Number of patients; INR=International normalized ratio; EF=Event free (normal) group; TE=Thromboembolic group.

The mean INR was 1.86±0.14 in the normal group and 1.80±0.11 in the event group, and the difference between these two was not significant (p=0.367) (Table 1). However, we analyzed the INR during the 4 months right before each event, and the mean INR of the normal group was 1.86±0.14 and that of the event group was 1.50±0.28. That means the event group had a significantly lower INR value (p≤0.001) (Table 1). The normal group did not have any complications, so we analyzed the value of the normal group for the whole period.

The INR measurement interval over the whole study period was 49.04±9.48 days in the normal group and 45.1±14.3 days in the event group. Therefore, there was no significant difference between the two groups (p=0.14) (Table 2). However, when we observed the INR measurement interval during the 6 months right before events, the mean interval of the event group was 65.89±44.88 days. That was significantly longer than the mean interval of the normal group, which was 49.04±9.48 days (p＜0.01) (Table 2).

DISCUSSION

INR, which is a standardized measurement of anticoagulation, has been used widely since the recommendation by the WHO [11]. In addition, in order to prevent the patients who have mechanical valves from experiencing thromboembolism, the need for adequate warfarin anticoagulation

has been addressed [12]. For this, it is essential to maintain the proper INR. The present study's results on the linearized occurrence rate of thromboembolism and actuarial event-free rates in the patients who maintained a low INR is similar to those of other reports [13-17].

There have been ongoing trials which use a low INR in the range of the lowest thromboembolism rate whenever possible. Furthermore, there have been reports that showed lower thromboembolic and bleeding rates with an INR between 2.0 and 3.0 [2,3]. Although the ACCP suggests 2.5 (2.0～3.0) as a target INR when the left atrium is not enlarged [1], the dosage of warfarin needed varies among ethnic groups. To maintain the same INR target, Asians require lower dosages of warfarin than other ethnic groups [6-9]. You et al. [8] reported ethnic differences in bleeding and thromboembolic rates in a study of Chinese patients in Hong Kong who had maintained an INR level from 1.8 to 2.4 and showed low rate of bleeding and thromboembolic complications. The optimum low intensity anticoagulation therapy has been reported in Korea. Jeong et al. [5] reported that there was no statistically significant differences in thromboembolism occurrence in the groups with an INR of 1.5 to 2.0, 2.0 to 2.5, and 2.5 to 3.0, and the bleeding rate was higher in the group with high intensity anticoagulation therapy. Kim and Kim [4] suggested that a lower INR from 1.5 to 2.5 would be optimal for patients who have mechanical prosthetic aortic valves. The authors have reported an optimal level from 1.5 to 2.5 in a previous study [10]. In the present study, the target INR was set at 1.5 to 2.5 for the patients who had undergone isolated mechanical aortic valve replacement. We used various types of valves, but we did not believe that the analysis of individual valves would be meaningful [18]. There were no differences in the rate of target INR maintenance or in the mean INR between the groups regardless of valve type. We assessed the INR during the four months before complications occurred, and this value was significantly different between the two groups. The INR of the event group was 1.50 and was significantly lower than that of the normal group, which was 1.86. This means that a certain period of very low INR, rather than the usual maintenance of the mean INR level, can bring on thromboembolic events.

We analyzed the differences in INR measurement interval between the normal and the thromboembolic event groups. We reviewed the 6 months just before the complications because there were no differences in the INR measurement interval of the two groups over the whole observational period. The INR measurement interval of the normal group was 49 days and that of the event group was 66 days. The event group showed lower patient compliance with taking anticoagulants.

To maintain INR in the target range for the patients who take warfarin, regular examinations are essential. Lidstone et al. [19] claimed that in some selected patients, they could elongate the INR measurement interval to 14 weeks or more safely; however, we believe this elongated interval is not optimal because the INR measurement interval just before the complications was 66 days and longer than that of the normal group. In addition, the INR level was lower, despite the fact that exams were performed every 4 to 8 weeks in this study. We conclude that a long INR measurement interval is poor for maintaining the target INR and a main cause of complications. We often observe a fluctuation in the INR even in the patients who have frequent INR measurements, so a long INR measurement interval is not optimal. However, when it comes to the INR measurement interval, further analysis and studies about the factors which can lower the INR are needed. Just as Kim et al. [4] emphasized the importance of patient compliance, it is suggested that clinicians regularly educate patients about the importance of taking warfarin daily.

Torella et al. [18] suggested that in the bi-leaflet mechanical aortic valve group, it would be safe to maintain a low intensity INR level from 1.5 to 2.5. Their mean INR was 1.94. According to the INR results from this study, because of the higher risk of thromboembolism, the target INR should be over 1.8 despite an application of low intensity anticoagulation therapy.

CONCLUSION

We suggest that to maintain an INR level over 1.8 and INR measurement interval of 7 to 8 weeks would be safe for preventing thromboembolic events when a low level of anti-

coagulation treatment is applied after isolated mechanical aortic valve replacement.

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