ORIGINAL ARTICLE

Control of Oral Anticoagulant Therapy using INR in Patients with Artificial Heart Valves

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ABSTRACT

Objective: To determine frequency of patients with artificial heart valves who are optimally anticoagulated, over anticoagulated or under anticoagulated based upon INR values.

Study Design: Descriptive, cross sectional study.

Place and Duration of Study: Pathology Department, Armed Forces Institute of Cardiology, Rawalpindi.

Materials and Methods: Five hundred patients who underwent heart valve replacement at AFIC were selected according to convenience sampling. Prothrombin time along with International Normalized Ratio (INR) was done in every case on automated Coagulation Laboratory (ACL). Patients were grouped into adequately anticoagulated, under anticoagulated and over anticoagulated according to INR values. Descriptive statistics were used to describe the frequencies and percentages. One way ANOVA followed by post Hoc Sheffe test was applied to compare mean values of INR across the three groups. The p-value less than 0.05 was considered significant.

Results: A total of 300 patients (60%) were adequately anticoagulated whereas 175 (35%) and 25 (5%) were under and over anticoagulated respectively. Fifteen patients (60%) of the over anticoagulated group had hemorrhagic complications. INR values of all the three groups were significantly different from each other p-value(<0.005).

Conclusion: Dose of oral anticoagulant (warfarin) should be adjusted according to the results of INR to avoid thromboembolic or hemorrhagic complications.

Keywords: *INR, warfarin, artificial heart valves, oral anticoagulation.*

Introduction

Artificial heart valves put the patients at risk of thromboembolism.[1] Lifelong anticoagulant therapy is, therefore, essential after artificial heart valve replacement. While oral anticoagulants reduce the risk of thromboembolism by inhibiting coagulation, they increase the risk of variable degree of hemorrhagic complications.[2] Indeed, for such patients, quality of life is dependent on the absence of anticoagulant related adverse events i.e. thromboembolic or hemorrhagic complications. The two extremes depend upon the dosage of anticoagulant and an optimal dosage is required for the desired outcome.[3] The thromboembolic hazards are not only related to the type of prostheses but also to a variety of concomitant patient related risk factors.[4] This seesaw of anticoagulation therapy is balanced by determining the optimal intensity of oral anticogulant where thromboembolic complications are effectively prevented without excessive bleeding. The optimal intensity is defined as the level at which the incidence of both thromboembolism and bleeding is lowest.[5] Warfarin is a commonly used anticoagulant drug in such patients which acts by inhibiting the synthesis of vitamin K dependent clotting factors i.e. factor II, VII, IX and X, and other proteins essential for clotting process.[6] Considering its mechanism of action, warfarin may act as 'double edged sword'. Over dosage will lead to bleeding tendency whereas under dosage will result in thromboembolic complications. It therefore follows that strict and accurate control of warfarin dosage is essential to avoid such events. This is achieved with the help of laboratory tests for coagulation like PT, PT ratio and INR.[7] The traditional expression of PT test results, either as percentage prothrombin activity or PT ratio, is inadequate for international communication and comparison because the values depend on the nature of thromboplastin test system used.[8] The WHO recommended; universal scale of reporting PT results is based on calibration of local thromboplastin systems against an International Reference Preparation (IRP). This scale is International Normalized Ratio (INR).[9]

Due to significant patient variability in response to warfarin therapy, the INR must be closely monitored until a steady state is reached.[10] Medications like antibiotics, birth control pills and other hormones

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can also affect the action of warfarin; necessitating the evaluation of the possible effect of the added medication on the INR.[11] Warfarin dosage changes may also be required in response to the INR results. However, until the patient reaches a steady state, INR fluctuations are expected. It may take up to one month to reach an optimal therapeutic level of warfarin for an individual patient.[12] Periodic monitoring, up to once every month, is necessary as long as the patient remains on anticoagulation therapy. More frequent routine monitoring may be required in some patients. Random variation of INR values may occur in a patient on stable oral anticoagulant dosage, as a result of both biological and analytic variation. It has been calculated that in a patient on fixed dose and steady state warfarin, a change in the INR is significant only if it is a change (increase or decrease) of greater than 0.28 times the previous INR value.[13] The American College of Chest Physicians and the National Heart Lung and Blood Institute revised their recommendations for intensity of warfarin therapy in 1995. An INR of 2.0 to 3.0 is recommended for all indications except mechanical prosthetic heart valves, for which an INR of 2.5 to 3.5 is recommended.[14] We planned this study to determine frequency of patients with artificial heart valves who are optimally anticoagulated, under anticoagulated and over anticoagulated based upon INR values.

Materials and Methods

A descriptive, cross sectional study was conducted at Pathology Department of Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi. A formal approval was acquired from medical ethics committee before commencement of the study. Written and informed consents were obtained from all the patients. Five hundred patients who underwent heart valve replacement at AFIC were selected according to convenience sampling. Prothrombin time along with International Normalized Ratio (INR) was done in every case on Automated Coagulation Laboratory (ACL). Commercial Kits; IL test PT-Fibrinogen along with IL test normal control plasma with range of 11.2-12.7 seconds were used. Patients were grouped into (Group A) adequately anticoagulated, (Group B) under anticoagulated and (Group C) over anticoagulated according to INR values. Statistical analysis was performed by using IBM SPSS statistics version 21. Descriptive statistics were used to describe the frequencies and percentages. One way ANOVA (analysis of variance) followed by post Hoc Sheffe test was applied to compare mean values of INR across the three groups. The p-value less than 0.05 was considered significant.

Results

Out of 500 patients 300 were optimally anticoagulated, 175 were under anticoagulated and 25 were over anticoagulated. INR values for adequate anticoagulation was 2.5 to 3.5 whereas the values below 2.5 was considered under anticoagulated and over 3.5 as over anticoagulated (Table I). Pie chart in Figure 1 shows the percentages of the patients in three groups.

One way ANOVA was applied on the three groups receiving anticoagulant therapy which showed significant difference in mean values of INR across the groups. p-value(<0.005) (Table II). Post Hoc Sheffe test revealed that mean INR values of adequately anticoagulated group were significantly different from those of over and under anticoagulated groups. p-value(<0.005) (Table 3).

Table I: Frequency of patients in different anticoagulation groups according to INR values (n-500)

Anticoagulation status	Frequency	INR
A. Adequately anticoagulated	300	2.5 – 3.5
A. Under anticoagulated	175	< 2.5
B. Over anticoagulated	25	> 3.5

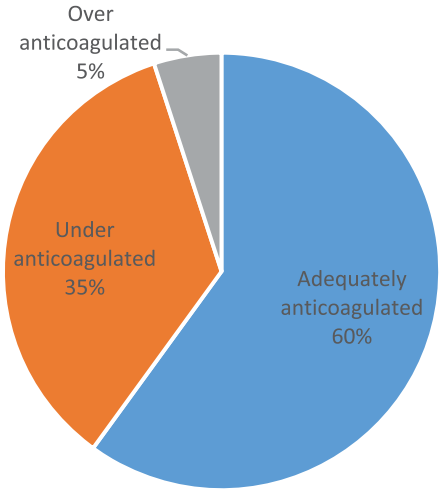

Fig 1: Percentage of patients according to anticoagulant status (n-500)

Table II: Comparison of mean INR values across the three groups (one way ANOVA test) (n-500)

Anticoagulation status	Mean INR ± SD	*p*-value
A. Adequately anticoagulated	3.10 ± 0.37	< 0.001*
B. Under anticoagulated	1.46 ± 0.47	
C. Over anticoagulated	5.22 ± 1.12	

***p-value significant (< 0.05)**

Table III: Comparison of mean INR values of adequately anticoagulated group with under and over anticoagulated groups (Post Hoc Sheffe test)

Anticoagulation status		*p*-value
A. Adequate	B. Under	< 0.001*
	C. Over	< 0.001*

***p-value significant (< 0.05)**

Discussion

Results of our study showed that 60% of the patients who underwent artificial heart valve replacement were adequately anticoagulated; while 35% being under and 5% were over anticoagulated. Fifteen patients (60%) out of the later group had evidence of critical bleeding.They had to be hospitalized and were managed successfully by immediate withdrawal of warfarin sodium and fresh frozen plasma (FFP) replacement therapy. Our results also confirmed significant difference between INR values of adequately anticoagulated group with each of the other two groups. This implies that warfarin dosage was 'out of range' in under and over anticoagulated groups. Cannegieter S et al carried out a study to find out optimal oral anticoagulant therapy in patients with mechanical heart valves.[15] Their study included 1608 patients with mechanical heart valves who were on oral anticoagulant therapy. They followed up their patients for a mean period (per patient) of 4 years. 45 of their patients developed thromboembolic disorders whereas 164 developed hemorrhagic complications during the follow up period. The optimal intensity of anticoagulation, at which the incidence of both complications was lowest, was achieved when the INR was between 2.5 and 4.9. This is in contrast with INR range of our study i.e. 2.5 to 3.5. Our study was a basic study to categorize out patients on anticoagulant therapy into above mentioned three groups; therefore it does not include the follow up of under and over anticoagulated groups for the incidence of thromboembolic or hemorrhagic complications. Mori T et al studied the effects of anticoagulant therapy after prosthetic valve replacement in Japanese patients.[16] Their study included 102 patients who had prosthetic heart valve replacement and had been followed up for the past 25 years. INR of these patients were regularly determined in the last three years of their study period. They observed no thromboembolic complications in their patients during the follow up period, however 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. This finding of More T et al study is comparable to our study where we found 15 (3%) patients in over anticoagulant group having major hemorrhagic complications. Mean INR values of their study were 3.8±2.0 and 3.2±1.0 at the onset of the complications. Interestingly, in the study population of Mori et al, hemorrhagic complications developed at INR value which is near normal as per recommendations of American Heart Association for patients with a prosthetic heart values. Mean values of INR in our study are also in consistence with the international standards. Mori at al made a very important conclusion that the 'normal values' of INR are high for Japanese patients. They recommended INR below 2.5 in their patients to avoid hemorrhagic complications. Hering D et al, conducted a study to record thromboembolic and bleeding complications following artificial heart valve replacement in German population.[17] They selected 2735 patients who underwent artificial heart valve replacement surgery.They observed 51 thromboembolic events, 22 of which were minor 10 were moderate and 19 were severe. They reported 1,687 patients with bleeding complications. The vast majority of bleeding complications (1509 patients) were classified into minor, 140 as moderate and 38 classified as severe. Besselaar VD carried out a survey of thromboplastin reagents used for prothrombin time testing to observe the international standardization of laboratory control of oral anticoagulant therapy.[18] He reported that although the prothrombin time is the primary test for control of oral anticoagulant treatment, it lacks standardization because the values depend on the nature of the thromboplastin test system used. The

WHO standardized PT results on the basis of calibration of local thromboplastin systems against an international reference preparation and this standardization is the International Normalized Ratio. The use of the INR for the control of oral anticoagulant therapy will facilitate international comparison of the results and consensus on optimal target values. The use of INR should be mandatory for better control of oral anticoagulant therapy to avoid complications in patients on long term anticoagulation such as with artificial heart valves.One of the limitations of our study is lack of follow up of our patients in under and over anticoagulated groups for thromboembolic and hemorrhagic complications respectively. However, the average INR values in these two groups showed significant variation from the normal mean value. This indicates that the actual number of patients with thromboembolic or hemorrhagic complications in our study might be high. This aspect is going to be the major component of our future study.

Conclusion

Anticoagulant therapy is an integral part of the treatment in patients with artificial heart valves. Dose of oral anticoagulant should be adjusted according to the results of INR to avoid complications.

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