

# Complications of warfarin in post operative heart valve surgery

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## Abstract:

**Introduction:** Thromboembolic complications and bleeding are the major complications of warfarin. The aim of the study was to focus on the complication of warfarin and monitoring post-valve surgery.

**Methods:** A combined retrospective and prospective study was done in post mechanical heart valve surgery patients at Manmohan Cardiothoracic Vascular and Transplant Center. The study was carried out for 4 months by interviewing patients with self administered structured questionnaire about any complications during their follow up in OPD and monitoring for their INR values.

**Results:** The majority of patients studied were male 42 and 56 were female. Fifty five patients underwent mitral valve replacement, 22 underwent double valve replacement and 46 underwent aortic valve replacement. There were a total of 59 cases of bleeding complications. Hemoptysis was the most common bleeding event. Pericardial bleeding was the most common major bleeding complication with 3.1%. In patients taking warfarin major bleeding complication was 10.2% and minor bleeding was 50%. Out of total INR reading 47% were out of the target INR range, with 19.5% above range and 27.5% below range.

**Conclusion:** Minor bleeding was the most common type of bleeding. A system for proper monitoring of warfarin can bring improvement in better dose adjustment to achieve more appropriate INR values and eventually minimizing warfarin related complications. Introducing pharmacist monitored anticoagulant clinic can reduce the work load of physicians and overcome the time barrier.

**Key word:** Minor bleeding, Major bleeding, INR, Thromboembolism

## Introduction

Rheumatic fever and RHD are the major public health problems. Only medical treatment does not solve the problems of patients with rheumatic heart disease sooner or later they have to undergo heart valve surgery. So once they have undergone heart valve replacement they require lifelong warfarin treatment

The most common cause of valve disease is Rheumatic heart disease (RHD). Heart valve surgery is conducted in patients with RHD. Studies have shown that second most common cause for open heart surgery was RHD that constitute 35 percent in Nepal. So RHD is one of the

leading causes of surgery in cardiothoracic and vascular surgery department of this country.<sup>2</sup>

Warfarin has a narrow therapeutic window and is commonly associated with adverse events. Subtherapeutic levels can lead to thromboembolic complications in patients, while supratherapeutic levels can lead to bleeding complications. Strategies to improve both the dosing and monitoring of this high-risk drug have potential to reduce the associated risks of bleeding or thromboembolic events.<sup>1</sup>

This study was focused on the complication of warfarin and monitoring post-valve surgery. It also focuses on

the risk factors for complication. If the risk factors for warfarin complication can be determined, there is chance of preventing complication related to warfarin in these groups.

## Methods

The survey was carried out at Manmohan Cardiothoracic Vascular and Transplant Center, IOM Maharajgunj, Kathmandu, Nepal. The study was carried out for the duration of 4 months from 23<sup>rd</sup> July 2012 to 12<sup>th</sup> November 2012. The research has adopted descriptive cross-sectional design and random sampling technique. The sample size was 98. Combined prospective and retrospective study. New patients and old patients who have undergone mechanical valve surgery and on warfarin therapy were included in the study.

The study was carried out by directly interviewing patients for the details as specified in the data collection sheet in order to investigate any complication when they come. The subjects had given in their informed consent to participate in the research and the study was in accordance to the Helsinki declaration of 1975 as revised in 2000. Follow up was done for 4 months i.e. for the duration of study period. Patients who were admitted in the hospital due to warfarin complication were also included. Warfarin was monitored by PT expressed as INR. The study variables are Age, Sex, warfarin induced Bleeding complications, Thromboembolic complications and types of valve replacement.

Patients under treatment with warfarin after undergoing valve surgery in MCVTC, Patients who began treatment during the study period (new patients) and Patients who had been undergoing treatment at the time of study (old patients) were included in the study.

Patient prescribed with anticoagulant other than warfarin, Patient with valve repair only, Patient under warfarin therapy besides mechanical valve replacement and Patients who are not willing to be included in the study are excluded in the study.

The patients who qualified the inclusion criteria were informed of the purpose of the study. Those patients willing to participate were directly interviewed for the details as specified in the data collection form in order to investigate any complication when they came for follow up in OPD. Follow up was done for 4 months i.e. for the duration of study period. Information on any past or current occurrence of complication related to warfarin was collected. Risk factor for complication related to warfarin was also identified. Patient's knowledge about the drug was

also assessed. Warfarin was monitored by PT expressed as INR. Patient's INR recording and dose adjustment made were also noted from patient's medication record and anticoagulation booklet. Patients who were admitted in the hospital due to warfarin complication were also taken.

The collected data were entered in SPSS data sheet and statistically analyzed using SPSS for windows, version 17.0. Chi-square test was used for analysis. It was also used to evaluate association between different other variables. A p-value less than 0.05 were considered statistically significant. Graphs were generated using Microsoft Excel 2007.

## Result

Ninety eight patients were studied 42 (42.9%) were male and 56(57.7%) were female. Mean age of the patients was 39.76(range 14-77 years).Fifty five (56.1%) patients underwent mitral valve replacement (MVR), 22 (22.4%) patients underwent double valve replacement (DVR) and 46 (24.8%) patients underwent aortic valve replacement (AVR). There were a total of 59 cases of bleeding complications. Hemoptysis was the most common bleeding event (15.3%) and menorrhagia (15.3%) was the most common amongst women (7.6 per patient-years). Pericardial bleeding was the most common major bleeding complication with 1.5 per 100 patient-years (3.1%). In patients taking warfarin major bleeding complication was 5.1 per 100 patient-years (10.2%) and minor bleeding was 24.7 per 100 patient-years (50%). The cumulative time spent by the patient is 198.6 patient-years.

**Table 1: Incidence of bleeding complication in patient-year and type of valve replacement**

| Type of valve replacement | Major | Minor |
|---------------------------|-------|-------|
| MVR                       | 3     | 9.1   |
| DVR                       | 1.5   | 3.5   |
| AVR                       | 0.5   | 3     |

The maximum numbers of patients who have under gone heart valve surgery were 27 of age group 41-50 years. The mean age is 39.76 years. Age group of 51-60 years had highest rate of major type bleeding complication (24.1%), where as age group 41-50 years had highest rate of minor type bleeding complication (33.3%).

**Table 2: Incidence of bleeding and age group**

| Age group (years) | Major bleeding |              | Minor bleeding |              |
|-------------------|----------------|--------------|----------------|--------------|
|                   | Occurred       | Not occurred | Occurred       | Not occurred |
| 11-20             | 0              | 8(100)       | 2(25)          | 6(75)        |
| 21-30             | 1(5.4)         | 17(94.4)     | 5(27.8)        | 13(72.2)     |
| 31-40             | 2(7.3)         | 24(92.3)     | 7(26.9)        | 19(73.1)     |
| 41-50             | 3(11.1)        | 24(88.9)     | 9(33.3)        | 18(66.7)     |
| 51-60             | 3(24.1)        | 10(76.9)     | 5(38.5)        | 8(61.5)      |
| 61-70             | 1(25)          | 3(75)        | 1(25)          | 3(75)        |
| 71-80             | 0              | 2(100)       | 2(100)         | 0            |

Out of 98 patients there were 37 hypertensive patients, 1 patient have major bleeding complication and 29 patients have minor bleeding complication and remaining 7 does not have any bleeding complication.

**Table 3. Risk factors and bleeding complications**

| Other risk factor    | Major  | Minor   | Total (n=98)(%) |
|----------------------|--------|---------|-----------------|
| Age>65               | 1(25)  | 3(75)   | 4(4.1)          |
| h/o stroke           | 1(25)  | 1(25)   | 4(4.1)          |
| h/GI bleeding        | 0      | 1(50)   | 2(2)            |
| Hematocrit<30%       | 1(5.6) | 7(38.9) | 18(18.4)        |
| SCreatinine>1.5mg/dl | 0      | 2(66.7) | 3(3.1)          |
| Diabetes mellitus    | 1(25)  | 1(25)   | 4(4.1)          |

There were 2 reported thromboembolic complication in patients who have undergone MVR. The patient with the age group 41-50 and 61-70 years had developed thromboembolic complications. Overall, out of total 632 INR readings 27.5 % ( 174) was below the target range and 19.5% (124) was above target range. Only 53% (334) INR were within target range. The mean INR at discharge was 2.59. Statistical analysis showed that there was significant association between dose adjustment and INR. In total, there were 297 INR reading outside the range among which there were 159 INR reading in which dose adjustment was done. Statistical analysis showed significant association ( $p<0.05$ ) between dose adjustment and INR fluctuation

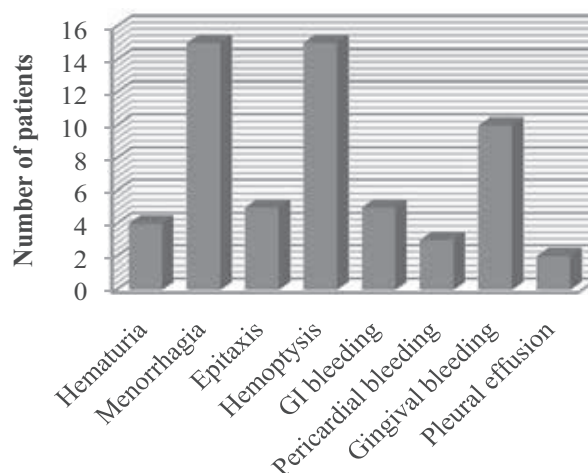
**Table 4: Doses adjustment and fluctuation in INR**

| INR range          | Dose adjustment Done | Not done |
|--------------------|----------------------|----------|
| Above range(n=123) | 73(59.3)             | 50(40.7) |
| Below range(n=174) | 86(49.4)             | 88(50.6) |

Chi-square =57.093;  $p=0.00$

## Discussion

Different studies showed variation in method of warfarin management and inconsistency in characterizing bleeding event. Due to the lack of standard for defining complications of warfarin, various criteria have been used to define bleeding events (e.g., fatal, major, minor, nuisance) and complications. This makes the comparability between the studies difficult.

**Figure 1. Type of bleeding complications**

Other causes of incomparability are differences in patient selection and method of follow up.

In this study 59 bleeding events (29.7 per 100 patient-years) occurred in 41 patients which is three half higher than that shown by other studies (20.5 per 100 patient-years).<sup>10</sup> The high incidence of bleeding seen in this study could be due to variation in defining bleeding events and insufficient patient number.

Studies have shown that epistaxis is a common bleeding event in patient's on warfarin which is also supported by this study, being the most common (16.8%) bleeding event.<sup>21, 22</sup> Study done in Turkey have shown that hematuria is the most common complaints in warfarin-induced renal and retroperitoneal hemorrhage, which could be the cause of hematuria (10.3%) in this study.<sup>11</sup> Evidence also suggests that serious, underlying occult lesions are the source of GI bleeding. This could be the reason for the observed GI bleeding (5.1%) in this study.<sup>12</sup> Beside this, hematuria occurred at the rate of 4.2% of the total bleeding events which was close (6.3%) to the finding of study conducted in Boston.<sup>13</sup>

A study at UK states that menorrhagia is common in women receiving oral anticoagulation. Similar findings were observed in this study with high incidence of menorrhagia in females. His study also shows that levonorgestrel releasing intrauterine device (LNG-IUS) is effective in reducing the duration and amount of menstrual bleeding in women with menorrhagia associated with warfarin.<sup>14</sup> So the use of LNG-IUS should be considered in patients who are excessively suffering from menorrhagia.

In this study, minor bleeding was the most common bleeding (24.7 per 100 patient-years). Major bleeding occurred at the rate of 5.1% per patient-year which is consistent with the results published in other studies.<sup>7</sup> Whereas, it is inconsistent with the finding of Palareti et al.<sup>4</sup> Minor bleeding occurred at the rate of 24.7% per patient-year which is four times as higher than that reported by other studies.<sup>4,7</sup> This difference in bleeding event could be due to variation in number of patients and patient years involved in the study. Moreover, it could also be due to the variation in bleeding categorization and warfarin management. Beside this, present study involved patient with restricted indication, valve replacement only.

The rate of major and minor for new and old patients were compared. Minor bleeding complication occurred slightly higher in new patients (36.4%) than in old patients (27.8%). Major bleeding occurred at slightly higher rate in new patients (11.4%) than in old patients (9.3%).

Statistical analysis did not showed association between

minor bleeding events and major bleeding events in new and old patients. However, the linearized incidence of bleeding shows that new patients are more likely to experience bleeding complication compared to old patients. These observations suggest that higher frequencies of bleeding occur during early course of warfarin therapy which is a constant finding in other literatures.<sup>4, 7</sup>

This study identified that patients with MVR had maximum incidence of minor type bleeding (32.7%) and patients with DVR had maximum incidence of major type bleeding (13.6%). No association between type of prosthesis and various types of bleeding complications were seen. However, patients with MVR had the more incidence of bleeding which is consistent with the other findings, which states that prosthesis in mitral position increased the risk bleeding almost twice as compared with the aortic position.<sup>3</sup>

Many patient characteristics are associated with bleeding complications during warfarin therapy.<sup>13</sup> Hypertension is known to increase the risk of bleeding.<sup>7</sup> The finding of this study also supports that there is increase in bleeding risk in patients with hypertension. Some studies have noted an increased frequency of bleeding in women treated with warfarin. However, this study found higher incidence of bleeding in male (74.4%) than female (60%).<sup>14</sup>

Several studies have suggested association of older age with bleeding complication.<sup>15</sup> In this study there is an increasing trend of minor bleeding complication with increasing age, with slight decline in minor bleeding complication after the age group 41-50. The probably reason for this could be due to dramatic decline in the patient number after this age-group. There were only 13 patients in the age group 51-60, only 3 patients in the age group 61-70 and 2 patients in the age group 71-80. So this could have underestimated the incidence of bleeding with increasing age in this age group.

Increasing trend of major bleeding with increasing age could be observed. There is increase in incidence of major type of bleeding with the age group but no incidence of major bleeding in age group 71-80, though there were only 10 major bleeding complications that occurred. This may be due to the reason of insufficient number of patient and long term studies could have overcome this variation.

Comorbid condition such as recent myocardial infarction (MI), renal insufficiency or severe anemia is also described as a risk factor.<sup>5</sup> a history of gastrointestinal bleeding also increases the risk of bleeding.<sup>12</sup> In this study there were no MI history patients interviewed. All four patients with age>65 years experienced bleeding, 8/18 patients with hematocrit<30% had experienced bleeding, 1/2 patients with history of GI bleeding experienced bleeding, 2/3 patients with serum creatinine<30% had experienced

bleeding and 2/4 patients with history of stroke had experienced bleeding. All these number shows more than 50% probability of having bleeding when the patients have these risk factors except 1/4 patient with diabetes mellitus experienced bleeding. However, there were not sufficient patients. So the conclusion could not be derived for their risk of bleeding when the patients have these risk factors.

The rate of thromboembolic complications (1% per pt-yr) seen in this study did not showed consistency with the finding of other study.<sup>3</sup> There are various factors which can influence the thromboembolic risk, including position of the prosthesis (mitral, aortic or both). Risk of thromboembolism is commoner with prosthetic mitral valves than aortic valves and in patients with double replacement valves compared with those with AVR.<sup>9</sup> Similar trend was seen in the present study but there was no incidence of thromboembolism in AVR and DVR. However, it is not consistent with the finding of Goldsmith et al.<sup>6</sup> that thromboembolic complications were higher with DVR than MVR. There were no incidence of thromboembolic complications in patients with DVR than in MVR could be due to small number of patients with DVR (n=22) than patients with MVR (n=55) in this study. So, the number of patients might have affected the result. Study had shown that thromboembolism is higher among men than women which contradict with our finding.<sup>16</sup> In fact, our study showed both female have almost equal risk of thromboembolism.

This study also supports a finding that age may increase the risk of thromboembolic complication.<sup>3</sup> There were clear indication of incidence thromboembolic complications in the age group 41 to 50 and 61 to 70 years, which showed one complication on each. The probable reason, might be due to patients failing to inform their incidence of thromboembolic complication, as it is more likely as this study is partly retrospective. Beside this, it could also be due to unavailability of patient's record of complication. This study had identified age group 41 to 50 and 61-70 be most commonly involved with thromboembolic complications. However, there was none of the patient with thromboembolic complication in the other age group which could be due to less number of patients in this age group. There were none of the patients with thromboembolic complication in the age group 11 to 20, which supports the findings.<sup>3</sup> The young age is probably the reason for less risk of thromboembolic complications. Study has stated that there is high incidence of thromboembolic complication among smokers, which is in support of our current finding.<sup>3</sup> As there were no currently smoking patients, the result of this study is questionable. However, former smoking patients (2.2%) in this study did not have any thromboembolic complications.

Overall, this study showed that 53% INR was within the target range which is little higher to the value of 40% reported.<sup>17</sup> 27.5% INR was below the target range which showed the practice of under-anticoagulation being more common than above the target INR range among the patients of MCVTC. Study had shown that 48% of thromboembolic complications occurred at INRs below therapeutic range.<sup>18</sup> As patients in this study had INR below the target range one fourth of the time (27.5%), they were at high risk of thromboembolic complication. However, thromboembolic events reported were very less in relation to INR being low. This could be because patients were using aspirin on and off basis which could have reduced the risk of thromboembolic events in them. The data of patients on warfarin could not be taken as the prescribing of aspirin was not regular and was mostly used short term. Moreover, there was lack of standard guideline for the use of warfarin in hospital.

There were 19.5% of INR readings which was above range causing high risk for bleeding. Among them there were 8.1% of patients who had INR more than five. Studies have shown that INR greater than 5 greatly increases the risk of hemorrhage.<sup>19</sup> So these patients have higher risk of hemorrhage. Most of the time (38.3%) INR was between 2 to less than 3.

This large fluctuation in INR as seen in the present study can increase risk of bleeding.<sup>8</sup> This unexpected fluctuation in INR could be due to one or more causes, such as change in diet, poor compliance, undisclosed drug use, alcohol consumption or self-medication. The underlying cause for the fluctuation in INR should be identified where possible which can prevent complication of warfarin. Beside this, achievement of INR in target range requires regular monitoring and follows up with proper patient counseling. Most of the patients in Nepal do not come for regular follow up which could also have resulted in poor management of INR and also there are less INR clinics.

In this study, dose adjustment was done most of the time (59.3%) when the INR was above the target range. However, when the INR was below the target range there seems to be negligence in dose adjustment (19.4%). This indicates that prescribers are more concerned about overwarfarinization than underwarfarinization. In 1995 the Agency for Healthcare Policy and Research (AHCPR) reported that warfarin is greatly underutilize and that the physicians are reluctant to prescribe warfarin, in part because they are not familiar with techniques for administering the drug safely and fear that the drug will cause bleeding.<sup>20</sup> This could be the reason for high incidence of under-anticoagulation in this study. Moreover, physician tends to neglect dose adjustment when the INR is close to the target range,

specially when INR is below the target range. This could be the reason for the low percentage of dose adjustment being done in patients whose INR is below the target range.

Patients in this study experienced wide variety of side effects of warfarin. Alopecia occurred at the highest rate (14.3%). This high incidence of alopecia seen in the patients could be due to concurrent administering of other drugs like metoprolol and various antibiotics. So the observed alopecia could be the additive effects of these drugs as well.

Allergic reaction and bruising was the second highest (9.2%) side effects experienced by patients, which can also be due to concomitant administration of other drugs which can also cause fever as a side effect. Fever was experienced by 4.1 %patients, which can also be due to concomitant administration of other drugs which can also cause fever as a side effect these drugs include cefadroxyl, ACE Inhibitor and benzathinepenicilline which were used commonly in these patients.

3.1% incidence of vomiting seen in the patients could also be due to other drugs beside warfarin. Patients with valve surgery are often given digoxin, cefadroxyl, benzathine penicillin and ACE Inhibitor which can also cause vomiting as a side effect. Nausea was seen in 3.1% and rashes were seen in 2% of patients on warfarin. Both of these side effects can be due to other drugs beside warfarin. These drugs could be digoxin, amiloride, cefadroxyl, metoprolol, benzathine penicillin and ACE Inhibitor which was also being used in most of these patients.

Of The 6 patients were admitted to the hospital with bleeding complication. Of 6 patients who bled, 4 patients had INR more than 4.5 which is different from a result which showed, sixteen of 17 bleeding patients had INR more than 4.5.<sup>19</sup>

On the other hand, only 2(8.3%) out of total 2 underwarfarinized patients developed thromboembolic complications. This shows that INR below the target range resulting in thromboembolic complications occur at the lower rate (8.3%) than bleeding (25.1%) which occurs with INR above the target range. This shows that overwarfarinization can easily cause bleeding compared to thromboembolic complications produced in patients who were underwarfarinized.

## Conclusions

The study demonstrated that there is high prevalence of complication related to warfarin in patients with mechanical valve replacement, with bleeding complication being the most common one. Majority of the bleeding complications were minor bleeding. There was also high fluctuation of

INR in patients and mostly INR was within the target range. Moreover, dose adjustment was not done one-fifth of times, mostly when the INR was below the target range there was also high incidence of requirement for hospitalization which could have been avoided by better monitoring.

This shows the need of a system for proper monitoring of warfarin which can bring improvement in better dose adjustment to achieve more appropriate INR values and eventually minimizing warfarin related complications. This is achieved by implementation of pharmacist monitored anticoagulation clinics which is lacking in Nepal.

## Conflict of interest

The authors declare that there is no conflict of interest associated with the study.

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