ANTICOAGULANT CONTROL RESULTS AMONG PATIENTS WITH MECHANICAL HEART VALVES AT MUHIMBILI NATIONAL HOSPITAL, TANZANIA

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Abstract

Background: Patients with mechanical heart valves receive life long, oral anticoagulant therapy to prevent thromboembolic complications, but this treatment is associated with an increased risk of bleeding [(1)]. However no study in Tanzania has been done to review the adequacy of anticoagulation monitoring and risk factors involved in the operated patients receiving warfarin.

Broad objective: The study aimed at reviewing the adequacy of anticoagulant control results among patients with mechanical heart valves attending the anticoagulation clinic at Muhimbili National Hospital (MNH).

Study design: This was a retrospective cohort study.

Study settings. The study was conducted in Dar es Salaam at the anticoagulation clinic, MNH.

Measure of outcome: Review of adequacy of anticoagulation control results was analyzed as percentages of all prothrombin ratio tests done during the whole period of follow up to determine the proportion of tests which were within the therapeutic level, below or above it. Basing on defined percentile levels, the number of patients who were adequately controlled was calculated. Univariate and Multivariate logistic regression was also done to assess factors such as warfarin dose, source, food habits and drugs that could be associated with the high level of anticoagulation

Subjects: The study involved all patients-receiving- warfarin with mechanical heart valves operated from 1990 to 2003 attending the anticoagulation clinic at MNH.

Methods: Assessment of anticoagulation adequacy was based on the prothrombin ratio measurements that were recorded in the anticoagulation booklets. Each prothrombin ratio measurement was assessed if it was within the therapeutic level, above or below it. Information on risk factors influencing the anticoagulation monitoring was obtained from medical records and interviews.

Findings: During study follow-up, a total of 10583 prothrombin ratio measurements were done among all 189 patients who were available for interview. Only 35.5% of the measurements were within the recommended therapeutic (normal) range, 33.4% above therapeutic and 31.1% below it. Thus, in only 35.5% of the follow-up prothrombin ratios, was adequate anticoagulation maintained. The study also only 23.8% (45/189 patients) of the patients were able to maintain adequate anticoagulation for more than 56.5% (more than 80 percentile) of their Prothrombin ratio measurements done during follow up. The occurrence of both thromboembolic and bleeding complications was only significantly reduced when the level of anticoagulation adequacy was above 80 percentile.

Conclusions and recommendations: Most of the Prothrombin Time results were out of therapeutic ranges reflecting high anticoagulation inadequacy. It was recommended to improve the anticoagulant adequacy among study patients.

Key Words Anticoagulation Adequacy, Mechanical Heart Valves

Introduction

Thromboembolic and anticoagulant related bleeding complications are the main causes of morbidity and mortality in patients with mechanical heart valves [(2)].

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Patients with mechanical heart valves receive life long, oral anticoagulant therapy to prevent thromboembolic complications, but this treatment is associated with an increased risk of bleeding [(1)]. The risks of thromboembolism and bleeding depend mainly on the adequacy of anticoagulation,[(1)] however other factors may play a role.

The efficacy of anticoagulant therapy was previously assessed with use of the prothrombin time, but variability in the sensitivity of the thromboplastin reagent prevented its standardization, so comparing results from different periods or laboratories was problematic. The prothrombin time is now converted to an International Normalized Ratio (INR)[(2'10)].

Despite the use of warfarin in patients with prosthetic valves to prevent thromboembolic complications with minimal bleeding several factors also may potentiate either of the complications. A study done by Wells PS et al [(3)] found the anticoagulant effect of warfarin was potentiated by cotrimoxazole, erythromycin, fluconazole and metronidazole; cardiac drugs such as amiodarone and propranolol; cimetidine and omeprazole. Three patients had a hemorrhage at the time of a potentiating interaction (caused by alcohol and isonizid). A study by Chan [(4)] showed that all NSAIDs can prolong bleeding time by inhibiting platelet function. High-dose aspirin has a direct hypoprothrombinaemic effect.

The influence of vitamin K-rich vegetables on effectiveness has also been documented in a number of studies [(1, 3, 7)]. Karlson B et al [(7)] found that when broccoli, cabbage, soyabean and spinach were given daily in variable and variable amount to patients receiving warfarin, the thrombotest values tended to rise above the upper therapeutic limit, requiring dose adjustment in patients.

Warfarin is the only anticoagulant used at MNH. The 5mg daily dose of warfarin is the recommended maintenance dose for most of the patients. A few patients receive a 5mg and 10 mg alternate dose.

Monitoring of adequacy of anticoagulation at Muhimbili National Hospital (MNH) is still based on measurements of prothrombin time ratio. It is recommended to maintain a Prothrombin ratio of 1.5-2 and 2-2.5 for mechanical valve on aortic and mitral positions, respectively [(1)]. The use of International Normalized Ratio has not been put into practice though this is done in a few private hospitals due to the difficulty in getting standardized commercial reagents.

Anticoagulation in patients with mechanical heart valves aims at minimizing thromboembolic complications. However no study in our setting has been done to assess the adequacy of anticoagulation monitoring and risk factors involved in the operated patients receiving warfarin. This study therefore addressed these problems, bearing in mind that the control of these complications would have a positive effect on the quality of life of our patients.

Methods and Materials

A retrospective cohort study was conducted in 2005 among patients with mechanical heart valves operated from 1990 to 2003 attending the Muhimbili National Hospital. The study aimed at reviewing the adequacy of anticoagulant control results and risk factors involved among patients with mechanical heart valves attending the anticoagulation clinic at Muhimbili National Hospital .The study included patients who were still attending clinic to the day of study. Exclusion criteria included refusal to give consent during interview and failure to trace records of surgery /complication. Information on anticoagulation adequacy and risk factors influencing its proper monitoring was obtained from medical records and interviews

The review of adequacy of anticoagulation control results was based on the prothrombin ratio measurements that were recorded in the anticoagulation booklets. Each prothrombin time ratio measurement was assessed if it was within the therapeutic level, above or below it. At a given time of anticoagulation monitoring, a prothrombin ratio of a patient was considered to be within therapeutic ranges if either its value was 1.5-2 times the control value (for the patient with aortic valve replacement) or a value was 2-2.5 times the control value (for patient with mitral , double valve replacement or other additional risk factor for thromboembolism).

During interview each patient was asked if he/she had been exposed to a number of possible factors that might affect adequacy of anticoagulation. Information collected in hospital records was also used. This included warfarin dose and where it is obtained or bought and whether there was concurrent use of warfarin with aspirin, amiodarone; consumption of cabbage and green leafy vegetables.

Statistical data analysis

The data was then compiled for statistical analysis using the SPSS package software. Version 12.0.1. Adequacy of anticoagulation was analyzed as percentages of all prothrombin ratio tests done during the whole period of follow up to determine the proportion of tests which were within the therapeutic level, below or above it. On further analysis, the level of anticoagulation was divided into four percentiles in which at 20 percentile the percentage of prothrombin ratio that was within the therapeutic was from 0-28.6% and at more than 80 percentiles, it was more than 56.5%. A percentile of more than 80 was considered to be a high level of anticoagulation. These different levels of anticoagulation were then analyzed in a univariate logistic regression to determine their influence on occurrence of thromboembolic and bleeding complications. Univariate logistic regression was also done to assess factors such as warfarin dose, source, food habits and drugs that could be associated with the high level of anticoagulation

Ethical consideration

Informed written consent was requested and granted from all subjects and the medical record section. Institutional ethical clearance was obtained from the Muhimbili University College of Health Sciences Ethical Committee.

Results

A total of 189 patients who appeared for interview with their anticoagulation booklets at MNH, were recruited in the study .The findings indicated that 123 (65 %) of patients were females and 66 (35%) were males. The mean age at valve replacement was 17.8±2.1 years (Table 1). The mean duration of the study follow-up was 4.3± 2.2 years with a total duration of 887 patient-years. It was also revealed that 103 (54.5%) subjects had valves implanted in mitral positions, 56(29.7%) in aortic positions and 30 (15.8) in both mitral and aortic positions. Bileaflet tilting disks were replaced in majority of the patients (48%).

Table 1 Baseline characteristics of patients with Mechanical Heart valves attending the MNH by position of valve replaced (N=189)

Variable	Total		Position of valve replacement					
	N	%	Aortic		Mitral		Aortic and Mitral	
			n	%	n	%	n	%
No of patients	189	(100)	56	(29.7)	103	(54.5	30	(15.8)
Mean age at valve replacement(years)	17.8±2.1		17.8±8.7		17.7±10.4		17.7±9.6	
Female sex	123*	(65.0)	38	(28.0)	62	(50.3)	23	(21.7)
Type of valve								
Ball caged	42	(22.2)	7	(16.7)	30*	(71.4)	5	(11.9)
Single tilting disk	56	(29.6)	28	(50.0)	18	(32.1)	10	(17.9)
Bileaflet tilting disk	91	(48.2	21	(21.9)	55	(60.4)	15	(16.5)
Place of Surgery								
India	167*	(88.4)	49	(29.3)	91	(54.5.)	27	(16.2)
Others	22	(11.6)	7	(31.8)	12	(54.5)	3	(13.7)

* Indicates p value < 0.05

During study follow-up, a total of 10583 prothrombin ratio measurements were done among all 189 patients who were available for interview with their anticoagulation booklets (category 2). Only 35.5% of the measurements were within the recommended therapeutic (normal) range, 33.4% above therapeutic and 31.1% below it (Table1). Thus, in only 35.5 % of the follow-up prothrombin ratios, was adequate anticoagulation maintained. Even when the level of anticoagulation adequacy was assessed for each individual based on the increasing percentages of Prothrombin Time ratio that were within the therapeutic target, still the majority of patients were not well controlled. Only 45 (23.8%) of the patients were able to maintain adequate anticoagulation for more than 56.5% (more than 80 percentile) of their Prothrombin ratio measurements done during follow up while the majority of them (76.2%) maintained their anticoagulation adequacy at low levels of less than 80 percentiles. Further analysis was done to determine the effect on anticoagulation adequacy at different levels on the incidence of thromboembolism and bleeding complications

(Table 2 and 3).The occurrence of both thromboembolic and bleeding complications was only significantly influenced when the level of anticoagulation adequacy was above 80 percentile. Thus there was a tendency that the high the level of anticoagulation adequacy, the lower the thromboembolic and bleeding complications. In Table 4, several food and drug items which might potentially interact with warfarin were analyzed with the high level of anticoagulant adequacy that was found to be statistically significant to reduce occurrence of complications in Table 2. Frequent use of a daily dose of 5mg warfarin was significantly associated ($p<0.05$) with a high level of anticoagulation adequacy. Concurrent use of warfarin with cabbage and green leafy vegetables also showed similar association. However, the amount of cabbage and vegetables had to be kept nearly constant and regular rather than being irregular and variable in amount. Concurrent use of warfarin with either aspirin or amiodarone had no statistically significant association with a high level of anticoagulation adequacy.

Table 2. Adequacy of anticoagulation based on the proportion of therapeutic values among anticoagulant control results (n=10583)

Prothrombin Time ratio tests	**No**	**%**
Therapeutic tests	3746	35.5
Supra therapeutic tests	3508	33.1
Sub therapeutic tests	3329	31.4
Total	10583	100

Table 3. The influence of level of anticoagulation adequacy on thromboembolism among patients with Mechanical Heart valves attending the MNH (n=47)

Level of anticoagulation adequacy (%)		Patients experienced thromboembolism		
		n	%	OR (95%CI)
0-25.7	20 percentiles	13	38.5	1.0
25.1-28.1	40 percentiles	13	33.3	0.8(0.4-3.9)
28.1-32.1	60 percentiles	10	31.3	0.7(0.4-3.6)
32.1-56.5	80 percentiles	7	21.9	0.4(0.1-2.7)
Above 56.5	Above 80 percentiles	4	8.8	0.1(0.01-0.8)*

*P value <0.05

Table 4 The influence of level of anticoagulation adequacy on bleeding events patients with Mechanical Heart valves attending the MNH (n=64)

Level of anticoagulation adequacy (%)		**Patients experienced bleeding**		
		n	**%**	**OR (95%CI)**
0-25.7	20 percentiles	16	50.0	1.0
25.7-28.1	40 percentiles	18	44.4	0.8(0.3-1.9)
28.1-32.1	60 percentiles	18	35.3	0.6(0.1-2.6)
32.1-56.5	80 percentiles	7	26.9	0.4(0.1-1.1)
Above 56.5	Above 80 percentiles	5	11.1	0.1(0.0-0.4)*

*P value <0.05

Table 5 Factors associated with high level of anticoagulant adequacy among patients with Mechanical Heart valves attending the MNH (n#)

Variable	**Univariate**			**Multivariate**
	Patients with high level of anticoagulant adequacy			
	n	**%**	**OR (95% CI)**	**OR (95% CI)**
Warfarin 5mg dose				
10mg	**8**	**16.1**	**1.0**	
5mg	**27**	**35.7**	**4.4(1.8-7.6)***	**2.6(1.3-6.4)***
Both	**10**	**20.1**	**1.1(0.2-3.1)**	
Obtaining warfarin from Govt. hospitals				
No	**26**	**14.1**	**1.0**	
Yes	**19**	**22.0**	**2.8(1.0-4.7)**	
Warfarin use with irregular and variable intake of cabbage	**8**	**20.9**	**1.0**	
Warfarin use with regular and constant intake of cabbage	**19**	**36.5**	**3.3(1.4-6.3)***	**2.1(1.2-4.9)***
Warfarin use with irregular and variable intake of green vegetables	**10**	**22.7**	**1.0**	
Warfarin use with regular and constant intake of green vegetables	**26**	**43.3**	**4.3(3.1-6.8)***	**2.9(1.7-5.7)***
Warfarin use with irregular and variable intake of soybeans	**17**	**43.0**	**1.0**	
Warfarin use with regular and constant intake of soybeans	**12**	**35.9**	**0.3(0.2-0.6)**	
Warfarin use with aspirin				
No	**12**	**32.8**		
Yes	**8**	**28.6**	**0.8(0.4-2.0)**	
Warfarin use with amiodarone				
Yes	**8**	**19.4**	**1.0**	
No	**5**	**13.2**	**0.6(0.09-0.89)**	

***p value<0.05. Only variables with p value <0.05 are shown in the multivariate analysis column n# variable basing on the responses**

Discussion

The study showed that most of the Prothrombin Time results were out of therapeutic ranges reflecting high anticoagulation inadequacy. In only 35.5 % of the follow-up prothrombin ratio was adequate anticoagulation maintained. This finding is higher than that reported by Ogendo SW in Kenya [5] where in only 18% of the follow-up time, was adequate anticoagulation controlled. However during this study, about 64.5% of all prothrombin ratios were out of the therapeutic range. This is contrast to the findings by Katsuhiko et al in which only 24 % of the intensity measurements were out of the target range [1]. These significant differences might be attributed to non-standardised postoperative anticoagulation regimens [1]. In this study, patients were managed by non- standardised regimens. The use of prothrombin ratio instead of INR at this centre made the anticoagulation adequacy assessment very difficult. Also this high poor level of anticoagulation monitoring may partly be due to the fact that Muhimbili National Hospital has been the only anticoagulation centre for all patients coming from all parts of the country until recently when a few private hospitals were able to provide this service. Thus it was presumed that patients were not regularly checked for anticoagulation adequacy because of long appointments at MNH and possibly unavailability of warfarin in the peripheral regions of the country.

This study also confirmed that a daily 5mg dose of warfarin is associated with good control of anticoagulation adequacy. This is consistent with other previous studies [6]. A 10mg dose of warfarin did not offer any benefit. . However this observation raises doubt as to whether the adjustment was made to the required dose which could easily fall outside 5mg and 10mg dose. Probably this was due to unavailability of warfarin tablets of other dose sizes other than 5mg.

Interaction of warfarin with food and other drugs also appeared to influence the high level of anticoagulation adequacy .As with other previous studies [7], regular and constant intake of green leafy vegetables was associated with high level of anticoagulation adequacy compared to irregular and variable intake. This emphasised the need to instruct the patients properly on the dietary restrictions so that they can allow a room for warfarin dosage modification keeping the prothrombin ratio under control.

The use of Aspirin and amiodarone appeared to make the control of anticoagulation adequacy difficult, thus they showed a tendency of being associated with low level of anticoagulation .In fact, addition of Aspirin to warfarin has been reported to be associated with high bleeding events [8,9,]. Also amiodarone has been reported to affect the pharmacokinetics of warfarin [3]. Even in a relatively low dose of warfarin, prothrombin time becomes prolonged. In this study, patients who were on both warfarin and amiodarone had low level of anticoagulant adequacy though the association was not statistically significant

The findings of this study were also limited by other factors. This was a retrospective study over period of time. This inevitably raises the concern of the availability of medical records and the ability to recall complications accurately. Although it is unlikely the major complications were missed, the registration and recall of minor complications might be limited despite the efforts to minimize it by supportive interview to some patients who were still alive and appeared in the clinic during the study. The reported minor events may therefore be underestimated and the proportion of major events consequently overestimated. Failure to trace some of the records might also influences the final results. However only 4.5% of the patients were excluded due to this limitation

The study also purely looked into thromboembolic and bleeding complications. In this study, patients were managed by non- standardized regimens. The use of prothrombin ratio instead of INR at this centre made the anticoagulation adequacy assessment very difficult.

Even with these limitations in mind, the observed incidence may still be a good reflection of true incidence of complications and the results would serve as a reference for further recommendations to improve anticoagulation care at MNH.

Conclusions and recommendations

Most of the Prothrombin Time results were out of the therapeutic range reflecting high anticoagulation inadequacy. Also, the frequent use of a daily 5mg-dose warfarin and maintaining constant and regular intakes of vegetables were associated with good anticoagulation control. It was recommended that MNH should ensure establishment of adequate system for adequate control of anticoagulation of all patients in additional to introducing INR tests. MNH as a national hospital should also make sure that different warfarin tablets of various dose sizes are available to at the centre. The Ministry of Health and Social Welfare should also establish a system of registration and follow up of all patients on oral anticoagulation therapy at appropriate anticoagulant clinics

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