THROMBOEMBOLIC AND BLEEDING COMPLICATIONS AMONG PATIENTS WITH MECHANICAL HEART VALVES ATTENDING THE MUHIMBILI NATIONAL HOSPITAL, TANZANIA

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Abstract

Background: Thromboembolic and anticoagulant related bleeding complications are the main causes of morbidity and mortality in patients with mechanical heart valves. A review of articles published since 1979 indicates that thromboembolic and bleeding complications account for about 75% of valve-related complications in patients with mechanical heart valves [(2)]. However, the magnitude of these complications in Tanzania has not been established.

Objective: This study was conducted to determine the incidence of thromboembolic and bleeding complications among patients with mechanical heart valves operated from 1990 to 2003 attending the Muhimbili National Hospital.

Study design: This was a retrospective cohort study conducted at the cardiac, anticoagulation clinics and medical records section.

Study settings: The study was conducted in Dar es Salaam at Muhimbili National Hospital in either the cardiac or anticoagulant clinics.

Measure of outcome: The incidence rate of complications was reported as the number of complications per patient year of observation. Survival curves were obtained using the method of Kaplan and Meier to determine the freedom (survival) rate from either thromboembolic or bleeding complications. The time taken to develop a first complication since valve replacement was used for analysis.

Subjects: All patients with mechanical heart valves who were operated from 1990 to 2003 attending the Muhimbili National Hospital

Methodology: Determination of complications involved tracing complications recorded in the file for all patients. This also included tracing their operational (surgical) notes to obtain their baseline demographical and surgical information .Additional collaborative information, by interview, was added for patients who were still attending the clinics

Results: Among the 232 study patients, 59 (25.4%) suffered a total of 83 thromboembolic episodes. The linearized incidence of minor (grade I and II) episodes was 5.5% person-years and 3.5 % person-years for major (grade III) episodes. The study also indicated that 87 (37.5%) patients suffered a total of 132 bleeding events. The linearized incidence rate of minor bleedings was 11.4% person-years while that of major bleeding was 2.9 % person-years.

Conclusion and recommendation: It was concluded that the incidence of both thromboembolic and bleeding complications was high among study patients. It was recommended to conduct further studies that will focus on the factors contributing to this high incidence

Key Words: Complications, Mechanical Heart Valves

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Introduction

Thromboembolic and anticoagulant related bleeding complications are the main causes of morbidity and mortality in patients with mechanical heart valves.[(1)] In the

US, thromboembolic complications occur in 13-17% of mechanical heart valves within five years of implantation and in 34-44% within fifteen years of implantation.[2] Anticoagulant-related bleeding complications of mechanical heart valves include major bleeding in 1-3% of patients per year and minor bleeding in 4-8% of patients per year.[3] In patients with mechanical valves, the incidence of major embolization (resulting in death or a persistent neurological deficit) is roughly 4 percent per patient-year in the absence of antithrombotic therapy, 2 percent per patient-year with antiplatelet therapy, and 1 percent per patient-year with warfarin therapy.[4] The majority of the systemic embolizations manifest as cerebrovascular event.[2] Katsuhiko et al[1] found the incidence of cerebral infarction to be 0.8% patient-years. Koertkel et al showed the incidence of major thromboembolic complications per observation year to be 2.8 %.[5] During the 7-year follow up period in GELIA 5 study, 18 among 553 patients had 21 thromboembolic events after mitral valve replacement. Of these 9 patients had 10 severe (2 grade II and 8 grade III) events. Linearized rates for grade II and III thromboembolic events were 0.16% patient-years and 0.62 per patient-years, respectively.[6]

Bleeding is the most common complication of warfarin treatment occurring in about 6-39% of recipients annually.[7] Casselman FP et al[7] studied 249 patients who had undergone mitral valve replacement1963-1964 and found that 25% had the ball valve was implanted and disc valve in 75% of the patients. The mean follow up was 19.5+_9.4 years and 100% of them completed the study. About 40% of all patients had at least one bleeding episode and 29% had two postoperative events. The incidence of events was higher in the first 5 years after surgery. It is notable that the incidence of bleeding complications is variable (0.2-7.4% patient-year) in most of the study populations.[6]

Methodology

Study setting

The study was conducted in Dar es Salaam at Muhimbili National Hospital in either the cardiac or anticoagulant clinics.Dar es Salaam (DSM) is the largest city in Tanzania. Muhimbili national Hospital is a national referral hospital within this city and until recently the hospital was the only centre in the country running anticoagulant clinic for all patients with prosthetic valves in the country. For the purpose of description of regions/ areas outside Dar es Salaam, the residency of patients was defined with reference to Dar es Salaam as follows; Near DSM was defined as residences close to DSM where the patient had to take 45min-3hrs to access the anticoagulant/cardiac clinic in DSM. Far from DSM defined as residences where the patient had to take 4-12hrs to access the anticoagulant/cardiac clinic in DSM by public transport. Very far from DSM was defined as residences where the patient had take more than 12hrs to several days to access the anticoagulant/cardiac clinic in DSM by public transport

Subjects, Study Design and Materials

All patients with mechanical heart valves operated from 1990 to 2003 attending the Muhimbili National Hospital either in the cardiac or anticoagulant clinics were recruited. The study was conducted in 2005 specifically to determine the incidence of thromboembolic and bleeding complications among these patients with mechanical heart valves. This was a retrospective cohort study in which information on occurrence of these complications was obtained from medical records and interviews in the cardiac clinic, anticoagulant clinic and cardiology records section at the Muhimbili National Hospital .The study included all patients those who had valve replacement from 1990 to 2003 and were attending or attended at the MNH. Exclusion criteria included patients in whom it was not possible to trace records of surgery /complications.

Determination of complications involved tracing complications recorded in the file for all patients. This also included tracing their operational (surgical) notes to obtain their baseline demographical and surgical information .Additional collaborative information, by interview, was added for patients who were still attending the clinics. This involved all complications that were related to warfarin. The time taken to develop the first complication from valve replacement was determined. Subsequent episodes that developed in the course of follow up were also recorded to obtain the cumulative events. Information collected by records and interviews was entered in a standard structured questionnaire.

The Thromboembolic and bleeding complications were graded according to the adapted GELIA criteria.[6] Minor thromboembolism (grade I and II) was defined as symptoms and signs of embolic cause that were observed and treated by the patient himself or treated in an outpatient mode. Major thromboembolism (grade III) was defined as symptoms and signs of embolic cause that necessitated hospitalization. Minor bleeding (grade I and II) was defined as any episode of bleeding such as minor epistasis, gum bleeding, purpura, bruising, menorrhagia etc that were observed and treated by the patients himself or treated in an outpatient mode and that was thought to be related to warfarin by the patient/ attending doctor. Major bleeding (grade III) was defined as any episode of bleeding in any system of the body that could lead to death, hospital admission or blood transfusion and that was thought to be related to warfarin by the attending doctor.

Statistical analysis

The data was then compiled for statistical analysis using the SPSS package software Version 12.0.1.The incidence rate of complications was reported as the number of complications per patient year of observation. The 95% confidence interval for the incidence rate was calculated using the Poisson distribution assumption.

Survival curves were obtained using the method of Kaplan and Meier to determine the freedom (survival) rate from either thromboembolic or bleeding complications. The

time taken to develop a first complication since valve replacement was used for analysis.

Ethical consideration

Informed written consent was requested from all interviewed subjects and the medical record section. Patients who were found to have complications at the time of interview were referred to a hematologist/cardiologist for further management.. Institutional ethical clearance was obtained from the Muhimbili University College of Health Sciences ethical committee.

Results

All 243 patients operated for mechanical heart valve replacement from 1990 to 2003 who were attending MNH were recruited in the study. Following lack of proper records 11 subjects were excluded from the study and 232 subjects met the inclusion criteria. A total of 143 (61.6%) of patients were females and 89 (38.4%) were males and the mean age at valve replacement was 18.8±9.8 years (Table 1). The mean duration of the study follow-up was 3.9± 2.2 years with a total duration of 919 patient-years. The majority of the patients (65%) were residing outside Dar es Salaam. One hundred and fourteen (49.1%) subjects had valves implanted in mitral positions, 66(28.4%) in aortic positions and 52 (22.4%) in both mitral and aortic positions (Table 1). Bileaflet tilting disks were replaced in the majority of the patients (44.8%). All patients were operated outside Tanzania with the majority of them (86.6%) being operated in India and a few (13.4%) in Europe, South Africa and America. The study revealed that among 232 patients studied, 59 (25.4%) suffered a total of 83 thromboembolic events of which 51 (61%) were minor (grade I and II) episodes and 32 (39%) were major (grade III) episodes. Among 83 episodes, 59(71%) were experienced as the first events (Table 3) from valve replacement. The linearized incidence for minor episodes was 5.5% person- years and 3.5 % person -years for major episodes (Table 2).

Table 1. Baseline characteristics by position of valve replaced

Variable	Total		Position of valve replacement					
			Aortic		Mitral		Aortic and Mitral	
	N	%	n	%	n	%	n	%
No of patients	232	(100)	66	(28.4)	114	(49.1)	52	(22.4)
Mean age at valve replacement(years)		18.8±9.8		17.8±8.7		19.9±10.4		17.7±9.6
Female sex	143*	(61.6)	40	(28.0)	72	(50.3)	31	(21.7)
Residence								
Dar es Salaam (DSM)	80*	(34.5)	21	(26.3)	38	(47.5)	21	(26.2)
Near DSM	40	(17.2)	15	(37.5)	13	(32.5)	12	(30.0)
Far from DSM	31	(13.4	12	(38.7)	13	(41.9)	6	(19.4)
Very far from DSM	42	(18.1)	07	(16.7)	29	(69.0)	6	(14.3)
Changed residence	39	(16)	11	(28.3)	21	(53.8)	7	(17.9)
Follow up clinic attended								
Cardiac only	35	(15.1)	9	(25.7)	22	(62.9)	4	(11.4)
Anticoagulation only	23	(09.9)	5	(21.7)	11	(47.8)	7	(30.4)
Both clinics	146*	(62.9)	46	(31.5)	66	(45.2)	34	(23.3)
Changed Clinics	28	(12.1)	6	(21.4)	15	(53.6)	7	(17.9)
Type of valve								
Ball caged	56	(24.1)	4	(07.1)	41*	(73.2)	1	(19.6)
Single tilting disk	72	(31.1)	34	(47.2)	23	(31.9)	1	(20.9)
Bileaflet tilting disk	104	(44.8)	28	(26.9)	50	(48.1)	2	(25.4)
Underlying valve pathology								
Rheumatic	201*	(86.6)	50	(24.9)	106	*(52.7)	45	(22.4)
Non Rheumatic	31	(13.4)	16	(51.6)	8	(25.8)	7	(22.6)
Place of Surgery								
India	191*	(81.6)	4	(24.6)	9	(50.8)	47	(24.6)
Others[1]	41	(18.4)	1	(46.3)	17	(41.5)	5	(12.2)
Past/coexisting medical condition								
Diabetes Mellitus	3	(1.3)	1	(33.3)	2	(66.7)	0	(0)
Hypertension	11	(4.3)	4	(30.0)	4	(40.0)	2	(20.0)
Ischemic heart disease	8	(3.4)	1	(12.5)	7	(87.5)	0	(0)
Stroke	5	(2.2)	0	(0)	5	(100.0)	0	(0)
Atrial fibrillation	73	(31.5)	15	(20.5)	51	(69.9)	6	(9.6)
Bleeding disorder	25	(10.8)	1	(44.0)	13	(52.2)	7	(4.0)

* Indicates p value < 0.05, [1] Europe, South Africa and America

The probability of surviving from the first thromboembolic events was 83.8±2.6% after 2 years, 70.3%±3.7% after 5 years and 39.4%±16.8% after 7 years of valve replacement (Figure 1). The majority of the thromboembolic complications were due to cerebral vascular accidents accounting for 69.4 % of all first events and 58.9 %(incidence rate of 5.5% patient-year) of all commulative events at the end of follow up (Table 3)

During follow-up, 87/232 (37.5%) patients suffered a total of 132 bleeding events (Table 2). Among 132 bleeding events, 87(66%) were experienced as first episode (Table 4) from the time of valve replacement, the remaining events occurred subsequently during the follow up period. There were 105(80%) minor bleeding events and 27(20%) major bleeding events. The linearised incidence rate of minor bleedings was 11.4% person years and 2.9 % person years for major bleedings (Table 2) The probability of surviving from the first major bleeding events was 94.5%±1.6% after 2 years, 86.7%±1.3% after 5 years and 76.6%±8.6% after 7 years (Fig 2). It was also found that the majority of the first bleeding events were gingival (40.2%), followed by nasal (12.6%) Patients with the first bleeding event had an increased rate of subsequent events (Table 4). Combined cerebral and gastrointestinal bleeding also contributed a major part (16.1% as first bleeding events)

Table 2. Linearized incidence of thromboembolic and bleeding complications during follow up

Variable	Patients experienced TE events		Number of TE events		Linearised incidence rate
	n	%	n	%	
Minor TE	38	16.3	51	(61)	5.5
Major TE	21	9.1	32	(39)	3.5
Combined TE	59	25.4	83	(100)	9.0
Minor bleeding	66	28.4	105	(80)	11.4
Major bleeding	21	9.1	27	(20)	2.9
Combined Bleeding	87	37.5	132	(100)	14.3

TE-Thromboembolic

Table 3. Frequency of different types of thromboembolic events

Type of TE episode	1st TE episode		Cumulative TE during follow up	
	n	%	n	%
Transient ischemic attack	29	49.1	37	42.5
Ischemic CVA	12	20.3	14	16.1
Ischemic heart disease	15	25.4	20	22.9
Prosthetic valve thrombosis	1	1.7	1	1.1
Other	2	3.4	11	12.6
Total	59	100	83	100

TE-Thromboembolic, CVA-Cerebral Vascular Accident

Table 4. Frequency of different types of bleedings complications

Type of bleeding episode	1st bleeding episode		Total bleeding episodes during follow up	
	n	%	n	%
Nasal bleedings	11	12.6	21	16.0
Gingival bleedings	35	40.2	54	40.9
Gastrointestinal bleedings	11	12.6	14	10.6
Genitourinary bleeding	17	19.5	20	15.1
Cerebral bleedings	3	3.4	3	2.2
Skin bleedings	7	8.0	14	10.6
Other bleedings	3	3.4	6	4.5
Total	**87**	**100**	**132**	**100**

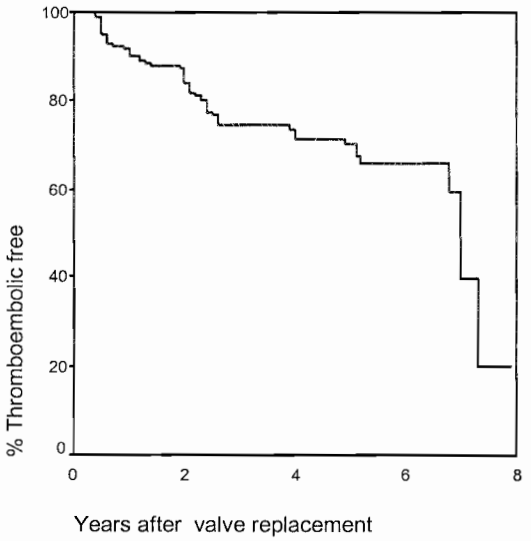

Figure 1. Time to first thromboembolic complications (Kaplan-Meier ploty

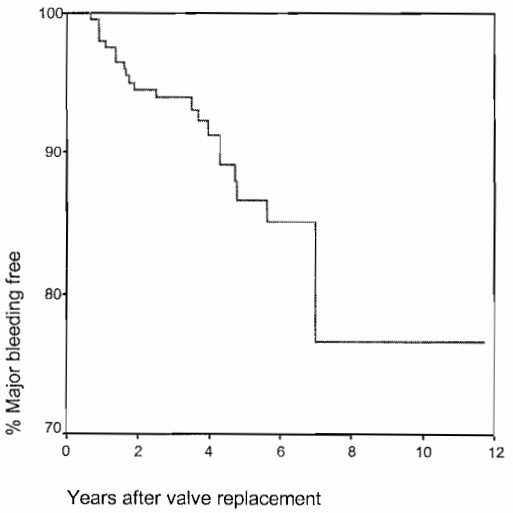

Figure 2. time to the first major bleeding complications (Kaplain – Meiier plots)

Discussion

In this study among the 232 study patients, 59 (25.4%) suffered at least one episode of thromboembolism with major events accounting for a linearised incidence of 3.5% person-year. This incidence is undoubtedly higher than most of the reported findings.[4] However other studies [8] revealed incidences are comparable to results of this study. Though it may be difficult to explain the high incidence in this study, some of the baseline factors may have contributed to this. It is well known that mechanical valves implanted in mitral valves position tend to have higher thrombogenicity than those placed in the aortic position.[4] In this study majority of the patients had valves implanted in mitral positions. It was also noted that most of the patients in this study were residing outside Dar es Salaam. This might have made their anticoagulation monitoring very difficult as they had to travel long distances from their homes to Muhimbili for the anticoagulation clinic thus predisposing them to thrombolic events. Other studies have reported dietary styles and variations may also influence the occurrence of these complications. However in most cases the anticoagulation level is adjusted according to the normal dietary lifestyle of the patients

The occurrence of thromboembolic events was mainly cerebral vascular with transient ischemic attacks occurring in the majority of the patients. This finding is consistent to other previous studies in which most of the thromboembolic events were manifesting as cerebral vascular accidents.[1, 7] The major difference with previous studies is the high incidence of these events in this study. However accurate estimation of ischemic cerebral vascular accidents in this study was limited by lack of diagnostic facilities such as CT scan in the early 1990's and this might have influenced the findings. It is mostly likely that the study has underestimated the events.

Freedom from a first thromboembolic event was 83.8% after 2 years, 70.3 after 5 years and 39.4% after 7 years of valve replacement. This indicated that, within 5-7 years, 30%-60% of the patients had experienced at least one thromboembolic episode. As with a previous study [3], patients who had a first thromboembolic event were at increased risk of subsequent events (Table 2).

This study also revealed that the incidence of bleeding complications was high during the study follow up. About 37.5% of the patients suffered at least one episode of bleeding complication with major events accounting for a linearised incidence of 2.9 % person-year. The incidence of total bleeding events was found to be 14.3% person-years. Findings from other studies have been variable. In a study done by Chiquitte E et al [9], the incidence of major to fatal bleeding among patients attending anticoagulation clinic was low (1.6% person- year). In one study the incidence was found to be 1.4% person year for major bleeding.[4] In Sweden it was reported to be 8.5% person-years.[10] However in most of the studies, the incidence of anticoagulant-related hemorrhagic complications of mechanical valves was generally 1-3% of patients per year for major haemorrhages and 4-8% of patients per year for minor haemorrhages.[2] A major problem in the interpretation and comparison of these studies is the inconsistency in the definitions used for reporting morbid events.[10]

The findings of this study were also limited by other factors. It has also to be noted that information on complications was obtained by records to all study patients and a few of them who were still attending the clinics during the study were also interviewed. It is likely that some information on complication might have been missed to patients whose information was based on records only, thus underestimating the incidence of complications.

Even with these limitations in mind, the observed findings may still be a good reflection of true situation and this study serves as a reference for further recommendations to improve the anticoagulation adequacy monitoring at MNH.

Conclusion and recommendations

The incidence of both thromboembolic and bleeding complications was high among study patients .It was recommended to conduct further studies that will focus on the factors contributing to this high incidence

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