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WARFARIN-RELATED BLEEDING FOLLOWING OPEN HEART SURGERY IN NAIROBI
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ABSTRACT

Objectives: **To review anticoagulant-related bleeding in heart valve patients on warfarin at the Kenyatta National Hospital and to determine the variables associated with anticoagulant-related bleeding.**
Design: **A combined retrospective and prospective review of patients operated at the Kenyatta National Hospital. Retrospective period from June 1973 to 31st July 1997, while prospective period from August 1st 1997 to June 1st 2000.**
Setting: **Surgical Outpatient Department, Kenyatta National Hospital, Nairobi.**
Main outcome measures: **Linearised occurrence rate of anticoagulant-related bleeding and the one- five- and ten- year bleed free rates. Independent risk factors associated with anticoagulant-related bleeding determined using Cox's proportional hazards.**
Results: **Thirty one bleeding episodes were recorded in 150 patients followed up for a total of 745 patient-years. The risk of occurrence of the first bleed was 16.0%; while the risk of a subsequent bleed increased thereafter with a 16.7%, 50% and 50% risk after the first, second and third bleeds respectively. The linearised rate for minor anticoagulant-related bleed was 4.16% per patient per year however, half the bleeds occurred within the first year of valve implantation or previous bleeding episode. The one-, five- and ten- year bleed free rates for all valves combined were 93%, 85% and 78% respectively. There was no statistically signicant difference between the curves comparing the bleed free rates for the first and second bleeding episodes (p=0.098). The number of valves implanted, the site of implant and the time to the occurrence of bleeding were independent risk factors associated with the occurrence of bleeding (p<.05).**
Conclusion: **The occurrence of anticoagulant-related bleeding is relatively common being slightly above the internationally reported range. Most episodes of bleeding will occur within one year of hospital discharge or the previous bleeding episode. The risk of another bleeding episode occurring increases with each episode with up to a 50% risk of re-bleed after the second bleeding episode. In this study, the number of valves implanted, their position and the time of occurrence of the bleed were risk factors to the occurrence of bleeding.**

INTRODUCTION

The morbidity associated with the use of anticoagulants in post-operative heart valve patients is a complex interaction between patient-related, prosthetic-related and managment-related factors. Thrombosis, embolism and haemorrhage account for up to 75% of all complications after heart valve replacement(1). Anticoagulant-related valve complications fall into two extremes. At one extreme is bleeding associated with excessive anticoagulation and the other, thrombosis due to too little anticoagulation. Anticoagulant management is thus a delicate balance between the two extremes. Anticoagulant related bleeding can be divided into two forms(1). The major bleed, or life threatening bleed, associated with the need for hospital admission and additional treatment thereafter; and minor bleeds such as epistaxis, haematuria or menorrhagia, which often respond to appopriate adjustements of warfarin therapy. Major bleeding is associated with a risk of death reaching nine per cent in the North American elderly(2).

There have been many reports on the incidence of bleeding in anticoagulated valve patients. A reported risk for major bleed of 0.8% per patient per year (ppy), for heart valve patients(3) is documented, while the incidence for minor bleed however is said to be about ten times greater than that for major bleeding. Risk factors associated with anticoagulant-related bleeding can be broadly divided into the four D's(1); namely the dose of anticoagulant medication, concurrent drug usage, other diseases the patient may suffer and demographic factors.

At the Kenyatta National Hospital (KNH), anticoagulant control as measured by the international normalised ratio (INR), is fairly poorly maintained with most patients being under anticoagulated. Only during

18% of their follow up time do patients maintain adequate INR levels(4). The aim of this study was to look at the occurrence of bleeding episodes in valve patients anticoagulated with warfarin at the KNH during their follow up.

MATERIALS AND METHODS

The study reviewed the occurrence of anticoagulant-related bleeding in the post-operative period for valve repair or replacement patients on warfarin being followed up at the KNH surgical outpatient clinic up to 1st June 2000. Patient data were obtained from the unit database. This database was established in August 1997 and data relating to events before that period was collected retrospectively from varoius sources. As not all files were retrieved from the records office initially, not all variables for patients were complete. From August 1997 onward, all patients data were collected on a prospective basis in the wards, theatres and outpatient clinics.

From August 1997, for all patients planned for theatre, data were collected prior to surgery and divided into four broad categories, namely general patient and surgical data, ECHO or catheterisation data and lastly patient demographic details.

During each outpatient clinic attendance, data relating to anticoagulant control and morbility were obtained. In addition, all patients operated on prior to mid 1997 had specific questioning on anticoagulant-related morbidities as well as a through re-scrutiny of their files for complications that may have been missed earlier.

There were eight variables chosen for multivariate analysis in this study. These variables included the occurrence of bleeding episodes, INR control, (only from 1991 onwards when KNH started to use INR on a routine basis), dates of clinic attendance and warfarin dose prescription. Addition information collected included the type of valves implanted per patient, their site of implantation and the type of valve(s) used. The type being divided into either the first generation or second generation valves(5). Age at the end point was calculated from the time of hospital discharge to the end point of follow up or the occurrence of a bleeding episode. Age and sex of the patient were used to constitute the demographic component of the data for this study.

All patients operated on in the hospital and with a follow up record within the surgical outpatient clinic (SOPC) were included in the study. Those patients operated on in the hospital and known to have been attending follow up elsewhere and those operated on outside KNH were not included in the study, even though the latter may have attended our follow up clinic.

Statistical analysis of data was done using Statistica software version 4.3. The Kaplan Mayer method was used to determine the one-, five- and ten- year bleed free rates. While the Gehan's Wilcoxon test was applied to determine if there was any significant difference between the bleed free curves generated. To determine the significance of the association of each of the eight risk factors to the occurrence of anticoagulant-related bleeding, multivariate analysis using Cox's propotional hazard model with casewise deletion of incomplete or missing data was used. (A p value of less than 0.05 is considered significant.)

For those patients with multiple bleeding episodes, each episode was entered into the analysis separately with the censor variable for each separate episode being dependent on the outcome at the end of that particular episode. All patients who failed to come back for follow up for more than twelve months were deemed to have fallen out to follow up.

RESULTS

During the study period, thirty one bleeding episodes were found among the patient population of 150 patients who fulfilled the criteria for inclusion. The mean age of these patients at the time of their surgery was 23.67 years while the mean age at their respective end points was 29.08 years. All episodes of bleeding were minor and consisted of epistaxis, menorrhagia, haematuria, gingival bleeding and haemarthrosis. The distribution of the bleeding episodes is illustrated in Table 1. One episode of major retroperitoneal bleeding presenting as an acute abdomen to the general surgeons, was documented during the period but the patient in question did not fulfill the criteria for inclusion in the study. Only one patient presented with different forms of bleeding subsequently. All the other multiple bleeders had the same form of bleed on different occasions. One patient with a bleeding episode had a thromboembolic episode also at some other time during his follow up.

Table 1

Distribution of bleeding episodes

Bleeding episode	Year bleed occurred						Total No. of episodes
	1988	1994	1995	1998	1999	2000	
Epistaxis	1	2	1	3	4	7	18
Menorrhagia	0	0	0	0	2	1	3
Haematuria	0	1	0	1	1	1	4
Haemarthrosis	0	0	0	1	0	1	2
Bleeding gums	0	0	0	1	1	0	2
Malaena stools	0	0	0	0	1	0	1
Bleed from sternotomy scar	0	0	0	1	0	0	1
Total	1	3	1	7	9	10	31

Of all the bleeds documented, fifteen occurred within the first year after valve implantation (or following the previous bleed), and six in the second year. Three bleeds occurred in the third year after implantion or the previous bleed. Similarly, seven bleeds occurred more than three years after implantion/last bleed. No mortalities that could be directly related to anticoagulaton were documented during the study period.

The total cumulative follow up time for the 150 patients during the study duration was 745.1 patient-years. This gives a linearised rate for minor anticoagulant related bleeding of 4.16% per patient per year (ppy). The majority of this (83.8%), was documented during the prospective phase of the study (Table1). The average occurrence rate for all bleeding episodes in the study averages 17.22%. However, following the first bleed, the risk of another bleed was noted to increase to a 50% risk of recurrent bleed following the second bleeding episode(Table 2).

Table 2

Bleeding events in the postoperative period

No. of bleeding episodes	Bleeds No. of patients at risk	No.	% age bleed in patients at risk of bleed
One	150	24	16.00%
Two	24	4	16.67%
Three	4	2	50.00%
Four	2	1	50.00%
Total	180	31	17.22%

The one-, five- and ten-year free rate of the first bleeding episode were 93%, 85% and 78% respectively for all valves combined (Figure 1). For the second bleeding episode the available data did not approach one year of follow up. There was, however, no statistically significant difference between the two graphs for the first and second bleeding episodes (p=0.09844). There were too few variables for analysis of three and four bleeding episodes.

Figure 1

Occurrence of bleeding in all valve patients

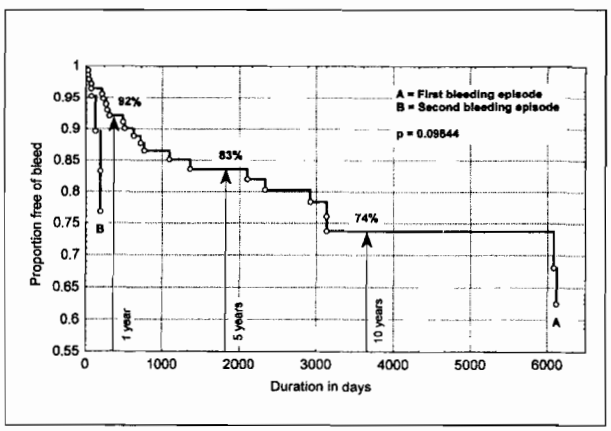

Table 3

Bleeding versus number of valves implanted

No. of valves	Bleed occurred	No. bleed	Total
Single	28	132	160
Double	5	15	20
Total	31	147	180

Table 4

Bleeding vs type of valve implanted irrespective of site

Type of valve	Bleeding occurred S	D	Total	No bleeding	age bleed (%)	Total
First generation mechanical	11	2	13	54	19.4	67
Second generation mechanical	10	2	12	41	22.6	53
Tissue valve	5	0	5	9	35.7	14
Combination of mechanical	0	0	0	2	0.0	2
Combination tissue and mechanical	0	0	0	1	0.0	1
MV repair	1	0	1	6	14.3	7
Total	27	4	31	113		144

S = single valve replacement; D = double valve replacement

Table 5

Variables associated with the occurrence of anticoagulation related bleed (Cox's regression analysis)

	Standard beta	Error	t-value
Age	-.028352	.015142	-1.87245
Sex	.243655	.337986	.72090
No. of valves implanted	.964054	.476742	2.02217**
Type of valve(s) implanted	1.248863	.327992	3.80760**
Average warfarin dosage prescribed	-.077153	.073628	-1.04787
Clinic attendance average interval between visit	.000366	.001985	.18421
Time to occurrence of bleed	-.000294	.000129	-2.27824**
Proportion of follow-up time INR>4.5	-.020344	.021187	-.96023

**P value<0.05
(For analysis of 120 patients at a 0.05 level of significance the t value should be more than (±1.960)

The occurrence of bleeding for the number of valves implanted is shown in Table 3. For single valve replacement patients, 17.5% had a bleeding episode as opposed to 25.0% for double valve replacement patients. In Table 4, the first-generation valves are seen to have a lower rate of bleeding episodes as compared to second-generation valves: 19.4% versus 22.6%. In this study tissue valves have a 35.7% rate of bleeding. Thirty six patients for whom no valve type was specified were omitted from the analysis. Results of analysing the data to determine independent risk factors associated with anticoagulant-related bleeding are shown in Table 5. Significant variables related to the occurrence of minor bleeding are, the number of valves implanted per patient and the type of valves implanted. The number of years from implantation, or previous bleed, to the next bleed for all valve(s) combined has a significant negative relationship to the occurrence of bleeding. The patient age just falls outside a p value of less than .05. Other variables that were insignificant included the sex of the patient, the average interval between clinic

visits and the proportion of time during follow up that the INR was recorded above 4.5.

DISCUSSION

Both thrombosis and bleeding are common and occur naturally in the general population in whom there is a fine balance between the two morbidities(1). Both these risks are increased in patients with prosthetic heart valves with or without anticoagulant therapy. The effective management of heart valve patients on warfarin is a fine balance between reducing the risk associated with thromboembolism on the one hand and spontaneous bleeding episodes on the other(1). For bleeding complications these can either be minor bleeds or life threatening bleeds like intracranial, gastrointestinal or retroperitoneal bleeds. The latter three constitute the commonest cause of death associated with anticoagulant-related bleeds(3,6,7).

There have been many reports in the past to try and highlight the occurrence of anticoagulant-related morbidity associated with valve patients on warfarin. These results have been associated with many difficulties due to differences in the types of valves used, differences in definitions of bleeding, different patient characteristics, definitions of complications, lack of placebo-controlled trials and differences in the expression of results amongst others(1). Giving a single internationally accepted figure for anticoagulant-related bleeding in valve patients from previous studies has been difficult. The generally quoted range for anticoagulant-related bleeding combining numerous studies is 2.4% - 3.4% ppy(8).

The over-all linearised rate for bleeding for this study was 4.16% ppy. This is a revised figure from the previous data analysis for our group of patients(9), and is slightly higher than the quoted international values. Our revised figure of 4.16% ppy for minor bleeding episodes as compared to the previously estimated 0.79% ppy, is a much more realistic estimation of the occurrence of bleeding in our patients. One striking observation from Table 1, is that the majority of bleeds (approximately 84%), occurred in the period of the study when data were collected prospectively. This demonstrates the problems that are associated with retrospective data collection. Missing files and poor documentation resulting in a lower reported incidence of bleeding was the most likely reason. In addition, the cardiac team has recently been actively looking out for anticoagulant-related morbidities.

Though no mortality related to major bleeding was documented for this study, Miller *et al*(10) found that one third of all their major bleeds resulted in mortality. We may never be able to determine how many of our patients may die of major bleed outside hospital.

The average five- and ten-year follow up period free of the first anticoagulant-related bleeding in the literature of 87% and 79% respectively(8), is very similar to the results of 85% and 78% in this study. Anticoagulant-related bleeding is associated with numerous factors. Due to the sample size and limitations with our database only the warfarin dosage, number of valves implanted, valve type, site of implantation and the demographic variables were examined using the Cox's regression model.

For this study the warfarin dosage prescribed is not a significant independent risk factor related to the occurrence of bleeding. The warfarin dosage prescribed is reflected indirectly as the INR result of the patient during the clinic visit(s). A more appropriate standardisation of this variable would have been warfarin dosage (mg), per unit of body mass/index or body surface area. This, however, is difficult to document in a study of this nature as the indices mentioned are very dynamic in such a young age group, and secondly, it is not possible to access such data each time an event occurs. It is, therefore, not a surprise that the actual dosage of warfarin is not a significant independent risk factor that is related to the occurrence of bleeding in our patients.

The occurrence of minor or major bleeding in long-term anticoagulated patients is a reflection of the INR at the time the bleed actually occurs(3,11). It is known that the INR tends to be higher on average in anticoagulated patients with bleeding as compared to those who do not exhibit any bleed. Whereas the use of warfarin is directly related to the occurrence of bleeding, the level of INR at which the bleed may occur varies widely. The INR though usually high during the occurrence of a bleed, may in some patients, be within the normal therapeutic range(1). This study did not look at the instantaneous INR at the time of bleeding, but instead, at the proportion of time the patients spent over-anticoagulated(4) as per the protocol of the British Association of Haematologists(12). As these two are not identical, it is not a suprise that the proportion of the follow up time the patients were over-anticoagulated was not a significant independent risk factor to the occurrence of bleeding. Indirectly related to the INR levels is the amount of dedication the patients put into the control of their INR. This is further reflected in the clinic attendance pattern. Clinic attendance pattern expressed as the average interval between each clinic visit for each patient was not significant in multivariate analysis.

The patient age has been documented as one of the independent risk factors associated with the occurrence of bleeding in patients on long-term anticoagulant therapy in many studies(13-15). Some authors have highlighted that with age there follows a natural increase of clotting factor concentration as well as increased platelet activation with a decline in fibrinolytic activity. It is a known fact that the warfarin dosage required to maintain an adequate INR falls with age(1). Could this greater bleeding associated with the elderly in fact be just a reflection of the increase usage of anticoagulation as age increases(16) and not the factor of age *per se?* Age is not a significant assoaciation in this study, probably as a result of our younger age group as compared to the earlier series.

The type of valve implanted is a significant independent risk factor to bleeding in our anticoagulated patients. Looking at Table 4, the first generation valves had a lower

incidence of bleeding epsiodes than the second generation by a factor of about 1.2. We maintain an INR of 2.0 - 2.5 and 2.5 - 3.0(17) for those with second generation valves in the aortic and mitral positions respectively, while for first generation the recommended INR of 3.0 - 4.5 is maintained(18). Based on this theory, the reversal of the bleeding rates for the first and second generation valves in our study was unusual. This is most likely influenced, firstly by the prospective component of the study from 1997 onward. This period is also around the time that second generation valves were introduced at KNH. As a result of prospective data collection, the information acquired is more accurate and more cases were captured than during the retrospective period. Secondly, as it seems most bleeds occur early after implantation most of the second-generation valve patients would have stabilised by this stage. Therefore this significant difference in the bleeding occurrence is not the result of the different types of valve *per se,* but the different INR recommendations for the different types of valve and the thoroughness of data collection. Thus, excluding the variable of different INR requirements, the risk of anticoagulant-related bleeding is known to be the same regardless of the type of mechanical or tissue valve implanted that provides the indication for warfarin(8).

Interestingly, Stanley *et al*(19) have reported a very low rate of non-fatal anticoagulant related bleeding of 0.09% ppy for patients with Starr-Edwards valves on a low intensity anticoagulant regime. Our unit has not tried out low intensity anticoagulation on our first generation valve patients. However, this author feels that given our current results and our type of patients, we are unlikely to reproduce results like those of Stanley *et al* (19) in our population.

In this study, the tissue valves had an unusually high rate of bleeding episodes even more than the double valve replacements with two mechanical valves. It is not immediately clear why this should be the case. It is possible that the relatively small number implanted, and the relatively longer time of follow up for these valves may account for this anomaly. It is known that the incidence of bleeding increases with increased duration of anticoagulation usage thus one per cent at six months, five per cent at aone year and seven per cent at three years(2). In the literature the increased risk of occurrence of thromboembolism earlier following valve implantation is well documented(20). No similar risk pattern has been documented for anticoagulant-related bleeding though this has not been studied extensively(8). Our data in this study indicate that the time of bleeding following implantation or previous bleed has a significant negative association with its occurrence. Therefore, most of our bleeding is experienced early following implantation or the previous bleed.

As per the study results looking at the time of occurrence of the bleed, this early bleeding pattern does in fact seem to be the case with half the bleeds occurring within the first year. However, this result may be influenced by an artificially created anomaly as most of the bleeds documented occurred after 1997 (Table 1). Prospective data collection within the last three years out of the previous twenty five years from the first surgery may result in an artificially created skew in the results. This skew may explain the apparent negative association mentioned. Should this issue of anticoagulant-related bleeding be revisited at another time with better data collection, a more accurate picture may emerge. This however, will require a long-term prospective follow up of ten years or more.

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