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Research Article

Predictors of Adequate Ambulatory Anticoagulation among Adult Patients in a Tertiary Teaching and Referral Hospital in Kenya

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Background: Local anticoagulation services are inadequate and substantially underutilized despite compelling evidence showing that their appropriate use significantly reduces the risk of thromboembolic complications.

Objectives: To determine the predictors of adequate ambulatory anticoagulation services in Kenyatta National Hospital.

Methodology: A cross sectional study between December 2014 and April 2015 among 102 adult outpatients on anticoagulation using consecutive sampling was done. Information abstracted into a predesigned data collection tool included participants' sociodemographic characteristics, regular sources of supply of anticoagulant, clinic pre-appointment reminders, indications of treatment and international normalized ratio tests. Data were analyzed using IBM Statistical Package for Social Sciences version 21.0 and logistic regression was used to determine independent predictors of adequate anticoagulation, which was defined as international normalized ratio ranging 2 - 3.

Results: Females were majority (76.5 %) and only 27.5 % of patients had adequate anticoagulation control. The indication of warfarin for heart valve surgery (p=0.014) and deep venous thrombosis (p=0.021) were associated with adequate anticoagulation. Age above 60 years was associated with poor anticoagulation (p=0.006). Logistic regression revealed that the independent predictor of adequate anticoagulation was warfarin use due to heart valve surgery (OR=3.1; 95% CI: 1.2 – 7.9, p=0.017).

Conclusions: Ambulatory anticoagulation control in the hospital is poor. Further investigation is required to find out the reasons behind adequate anticoagulation in heart valve surgery patients.

Key Words: Ambulatory anticoagulation, anticoagulant, outpatient, international normalized ratio tests.

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1. Introduction

Anticoagulation medications are high risk treatments that commonly require complex dosing and monitoring of effects to optimize therapy (Ageno et al, 2012). Vitamin K antagonists (VKA), for example warfarin, are the most widely prescribed ambulatory anticoagulants in Kenya (Ogendo, 2000) and the rest of the world (Pham and Pham, 2007). Despite their effectiveness, VKAs have unpredictable and highly variable effect in

coagulation, with a high risk of under and over-treatment (Ageno et al, 2012). The activity of these ambulatory anticoagulants has to be closely monitored by maintaining the international normalized ratio (INR) between 2-3 and to ensure an adequate yet safe dose is taken (Ansell et al, 2004; Pham and Pham, 2007).

Dosing of warfarin is complicated by the fact that it has a narrow therapeutic index (Holbrook et al, 2012). Consequently, in order to optimize its therapeutic effect without risking dangerous side effects such as bleeding, close monitoring of the degree of anticoagulation is required (Gage et al, 2006) as well as identification of other factors which could impact on therapy.

Globally, unavailability of local clinical guidelines has been suggested to contribute to suboptimal therapy as their appropriate utilization improves the process and outcomes of anticoagulation (Ageno et al, 2012). Furthermore, lack of protocols may also hinder translation of knowledge into clinical practice (Grimshaw and Russell, 1993). In addition, anticoagulation could substantially be underutilized, especially in the absence of local clinical guidelines (Ageno et al, 2012), as it is in our setting.

Locally, several studies have revealed that ambulatory anticoagulation control is poor (Kibiru, 2012; Mariita et al, 2016; Ogendo, 2000). Some studies have implicated patient factors such as poor knowledge on anticoagulation and sociodemographic variables (Mariita et al, 2016) while others point towards poor warfarin dosing methods (Ogendo, 2000). These studies suggest that independent predictors which could optimize anticoagulation services need to be sought to avoid fatal and disabling complications such as bleeding disorders associated with VKAs (Seet et al, 2013). Furthermore, compelling evidence shows that appropriate use of anticoagulation services significantly reduces the risk of thromboembolic complications and all-cause mortality (De Caterina et al, 2012).

This study sought to determine the factors which can predict adequate ambulatory anticoagulation practices at the Kenyatta National Hospital (KNH) with a view to improving the practice.

2. Methods

2.1 Study Design and Area

This was cross-sectional study conducted at KNH, the largest teaching and referral hospital in Kenya that also serves as a primary healthcare facility for the communities around it. Data were collected from KNH cardiothoracic surgery, haemato-oncology and medical clinics where most of the patients on long term warfarin therapy are managed. In addition, anticoagulation referrals of patients requiring specialized care on anticoagulation therapy are usually to the three clinics. In the year 2012 alone, there were 2467 and 8202 outpatients in cardiothoracic and haemato-oncology clinic, respectively.

2.2 Study Population

The study was carried out among male and female patients. Only freely consenting patients were invited to participate in the study. Patients were eligible if they were on warfarin therapy, had attained at least 18 years of age and signed written, informed consent. Patients were excluded if they had a contraindication of warfarin therapy such as peptic ulcer disease and pregnancy.

2.3 Sample Size and Sampling Method

The primary endpoint of the current study was the proportion of patients with adequate anticoagulation controls (appropriate INRs of 2-3). Local studies on anticoagulation control had revealed that only 6.9 % of patients were able to maintain adequate anticoagulation for ≥ 50 % of their follow up time (Ogendo, 2000), therefore, a prevalence of 6.9 % was used for sample size estimation. By using Cochran equation (Cochran, 2007) to yield a representative sample for the population, the sample size was estimated at ninety eight but a 10 % was added to cater for data losses and non-responders to get a sample of 110 patients. Patients were recruited consecutively as they came for their appointments during the clinic days.

2.4 Data collection

Patients were recruited on the day they came for clinic appointments after they had been attended by the clinician. Once they consented, the questionnaire was administered. Every study tool was allocated a unique alphanumeric serial number to avoid confusion and duplication of the data. Demographic characteristics including age, gender, education level, marital status and details of warfarin therapy such as indication as well as regular sources of drug supply were obtained through patient interviews and a review of patients' files by researcher.

Once the patient had been taken through recruitment, consenting and the questionnaire administration, he/she was handed over to a trained, qualified and experienced phlebotomist who was in charge of drawing the blood specimens for INR determination. This was done at the haemato-oncology clinic bleeding centre. The sample was immediately put in a vacutainer with citrate, labelled with the serial number corresponding to the participant's questionnaire and taken for INR testing in the University of Nairobi haematology laboratory. INR testing was done within 2 hours to prevent haemolysis which could give erroneous readings. The results of INR were immediately communicated to the attending clinicians for decision making on warfarin dose adjustments.

2.5 Data Entry and Statistical Analysis

Data collected was captured into the computer database using Microsoft Access version 2013. It was then exported to IBM Statistical package for social sciences (SPSS) version 21 for analysis. All data was verified before analysis.

Exploratory data analysis was carried out to describe the study population in terms of socio-demographic and clinical characteristics. Descriptive statistics were done for categorical variables such as gender, education level, marital status and warfarin indications. For continuous variable such as age, anticoagulation measurement and doses of warfarin, measures of central tendency

including mean, standard deviations, median, ranges were used. Anticoagulation control for each patient was reflected by the measured INR value being within, below or above the therapeutic range of 2-3 as recommended in the international guidelines (Ageno et al, 2012). Bivariate analysis was done to determine associations between predictor and outcome variables. Chi-squared tests were adopted to determine the association of outcome variables with nominal factors. To adjust for potential confounders, stepwise backward binary logistic regression model was used starting with initial predictors of INR control on bivariate analysis to determine independent predictors of adequate ambulatory anticoagulation. Odds ratios (ORs) were computed and statistical significance was set at 95% confidence limit. Values with p ≤0.05 were considered statistically significant.

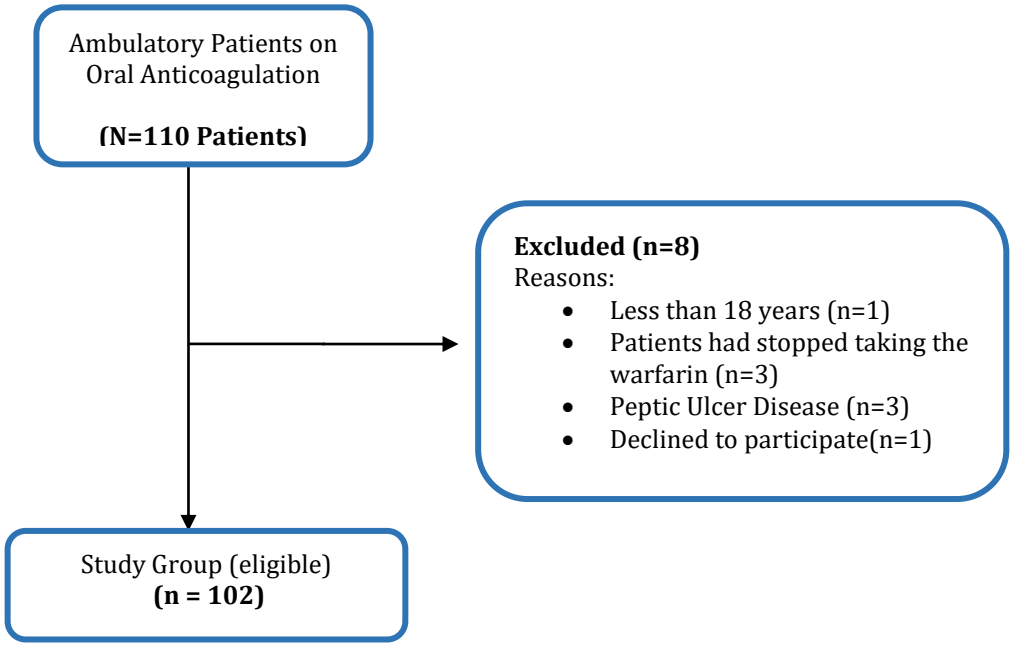

Figure 1: Flow diagram showing patient eligibility and reasons for exclusion

Table 1: Socio-demographic Characteristics of the Study Patients (N=102)

Variable	Category	n	%
Gender	Male	24	23.5
	Female	78	**76.5**
Mean Age in years (SD)	42.0 (± 13.4)		
Age group(Years)	18 - 30	24	23.8
	31 - 40	22	21.8
	41 - 50	33	**32.7**
	51 - 60	14	13.9
	>60	8	8.0
Marital status	Single	26	25.5
	Married	59	**57.8**
	Divorced	8	7.8
	Widowed	9	8.8
Occupation	Unemployed	27	26.5
	Salaried	33	32.4
	Self-employed	40	**39.2**
	Student	2	2.0
Education Level	College /University	24	23.5
	Secondary	41	**40.2**
	Primary	17	16.7
	Non –formal	20	19.6

Key: SD-Standard Deviation

2.6 Ethical considerations

Study approval was obtained from Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC) and study reference number **KNH-ERC/A/280** was given. All patients provided informed consent prior to recruitment. All the information acquired was treated in strictest confident without sharing with the third party. The filled study forms were filed and locked securely where only the researcher had access.

3. Results

A total of one hundred and ten participants were screened. However, data were analyzed from 102 participants because eight participants were not eligible due to various reasons (**Figure 1**).

The mean age (SD) of the study population was 42.0(±13.4) years. There was female predominance at 78(76.5 %). Majority of the participants were self-employed (39.2 %) and had attained secondary level of education (40.2 %) (**Table 1**).

The main indication of warfarin among the study participants was for managing DVT at 57 (55.9%) followed by major surgery (39.2 %) and rheumatic heart disease (8.8 %). Other less common uses included atrial fibrillation, pulmonary embolism and cerebrovascular events, all accounting for 5.9 %. Three quarters of the patients were getting their regular drug supply from outside the hospital (**Table 2**).

The study sought to find out what reminds the patients of the next clinic appointment as this could have an impact on the level of anticoagulation control among the patients. Almost three-quarters of the patient used the calendar as a reminder for their next clinic appointments. Those who relied on their clinic cards and caregivers as reminders for the appointments accounted for 13% and 10%, respectively. The rest were using mobile alerts (3%), relatives (1%) or diaries (1%) as reminders for the next clinic appointment (**Figure 2**).

At the time of the study, almost a third (27.5%) of the participants had INR levels within therapeutic range of 2-3 (**Figure 3**).

Table 2: Indications and Sources of Warfarin Supply

Indications of Warfarin	**n**	**%**	**Sources of Warfarin**	**n**	**%**
DVT	57	**55.9**	**Last Supply**		
Major Surgery (Valve repair/replacement)	40	**39.2**	KNH	21	24.4
RHD	9	8.8	Other sources	65	75.6
Atrial Fibrillation	3	2.9	**Regular Supply**		
Pulmonary Embolism	1	1.0	KNH	21	24.1
Other Indications (CVAs)	2	2.0	Other sources	66	75.9

*CVAs-Cerebral Vascular Accidents; DVT-Deep Vein Thrombosis; KNH-Kenyatta National Hospital; RHD-Rheumatic Heart Disease.

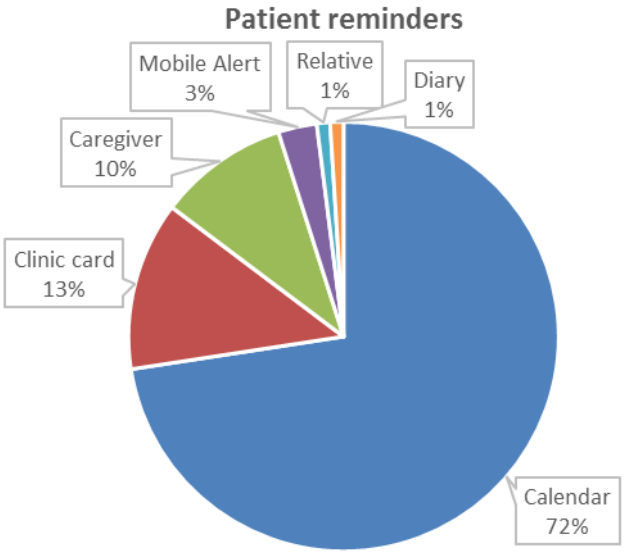

Figure 2: Clinic pre-appointments reminders

Bivariate analysis was done to determine relationships between the predictor and outcome variables. Demographic characteristics, sources of warfarin supply, indications of the drug and patients' reminders were explored to determine the factors which impacted on anticoagulation control. Patients' age was statistically significantly associated with the level of anticoagulation, with most patients above 60 years being outside therapeutic INR (p=0.006). Patients' marital status, occupation and sources of warfarin supply did not show any statistically significant relationship with the level of anticoagulation (P>0.05). The proportion of males with adequate anticoagulation control was higher than that of females but this was not statistically significantly associated with the level of anticoagulation (p=0.217). There was no statistically significant difference between the patients' clinic appointment reminder mechanisms and the level of anticoagulation control (p>0.05).

There was statistically significant relationship between the level of anticoagulation control and patients who had had DVT (p=0.021) and major surgery (p=0.014) (**Table 3**). Stepwise backward binary logistic regression model was used starting with age group, clinic card reminder, major surgery and DVT as initial predictors of adequate INR control on bivariate analysis. Patients who had undergone major surgery were three times more likely to have adequate INR control than those who had not (OR=3.1 95% CI of OR [1.2 – 7.9], p=0.017).

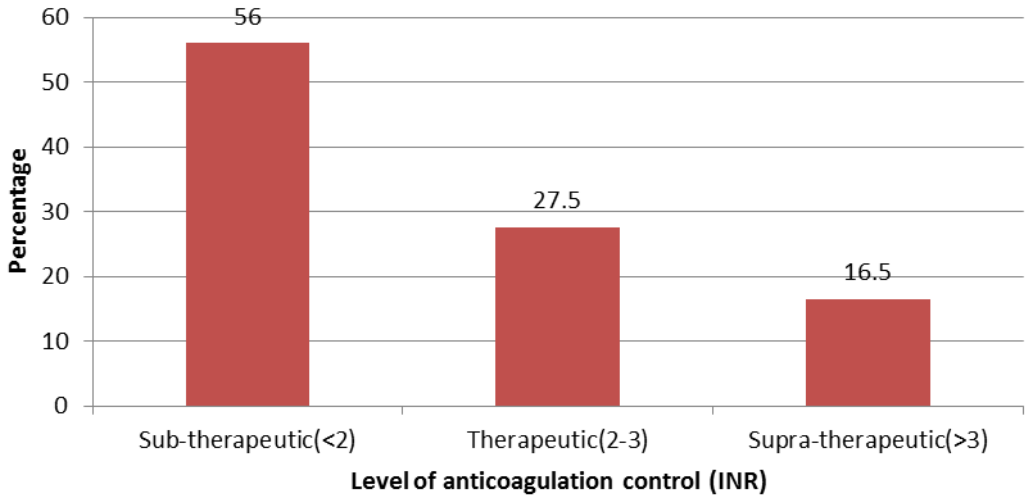

Figure 3: Level of anticoagulation control at the time of study

Table 3: Relationship between levels of anticoagulation control versus indications for warfarin therapy

Indications of Warfarin		INR Control				p-value
		INR controlled		INR not controlled		
		n	%	n	%	
Major Surgery	No	10	16.1	52	83.9	**0.014**
	Yes	15	37.5	25	62.5	
DVT	No	16	35.6	29	64.4	**0.021**
	Yes	9	15.8	48	84.2	
Pulmonary Embolism	No	25	24.8	76	75.2	0.567
	Yes	0	0	1	100.0	
RHD	No	21	22.6	72	77.4	0.145
	Yes	4	44.4	5	55.6	
Atrial Fibrillation	No	24	24.2	75	75.8	0.718
	Yes	1	33.3	2	66.7	
Transient Ischaemic Attacks	No	25	24.5	77	75.5	-
	Yes	0	0	0	0.0	

Key: DVT-Deep Vein Thrombosis; INR- International Normalized Ratio; RHD-Rheumatic Heart Disease. Major surgery included valve repair or valve replacement.

4.0 Discussion

This study has revealed that ambulatory patients who received anticoagulation due to DVT or heart valve surgery were better anticoagulated. Utilization of anticoagulation to prevent thrombosis among patients who have undergone heart valve surgery has been associated with optimal INR control (Mariita et al, 2016). Unlike other participants, this group of patients was using predesigned cards as clinic appointment reminders which could have facilitated the improvement in the observed anticoagulation control.Patients' appointment reminder systems improve patients' adherence to screening, diagnosis,

and treatment. Studies have revealed that pre-appointment patients' reminders proved sensible and beneficial additions to treatment programme (Liu et al, 2014).

We observed that, unlike for other warfarin indications, patients who had undergone heart valve surgery were using the predesigned clinic pre-appointment cards which contained detailed information on warfarin use. This suggested that these patients had opportunities to understand and monitor their treatments unlike their counterparts, thus giving them a benefit of optimal control. Additionally, there are also possibilities that previous reports (Ogendo, 2000) on poor anticoagulation control among the heart surgery patients led to improvement in anticoagulation services.

The proportion of adequately anticoagulated patients in our study was low at 27.5% though comparable with 25% found in Malaysia (Yahaya, 2009), 33% in Saudi Arabia (Mayet, 2015) and 31 % previously (Kibiru, 2012). Although our figure was low, it represents an improvement from a previous study done in the same hospital which found adequate anticoagulation at 6.9 % (Ogendo, 2000). Probably the fact that latter study used the Rosendaal method that has been reported to underestimate INR (Schmitt et al, 2003) was the reason for the small proportion of adequately anticoagulated patients. Additionally, Ogendo et al (2000) only reported the proportion of patients who achieved adequate anticoagulation for 50% or more of the follow up time. Our finding, however, contrasts another study done by Khudair et al, which showed 41% of their patients having INRs within range (Khudair and Hanssens, 2010).

Our study revealed female predominance at 76.5%, although gender did not impact on the level of anticoagulation. Several studies on anticoagulation control have shown similar female preponderance and young population aged around 40 years (Davis et al, 2005; Kibiru, 2012; Mayet, 2015; Ogendo, 2000). These findings are probable because it has been suggested that most of the conditions requiring anticoagulation start developing from the age of 40 years(Cushman, 2007). However, poor anticoagulation control was more common among the elderly patients (> 60 years) ($p=0.006$). Khan et al have revealed that the elderly patients are more likely to be poorly anticoagulated(Khan et al, 2004). Similarly, Paralleti et al (Tran et al, 2014) in a case-control study in Italy found that the odds ratio of INR instability was significantly higher in those who had poor comprehension of anticoagulation therapy, as may be seen in elderly. Contrary Witt et al found that elderly patients above 70 years and on chronic anticoagulation had more stable INRs (Witt et al, 2009).

Warfarin was used mostly for the management of DVT (55.9 %) and prevention of complications associated with heart valve surgery (39.2%). Similar findings were revealed by other local studies (Kibiru, 2012; Mariita et al, 2016). Kibiru found the prevalence of DVT and heart valve surgery at 66% and 21 % (Kibiru, 2012) while Mariita found 48.6% and 32.9 % (Mariita et al, 2016), respectively. Although there were slight variations in the proportions observed, those were the main indications for warfarin anticoagulation. The differences in the proportions may have been attributed to differences in study periods which could have affected the patients' appointment schedules.

Slightly over three quarters of the patients who indicated their regular sources of drug supply got their medicine from facilities outside the hospital. Probably long queues at the hospital pharmacies could have influenced the choice of where to purchase the drugs. Sources of warfarin, however, could not predict the adequacy of anticoagulation among patients.

The main limitation in our study was that as common with cross-sectional studies that involve interviews, patients may have underreported or over reported their experiences but this was minimized by counterchecking information from patients' files. Secondly, we relied on single measurement of INR.

5.0 Conclusion

Ambulatory anticoagulation with vitamin K antagonists still remains poor in KNH with almost 75% of the patients being inadequately anticoagulated, especially the elderly. However, optimal anticoagulation control was associated with prevention of thromboembolic disorder following heart valve surgery. Further investigation is required to find out why patients with heart valve surgery are better anticoagulated than others. Larger studies, however, should be carried out to explore the prescriber and hospital contextual factors which may impact on anticoagulation.

Conflict of Interest declaration

The authors declare no conflict of interest.

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Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the US National Institutes of Health.

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