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Quality of Anticoagulation Management with Warfarin among Patients in Orotta National Referral Hospital, Asmara, Eritrea: A Retrospective Cross-Sectional Study

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ABSTRACT

Introduction:
To analyze the quality of anticoagulation management with warfarin in Orotta National Referral Hospital, Asmara, Eritrea.

Materials and Methods:
A retrospective cross sectional study was conducted on patients aged 18 years and above who had received warfarin for Deep Vein Thrombosis and Valvular Heart Disease for at least 30 days. Data were collected by reviewing patients' medical records. Time in Therapeutic Range (TTR) and International Normalized Ratio (INR) were used to analyze the quality and factors that affect the anticoagulation management.

Results:
Out of the 336 patients studied, 24.5% and 28.8% of patients, with Deep Vein Thrombosis (DVT) and Valvular Heart Diseases (VHD) respectively, had INR measurements within therapeutic range. The mean TTR was 25.1%, while the mean duration of INR monitoring for all patients was 40 days with a standard deviation of 43 days. The daily dose of warfarin was increased in 35.4% of participants following subtherapeutic INRs, and decreased in 50.6% following supratherapeutic INRs. No association was found between optimal TTR outcome and concomitantly used medications as well as comorbid conditions. However, the use of alternate dose regimen was found to be significantly associated with in-range (therapeutic) INR measurements.

Conclusion:
The study concluded that the quality of anticoagulation management with warfarin among patients in Orotta National Referral Hospital was suboptimal. This was demonstrated by low mean TTR, longer INR monitoring frequency and unsatisfactory measures taken to adjust warfarin dose after occurrences of non-therapeutic INRs.

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Introduction

Ever since its discovery in 1948, warfarin, has become one of the most extensively used anticoagulant drugs worldwide (1). Warfarin is commonly used in general practice to treat and prevent thromboembolic complications in a range of clinical settings. It acts by interfering with the activation of vitamin K dependent clotting factors and halting other naturally occurring anticoagulant proteins. The most common indications for this drug are Deep Vein Thrombosis (DVT), and Valvular Heart Diseases (VHD) (2). Although warfarin is still considered among the frontiers of oral anticoagulant therapy, it is quite challenging to manage its effects due to its narrow therapeutic index. Warfarin is a special target of intensive research mainly because patients are at increased risk of bleeding if the International Normalized Ratio (INR) is supratherapeutic and at risk of thromboembolic complications if INR is subtherapeutic. Furthermore, it significantly interacts with diet and various medications; and its effect is influenced by genetic and comorbid conditions.In a South African study, warfarin was the fourth most commonly implicated medication in preventable adverse drug reaction-related admissions (3); so, it is imperative that due consideration is given to determine the quality of anticoagulation with warfarin. Inappropriate management of patients taking warfarin can lead to serious complications such as fatal bleeding, increased toxicity and mortality (4,5). However, the overall rationality of anticoagulation therapy with warfarin can be enhanced if it is strictly monitored using various laboratory approaches in conjunction with effective patient counseling .INR was developed to standardize the report of anticoagulation levels around the world (6). Since then, INR monitoring became the main laboratory parameter used to determine the effects of oral anticoagulants. It is determined by dividing the prothrombin time of a patient to the mean prothrombin time of a normal person multiplied by international sensitivity index (ISI) (6). Another endorsed parameter to estimate outcomes of anticoagulation therapy is Time in Therapeutic Range (TTR). It is recommended that the TTR should be maintained above a goal of 50%, to achieve benefit (7). Therefore, conducting this study is of common interest as it investigates the extent of the problem and approaches of management associated with warfarin use. The major aim of this study was to systematically assess the quality of anticoagulation management with warfarin by measuring the outcomes of INR, the proportion of patients achieving the optimum TTR, the factors associated with poor anticoagulation and evaluation of warfarin's dose adjustments practices in a national referral hospital in Eritrea, Orotta.

Materials and Methods

Study Design and Setting

A retrospective cross-sectional study design was employed, where data was collected by reviewing patient's medical record. The study was conducted in medical ward and cardiology clinic in Orotta national referral hospital (ONRH), the largest tertiary teaching hospital in Eritrea. It is the main medical, surgical, pediatric and obstetrics and gynecology referral hospital in the country.

Sample selection criteria

Medical records of patients admitted to medical ward and cardiology clinic of the referral hospital from 2012 to May 2019 were reviewed. Patients aged 18 years and above with DVT and/or VHD who had been on warfarin therapy for at least 30 days were eligible for the study.

This is because of the fact that anticoagulation effects of warfarin could not be measured reliably prior to this time. Final number of patients eligible for the study is shown in Figure1. Patients who were on anticoagulant other than warfarin, under 18 years of age. with missed or no information on cards, and those having only one or no recorded INR measurements were excluded from the study.

TTR calculation

The TTR was calculated using fractions of INR in-range as shown below (8,9):

$$TTR = \frac{\text{the number of INRs within the target range for all patients}}{\text{Total number of INRs during the selected interval of time}}$$

TTR was calculated for individual patient record and categorized into optimal (TTR 50% and above) and sub-optimal for use in subsequent analysis. When performing data analysis, the INR therapeutic targets were 2–3 for DVT, whereas INR target of 2.5–3.5 was endorsed for VHD such as rheumatic heart disease, mechanical valve replacement in mitral position, and for dual aortic and mitral mechanical valve replacement (10).

Statistical analysis

Data was checked for completeness, validated and entered using CS-Pro version 7.2. Descriptive analysis for the factors that affect the quality of management such as sociodemographic characteristics of the patients, concomitantly used medications, comorbid diseases and warfarin dose adjustment practices were analyzed using SPSS version 22. The first three factors were analyzed for association with quality of anticoagulation management using TTR outcome. Possible association between warfarin dose regimen* (alternate or single) and INR range were also computed. Chi square and logistic regression tests were used to obtain relationships and statistical significance between the collected variables. The p-value for significance was taken < 0.05 and Confidence interval of 95%.*Warfarin dose regimen: the dose/s of warfarin given following INR measurement. It can either be single dose where similar doses of warfarin are given until the next INR measurement (e.g. only 5 mg, or only 2.5 mg) or alternate dose in which different doses of warfarin are given until the next INR measurement (e.g. 5 mg first day, then 7.5 mg second day, 2.5 mg the next day and so on)

Results

Socio-demographic and clinical characteristics of the study population

Of the 336 study participants; 223 (66.4%) were females. The mean age of participants was 42.36 years (SD =18.60) with majority of the patients falling in the range of 18-35 years (44.9%). DVT and heparin constituted for more than half of the reviewed indications and concomitant medications respectively; while more than a quarter of the concomitantly prescribed medications were antibacterial, as shown in Table 1.

Table 1: Socio-demographic and clinical characteristics of the patients on warfarin therapy

Variables	Frequency	Percentage
Sex		
Male	112	33.3
Female	223	66.4
Missing	1	0.3
Age		
18-35	151	44.9
36-65	132	39.3
>65	53	15.8
Indication		
DVT	243	72.3
VHD	93	27.7
Comorbidities		
Hypertension	19	5.7
Congestive Heart Failure	18	5.4
Diabetes Mellitus	16	4.8
Urinary Tract Infection	14	4.2
Concomitant Drugs		
Heparin	222	66.1
Antibacterial	127	37.8
Diuretic	89	26.5
Aspirin	72	21.4
Beta blockers	62	18.5
ACE inhibitors	51	15.2
Digoxin	53	15.8
Others*	67	19.9

*Other drugs: Antivirals, Non-steroidal anti-inflammatory agents, Opioids, Statins, Corticosteroids, Proton Pump Inhibitors, Histamine 2 Receptor Antagonists and Antidiabetics

Outcomes and duration of INR measurements

Almost half of the patients with DVT fell in the subtherapeutic range, and 18.1% in supratherapeutic range. Similarly, 50.3% VHD INR measurements were in subtherapeutic range, while28.8% were in therapeutic. The overall mean monitoring interval between two INR tests was 40 days with a standard deviation of 43 days.

Warfarin dose adjustment practices

Two hundred eighty four (50.6%) INR measurements of the patients in supratherapeutic range were managed by decreasing the dose of warfarin, 171 (30.5%) continued with the same dose and 106 (18.9%) with increased dose. After occurrences of therapeutic INRs, the proceeding doses were unchanged in 535 (69.5%) cases, reduced in 132 (17.1%) and increased in 103 (13.4%) cases. 260 (17.4%) subtherapeutic INR measurements were treated by lowering the doses while 706 (47.2%) and 529 (35.9%) continued with the same and increased doses respectively.

TTR outcomes

Out of the total patients, 81.5% had suboptimal TTR (TTR measurement below 50%). The mean TTR computed from individual patient TTRs was found to be 25.1% with standard deviation of 27%. While mean TTR for DVT and VHD patients was 24.9% (SD=31.4%) and 25.5% (SD=14.8%) respectively.

Factors affecting anticoagulation outcomes

No statistically significant association was found between TTR outcome and the three factors i.e sociodemographic characteristics of the patient, concomitant drugs administered and comorbid diseases as shown in Table 2. However, patients who were on alternate dose regimen were found to be associated with therapeutic INR range ($p < 0.001$).Using logistic regression,INR measurements following alternate dose regimen were 2.241 times more likely to be with in therapeutic range compared to INRs values following single dose regimen ($p<0.001$)

Table 2: Factors that affect the TTR outcome

Variables	Suboptimal TTR (n)	Optimal TTR (n)	*p value*
Age group	274	62	0.092
18-35	129	21	
36-65	104	26	
>65	41	15	
Sex	273	62	0.329
Male	88	24	
Female	185	38	
Comorbidity	274	62	0.167
Yes	159	30	
No	115	32	
Concomitant drugs	274	62	0.080
Yes	261	62	
No	13	0	

Table 3: Dose regimen and INR range

Variables	Crude Odds Ratio	95% Confidence Interval	*p* value
Alternate dose regimen	2.241	1.855-2.707	< 0.001
Single dose regimen	*Ref**		

Ref: reference range*

Discussion

According to our study, low mean TTR, longer INR monitoring, and unsatisfactory dose adjustment practices in subtherapeutic INRs are the core reasons for the poor anticoagulation outcomes. In Orotta national referral hospital the mean TTR(25.1%) was low in comparison to the standard TTR ≥ 50% which was lower than the value (mean TTR of 29%) revealed by an Ethiopian study that assessed the quality of anticoagulation with warfarin in the largest hospital in Addis Ababa (10). A similar study in Kenyatta national hospital in Nairobi reported a mean TTR of 31.1% which was also higher than the findings in this study (11). Even though the study population, sample size and context of the studies differ; the quality of anticoagulation management in all three studies was relatively poor as reflected by lower mean TTR than the standard.

INRs recorded for VHD patients were more in the therapeutic range than INRs for DVT patients. This could be due to the wide practice of alternate dose regimen with warfarin and the presence of a separate cardiac clinic that provides a close monitoring of VHD patients.

The American College of Chest Physicians, American Heart Association and other studies suggest that INR should be monitored at an interval of no longer than every 28 days for stable patients receiving warfarin (12-14). The mean duration of INR monitoring between two INR tests was found to be remarkably longer in this study compared to a finding revealed by a study conducted in the United States that showed a mean number of 6.2 days between two INRs measurements (15).

The deterrents to more INR monitoring frequency are potentially lack of adequate technical staff and possibly patient's lack of awareness in the importance of frequent INR measurement. Other possible reason might also be the lack of anticoagulation clinic for patients with DVT; given the institution's workload. The Orotta national referral hospital has shortage of technical staff and this issue can be addressed by the possible incorporation of pharmacists in the patient management process. As pharmacists' responsibilities are evolving towards patient centered clinical care, their engagement can have positive impact in the patient management process. (16).

Subtherapeutic INRs were mostly managed by continuing the same daily dose of warfarin in most of the cases. This is different from the management shown in a study by Aspinall et al, reporting that 75% of subtherapeutic cases were managed by increasing warfarin dose (7).

This can greatly influence the quality of anticoagulation as patients are supposed to get increased dose of warfarin following their subtherapeutic INRs. The reason behind the reluctance to increase the doses could be the lack of varied doses of warfarin, which leaves the staff with no alternatives (e.g. 2 mg and 3 mg) to adjust, but to break the available 5 mg tablets. In cases of supratherapeutic INRs, the doses were decreased in only half of the cases, and although this number is still low, the practices are partially satisfactory as compared with subtherapeutic INRs.

Logistic regression analysis found that alternate dose regimen was significantly more in the target INR range than single dose regimen. Although the possible reason behind this finding is unknown, the authors suggest that the provision of varying dose of warfarin (by breaking the only available dose of 5 mg into different doses) maintains the desired level of the drug in the blood in similar way to the different manufactured doses of warfarin (e.g. 1 mg, 2 mg, 3 mg and so on). So, it is strongly recommended that the Orotta national referral hospital considers procurement of different prefabricated doses of warfarin or to encourage the use of alternate doses of warfarin with extreme precautions when breaking the tablets. Similar to this study, reports from Botswana and Kenya, have found no association between sex and poor anticoagulation outcome (11,17). However many other studies have found an association with sex (18, 9). In contrary to this study, Salome, 2016 found an association with age of less than 65 years and low TTR outcome (11). The study in Botswana found a significant relationship with the comorbid condition, hypertension, while the current study found no relationship (17).

3.1 Limitations and Recommendations

As this was a retrospective study relying on patient medical records and verification of the accuracy of recorded information was not possible there might have been a sort of information bias. In many cases, physicians' hand writing was illegible and created a major problem in the interpretation of patient medical records which might have consequently led to the loss of some data and thus affecting representativenes.

Other potential risk factors, such as diet, alcohol consumption and smoking status weren't included, because of the unavailability of information and retrospective nature of the study. Since most of the data in Orotta national referral hospital anticoagulation clinic was non-computerized, fractions of INR in-range was used instead of Rosendaal method to calculate the TTR.

As this study involves one national referral hospital the results cannot be generalized. The authors, depending on the unsatisfactory findings of the study, recommend establishing a separate anticoagulation clinic and involvement of relevant healthcare professionals in the management process. Besides, alternate dose regimen showed strong association with good INR management, thus procurement and distribution of different warfarin doses is recommended.

Conclusion

The study indicates that the quality of anticoagulation management among patients who received warfarin in Orotta national referral hospital was poor.

This was reflected by the low mean TTR value, significant suboptimal TTRs, longer duration of INR monitoring, and unsatisfactory warfarin dose adjustment practices. The study also found a significant association between alternate dose regimens and better outcomes of warfarin treatment.

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