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Conservative Management of Overanticoagulation in Patients With Low–Moderate Risk for Bleeding Complications

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Abstract

Despite long-standing experience with warfarin, anticoagulation clinic services are often confronted with the challenging clinical situation of patients with overanticoagulation. This requires repeat international normalized ratio (INR) monitoring and in some cases administration of vitamin K to minimize the risk of bleeding. A study was performed to determine the safety and efficacy of outpatient management in order to provide guidance on the management of patients with prolonged INRs. Patients on stable warfarin therapy for more than 1 month attending a dedicated academic hospital anticoagulation clinic who had an INR $\geq$5 were identified over a 1-year period. Follow-up INR results and outcomes were recorded for 30 days. One hundred and ninety-five episodes of overanticoagulation in 148 patients were identified. Patients were classified as low risk (n = 85, 57.4%) and moderate risk of bleeding (n = 63, 42.6%). The mean index INR was 7.22 (1.88). Management with low-dose oral vitamin K (n = 32, 16.4%) did not significantly result in a more rapid correction of the INR when compared to conservative management (n = 163, 83.6%; $P = .103$). Follow-up INR testing was performed at a mean of 11.1 (8.9) days from the index measurement. A mean of 1.6 (0.9) follow-up INR tests were performed per episode. During the 30-day follow-up, there was 1 (0.5%) episode of major bleeding and 1 (0.5%) death. The management of asymptomatic outpatients with overanticoagulation is associated with a low risk of major bleeding within 30 days. Conservative management of overanticoagulation is as effective as utilizing low-dose oral vitamin K.

Keywords

INR monitoring, warfarin, bleeding, anticoagulation clinic

Background

Warfarin, discovered almost 80 years ago, is the most widely used anticoagulant in the developing world. However, there are many practical challenges. Warfarin has a narrow therapeutic range and thus requires regular monitoring of the international normalized ratio (INR) to determine the dose required to achieve a therapeutic benefit while at the same time reducing the risk of bleeding complications. Despite regular monitoring, overanticoagulation is frequently observed in patients on warfarin attending dedicated anticoagulation clinic services. A change in dietary habits, new medications, noncompliance, dosing errors, decompensated heart failure, alcohol use, and liver disease are some of the risk factors for overanticoagulation.[1]

Previous studies have demonstrated that an INR >5 is significantly associated with an increased risk of intracerebral hemorrhage.[2] The American College of Chest Physicians guidelines suggest reducing the length of time in which the INR is elevated in order to avoid bleeding complications. It is recommended that asymptomatic patients with overanticoagulation omit warfarin until the INR has returned to the

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therapeutic range and/or be given vitamin K (phytonadione).[3] For patients at high risk of bleeding or with INR >10, oral vitamin K is recommended in order to ensure a more rapid INR correction.[4] Increased frequency of INR monitoring is advised until the INR has returned to the therapeutic range. Some studies have demonstrated that it takes an average of 2.5 days for an INR of 6 to 10 to decline to <4 when warfarin alone is withheld, whereas it takes an average of 1.4 days for the INR to decline when oral vitamin K 1 to 2.5 mg is administered.[5] However, other studies have indicated that the rate of INR decline after discontinuation of warfarin is variable thus requiring daily monitoring.[6]

In order to improve the safety and efficacy of warfarin, various dosing algorithms, based on clinical and pharmacogenetic patient information, are used at many anticoagulation clinics. At anticoagulation clinics in South Africa, pharmacogenetic studies are not routinely requested. A study performed locally demonstrated that clinical characteristics such as age, ethnic group, and drugs were better predictors of warfarin dose requirements and overanticoagulation than genotype in this population group.[7] In South Africa, anticoagulation clinic services for state patients are centralized at large academic hospitals. Frequent monitoring of outpatients with overanticoagulation is often not feasible, predominantly as a result of limited patient accessibility. We therefore studied the day-to-day management of overanticoagulation at a dedicated academic hospital anticoagulation clinic service. The secondary aim was to define the 30-day major bleeding risk in outpatients with overanticoagulation in order to provide guidance to local health-care professionals caring for patients on warfarin therapy.

Methods

Study Design

An average of 1500 patients attend the dedicated academic hospital anticoagulation clinic at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). This serves the greater Johannesburg patient population. Hospital anticoagulation clinic patients consist of the following indications: 25% with mechanical valve replacements (MVRs) on lifelong anticoagulation therapy, 20% with a history of venous thromboembolism (VTE), and 35% anticoagulated for prevention of arterial embolism due to atrial fibrillation (AF).[7] Patients are assessed at a maximum of 1-month intervals and followed up by dedicated nursing staff trained in the management of anticoagulation therapy.

Study Protocol

Patients attending the anticoagulation clinic on daily warfarin (warfarin; Cipla/Aspen, Cape Town, South Africa) for more than 1 month with an INR $\geq$5 were identified over a 1-year period from February 2017 to February 2018. The baseline demographic, clinical, and routine laboratory data were collected from the patients' medical records. Active cancer was defined as cancer at initial diagnosis, recurrent or metastatic cancer, or treatment in the previous 6 months for cancer. The associated bleeding risk was defined according to the outpatient bleeding risk index (OBRI) which included age >65 years, past history of gastrointestinal bleeding, past history of cerebrovascular incident, and at least 1 comorbid condition (myocardial infarction, diabetes, hematocrit <30%, and creatinine >1.5 mg/dL.[8,9] Management was classified as conservative (interruption of warfarin alone) or nonconservative (oral vitamin K or hospital admission at the discretion of the treating doctor). Vitamin K was administered as Pediatric Konakion (Roche, Welwyn Garden City, UK; vitamin K 2 mg/0.2 mL) orally. Follow-up INR results and outcomes were recorded for 30 days after the index INR measurement. Major bleeding was defined in accordance with the international society of thrombosis and hemostasis criteria.[10] The definition included clinically overt bleeding associated with a decrease in hemoglobin by >20 g/L; bleeding requiring transfusion of >2 units of packed red cells; and bleeding at a critical site or bleeding associated with mortality. All other bleeding was considered as minor.

Laboratory Analysis

Laboratory testing was performed at the National Health Laboratory Service Hematology Laboratory at CMJAH. The INR testing was performed by venepuncture collected in citrate tubes (Becton-Dickinson, Oxford, United Kingdom) and measured within 2 hours of collection on the STA-R evolution coagulation analyzers (Diagnostica Stago, Asnières, France) with Neoplastin (Diagnostica Stago) reagents with an international sensitivity index of $\sim$0.94. All INR measurements $\geq$5 were checked manually.

Ethics

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (approval number M170605).

Statistical Analysis

Descriptive analysis was performed using Graphpad Prism software (Graphpad Prism v4, La Jolla, California). Statistical comparisons were performed using the χ^2 for categorical variables and the parametric independent t test or nonparametric Mann-Whitney U test for continuous parameters depending upon normality. Statistical significance was set at a P value of .05 or less.

Results

Study Population

During the 1-year observation period, there were 195 episodes of overanticoagulation in 148 patients (Figure 1). The baseline characteristics of the study population are summarized in Table 1. The most common indication for warfarin was for the

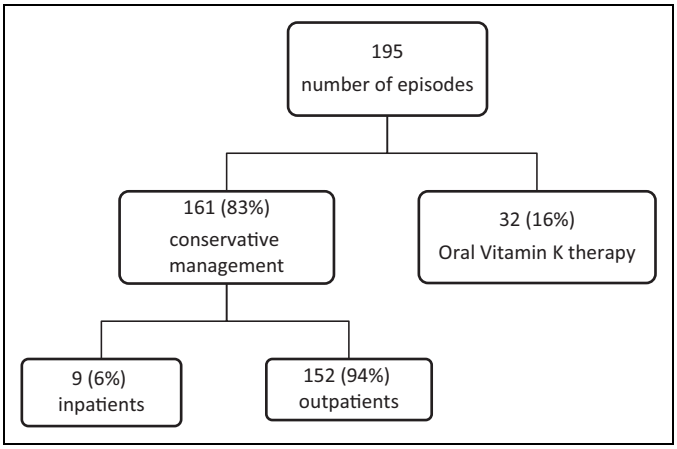

Figure 1. Flow diagram of patient management.

Table 1. Patient Characteristics.

Characteristic	N = 148
Demographics	
Male	54 (36.5%)
Female	94 (63.5%)
Age, mean (SD), years	55 (16)
Indication for Anticoagulation	
Venous thromboembolism	46 (31.1%)
Atrial fibrillation	44 (29.7%)
Mechanical valve replacement	37 (25%)
Other	21 (14.2%)
Target INR (range)	
2.5 (2-3)	111 (75.0%)
3 (2.5-3.5)	37 (25.0%)
Duration of warfarin	
>1 month and <6 months	37 (25.0%)
≥6 months	111 (75.0%)
Bleeding Risk	
Age >65 years	52 (35.1%)
Past gastrointestinal bleeding	2 (1.4%)
Past cerebrovascular incident	10 (6.8%)
Myocardial infarction	11 (7.4%)
Diabetes	4 (2.7%)
Hematocrit <30%	1 (0.7%)
Creatinine >1.5 mg/dL	3 (2.0%)
Active cancer	1 (0.7%)
Antiplatelet therapy	12 (8.1%)

Abbreviation: INR, international normalized ratio.

management of VTE (31%). In this cohort, 85 (57%) patients with no risk factors for bleeding were classified as low risk, and 63 (43%) patients with ≥ 1 risk factor for bleeding were classified as moderate risk. No patients were classified as high risk. Overall, 52 (35%) of the patients were older than 65 years, of which 5 (3%) were ≥80 years. The majority were on stable warfarin therapy for more than 6 months (n = 111, 75%).

Entry INR Results

The mean index INR was 7.22 (1.88). An INR >10 was recorded in 57 (29%) episodes. The suspected reasons for INRs ≥5 are presented in Table 2. Analgesics and anti-inflammatory medications for pain were the most common interacting drugs (n = 30, 42%). Other frequent drug interactions included antibiotic therapy (n = 12, 17%), a change in chronic medication dosage (n = 13, 18%), and the use of traditional medicines (n = 4, 6%). There were 11 (6%) reports of minor bleeding and no reports of major bleeding. Minor bleeding included 6 cases of purpura and hematomas, a case of gum bleeding, and 4 cases of abnormal vaginal bleeding which were all self-limited. Of the patients with minor bleeds, 3 (27%) were older than 65 years. The one major bleeding event in this study prevented assessment of the relationship between conservative and nonconservative management and the risk of major bleeding.

Table 2. Suspected Reasons for Index INR ≥5.[a]

Reason	n (%)
Drug interactions	71 (36.4%)
Dietary interactions	7 (3.6%)
Noncompliance with taking warfarin	25 (12.8%)
Illness	31 (15.9%)
Warfarin dosing errors	23 (11.8%)
Decompensated heart failure	7 (3.6%)
Liver failure	5 (2.6%)
Alcohol use	2 (1.0%)
No documented reason	62 (3.2%)

Abbreviation: INR, international normalized ratio.
[a]Total exceeds 195 episodes as some patients had more than 1 suspected reason.

Warfarin was stopped for a mean of 3 (1) days. The majority of episodes were treated conservatively (n = 161, 83%; Table 3). Oral vitamin K was prescribed at dose of 2 mg in 32 (16%) episodes. In the vitamin K group, the index INR was >10 (94%) in 30. Three (9%) of these episodes presented with minor bleeding. Nine (16%) patients with MVRs and INR >10 with no signs of bleeding were admitted to the CMJAH for observation and temporary interruption of warfarin for a mean of 4 (2) days. In 17 (30%) episodes with INR >10, patients were contacted telephonically with results, and vitamin K, which is not readily available, could not be administered. Patients were advised to increase their dietary intake of green leafy vegetables in addition to interruption of warfarin. In this subgroup, the follow-up mean INR was 3 (1) at a mean of 5 (4) days as compared to the group treated with oral vitamin K (INR was 3.06 [2.63] at a mean of 4 [3] days; $P = .595$).

Follow-Up Over 30 Days

Follow-up INR measurements for the next 30 days were not available for 5 episodes (4 missed the scheduled follow-up within 30 days and 1 was transferred to another anticoagulation clinic service). Patient 1 returned after 166 days with an INR >10, patient 2 returned after 31 days with an INR of >10, patient 3 returned after 112 days with an INR of 1.11, and patient 4 returned after 35 days with an INR of 2.16. There were no adverse events in these 4 patients. Follow-up analysis

Table 3. Management of Episodes of Overanticoagulation.

Characteristics	Conservative (n = 163, 83.6%)	Nonconservative (n = 32, 16.4%)	*P* Value
INR, mean (SD)	6.71 (1.59)	9.82 (0.70)	<.0001
Bleeding			
Minor, n (%)	8 (4.9)	3 (9.4)	–
Major, n (%)	1 (0.6)	0 (0)	–
Number of days warfarin omitted, mean (SD)	2. 6 (0.8) days	3.4 (1.0) days	<.0001
Follow-up INR if retested within 72 hours, mean (SD)	3.37 (1.23)	3.89 (2.97)	.103
Number of follow-up INR in 30 days	1.5 (0.8)	2.1 (1.3)	<.0007
Number of follow-up INR below the therapeutic range,[a] n (%)	49 (31.0)[b]	15 (46.9)	.078
Number of follow-up INR above the therapeutic range,[a] n (%)	35 (22.2)[b]	7 (21.9)	.581
Number of days to a therapeutic INR, mean (SD)	19.1 (10.2)	18.2 (11.9)	.658

Abbreviations: INR, international normalized ratio; SD, standard deviation.
[a]Therapeutic range as specified by treating clinician 2 to 3 or 2.5 to 3.5.
[b]No follow-up in 1 patient transferred and 4 patients with no subsequent follow-up (n = 158).

has been performed on 190 episodes. Follow-up INR testing was performed at a mean of 11 (9) days from the index measurement. These results were supratherapeutic in 42 (22%), within the therapeutic range in 84 (44%), and subtherapeutic in 64 (34%). A mean of 2 (1) follow-up INR tests were performed per episode over the next 30 days. In the majority (n = 120, 82%) follow-up, INR testing was performed once during the next 30 days. In 47 (25%) patients, follow-up INRs were performed on 2 occasions, in 15 (8%) on 3 occasions, and in 8 (4%) on ≥4 occasions. The mean number of days to achieve a therapeutic INR (range as specified by the treating clinician) was 19 (11) days.

A follow-up INR measurement was performed within 72 hours in 28 (15%) episodes. The mean INR measured within 72 hours was 3.67 (2.15). Overall, 10 (36%) INRs were in the supratherapeutic range and 3 (11%) were in the subtherapeutic range. Of the episodes in which the first follow-up INR occurred 72 hours after the index INR, 19 (10%) missed an earlier scheduled appointment, 59 (31%) episodes were retested within the first week, and 62 (33%) episodes were retested within the second week. In 42 (22%) episodes, testing was performed after 2 weeks: 24 (57%) cited no transport funds and 18 (43%) had no documented reason for the follow-up interval chosen. Of the patients retested within the first week, the mean INR was 2.13 (1.01) at a mean follow-up of 5 (1) days. The INR was subtherapeutic in 34 (58%), therapeutic in 19 (32%), and supratherapeutic in 6 (10%).

Outcomes

During the first 30 days after the index INR, there was 1 (0.5%) major gastrointestinal bleed and 1 (0.5%) minor epistaxis. The patient with the major bleeding was a 48-year-old male with diabetes mellitus on warfarin ≥6 months for AF. His INR at presentation was 6 and was treated conservatively with warfarin interruption for 2 days. He presented within 14 days of the elevated INR with rectal bleeding and an INR of 1.34. Endoscopic biopsies revealed no evidence of malignancy or inflammation. There were no recorded incidents of VTE. One (0.5%) patient died. The patient was a 32-year-old female on lifelong warfarin for a mitral MVR. Her index INR was >10, and she was treated conservatively as an outpatient with warfarin interruption for 3 days. Follow-up INR testing was performed on day 6 (INR: 5.85), day 12 (INR: 4.70), and day 18 (INR: 1.86). She collapsed on day 43 after the index INR. The cause of death was undetermined.

Discussion

The major safety concern related to the use of warfarin is the risk of bleeding complications. In the developed world, there is an increase in the use of the new direct oral anticoagulants because of the higher absolute incidence of major bleeding associated with a more severe clinical course with the use of warfarin.[11-13] However, in the developing world, access is restricted by cost and availability. Reassuringly, in the present study in patients on warfarin treatment, there was only 1 major bleed, 4 minor bleeds, and 1 related death. The findings of this study performed at a dedicated academic hospital anticoagulation clinic added to the evidence that outpatient management of overanticoagulation is safe.

A number of models have been developed to identify risk factors and predict bleeding complications specifically on warfarin.[8,14] Most of these models, however, have been validated in patients with AF. This limits the use of these scoring systems in study populations in the developing world, where MVR for rheumatic heart disease is still prevalent. In this cohort, the patient age (55 [16] years) and the prevalence of indications for anticoagulation (VTE = 31%, AF = 30%, MVR = 25%, and other = 14%) were representative of anticoagulation clinic services in the developing world. This differs considerably from cohorts described in the developed world that predominantly consist of elderly patients with AF.[15] According to the OBRI model applied in this study, the majority of the study patients (n = 85, 57%) had no risk factors for bleeding and would have been classified as low risk. In addition, there were 63 (42%) with ≥1 risk factor classified as moderate risk. The small number of major bleeding events (n = 1) in this study prohibited further analysis, which is a limitation of this study. The accuracy of the OBRI model to predict major bleeding has,

however, previously been demonstrated in cohorts with VTE and AF. Di Nisio et al evaluated a number of prediction models in 4122 patients on warfarin for VTE in the Hokusai-VTE study. In this cohort, the OBRI model was an effective discriminator of major bleeding as indicated by the area under the curve of 0.64 (95% confidence interval: 0.58-0.7). There was an increase in the bleeding rate in the moderate (2.17%) and high-risk categories (5.83%) when compared to the low-risk category (0.74%).[16]

Management of INR >10 with low-dose oral vitamin K did not significantly reduce the risk of major bleeding compared to conservative management during the 30 days of follow-up. However, the small number of bleeding events precluded definitive assessment. Furthermore, although studies have demonstrated that low-dose oral vitamin K results in a more rapid correction of the INR to the desired range,[5,17] in this cohort no significant difference was observed. In accordance with local guideline recommendations, episodes of INR >10 (n = 57, 29%), associated with a higher risk of bleeding, were treated with low-dose oral vitamin K. The mean follow-up INR within 72 hours was 3.37 (1.23). Testing within 24 hours was not feasible in the majority (n = 28, 88%) owing to limited patient access to the anticoagulation clinic. In addition, there were 17 (30%) episodes of INR >10, in which patients were unable to access the clinic/hospital for vitamin K. Of interest, these patients treated conservatively were advised to increase their dietary intake of green vegetables with a medium content of vitamin K, in particular avocados in addition to interruption of warfarin. The mean follow-up INR in the group treated conservatively was 2.71 (0.74) which was not significantly different from the group treated with low-dose oral vitamin K ($P = .595$). Increased intake of green vegetables may be recommended in settings, where oral vitamin K is not readily available or patient access to anticoagulation clinic services is limited. However, further randomized controlled trials are indicated. A safety concern with low-dose oral vitamin K is the risk of over reversal in 10%, which predisposes to valve thrombosis in patients with mechanical heart valves.[18] In this study, patients with MVR (n = 6) and INR >10 were therefore preferentially admitted to hospital for daily monitoring and conservative management in order to avoid the risk of a subtherapeutic INR associated with oral vitamin K use. In this study, there was 1 (0.5%) death in a patient with an MVR who presented with a subtherapeutic INR on follow-up testing. This patient had been managed as an outpatient and did not achieve a therapeutic INR on follow-up over the next 30 days. Her cause of death was undetermined. However, it may have been secondary to a bleed or thrombotic event.

As described previously,[15] low-dose oral vitamin K was infrequently prescribed for patients with INR of 5 to 9. In this study, oral vitamin K was prescribed in 2 patients with INR of 5 to 9. The risk of warfarin overreversal, the practical difficulties with the use of vitamin K in outpatients, and the failure of randomized controlled trials to show improved efficacy most likely explain the uncommon use of oral vitamin K by anticoagulation clinic services.[17]

Studies have demonstrated that the rate of INR decline after interruption of warfarin is variable thus increased frequency of INR monitoring is advised until the INR has returned to the desired range.[6]

In this study, retesting within 1 week of the index INR measurement was feasible in <50% of the episodes and 33% (n = 62) were retested within 2 weeks. Of these, a follow-up INR was performed within 72 hours in only 28 (15%) episodes. An earlier scheduled appointment was missed in 10.0% (n = 19). In addition, on follow-up during the next 30 days, the frequency of INR testing was increased in only 37% (n = 70) of episodes. This was predominantly as a result of limited patient access because of the distance to anticoagulation clinics which are centralized at large academic hospitals and financial constraints. However, this level of monitoring was not associated with thrombotic events or increased major bleeding.

Finally, on review of the suspected reasons of overanticoagulation, drug interactions (n = 71, 36%) were the major cause. Over-the-counter analgesics were the most common interacting drugs (n = 30, 42%) highlighting the need for focused patient education. This was followed by antibiotic therapy (n = 12, 17%) and a change in chronic medication dosage (n = 13, 18%) by clinicians. Clinicians need to carefully consider the use of concomitant drugs that potentially interact with warfarin, and patients need to remind their attending physicians that they are taking warfarin.

Conclusion

Although the sample size is small, the results of this study, which represent a broad spectrum of patients, are important because they represent clinical practice in developing countries where frequent monitoring and genotypic analysis are often not feasible. The findings of this study support the conservative management of outpatients with INR $\geq$5 and a low–moderate risk for bleeding complications with interruption of warfarin therapy and reinstitution once the INR has decreased to the therapeutic range. The low risk of major bleeding (0.5%) and the cumulative mortality (0.5%) in asymptomatic outpatients with an INR $\geq$5 within 30 days is comparable to large multicenter studies.[6,15] Administration of low-dose oral vitamin K for INR >10 was safe. However, the small number of bleeding events precluded definitive assessment of its efficacy. We are of the opinion that asymptomatic patients with MVR and INR >10 should preferentially be admitted for observation and temporary interruption of warfarin.

Authors' Note

E.S. contributed to study design, manuscript author, data entry and analysis. S.L. contributed to study design and critical review. J.S. contributed to data collection. M.M. contributed to study design and data collection. B.J. critically revised the manuscript.

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