Time in Therapeutic Range and Adverse Outcomes among Patients Receiving Warfarin Therapy at Tertiary Care Hospital

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ABSTRACT

Background

Warfarin has a narrow therapeutic index and needs regular international normalized ratio monitoring and dose adjustment. Poor quality of warfarin dosing can lead to an increased risk of adverse events.

Objective

To find out the overall quality of the international normalized ratio expressed in terms of time in therapeutic range and adverse outcomes associated with the use of warfarin.

Method

A descriptive cross-sectional study among 150 patients attending a tertiary care center receiving warfarin therapy from December 2022 to June 2023. Patients receiving warfarin at least for 6 months and with at least three international normalized ratio values were enrolled. Indications, average daily dosing, international normalized ratio, and adverse effects were recorded using convenient sampling. Data were analyzed by using SPSS, version 20.

Result

The mean age was 46.41±13.96 years. Indications for warfarin were valvular and nonvalvular atrial fibrillation in 104 (69.33%), deep vein thrombosis 21 (14%), and pulmonary embolism 6 (4%). The majority of patients 100 (66.6%) received 5 to 10mg of warfarin per day. The mean duration of warfarin use was 18.11±21.93 months. The mean time in the therapeutic range (%) was 62.43±27.52. Sixty patients (40%) had time in the therapeutic range below 60%. Among the adverse effects, minor bleeding was present in 25 (16.66%). The ischemic event was present in 7 (4.7%).

Conclusion

Our patients had lower time in the therapeutic range than recommended in the guidelines. They had a longer time in the sub-therapeutic range.

KEY WORDS

Atrial fibrillation, International normalized ratio, Treatment outcome, Warfarin

INTRODUCTION

Warfarin has been used as an anticoagulant for more than 60 years. It has a narrow therapeutic index and needs regular international normalized ratio (INR) monitoring and dose adjustment. INR value fluctuates due to various reasons like drugs and food interactions, presence of co-morbid conditions, alterations of the doses of the same or other concomitant medications, etc.[1] Despite these challenges, warfarin is still a popular oral anticoagulant due to its availability and affordability in our healthcare settings. It has been approved for use in the prevention of stroke and systemic embolism in at-risk patients with atrial fibrillation (AF), or mechanical heart valves, as well as for treating deep vein thrombosis (DVT) and pulmonary embolism (PE).[2]

The time in the therapeutic range (TTR) is an important measure in evaluating the efficacy of warfarin therapy for patients with various medical conditions. It represents the percentage of time in which the INR remains in the target range of 2.0 and 3.0 across time, although the specific range may vary based on the individual patient's medical history and other factors.[3] If the INR levels are outside the therapeutic range, the risks of adverse outcomes such as bleeding or clotting increase.

Patients with higher TTR values have been reported to have better outcomes such as a lesser number of strokes, major hemorrhagic events, and mortality.[4] To achieve the optimal clinical outcome, the TTR should be at least 65%.[5] Studies have found that patients with a TTR of less than 60% had a significantly higher risk of major bleeding and thrombo-embolism compared to patients with a TTR of 60% or higher.[6] This study aimed to find out the overall quality of INR control expressed in terms of TTR and to study the adverse effects associated with the use of warfarin.

METHODS

This was a descriptive cross-sectional study among 150 patients attending outpatient departments or admitted under different specialties of internal medicine at tertiary care hospitals receiving warfarin therapy for different indications from December 2022 to June 2023. All patients receiving warfarin at least for the previous six months and having at least three INR values were enrolled. Demographic profile, indications of warfarin use, average monthly dosing, and duration of use were recorded based on the pre-structured questionnaires. The overall quality of INR control was categorized as therapeutic (INR between 2 and 3), sub-therapeutic (INR < 2), or supra-therapeutic (INR > 3). TTR was calculated by the traditional method as the percentage of time a patient's INR is within the desired therapeutic range (INR between 2 and 3). The traditional method calculates TTR as the proportion of in-range INR values to the total number of INR values.[7] Adverse events were noted as minor or major bleeding, hypersensitivity, and systemic thromboembolism. The main objectives of this study were to find out the overall quality of INR control expressed in terms of TTR and to study the adverse effects associated with the use of warfarin. Ethical approval was obtained from the institutional review committee of Nobel Medical College (NMCTH ref no. 723/2022) before conducting the study. Convenient sampling was done.

The sample size (n) was calculated as follows,

$n = Z^2 \times p \times q/e^2$

$= (1.96)^2 \times 0.1 \times 0.9/ (0.05)^2$

$= 138$

Where,

Z= 1.96 for a 95% confidence interval

p= Average number of patients receiving warfarin per day = 10 (Educated guess)

q= 1-p

e= margin of error = 5%

The sample size was calculated to be 138. However, we enrolled 150 patients.

Data were entered in Microsoft Excel 2007 and analyzed by IBM Statistical Package for the Social Sciences (SPSS) data editor, version 20. Continuous and categorical variables were presented as a mean, percentage, and standard deviation. The tabular presentation was made for different variables.

RESULTS

The mean age was 46.41 ± 13.96 years (range 15 to 77 years) with a majority of age groups between 30 and 60 years 106(70.66%). The females 88 (58.7%) outnumbered the male 62 (41.3%) with a ratio of 1.41. Among co-morbidities, hypertension was in 15 (10%), diabetes mellitus in 10 (6.7%), heart failure in 10 (6.7%), and stroke in 9 (6%) The baseline characteristics of patients receiving warfarin are shown in table 1. Indications for warfarin were the presence of valvular AF in 87 (58%) and mitral valve replacement (MVR) in 44 (29.3%), DVT in 21 (14%), aortic valve replacement (AVR) in 20 (13.3%), non valvular AF in 17 (11.3%) and pulmonary embolism in 6 (4%). Different indicators of warfarin use and INR are illustrated in table 2. The majority of patients 100 (66.6%) received 5 to 10 mg of warfarin per day. Forty-eight (32%) patients received less than 5 mg and only 2 patients received more than 10 mg of warfarin per day. The mean duration of warfarin use was 18.11 ± 21.93 months ranging from 60 to 132 months. The mean TTR was 62.43 % ± 27.52 (range from 0 to 100). Sixty patients (40%) had TTR below 60%. Six patients (4%) had zero TTR and 28 (18.7%) had 100% TTR.

Table 1. Baseline characteristics of patients receiving warfarin (n=150)

Variables	Frequency (%)
Age (years):	
<30	20 (13.3)
30-60	106 (70.6)
>60	24 (16)
Gender	
Male	62(41.3)
Female	88 (58.7)
Co-morbidities	
Hypertension	15 (10)
Type 2 diabetes mellitus	10 (6.7)
Stroke	9(6)
Heart failure	10(6.7)
Indications for warfarin	
Valvular AF	87 (58)
Non valvular AF	17(11.3)
Mitral valve replacement	44 (29.3)
Aortic valve replacement	20(13.3)
Deep vein thrombosis	21 (14)
Pulmonary embolism	6 (4)
Drugs	
Diuretics	97(64.7)
Beta-blockers	91(60.7)
Calcium channel blockers	28 (18.7)
ACEI/ARB	30 (20)
Digoxin	26 917.3)
Aspirin	14 (9.3)
	Mean ± SD
Mean age (years)	**46.41±13.96**
Mean SBP (mmHg)	**118.02±14.60**
Mean DBP (mmHg)	**76.30±18.90**
Mean heart rate (beat/min)	**84.60±12.08**
Mean hemoglobin (gm/dl)	**12.89±6.95**

AF: Atrial Fibrillation, ACEI: Angiotensin Converting Enzyme Inhibitor ARB: Angiotensin Receptor Blocker, SBP: systolic blood pressure DBP: Diastolic Blood Pressure

Table 2. Indicators of warfarin use and INR n=150)

Indicators	Frequency (%)
Dose	
< 5 mg	48 (32)
5-10 mg	100 (66.66)
>10 mg	2 (1.4)
All INR values in the therapeutic range	28 (18.7)
At least one INR in the sub-therapeutic range	98(65.33)
At least one INR in the supra-therapeutic range	49 (32.7)
Time in the therapeutic range	
0%	6(4)
<50%	34(22.7)
<65%	62(41.33)
100%	28(18.7)
	Mean ± SD
The average daily dose of warfarin is	4.99 ± 1.46
The mean duration of warfarin use (in months)	18.11 ± 21.93
The mean number of INR values per patient	4.1 ± 1.18
Mean TTR (%)	62.43 ± 27.52

Table 3. Adverse events related to warfarin use

Variables	Frequency (%)
Minor bleeding	
Ecchymosis	22 (14.7)
Hematoma	1 (0.7)
Epistaxis	1 (0.7)
Excess menstrual bleeding	1 (0.7)
Major bleeding	
Thigh hematoma	1 (0.7)
Gastrointestinal	1 (0.7)
Hypersensitivity	1 (0.7)
Ischemic events	
Stroke	7 (4.7)
Valve thrombosis	2 (1.3)

The adverse effects of warfarin use are shown in table 3. Among the adverse effects, minor bleeding events were more common 25 (16.66%). Ecchymosis was present in 22 (14.7%) patients. Major bleeding including thigh hematoma and gastrointestinal bleeding was present in two patients. The ischemic event in the form of stroke was present in 7 (4.7%) and mechanical valve thrombosis was present in 2 (1.3%).

DISCUSSION

Our study showed a mean TTR of 62.43% ± 27.52 with around 25% adverse events mainly limited to minor bleeding manifestations like ecchymotic patches. Maintaining a high TTR is critical for minimizing the risk of adverse outcomes such as bleeding or clotting events. Poor TTR, defined as TTR < 65%, has been shown to have an increased risk of ischemic events, major bleeding, intracranial bleeding, and mortality.[8]

Vitamin K antagonist (VKA) like warfarin is the most commonly used oral anticoagulant (OAC) for stroke prevention among patients with valvular atrial fibrillation (VAF) and non-valvular atrial fibrillation (NVAF). Although major practice guidelines generally recommend direct oral-acting anticoagulants (DOACs) over VKA for the prevention of stroke or other systemic embolism among patients with NVAF, warfarin remains the most commonly used OAC in low and middle-income countries like Nepal. TTR is an essential measure in evaluating the efficacy of warfarin

therapy for patients with various medical conditions. It is recommended that TTR be used as a guide for assessing the quality of warfarin therapy among patients receiving warfarin for stroke prevention. To achieve the optimal clinical result, the TTR should be targeted for at least 65% or, ideally should be ≥ 70%.[9,10] Low-income countries like Nepal still use warfarin for the indications where DOACs can be used due to easy availability, limited healthcare budget, and affordability compared with DOACs. GARFIELD registry on Asian and non-Asian populations in 2010-2013 demonstrated that Asian populations had a lower proportion of patients with TTR within a target INR range between 2 and 3 (31.1% vs. 54.1%) when compared with data from other parts of the world.[11] In our study, the mean TTR was 62.43% ± 27.52, indicating the improvement in INR control in our patient population. Possible reasons for the low observed TTR in our populations could be to lack of regular monitoring of INR and dose adjustment, poor compliance to drugs and foods interacting with warfarin, genetic predisposition, perceived fear of bleeding among treating physicians, etc.[12] Indeed, a fear of bleeding among physicians and patients could be the reason for maintaining a low INR.

Complications related to supra-therapeutic INR include major bleeding, hemorrhagic stroke, and mortality which are the common reasons for hospitalization.[13] There is also a higher risk of ischemic stroke and systemic embolism associated with sub-therapeutic INR.[14]

Morgan et al. studied 6108 AF patients and found that there was a significant reduction in stroke events in those patients with TTR > 70% with INR between 2.0 to 3.0 compared with the non-warfarin treatment group.[15] Our study revealed that patients with TTR < 65% not only had a longer time in the sub-therapeutic range but also had a longer time in the supra-therapeutic range. Patient with at least one INR in the sub-therapeutic range was nearly double (65%) than patients in the supra-therapeutic range (32%). Similarly, data from the the FUSHIMI[16] and the GARFIELD AF[11], registry also showed that Asian populations had a higher proportion of the INR in the sub-therapeutic range. Despite a longer time in the sub-therapeutic range, the rate of major bleeding was high though our study demonstrated a higher number of minor bleeding episodes mainly limited to ecchymotic patches.[14] Results from our study indicated that the risk of ischemic stroke in 4.7% and two patients with mechanical valve thrombosis may be associated with a higher time in the sub-therapeutic range of INR. Patients who have a lower TTR also have an increased risk of major bleeding which is related to the longer time in the supra-therapeutic range (INR > 3.0). Studies have shown that Asian populations with AF on warfarin therapy are at higher risk for intracranial hemorrhage (ICH) than the white population, and likewise, the TTR in Asian patients on warfarin has generally been found to be lower than whites.[17,18] Possible reasons for an increased risk of bleeding in Asian populations could be a genetic polymorphism, affecting warfarin metabolism that predisposes to bleeding risk.[19,20] The frequency of the INR measurement could also be a factor affecting TTR results.[21] Frequency of INR measurement also correlates with the quality of OAC therapy. The INR measurement interval in Asian populations is longer than in white populations, due to different factors.[22] In our study, the mean number of INR values per patient was 4.1 ± 1.18. Our study showed that major bleeding was present only in two patients which may be associated with a shorter time in the supra-therapeutic range compared to the sub-therapeutic range of INR.

This study has some limitations. First, we enrolled a limited number of patients from a single tertiary care center by convenient sampling from the eastern part of Nepal which cannot be generalized across the country due to discrepancies in the health care access in different geographic locations. This is a cross-sectional study, we noted at least three or more INR values from the previous records, which may not be the consecutive values and might have missed the normal INR range in between.

CONCLUSION

We found that the mean TTR was not as par with the guidelines. Our patients had a longer time in the supra-therapeutic range. Minor bleeding events were more compared to major bleeding or ischemic events. There is a need for better INR control and effort must be made to achieve good clinical outcomes.

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