



Determination of the Percentage of Patients Using Warfarin to Reach Target INR

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History

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ABSTRACT

Objective: Warfarin is the most commonly used oral anticoagulant in the treatment and prophylaxis of thromboembolic diseases. In order to prevent thrombosis and to avoid hemorrhagic complications, the patient's International Normalized Ratio (INR) is kept within a certain range according to the indication and monitored at certain intervals. Our aim in our study is to determine the percentage of patients using warfarin for various indications reaching target INR values.

Methods: Patients who used warfarin for various indications at our hospital's Internal Medicine outpatient clinic between May 2023 and November 2023 were included in our study, and their INR results were recorded by retrospectively scanning them.

Results: A study group was formed with a total of 130 patients. Patients using warfarin due to metallic heart valve replacement, AF, PTE and CVD were evaluated separately according to the target INR value. The percentage of patients with metallic heart valve replacement reaching the target INR value of 2.5-3.5 was calculated as 38.5% (n: 27). The percentages of patients with AF, PTE and CVD reaching their target INR values of 2-3 were calculated as 40% (n:16), 54% (n:7), 70% (n:5), respectively. Considering the entire study group, the percentage of reaching the target INR was calculated as 42% (n: 55).

Conclusion: As a result, warfarin not being within the therapeutic range causes serious morbidity and mortality. In our study, the percentage of patients reaching the target INR was found to be 42%. This percentage is very low, and in order to increase this rate, it is necessary to increase patient awareness, increase the frequency of follow-up of patients and develop more effective follow-up strategies.

Keywords: Warfarin, INR, Thrombosis, Bleeding

Varfarin Kullanan Hastaların Hedef INR'ye Ulaşma Yüzdesinin Belirlenmesi

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ÖZET

Amaç: Varfarin tromboembolik hastalıkların tedavisinde ve profilaksisinde en sık kullanılan oral antikoagülandır. Trombozun oluşmasını engellerken aynı zamanda hemorajik komplikasyonlardan kaçınmak için hastanın Uluslararası Normalleştirilmiş Oranı (INR) endikasyonuna göre belirli aralıkta tutulur ve belirli aralıklarla takip edilir. Bizim çalışmamızdaki amacımız çeşitli endikasyonlarda varfarin kullanan hastaların hedef INR değerlerine ulaşma yüzdesinin saptanmasıdır.

Yöntem: Çalışmamıza hastanemize Mayıs 2023 ile Kasım 2023 tarihleri arasında İç Hastalıkları polikliniğine çeşitli endikasyonlar sebebiyle varfarin kullanan hastalar dahil edilmiş ve retrospektif olarak taranarak INR sonuçları kayıt altına alınmıştır.

Bulgular: Toplam 130 hasta ile çalışma grubu oluşturulmuştur. Metalik kalp kapak replasmanı, AF, PTE ve SVH nedeniyle varfarin kullanan hastalar ayrı ayrı hedef INR değerine göre değerlendirilmiştir. Metalik kalp kapak replasmanlı hastaların hedef INR'ye ulaşma yüzdesi %38,5 (n: 27) olarak, AF, PTE ve SVH'li hastaların hedef INR'lerine ulaşma yüzdeleri sırasıyla %40 (n:16), %54 (n:7), %70 (n:5) olarak tespit edildi. Tüm çalışma grubu göz önüne alındığında ise hedef INR'ye ulaşma yüzdesi %42 (n:55) olarak hesaplandı.

Sonuç: Sonuç olarak varfarinin terapötik aralıkta bulunmaması ciddi morbidite ve mortaliteye yol açmaktadır. Çalışmamızda hedef INR'ye ulaşan hasta yüzdesi %42 olarak saptanmıştır. Bu yüzde çok düşük olup, bu oranı artırmak için hasta farkındalığının artırılması, hastaların takip sıklığının artırılması ve daha etkili takip stratejileri geliştirilmesi gerekmektedir.

Anahtar Kelimeler: Varfarin, INR, Kanama, Tromboz

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Introduction

Warfarin, a vitamin K antagonist, is used as an oral anticoagulant for primary and secondary antithrombotic prophylaxis.¹ The anticoagulant effect of warfarin is due to its structural similarity to vitamin K. It achieves this effect by inhibiting vitamin K epoxide reductase, the enzyme that converts vitamin K epoxide back into vitamin K. Thus, an anticoagulant effect is achieved by reducing the amount of active vitamin K available for the activation of clotting factors II, VII, IX and X.² The anticoagulation effectiveness of vitamin K antagonists is monitored by the international normalized ratio (INR). The INR is kept within a determined therapeutic range for the balance between preventing thromboembolic events and preventing hemorrhagic complications.³ In diseases such as atrial fibrillation (AF) and venous thromboembolism (VTE), the INR is targeted to be 2-3. Many high-quality randomized studies have shown that aiming for a lower INR target range, such as 1.5-2, provides inadequate protection against thromboembolism without any reduction in major bleeding rates.⁴ In addition, patients with mechanical heart valves must use anticoagulants for life to protect themselves from thromboembolic complications. Considering the patient's valve and risk status, the INR value is desired to be between 2.5-3.5. Therefore, clinically stable patients are usually monitored with INR every 4-6 weeks, and unstable patients are monitored with INR at shorter intervals such as every week or every few days.⁵ Studies have shown that even patients with very careful and optimal follow-up have difficulty reaching therapeutic INR. The reasons for this difficulty in reaching the target INR are many actors have been shown, such as inadequate compliance with warfarin treatment, irregularity in dietary vitamin K intake, interaction with other drugs, and genetic differences between patients.⁶

Our study aimed to determine the percentage of patients using warfarin for various indications reaching target INR values.

Material and Method

In our study, the INR results of patients who came to our hospital for INR monitoring due to warfarin use at the Internal Medicine outpatient clinic between May 2023 and November 2023 were scanned using the hospital information management system. Ethics committee approval was obtained before the study. Patients using warfarin due to indications such as metallic heart valve replacement, AF, cerebrovascular disease (CVD), pulmonary embolism (PTE) were included in

our study. The patients included in the study were selected from patients using warfarin for more than 6 months and were recorded based on the last INR value during follow-up. A study group was formed with 130 patients who met these criteria.

Previously studied INR results due to warfarin use were scanned and recorded. Target INR value of the patients included in the study; It was evaluated as 2.5-3.5 in patients with mechanical prosthetic valves, and as 2.0-3.0 in patients with AF, PTE, deep vein thrombosis and CVD. Then, the percentages of patients whose results were at the target INR value were calculated according to the indication for warfarin use. Analysis of study data was performed using Statistical Package for Social Sciences (SPSS) software, Version 25.0 (Armonk, NY: IBM Corp.) on Mac OS. Demographic and clinical characteristics of the participants were examined with descriptive statistical analyzes such as numerical, percentage, mean and standard deviation. Chi-square test was used to evaluate the relationship between categorical variables. The Kolmogorov-Smirnov test was preferred to determine the suitability of the data for normal distribution. Independent samples t test was applied to evaluate the difference between independent variables that were suitable for normal distribution. $p < 0.05$ was considered significant.

Results

130 patients who were followed up due to warfarin use in the Internal Medicine outpatient clinic were included in the study. While 54% (n:70) of these patients were women, 46% (n:60) were men. The average age was calculated as 63.93 ± 12.78 (range 20-90). The average INR of the study group was determined as 3.15 ± 1.31 (1.4-9.81 INR range). Indications for warfarin use in the patients included in the study were metallic heart valve replacement, AF, CVD and PTE. The number of patients and percentages of these indications are shown in Table 1.

The percentage of patients with metallic heart valve replacement reaching the target INR value of 2.5-3.5 was calculated as 38.5% (n: 27). The percentages of patients with AF, PTE and CVD reaching their target INR values of 2-3 were calculated as 40% (n:16), 54% (n:7), 70% (n:5), respectively. Considering the entire study group, the percentage of reaching the target INR was calculated as 42% (n: 55). The percentages of reaching the target INR by indication and the percentages of patients with subtherapeutic and supratherapeutic INR are shown in Table 2.

No statistically significant difference was detected in reaching the target INR according to the indications. ($p > 0.05$)

Table 1. Percentages and numbers of patients using warfarin according to indication

Indication	%	Number (n)
Metallic Heart Valve Replacement	54	70
AF	30.7	40
PTE	10	13
CVD	5.3	7

Table 2. Percentages of reaching target INR by indication

Indication	Target INR	Subtherapeutics	Supratherapeutics
Metallic Heart Valve Replacement	38.5% (n:27)	33% (n: 23)	28.5% (n:20)
AF	40% (n:16)	15% (n:6)	45% (n:18)
PTE	54% (n:7)	8% (n:1)	38% (n:5)
CVD	70% (n:5)	15% (n:1)	15% (n:1)
Total	42% (n:55)	24% (n:31)	34% (n:44)

Discussion

Warfarin is the most commonly used oral anticoagulant in the treatment and prophylaxis of thromboembolic diseases. In order to prevent thrombosis and to avoid hemorrhagic complications, the patient's INR should be kept within a certain range according to the indication. Therefore, warfarin has a narrow therapeutic range and the drug has a complex dose-response relationship that makes safe and effective use difficult. Considering the interactions of warfarin with other drugs and foods and genetic differences, careful INR monitoring and treatment management are required, especially in elderly patients.⁷

In a multicenter, prospective study with 4987 patients, patients using warfarin for various indications were included in the study and the awareness of these patients, time in therapeutic range (TTR) and safety of warfarin treatment were investigated. The indications for using warfarin were mechanical valve in 42.6%, AF in 38.4%, and other warfarin indications in 19%. It was observed that awareness of warfarin decreased in older age groups, and it was determined that only patients with knowledge about food-drug interactions of warfarin constituted 55% of the study group. People with higher warfarin awareness were observed to have higher TTR levels. In this study, 70.9% of INRs were above the therapeutic range, 24.6% were in the therapeutic range, and 4.6% were below the therapeutic range. As a result of the study, the patients' average TTR rates and awareness of warfarin treatment were found to be low, and it was thought that the reason for the low TTR might be due to food-drug interactions of warfarin, in sufficient awareness of patients about warfarin, and the high rate of comorbidities. In our study, INR was found to be 42% in the therapeutic range, and similar to this study, it is note worthy that the percentage of patients in the target INR was low.⁸

In a study conducted with a large patient group consisting of 29,717 AF and 19,113 VTE patients, it was observed that 43% of patients with AF and 36% of patients with VTE could reach the target INR. In this study, attention was drawn to the low level of reaching the target INR and it was stated that closer monitoring or innovative strategies were needed to optimize the results of oral anticoagulant treatment.⁹

In another study, the percentages of patients using warfarin for various indications reaching the effective INR were calculated and it was observed that 47.6% of the

patients had an effective INR. In this study, it was emphasized that INR should be monitored more frequently, taking into account other medications used by the patients and their nutritional habits.¹⁰

In a study where the optimal INR range was taken as 2-3, the percentage of patients in the target INR range was determined as 50%. However, in this study, the therapeutic INR range was determined as 2-3 for all indications, and accordingly, the percentage of patients in different indications reaching the target INR was not determined. In addition, in this study, the INR range with the lowest risk of bleeding and thromboembolic events due to warfarin was determined as 1.8-2.4, a result different from the literature.¹¹

In some studies conducted with patients with AF, the percentage of reaching the target INR was found to be 61-70%.^{12,13} In our study, this was found to be 40%. The percentage of patients reaching the target in the above-mentioned studies is different from the literature, and it is thought that the reason why it is high is that the studies are prospective and are carried out in the form of clinical trials, resulting in better and more effective follow-up.

In a meta-analysis, it was stated that the percentage of patients using warfarin reaching the target INR varied between 58% and 68%, depending on the median follow-up period. In this meta-analysis, warfarin was compared with new oral anticoagulants; New oral anticoagulants have been reported to have a favorable risk-benefit profile. New oral anticoagulants have been shown to have significant reductions in stroke, intracranial bleeding and mortality, but it has been emphasized that, similar to warfarin, they cause major bleeding and increase gastrointestinal bleeding. The advantage of this drug group is that it is more effective than warfarin, especially in stroke, and there is no need for INR monitoring, unlike warfarin. However, it has been stated that there is no clear superiority over warfarin in other indications, and much more experience and studies are needed for this group of drugs.¹⁴

In other studies in the literature, the percentage of reaching the target INR was found to be between 36.5-54%.¹⁵⁻¹⁷ In our study, the percentage of reaching the target INR was found to be 42% in the total patient group, and when considered on the basis of indication, it was found to be 38.5% in patients with valve replacement, 40% in patients with AF, 54% in PTE patients and 70% in CVD patients. Although the results obtained from our study are generally compatible with the literature, the

percentage of reaching the target INR was found to be low, especially compared to studies conducted with prospective and clinical follow-up. The limitations of our study are that the number of patients diagnosed with PTE and CVD is small and that the factors affecting reaching the target INR, patient awareness and TTR cannot be determined due to the fact that our study is retrospective.

Conclusion

As a result, warfarin is a very frequently used drug today, and while the risk of thromboembolic events increases in patients with INR in the subtherapeutic range, serious bleeding is observed in cases with supratherapeutic INR. This causes serious morbidity and mortality. In our study, the percentage of patients reaching the target INR was found to be 42%. This rate is very low for such an important disease group, and in order to increase this rate, it is necessary to increase patient awareness, increase the frequency of follow-up of patients and develop more effective follow-up strategies.

Conflicts of Interest

There are no conflicts of interest in this work.

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