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Does the Timing of Warfarin Ingestion Affect the Time in Therapeutic Range in Patients with Metallic Prosthetic Valve?

Varfarin Kullanım Zamanı Metalik Protez Kapaklı Hastalarda Terapötik Aralıktaki Zaman Yüzdesini Etkiler Mi?

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Abstract

Aim: Warfarin as the only approved oral agent to provide anticoagulation in patients with metallic prosthetic valves is a vitamin K antagonistt. Since effectively initiating and maintaining anticoagulation is challenging due to various factors, those patients undergo frequent periodic INR testing. We sought to investigate the effect of timing of warfarin intake on anticoagulation stability.

Material and Method: A total of 60 patients with metallic prosthetic valves were included in the study. Patients were informed to take warfarin between 7:30 and 08:00 P.M during the first month, and then to take warfarin between 09:30 and 10:00 A.M during the second month. All the patients were evaluated with INR monitoring once every 15 days during the follow-up period. The time in therapeutic range (TTR) values for the first month and second month (referred to as 'first TTR' and 'second TTR', respectively) were calculated separately using the Rosendaal method.

Results: The mean age (±SD) of the patients was 59.6±9.6 years and 36.7% (n=22) were male. There was no significant difference between the first TTR (in the month when warfarin ingested in the evening) and second TTR(in the month when warfarin ingested in the morning) values of our study group (66.23±40.7% vs 64.12±41.13%, p=0.783). The mean INR value in the first month was found to be significantly lower according to the value in the second month (2.73±0.53 vs 3.06±0.47, p=0.001).

Conclusion: The study results showed that the timing of warfarin ingestion did not affect the stability of anticoagulation despite the higher INR values achieved with a morning dose of warfarin,indicating evening warfarin ingestion is not a necessity.

Keywords: Warfarin, international normalized ratio, pharmacokinetic

Öz

Amaç: K vitamin antagonisti olan Varfarin metalik kalp kapaklı hastalarda onaylanmış oral antikoagulan tedavidir. Etkin antikoagulan tedaviyi sürdürmeyi zorlayan birçok faktör nedeniyle bu hastaların sık aralıklarla INR takibine alınması önerilmektedir. Bu çalışmanın amacı varfarin kullanma zamanının antikoagulasyona etkisi olup olmadığını araştırmaktır.

Gereç ve Yöntem: Metalik protez kapaklı toplam 60 hasta çalışmaya dahil edildi. Tüm hastalara ilk ayda varfarini saat 19:30 -20:00 arasında, ikinci ayda saat 09:30 ve 10:00 arasında alması söylendi .Hastalardan takip süresinde 15 günde bir INR ölçümü yapıldı. Birinci ve ikinci ay terapötik aralıktaki zaman yüzdesi (TTR) değerleri (sırasıyla birinci ve ikinci TTR) Rosendaal metoduyla hesaplandı.

Bulgular : Ortalama yaş 59.6±9.6 yıldı.%36,7'si (n:22) erkekti. Warfarinin gece alındığı ayda hesaplanan birinci TTR ile ve warfarinin gündüz alındığı ayda hesaplanan ikinci TTR değerleri arasında anlamlı fark bulunmadı (66.23±40.7% vs 64.12±41.13%, p=0.783). Birinci aydaki ortalama INR değeri ikinci aydakinden anlamlı olarak daha düşüktü (2.73±0.53 vs 3.06±0.47, p=0.001).

Sonuç: Çalışma sonuçları varfarin kullanma periyodunun etkin antikoagulasyon sağlanan toplam zamana bir etkisi olmadığını göstermiştir. Bunun birlikte sabah varfarin kullanımı daha yüksek INR değerlerine neden olmaktadır. Çalışmada akşam warfarin alımının bir zorunluluk olmadığına işaret edilmiştir.

Anahtar Kelimeler: Warfarin, uluslararası normalleştirilmiş oran, farmakokinetik

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INTRODUCTION

Warfarin, a vitamin K antagonist, is the only approved oral agent to provide anticoagulation in patients with a metallic prosthetic valve. Warfarin significantly reduces the risk of thromboembolic events such as stroke and pulmonary embolism. The effective initiation and maintenance of anticoagulation can be challenging depending on the variability of serum warfarin concentrations that is susceptible to the person's metabolic status, diet, and additional drugs used.[1-5] Because of the metallic prosthetic valve-related problems ,e.g, lifelong treatment, absence of an alternative treatment such as non-vitamin K antagonist oral anticoagulants (NOAC), lifelong risk of fatal prosthetic valve thrombosis and thromboembolism, effective anticoagulan therapy becomes mainstay in this population.[6]

The safety and efficacy of warfarin is assessed by measuring the international normalized ratio (INR). Desired therapeutic range of INR is determined by prosthetic valve type. In current guidelines, the therapeutic range is between 2-3 for Aortic Valve Replacement (AVR) and between 2.5-3.5 for Mitral Valve Replacement (MVR).[7] The time in therapeutic range (TTR) is a parameter which defines what percentage of total follow-up time is within the therapeutic range. A TTR value of ≥70% indicates both effective and safe anticoagulation.[8-10]

The aim of this study was to investigate whether or not the time period (morning vs evening) to ingest warfarin affects TTR and INR values in patients with a metallic prosthetic valve.

MATERIAL AND METHOD

Ethics Committee Approval

The study was approved by a local clinical research ethics committee with the decision number 2011-KAEK-25 2020/02-08 dated February 5, 2020.The study was initiated just after obtaining approval from the ethics committee.

Study Design

The study was prospective in design and conducted in a single center. Patients with metallic prosthetic valves who visited the outpatients clinics for INR testing between March 1, 2020 and May 31, 2020 were identified. The study inclusion criteria were defined as age >18 years, and having undergone INR testing at least once a month during the last six months. Patients were excluded from the study if warfarin had been discontinued due to any indication during the last six months. After implementing the criteria, 70 patients were eligible for the study. Informed consent was obtained from all those patients.

As stated above, the therapeutic ranges of INR were determined as between 2 and 3 for Aortic Valve Replacement (AVR) and between 2.5-3.5 for Mitral Valve Replacement (MVR). The TTR values were calculated using the Rosendaal Method.The Rosendaal method is a computer based linear interpolation method which assumes there is a linear decrease or increase between two measured INR values. It determines an INR value for each day between those two INRs and calculates TTR using all measured and determined INRs in the follow up period.[11] Baseline TTR was calculated from the last two INR values for each patient. INR testing was performed every 15 days throughout the 2-month follow-up period. There was no patients who had a INR test before 15 days. The INR levels were measured from blood samples taken at 09:00 A.M. The patients were instructed to take warfarin between 7:30 P.M and 08:00 P.M in the first month of the study, then between 09:30 A.M and 10:00 A.M for the second month. The patients were assessed for any symptoms and newly used drugs at each INR testing. Finally, the TTR values for the first month and second month (referred to as 'first TTR' and 'second TTR') were calculated separately.

A further 10 patients were excluded from the study; 4 because the calculated TTR values were <40%, 1 because of gastrointestinal bleeding in the first week, and 5 because of a significant change in weekly tablet use. Therefore, the study was completed with 60 patients.

The INR Measurement Procedure

Blood samples were withdrawn from any vein in the forearm into 2 ml sodium citrate tubes, then the samples were centrifuged at 5000 rpm for 10 minutes. INR analysis was performed using a Sysmex CS-5100 model device with Dade Actin FS Activated PTT reagent and thromborel reagent.

Data obtained in the study were analyzed statistically using SPSS version 22.0 software (IBM-SPSS Inc., Armonk, NY, USA). The Shapiro Wilk test was used to evaluate whether the variables conformed to normal distribution. The descriptive statistics used to report demographic data were expressed as mean±standard deviation values for normally distributed continuous variables and as number and percentage for categorical variables. To conduct the comparisons between two groups based on gender (male /female), the independent sample t-test was used for continuous variables and the chi squared test was used for categorical variables. The Paired Samples t-test was used to compare the calculated variables (TTR, INR and number of tablets per week). A value of $p<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Our group comprised 38 (63.3%) females and 22 (36.7%) males with a mean age of 59.6±9.6 years. The study population consisted of 15 (25%) patients with AVR, 35 (58.3%) with MVR, and 10 (16.7%) with AVR+MVR. In the echocardiographic examinations of the patients, left ventricle ejection fraction (LVEF) of <50% was determined in 16 (26.7%) patients. Atrial fibrillation was observed in 13 (21.7%) patients. It was stated by 55 (91.6%) patients that warfarin use was in the evening hours. The demographic and clinical characteristics of the patients, and medications used are shown in **Table 1**.

Table 1: Demographic and Clinic Characteristics of the Patients

Study population (n=60)	
Age, Years (mean±SD)	59.62±9.67
Sex, n (%)	
Male	22 (36.7%)
Female	38 (63.3%)
Diabetes, n (%)	6 (10%)
Hypertension, n (%)	15 (25%)
Smokers, n (%)	6 (10%)
Coronary artery disease, n (%)	8 (13.3%)
LVEF (%)	
>%50	44 (73.3%)
%50-%40	15 (25%)
<%40	1 (1.7%)
Atrial fibrillation, n (%)	13 (21.7%)
BMI (kg/m²) (mean±SD)	
Male	25±2.2
Female	26.6±3.9
Medications, n (%)	
Aspirin	14 (23.3%)
NSAI	8 (13.3%)
Antibiotic	3 (5%)
Basal TTR value, % (mean±SD)	69.98±24
Weekly warfarin tablet (5mg) use (mean±SD)	6.38±2.45
Duration of warfarin , year (mean±SD)	9.9±6.6

BMI: Body mass index, LVEF: Left ventricular ejection fraction, NSAI: Nonsteroidal anti-inflammatory, TTR: Time in therapeutic range

The mean number of warfarin tablets (5mg) used in a week was determined as 6.38±2.45, and the mean duration of warfarin use was 9.9±3.6 years (Table 1).

The mean age of the female patients was significantly lower than that of male patients (56.8±8.7 years vs 64.4±9.5 years, p=0.004). The female patients had lower mean systolic blood pressure values than the males (118.29±11.5 vs 128.18±13, p=0.005). The mean second TTR was higher in the male patients than in the female patients (82.68+23.0 % vs 56.71+45.5 % p:0.005). The comparisons of the characteristics based on gender are shown in **Table 2**.

The mean baseline TTR value was calculated as 69.98±24.4%. The mean baseline INR value (the mean of the last two INR values) was 2.77±0.7. There was no significant difference between the mean TTR value in the first month (first TTR) and the mean TTR value in the second month (second TTR) (64.12%±31% vs 66.23%±30%, p: 0.783). The mean INR value in the first month was determined to be significantly lower than the mean INR value in the second month(2.73±0.53 vs 3.06±0.4, p:<0.001). The number of tablets taken weekly was seen to be similar in both months (6.39±2.3 vs 6.43±2.46, p: 0.070) (**Table 3**).

Table 2. Comparisons of the Demographic and Clinic Characteristics based on gender

	Female (n=38)	Male (n=22)	p value
Age, year mean±SD	56.8±8.7	64.4±9.5	0.004
SBP, mmhg mean±SD	118.29±11.5	128.18 ±13	0.005
DBP, mmHg mean±SD	75.53 ±8.1	79.55±8.5	0.082
Heart rate bpm , mean±SD	77.7±6.9	74.3±8.5	0.007
Duration of warfarin, years (mean±SD)	9.53±6.7	7.77±6.3	0.321
HT, n (%)	9 (23.7%)	6 (27.3%)	0.757
DM, n (%)	4 (10.5%)	2 (9.1%)	0.858
CAD, n (%)	5 (13.2%)	3 (13.6%)	0.958
AF, n (%)	6 (15.8%)	7 (31.8%)	0.146
Smoking, n (%)	2 (5.3%)	4 (18.2%)	0.108
BMI kg/m2 ,mean±SD	26.6±3.9	25.0±2.2	0.056
Weekly warfarin tablet (5mg) use (mean±SD)	6.39±2.3	6.3±2.24	0.909
Baseline TTR , % mean±SD	71.6+21.1	67.9+29.5	0.529
First TTR, % mean±SD	63.37+41.8	65.41+41.2	0.855
Second TTR % mean±SD	56.71+45.5	82.68+23.0	0.005
Baseline INR mean±SD	2.78+0.74	2.75+0.86	0.884
INR in the first month mean±SD	2.73+0.5	2.74+0.5	0.942
MVR N (%)	12 (20%)	23 (38.3%)	0.215
AVR N(%)	8 (13.3%)	7 (11.7%)	0.215
MVR+ AVR N(%)	2 (3.3%)	8 (13.3%)	0.215

AF:Atrial fibrillation, AVR: Aort valve replacement ,BMI: Body mass index , CAD:Coronary heart disease ,DBP: Diastolic blood pressure , DM: Diabetes mellitus, HT:Hypertension,MVR: Mitral valve replacement SBP: Systolic blood pressure ,TTR : Time in therapeutic range

DISCUSSION

The aim of this study was to investigate the effect of timing of warfarin intake on anticoagulation stability based on TTR and INR values in patients with a metallic prosthetic valve. The mean INR values of the patients were found to be significantly higher when warfarin ingestion occured in the morning. Although there was no difference in the calculated TTR values between morning and evening warfarin ingestion, it was observed that male patients had better TTR values with morning warfarin use according to the female patients.

Since most of the patients were already taking warfarin in the evening, it was not suprising that there was no significant difference between the baseline TTR and the first TTR.

The mean baseline TTR (69.98%±24.4) in this study was higher than the mean TTR reported in the study of Yee Tan et al.[12] (57.11%) and that in the study of Boonyawat et al.[13] (54.6%). This difference could be attributed to the use of more INR values to calculate TTR than in those previous studies.

Table 3: Comparison of INR and TTR values in morning and evening ingestion

	Basal measurement	Evening ingestion	Morning ingestion	Basal measurement vs Evening ingestion (p value)	Evening ingestion vs Morning ingestion (p value)
INR, mean±SD	2.77±0.7	2.73±0.53	3.06±0.4	0.709	<0.001
TTR, % (mean±SD)	69.98±24.4	64.12±41	66.23±40	0.312	0.783
Number of tablets per week, mean±SD	6.40±2.3	6.39±2.3	6.43±2.46	0.990	0.070

TTR: Time in therapeutic range, SD: Standard deviation

The current study consisted of a younger population compared to the Influence of Duration of Warfarin Administration on Anticoagulation Stability (INRange) study designed by Garrison et al.[14] in which the mean age was 73 years. In addition, the rate of left ventricle ejection fraction (LVEF) of ≥50% was found to be higher in the current study. The fact that younger people and patients with higher LVEF values constitute the current study population, unlike other studies, may be due to rheumatic valve disease, which is one of the most common indications for prosthetic valve surgery in Turkey.[15] Acute rheumatic fever (ARF), which affects children and adolescents, remains the leading cause of rheumatic valve diseases in Turkey.[16] Since the patient population in this study was younger than the patients included in other prosthetic valve studies, the rates of hypertension, diabetes and coronary artery disease were found to be quite low.

Although patients are generally advised to take warfarin in the evening, it is not clear whether the timing of warfarin ingestion changes the level of anticoagulation. In an extensive literature search (PubMed search for warfarin [MESH] and filtering for clinical trials), none of the 1,642 articles examined the effect of warfarin administration time on TTR. In the INRange study, current warfarin users were randomly assigned to use warfarin in the evening or morning. When compared to the baseline values, the changes in the TTR values were not statistically significant in both groups defined according to warfarin timing (morning or evening). Different from our study, they included patients using warfarin for any indication. The indications for warfarin use are primarily AF, followed by deep vein thrombosis and pulmonary embolism. Since warfarin interacts with the patient's general condition and any comorbidities, such a heterogenity in the study population might have affected the results. The therapeutic INR range was determined as 2 – 3 for most of the patients in that study, which may explain the higher mean TTR value (72.2%) observed.[13] The design of the current study differed from the INR range study as both morning and evening warfarin administration was applied to a single population in order to minimize the effect of the confounding variables. Moreover, the study was completed within the 3-month period of March-April-May to minimize the effect of seasonal changes on diet and metabolism. When the demographic characteristics of the study populations were examined, no significant difference was found between the two studies in the amount of daily warfarin use and the baseline TTR values were observed to be similar in both studies.

Mean second TTR (in the month when warfarin ingested in the morning) was higher in males than the females in our study. Findings regarding the effect of gender was similar to the results of the study of Averello et al.[17] However,it should be emphasized that their study was retrospective in design including the patients taking vitamin K antagonists (VKA) - either acenocoumarol or warfarin-regardless of VKA ingesting time.

The pharmacokinetic/pharmacodynamic characteristics of warfarin such as having a very long half life (approximately 35 hours) and having very small fluctuation in plasma concentration after ingestion may explain why the change in the warfarin ingestion time did not affect TTR.[18]

There were some limitations to this study, primarily the relatively low number of participants. A second limitation was that many confounding factors such as diet were not evaluated. 2 month period may be a bit short to optimize TTR. Finally, since the Rosendaal method of TTR calculation is based on linear change between consecutive INR checks, more than two INR visits might be required to be able to obtain more reliable TTR values.

CONCLUSION

The results of this study demonstrated that INR values were significantly higher when warfarin ingestion occurred in the morning in patients with a metallic prosthetic valve. However , no significant difference was observed in TTR after a change in warfarin ingestion time. The study has highlighted that evening warfarin ingestion is not a necessity and morning warfarin ingestion may be offered to patients with INR levels below the target range. Future research is needed to confirm those results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital Ethics Committee (Date: 05.02.2020, Decision No: 2011-KAEK-25 2020/02-08) .

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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