The Effect of COVID-19 Pandemic on Time in Therapeutic Range in Patients Using Warfarin

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Abstract

Introduction: Patients receiving anticoagulant therapy experience a serious problem at a time when the rates of outpatient visits for the international normalized ratio (INR) monitoring are gradually decreasing owing to the risk of virus transmission during the pandemic. The aim of this multicenter study was to investigate how the coronavirus disease 2019 pandemic affected the time in therapeutic range (TTR) value, which shows the use of effective doses of warfarin, and its monitoring in patients using warfarin. **Materials and Methods:** A total of 158 patients with 3 consecutive prepandemic INR levels and at least 3 postpandemic INR levels without time limitation were retrospectively evaluated. TTR values were calculated and the preepidemic and postepidemic values were compared. TTR was obtained using the conventional method. **Results:** The mean preepidemic and postepidemic TTR values were found to be 64.4 (61.8%–67.0%) and 34.9 (30.8%–39.0%), respectively. TTR rate was statistically significantly lower in the postpandemic period than in the prepandemic period ($P < 0.001$). While the prepandemic TTR of 68 (43%) patients was <60, the postpandemic TTR of 125 (79%) patients was <60. **Discussion and Conclusion:** Patients using warfarin were found to have lower TTR values during the pandemic. One of the most important reasons for this result is patients' delayed admission to the hospital due to fear of infection. The importance of regular follow-ups and alternative solutions should be emphasized for the effective treatment of these patients.

Keywords: COVID-19, ınternational normalized ratio, prothrombin time, time in therapeutic range, warfarin

Introduction

In late 2019, a type of virus that was found to cause pneumonia was identified in Wuhan City, Hubei Province of China. This virus was defined as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and in February 2020, the disease was named coronavirus disease 2019 (COVID-19) by the World Health Organization. It became a serious public health issue and was considered a pandemic in a short period. Due to the significant differences in surveillance, diagnostic tests, and practices worldwide, it is thought that there are more cases of COVID-19 than the number of detectable COVID-19 cases.

[1] While the medical community was directing their studies and health-care services to this problem in this period, the care and follow-up of patients with chronic diseases could have been endangered.[2] The importance and awareness of social distancing to prevent the spread of COVID-19 are increasing. Especially in his past medical history; patients with prosthetic heart valves, atrial fibrillation, and thromboembolism use warfarin. The international normalized ratio (INR) is of great

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importance for the follow-up of these patients, and routine follow-up requires regular contact. Data obtained from clinical studies show that even in a controlled study environment with adequate monitoring and follow-up and special study nurses, the time in therapeutic range (TTR) values achieved by patients are between 55% and 64%.[3,4] Moreover, a large retrospective cohort study of more than 50,000 patients with atrial fibrillation who were on warfarin showed that only 40,570 patients had adequate INR results to assess TTR, and less than half (41%) of these patients had a TTR value ≥65%.[5] Some studies have also demonstrated the importance of providing service options such as telehealth to maintain social distance while continuing the management of chronic diseases, including the management of anticoagulant therapy.[2,6,7] In a period when the importance of social distance is increasing and the rate of outpatient visits for INR monitoring is decreasing due to the risk of virus transmission, patients receiving anticoagulant therapy experience a serious problem.

The aim of this multicenter study was to investigate how the COVID-19 pandemic affected the TTR value, which shows the use of effective doses of warfarin, and its monitoring in patients using warfarin.

MATERIALS AND METHODS

While patients were included in the study; they were selected from outpatient clinic applications from four different centers in Turkey and in a single geographical region between May 1 and July 30, 2020. One hundred and eighty-five patients using warfarin for any reason were reviewed retrospectively. Patients were selected sequentially. INR levels and other laboratory parameters of patients were recorded. Prepandemic INR levels and other laboratory parameters of the same patients between May 1 and July 30, 2019, were recorded. Demographic and clinical characteristics of the selected patients, and the reason for using warfarin were obtained from the hospital registry system. Exclusion criteria were as follows: younger than 18 years old, using warfarin less than 2 years, patients with no follow-up data, pregnancy, patients on routine hemodialysis, and active malignancies. In the prepandemic period, 3 consecutive INR levels were recorded at the time of admission to the hospital at periodic intervals of 2 or 3 weeks. In the pandemic period, admissions to hospitals were somewhat less frequent. Furthermore, according to the course of the pandemic, admissions to hospitals were irregular. Therefore, INR levels could not be reported at frequent and regular periodic intervals. During the pandemic period, the 3 INR levels obtained during the time the study was determined were recorded. One hundred and fifty-eight patients who met the criteria were included in the study. Twenty-seven patients were excluded from the study. TTR values were calculated and the prepandemic and postpandemic values were compared. Percentage of time in the therapeutic INR range was calculated according to the Rosendaal method, assuming changes between consecutive INR measurements were linear with time.[8] The study was conducted in accordance with the principles of the Helsinki Declaration (2013) and the study protocol was approved by the local ethics committee.

Statistical analysis

IBM SPSS version 24.0 software package was used for analyses. The histogram and Shapiro–Wilk test were used to confirm the normal distribution of the data. Baseline continuous variables were presented as mean ± standard deviations or median and first and third quartiles (Q1-Q3) depending on the distribution of data. Wilcoxon test was used for two measurements of dependent variables. Categorical variables were expressed as frequency and percentage. A $P < 0.05$ was considered statistically significant for all tests.

RESULTS

The mean age of 158 patients included in the study was 52.6 ± 14.3 years, and 87 (55.1%) of them were females. Forty-three patients (27.2%) were receiving warfarin therapy for AVR, 52 patients (32.9%) for MVR, 15 patients (9.5%) for aortic valve replacement + mitral valve replacement (AVR + MVR), 3 patients for deep vein thrombosis, 3 patients for pulmonary embolism, 36 patients for atrial fibrillation, and 6 patients for other reasons [Table 1]. The mean prepandemic and postpandemic TTR were found to be 64.4 (61.8%–67.0%) and 34.9 (30.8%–39.0%), respectively. TTR rate was statistically significantly lower in the postpandemic period than in the prepandemic period ($P < 0.001$). While the prepandemic TTR of 68 (43%) patients was <60, postpandemic TTR of 125 (79%) patients was <60. There was no statistically significant difference between the patients' prepandemic and postpandemic glucose, creatinine, aspartate transaminase, alanine transaminase, leukocyte, hematocrit, platelet, albumin, and lactate dehydrogenase values [Table 2].

DISCUSSION

In this study, we examined the effect of the COVID-19 pandemic on TTR rates of patients with chronic warfarin use who presented to the outpatient clinics of 5 different health institutions. We found that patients had significantly lower TTR rates during the pandemic period compared to the prepandemic period. We are of the opinion that the most important reason for this result is the fear of viral transmission, national restrictions, and changing health-care priorities during the pandemic period, which affected outpatient visits. In a recent study by Emren *et al*., they found the mean TTR value during the COVID-19 pandemic to be significantly lower than during the pre-COVID-19 pandemic period. Furthermore, in this study, the vast majority of patients did not seek medical help even in case of bleeding.[9] In this respect, the results of the study also support our study. Restriction of access to care for patients in need of care with warfarin use also constituted a serious problem in this period. In addition, the change in eating habits during the pandemic, sleep, and stress disorders during the quarantine period may have also affected this situation. Furthermore, it can be thought that the lack of access

Table 1: Warfarin therapy indications and demographic data of patients

Parameters	All Patients
Age, years	52.6±14.3
Gender, *n* (%) (female-male)	87 (55.1)-71 (44.9)
MVR, *n* (%)	52 (32.9)
AVR, *n* (%)	43 (27.2)
MVR + AVR, *n* (%)	15 (9.5)
DVT + pulmonary embolism, *n* (%)	6 (3.8)
AF, *n* (%)	36 (22.8)
Other, *n* (%)	6 (3.7)

MVR: Mitral valve replacement, AVR: Aortic valve replacement, DVT: Deep vein thrombosis, AF: Atrial fibrillation

Table 2: Time in therapeutic range and other laboratory parameters of patients

	Pre-COVID-19	Post-COVID-19	*P*
TTR, %	64.4 (61.8-67.0)	34.9 (30.8-39.0)	<0.001
Glucose, mg/dl	106.7±29.8	104.3±27.5	0.677
Creatinine, mg/dL	0.83±0.5	0.81±0.5	0.321
AST, U/L	24 (19-30)	25 (21-28)	0,224
ALT, U/L	20 (15-29)	22 (19-27)	0,251
Leukocyte, 10^3/uL	8.02±2.25	7.90±2	0.152
Hematocrit	41.2±5.4	38.3±4.7	0.013
Platelet, 10^3/uL	253±71.7	249±69.5	0.183
Albumin, g/L	40±5.5	42±4.8	0.304
LDH, U/L	300±120.3	295±118.4	0.181

TTR: Time in therapeutic range, AST: Aspartate transaminase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase

to health-care services due to the spread of the COVID-19 pandemic among laboratory technicians may have led to this situation. However, we did not encounter such a problem in the centers included in the study. There was no difference in the test kit and tubes, with which INR levels were measured, between the prepandemic and postpandemic periods.

We do not have data on whether these patients were exposed to the COVID-19 virus during their follow-ups. The patients included in the study during the pandemic period might have had COVID-19 infection during the period of INR follow-up, inducing coagulopathy.[10,11] We know that warfarin is eliminated through hepatic metabolism and that acute and chronic liver diseases affect INR levels. We could not definitively exclude whether patients developed any additional liver disease during the postpandemic INR follow-up intervals. We believe that the use of prophylactic drugs that have not yet been scientifically proven, and the use of food supplements to strengthen the immune system during the pandemic and quarantine period may also interact with warfarin.

If there are no obstacles such as health policies and persuasion of the patient in such pandemic and emergency situations, switching to new generation oral anticoagulants can be considered for eligible patients. For patients who have to use warfarin, safe health-care service conditions of health centers can be supported by increasing measures such as the use of masks, social distancing, and personal hygiene. A separate unit can be established in hospitals for patients to be provided with INR monitoring service so that INR can be monitored more frequently and the time spent in health institutions can be minimized. Another solution suggestion is to take blood samples from the patients at home and carry out the INR monitoring without visiting health institutions.[12] However, we are of the opinion that it will not be effective in terms of both establishing suitable conditions for delivery and transfer of the samples to health institutions. It is important to provide telemedicine health-care services to patients in such periods. It is also important to increase the patient adherence to warfarin therapy, to inform the patients correctly and safely, and to make appointments for face-to-face meetings in health institutions in safe conditions when necessary. In our study, we attempted to determine the results of INR follow-ups and TTR rates and the reasons for the lack of follow-up in this specific patient population during the pandemic and emergency situations; however, there is a need for further studies in terms of clarification of these reasons and solution suggestions.

Study limitations

The study has several limitations. First, the study may have led to subjective and not generalizable results since it had a retrospective design and the centers where the study was conducted included a relatively small-scale geographical region and race. The fact that the data obtained in this study were based on hospital records and patient information may have led to biased and inaccurate results. Another important limitation was that TTR calculations in a short period such as 3 months may be less informative than 6-or 12-month TTRs.[13]

CONCLUSION

Patients using warfarin were found to have lower TTR values during the pandemic. One of the most important reasons for this result is patients' delayed admission to the hospital due to fear of infection. The importance of regular follow-ups and alternative solutions should be emphasized for the effective treatment of these patients as TTR rates are associated with increased bleeding or thrombosis.

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Conflicts of interest
There are no conflicts of interest.

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