İstanbul Med J 2022; 23(4): 301-5
DOI: 10.4274/imj.galenos.2022.49035

Does Previous Anti-thrombotic Use Affect the Course of Coronavirus Disease-2019?

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ABSTRACT

Introduction: Proinflammatory cytokines, produced as an immune response in severe acute respiratory syndrome-coronavirus 2 infection, activate the coagulation cascade as well. In this study, we investigated the difference in the clinical course of patients who had been already using anti-thrombotic therapy before coronavirus disease-2019 (COVID-19) for any reason compared to the group who had not.

Methods: In this retrospective, multicenter study; patients who were hospitalized between March 11 and July 1, 2020 were divided into two main groups as who had been on anti-thrombotic therapy for any indication use previously at the time of admission or who had not been on anti-thrombotic therapy at the time of admission, and their selected clinical parameters were compared.

Results: After analyzing the study population of 124 patients with a homogeneous distribution in terms of age and gender, the comparison of anti-thrombotic users and non-users showed no significant difference in hospitalization. There was a statistically significant decrease in mechanical ventilation apply rate, intensive care unit duration and mortality rate between the group using anti-thrombotic compared to the group not using it ($p<0.05$).

Conclusion: It has already been shown that COVID-19 patients are more prone to thromboembolic events as it activates the coagulation cascade with the cytokine storm it creates and thus the mortality of COVID-19 infection increases significantly. Parallel to this fact the results of our study demonstrated that using anti-thrombotic therapy for any reason may affect the bad prognosis of the disease positively.

Keywords: SARS-CoV-2, COVID-19, anti-trombotic treatments

Introduction

Coronavirus disease-2019 (COVID-19) spread rapidly worldwide and caused an inevitable pandemic. While most of the COVID-19 patients are in a mild clinical form, 6-19% of the patients develop a serious disease course (1,2). Although there has been a big obscurity about the disease, it has been getting enlightened over time and currently the pathophysiology of the disease is considered to be associated with the inflammatory cytokine storm (3-5).

Proinflammatory cytokines that are released as an immune response to infection are thought to activate the coagulation cascade as well (6). Thrombin is well known to be mainly responsible for the clot formation by activating the platelets. It provides protein kinase activator receptor accumulation with multiple cellular actions as well and primarily creates protease-activated receptor-1. The thrombin formation is under strict control of anti-thrombin 3 factors, tissue factor inhibition and protein C system and physiological and negative feedback mechanisms (6). With an increase in the inflammatory response, control mechanisms deteriorate and procoagulant-anti-coagulant balance gets impaired. As a result, microthrombus, diffuse intravascular coagulation, and thus D-dimer increase are observed. These markers indicate the poor prognostic course and severe organ failure in COVID-19 pneumonia (7,8). In the autopsy series of COVID-19 patients, deep vein, arterial, cardiac and pulmonary artery thrombosis were observed (9-12). In addition, alveolocapillary microthrombi are seen in patients with COVID-19 nine times more than that of influenza patients, suggesting that it leads to severe lung damage and hypoxemia (13).

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Cite this article as: Önur İ, Tural Önür S, Günlüoğlu G, Bingöl G, Sökücü SN, Özden Ö, Nasifov M, Bolat E, Toptaş M, Altın S. Does Previous Anti-thrombotic Use Affect the Course of Coronavirus Disease-2019? İstanbul Med J 2022; 23(4): 301-5.

Received: 20.03.2022
Accepted: 28.10.2022

Regrettably, neither anti-inflammatory drugs nor anti-coagulant drugs have sufficient studies on the course of COVID-19 disease. In our study, we investigated the prognosis of patients who had been using anti-thrombotic therapy for any reason in terms of hospital stay, intubation, and death by comparing it with the patients who had not been using that therapy.

Methods

In our study, 124 patients who were hospitalized between March and July 2020 for COVID-19 according to WHO interim guidance in 2 hospitals were retrospectively analyzed. One hospital was a training and research hospital and the other one was a private hospital, which were designated as pandemic hospitals. Forty-six patients who had been using anti-thrombotic therapy for any indication (such as a previous cerebro vascular event, cardiac arrhythmia, heart valve replacement) before hospitalization were included in the study. Acetylsalicylic acid, vitamin K antagonist, new generation oral anti-coagulant, clopidogrel and ticagrelol, which are used as anti-aggregant and anti-coagulantss, have been accepted as anti-thrombotic therapy (14). Since death was the primary endpoint of the population included in the study, the anti-thrombotic treatment group and the control group not using it were divided into those who died and those who did not. This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (approval number: 2020-03, date: 06.08.2020). Written informed consent was obtained from all patients.

The demographic data of the patients, medical histories and laboratory findings, radiological Images were retrospectively obtained through the hospital electronic information system. While taking the medical history of the patients, the drugs that they declared they used before were checked through the social security reporting and the prescription system. Hemogram data of the patients included in the study were studied with the Sysmex XT4000i device and biochemical examinations were performed with the Beckman Coulter AU2700 device in the hospital laboratory. Polymerase chain reaction were examined in the hospital laboratory where SARS-CoV-2 laboratory validation was performed. Swap samples were taken from the upper respiratory tract at the time of admission to the hospital and transported with viral transport medium to the laboratory. Whole RNA Extraction in the respiratory sample, which took 2 h, the Genmak RNA isolation kit was obtained using the Genome by the method previously described for SARS-CoV-2 (15).

Statistical Analysis

Descriptive and demographic statistics were applied for the investigated parameters and the chi-square test and Fisher's exact test were performed for categorical variables where appropriate. For group comparisons, Kolmogorov-Smirnov test was used to determine whether data were normally distributed. The Mann-Whitney U test was used due to the abnormal distribution of data. Logistic regression analysis was used to predict confounders and risk factors for COVID-19. All statistical tests were two-tailed and $p<0.05$ was considered statistically significant. The Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 21.0) was used.

Results

Our study population consists of 124 patients, whose demographic data can be appreciated in Table 1, shows a homogeneous distribution in terms of age and gender. A statistically significant difference was found in favor of those using anti-thrombotic for death ($p<0.05$) (Table 1). The rate of anti-thrombotic use is higher in the control group. In other words, the mortality rate is higher in those who do not use anti-thrombotics. Anti-thrombotic use was found to be significantly different in patients with chronic obstructive lung disease and cardiovascular disease comorbidity depending on the current comorbidity (respectively $p=0.019$ and $p=0.001$). The use of statins, angiotensin-converting enzyme (ACE)

Table 1. Comparison of demographic and clinical characteristics of anti-thrombotic users and non-users before hospitalization

Variables	Total	Anti-thrombotic (+)	Anti-thrombotic (-)	p-value
		(n=46)	(n=78)	
Age groups-No. (%)				
<30 years	4 (3.2)	1 (2.2)	3 (3.8)	0.105
30-49 years	13 (10.5)	1 (2.2)	12 (15.4)	
50-69 years	69 (55.6)	27 (58.7)	42 (53.8)	
≥70 years	38 (30.6)	17 (37.0)	21 (26.9)	
Sex - No. (%)				
Male	77 (62.1)	32 (69.6)	45 (57.7)	0.188
Female	47 (37.9)	14 (30.4)	33 (41.3)	
Group - No. (%)				
Control	69 (55.6)	33 (71.7)	36 (46.2)	0.006
Death	55 (44.4)	13 (28.3)	42 (53.8)	
Intube group - No. (%)				
Intube	46 (37.1)	10 (21.7)	36 (46.2)	0.007
Non-intube	78 (62.9)	36 (78.3)	42 (53.8)	
RT-PCR - No. (%)				
Negative	73 (60.8)	31 (68.9)	42 (56.0)	0.161
Positive	47 (39.2)	14 (31.1)	33 (44.0)	
Comorbidity - No. (%)				
COPD	22 (17.7)	13 (28.3)	9 (11.5)	0.019
HT	24 (19.4)	10 (21.7)	14 (17.9)	0.606
DM	3 (2.4)	1 (2.2)	2 (2.6)	0.891
CVD	14 (11.3)	13 (28.3)	1 (1.3)	0.001
Pneumonia	31 (25.0)	10 (21.7)	21 (26.9)	0.520
Lung cancer	5 (4.0)	1 (2.2)	4 (5.1)	0.419
Medications - No. (%)				
Statin	24 (19.4)	17 (37.0)	7 (9.0)	0.001
ACE inhibitors	12 (9.7)	8 (17.4)	4 (5.1)	0.026
Beta blockers	32 (25.8)	25 (54.3)	7 (9.0)	0.001
Hospitalisation-median (IQR)/day	9.0 (8.0)	7.5 (7.0)	10.0 (9.0)	0.053
ICU-median (IQR)/day	1.0 (6.0)	0.0 (0.0)	1.0 (10.0)	0.001

RT-PCR: Real-time polymerase chain reaction, COPD: Chronic obstructive lung disease, HT: Hypertension, DM: Diabetes mellitus, CVD: Cardiovascular disease, ACE: Angiotensin-converting enzyme, IQR: Interquartile range

inhibitors and beta blockers in patients using anti-thrombotic therapy due to their existing comorbidities during hospitalization was also significant (respectively p=0.001, p=0.026, and p=0.001). No significant difference was found in patients using anti-thrombotic compared to those who did not use them during the total length of hospital stay. However, there was a tendency for a significant difference (p=0.053). It has also been shown that ICU stay duration was significantly shorter in the anti-thrombotic drug user group (p=0.007).

A comparison of the study groups with hemograms and biochemical laboratory results can be seen in Table 2. D-dimer, troponin, ferritin, and alanine aminotransferase values were found to be statistically significantly different between two groups ($p<0.05$). These values were higher in those who did not use anti-thrombotic. These results support our prediction of COVID-19 patients who do not use anti-thrombotic s have a worse prognosis.

When we examine the logistic regression analysis results of the independent variables in Table 3, the deaths of patients using anti-thrombotic and statin were found to be less than COVID-19, and no effect of ACE inhibitor and beta blocker use was detected.

Discussion

COVID-19 pandemic caused by SARS-CoV-2 has become a disease with its numerous unknown aspects of humanity. It is thought that the progression of the disease worsens with the formation of microthrombus and thrombosis, which causes disruption of the balance between the procoagulant and anti-coagulant systems with the widespread cytokine release. We determined that the anti-thrombotic therapy used in the patient group with comorbidity in which the disease progressed worse, depending on the existing comorbidity, may affect the duration of hospitalization, intubation and the course leading to death.

Anti-phospholipid syndrome of disseminated intravascular coagulation, activation of complement cascade and formation of endothelial dysfunction as a feature of the virus, constitutes the basis of the procoagulant pathophysiology (16,17). The tropism of the SARS-CoV-2 virus to angiotensin-converting enzyme 2 found in type 2 pneumocytes causes an inflammatory cascade causing generalized pulmonary hypercoagulability (18). In our study, we believe that our inability to determine the effect of ACE inhibitors on the mortality of the disease on intubation and length of stay was due to the small sample size.

In the literature, it has been shown that systemic anti-coagulant therapy reduces the mortality of COVID-19 patients on mechanical ventilation (19). Similar to our results, Chow et al. (20) compared the patient group using aspirin up to seven days before their hospital admission with non-users and found that hospitalized patients due to COVID-19 had lower mechanical ventilation, intensive care admission and hospital mortality (20). Additionally, the potential benefits of acetylsalicylic acid in lung damage reduce interleukin-6 production, platelet-neutrophil aggregation, inflammation and increase lipoxin formation, which improves pulmonary endothelial cell function (21,22).

In a multi-center observational study by Russo et al. (23) in Italy, it has been demonstrated that pre-admission anti-thrombotic treatment did not affect acute respiratory distress syndrome (ARDS) and death due to COVID-19.

In our study, we found that while the duration of hospitalization was not associated with the use of anti-thrombotic therapy before hospitalization, it had a positive effect on intubation and mortality. We think that a larger sample size is needed to the effect of patients using anti-thrombotic therapy before hospitalization on the length of hospital stay.

It is emphasized in the relevant guidelines that patients who use ACE inhibitors or angiotensin II receptor blocker (ARBs) due to their chronic diseases, continue their current treatment even if they have COVID-19 disease (24,25). Mehta et al. (26) investigated 18,472 COVID patients and found no relationship between the use of ACE inhibitors or ARBs during the pandemic process, and the positivity of COVID-19 tests, and findings supporting the recommendations of the guidelines were found. In the secondary analyses of the same study, no significant difference

Table 2. Comparison of laboratory parameters between anti-thrombotic users and non-users before hospitalization

Variables	Total (n=124) Median (IQR)	Anti-thrombotic (+) (n=46) Median (IQR)	Anti-thrombotic (-) (n=78) Median (IQR)	p-value
D-dimer	0.92 (1.05)	0.88 (0.64)	0.94 (1.3)	0.040
Troponin	6.6 (11.7)	5.7 (10.2)	8.6 (13.3)	0.033
Ferritin	298.2 (313.05)	283.1 (245)	304.0 (290.8)	0.048
Fibribojen	484.9 (217.2)	490.5 (231.8)	483.85 (206.5)	0.248
Procalcitonin	0.1 (0.23)	0.08 (0.21)	0.1 (0.27)	0.361
Albumine	37.35 (6.25)	36.65 (5.4)	37.4 (6.5)	0.934
CRP, (mg/L)	88.45 (97.6)	88.45 (87.9)	91.5 (109.6)	0.616
WBC, (×10e3/uL)	7.93 (8.05)	7.18 (3.64)	9.13 (11.72)	0.008
Hb, (g/dL)	13.1 (2.35)	12.9 (1.8)	13.3 (2.5)	0.677
Hct, (%)	38.35 (5.55)	37.85 (4)	38.75 (6.4)	0.629
LY, (×10e3/uL)	1.14 (0.67)	1.17 (0.93)	1.12 (0.61)	0.523
LY, (%)	16.5 (13.65)	17.15 (15.0)	16.35 (13.1)	0.687
LDH, (U/L)	381.0 (199.0)	363 (209.0)	397.0 (180.0)	0.291
AST, (U/L)	39.0 (28.0)	36.5 (23.0)	40.0 (38.0)	0.143
ALT, (U/L)	25.5 (21.0)	23.0 (15.0)	32.0 (23.0)	0.012

IQR: Interquartile range, CRP: C-reactive protein, WBC: White blood cell count, Hb: Hemoglobin, Hct: Hematocrit, LY: Lymphocyte count, LY: Lymphocyte count, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 3. Logistic regression analysis of factors affecting COVID-19 death

Independent variables	OR	95% CI	p-value
Anti-thrombotic	0.338	0.155-0.737	0.001
Statin	0.347	0.127-0.947	0.001
ACE	0.598	0.170-2.101	0.423
Beta	0.571	0.248-1.319	0.190

COVID-19: Coronavirus disease-2019, OR: Odds ratio, CI: Confidence interval, ACE: Angiotensin-converting enzyme

was found in the need for mechanical ventilation in patients using ACE inhibitors or ARB compared with those who did not (26). Reynolds et al. (27) showed that, in a large-scale observational study an increase in the probability of positive test result in patients who used 5 groups of anti-hypertensive (ACE inhibitor, ARB, beta blocker, Calcium channel blocker, or thiazide diuretic) but an increase in the severity of the disease was not detected in patients with positive test results (27). In our study; in accordance with the literature, ACE I and ARB and beta blockers used for comorbidity of the patients have been shown not to increase mechanical ventilation, ICU need and mortality.

In the meta-analysis of 4 large-scale studies involving 8,990 patients, in which the effects of statin use on the development of mortality and/or serious disease in patients with COVID-19 infection was evaluated and it was shown that the use of statin significantly reduced the rate of death and serious disease by 30%. Although more information is needed on statin regimens in COVID-19, evidence has shown that medium and high-dose statin therapy is effective (28). In our study, we found that patients using statin alone had decreased mechanical ventilation, ICU need and mortality.

Study Limitations

The main limitations of our study are its retrospective nature and small sample size. We believe that the use of pre-admission anti-thrombotic therapy should be investigated in a prospective controlled study group with a larger sample size, which will help prove with a stronger level of evidence that it may affect the course of the disease.

Conclusion

It has been shown that the use of anti-platelet therapy before hospital admission does not affect the duration of hospital stay in the clinical presentation of COVID-19, but significantly affects the intubation of the patient and the death. In the pathophysiology of COVID-19 pneumonia, we think that microvascular pulmonary thrombosis supports the existence of a complex relationship between the immune-mediated inflammatory response and the activation of the coagulation system during ARDS.

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (approval number: 2020-03, date: 06.08.2020).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices: İ.Ö., S.T.Ö., G.G., G.B., S.N.S., Ö.Ö., M.N., E.B., M.T., S.A.; Concept: İ.Ö., S.A., M.T., M.N.; Design: İ.Ö., G.G., E.B., G.B.; Data Collection or Processing: M.N., G.G., S.A. M.T.; Analysis or Interpretation: S.T.Ö., E.B., S.N.S., S.A.; Writing: Ö.Ö., E.B., M.N., S.N.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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