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Prophylactic Anticoagulant Treatment Might Have an Anti-inflammatory Effect and Reduce Mortality Rates in Hospitalized COVID-19 Patients?

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ABSTRACT

Objectives: COVID-19 associated coagulopathy and prophylactic anticoagulant therapy (PAT) are ongoing topics globally. Using PAT for anti-inflammatory effect may prevent thromboembolic events (TEEs). The objective of this study was to determine the anti-inflammatory effects of PAT in hospitalized COVID-19 patients. ***Methods***: We conducted a retrospective observational study in a tertiary pandemic hospital. Patients were divided into two categories according to their PAT therapy status (PAT (+) and PAT (-)) and into three categories according to clinical features (mild: group 1; moderate: group: 2; and severe: group 3). We then evaluated laboratory parameters and clinical courses. ***Results:*** We included 662 hospitalized COVID-19 patients in this study. Enoxaparin sodium was given to all patients as PAT therapy. TEE was developed in five patients in the PAT (+) group. Pulmonary embolism developed in 3/5 patients and deep venous thrombosis in 2/5 patients. Disseminated intravascular coagulation (DIC) was detected in 54 patients in group 3. No statistically significant difference was found in 28-day mortality, development of DIC rates, intubation rates, and TEEs. ***Conclusions:*** The use of PAT in critically ill patients was not effective in reducing C-reactive protein, which is one of the biomarkers of inflammation.

Globally, research has been ongoing into the treatment of COVID-19, which has caused almost 2.1 million deaths since its declaration as a pandemic.[1] Conditions such as thrombocyte activation, inflammatory status, and endothelial dysfunction, especially in COVID-19 patients requiring hospitalization, predispose for arterial and venous thrombosis. Thromboembolic events (TEEs) have been observed with COVID-19 by various mechanisms. Possible mechanisms for TEE development are related to the binding of the virus to the angiotensin-converting enzyme 2 (ACE2) receptor and/or directly to endothelial damage. It is thought to be associated with vascular microthrombotic disease observed in sepsis (endothelial damage with complement activation and activation of the inflammatory and microthrombotic pathway) and disease-related immobilization.[2,3]

The prevalence of venous thromboembolism in COVID-19 patients is 10%–35%, and venous thromboembolism is detected up to 60% in the autopsy series.[4] There is literature stating that the picture of COVID-19 associated coagulopathy may even develop under prophylaxis and cause mortality or morbidity.[3,4] Studies have shown that mortality significantly decreases with heparin use in patients with COVID-19.[2,3] In addition to its anticoagulant effect, the role of heparin in binding inflammatory cytokines, inhibiting neutrophil chemotaxis and leukocyte migration, neutralizing positively charged peptide C5a, and sequestrating acute phase proteins have been reported.[2,4,5]

Turkey's Ministry of Health COVID-19 Diagnosis and Treatment Guidelines currently recommend thromboprophylaxis in COVID-19 patients.[6] Coagulopathy and anticoagulant treatment, which were not considered in the early days of the epidemic, have become more important. Globally, research continues on prophylactic anticoagulant treatment (PAT).[2] Comprehensive and detailed studies are still needed on this subject.

Our study aimed to determine the anti-inflammatory effectiveness of PAT therapy and compare the clinical outcomes, prognosis, and 28-day mortality rates in hospitalized COVID-19 patients.

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METHODS

We conducted a retrospective, observational study in a tertiary pandemic hospital. All the patients included in the study had positive reverse transcriptase–polymerase chain reaction (RT-PCR) results for SARS-CoV-2 virus. All hospitalized COVID-19 patients admitted between 12 March and 1 June 2020 were included in the study. PAT treatments were given according to the Turkish Ministry of Health guidelines. These guidelines did not recommend PAT treatment before the date 12 April 2020. All patients admitted before 12 April 2020 did not receive PAT, whereas those admitted after this date received PAT according to the guidelines. Thus, in our study, we selected patients who received and did not receive PAT in this way, without any intervention.

Patients were divided into three groups according to clinical features (mild, moderate, and severe). The groups' selection was made according to the clinical findings at the time of first admission, radiological findings (according to the involvement rate), and the place they were hospitalized (wards or intensive care unit (ICU)). No intervention was made.

Group 1 was patients with mild symptoms of viral upper respiratory tract infection or parenchymal infiltration (< 50.0%) at thorax computed tomography (CT), but with a normal O_2 saturation (> 94%) in room air with mild symptoms.

Group 2 was patients with parenchymal infiltration (> 50.0%) at thorax CT and/or with a low O_2 saturation (90.0–94.0%) in room air with moderate to severe symptoms.

Group 3 was patients hospitalized in the ICU. Patients with severe symptoms, intubated or unconscious referral, or those with tachypnea (30 breaths/min), those with saturation O_2 < 90% despite receiving O_2 at 5 L/min through nasal or mask, or hypotension (patients with systolic blood pressure < 90 mmHg, mean arterial pressure < 65 mmHg, and heart rate 100/min).

Additionally, the patients in all groups were divided into two groups according to PAT.

Patients under the age of 18, had a negative PCR result for SARS-CoV-2, received anticoagulant treatment previously, and outpatients with a diagnosis of COVID-19 were not included in the study.

The hospital automation system and patient epicrisis were used to access electronic patient records. The laboratory parameters (international normalized ratio (INR), di-dimer, C-reactive protein (CRP), platelet, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, thorax CT scans, PCR results, clinical conditions, duration of hospitalization, disseminated intravascular coagulation (DIC), and status of TEE development and outcome (such as discharge, transfer to ICU, and exitus)) were evaluated. The data were transferred to Excel forms created by the researchers.

The data were analyzed with the SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Number, percentage, mean, standard deviation, median, minimum, and maximum were used to present descriptive data. Chi-square test was used to compare categorical data. The compliance of the data to normal distribution was evaluated with the Shapiro-Wilk and Kolmogorov-Smirnov Test. The significance test of the difference between two means was used to compare variables that fit the normal distribution. We used the Mann-Whitney U to compare variables that were not compatible. For statistical significance, $p < 0.05$ was accepted.

The study was carried out in accordance with the principles of the revised 2013 Helsinki Declaration. We received approvals dated 4 May 2020 from the COVID-19 Scientific Research Evaluation Commission of the General Directorate of Health Services of the Ministry of Health and dated 3 June 2020 from the Clinical Research Ethics Committee of Canakkale Onsekiz Mart University.

RESULTS

A total of 662 patients hospitalized with COVID-19 infection were included in the study. There were 356 patients in group 1 (patients with mild illness), 245 in group 2 (patients with moderate or severe illness), and 61 patients in group 3 (patients with critical illness). All patients were given low molecular weight heparin (enoxaparin sodium) treatment according to the Turkish Ministry of Health COVID-19 Treatment Guidelines. Over half (54.5%) of group 1 patients, 66.9% of group 2 patients, and 72.1% of group 3 patients received PAT. Statistically, a significant difference was found between the groups in terms of PAT usage ($p = 0.001$) [Tables 1, 2, and 3], and this difference was due to the patients

Table 1: Evaluation of prophylactic anticoagulant treatment (PAT) status in the groups.

PAT	Group 1 (n = 356)	Group 2 (n = 245)	Group 3 (n = 61)	*p*-value
	n (%)	n (%)	n (%)	
Negative	162 (45.5)	81 (33.1)	17 (27.9)	0.001
Positive	194 (54.5)	164 (66.9)	44 (72.1)	

Table 2: Summary of essential variables in group 1 patients.

Variables	PAT (-) (n = 162)	PAT (+) (n = 194)	*p*-value
	n (%)	n (%)	
Gender			0.082
Female	74 (45.7)	71 (36.6)	
Man	88 (54.3)	123 (63.4)	
Infiltration in CT			< 0.001
No	36 (40.0)	51 (98.1)	
Yes	54 (60.0)	1 (1.9)	
PCR result			0.064
Negative	102 (63.0)	140 (72.2)	
Positive	60 (37.0)	54 (27.8)	
Transfer from group 1 to 2, progression in lung involvement			0.781
No	154 (95.1)	182 (93.8)	
Yes	8 (4.9)	12 (6.2)	
Thromboembolic event	1 (0.6)	1 (0.5)	1.000
Intubation-transfer to ICU			0.073
No	153 (94.4)	191 (98.5)	
Yes	9 (5.6)	3 (1.5)	
Result			0.072
Discharged with healing	146 (94.2)	183 (98.4)	
Mortality (in 28 days)	9 (5.8)	3 (1.6)	
	Mean ± SD	**Median value (min-max)**	**Mean ± SD**	**Median value (min-max)**	
Age, years	51.8 ± 18.3	49.0 (19.0–94.0)	50.9 ± 19.8	48.0 (18.0–96.0)	0.538*
INR, s	1.1 ± 0.2	1.0 (0.9–2.8)	1.2 ± 0.8	1.0 (0.8–10.2)	0.237*
Platelet count, × 10^9/L	230 906.3 ± 80 039.9	219 500.0 (850 00.0–693 000.0)	220 077.3 ± 93 473.0	208 000.0 (62 000.0–930 000.0)	0.049*
D-dimer, µg/mL	353.4 ± 492.2	14.3 (0.3–1216.0)	319.3 ± 501.9	170.0 (0.3–3416.0)	0.098*
ALT, IU/mL	27.3 ± 41.0	19.0 (4.3–473.5)	25.0 ± 30.8	18.0 (4.6–361.0)	0.686*
AST, IU/mL	29.1 ± 35.2	20.7 (8.5–357.8)	27.5 ± 34.1	20,8 (9.3–425.0)	0.673*
CRP, mg/dL	1.2 ± 0.2	4.0 (0.9–10.2)	5.9 ± 1.8	1.8 (0,6,0–8.8)	0.578*

PAT: prophylactic anticoagulant treatment; CT: computed tomography; PCR: polymerase chain reaction; ICU: intensive care unit; INR: international normalized ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein.
**Mann-Whitney U test.*

Table 3: Summary of essential variables in group 2 patients.

Variables	PAT (-) (n = 81)		PAT (+) (n = 164)		*p*-value*
	n (%)		n (%)		
Gender					0.083
Female	39 (48.1)		60 (36.6)		
Male	42 (51.9)		104 (63.4)		
Infiltration in CT					< 0.001
No	4 (10.5)		40 (90.9)		
Yes	34 (89.5)		4 (9.1)		
PCR test result					0.010
Negative	64 (79.0)		101 (61.6)		
Positive	17 (21.0)		63 (38.4)		
Progression in lung involvement					0.255
No	79 (97.5)		163 (99.4)		
Yes	2 (2.5)		1 (0.6)		
Thromboembolic event	2 (2.5)		1 (0.6)		0.255
Intubation-transfer to ICU					0.536
No	74 (91.4)		144 (87.8)		
Yes	7 (8.6)		20 (12.2)		
Result					0.744
Discharged with healing	66 (88.0)		141 (90.4)		
Mortality (in 28 days)	9 (12.0)		15 (9.6)		
	Mean ± SD	**Median value (min-max)**	**Mean ± SD**	**Median value (min-max)**	
Age, years	64.8 ± 17.6	68.0 (24.0–92.0)	65.9 ± 14.2	67.0 (21.0–93.0)	0.941*
INR, s	1.2 ± 0.4	1.1 (0.9–3.8)	1.2 ± 0.5	1.1 (0.8–6.7)	0.05*
Platelet count, × 10^9/L	240 061.7 ± 109 262.6	221 000.0 (440 00.0–527 000.0)	238 219.5 ± 104 590.5	222 000.0 (36 000.0–809 000.0)	0.913*
D-dimer, µg/mL	1286.9 ± 3858.3	2.8 (0.4–16724.0)	663.6 ± 934.9	368.0 (0.1–7456.0)	0.001*
CRP, mg/dL	19.2 ± 25.2	19.0 (6.0–21.2)	22.9 ± 2.8	18.8 (9.0–22.1)	0.618*
ALT	23.9 ± 22.8	15.8 (4.2–155.9)	23.9 ± 26.8	15.9 (3.6–239.2)	0.577*
AST	32.3 ± 23.9	23.9 (9.4–147.9)	32.2 ± 29.4	21.2 (7.0–215.9)	0.252*

PAT: prophylactic anticoagulant treatment; CT: computed tomography; PCR: polymerase chain reaction; ICU: intensive care unit; SD: standard deviation; INR: international normalized ratio; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase.
**Mann-Whitney U test.*

in group 1. In group 1 patients, no statistically significant difference was found between the groups that received and did not receive PAT in terms of gender, PCR results, transfer from Group 1 to 2, progression in the thorax, CT involvement, transfer to ICU or intubation, prognosis, and development of TEEs ($p > 0.05$). There was no significant difference in age, INR, di-dimer, CRP, AST, and ALT values between the two groups. The median platelet value was statistically higher in the PAT (-) group ($p = 0.049$) [Table 4].

In patients in group 2, we saw no difference in gender, progression in the lung involvement, transfer to ICU/intubation, and prognosis between the two groups. Also, there was no statistically significant difference in TEE development ($p > 0.05$). PCR and thorax CT positivity was statistically higher in the PAT (+) group ($p = 0.01$, $p < 0.0001$). There was no

Table 4: Summary of essential variables in group 3 patients.

Variables	PAT (-) (n = 17)		PAT (+) (n = 44)		*p*-value
	n (%)		n (%)		
Gender					0.394
Female	5 (29.4)		20 (45.5)		
Male	12 (70.6)		24 (54.5)		
Infiltration in CT					0.103
No	0 (0.0)		4 (44.4)		
Yes	6 (100)		5 (55.6)		
PCR test result					0.481
Negative	13 (76.5)		37 (84.1)		
Positive	4 (23.5)		7 (15.9)		
Intubation					0.175
No	17 (100)		37 (84.1)		
Yes	0 (0.0)		7 (15.9)		
Thromboembolic event	0 (0.0)		0 (0.0)		1.000
DIC	17 (100)		37 (84.1)		1.000
Result					1.000
Discharged with healing	6 (35.3)		15 (34.9)		
Mortality (in 28 days)	11 (64.7)		28 (65.1)		
	Mean ± SD	**Median value (min-max)**	**Mean ± SD**	**Median value (min-max)**	
Age, years	66.7 ± 12.2	67.0 (38.0–87.0)	71.9 ± 12.1	72.5 (46.0–93.0)	0.135**
INR, s	1.2 ± 0.2	1.2 (0.9–1.5)	1.7 ± 1.7	1,2 (0.9–11.5)	0.953*
Platelet count, × 10^9/L	2400 00.0 ± 112 539.4	287 000.0 (47 000.0–406 000.0)	259 045.5 ± 119 631.9	253 500.0 (47 000.0–664 000.0)	0.573**
CRP, mg/dL	25.6 ± 55.5	15.8 (4.2–55.9)	5.2 ± 19.1	5.9 (3.6–39.2)	< 0.001
ALT	58.6 ± 53.4	37.1 (7.8–177.6)	140.9 ± 498.4	20.9 (5.5–3290.7)	0.381*
AST	81.8 ± 62.4	70.1 (14.7–226.9)	283.7 ± 1120.2	32.5 (14.6–7389.4)	0.187*

PAT: prophylactic anticoagulant treatment; CT: computed tomography; PCR: polymerase chain reaction; DIC: disseminated intravascular coagulation; INR: international normalized ratio; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase.
**Mann Whitney U test. **Significance test of difference between two means.*

significant difference in age, INR, platelet, AST, and ALT levels between the two groups. The median of di-dimer value was higher in the PAT (+) group, and this difference was statistically significant ($p = 0.001$).

We found no statistically significant difference between the two PAT groups in group 3 patients according to gender, thorax CT, PCR results, intubation, TEE development rate, and prognosis ($p > 0.05$). There was also no significant difference between the two groups according to INR, platelet, di-dimer, AST, and ALT levels. However, CRP values were statistically significantly higher in patients who did not receive PAT.

DISCUSSION

COVID-19 is a disease characterized by activation of the coagulation system and endothelial dysfunction. TEEs are suggested to contribute to the high mortality rates.[4–6] Lodigiani et al,[7] reported that a TEE developed in 28 (7.7%) patients diagnosed with COVID-19; 8 (27.6%) patients hospitalized patients in the ICU, and 20 (6.4%) patients in other departments. The TEEs developed in the first 24 hours of admission in half of the patients. The frequency of ischemic stroke and acute coronary syndrome was detected in nine patients (2.5%) and four patients (1.1%), respectively. DIC criteria

were determined in eight patients (2.1%). In our study, TEE developed in only three patients in group 2 (two patients in PAT (-) group and one patient in PAT (+) group) and two patients in group 1 (one patient in PAT (-) group and one patient in PAT (+) group) and there were no statistically significant findings. Three of these five patients had a pulmonary embolism (PE), and two had deep vein thrombosis (DVT). No TEE was detected in group 3. Evaluation according to DIC criteria was found only in 54 patients in group 3. It could not be evaluated because it was not investigated in other groups as our study was retrospective. In addition, DIC criteria were not tested other than group 3 as this study was a non-intervention study, and the guidelines did not recommend it at the study time.

In a study conducted in France, concomitant PE was detected in 20.6% of 107 patients with COVID-19 pneumonia.[8] The prevalence of PE rates was two times higher in patients with COVID-19 pneumonia than non-COVID-19 diagnosed ICU patients. It has been emphasized that there is a high incidence of PE.[8] Since patients with PE were excluded from our study, this assessment could not be made. We did not detect PE in any patient who received prophylaxis in group 3. However, PE was detected in three patients of group 2. Since not all patients were screened for PE during their hospitalization, cases may have been missed.

A nationwide cohort study in the USA included 4297 COVID-19 patients.[9] This study reported that prophylactic heparin-based anticoagulation therapy was initiated within 24 hours of the first hospitalization; the 30-day mortality rate was 27% lower in patients receiving PAT.[9]

In another cohort study from the USA with 2785 hospitalized COVID-19 patients, the mortality rate of patients receiving PAT was significantly lower than the aspirin cohort.[10] We found no statistically significant difference between mortality rates among all groups.

The French Working Group on Perioperative Hemostasis and French Study Group on Hemostasis and Thrombosis also recommend PAT in COVID-19 patients.[6,11] However, in Turkey, this recommendation was not available due to the high number of uncertainties regarding the disease before 12 April 2020. This allowed the control group to be formed without intervention in our study.

In a study conducted with patients hospitalized in the ICU in France, high-dose PAT was reported as associated with a significantly reduced risk of TEEs without increasing the risk of bleeding.[12] In our study, patients were not evaluated in terms of bleeding.

Klok et al,[13] reported in their studies that PAT treatment should be adjusted according to the patient's body weight and underlying disease. The standard dose was not given to all patients in our study. The dose was adjusted according to our guide, similar to the recommendation of Klok et al.[13] The risk of DVT was evaluated in COVID-19 patients in a cohort study including 121 patients. The risk factors related to DVT were age (odds ratio (OR) = 1.05; p = 0.0306), higher admission CRP (OR = 1.02; p = 0.0040), and D-dimer (OR = 1.42; p = 0.0010) levels. Significant increases were seen in COVID-19 patients with DVT in CRP, D-dimer levels, and neutrophil counts.[14]

Although there are studies in the literature showing that PAT reduces mortality, there is no study investigating its anti-inflammatory activity.[15–19]

As the number of cases seen increases, COVID-19 causes very different thromboembolic complications.[20,21] However, the disease mechanisms are still not fully understood.

There are no studies investigating detailed anti-inflammatory effects according to biomarkers and inflammatory effects of PAT use in COVID-19. Therefore, our study findings could not be discussed with other studies.

This study was single center and retrospective. The lack of significant results could be due to the sample size; insufficient sample size may cause bias between groups in terms of results. Our study would benefit from larger sample sizes. In this context, CRP may not be a major endpoint.

CONCLUSION

The use of PAT in COVID-19 patients was not effective in reducing 28-day mortality, intubation, DIC, TEE development rates, and CRP levels among patients hospitalized other than in the ICU. The use of PAT in critically ill patients was not effective in reducing CRP levels, which is one of the biomarkers of inflammation. Further randomized controlled prospective studies with other biomarkers of inflammation are urgently needed.

Disclosure
The authors declared no conflicts of interest. No funding was received for this study.

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