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

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ABSTRACT

Objectives: Coronavirus disease-19 (COVID-19) associated coagulopathy and prophylactic anticoagulant therapy (PAT) is an ongoing topic globally. Using PAT for anti-inflammatory effect may prevent thromboembolic events (TEE). The objective of this study was to determine the anti-inflammatory effectiveness of PAT in hospitalized COVID-19 patients.

Methods: A retrospective observational study was carried out in a tertiary pandemic hospital. Patients were divided into two categories according to their PAT therapy status (PAT+ and PAT-), and also into 3 categories according to clinical features (mild: Group 1, moderate: Group:2, severe: Group 3). Laboratory parameters and clinical courses were evaluated.

Results: Totally 662 hospitalized COVID-19 patients were included in the study. Enoxaparin sodium was given to all patients as PAT therapy. TEE was developed in a total of 5 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 only detected in 54 patients in Group 3. There was no statistically significant difference was found in 28-day mortality, development of DIC rates, intubation rates and TEEs.

Conclusion: The use of PAT in critically ill patients was not found effective to reduce CRP which is one of the biomarkers of inflammation.

Keywords: COVID-19, prophylactic anticoagulant therapy, mortality, anti-inflammatory effect**.**

BACKGROUND

Researches have been globally ongoing on the treatment of Coronavirus disease-19 (COVID-19), which has caused almost 2.1 million deaths since its declaration as a pandemic .[1] It has been reported that conditions such as thrombocyte activation, inflammatory status, endothelial dysfunction, especially in COVID-19 patients requiring hospitalization, predisposition for arterial and venous thrombosis. Thromboembolic events have been observed

in the course of COVID-19 by various mechanisms. According to our knowledge, possible mechanisms for thromboembolic event development; 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]

It has been reported that the prevalence of venous thromboembolism in the COVID-19 patients is 10-35%, and venous thromboembolism is detected up to 60% in the autopsy series.[4] There is literature information stating that the picture of COVID-19 associated coagulopathy which may even develop under prophylaxis and cause mortality or morbidity. [3,4] Studies have shown that mortality significantly decreases with the use of heparin 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]

The current The Republic of Turkey Ministry Of Health's COVID-19 Diagnosis and Treatment Guideline recommends thromboprophylaxis in COVID-19 patients. [6]

Also, coagulopathy and anticoagulant treatment, which were not considered too much in the early days of the epidemic, have become more important. And globally it continues to be a research subject on prophylactic anticoagulant treatment (PAT) in COVID-19.[2] Comprehensive and detailed studies are still needed on this subject.

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

METHODS

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

Patients were also divided into 3 groups according to clinical features (mild, moderate, severe). The groups' selection were made according to the clinical findings at the time of first admission, radiological findings (according to the rate of involvement), and the place they were hospitalized (wards or intensive care unit). No intervention was made.

a. Group 1: Patients with mild symptoms of viral upper respiratory tract infection or parenchymal infiltration (less than 50%) at thorax computed tomography (CT), but with a normal O2 saturation (> 94%) in room air with mild symptoms.

b. Group 2: Patients with parenchymal infiltration (more than 50%) at thorax CT, and/or with a low O2 saturation (between 90-94%) in room air with moderate to severe symptoms.

c. Group 3: (Patients those hospitalized in the intensive care unit (ICU)) [Patients with severe symptoms, intubated or unconscious referral, or those with tachypnea (30 / min) and/or those with saturation O2<90% despite receiving O2 at 5 lt / min through nasal or mask, hypotension (patients with systolic blood pressure <90mmHg or mean arterial pressure <65 mmHg, heart rate 100/min)].

And also the patients in all groups were divided in 2 groups according to PAT.

Patients who were under the age of 18, the patients had a negative PCR result for SARS-CoV-2, who were also receiving 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 patient electronic records. The laboratory parameters (International Correction Ratio (INR), di-dimer, C-reactive protein (CRP), platelet (PLT), Aspartate Aminotransferase (AST) and Alanine aminotransferase (ALT) levels), the thorax CT scans, polymerase chain reaction (PCR) results, clinical conditions, duration of hospitalization, Disseminated intravascular coagulation (DIC), status of thromboembolic event development and outcome (such as discharge, transfer to ICU, exitus) were evaluated. The data were transferred to Excel forms created by the researchers.

Statistical analysis

The data analyzed with the SPSS statistical package program (SPSS, 20.0 for Windows Version, Chicago, IL). Number, percentage, mean, standard deviation, median, minimum, and maximum were used in the presentation of 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, and the Mann Whitney U test was used to compare variables that were not compatible. For statistical significance, $p < 0.05$ was accepted.

Ethical approval

The study was carried out in accordance with the principles of the revised 2013 Helsinki Declaration. In order for the study to be done; approvals dated 04.05.2020 from the COVID-19 Scientific Research Evaluation Commission of the General Directorate of Health Services of the Ministry of Health and dated 03.06.2020 from the Clinical Research Ethics Committee of Canakkale Onsekiz Mart University, were received.

RESULTS

662 patients hospitalized with a diagnosis of 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). As a PAT, all patients were given low molecular weight heparin (enoxaparin sodium) treatment according to the Turkish Ministry of Health COVID-19 Treatment Guideline. 54.5% of Group 1 patients, 66.9% of Group 2 patients and 72.1% of Group 3 patients were receiving PAT.

Statistically, a significant difference was found between the groups in terms of PAT usage (p = 0.001) (Table 1), and this difference was due to the patients 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, development of thromboembolic events (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 1: Evaluation of PAT status in the groups.

	Grup 1 (n=356)	**Grup 2(n=245)**	**Grup 3(n=61)**	
	n (%)	**n (%)**	**n (%)**	***p***
PAT (-)	162 (45,5)	81 (33,1)	17 (27,9)	***0,001***
PAT (+)	194 (54,5)	164 (66,9)	44 (72,1)	

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

Variable	**PAT (-) (n=162)**	**PAT (+) (n=194)**	
	n (%)	**n (%)**	**p**
Gender			0,082
Female	74 (45,7)	71 (36,6)	
Man	88 (54,3)	123 (63,4)	
Infiltration in CT			***0,0001***
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
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 ± ss	**Median value (min-max)**	**mean ± ss**	**Median value (min-max)**	
Age	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 ($\times 10^9$/L)	230906,3±80039,9	219500,0 (85000,0-693000,0)	220077,3±93473	208000,0 (62000,0-930000,0)	***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*

%: column percentage, p: Chi-Square test, p *: Mann Whitney U Test

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

Variables	**PAT (-) (n=81)**	**PAT (+) (n=164)**	
	n (%)	**n (%)**	**p**
Gender			0,083
Female	39 (48,1)	60 (36,6)	
Male	42 (51,9)	104 (63,4)	
Infiltration in CT			***0,0001***
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 ± ss	**Median value (min-max)**	**mean ± ss**	**Median value (min-max)**	
Age	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)	0,050*
Platelet count ($\times 10^9$/L)	240061,7±109262,6	221000,0 (44000,0-527000,0)	238219,5±104590,5	222000,0 (36000,0-809000,0)	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*

%: column percentage, p: Chi-Square test, p *: Mann Whitney U Test

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

Variable	**PAT (-) (n=17)**	**PAT (+) (n=44)**	
	n (%)	**n (%)**	**p**
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 (100,0)	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 (100,0)		37 (84,1)		
Yes	0 (0,0)		7 (15,9)		
Thromboembolic event	0(0)		0(0)		1,000
DIC	17 (100,0)		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±ss	**Median value (min-max)**	**mean±ss**	**Median value (min-max)**	
Age	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 ($\times 10^9$/L)	240000,0±112539,4	287000,0 (47000,0-406000,0)	259045,5±119631,9	253500,0 (47000,0-664000,0)	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)	**p<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*

*%: column percentage, p: Chi-square Test, p *: Mann Whitney U Test, **: Significance Test of Difference Between Two Means*

In group 2 patients; there was no difference according to gender, progression in the lung involvement, transfer to ICU/intubation and prognosis between the two groups. Also, there was no statistically significant difference in terms of thromboembolic event development (p> 0.05). PCR and thorax CT positivity was statistically higher in PAT (+) group (p = 0.010, p = 0.0001). There was no 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).

In group 3 patients; no statistically significant difference was found between the two groups according to gender, thorax CT and PCR results, intubation and thromboembolic event development rate, and prognosis (p> 0.05). And also; there was no significant difference according to; INR, platelet, di-dimer, AST, and ALT levels between the two groups.

However, CRP values were statistically significantly higher in patients who did not receive PAT.

DISCUSSION

The COVID-19 is a disease characterized by activation of the coagulation system and endothelial dysfunction. Thromboembolic events are suggested to contribute to the high mortality rates.[4-6] Lodigiani et al.[7] reported that a thromboembolic events developed in 28 (7.7%) of all patients diagnosed with COVID-19, 8 (27.6%) of hospitalized patients in the ICU, and 20 (6.4%) of the hospitalized patients other than ICUs. The thromboembolic events developed in the first 24 hours of admission in half of the patients. The frequency of ischemic stroke and the acute coronary syndrome was detected in 2.5% (9 patients) and 1.1% (4 patients), respectively. Disseminated intravascular coagulation (DIC) criteria were determined in 8 patients (2.1%). In our study, the thromboembolic event had developed in only 3 patients in Group 2 patients (two patients PAT (-) group and one patient PAT (+) group and two patients in Group 1 (one patient in group PAT (-) group and one patient in PAT (+) group) and there was no statistically significant findings. Three of these five patients had a pulmonary embolism and two had deep vein thrombosis. No thromboembolic event was detected in group 3 patients. 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 guideline did not recommend it at the study included time.

In a study conducted in France, patients hospitalized in an intensive care unit (ICU) with COVID-19 were elevated. According to this study; 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 compared with non-COVID-19 diagnosed ICU patients. It has been emphasized that there is a high incidence of PE. [8] In our study, since patients with PE on admission were excluded from the study as they were treated with anticoagulants, this assessment could not be made. In our study, PE was not detected in any patient who received prophylaxis in Group 3 (ICU). However, PE was detected in three of Group 2 patients. Since not all patients were screened for pulmonary embolism (eg, CT angiography) during their hospitalization, PE cases may have been missed in this retrospective study.

A nationwide cohort study in the United States of America (USA) was conducted by Rentsch et al. [9] included 4,297 COVID-19 patients. This study reported that prophylactic heparin-based anticoagulation therapy was initiated within 24 hours of the first hospitalization. In this cohort, it was determined that the 30-day mortality rate was 27% lower in patients who were receiving PAT.[9] In another cohort study with 2785 hospitalized COVID-19 patients were from the USA; the mortality rate of patients receiving PAT was found to be statistically significantly lower, compared to the aspirin cohort.[9] In our study, 28-day mortality was evaluated. However, no statistically significant difference was found between mortality rates among all groups.

The French group's Interest Group in Perioperative Hemostasis and French Group of Studies of Hemostasis and Thrombosisalso recommend PAT in COVID-19 patients as in our Ministry of Health COVID-19 guide.[6,11] However, this recommendation was not available due to the high number of uncertainties regarding the disease in the period before April 12th 2020, in our country. 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 thromboembolic events 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, too. The dose was adjusted according to our guide, similar to his recommendation of Klok et al. [13] In a cohort study included 121 patients, the risk of DVT was evaluated in COVID-19 patients. This study reported that, the risk factors related to DVT were age (OR, 1.05; p=.0306), higher admission CRP (OR, 1.02; p = .0040) and D-dimer (OR, 1.42; p = .0010) levels, as a result of multivariate logistic regression analyzes. And the significant increases were seen in COVID-19 patients with DVT in terms of 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, it is reported that COVID-19 causes very different thromboembolic complications.[20,21] However, the disease mechanisms are still not fully elucidated.

In the available literature; there are no studies investigating detailed anti-inflammatory effects according to biomarkers and inflammatory effects of PAT use in COVID. Therefore, our study findings could not be discussed with other studies.

Conclusion

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

Limitations: This study was single center and retrospective study. In addition, the lack of significant results can be due to the sample size. Insufficient sample size may cause bias between groups in terms of results. The study should be expanded with larger sample sizes. In this context CRP may not be a major endpoint

Conflict of interest: The authors declare no personal or financial conflict of interest.

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