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ORIGINAL ARTICLE

Evaluation of the Results of the Use of two Different Anticoagulants in COVID-19 Patients who Were Followed-Up and Treated in the Intensive Care Unit

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Abstract

Introduction: The risk of thromboembolism increases due to tendency to coagulopathy, excessive inflammation, hypoxia, and immobility in patients who are treated of COVID-19 in Intensive Care Units (ICU). Therefore, thromboembolism prophylaxis (anticoagulant therapy) is recommended. There is no clear recommendation in the literature regarding the dose and duration of anticoagulant therapy. In this study, we evaluate of two different anticoagulant administrations in terms of prognosis and mortality in COVID-19 patients who were followed up and treated in the ICU.

Methods: After the approval of the Ethics Committee, the study was carried out by retrospectively in ICU affiliated to three different centers. The patients were divided into two groups as those using anticoagulant at a prophylactic dose (Group 1) and treatment dose (Group 2). Various parameters of the patients were evaluated.

Results: Of the 91 patients included in the study, 61.5% received prophylactic and 38.5% therapeutic anticoagulants. The rate of male patients 73.9% was found to be significantly higher in the mortal group (p=0.014). About 75.9% of the patients who received mechanical ventilation treatment and 13.59% of the patients who were not applied died (p<0.001). Mortality was higher in the group using prophylactic anticoagulants (58.39% vs. 37.1% p;0.043). Patients using prophylactic doses of anticoagulants had 2.42 times more mortality (Odds Ratio=2.42). Hb levels were found to be lower (p=0.017) and prothrombin time and partial prothrombine time values were long (p=0.048 and 0.038, respectively) in patients who received anticoagulants at the treatment dose.

Discussion and Conclusion: Despite the increased tendency for thrombosis in COVID-19, there is no clear preventive or protective treatment. Hence, if there is no contraindicated situation, we believe that anticoagulants can be used safely at the treatment dose to avoid possible thromboembolic complications and reduce the risk of mortality. There is a need for large-scale studies on dose selection in terms of prophylaxis.

Keywords: Anticoagulant; COVID-19; intensive care unit.

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A new infectious disease was detected in Wuhan, China in December 2019. This disease that was caused by a new type of coronavirus has been named COVID-19 by the World Health Organization (WHO). The disease that progresses firstly with respiratory tract involvement has spread rapidly to many countries. The number of severe patients in China exceeded 60,000 in mid-February 2020.[1] During the same period, more than 81,000 cases were reported all around the world.[2,3] The emerging outbreak was declared as a pandemic by the WHO on March 11, 2020, causing the death of more than 4000 people.[4,5]

The disease is extremely infectious and the main symptoms include fever, dry cough, muscle pain, sore throat, headache, shortness of breath, weakness, diarrhea, fatigue, and poor appetite.[3,6]

Venous and arterial thromboembolism, especially pulmonary and cerebrovascular embolism, may become cardiovascular involvement due to COVID-19-related coagulopathy and disseminated intravascular coagulation (DIC).[2] In general, while this kind of complication is 13.6%, it may reach higher rates (31%) in patients treated in Intensive Care Unit (ICU).[4]

Coagulopathy tendency and the risk of thromboembolism increase in these patients due to previous cardiovascular diseases, severe inflammation, platelet activation, endothelial dysfunction, stasis, hypoxia, standing still during long-term treatments, and applied medical treatments.[2,6] Abnormally high D-dimer in the disease is directly associated with coagulopathy and DIC mortality. Therefore, anticoagulant (Low-molecular-weight heparin [LMWH]) therapies are recommended routinely (in patients who have a tendency, antiagregants such as acetylsalicylic acid [ASA] and clopidogrel), especially in severe COVID-19 cases if there is no contraindication.[2,7] There is not any recommendation related to the dose and duration of anticoagulant therapy in the literature.

This study aims to determine the efficiency and to reveal the relationship with mortality of the use of anticoagulants in two different doses in COVID-19 patients who are followed up and treated in the ICU.

Materials and Methods

After the approval of hospital administration and Local Non-Pharmaceutical Clinical Research Ethics Committees (2020/53) were obtained for the study, ICU patients who were followed up and treated with the diagnosis of COVID-19 between March 15, 2020, and June 15, 2020, were included in the study. The study was conducted by retrospectively evaluating physical files and electronic file records of the 96 patients in three different ICU. Those who have cardiovascular disease, who have had anticoagulant therapy before the diagnosis of COVID-19, who have bleeding disorders, whose anticoagulant therapy related to hematologic problems is contraindicated are excluded from the study. We grouped the patients in whom we use Enoxaparin Sodium (Clexane® 0.4 mL Sanofi aventis İlaçları Ltd. Şti, No: 209, 4. Levent-Istanbul) drug as LMWH (which can be used in two different doses) in prophylactic dose as 0.5 mg/kg as Group 1 and the patients in whom we use treatment dose as 1mg/kg as Group 2 by considering the additional and comorbid diseases according to treatment protocol in the clinic they were treated.

Laboratory results at the time of the admission of the patient to ICU were admitted as basal values. All patients included in the study underwent Thorax Computed Tomography (CT) within the scope of the routine procedure before admission to ICU. Patients whose Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) tests were positive in the oral and nasal samples collected combined were admitted to the study group. Furthermore, those who had characteristic findings in Thorax CT (when evaluated by the senior specialist radiologists with at least 10 years of experience) among the ones whose RT-PCR tests are negative (in the first, second, or third sample) were included in the study. The presence of peripheral bilateral severe ground-glass opacity and/or consolidation areas was accepted as a characteristic lesion.

Patients' parameters such as age, sex, comorbid diseases, length of ICU stay, non-rebreather mask treatment duration, length of invasive and non-invasive mechanical ventilation (MV) period, D-dimer, prothrombin time (PT), partial prothrombine time (aPTT), international normalized ratio, white blood cell count, hemoglobin (Hb), platelets, pa oxygen/fractional oxygen ratio, peripheral oxygen saturation values, and mortality rates were evaluated.

Statistical evaluation was carried out using the following tests in SPSS 20.0 software. Compliance with the normal distribution of the data was established using the Kolmogorov–Smirnov test. The Student's t-test was used for independent variables in the data conforming to the normal distribution, and the Mann–Whitney U-test was used for independent variables in the data that did not comply with the normal distribution. Chi-square or Fisher's Exact Chi-Square tests were used for the evaluation in the analyses of the categorical variables such as sex, invasive MV, non-invasive MV, and patient outcome. The data obtained by measurement were expressed as mean±standard deviation. The data obtained by counting were expressed

as numbers (n; %). $p<0.05$ was the statistical significance threshold.

Results

Ninety-six patients who were followed up and treated in ICU with the diagnosis of COVID-19 were included in the study, five patients were excluded as their data were not complete, and the data of the 91 patients are given in Table 1 in detail. It was seen that 61.5% of the 91 patients included in the study had received a prophylactic dose of anticoagulant and 38.5% had received treatment dose 46 (50.5%) of the patients died. While 58.9% of the exitus patients had received anticoagulant therapy in prophylactic dose, 37.1% received anticoagulant therapy in treatment dose (p=0.043). The patients who had received anticoagulant therapy in prophylactic dose had a 2.42 times higher risk of mortality (Odds Ratio=2.42). Out of the patients treated in ICU in the study, 73.9% of those who progressed mortal were male,

Table 1. Data of the patients followed-up in the intensive care unit due to COVID-19 and applied procedures (mean±SD, n, %)

	Mean±SD, n (%)
Age	
Year	70.00±14.30
Sex	
Male	56 (61.5)
Female	35 (38.5)
Intensive care unit	
Day	7±13.05
D-dimer	
mcg/mL (0-0.5)	1.2±2.31
Prothrombin time	
sec (10.4-12.6)	14±7.24
Partial prothrombine time (aPTT)	
sec (22.1-28.1)	29.8±15.74
International normalized ratio (0.8-1.2)	1.18±0.52
White blood cell count	
K/uL (3.7-10.1)	9.36±5.37
Hemoglobin	
g/dL (12-17)	11.8±2.13
Platelets	
K/uL (100-400)	232.5±89.9
Pa oxygen/fractional oxygen ratio (Pa/FiO_2)	140±70.49
Peripheral oxygen saturation (SPO_2)	
%	92±8.4
Mechanical ventilation	
Yes	56 (61.5)
None	35 (38.5)
Invasive MV treatment	
Day	54 (59.3)
Non-invasive MV treatment	
Day	21(23.07)
Non-rebreather mask	
Day	66(63.52)
End	
Ex	46 (50.5)
Discharge	45 (49.5)
Acetylsalicylic Acid	
1x100	22 (24.1)

Table 2. Data of the patients followed-up in the intensive care unit with a different dose of LMWH treatment applied procedures (mean±SD, n, %)

	Group 1 (n=56) (61.5)	Group 2 (n=35) (38.5)	p
Age (years)	68.75±13.59	68.65±15.57	0.97
(Sex (M/F)	38 (63.8)/18 (36.2)	18 (53.6)/17(46.4)	X^2=2.45; 0.117
Length of Intensive Care Unit stay (day)	11.61±14.30	11.68±10.88	0.5
D-dimer (mcg/mL)	1.75±1.53	2.26±3.20	0.402
PT (sec)	14.27±3.18	18.06±10.65	0.048
aPTT (sec)	29.43±11.92	37.30±19.65	0.038
INR	1.19±0.23	1.41±0.77	0.36
WBC (K/uL)	10.58±5.50	10.48±5.23	0.93
Hb (g/dL)	11.93±2.28	10.84±1.71	0.017
Platelets (K/uL)	226.14±89.59	251.95±89.43	0.184
Pa/Fi	153.01±70.38	144.50±71.37	0.578
sPO_2 (%)	89.62±6.34	89.80±11.04	0.92
MV treatment (yes/no)	33 (56.9)/25 (43.1)	17 (60.7)/11 (39.3)	X^2=0.113: 0.737
Invasive MV treatment (day)	33 (58.9)	21 (60)	X^2=0.01: 0.919
Non-invasive MV treatment (day)	13 (23.21)	7 (20)	X^2=0.08: 0.771
Non-Rebreather Mask	42 (75)	24 (68.5)	X^2=0.447: 0.504
Outcome (ex/discharge)	33 (58.9)/23 (41.1)	13 (37.1)/22 (62.8)	X^2=4.09: 0.043 (OR=2,42; 95%=1.019-5.784)

ICU: Intensive Care Unit; PT: Prothrombin Time; aPTT: Partial Prothrombine Time; INR: International Normalized Ratio; WBC: White Blood Cell Count; Hb: Hemoglobin; Pa/Fi: Pa oxygen/Fractional Oxygen ratio; SPO_2: Peripheral Oxygen Saturation; MV: Mechanical Ventilation; LMWH: Low Molecular Weight Heparin; p<0.05: accepted as significant.

and 26.1% were female. The ratio of the male patients was found to be significantly high in the mortal group (X^2=6.018; p=0.014). About 75.9% of the patients who received invasive MV and 13.59% who did not receive invasive MV died. The ratio of the patients who received invasive MV was found to be significantly high in the mortal group (X^2=34.2; p<0.001). Hb level was found to be significantly low (p=0.017) and PT and aPTT values were found to be prolonged (respectively, p=0.048 and 0.038) in the patients who received anticoagulant in treatment dose. It was seen that four patients using anticoagulant in prophylactic dose had sudden cardiac arrest, and two patients had mild gastrointestinal bleeding related to the use of anticoagulant in treatment dose. Other data were found to be similar between the groups (Table 2).

Discussion

Early diagnosis and treatment decrease the severity and mortality of the disease in COVID-19 cases. In the previous studies, while 58–70% of the patients visiting a hospital were male, 5% needed for ICU, 2.3% needed for MV, and 1.4% had severe disease with mortality.[5]

Endothelial dysfunction with systemic involvement progresses with an increase in coagulation as a result of an increase in thrombin production and a decrease in fibrinolysis in COVID-19 patients.[8,9] In addition, it causes an increase in vascular viscosity and thrombosis tendency in the hypoxia condition frequently observed in COVID-19 patients.[10] Elevated D-dimer and coagulopathy-related mortality have higher rates among the patients admitted to ICU.[11] For thrombosis prophylaxis in COVID-19 patients who lied still in ICU, anticoagulants were used in prophylactic dose as there was not sufficient evidence in the early period of the pandemic. Anticoagulant therapy recommendations started to be clearer on receiving evidence-based data. The recommendation of using LMWH in treatment dose rather than prophylactic dose especially in the risk groups in ICU was started to be widely accepted following an increase in thrombotic complications during pandemic.[4] In our study, it was detected that the mortality rate was low when a high dose (treatment dose) of LMWH was used (p=0.043), while mortality was 2.42 times higher in patients using anticoagulant in prophylactic dose.

In COVID-19, the main involved organ is the lung; however, there is also a risk of systemic coagulopathy. While planing anticoagulant treatment, D-dimer elevation should be

taken into account as well as platelet count.[7,11,12] While there are studies defending that an increase in the D-dimer level may be associated with the severity of the disease and mortality,[6] on the other hand, there are also studies defending that there is not any correlation between D-dimer levels and the severity of the disease.[1,13] Furthermore, there are studies reporting that D-dimer level is higher in those with high pulmonary embolism.[1,3] It is also reported that low platelet number and high PT are also directly associated with mortality. In a previous study,[7] just 40–60 mg heparin had been used, and when it was evaluated in terms of 28-day mortality, it was reported that the mortality significantly decreased with the use of heparin in those especially having D-dimer >3 mcg/mL (6 times of upper limit) and Sepsis-induced coagulopathy (SIC, platelet count, PT, INR, and SOFA-Sequential Organ Failure Assessment-) ≥4. In another study,[14] it is reported that those with D-dimer >1 mcg/mL have an independent risk factor for hospital mortality and this increases the risk of mortality up to 18 times. Furthermore, in our study, the D-dimer level was found to be higher (1.2 mcg/L) than normal and it is correlated with similar studies in the literature.[3,11] In our study, D-dimer levels averages were not found to be different in the use of prophylactic-dose and treatment-dose anticoagulation.

The mortality rate is high in COVID-19 due to reasons such as using MV, being male, infection, sepsis, acute respiratory distress syndrome, and multiple organ failure as well as thromboembolic events in ICU patients. Mortality rates may also vary depending on some factors such as ICU admission criteria, access to health-care services, patient profile, treatment protocols, physical conditions, medical opportunities, and professionalism of the healthcare workers while providing service during the pandemic. While mortality data of the centers providing COVID ICU treatment are limited, our 50% rate is correlated with similar studies.[4] On the other hand, we believe that variable mortality rates (11.5–71%) in the previous studies result from the severity of the disease, sex, age, and comorbid diseases such as organ failure, diabetes, and hypertension of the population included in the study.[6]

Complications such as bleeding associated with the use of LMWH can be seen. The bleeding complication occurs in the gastrointestinal system mostly as well as skin, mucosa, and urinary system. It is estimated that gastrointestinal bleeding risk associated with the use of systemic anticoagulant increases by 4.5–8%.[15] In our study, mild GI bleeding was observed in two patients and it did not cause a problem in terms of clinic and mortality. As our study was designed retrospectively if it is considered that the use of treatment-dose LMWH is preferred mostly in the patient group with additional and comorbid disease, the presence of low Hb (due to advanced age, an additional disease, and comorbidity) is an expected situation. Close follow-up, appropriate prophylactic medication (H2 receptor blockers or proton-pump inhibitors), and, when necessary, replacement of decreasing blood products will be a proper approach.

The most common (81%) thrombotic complication in ICU patients is pulmonary embolism and it is followed by venous and arterial embolism events.[4] In the previous studies, it is reported that venous thromboembolism in ICU is 5–33%.[16] Even though a sudden cardiac arrest in four patients using prophylactic LMWH could not be exactly determined as etiological diagnostic imaging could not be performed in our study, it implies pulmonary embolism due to rapid progress of the event, the lack of previous cardiovascular history in the patients, the lack of providing inotropic support, hypoxemic progress, and failure to respond to resuscitation.

Our study has some limitations. It was initially conducted as a retrospective observational study. As it was conducted in the early period of the pandemic in our country, there was limited information, and treatment recommendation protocols had not been created yet. The number of patients included in the study was relatively limited. Furthermore, randomization cannot be completely provided as the selection of anticoagulant therapy changes depending on the comorbid diseases of the patients and the practice of the physician. As the use of ASA is very low, it was ignored. In addition, as the stage and severity of the disease at the time of the first admission of the patient to ICU were different, examined laboratory initial values cannot be standardized.

We believe that treatment-dose LMWH can be used safely if there is not any contraindicated event to avoid possible thromboembolic complications and to decrease the mortality risk as there is not any preventive and protective treatment despite the increase in thrombosis tendency in COVID-19. Larger studies are needed, related to the appropriate medication and dose selection in terms of thromboembolism prophylaxis and possible complications.

Ethics Committee Approval: After the approval of hospital administration and Local Non-Pharmaceutical Clinical Research Ethics Committees (2020/53) were obtained for the study, ICU patients who were followed up and treated with the diagnosis of COVID-19 between March 15, 2020, and June 15, 2020, were included in the study.

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