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INFLUENCE OF ANTICOAGULANT THERAPY ON THE COAGULATION PROFILE OF PATIENTS WITH CORONAVIRUS INFECTION (COVID-19)

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ABSTRACT

In order to conduct a comparative assessment of the effect of anticoagulant therapy on the coagulation profile and the outcome of coronavirus infection (COVID-19), were examined 372 patients with laboratory-confirmed COVID-19 (moderate-to-severe) in the Specialized Hospital from August to December 2020. The ratio of men and women was 1.6 / 1; the average age was 57.4 ± 6.77 years. In the course of the study, the antithrombotic and hemorrhagic effects of the oral anticoagulant Rivaroksaban Nobel (n = 122) in comparison with the parenteral anticoagulant Enoxaparin sodium (Clexane) (n = 250) were evaluated in a comparative aspect. Based on the risk of venous thromboembolism, standard treatment doses were used for oral Rivaroksaban Nobel 20 mg / day and Enoxaparin sodium (Clexane) is 8,000 IU (80 mg) once daily by subcutaneous (SC) injection. The study found that the incidence of both thromboembolic outcomes and bleeding events did not show statistically significant differences between the clinical and laboratory parameters of patients with COVID-19 with the recommended anticoagulant therapy Rivaroksaban NOBEL, compared with Enoxaparin sodium (Clexane). However, Enoxaparin sodium (Clexane) has shown more significant clinical efficacy compared to Rivaroksaban Nobel. On the other hand, during the use of Rivaroksaban Nobel, there were no significant differences in the incidence of acute respiratory distress syndrome and deaths compared with Enoxaparin sodium (Clexane). Thus, our study confirms the hypothesis about the safety and efficacy of the oral anticoagulant Rivaroksaban Nobel for the prevention of venous thromboembolism in hospitalized patients with moderate to severe COVID-19.

KEYWORDS: Coronavirus infection (COVID-19), coagulation profile, anti-coagulant therapy, direct oral anticoagulants, unfractionated heparin, low-molecular-weight heparins, rivaroksaban, enoxaparin.

INTRODUCTION

The emergence of a new coronavirus infection, COVID-19, has posed challenges for healthcare professionals to quickly diagnose and provide medical care to patients. At present, an intensive study of the clinical and epidemiological characteristics of the disease continues, the development of new means of its prevention and treatment.[4,8,9] The most common clinical manifestation of a new variant of coronavirus infection is bilateral pneumonia (viral diffuse alveolar injury with microangiopathy); acute respiratory distress syndrome (ARDS) was recorded in 3-4% of patients. Some patients develop hypercoagulable syndrome with thrombosis and thromboembolism, other organs and systems are also affected (central nervous system, myocardium, kidneys, liver, gastrointestinal tract, endocrine and immune systems), and sepsis and septic shock may develop.[1]

The finding of elevated D-dimer and fibrinogen levels in COVID-19 patients has raised questions about the coexistence of venous thromboembolism, ventilation / perfusion disorders with a predominance of pulmonary embolism. The complex interaction between inflammation and coagulation can significantly affect the progression of the disease, leading to poor outcomes.[5,9,13]

Coagulation disorders in COVID-19 not only lead to the occurrence of clinically significant thrombotic complications, but also play a role in the pathogenesis of coronavirus infection, including with lung damage. Microcirculation disorders due to microthrombosis can significantly aggravate the course of acute respiratory failure in patients with COVID-19. Therefore, the treatment of COVID-19 must necessarily include measures aimed at correcting hemostasis disorders. The study of the mechanisms of coronavirus-induced coagulopathy allows not only to better understand the pathogenesis of the disease, but also to improve the diagnosis, open up new horizons for its treatment.[10,11]

Due to the dominance in the pathogenesis of acute distress syndrome and pneumonia caused by COVID-19, violations of oxygen delivery associated with intra-erythrocyte and microcirculatory disorders, as well as intravascular coagulation, hemolysis of erythrocytes, microthrombus formation in the vessels of the lungs and intraalveolar within the framework of chronic hemolytic microthrombovasculitis and secondary chronic disseminated intravascular coagulation syndrome. An advanced preventive use of antithrombotic therapy and an individualized approach is required.[2]

Patients with pneumonia caused by the SARS-CoV-2 virus need early anticoagulant and antiplatelet therapy to prevent the development of acute respiratory distress syndrome and chronic disseminated intravascular coagulation syndrome, to protect erythrocyte membranes and endothelium. The dynamics of the development of the disease allows it to begin before the development of pneumonia, already in the first and second days of the development of the disease. The use of therapeutic doses of anticoagulants (unfractionated heparin and low molecular weight heparins) for the preventive therapy of coagulopathies associated with the development of multiple microthrombosis, intraalveolar fibrin formation and venous thromboembolism. It is advisable to use prophylactic doses only in patients at risk of hemorrhagic complications. Early prevention with unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs) is necessary in patients of the older age group, in patients with diabetes, hypertension, coronary heart disease, cancer and chronic rheumatologically diseases, diseases with impaired liver and kidney function, allergic diseases.[2] Also, prolonged anticoagulant prevention with the use of direct oral anticoagulants (DOACs) during the rehabilitation period in patients with moderate and severe COVID-19 is recommended.[1]

According to the American Society of Hematology (ASH), there are currently no unambiguous data that would show the comparative effectiveness of different types of anticoagulants. The choice of a particular remedy may be based on availability, ease of use, patient contraindications, and other factors. As the authors of the recommendations note in the course of the interim results of three clinical trials of anticoagulants for COVID-19, such as REMAP-CAP, ACTIV-4 and ATTACC, which were recently presented. ASH is awaiting the final results of these tests, based on which it will further update the current recommendations. Therapeutic doses of anticoagulants showed no benefit in critically ill participants with coronavirus infection, but improved the condition of patients with moderate disease.[3]

The use of anticoagulant therapy with low molecular weight heparins (LMWH) has been shown to reduce mortality in hospitalized patients with severe COVID-19, probably due to its anti-inflammatory and antiviral properties.[5] There is no proven benefit of any one LMWH over others. If the development of venous thromboembolic complications is suspected, anticoagulant therapy in therapeutic doses can be started before the diagnosis is confirmed: during the period of inpatient treatment, preference should be given to LMWH, especially Enoxaparin sodium Clexane or UFH, after discharge from the hospital, it is recommended to transfer to direct oral anticoagulants, in particular Rivaroksaban NOBEL for a period of at least 3 months.[1]

In addition to their anticoagulant effect, DOACs, especially a factor Xa inhibitor, may have an anti-inflammatory effect in COVID-19. As previously shown, Rivaroksaban Nobel prevents arterial and venous thrombosis in patients with comorbid cardiovascular diseases.[14,18] In addition, Rivaroksaban Nobel and Betriksaban reduce the risk of venous thromboembolism. In this regard, DOACs is being considered for the treatment of patients with COVID-19.[21]

Even though Enoxaparin sodium (Clexane) and Rivaroksaban Nobel have the same clinical indications for the treatment of venous thromboembolism, there are currently no data on the use of Rivaroksaban Nobel in terms of safety, efficacy and impact on the clinical prognosis among patients with COVID-19.[7,12]

The purpose of this work is to conduct a comparative assessment of the effect of anticoagulants on the clinical and laboratory course and the outcome of coronavirus infection (COVID-19).

MATERIAL AND METHODS

In the 1-Zangiata Infectious Disease Clinic from August to December 2020, 372 patients with laboratory-confirmed COVID-19 of the moderate course were studied. The age of the patients ranged from 29 to 85 years old, with an average age of 57.4 ± 6.77 years. The ratio of men and women was 1.6 / 1. The studies included patients hospitalized with moderate to severe COVID-19 who underwent a course of venous thrombosis prevention in accordance with current international guidelines. During hospitalization and during the observation period, were studied the clinical status, laboratory parameters, instrumental (MSCT and chest ultrasound) data of patients with coronavirus disease.

In the course of the study, the antithrombotic and hemorrhagic effects of the oral anticoagulant Rivaroksaban Nobel (n = 122) in comparison with the parenteral anticoagulant Enoxaparin sodium (Clexane) (n = 250) were evaluated in a comparative aspect. Based on the risk of venous thromboembolism, standard treatment doses were used for Rivaroksaban Nobel 20 mg / day and Enoxaparin sodium (Clexane) sc 80 mg / day. The compared groups of patients were comparable in terms of age, concomitant diseases, risks of thromboembolic and hemorrhagic complications. The results were statistically processed using the Excel 2017 computer

program. To compare the mean values, was used the Student's t-test. Nonparametric features were compared by contingency tables using the $\chi 2$ test. The level of reliability of statistical indicators was taken as $p < 0.05$.

RESULTS

In order to monitor the effectiveness of anticoagulant therapy in patients with coronavirus infection with a risk of venous thromboembolism, coagulogram indicators were determined - Activated partial thromboplastin time (APTT), prothrombin time (PT); prothrombin index (PI), international normalized ratio (INR), thrombin time (TT), fibrinogen (FIB) and blood clotting time (CT) (Table 1.) upon admission and during treatment with Enoxaparin sodium (Clexane) and Rivaroksaban Nobel for 10-12 days.

Table 1: Coagulation profile of the studied groups before and after treatment (M ± m).

Indicators	1st group - Rivaroksaban Nobel (n=120)		2nd group - Enoxaparin sodium (Clexane) (n=250)	
	Before treatment	After treatment	Before treatment	After treatment
APTT, sec	25,6±0,99	37,2±1,40	25,19±0,93	38,7±1,62
TT, sec	21,0±1,31	23,3±1,27	20,36±1,28	22,8±1,09
FIB, mg/dl	456,3±16,11	318,1±11,43	458,7±16,96	309,7±10,12
PT, sec	10,59±0,66	15,3±1,04	10,41±0,67	16,3±1,32
PI, %	116,1±5,31	85,2±7,28	115,7±5,12	83,2±6,98
INR	0,93±0,04	1,5±0,12	0,95±0,04	1,5±0,11
CT, sec	1.50-2.20	4.20-4.50	1.55-2.25	4.40-5.10

Analysis of the results obtained during the study showed that the main parameters of the coagulogram, in particular APTT, FIB, PT, PI and INR against the background of anticoagulant therapy in dynamics, reached reference values, the average value of which did not make a significant difference between the group using Enoxaparin sodium Clexane) and a group with Rivaroksaban Nobel ($p > 0.05$). It is noteworthy that the recommended increase in the APTT indicator by 1.5-2.5 times from the upper limit of the norm was achieved both in the first group and in the second group of the studied in 82% (n = 98) and 87% (n = 217) cases, respectively. It should be noted that practicing physicians quite often (in 50% of patients) to assess the effectiveness and safety of heparin therapy determined such a laboratory parameter as CT. Thus, the CT in the group against the background of DOACs therapy increased from 1.50-2.20 sec to 4.20-4.50, and in the group with LMWH increased from an average value of 1.55-2.25 sec to 4.40-5.10 sec, which also did not turn out to be statistically significant differences between the groups ($p > 0.05$).

According to the indicators of blood coagulation balance in patients with COVID-19, upon admission, there was a tendency to hypercoagulation due to an increased level of D-dimer in the study groups, 856 ng / ml and 872 ng / ml, respectively. In the dynamics of anticoagulant therapy in COVID-19 patients taking Rivaroksaban Nobel, the average D-dimer value decreased 2.2 times, whereas in patients receiving Enoxaparin sodium (Clexane) injections, the average values decreased 2.5 times. Thus, in both groups, was achieved a significant decrease in the level of D-dimer, a key biomarker of the risk of thromboembolic complications and poor outcome in patients with COVID-19, When assessing the development of adverse outcomes in patients with coronavirus infection during the study, thromboembolic complications were observed in 26 (7%) of the studied patients with COVID-19. In a comparative aspect, in the group of patients receiving Enoxaparin sodium (Clexane), thromboembolic complications were observed in 6.8% (n = 17) cases, and in the Rivaroksaban Nobel group - 7.4% (n = 9) ($\chi 2 = 0.042$, $p = 0.84$). The risk of developing (OR) thromboembolic complications was 1.092.

Further, we analyzed the development of hemorrhagic complications against the background of anticoagulant therapy using LMWH and DOACs. Bleeding was observed in 12 (3.2%) hospitalized patients. The main sources of bleeding were duodenal ulcers and hemorrhoids. The overall bleeding rate was 4% (n = 10) in the Enoxaparin sodium (Clexane) group versus 1.6% (n = 2) in the Rivaroksaban Nobel group ($\chi 2 = 1.46$, $p = 0.23$). According to these data, the probability of the risk of bleeding was 0.4, which indicates the safety of the use of both anticoagulants.

According to the assessment of the development of unfavorable outcomes of COVID-19 during the observation period, 42 (11.3%) patients developed acute respiratory distress syndrome (ARDS). The overall incidence of ARDS was 9.6% (n = 24) in the Enoxaparin sodium (Clexane) group versus 14.8% (n = 18) in the Rivaroksaban Nobel group ($\chi 2 = 2.17$, $p = 0$,14). At the same time, the risk of developing ARDS was 1.63. Among the studied patients, 24 (6.5%) died during the observation period. The all-cause mortality rate was 6% (n = 15) in the Enoxaparin group compared to 7.4% (n = 9) in the Rivaroksaban Nobel group ($\chi 2 = 0.26$, $p = 0.61$). The risk of developing a lethal outcome was equal to -1.25.

Thus, the use of one or another anticoagulant drug for the prevention of venous thromboembolism did not significantly increase or decrease the risk of thrombosis, bleeding, ARDS, or hospital mortality among patients with COVID-19.

DISCUSSION

A high incidence of coagulopathy and venous thromboembolism among hospitalized patients with COVID-19 has been shown by several studies.[11] However, little is known about the potential link between antithrombotic therapy and the clinical picture of COVID-19. The World Health Organization recommends the use of pharmacological prevention with LMWH to prevent thrombosis in patients with COVID-19,[7,9]

However, despite the systematic prevention of thrombosis with LMWH, the incidence of thrombosis among patients with COVID-19 remains very high compared to other clinical conditions characterized by disseminated intravascular coagulation,[6,12] A recent meta-analysis by Fontana et al.[5] showed that the risk of thromboembolic complications ranges from 4.4 to 8.2% among all hospitalized patients with COVID-19. The highest risk, up to 53.8%, was reported among critically ill patients with COVID-19 pneumonia admitted to intensive care.

The high frequency of observations of venous thromboembolism, despite the pharmacological thromboprophylaxis of UFH / LMWH, can be explained by the multifactorial genesis of COVID-19-associated coagulopathy. In particular, the excessive release of many inflammatory cytokines and chemokines such as tumor necrosis factor-α, interleukin (IL) -1, IL-6 and IL-8[4,5,7,13], which leads to pulmonary microvascular thrombosis, edema of blood vessels and hemorrhagic consequences. The relatively high cumulative incidence of bleeding (3.2%) is likely due to several common concomitant cardiovascular diseases such as diabetes, stroke, and hypertension, predisposing to frequent bleeding.[10,11]

At present, it is still not known about the prognosis of the risk of development among hospitalized patients with moderate to severe degree of COVID-19, and there is no data on the effectiveness of the use of DOACs, in particular Rivaroksaban Nobel in this group of patients with COVID-19.

We conducted a study to evaluate the effectiveness and impact on the outcome of COVID-19 of anticoagulant therapy, in the comparative aspect of the use of LMWH - Enoxaparin sodium (Clexane) and DOACs - Rivaroksaban Nobel. Based on the results obtained in the course of this study, we can assume the clinical and laboratory effectiveness of both Enoxaparin sodium (Clexane) and Rivaroksaban Nobel in relation to the risk of thrombosis and correction of hypercoagulable disorders in patients with moderate to severe COVID-19. When assessing the safety of anticoagulant therapy in patients with coronavirus infection, there were no statistical differences in the development of hemorrhagic complications and adverse outcomes in patients who received LMWH and DOACs, which makes it possible to recommend DOACs along with LMWH in order to prevent thrombosis associated with COVID-19.

It should be noted that one of the potential problems with the use of UFH is the use of such a laboratory test as activated partial thromboplastin time (APTT) for monitoring heparin therapy. In patients with COVID-19, there is a heterogeneity of response when determining aPTT. This may be due to high levels of factor VIII, fibrinogen, or the presence of a lupus anticoagulant. When LMWH is administered, it is necessary to measure the level of anti-Xa factor in order to ensure that the therapeutic level of heparin has been reached[17-18]. These conditions of anticoagulant therapy with the use of LMWH, which determines the choice of the use of POAC in the prevention of thrombogenic complications in patients with COVID-19 in cases of the preferred use of oral forms of anticoagulants, followed by prolonged thromboprophylaxis during the rehabilitation of patients in the postcoid period.

Findings

The study found that the incidence of both thrombogenic outcomes and bleeding events did not show statistically significant differences between the clinical and laboratory parameters of patients with COVID-19, with the recommended thromboprophylaxis Rivaroksaban Nobel, compared with Enoxaparin sodium (Clexane). However, Enoxaparin sodium (Clexane) has shown more significant clinical efficacy compared to Rivaroksaban Nobel. On the other hand, there were no significant differences in the incidence of ARDS and deaths when using Rivaroksaban NOBEL compared to Enoxaparin sodium (Clexane). Thus, our study confirms the hypothesis about the safety and efficacy of the use of DOACs -Rivaroksaban Nobel for the prevention of venous thromboembolism in hospitalized patients with moderate to severe degree of COVID-19.

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