ASSESSMENT OF THE INFLUENCE OF ANTICOAGULANT THERAPY ON COVID-19 COURSE AND OUTCOME


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ABSTRACT

The advent of COVID-19 has given the tasks to healthcare professionals of quickly diagnosing and providing medical care to patients. Currently, an intensive study of the clinical and epidemiological characteristics of the disease is being carried out, and the new ways of its prevention and treatment are being developed. The most common clinical manifestation of a new variant of coronavirus infection is bilateral pneumonia (viral diffuse alveolar damage with microangiopathy); the development of acute respiratory distress syndrome (ARDS) was recorded in 3-4% of patients. Hypercoagulable syndrome with thrombosis and thromboembolism are developing in some organs of patients, other organs and systems are also affected (central nervous system, myocardium, kidneys, liver, gastrointestinal tract, endocrine and immune systems); the development of sepsis and septic shock is possible [1]. The use of anticoagulant therapy with low molecular weight heparins (LMWH) reduces mortality in hospitalized patients with severe form of COVID-19, likely due to its anti-inflammatory and antiviral properties [5]. There is no proven benefit of one LMWH over another. In the suspicion of the development of venous thromboembolic complications, anticoagulant therapy can be started in therapeutic doses before the diagnosis is confirmed; during the period of inpatient treatment, LMWH should be preferred, especially Enoxaparin sodium (Clexane) or UFH, and after discharge from the hospital, it is recommended to switch to direct parenteral anticoagulants, in particular Rivaroksaban NOBEL for a period of at least 3 months [1].

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

Key words: anticoagulant therapy, COVID-19, diffuse alveolar damage, respiratory distress syndrome, venous thromboembolism

I. INTRODUCTION

The emergence of elevated levels of D-dimer and fibrinogen 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 disease progression, leading to adverse 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 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 diagnosis, open up new horizons for its treatment [10,11].
In the 1-Zangiata Clinic of Infectious Diseases from August to December 2020, 372 patients were studied who had laboratory-confirmed COVID-19 of the moderate-severe course. 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 study included patients hospitalized with COVID-19 who underwent a prevention course of venous thrombosis in accordance with current international guidelines. During hospitalization and during the observation period, the clinical status, laboratory parameters, instrumental (MSCT and ultrasound of the chest) data of patients with coronavirus disease were studied. 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) - subcutaneously 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 software program Excel 2017. Student’s t-test was used to compare the mean values. Nonparametric features were compared by contingency tables using the χ² test. p <0.05 was taken as the level of reliability of statistical indicators.

II. MATERIAL AND METHODS

Analysis of the results obtained during the study showed that the main parameters of the coagulogram, in particular APTT, FIB, PT, PTI 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 and the second groups in 82% (n = 98) and 87% (n = 217) of studied cases, respectively.

It should be noted that such a laboratory parameter was determined by practicing physicians quite often (in 50% of patients) to assess the efficacy and safety of heparin therapy, such as BCT. Thus, the BCT in the group of POAG therapy increased from 1.50-2.20 sec to 4.20-4.50, and in the group with LMWH, it increased from an average value of 1.55-2.25 sec to 4.40-5.10 sec, that the differences in indicators in the groups were not statistically significant (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 course of anticoagulant therapy in COVID-19 patients who took Rivaroksaban NOBEL, the average D-dimer value decreased 2.2 times, while in patients who received Enoxaparin sodium (Clexane)
injections, the average values decreased 2.5 times. Thus, in both groups, a significant decrease was achieved in the level of D-dimer - a key biomarker of the risk of thromboembolic complications and adverse outcome in patients with COVID-19.

In 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 who received Enoxaparin sodium (Clexane), thromboembolic complications were observed in 6.8% (n = 17) cases, and in the group with Rivaroksaban NOBEL - 7.4% (n = 9) (χ2 = 0.042, p = 0.84). And the risk of the development (OR) of thromboembolic complications was 1.092.

Further, we analyzed the development of hemorrhagic complications of anticoagulant therapy using LMWH and POAG. 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 group received Enoxaparin sodium (Clexane) versus 1.6% (n = 2) in the Rivaroksaban NOBEL group (χ2 = 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 adverse 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 (χ2 = 2.17, p = 0.14). And the risk of the development of 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 (χ2 = 0.26, p = 0.61). The risk of the development of a lethal outcome was equal to -1.25.

Thus, the use of the first or the other 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.

IV. DISCUSSION

High rates of coagulopathy and venous thromboembolism among hospitalized patients with COVID-19 have 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 prophylaxis with LMWH to prevent thrombosis in COVID-19 patients [7, 9].

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 hospitalized patients in intensive care with COVID-19 pneumonia.

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 bleeding rate (3.2%) is likely due to several common concomitant cardiovascular diseases such as diabetes, stroke, and hypertension, which predispose to frequent bleeding [10,11].

Currently, it is still unknown about the prognosis of the risk of development among hospitalized patients with moderate-severe degree of COVID-19, and there is no data on the effectiveness of the use of POAG, in particular Rivaroksaban NOBEL in this group of patients with COVID-19.

We conducted a study to evaluate the effectiveness and the influence on the outcome of COVID-19 of anticoagulant therapy, in the comparative aspect of the use of LMWH - Enoxaparin sodium (Clexane) and POAG - 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 the development of thrombosis, and the correction of hypercoagulable disorders in patients with moderate-severe form
of COVID-19. In 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 POAG, which makes it possible to recommend POAG 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 heparin therapy with such a laboratory test as activated partial thromboplastin time (APTT) for monitoring. Patients with COVID-19 have a heterogeneous response in determining APTT. This may be due to high levels of factor VIII, fibrinogen, or the presence of a lupus anticoagulant. When LMWH is administered, the anti-Xa factor should be measured to make sure if the therapeutic level of heparin has been achieved [17-18]. These conditions of anticoagulant therapy with the use of LMWH determine the choice of the use of POAG in the prevention of thrombogenic complications in patients with COVID-19 in cases of the preferred use of parenteral anticoagulants, followed by prolonged thromboprophylaxis during the rehabilitation of patients in the post COVID period.

V. CONCLUSION

The main conclusion of our study is that the incidence of both thrombogenic outcomes and bleeding events did not show statistically significant differences between the clinical-laboratory parameters of COVID-19 patients with the recommended thromboprophylaxis Rivaroksaban NOBEL compared to Enoxaparin sodium (Clexane). However, Enoxaparin sodium (Clexane) has shown more significant clinical efficacy compared to Rivaroksaban NOBEL. On the other hand, Rivaroksaban NOBEL was not significantly different from Enoxaparin sodium (Clexane) in ARDS incidence and lethal outcomes. Thus, our study confirms the hypothesis of the safety and efficacy of the use of POAG-Rivaroksaban NOBEL for the prevention of venous thromboembolism in hospitalized patients with COVID-19.

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