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Treatment of Hypercoagulation Syndrome with Anticoagulant Drug in Patients with Covid-19

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Summary

The paper presented the safety and efficacy of Rivaroxaban in the prevention of venous thromboembolism in hospitalized patients with COVID-19.

Keywords: COVID-19, prothrombin index, ferritin, enoxaparin.

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Introduction: The emergence of COVID-19 has posed challenges for healthcare professionals related to rapid diagnosis and provision of medical care to patients. Currently, intensive study of the clinical and epidemiological features of the disease, development of new means of its prevention and treatment continues. The most common clinical manifestation of the new variant of coronavirus infection is bilateral pneumonia (viral diffuse alveolar damage with microangiopathy), acute respiratory distress syndrome (ARDS) is registered in 3-4% of patients. Some patients develop hypercoagulation syndrome with thrombosis and thromboembolism, other organs and systems are also affected (central nervous system, myocardium, kidneys, liver, gastrointestinal tract, endocrine and immune systems), sepsis and septic shock may develop [1].

According to the American Society of Hematology (ASH), there is currently no clear data showing the comparative effectiveness of different types of anticoagulants. The choice of a particular drug 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 presented recently. ASH is awaiting the final results of these trials, based on which it will subsequently update the current recommendations. Therapeutic doses of anticoagulants did not show benefits in participants with critical coronavirus infection, but improved the condition of patients with moderate disease [3].

The use of anticoagulant therapy with low molecular weight heparins (LMWH) reduces mortality in hospitalized patients with severe COVID-19, probably due to its anti-inflammatory and antiviral

properties [5]. There is no proven advantage of any one LMWH over others. If venous thromboembolic complications are suspected, anticoagulant therapy in therapeutic doses can be initiated before diagnosis is confirmed: during inpatient treatment, preference should be given to LMWH, especially Enoxaparin sodium or UFH, after discharge from hospital, it is recommended to switch to direct oral anticoagulants, in particular Rivaroksaban for at least 3 months [1].

Scientific novelty:

The scientific article presented for the first time the safety and efficacy of using the DOAC Rivaroksaban for the prevention of venous thromboembolism in hospitalized patients with COVID-19.

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

Material and research methods

In the 1-Zangiata Infectious Diseases Clinic, 372 patients with laboratory-confirmed moderate COVID-19 were studied from August to December 2020. The patients' age ranged from 29 to 85 years, the average age of which was 57.4 ± 6.77 years. The ratio of men to women was 1.6/1. The study included patients hospitalized with COVID-19 who underwent a course of venous thrombosis prevention in accordance with current international recommendations. During hospitalization and during the observation period, the clinical status, laboratory parameters, instrumental (MSCT and chest ultrasound) data of patients with coronavirus disease were studied. The study assessed the antithrombotic and hemorrhagic effects of the oral anticoagulant Rivaroksaban (n=122) in comparison with the parenteral anticoagulant Enoxaparinsodium (n=250). Based on the risk of venous thromboembolism, standard therapeutic doses were used for Rivaroksaban (Serban) at 20 mg/day and Enoxaparinsodium (Enoxel) subcutaneously at 80 mg/day. The compared patient groups were comparable in age, concomitant diseases, and risks of thromboembolic and hemorrhagic complications.The results were statistically processed using the Excel2017 computer program. Student's t-test was used to compare mean values. Nonparametric features were compared using contingency tables of features using the $\chi 2$ criterion. The level of reliability of statistical indicators was $p < 0.05$.

Research results

In order to monitor the effectiveness of anticoagulant therapy in patients with coronavirus infection at risk of developing venous thromboembolism, the following coagulogram parameters were determined: Activated partial thromboplastin time (APTT), prothrombin index (PTI), prothrombin time (PT); thrombin time (TT), international normalized ratio (INR), fibrinogen (FIB) and blood clotting time (BCT) (Table 1) upon admission and during treatment with Enoxaparinsodium and Rivaroksaban for 10-12 days.

Table 1. Coagulogram indicators in the study groups on admission and in dynamics (M±m)

Indicators	**1 group–** Rivaroksaban **(n=120)**		**2 group -** Enoxaparin sodium – (n=250)	
	Exodus	In dynamics	Exodus	In dynamics
APTT, sec	25.6±0.99	37.2±1.40	25.19±0.93	38.7±1.62
TB, 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
PV, sec	10.59±0.66	15.3±1.04	10.41±0.67	16.3±1.32
PTI, %	116.1±5.31	85.2±7.28	115.7±5.12	83.2±6.98
MNO	0.93±0.04	1.5±0.12	0.95±0.04	1.5±0.11
VSK, sec	1.50-2.20	4.20-4.50	1.55-2.25	4.40-5.10

The analysis of the results obtained during the study showed that the main parameters of the coagulogram, especially 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 reliable difference between the group using Enoxaparin sodium and the group with Rivaroksaban ($p > 0.05$). 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 subjects in 82% (n = 98) and 87% (n = 217) of cases, respectively.

It should be noted that practicing physicians quite often (in 50% of patients) determined such a laboratory parameter as the ISCV to assess the effectiveness and safety of heparin therapy. Thus, the ISCV in the group with DOAC 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, which also did not prove statistically significant ($p > 0.05$).

According to the indicators of blood hemocoagulation balance in patients with COVID-19 upon admission, a tendency towards hypercoagulation was noted 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, the average D-dimer value decreased by 2.2 times, while in patients receiving Enoxaparinsodium injections, the average values decreased by 2.5 times. Thus, in both groups, a reliable decrease in the level of D-dimer, a key biomarker of the risk of developing thromboembolic complications and an unfavorable outcome in patients with COVID-19, was achieved.

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 who received Enoxaparin sodium, thromboembolic complications were observed in 6.8% (n=17) of cases, and in the Rivaroksaban group - 7.4% (n=9) ($\chi2=0.042, p=0.84$). The risk of developing thromboembolic complications (OR) was 1.092.

Further analysis of the development of hemorrhagic complications against the background of anticoagulant therapy with the use of LMWH and DOAC was performed. Bleeding was observed in 12 (3.2%) hospitalized patients. The main sources of bleeding were duodenal ulcers and hemorrhoids. The overall incidence of bleeding was 4% (n=10) of cases in the group of patients who received Enoxaparin sodium compared with 1.6% (n=2) of cases in the group with Rivaroksaban ($\chi2=1.46, p=0.23$). According to these data, the probability of the risk of bleeding was 0.4, which indicates the safety of using both anticoagulants.

According to the assessment of the development of adverse outcomes of COVID-19 during the observation period, acute respiratory distress syndrome (ARDS) developed in 42 (11.3%) patients. The overall incidence of ARDS was 9.6% (n=24) of cases in the group of patients taking Enoxaparin sodium versus 14.8% (n=18) of cases in the Rivaroksaban group ($\chi2=2.17, p=0.14$). 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 with 7.4% (n=9) in the Rivaroksaban group ($\chi2=0.26, p=0.61$). The risk of developing a fatal outcome was equal to -1.25.

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

Discussion

High rates of coagulopathy and venous thromboembolism have been shown in several studies among hospitalized patients with COVID-19 [11]. However, little is known about the potential association between antithrombotic therapy and the clinical presentation of COVID-19. The World Health Organization recommends the use of pharmacological prophylaxis with LMWH for the prevention of thrombosis in patients with COVID-19 [7, 9].

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

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

We conducted a study to assess the effectiveness and impact on the outcome of COVID-19 anticoagulant therapy, in the comparative aspect of the use of LMWH - Enoxaparinsodium and DOAC - Rivaroksaban. Based on the results obtained during this study, we can assume the clinical and laboratory effectiveness of both Enoxaparin sodium and Rivaroksaban in relation to the risk of thrombosis and correction of hypercoagulation disorders in patients with moderate COVID-19. When assessing the safety of anticoagulant therapy in patients with coronavirus infection, no statistical differences were noted in the development of hemorrhagic complications and adverse outcomes in patients who received LMWH and DOAC, which makes it possible to recommend DOAC along with LMWH for the prevention of 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) to monitor heparin therapy. In patients with COVID-19, there is heterogeneity in the response to determining APTT. This may be due to high levels of factor VIII, fibrinogen, or the presence of a lupus anticoagulant. When administering LMWH, it is necessary to measure the level of anti-Xa factor to ensure that the therapeutic level of heparin has been achieved (17-18). These conditions of anticoagulant therapy using LMWH determine the choice of using DOACs in the prevention of thrombogenic complications in patients with COVID-19 in cases of preferable use of oral forms of anticoagulants, followed by extended thromboprophylaxis during the rehabilitation period of patients in the post-COVID period.

Conclusions

The main finding of our study was 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 of Rivaroksaban, compared with Enoxaparinsodium, but Enoxaparinsodium showed more significant clinical efficacy compared with Rivaroksaban. On the other hand, in the process of using Rivaroksaban, there were no significant differences in the incidence of ARDS and death, compared with Enoxaparinsodium. Thus, our study confirms the hypothesis of the safety and efficacy of using DOAC-Rivaryloksaban for the prevention of venous thromboembolism in hospitalized patients with COVID-19.

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