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**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

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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 Rivaroxaban 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).

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

抽象的

COVID-19 的出现赋予了医疗保健专业人员快速诊断和为患者提供医疗服务的任务。目前，正在对该病的临床和流行病学特征进行深入研究，并正在开发新的防治方法。新型冠状病毒感染最常见的临床表现是双侧肺炎（病毒性弥漫性肺泡损伤伴微血管病）；3-4%的患者出现急性呼吸窘迫综合征（ARDS）。患者的某些器官出现血栓形成和血栓栓塞的高凝综合征，其他器官和系统也受到影响（中枢神经系统、心肌、肾脏、肝脏、胃肠道、内分泌和免疫系统）；脓毒症和感染性休克的发展是可能的 [1]。使用低分子量肝素（LMWH）抗凝治疗可降低 COVID-19 重症住院患者的死亡率，这可能是由于其抗炎和抗病毒特性 [5]。没有证明一种 LMWH 优于另一种。怀疑发生静脉血栓栓塞并发症时，可在确诊前开始治疗剂量的抗凝治疗：住院治疗期间应首选低分子肝素，尤其是依诺肝素钠（Clexane）或UFH，出院后在医院，建议改用直接肠外抗凝剂，尤其是 Rivaroxaban NOBEL 至少 3 个月 [1]。

这项工作的目的是对抗凝剂对临床和实验室过程以及冠状病毒感染（COVID-19）结果的影响进行比较评估。

关键词：抗凝治疗，COVID-19，弥漫性肺泡损伤，呼吸窘迫综合征，静脉血栓栓塞

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].

Material And Methods

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 Rivaroxaban 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 Rivaroxaban 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 χ^2 test. $p < 0.05$ was taken as the level of reliability of statistical indicators.

RESULTS

In order to monitor the effectiveness of anticoagulant therapy in patients with coronavirus infection with a risk of developing venous thromboembolism, 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 (Table 1.) upon admission and in the course of treatment with Enoxaparin sodium (Clexane) and Rivaroxaban NOBEL for 10-12 days.

Table 1. Coagulogram indicators in the study groups upon admission and in the course (M \pm m)

Indicators	1 st group - Rivaroksaban NOBEL (n=120)		2 nd group - Enoxaparin sodium (Clexane) (n=250)	
	Outco me	In the course	Outco me	In the course
APT T, 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
PTI, %	116,1± 5,31	85,2±7, 28	115,7± 5,12	83,2±6, 98
INR	0,93±0, 04	1,5±0,1 2	0,95±0, 04	1,5±0,1 1
BCT, 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, 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% ($n = 9$) ($\chi^2 = 0.042$, $p = 0.84$). 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 ($\chi^2 = 1.46$, $p = 0.23$). 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 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 ($\chi^2 = 2.17$, $p = 0.14$). 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 ($\chi^2 = 0.26$, $p = 0.61$). 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.

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 Rivaroxaban 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 thrombotic 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.

Conclusion

The main conclusion of our study is that the incidence of both thrombotic outcomes and bleeding events did not show statistically significant differences between the clinical-

laboratory parameters of COVID-19 patients with the recommended thromboprophylaxis Rivaroxaban NOBEL compared to Enoxaparin sodium (Clexane). However, Enoxaparin sodium (Clexane) has shown more significant clinical efficacy compared to Rivaroxaban NOBEL. On the other hand, Rivaroxaban 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-Rivaroxaban NOBEL for the prevention of venous thromboembolism in hospitalized patients with COVID-19.

References:

1. Временные методические рекомендации по профилактике, диагностике, лечению и реабилитации при коронавирусной инфекции (COVID-19), Версия 8, 2020. (03.09.2020).
2. Громов А.А., Кручинина М.В., Рабко А.В. Коронавирусная болезнь COVID-19: неиспользованные возможности терапии. РМЖ. 2020, №9. С.2-6.
3. Cuker A., Tseng EK., Nieuwlaat R. et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv* (2021) 5 (3): 872–888.
4. Di Micco P, Russo V, Carannante N, Imperato M, Rodolfi S, Cardillo G, et al. Clotting factors in COVID-19: epidemiological association and prognostic values in different clinical presentations in an Italian Cohort. *J Clin Med*. (2020) 9:1371.

5. Fontana P, Casini A, Robert-Ebadi H, Glauser F, Righini M, Blondon M. Venous thromboembolism in COVID-19: systematic review of reported risks and current guidelines. *Swiss Med Wkly.* (2020) 150:w20301.
6. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med.* (2020) 8:e46–7.
7. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. ESC Scientific Document Group developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J.* (2020) 41:543–603.
8. M. Levi, M. Scully, How I treat disseminated intravascular coagulation. *Blood.* (2018) 131:845–54.
9. McCloskey B, Heymann DL. SARS to novel coronavirus: old lessons and new lessons. *EpidemiolInfect.* (2020) 148:e22.
10. Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, et al. Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST guideline and expert panel report. *Chest.* (2020) 158:1143–63.
11. Russo V, Bottino R, Carbone A, Rago A, Papa AA, Golino P, et al. COVID-19 and heart: from clinical features to pharmacological implications. *J Clin Med.* (2020) 9:E1944.
12. Russo V, Rago A, Carbone A, Bottino R, Ammendola E, Della Cioppa N, et al. Atrial fibrillation in COVID-19: from epidemiological association to pharmacological implications. *J Cardiovasc Pharmacol.* (2020) 76:138–45.
13. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* (2020) 18:1094–9.
14. Mega JL, Braunwald E, Wiviott SD, et al; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;366(01):9–19.
15. Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377(14):1319–1330.
16. Cohen AT, Spiro TE, Büller HR, et al; MAGELLAN Investigators. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med* 2013;368(06):513–523.
17. Spyropoulos AC, Ageno W, Albers GW, et al; MARINER Investigators. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. *N Engl J Med* 2018;379(12):1118–1127.
18. Cohen AT, Harrington RA, Goldhaber SZ, et al; APEX Investigators. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med* 2016;375(06):534–544.