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ANTICOAGULANT THERAPY IN PATIENTS WITH COVID-19 FOR THE PREVENTION OF THROMBOPHILIA DEVELOPMENT

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Introduction

The emergence of COVID-19 has posed major challenges for healthcare professionals, particularly in the areas of rapid diagnosis and the provision of medical care to affected patients. Intensive research continues on the clinical and epidemiological features of the disease, as well as on the development of new methods for its prevention and treatment. COVID-19 causes a state of temporary acquired thrombophilia — an increased tendency of the body to form blood clots due to systemic inflammation and the direct effect of the virus on blood vessels.

The most common clinical manifestation of the novel coronavirus infection is bilateral pneumonia (viral diffuse alveolar damage with microangiopathy), while 3–4% of patients develop acute respiratory distress syndrome (ARDS). Some patients develop hypercoagulable syndrome with thrombosis and thromboembolism; other organs and systems may also be affected, including the central nervous system, myocardium, kidneys, liver, gastrointestinal tract, and the endocrine and immune systems. Sepsis and septic shock may also occur [1].

According to the American Society of Hematology (ASH), there is currently no conclusive evidence regarding the comparative efficacy of different types of anticoagulants. The choice of a particular drug may depend on availability, ease of use, patient contraindications, and other factors. As noted by the authors of the interim analyses of three clinical trials of anticoagulants in COVID-19 (REMAP-CAP, ACTIV-4, and ATTACC), therapeutic doses of anticoagulants did not demonstrate benefit in critically ill COVID-19 patients but improved outcomes in those with moderate disease severity [3].

The use of low-molecular-weight heparin (LMWH) therapy has been shown to reduce mortality among hospitalized patients with severe COVID-19, likely due to its anti-inflammatory and antiviral properties [5]. No single LMWH has demonstrated superiority over others. In cases where venous thromboembolic complications are suspected, therapeutic-dose anticoagulant therapy may be initiated before diagnosis is confirmed. During hospitalization, LMWH—particularly enoxaparin sodium or unfractionated heparin (UFH)—is preferred, whereas after discharge, switching to a direct oral anticoagulant (DOAC), specifically rivaroxaban, is recommended for a minimum of three months [1].

Scientific Novelty

This study is the first to present data on the safety and efficacy of the direct oral anticoagulant rivaroxaban for the prevention of venous thromboembolism in hospitalized COVID-19 patients.

Objective

To conduct a comparative assessment of the effects of different anticoagulants on the clinical and laboratory course and outcomes of coronavirus infection (COVID-19).

Materials and Methods

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From August to December 2020, a total of 372 patients with laboratory-confirmed, moderately severe COVID-19 were studied at the 1st Zangiata Infectious Diseases Clinic. Patients ranged in age from 29 to 85 years (mean age 57.4 ± 6.77 years); the male-to-female ratio was 1.6:1. All patients received venous thrombosis prophylaxis in accordance with current international guidelines.

Clinical status, laboratory parameters, and instrumental findings (MSCT and chest ultrasound) were assessed during hospitalization and follow-up.

Antithrombotic and hemorrhagic effects of the oral anticoagulant rivaroxaban (n = 122) were compared with those of the parenteral anticoagulant enoxaparin sodium (n = 250). Standard therapeutic doses were used: rivaroxaban (Serban) 20 mg/day orally and enoxaparin sodium (Enoxel) 80 mg/day subcutaneously. The study groups were comparable in age, comorbidities, and risk of thromboembolic and hemorrhagic complications.

Statistical analysis was performed using Excel 2017. Student's *t*-test was used for comparing means, and nonparametric data were analyzed using contingency tables and the χ^2 test. A p-value < 0.05 was considered statistically significant.

Results

To monitor anticoagulant therapy efficacy, coagulation parameters—activated partial thromboplastin time (APTT), prothrombin index (PTI), prothrombin time (PT), thrombin time (TT), international normalized ratio (INR), fibrinogen (FIB), and clotting time (CT)—were evaluated upon admission and after 10–12 days of treatment with enoxaparin sodium or rivaroxaban (Table 1).

Table 1. Coagulation parameters in study groups at baseline and during therapy (M ± m)

Parameter	Group 1: Rivaroxaban (n=120)	Group 2: Enoxaparin sodium (n=250)
APTT (s)	25.6 ± 0.99 → 37.2 ± 1.40	25.19 ± 0.93 → 38.7 ± 1.62
TT (s)	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 (s)	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 ± 0.12	0.95 ± 0.04 → 1.5 ± 0.11
CT (s)	1.50–2.20 → 4.20–4.50	1.55–2.25 → 4.40–5.10

Analysis showed that major coagulation parameters (especially APTT, FIB, PT, PTI, and INR) reached reference values during therapy, with no statistically significant differences between the enoxaparin and rivaroxaban groups (p > 0.05).

D-dimer levels, elevated at admission (856 ng/mL and 872 ng/mL, respectively), decreased significantly in both groups after anticoagulant therapy—by 2.2 times in the rivaroxaban group and 2.5 times in the enoxaparin group—indicating effective correction of hypercoagulation.

Thromboembolic complications were observed in 26 (7%) patients overall—6.8% (n = 17) in the enoxaparin group and 7.4% (n = 9) in the rivaroxaban group ($\chi^2 = 0.042$, p = 0.84). The odds ratio (OR) for thromboembolic complications was 1.092.

Bleeding events occurred in 12 (3.2%) patients: 4% (n = 10) in the enoxaparin group and 1.6% (n = 2) in the rivaroxaban group ($\chi^2 = 1.46$, p = 0.23; OR = 0.4), indicating good safety for both agents.

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ARDS developed in 42 (11.3%) patients: 9.6% (n = 24) with enoxaparin versus 14.8% (n = 18) with rivaroxaban ($\chi^2 = 2.17$, $p = 0.14$; OR = 1.63).
Overall mortality was 6% (n = 15) for enoxaparin and 7.4% (n = 9) for rivaroxaban ($\chi^2 = 0.26$, $p = 0.61$; OR = 1.25).

Thus, the use of either anticoagulant did not significantly alter the risks of thrombosis, bleeding, ARDS, or in-hospital mortality among COVID-19 patients.

Discussion

A high incidence of coagulopathy and venous thromboembolism among hospitalized COVID-19 patients has been confirmed in several studies [11]. However, little is known about the relationship between antithrombotic therapy and COVID-19 clinical outcomes. The WHO recommends pharmacological thromboprophylaxis with LMWH for all hospitalized COVID-19 patients [7, 9].

Despite systematic LMWH prophylaxis, the incidence of thrombosis remains higher than in other clinical conditions associated with disseminated intravascular coagulation [6, 12]. Fontana *et al.* found that thromboembolic risk ranges from 4.4% to 8.2% in hospitalized COVID-19 patients and up to 53.8% in critically ill patients in intensive care.

The high rate of thromboembolic events despite heparin prophylaxis may be explained by the multifactorial nature of COVID-19–associated coagulopathy, characterized by excessive cytokine and chemokine release (TNF-α, IL-1, IL-6, IL-8) [4, 5, 7, 13], leading to pulmonary microvascular thrombosis, vascular edema, and hemorrhagic complications. The relatively high bleeding rate (3.2%) may reflect frequent comorbid cardiovascular conditions such as diabetes, stroke, and hypertension [10, 11].

Our study compared LMWH (enoxaparin sodium) and the DOAC (rivaroxaban) in terms of efficacy and impact on COVID-19 outcomes. The findings indicate that both agents effectively reduce thrombotic risk and correct hypercoagulability in moderately severe COVID-19. No significant differences in bleeding or adverse outcomes were found, suggesting that DOACs can be safely recommended alongside LMWH for COVID-19–associated thrombosis prophylaxis.

Monitoring LMWH therapy via activated partial thromboplastin time (APTT) can be problematic in COVID-19 patients due to variability caused by elevated factor VIII, fibrinogen, or lupus anticoagulant. Measuring anti-Xa activity is preferable to confirm therapeutic heparin levels [17–18]. These limitations favor the use of DOACs, such as rivaroxaban, especially for extended thromboprophylaxis during the post-COVID rehabilitation period.

Conclusions

The frequency of thrombotic and bleeding events did not differ significantly between patients treated with rivaroxaban and those treated with enoxaparin sodium. However, enoxaparin demonstrated slightly greater clinical efficacy.
At the same time, rivaroxaban showed comparable safety, with no increase in ARDS or mortality rates. Thus, our study supports the hypothesis that the direct oral anticoagulant rivaroxaban is both safe and effective for the prevention of venous thromboembolism in hospitalized COVID-19 patients.

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