DOI: 10.17816/KMJ2020-485

Recommendations for the prevention and correction of thrombotic complications in COVID-19

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Abstract

The new coronavirus infection caused by the SARS-CoV-2 virus (COVID-19) is characterized by a high frequency of thrombotic complications varying from venous or, more rarely, arterial thrombosis to the development of disseminated intravascular coagulation (DIC) and/or diffuse pulmonary vascular microthrombosis, which aggravates the disease and becomes one of the leading causes of deaths. Timely and personalized anticoagulant thromboprophylaxis with low-molecular-weight heparins may prevent a severe course of the disease and improve outcomes. This applies to outpatients, hospitalized patients and patients in the early post hospital period. In the future, to develop comprehensive and evidence-based guidelines on the management of patients with COVID-19, it is necessary to conduct comprehensive systematic studies and comparative clinical trials of prophylaxis and treatment of hemostatic disorders in patients with COVID-19.

Keywords: coronavirus disease 2019, SARS-CoV-2, thrombosis, hemostatic disorders, anticoagulant therapy.

For citation: Safiullina S.I., Litvinov R.I. Recommendations for the prevention and correction of thrombotic complications in COVID-19. *Kazan Medical Journal.* 2020; 101 (4): 485–488. DOI: 10.17816/KMJ2020-485.

The disease caused by the SARS-CoV-2 coronavirus, known as COVID-19 (Coronavirus Disease 2019), is characterized by a frequent combination of respiratory disorders and coagulopathies in patients with a moderate or severe course of the disease. Thromboembolic complications in this category of patients represent one of the reasons for the severity of the condition and the probability of a lethal outcome [1].

In COVID-19, hemostatic disorders vary widely from latent hypercoagulation detected only by laboratory tests to severe clinical manifestations in the form of cerebral or coronary arterial thrombosis or venous thrombosis complicated by pulmonary artery thromboembolia, as well as regional microthrombosis or disseminated intravascular coagulation (DIC) syndrome [2,3]. It is the preterminal DIC that most often causes progressive multiorgan failure, although, unlike sepsis and other acute pathological conditions, DIC in COVID-19 is not usually accompanied by consumption coagulopathy and hemorrhagic diathesis [4].

Intravascular thrombogenesis in COVID-19 is located most often in the lung vessels. It is known that the activation of the blood coagulation system and the formation of clots in the inflammation foci represent a defense mechanism aimed at the physical delimitation of the focal point of infection, preventing the invasion of the pathogen and its spread in the body [5–7].

The primary target of SARS-CoV-2 is the respiratory epithelium cells, in which the lesion is accompanied by the activation of alveolar macrophages, and the inflammatory "cytokine storm" caused by them provokes endothelial hyperactivation in the pulmonary microcirculation, followed by microthrombosis, which aggravates the syndrome of acute respiratory failure [8]. It should be noted that fibrin can accumulate in the vessels of the lungs and alveolar exudate even before the detection of radiographic symptoms, which are defined as COVID-19 pneumonia. Regardless of the cause, diffuse immunothrombosis of microvessels prevents blood oxygenation, including during artificial lung ventilation [9].

Considering the exceptional danger of the thrombotic complications in COVID-19 and based on the literature data as well as on contemporary scientific concepts and our own clinical experience in managing patients with coagulopathies, we have formulated the following proposals for the prevention and treatment of hemostatic disorders

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Table 1. Recommended doses of low molecular weight heparins for anticoagulant prophylaxis or treatment according to the patient's body weight

Low preventive dose corresponding to the patient's body weight (kg) below	Enoxaparin sodium	Dalteparin sodium	Nadroparin calcium
<50	20 mg	2,500 U	2,850 U
51–90	40 mg	5,000 U	3,800 U
91–130	60 mg	7,500 U	5,700 U
130–170	80 mg	10,000 U	7,600 U
>170	0.6 mg/kg per day	75 U/kg per day	42 U/kg per day
High preventive dose (with a body weight of 51–90 kg)	40 mg, 2 times a day (or 0.5 mg/kg, 2 times a day)	5,000 U 2 times a day	3,800 U, 2 times a day
Therapeutic dose	1 mg/kg, 2 times a day	100 U/kg, 2 times a day	86 U/kg, 2 times a day

in COVID-19. These proposals do not contradict the temporary recommendations of the Ministry of Health of the Russian Federation [10]; however, they expand the indications for thromboprophylaxis, while facilitating the selection and calculation of the dose of anticoagulants.

Outpatients with mild COVID-19

Due to the fact that thrombosis has a latent phase and manifests itself clinically only when the functions of the lungs and/or other organs are significantly impaired as a result of impaired blood circulation, drug anticoagulant prophylaxis for all COVID-19 patients, including outpatients at the onset of the disease, seems reasonable. Such prophylaxis aims to prevent the progression of the disease to a moderate or severe course due to the development of thrombotic complications. This recommendation is not applicable to patients with asymptomatic COVID-19 and those with contraindications to anticoagulant administration (see Appendix). Immediate thromboprophylaxis is especially relevant for COVID-19 patients who have premorbid risk factors for thromboembolic complications, such as a compromised family and/or personal thrombotic anamnesis, obesity, smoking, varicose veins of the lower extremities, etc. Regardless of the drug prescriptions, non-drug thromboprophylaxis is strongly recommended for all COVID-19 outpatients, namely wearing of compression garments and other methods of controlling venous congestion in the lower extremities.

Low molecular weight heparin (LMWH) is the drug of choice for thromboprophylaxis in COVID-19 for the following reasons:

a) LMWH has an anti-inflammatory effect in addition to its anticoagulant effect;

b) As a rule, the administration of preventive doses of LMWH does not require laboratory control;

c) unlike oral anticoagulants, the active concentration of LMWH can be quickly adjusted, both to increase or to decrease in case of cancellation;

d) the use of LMWH is rarely complicated by heparin-induced thrombocytopenia, whereas with the administration of unfractionated heparin, the risk of heparin-induced thrombocytopenia is increased many times;

e) compared with unfractionated heparin, the incidence of hemorrhagic complications with LMWH is significantly lower.

Preventive administration of LMWH is also possible without a laboratory study of hemostasis indicators. However, under conditions of outpatients with a clinical presentation of COVID-19, dynamic laboratory monitoring of hemostasis is recommended, regardless of whether patients receive heparin or not. The recommended minimum coagulogram includes fibrinogen and D-dimer levels, and a complete blood test with platelet counts to rule out heparin-induced thrombocytopenia. Analyses are recommended to be performed at least 2 times a week, or even more often in case of negative dynamics. Monitoring the hemostasis system will identify patients with latent hypercoagulation and a high risk of a mild disease transformation into a more severe form, especially in patients with concomitant pathology. Progressive hyperfibrinogenemia and high levels of D-dimer (including the presence of thromboprophylaxis) are unfavorable prognostic factors that may justify more aggressive therapy and hospitalization.

The preventive dose of LMWH should be individualized based on the severity of clinical symptoms and the patient's body weight, as well as taking into account the activity of different LMWHs (Table 1). The recommended mode of administration is subcutaneously, 1 time per day. The duration of anticoagulant thromboprophylaxis is determined individually. As a rule, if hospitaliza-

tion is not required, LMWH is recommended to be used for at least 2 weeks after the disappearance of clinical symptoms or until the D-dimer and fibrinogen level is normalized.

Hospitalized patients with COVID-19 and patients in the early post-hospital period

Given the mortal danger of thromboembolic complications that develop in the absence of thromboprophylaxis or in cases of its ineffectiveness, LMWH at a high prophylactic or therapeutic dose is recommended to all hospitalized COVID-19 patients. Table 1 can be used when determining the dose. Administration schedule comprises 2 subcutaneous injections per day with an interval of 12 h. In patients with concomitant diseases and to exclude incompatibility with other drugs, individual selection of the LMWH dose under the control of anti-Xa activity is possible.

In hospitalized patients, daily monitoring of hemostasis indices is recommended, including at least fibrinogen, D-dimer levels, and a general blood analysis with platelet count. A progressive increase in the D-dimer and fibrinogen levels is a sign of an insufficient anticoagulant dose and the reason for its increase under continuous (daily or several times a day) laboratory control. In order to avoid hemorrhages, increasing the LMWH dose is advisable under the control of global hemostasis tests, such as thrombodynamics and thromboelastography (thromboelastometry).

Given that COVID-19 patients are at a high risk of thrombotic complications, patients need to continue thromboprophylaxis after discharge from the hospital. The LMWH drugs (the same that the patient received in the hospital) in a standard prophylactic dose (see Table 1) are preferable. An alternative to LMWH is direct oral anticoagulants, which are used according to the same protocols that are used in orthopedic surgery to prevent postoperative thrombosis. The duration of post-hospital thromboprophylaxis is determined individually, taking into account the risk factors for thrombosis until the D-dimer and fibrinogen parameters normalize, but not less than 2 weeks after discharge. Non-drug methods of thromboprophylaxis are recommended to all patients with a history of COVID-19.

In conclusion, it should be emphasized that the proposals presented for prevention and treatment of thrombotic complications of COVID-19 are absolutely advisory in nature. These recommendations summarize a significant part of the information accumulated and published in the relatively short time of the COVID-19 pandemic spread, which prompts more active prevention and treatment of thrombotic complications with direct anticoagulants. It should be noted that all the existing studies on coagulopathies in COVID-19 patients, performed at the height of the pandemic, are preliminary in nature, and their results may be revised in the future after a thorough retrospective analysis of the cumulative clinical experience and in the light of new data on COVID-19 pathogenesis.

Appendix

Contraindications for the administration of anticoagulant thromboprophylaxis to COVID-19 outpatients:

- hypersensitivity to LMWH or any other component of the drug;
- kidney disease, since LMWH unlike unfractionated heparin, is excreted in urine;
- a history of heparin-induced thrombocytopenia type I or II;
- current thrombocytopenia of any etiology;
- hemorrhage or an increased risk of bleeding associated with hereditary or acquired disorders of hemostasis;
- organic lesions of internal organs with a tendency toward hemorrhage;
- a history of intracranial hemorrhage;
- uncontrolled arterial hypertension (>180 mmHg).

Authors' contributions. S.S.I. and R.I.L. wrote the text.

Funding. Competitiveness Enhancement Program of the Crimean Federal University.

Conflict of interest. The authors declare no conflict of interest related to the article presented.

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