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PROBLEMS AND WAYS TO CORRECT ANTICOAGULANT THERAPY IN PATIENTS WITH CORONAVIRUS INFECTION

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Annotation. *Patients with COVID 19 have a hypercoagulable state, which increases the risk of thrombosis and thromboembolic complications. This condition is also called COVID 19 associated coagulopathy, which manifests as increased fibrinogen and D-dimer levels, prolongation of aPTT (Activated Partial Thromboplastin Time) and PT (Prothrombin time), changes in platelet levels in the early stage of the disease. This article discusses issues and problems of rational anticoagulant therapy in patients with coronavirus infection.*

Key words: *COVID 19 associated coagulopathy, anticoagulant therapy, heparin, low molecular weight heparins, D-dimer*

Since the beginning of 2020, the attention of the international medical community has been focused on the problem of diagnosis and therapy of patients with COVID-19. One of the most significant adverse prognostic features for patients with COVID-19 is the development of abnormalities in the hemostasis system. Patients with COVID 19 have conditions associated with hypercoagulation, which increases the risk of thrombosis and thromboembolic complications. This condition is also called COVID 19-associated coagulopathy. In COVID-19-associated coagulopathy, there is widespread inflammation and endothelial cell dysfunction, abnormal blood flow dynamics and activated platelets, high concentrations of Willebrand factor, free cellular DNA,

histones, and viral RNA, which together cause factor XI activation, thrombin generation and fibrin formation. Initial COVID-19 coagulopathy is represented by markedly elevated D-dimer and fibrin/fibrinogen degradation products, whereas abnormalities of prothrombin time, partial thromboplastin time and platelet count are relatively rare in the initial manifestations. Coagulopathy characterizes up to 55% of hospitalized patients with COVID-19. Thrombosis and coagulopathy associated with COVID-19 are a major cause of morbidity and mortality.

It is assumed that several mechanisms underlie the prothrombotic changes in COVID-19. These are disseminated intravascular coagulation (DIC), pulmonary intravascular coagulopathy or microcirculatory obstructive pulmonary thrombotic syndrome, secondary hemophagocytic lymph histiocytosis, thrombotic microangiopathy and endotheliosis. Most likely, DIC syndrome underlies the progression of multiple organ failure, which occurs faster in the absence of anticoagulant prophylaxis, and may also be due to the occurrence of septic complications.

Scientific evidence suggests prothrombotic changes in the hemostatic system, occurring mainly in hospitalized patients with moderate to severe forms of the disease. The main laboratory markers are increased levels of D-dimer and fibrinogen, prolongation of aPTT and prothrombin time (PT), thrombocytopenia or thrombocytosis. These results may have prognostic value and influence decisions regarding therapy and additional diagnostics required. One of the main laboratory indicators to guide the physician in prescribing anticoagulant therapy is the blood D-dimer level. D-dimer is a product of fibrin breakdown, a small fragment of protein present in blood after clot breakdown. Elevated D-dimer levels (above 1 mg/ml) are one of the serious independent risk factors for death in the population. An increased D-dimer level has now been proven to be associated with high mortality in patients with COVID-19. Due to the fact that coagulopathy may develop in the late stages of hospitalization, routine periodic blood clotting measurements should be performed in all patients with coronavirus infection.

This has led to considerable interest in the potential of anticoagulants in COVID-19 patients. Anticoagulants are administered to all hospitalized patients (if there are no

contraindications) at a prophylactic dose for the duration of the COVID-19 hospitalization and should be continued at least until discharge. Low molecular weight heparin is preferred unless contraindicated, such as acute renal injury (ARI), in which unfractionated heparin is more appropriate.

Increasing the dose of heparin and low molecular weight heparin to an intermediate or therapeutic dose may be considered in patients with high and extremely high D-dimer levels, in the presence of additional risk factors for venous thromboembolic complications, and in severe COVID-19 manifestations.

Start therapy with therapeutic doses is used when patients have received anticoagulants before hospitalization due to atrial fibrillation, after an acute episode of venous thromboembolic complications, after implantation of mechanical heart valve prostheses.

Heparin and low molecular weight heparins in addition to their anticoagulant activity have anti-inflammatory, anti-viral, and other properties. Heparin binds to many proteins and modulates their activity that mediates inflammation, including interleukin-8, platelet growth factor 4, neutrophil elastase, P- and L-selectin. Heparin can also attenuate inflammation by interacting with key inflammatory mediators, since it is itself a physiological antagonist of serotonin and histamine. SARS-CoV-2 penetration into endothelial and epithelial cells is thought to depend on its interaction with cell surface heparan sulfate. Thus, heparin or its synthetic heparin-like preparations, can inhibit this interaction and block virus penetration.

Peroral anticoagulants, which are direct inhibitors of activated clotting factor Xa, (rivaroxaban, apixaban) are recommended for patients with asymptomatic, mild, and moderate COVID-19 in the presence of risk factors of venous thromboembolic complications and minimal risk of bleeding. Peroral anticoagulants, in addition to their anticoagulant effects, may also have anti-inflammatory effects in COVID-19. Rivaroxaban prevents arterial and venous thrombosis in patients with a history of acute coronary syndrome, However, there are concerns about the use of peroral anticoagulants in patients with acute renal failure. Peroral anticoagulants are not prescribed in patients with COVID-19 who have severe renal dysfunction, mechanical heart valves, and

antiphospholipid syndrome.

When prescribing anticoagulant therapy for patients with COVID-19 to date, there are several problems:

1. One potential problem with the use of unfractionated heparin is the use of an aPTT to monitor heparin therapy. Patients with COVID19 have a heterogeneous response when determining the aPTT (as there is a prolongation of this aPTT index in the disease). This may be due to high levels of factor VIII, fibrinogen, or the presence of lupus anticoagulant.

2. When low molecular weight heparin is introduced, anti-Xa factor levels should be measured to see if therapeutic heparin levels are reached. But many clinics and hospitals do not determine this laboratory indicator (measurement of anti-Xa factor level).

3. The use of heparin as a therapeutic anticoagulant is associated with a risk of bleeding (in 3-5% of patients). When unfractionated heparin is used, heparin-induced thrombocytopenia may occur in a small proportion of patients. First of all, these are patients with a history of allergic processes or with the presence of hemolysis. Factors that may increase the risk of bleeding are older age, comorbid conditions, recent trauma or surgery, prolonged hospitalization, and decreased white blood cell and platelet counts. Many of these risk factors are seen in patients with COVID-19.

4. The evaluation of the interaction of anticoagulants with other drugs is not considered.

Table 3 - Interaction of anticoagulants with other drugs

Combination of medicines	Expected outcome
UFH/ LMWH+ gentamicin, cephalosporins	anticoagulant effect increases
UFH/LMWH + tetracyclines, polypeptides, GC	anticoagulant effect decreases
UFH/LMWH + carbenicillin, piperacillin/tazobactam, antiaggregant	the risk of bleeding increases
UFH/LMWH + NSAIDs (Nonsteroidal anti-inflammattory drugs) and GCs(glucocorticosteroids)	increased risk of ulcerogenic effects and bleeding in the gastrointestinal tract
UFH/LMWH + selective serotonin reuptake inhibitors, antiaggregant	anticoagulation effect increases
UFH/LMWH + Oral contraceptives	anticoagulant effect decreases
UFH/LMWH + ACE inhibitors, ARBs, potassium-saving diuretics	hyperkalemic effect increases

Conclusion:

SARS-CoV-2/COVID-19 infection often causes hypercoagulation with inflammation, accompanied by increased levels of clotting factors and disruption of normal vascular endothelial cell hemostasis, leading to local thrombus formation and systemic coagulation disorder, leading to large vessel thrombosis and thromboembolic complications in severe patients. COVID-19-associated coagulopathy is manifested by increased levels of fibrinogen and D-dimer, and prolongation of aPTT and PV, changes in platelet levels in the early stage of the disease. High D-dimer level is associated with increased mortality of patients, and further progression of its level precedes the development of multiple organ failure and DIC.

Thus, to eliminate the problems of anticoagulant therapy it is necessary to:

1. Carefully collect the pharmacological anamnesis.

2. Rule out contraindications to anticoagulant therapy.

3. Avoid dangerous combinations if possible. Increase monitoring for side effects (e.g., bleeding) if concomitant use of such combinations is necessary.

4. Conduct drug monitoring of anticoagulant therapy (monitoring the efficacy and safety of drug administration).

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