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EDITORIAL

Thrombosis and anticoagulation in COVID-19

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Coronavirus disease 2019 (COVID-19) has recently been described, and it has been reported that 15% of patients with the disease develop the severe form.[1] Because the lungs are the organs most often affected, clinical deterioration can occur, with progression to hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS), within a few days after symptom onset. In the context of a pandemic that has important prognostic implications, the investigation of new treatments is justified.

Studies on pharmacological treatment, including systemic corticosteroid therapy, have recently been published. The practices employed in patients with ARDS should also be prioritized in the supportive care of patients with COVID-19 in the ICU, such as protective strategies for mechanical ventilation, neuromuscular blocks, prone positioning, and conservative fluid administration. However, although COVID-19 is pathologically similar to ARDS, most patients with COVID-19 present with slightly impaired ventilatory mechanics and reduced potential of recruitment, despite significant hypoxemia.[2,3] The discrepancy between changes in gas exchange, radiological findings, and findings regarding respiratory mechanics might indicate a vascular component of the disease, as evidenced by a high shunt fraction[4] and the presence of thrombi in the microcirculation, which have been identified in autopsy studies.[5]

In this context, a state of hypercoagulability and hematological changes have been described in up to one third of the patients, the increase in D-dimer levels being an important marker of unfavorable outcomes.[6] Therefore, some retrospective studies have investigated the occurrence of venous thromboembolism (VTE) in patients with COVID-19, identifying it in up to 40% of those patients.[7] If an active search for VTE, by means of ultrasound venous mapping of the lower limbs, is performed, that rate is nearly 70% among ICU patients with COVID-19.[8]

It is of note that D-dimer is a fibrin degradation product that might be elevated due to the simultaneous activation of fibrinolysis during the formation of thrombi. The determination of D-dimer levels is nonspecific, and those levels might be increased in other situations, such as in cancer, after surgery, in infections, or during pregnancy. As described above, an increase in the levels of this marker is common in patients with COVID-19, which makes it difficult to use in the investigation of VTE in those patients. Therefore, in patients with COVID-19 and a high pre-test probability of thrombotic events, especially in those with disproportionate hypoxemia, D-dimer levels should not contribute to the clinical decision-making to continue the investigation, because this test is more important for excluding the disease in populations with a low prevalence of VTE (< 10%). Likewise, because this test has low specificity in populations with a high prevalence of VTE (> 50%), it should not influence the diagnosis in this situation.

Although there is clear evidence of an increased risk of VTE in COVID-19, the use of full anticoagulation in all COVID-19 patients has been questioned and is not currently recommended by international societies.[9] In suspected cases of VTE, it is suggested that the use of empirical anticoagulation be carefully evaluated, especially when we consider the risk-benefit ratio according to the clinical probability, and the diagnosis should be made as soon as possible to minimize the risk of bleeding. More importantly, the determination of D-dimer levels is of little use for the diagnosis of VTE when analyzed in isolation, especially in this high-risk population, in which the positive predictive value of the test is low. This is even more relevant in ICU patients who have a high inflammatory response. However, for patients in whom the clinical probability is higher (e.g., in those with worsened hypoxemia despite improved radiological findings and infection control), the determination of D-dimer levels can be useful. It is possible that future studies will identify higher cutoff points that might increase the specificity of this test for COVID-19. It is important to highlight the association between increased levels of D-dimer and systemic inflammation, as demonstrated by the correlation between high serum C-reactive protein levels and high D-dimer levels, even in patients with COVID-19.[10]

If the empirical treatment of macrovascular events is controversial, there is even less evidence to support its use in the treatment of microthrombi. A procoagulant state has been widely described in patients with sepsis and ARDS, as well as in those with other types of viral pneumonia, such as that caused by influenza. In fact, vascular lesions have been identified in patients with ARDS, not only in autopsy studies but also in ICU patients by means of pulmonary angiography. Patients with microthrombosis are not necessarily diagnosed with disseminated intravascular coagulation, and there is no evidence to support the use of full anticoagulation in this clinical situation.

Although some researchers recommend the prophylactic use of moderate doses of anticoagulants, that approach has not been shown to be beneficial in reducing mortality in patients without cancer. As expected, the incidence of VTE is lower when that therapy is employed, although there might be a greater chance of adverse hemorrhagic

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events.[11] In patients with COVID-19, this can be aggravated by the presence of other risk factors for bleeding, such as renal dysfunction and stroke, even in young patients.[12]

To date, the best approach to treat patients with COVID-19 is to underscore the approach recommended for diseases with a high thrombotic risk: performing routine thromboprophylaxis in all hospitalized patients and increasing surveillance and clinical suspicion, especially in patients with gas exchange alterations disproportionate to the degree of systemic inflammation and the radiological findings. While we await the results of clinical trials studying the use of higher doses of anticoagulants in COVID-19, we recommend greater surveillance and screening in the presence of additional risk factors, such as the use of mechanical ventilation.

Results of studies on anticoagulation in COVID-19 are expected to be published soon; however, we cannot stop to wait for good evidence to guide us if it is still unavailable. Appropriate, personalized clinical judgment supersedes "cookie-cutter" solutions and helps ensure that the patient receives high-quality care. However, clinical decision-making must be based on the best evidence available for similar diseases, rather than on just any evidence, taking into consideration not only the benefits but also the risks that that chosen course of action might carry.

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