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Thrombotic Events in COVID-19: Inquires About the Deleterious Procoagulant Effect of Corticosteroid Therapy

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The novel coronavirus disease (COVID-19) pandemic probably has all the potential to become a potent candidate for the 21st-century disease award since it demonstrated an incredible ability to disguise symptoms and emulate pathology without precedent in viral disease. From the early-described Acute Respiratory Distress Syndrome (ARDS)-associated microemboli[1] to the venous thromboembolism (VTE) and deep venous thrombosis (DVT), coagulation disorders have been the primordial target of treatment. Anticoagulants have probably been the most constant therapeutical certainty present in all COVID-19 management guidelines throughout the world.

Since the beginning of the pandemic, associating corticosteroids with the COVID-19 treatment has been a subject of debate. However, there is sufficient data to support that corticoid therapy proved to be efficient in reducing mortality and preventing evolution toward severe forms,[2] especially in patients requiring oxygen supplementation. Still, this debate continues at a more specific level since there is evidence of no significant reduction in mortality on patients receiving methylprednisolone during hospitalization,[3] and associating with a higher thrombosis risk has been raised around corticoid administration.

In Clinical and Applied Thrombosis/Hemostasis, we recently noticed a meta-analysis related to deep vein thrombotic events in COVID-19 patients with corticosteroid treatment.[4] The authors describe the pathophysiology of COVID-19-induced thromboembolism and highlight its frequent concomitance with the moderate to severe pulmonary forms of the disease that need corticosteroid treatment. Given the immune-thrombotic characteristic of this disease, the study describes the challenging "fine line" of treating acute respiratory suffering with an underlying coagulopathy. They conclude that, despite respiratory benefits, corticosteroids may cause VTE in patients with severe forms of COVID-19 and elevated D-dimers levels. Monitoring D-Dimers and constantly use of thrombotic risk-assessment tools seem to become required standards when treating severe forms. Nevertheless, we believe that this subject deserves further discussion and more questions on the matter.

It has been stated before that a pro-coagulation state is induced by corticoid administration, especially in patients with chronic inflammatory diseases. Corticotherapy seems to interfere with coagulation factor IX, X, XII causing increased expression of the first and decreased expression of the latter while preserving the prothrombin time but shortening the activated partial thromboplastin time. This interference demonstrates that the hypercoagulability state of COVID-19[5] extends beyond the pulmonary viral aggression and opens a whole new pathological expression of SARS-COV-2, qualifying COVID-19 more a systemic disease rather than viral pneumonia with high potential for severity.

Although salvatory in the acute respiratory phase, corticosteroids may also be triggers for the "devil within" as there is sufficient data in case reports throughout the world that suggests an acute episode of severe clinical degradation in patients that initially had a favorable clinical course. More often, cases of severe acute neurological and cardiovascular onsets (such as stroke or myocardial infarction) are reported in patients with moderate to severe forms of COVID-19 outside their acute pulmonary phase.

Another debatable aspect is the prominent association between corticotherapy and anticoagulants, a combination used

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to prevent severe outcomes that deliver significant clinical success on a short-term basis. However, a long-term course seems to interfere with the international normalized ratio (INR). Methylprednisolone acts as a vitamin K inhibitor but with an unclear mechanism, while this seems not to be the case in COVID-19 patients as thrombotic events occur via an alternative mechanism.[5]

As one progresses in understanding this disease, we find ourselves in the "tight-rope walker" position, on the one hand with the need of preventing or relieving the high inflammatory consequences of the viral aggression with corticoid therapy and, on the other hand, assuming little-known mechanisms of interference that could trigger a systemic-wide catastrophe with underlying subtleties that elude us.

Implications of genetics and the apparent link with thrombophilia-involved genes[5] support the theory that there is a strong correlation between the patient's genetic profile and the risk for thrombosis. However, a pertinent question arises: are corticosteroids a friend or a terrible foe for patients with a congenital or acquired predisposition to thrombosis? Furthermore, as a subsequent inquiry, we have to ask ourselves: how efficient is the prophylactic anticoagulation therapy for patients with previous risk factors and severe forms of COVID-19, significantly as these patients have very reduced (or none) mobility? There are case reports of distant severe thrombotic events in patients with previous moderate to severe forms of COVID-19 (despite prophylactic anticoagulant therapy during the acute phase). So, as hazardous as it may seem at this point, clinicians should consider a "leap of faith" and prescribe therapeutical doses of anticoagulants, monitoring the APTT (or complete coagulation tests, if available), and then continue with a prolonged cure. This proposal is supported by literature data that suggests a tendency to reduce the mortality of severe patients.[6] As far as "long COVID" is known at this point, the prevention of thrombotic events distant to the acute pulmonary phase, along with pulmonary rehabilitation, seems to be a valid therapeutic objective.

In conclusion, cohort studies with mandatory genetic profiling of the subjects may elucidate this possible interference mechanism between corticoid administration and the potential of triggering thrombotic events that can cause permanent damage or even death on patients considered to have overcome the worst as their pulmonary state stabilized. A simple clinical tool, such as thrombotic assessment questionnaires, may help orientate the clinician and evocate the possibility of a thrombotic event associated with corticosteroids treatment in COVID-19 disease.

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