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Coagulopathy and Plausible Benefits of Anticoagulation Among COVID-19 Patients

Syed Imran Ahmed, MClinPharm, PhD, MRSPH, and Shahzad Khan, MBBS, PhD

Abstract: The exceptional outbreak of COVID-19 pandemic has let the scientific community to work closely and quickly learnt things in a very short period of time. This has let us recognize that thromboembolic complications are responsible for morbidity and mortality among the COVID-19 infected patients. Available data have suggested a possible multifactorial basis of these complications, and while efforts are being made to treat this infection, preventive measures with the use of systemic anticoagulation were quickly adopted to deal with this issue. Despite obvious benefits as appeared with the use of systemic anticoagulation, most of the emerged data were retrospective, hence raise questions on the possible interplay of the confounders as well as long-term benefits and safety of systemic anticoagulation. (Curr Probl Cardiol 2020;45:100648.)

COVID19 Pandemic and the Global Response

The unprecedented pandemic of Novel Corona Virus Infectious Disease-19 (COVID-19) has now affected almost every part of the world, with variable degrees of health, social, psychological, and economic impacts. Aristotle famously wrote, “The more you know, the more you realize you don’t know.” But we can modify this notion for

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the case of COVID-19 as the more we are understanding the pathophysiology of COVID-19, hope is increasing that COVID-19 can be managed more effectively. Due to the swift global responses in terms of sharing data, we have gained substantial knowledge about this unique pandemic in a rather short period. Many large-scale retrospective cohort studies from China as well as from the United States have mentioned that besides pulmonary involvement, coagulopathy remains one of the most important secondary causes of mortality among patients with COVID-19.¹⁻⁴

Thromboembolic Complications in COVID-19 Patients

Although severe viral pneumonia and its complication such as acute respiratory distress syndrome and sepsis are the main causes of high mortality in COVID-19 observed globally, as we are getting more data, role of coagulation abnormalities in COVID-19 are becoming more obvious. Nearly all recently conducted retrospective studies have mentioned various degrees of increased thromboembolic events among COVID-19 victims. Among the very first of the studies conducted in China, increased odds of death in hospitalized patients were found to be associated with D-dimer levels $>1 \mu\text{g/mL}$ ($P = 0.0033$). Likewise, 50% of nonsurviving patients had coagulopathies as compared to only 7% in surviving patients ($P < 0.0001$).² Although sepsis seems to be the most obvious link to these coagulation derangements, data showed that only 70% of the nonsurviving patients had sepsis which emphasizes that sepsis is not the only necessary preceding condition responsible for coagulopathy in COVID-19.^{2,4}

Probable Mechanisms of Coagulopathies

The idea of isolated coagulopathies in COVID-19 was strengthened by the observation that disseminated intravascular coagulopathy (DIC) commonly occurs in sepsis, has marked thrombocytopenia decreased fibrinogen levels and increased prothrombin time, while observations show that in COVID-19 sepsis has relatively normal platelets and prothrombin time. In fact, a recent US study has reported significantly elevated D-dimers and fibrinogen levels but relatively normal platelet counts observed in COVID-19 patients.⁴

The mechanism of hematopathology and coagulopathy is complex and multifactorial in COVID-19. It may involve all or any of the documented common pathways seen in other viral illness and in severely ill hospitalized patients such as endothelium cell damage by viral antigens, upregulation of von Willebrand factor, Toll-like receptors, all play a role in the

coagulant state of viral infections which may lead to uncontrolled coagulations similar to DIC with the formation of excess fibrin clots. When these fibrin clots are degraded by the body's own anticoagulant system fibrin degradation products are produced, among which D-dimer (2 D fragments of the fibrin protein joined by a cross-link) is the one commonly tested in laboratories. The importance of this coagulopathy and association of it with COVID-19 is so strong that a recent study has declared that a 4-fold increase in D-dimer is a strong indicator of mortality COVID-19 patients.⁵

Besides DIC, local coagulopathies such as venous thromboembolism due to venous stasis has also been implicated in COVID-19 patients. Furthermore, generation of localized tissue factor-mediated thrombin, depression of bronchoalveolar plasminogen activator-mediated fibrinolysis via in lungs has been documented.⁶ This discovery is supported by a study that showed lung microthrombi and venous thromboembolism in COVID-19 patients without documented DIC.⁷

Role of Anticoagulation Therapies

Regardless of the certainty of the mechanism involved in COVID-19 related coagulopathy, the role of coagulation-related disorder in COVID-19 illness is obvious and therefore, the use of anticoagulation therapy is currently practiced prophylactically and therapeutically in COVID-19 patients.¹ Interestingly, besides the classical anticoagulation mechanism of heparin via binding and enhancing antithrombin III, it has been reported to alleviate inflammation through binding adhesion molecules L- and P-selectin^{8,9} and downregulating interleukin-6 as well.¹⁰

Additional intriguing role of heparin antiviral properties has been tested in experimental models. Heparin has shown to bind host cell surface glycoproteins and can inhibit viral attachment.⁶ In Italy, such a role of heparin has been verified successfully in experimental models.¹¹ Another recent study has shown that heparin binds to COVID-19 surface spike protein.¹² These secondary antiviral properties need to be clinically proven but still increase the importance of heparin in COVID-19 management. On the other hand, there is an opinion which opposes the use of early or prophylactic use of anticoagulant therapy in patients without significant coagulopathy mainly because of the fact that activation of coagulation contributes to wall-off or compartmentalize the pathogens and decreases their invasion and propagation.¹³ As of now unfractionated heparin and low-molecular weight heparin (LMWH) is being used in the standard management of COVID-19 induced sepsis. A recent study on 449 COVID19 patients who received LMWH for

7 days or longer has shown lower 28-day mortality in heparin-treated patients who had D-dimer >6-fold of the upper limit of the normal (32.8% vs 52.4%, $P=0.017$) but the same study showed no difference in 28-day mortality between heparin users and nonusers (30.3% vs 29.7%, $P=0.910$) when they did not have markedly elevated D-dimer. This study further revealed that D-dimer, prothrombin time, and age were positively correlated with 28-day mortality, and platelet count was negatively correlated with 28-day mortality.⁷

The Outcomes

A recent study in the United States has investigated the association between in-patient anticoagulant use and survival in a large cohort of COVID-19 patients. Based on the findings of this study, those who received anticoagulants were more likely to require invasive mechanical ventilation (29.8% vs 8.1%, $P < 0.001$), and among the mechanically ventilated patients the mortality rate was 29.1% as compared to 62.7% who were not treated with anticoagulants.¹ The study also examined the risk of bleeding, which confirms 1.9% of anticoagulants-treated patients had bleeding events and the risk of bleeding was more in intubated patients after anticoagulants use.¹ Although these findings confirm the apparent benefits of systemic anticoagulants use, however, it did not overrule the risk of bleeding, thus requiring measurement of individualized risk calculation for thrombosis as well as bleeding among COVID-19 patients. Furthermore, the data account for systemic use of anticoagulants, but not reflective of the specific types such as unfractionated heparin or low-molecular-weight heparin (LMWH) or LMWH derivatives like derivatives like enoxaparin, dalteparin, or tinzaparin, which could also be essential while choosing among high-risk patients.

Summary

In summary, COVID-19 related morbidities and mortalities are possibly contributed by thromboembolic events, and based on the suggestive data use of anticoagulants is associated with improved outcomes. However, the risk for thromboembolic events and benefits from anticoagulants must be individualized against the risk of bleeding. Is there a requirement of higher than the prophylactic dose of anticoagulants in patients with higher D-dimers levels, or there should be a dose adjustment depending on invasive or noninvasive mechanical ventilation, can heparin be considered independently or as an adjuvant therapy due to its anti-inflammatory and antiviral properties? These and many other questions still need more clarification. Moreover, reported data are retrospective, which cannot establish the impact of potential confounders and establish

causality, requiring prospective studies on the subject. We may also need to study the benefits and risks with the use of available anticoagulants, as they vary significantly in terms of their safety profiles.

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