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Coronavirus disease-19 pneumonia: The impact of coagulopathy

Neumonía por COVID-19: el impacto de la coagulopatía

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Abstract

The development of coagulopathy is emerging as one of the most significant poor prognostic features in coronavirus disease (COVID)-19 pneumopathy. D-dimer, a protein product of fibrin degradation, has been found elevated in the most severe cases and correlated to mortality. Potentially involved factors in the impairment of coagulation caused by viral infection include the dysregulated inflammatory response, platelet, and endothelial dysfunction with impaired fibrinolysis. Heparin is an anticoagulant molecule that also showed anti-inflammatory properties and a potential antiviral effect. The use of low-molecular-weight heparin could prevent thromboembolic complications in COVID-19 pneumopathy. However, the correct timing of prophylaxis according to the stage of COVID-19 disease and the appropriate therapeutic dosage to use in severe cases needs further researches.

Key words: *Coronavirus disease-19. Thrombosis. Coagulopathy. D-dimer. Low-molecular-weight heparin.*

Resumen

El desarrollo de coagulopatía se reconoce como una de las complicaciones y características clínicas más significativas asociadas a un pronóstico desfavorable en la neumopatía por enfermedad por coronavirus (COVID)-19. El dímero D, un producto proteico de la degradación de la fibrina se ha encontrado elevado en los casos más graves y correlacionado con elevación en la mortalidad. Los factores potencialmente involucrados en el deterioro de la coagulación causada por una infección viral incluyen una respuesta inflamatoria desregulada, las plaquetas y la disfunción endotelial con fibrinolisis alterada. La heparina es una molécula anticoagulante que también ha mostrado propiedades antiinflamatorias y un posible efecto antiviral. El uso de heparina de bajo peso molecular podría prevenir complicaciones tromboembólicas en la neumopatía por COVID-19; sin embargo, el momento correcto de la profilaxis de acuerdo con la etapa de la enfermedad COVID-19 y la dosis terapéutica adecuada para usar en casos severos requiere todavía más investigación.

Palabras clave: *COVID-19. Trombosis. Coagulopatía. Dímero D. Heparina de bajo peso molecular.*

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In December 2019 in the city of Wuhan, China, a novel coronavirus infection (coronavirus disease [COVID]-19) developed causing significant mortality in many countries and becoming a pandemic disease[1]. The main symptoms of COVID are related to respiratory involvement that in the most severe cases worsen to acute respiratory distress syndrome (ARDS) and systemic disease with multiorgan failure[2]. In such a clinical scenario, the activation of the coagulation system with thromboembolic manifestations has been described[3]. Recently, 31% incidence of thrombotic complications in intensive care unit patients with COVID-19 has been reported despite systematic thrombosis prophylaxis. The most frequent complication was pulmonary embolism (81%), however, arterial thrombotic events occurred in 3.7% of patients[4]. Moreover, the development of disseminated intravascular coagulation (DIC) has been described by Tang et al. Indeed, they found alterations in laboratory parameters according to diagnostic criteria for DIC on 15 (71.4%) deaths by COVID-19 disease[3].

Several factors could be involved in the impairment of coagulation caused by COVID-19: the dysregulated immune response that triggers the activation of coagulation cascade, thrombocytopenia, endothelial dysfunction, and impaired fibrinolysis.

Dysregulated immune response

The viral infection induces an inflammatory state through the activation of endothelial cells, platelets, and leukocytes[5]. A "cytokines storm" with overexpression of interleukin (IL)-6, IL-8, and tumor necrosis factor-alpha has been described during viral infection[6]. The severe inflammatory response induces a procoagulant state through the expression of tissue factor and von Willebrand factor. Result is the activation of the coagulation cascade with final generation of fibrin. In SARS-CoV infection, evidence of fibrin clots in the alveoli has been found[7]. Fibrin accumulation in the lung is a hallmark of acute lung injury and ARDS, and a reduced capacity to cleave and remove fibrin deposits corresponded to a poor clinical patient outcome[8]. Similar findings have been described in patients who died from COVID-19 disease. Histopathological examination revealed fibrin exudation in alveoli and, notably, formation of hyaline thrombus in small vessels in other organs and tissues[9].

Thrombocytopenia and platelet dysfunction

In viral infections, platelet dysfunction, destruction, or a reduced platelets production have been reported[5]. A recent meta-analysis of nine studies including nearly 400 patients with severe COVID-19 disease identified that the platelet count was significantly lower in severe cases[10]. Although pathogenesis of thrombocytopenia in COVID-19 disease has not been fully clarified, thrombocytopenia caused by autoantibodies and a reduced platelets production has been described in other respiratory infections such as SARS-CoV and influenza[5,11]. Another described mechanism is the binding of the virus to platelets followed by their activation, exposure of P- selectin on the platelet surface that triggers the formation of platelet-leukocyte aggregates. Subsequently, endothelial cells are activated and an increase in von Willebrand factor can be found[5].

Endothelial dysfunction and impaired fibrinolysis

Endothelial cells play a crucial role in the regulation of coagulation, both producing and presenting anticoagulant markers and procoagulant factors.

The direct endothelial cells involvement in COVID-19 could be hypothesized because the virus accesses host cells through the protein angiotensin-converting enzyme 2[12] that is also expressed by endothelial cells[13]. Viral infection activates endothelial cells causing the activation of coagulation that is mainly marked by an increase in von Willebrand factor secretion, which can bind platelets after vessel wall damage[14].

In COVID-19 infection, fibrinolysis can be impaired and the pathogenesis could be the same as SARS. In this infection, increased levels of plasminogen activator inhibitor-1 and increased plasma concentrations of tissue plasminogen activator and soluble thrombomodulin were found[15,16].

Role of anticoagulation as a therapy for COVID-19

As discussed before, COVID-19 infection could cause a coagulopathy through severe inflammatory state, endothelial dysfunction, and impaired fibrinolytic activity. Therefore, anticoagulant therapy is emerging as one potential adjunctive treatment for COVID-19 disease.

Heparins are anticoagulant drugs used for the prophylaxis and therapy of venous thromboembolism. In a retrospective analysis conducted by Tang et al. on 449 Chinese patients affected by severe COVID- 19,

a favorable outcome was reported thanks to the use of heparin. In particular, 94 patients received low-molecular-weight heparin (LMWH, 40-60 mg enoxaparin/day) and 5 received unfractionated heparin (UFH, 10,000-15,000 U/day). Heparin therapy significantly reduced mortality in patients with sepsis-induced coagulopathy (SIC) score ≥ 4 but not in those with SIC score < 4[17]. Apart from the well-known anticoagulant action, anti-inflammatory properties have also postulated: binding with inflammatory cytokines, inhibition of neutrophil chemotaxis and leukocyte migration, and antagonization of histones released from damaged cells[18-20]. A potential antiviral role has been questioned and an interaction with the binding domain of the spike S1 SARS-CoV-2 protein receptor has been recently investigated[21]. In summary, heparin could protect from thrombotic complications, microcirculatory dysfunction and possibly decrease multiorgan damage. However, large-size studies and higher-quality data are lacking to provide definitive indications for anticoagulant use. Future researches should focus on how COVID-19 infection triggers thrombotic diseases in some patients while in most of cases, infection remains asymptomatic, what are the patient's clinical characteristics that raise thrombotic risk, who benefits from early thrombotic prophylaxis, who needs to continue the treatment after hospital discharge, what is the appropriate dose of heparin, and how to monitor efficacy of anticoagulant treatment.

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Conflicts of interest

The authors declare no conflicts of interest.

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