Editorial

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Antithrombotic prophylaxis in COVID-19

Profilaxis antitrombótica en COVID-19

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José Javier Elizalde-González*

Venous thromboembolic disease is common, associated with recurrence and mortality, costly and sometimes producing long-term sequelae in the form of postphlebitic syndrome and chronic thromboembolic pulmonary hypertension.

Thrombosis is a complex phenomenon that has been described in ARDS for decades. Tomasensky reported its presence in these cases in 1972 and since then, it has been relatively common for the intensive care community.

However, it is assumed that COVID-19 is more frequently associated with this complication, since as Peter Libby says, it is ultimately an endothelial disease, an omnipresent element throughout the economy.

Infection-induced endothelial cell dysfunction results in excess thrombin generation and blackout of fibrinolysis, indicative of a hypercoagulable state in patients with SARS-CoV-2 infection. In addition, the hypoxia found in severe COVID-19 can stimulate thrombosis through not only the increase in blood viscosity, but also through the hypoxia-inducible transcription factor-dependent signaling pathway. There is evidence of microthrombosis formation and occlusion of pulmonary small vessels of critical patients with COVID-19. There are almost 80 registered clinical trials of different antithrombotic strategies with different agents in COVID-19 patients, the majority involving the use of heparin or LMWH.

In a particular study it was observed in mechanically ventilated coronavirus disease 2019 patients, who underwent CT pulmonary angiography because suspicion of PE upon admission and/or an acute deterioration of hemodynamic/respiratory status, a 33% of pulmonary embolism (PE); a figure that, although probably overestimated, is clearly higher than that of other clinical entities complicated with thrombosis phenomena. Researchers reported that the use of high-regimen thromboprophylaxis (subcutaneous enoxaparin 4,000 IU twice daily or continuous therapeutic infusion of unfractioned heparin in case of renal replacement therapy and/or ECMO) was associated with a lower occurrence of PE (2/18; 11%) than standard regimen (subcutaneous enoxaparin 4000 IU once daily) (11/22, 50% -odds ratio 0.13 [0.02-0.69]; p = 0.02); this difference remained significant even after adjustment for confounders. Six patients with PE (46%) and 14 patients without PE (52%) died at ICU discharge (odds ratio 0.79 [0.24-3.26]; p = 0.99). One way or another, we know that every critical patient should receive pharmacological and mechanical prophylaxis.

A systematic review and meta-analysis aimed at evaluating available data of 86 different series with a high heterogenicity and estimating the prevalence of venous thromboembolism (VTE) in almost 30,000 patients with COVID-19, concluded that it occurs in 22.7% of patients with severe COVID in ICU, but the risk was also increased in less serious patients admitted in general wards (7.9%).

Speaking specifically of PE, it was observed in ICU patients in a 13.7% and in wards in a 3.5%. Those who developed VTE have higher levels of DD (mean difference of 326 mg/mL) and authors called for the evaluation of different thromboprophylaxis strategies to improve VTE prevention.

Similar data were reported among hospitalized patients with COVID-19, with an estimated pooled incidence of 17.0% (95% CI, 13.4-20.9) for VTE, 12.1% (95% CI, 8.4-16.4) for DVT, 7.1% (95% CI, 5.3-9.1) for PE, 7.8% (95% CI, 2.6-15.3) for bleeding, and 3.9% (95% CI, 1.2-7.9) for major bleeding. Higher rates of VTE were noted with the use of routine screening, inclusion of distal deep venous thrombosis (DVT), and subsegmental PE, in critically ill patients and in prospective studies. Bleeding events were observed in 7.8% of patients and were sensitive to use of escalated doses of anticoagulants and nature of data collection.

In a multicentric prospective cohort study performed in four intensive care units (ICUs) from two centers of a French tertiary hospital the diagnosis of sixty-four clinically relevant thrombotic complications were reported in 150 patients, mainly pulmonary embolisms (16.7%). 28/29 patients (96.6%) receiving continuous renal replacement therapy experienced circuit clotting. Three thrombotic occlusions (in two patients) of centrifugal pump occurred in 12 patients (8%) supported by ECMO, where anticoagulation is necessary and usually achieved by continuous IV heparin infusion, targeted to an activated PTT of 45 to 60 seconds and/or to an activated clotting time of 1.5 to 2 times normal. Most patients (> 95%) had elevated D-dimer and fibrinogen. No patient developed disseminated intravascular coagulation. Von Willebrand (vWF) activity, vWF antigen and FVIII were considerably increased, and 50/57 tested patients (87.7%) had positive lupus anticoagulant. Comparison with non-COVID-19 ARDS patients (n = 145) confirmed that COVID-19 ARDS patients (n = 77)

* Instituto Nacional de Ciencias Médicas y Nutrición «Salvador Zubirán». UNAM. Mexico.

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developed significantly more thrombotic complications, mainly pulmonary embolisms (11.7 vs 2.1%, p < 0.008).

They concluded that as despite anticoagulation (AC) treatment, a high number of patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications, higher anticoagulation targets than in usual critically ill patients should therefore probably be suggested, which sounds reasonable.

One series enrolled a group of 449 patients with severe COVID-19, 99 of them received heparin (mainly with low molecular weight heparin) for seven days or longer. D-dimer, prothrombin time, and age were positively, and platelet count was negatively, correlated with 28-day mortality in a multivariate analysis. No difference in 28-day mortality was found between heparin users and nonusers (30.3% vs 29.7%, p = 0.910). But the 28-day mortality of heparin users was lower than nonusers in patients with the sepsis-induced coagulopathy (SIC) score ≥ 4 (40.0% vs 64.2%, p = 0.029) (entity proposed by the International Society of Thrombosis and Haemostasis as a new category to identify an early stage of disseminated intravascular coagulation associated with sepsis), or D-dimer > 6-fold of upper limit of normal (32.8% vs 52.4%, p = 0.017), so it seems that AC therapy mainly with low molecular weight heparin appears to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer.

Mount Sinai Health System clinicians in New York City assessed the association between administration of in-hospital AC and survival in a large cohort of hospitalized patients with COVID-19. In those who required mechanical ventilation (n = 395), in-hospital mortality was 29.1% with a median survival of 21 days for those treated with AC as compared to 62.7% with a median survival of nine days in patients who did not receive treatment-dose AC. In a multivariate proportional hazards model, longer duration of AC treatment was associated with a reduced risk of mortality (adjusted HR of 0.86 per day; 95% confidence interval: 0.82 to 0.89; p < 0.001). Among those who did not receive treatment-dose AC, 38 (1.9%) individuals had bleeding events, especially in the intubated ones, compared with 24 (3%) among those who received treatment-dose AC (p = 0.2).

That is why doses adjusted to body weight and renal function have been suggested, particularly in cases identified as high risk for thrombosis in severe COVID-19 (RPC > 150, DD > 1,500, IL-6 > 40, ferritin > 1,000, lymphopenia < 800), providing prophylaxis at intermediate doses of LMWH (enoxaparin 1 mg/kg of body weight, SC, every 24 hours), plus mechanical devices.

In cases of documented PE, there are excellent stratification and management guidelines depending on the level of the risk signal for acute death.

A retrospective analysis in 4,389 COVID patients, examined the association of AC with mortality, intubation, and major bleeding. Subanalyses were also conducted on the association of therapeutic versus prophylactic AC initiated ≤ 48 h from admission. In this study, AC was associated with lower mortality and intubation among hospitalized COVID-19 patients. Compared with prophylactic AC, therapeutic AC was associated with lower mortality, although not statistically significant.

On the other hand, efforts have been made to evaluate the effects of A-C at intermediate doses vs standard prophylactic doses in patients with COVID-19 admitted to the ICU. In an open multicenter randomized trial with a 2 × 2 factorial design performed in 10 academic centers in Iran, in patients admitted to the ICU with COVID-19, intermediate-dose prophylactic A-C, compared with standard-dose prophylactic A-C, did not result in a significant difference in the primary outcome of a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days. These results do not support the routine empirical use of intermediate-dose prophylactic A-C in unselected patients admitted to the ICU with severe COVID-19.

In the preprint RAPID trial 465 non-ICU hospitalized patients with moderate COVID and an elevated D-dimer were randomized to A-C with therapeutic or prophylactic heparin. The primary composite outcome was death, invasive mechanical ventilation, non-invasive mechanical ventilation or ICU admission. Safety outcomes included major bleeding. Analysis was by intention-to-treat. Full A-C (therapeutic) not significantly reduce the primary outcome but decreased the odds of death at 28 days.

The meta-analyses of two trials of moderately ill COVID patients, RAPID and the multiplatform trial integrating the antithrombotic therapy to ameliorate complications of COVID-19 (ATTACC), accelerating COVID-19 therapeutic interventions and vaccines-4 antithrombotics inpatient platform trial (ACTIV-4a) and the randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP), showed no significant reduction in all-cause death (odds ratio, 0.74; 95% CI, 0.54 to 1.02), but significant reductions in the composite of death or invasive mechanical ventilation (odds ratio, 0.77; 95% CI, 0.60 to 0.99), death or organ support (odds ratio, 0.77; 95% CI, 0.63 to 0.93), death or major thrombotic event (odds ratio, 0.64; 95% CI, 0.48 to 0.86), and major thrombotic events (odds ratio, 0.47; 95% CI, 0.25 to 0.87) were seen with the therapeutic scheme. Ventilator-free days alive (odds ratio, 1.30; 95% CI, 1.05 to 1.61) and organ support-free days alive (odds ratio, 1.31; IC 95%, 1.08 to 1.60) were significantly increased with the therapeutic heparin dose. There was also a non-significant increase in major bleeding. In such a way that a significant interaction of treatment by-subgroups was found with the severity of illness for all-cause death, all-cause death or major thrombosis and organ-support-free days alive, with evidence of benefit only

with therapeutic heparin in moderately ill ward patients, but not in severely ill ICU patients.

In an international, multiplatform, randomized, open-label clinical trial with one thousand critically ill patients (defined as that with organic support requirement with high flow nasal cannula, non-invasive ventilation, invasive ventilation, vasopressors, or inotropes) with confirmed COVID-19 were randomized to receive therapeutic anticoagulation with heparin or pharmacological thromboprophylaxis. The investigators concluded that the therapeutic anticoagulation regimen does not improve survival or days free of organ support and has an 89% probability of being inferior to the usual drug thromboprophylaxis. They described that there is an 81% probability that the A-C therapeutic dose actually reduces survival to hospital discharge in comparison to usual care pharmacological thromboprophylaxis. Furthermore, these findings suggest that starting an A-C treatment once the patient has developed a severe COVID-19 may be too late to reasonably alter sufficiently the pathophysiological consequences of an established condition. Bleeding complications were infrequent in both groups.

In addition, the effectiveness of A-C also seems to depend on the type of anticoagulant selected: the anticoagulation coronavirus (ACTION) trial used 15 to 20 mg of oral rivaroxaban in 94% of patients assigned to therapeutic A-C and found no benefit and resulted in an increase in bleeding complications when compared to regular heparin thromboprophylaxis. Rivaroxaban (and probably the rest of the newer direct-acting oral anticoagulants) is unlikely to have the anti-inflammatory and antiviral properties attributed to heparin. Secondly, ACTION allowed intermediate doses of enoxaparin in the control group.

Of particular interest is the nice work recently published by the ATTACC, ACTIV-4a and REMAP-CAP researchers that reported among 2,219 noncritically ill patients with COVID-19, that an initial strategy of therapeutic-dose A-C with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with usual-care thromboprophylaxis, with a final probability of the superiority of therapeutic-dose anticoagulation over usual-care thromboprophylaxis of 97.3% in the high d-dimer cohort, 92.9% in the low d-dimer cohort, and 97.3% in the unknown d-dimer cohort. Major bleeding occurred in 1.9% of the patients with receiving therapeutic-dose anticoagulation and in 0.9% of those receiving thromboprophylaxis.

Reconciling different results in different populations and with unequaled disease progression and severity is a complex work; one article of these three focuses on patients with severe illness and the other on those with moderate illness. In the two articles, the potential benefits and risks of therapeutic-dose heparin or LMWH (with the latter being used in > 90% of the patients in both groups) are assessed against standard thromboprophylaxis. The main findings were that therapeutic-dose heparin or LMWH did not improve the primary outcome of days without organ support in the critically ill patients and was associated with more major bleeding complications than usual-care prophylaxis (3.8% vs 2.3%). In contrast, in the moderately ill patients, therapeutic-dose heparin or LMWH appeared to increase the probability of survival until hospital discharge with a reduced need for organ support. It is to be noted that the method of standard prophylaxis was left to the discretion of the physicians, which resulted in a mix of conventional prophylaxis doses and intermediate doses within the treatment groups; nevertheless the available evidence does not support use of full therapeutic-dose heparin or LMWH for thrombosis prevention in COVID-19 critically ill patients.

Different guides and recommendations emanating from different collegiate bodies are available for those interested in the subject, each with its particular characteristics, limitations and biases. Among others, the ASH recommendations suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19–related critical illness who do not have suspected or confirmed VTE, and the same for patients with COVID-19–related acute illness (non-ICU patients), establishing a classification of the different anticoagulation regimens according to their intensity: prophylactic, intermediate and therapeutic for all available molecules.

On the other hand, those of the ISTH, indicate that it should be considered in all patients (including non-critical ones) that require hospital admission for COVID-19, in the absence of contraindication.

Although the evidence is under construction, we can conclude that there is enough information to support the use of thromboprophylaxis in severe COVID-19 complicated with acute respiratory failure, although the optimal scheme to carry it out has not yet been described, nevertheless we know that its start must be timely. The early use of therapeutic heparin regimens can decrease the thromboinflammation process and the risk of critical illness and death.

In moderate forms of COVID-19, data appears to favor full A-C, not so in severe COVID-19 where the evidence points to the use of only conventional thromboprophylaxis. Until now, the use of direct anticoagulants is not recommended, since their mechanism of action is not in line with the pathophysiology of the process and they have been associated with adverse outcomes in COVID-19. And finally, we require more information that only prospective and methodologically correct research will be able to provide us in the future.

Correspondence:
José Javier Elizalde-González, MD
E-mail: jjeg@unam.mx