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LETTER TO THE EDITOR

Pharmacologic therapeutic options for thromboprophylaxis in COVID-19

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To the editor,

Recent interim clinical guidance of anticoagulant therapy amid novel coronavirus disease 2019 (COVID-19) pandemic by Barnes et al. [1] came timely since the existence of coagulopathy and the subsequent increased risk of venous thromboembolism (VTE) among patients with COVID-19 has increasingly been recognized by the medical community. Their effort to propose anticoagulant-based management strategy for thromboembolism among hospitalized COVID-19 patients must be complimented, where they tailored and individualized the intensity of anticoagulation according to different circumstances (critically ill versus non-critically ill).

We acknowledged the role of parenteral anticoagulant, especially heparin-based regimen (unfractionated heparin, low-molecular-weight heparin) in thromboprophylaxis for hospitalized patients with COVID-19. Nevertheless, as pointed out by the authors, the rate of thromboprophylaxis failure may be higher among COVID-19 patients. Clinicians managing hospitalized patients with COVID-19 are also concerned with the findings in a recent study [2] which reported that about 20% of the included hospitalized COVID-19 patients had VTE despite routine thromboprophylaxis with low-molecular-weight heparin. In addition, a study that systematically evaluated 71 patients hospitalized with COVID-19 for more than 48 h by performing bilateral lower extremity duplex ultrasounds at the time of discharge found deep vein thrombosis in 21% (15/71) of patients [3]. In fact, all but one were receiving prophylactic anticoagulation with daily administration of weight-appropriate enoxaparin. Pulmonary embolism also occurred in 10% (7/71) of patients, one of which was fatal. Such a high thromboprophylaxis failure rate with heparin-based regimen should prompt us to determine the adequacy of the current thromboprophylaxis approach.

Therefore, alternative pharmacological thromboprophylaxis approach with oral factor Xa inhibitors should not be left out in the discussion of thromboprophylaxis among COVID-19 patients. Betrixaban and rivaroxaban have been approved for thromboprophylaxis in hospitalized medically ill patients. In a study of 7513 hospitalized medically ill patients (APEX trial), compared with enoxaparin, the composite outcome of asymptomatic and symptomatic VTE plus VTE-related death was significantly reduced in patients taking betrixaban (4.87%) compared with subcutaneous enoxaparin (7.06%) (relative risk reduction = 0.30, 95% confidence interval 0.13–0.44; p = 0.001), without any increase in the bleeding rate [4].

Perhaps a subgroup analysis of patients hospitalised for acute infectious diseases in the MAGELLAN study [5] is more related to COVID-19 patients, where the authors evaluated prolonged prophylaxis with rivaroxaban 10 mg daily for 35 days compared with enoxaparin 40 mg daily for 10 days. Among 3173 patients with acute infectious diseases leading to hospitalization randomized to either rivaroxaban (n = 1585) or enoxaparin (n = 1588), primary composite efficacy outcomes (asymptomatic proximal or symptomatic VTE) at day 10 though did not differ between two prophylaxis strategies, authors reported significantly fewer VTE events with rivaroxaban (4.2%) than with enoxaparin (6.6%) at day 35 (relative risk = 0.64; 95% confidence interval 0.45–0.92; p = 0.014). Specifically, among patients with pulmonary infections who were randomized to rivaroxaban (n = 936), the effect size was greater, where they had a significantly lower incidence of VTE both at day 10 (relative risk = 0.50; 95% confidence interval 0.28–0.90; p < 0.05) and at day 35 (relative risk 0.54; 95% confidence interval 0.33–0.87; p < 0.05) compared to their counterparts receiving enoxaparin. Whilst primary safety outcome events were

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increased with rivaroxaban (relative risk = 2.42; 95% confidence interval 1.60–3.66; $p < 0.05$), there was no significant difference in major bleeding events (relative risk = 2.96; 95% confidence interval 0.96–9.14; $P > 0.05$) among patients with pulmonary infections randomized to rivaroxaban or enoxaparin.

Oral administration of anticoagulants could potentially ease the workload of nursing staff compared to subcutaneous administration amid the COVID-19 pandemic. Besides, patients with COVID-19 may require the administration of vasopressors, and the associated reduction in peripheral circulation with vasopressors could limit the bioavailability of heparin-based regimen administered via the subcutaneous route. We too feel that the potential antiviral mechanism of oral factor Xa inhibitors should be recognised. Factor Xa, which functions as a protease, has been shown to facilitate the entry of severe acute respiratory syndrome coronavirus (SARS-CoV) into the host cells through cleavage of S1–S2 subunits of viral spike protein to expose S2 for fusion to the cell membrane [6]. Therefore, oral factor Xa inhibitors can too be candidates for targeting protease cleavage and the cellular entrance of SARS-CoV-2, the pathogen responsible for COVID-19.

Nevertheless, we recognized that patients receiving drugs that strongly inhibit both CYP3A4 and P-glycoprotein such as lopinavir and ritonavir that may be used in COVID-19 patients should not receive oral factor Xa inhibitors. In addition, the administration of oral factor Xa inhibitors may not be feasible in critically ill patients in intensive care units who are mechanically ventilated or intubated, or require mechanical circulatory support, compared to parenteral anticoagulant administration [7]. The long half lives of these agents also preclude their use in patients for whom invasive procedures are likely. Despite few limitations, we feel that the thromboprophylaxis role of oral factor Xa inhibitors should not be denied since most other hospitalized patients with COVID-19 would be suitable for thromboprophylaxis regimen with oral factor Xa inhibitors. In fact, since COVID-19 patients may present with venous thrombosis at discharge as described above and not all facilities would screen their patients for the presence of thrombosis at discharge, oral factor Xa inhibitors can be used for extended thromboprophylaxis in those with high risk such as immobility and older age (similar to criteria in APEX and MAGELLAN trials). Efficacy of oral factor Xa inhibitors should be tested in clinical trials or observational studies to establish its role relative to the heparin-based regimen in the prophylaxis of VTE among hospitalized COVID-19 patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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