Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Thrombosis Research 203 (2021) 72–73

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Letter to the Editors-in-Chief

Therapeutic anticoagulation in COVID-19 patients

ARTICLE INFO

Keywords
COVID-19
Anticoagulant treatment
Coagulopathy

Our pilot investigation [1] was performed in an early phase of this pandemic when the first SARS-CoV-2 infected patients emerged in our region.

We thank your interest in our research, and we clarify some questions raised. First, about the prophylactic anticoagulation, our institutional protocol indicated these two treatment regimens (enoxaparin or unfractionated heparin); thus, enoxaparin was not used for all patients. There were no pre-defined criteria to choose between the two regimens, and we respected the doctors' option.

Second, all the patients were evaluated for enrollment in the emergency department immediately after admission. Most of the patients were randomized in the first 24 h after admission, and they received the first dose anticoagulant during this period.

Third, the control and intervention group had similar baseline characteristics. The tidal volume (TV) per Kilograms of predicted body weight and the positive end-expiratory pressure (PEEP) were not statistically different between these two groups. They exhibited the same average value for the TV per Kg of predicted body weight and only 1 cm of water of difference in the PEEP relation, which is not clinically significant to distinguish different severities between them. The number of patients submitted to prone positioning was similar between the groups (80% vs. 70%; $p = 0.606$); however, the prophylactic group required a higher number of prone positioning sessions because they did not improve the gas exchange over time.

We want to highlight that early endotracheal intubation and mechanical ventilation were preconized in the initial phase of this pandemic. The experience acquired during the pandemic course has shown that several patients could be maintained in the high-flow nasal cannula or non-invasive ventilation. Therefore, some patients included in our investigation would currently not meet the criteria for mechanical ventilation.

Fourth, we excluded seven patients before randomization, and the two patients with circulatory shock who required high doses of vasopressors were excluded before the enrollment. Despite this, four patients in the prophylactic group and two patients in the therapeutic group developed late severe circulatory shock after randomization; however, they were not excluded from this intention-to-treat analysis.

Fifth, the bleeding was evaluated through the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria [2]. The bleeding requiring medical attention was defined as any sign of hemorrhage necessitating intervention, prolonged hospitalization, or need for prompt evaluation and did not meet major or minor bleeding criteria. A high proportion of patients presented an isolated drop in hemoglobin levels, without any clinically evident sign of hemorrhage; consequently, these events were not classified as minor or major bleeding. There is significant heterogeneity among different bleeding definitions. For example, the International Society of Thrombosis and Haemostasis (ISTH) considers an isolated fall in hemoglobin level of 2 g/dl as major bleeding [3]. If we had considered this last definition, we would have had two major bleeding in the prophylactic group and four major bleeding in the therapeutic group. Two patients required blood transfusion in the therapeutic anticoagulation group and one patient in the prophylactic anticoagulation group. We think that the most important thing is that the occurrence of symptomatic bleeding in a critical organ is very low in COVID-19 patients.

Lastly, everyone is anxiously waiting for publication of the results of these clinical trials about therapeutic and intermediate dose of anticoagulation in COVID-19 patients. The interim analysis of the three multicenter (ATTACC, REMAP-CAP, ACTIV-4a) randomized, open-label trials showed that therapeutic dose anticoagulation decreased the need for organ support and mortality in moderately ill COVID-19 patients, on the other hand, therapeutic-dose anticoagulation did not decrease organ support and mortality in critically ill COVID-19 patients. [4]

Despite the uncertainties, we cannot forget that all severely ill patients were previous moderately ill; it is only a time question. We think an intermediate dose of anticoagulation is insufficient to mitigate this hypercoagulable state, as demonstrated in the INSPIRATION clinical trial. [5] Furthermore, the antithrombotic intervention could be too late in the severe COVID-19 patients admitted to the intensive care unit to improve their clinical condition. From our point of view, early hospitalization of COVID-19 patients with dyspnea and mild reduction in the arterial oxygen saturation (moderately ill patients) with prescription of anti-inflammatory drugs (corticosteroids, tocilizumab, etc.) [6,7], antiviral drugs, and therapeutic anticoagulation in selected patients with low risk of bleeding are the available strategies to prevent the worsening of this disease.

https://doi.org/10.1016/j.thromres.2021.04.027
Received 3 March 2021; Received in revised form 22 April 2021; Accepted 26 April 2021
Available online 3 May 2021

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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