Is thromboprophylaxis with high-dose enoxaparin really necessary for COVID-19 patients? A new "prudent" randomised clinical trial

Marco Cattaneo[1,2], Nuccia Morici[3,4]

[1]*Department of Health Sciences, University of Milan, Milan, Italy;*
[2]*"Unità di Medicina 2, ASST Santi Paolo e Carlo", Milan, Italy;*
[3]*Intensive Cardiac Care Unit and "De Gasperis" Cardio Center, "ASST Grande Ospedale Metropolitano Niguarda", Milan, Italy;*
[4]*Department of Clincal Sciences and Community Health, University of Milan, Milan, Italy*

Dear Sir,

We enjoyed reading the position paper by the Italian Society on Thrombosis and Haemostasis (SISET) that was recently published in Blood Transfusion[1]. It stands out as a rational and well-balanced document in a time of often confused and emotionally-charged initiatives in the management of COVID-19, a severe disease about which still not enough is known[2]. We would like to focus our attention on the recommendation to urgently organise randomised clinical trials (RCT), hopefully supported by the Italian drug agency (AIFA), comparing standard low-dose unfractionated or low molecular weight heparin (LMWH) with higher doses for thromboprophylaxis of COVID-19 patients, who are apparently at very high risk for venous thromboembolism (VTE)[3].

In partial disagreement with the authors, we think that RCT are necessary not only to validate the full anticoagulant dose, but also the intermediate-low dose LMWH (enoxaparin 4,000 IU subcutaneously b.i.d.). We have designed an RCT, X-COVID 19, which has been approved by the AIFA. It will compare efficacy (prevention of VTE) and safety (incidence of major/clinically relevant bleeding) of the standard prophylactic dose of subcutaneous enoxaparin (4,000 IU o.d.) with those of a higher dose (4,000 IU b.i.d.).

We plan to randomise 2,712 COVID-19 patients, hospitalised on non-Intensive Care Unit (ICU) wards. The primary endpoint will be incidental events of asymptomatic or symptomatic deep vein thrombosis (DVT) diagnosed by serial compression ultrasonography (CUS) or symptomatic pulmonary embolism diagnosed by computed tomography angiography (CTA). We will also evaluate the possibility that double-dose enoxaparin favourably impacts the natural history of the disease, perhaps decreasing the incidence of the organ dysfunction associated with the formation of microthrombi in vital organs[4].

Regarding this last point, we would like to question the view that most of the pulmonary occlusions that are detected in COVID-19 patients are caused by pulmonary emboli, originating from peripheral venous thrombi. None of the over 300 COVID-19 patients hospitalised on our wards (all treated with 4,000 IU enoxaparin o.d.), including those with evidence of pulmonary artery occlusions, displayed signs and symptoms of DVT; some of them underwent CUS, which failed to detect asymptomatic DVT[5]. More

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Correspondence: Nuccia Morici
e-mail: nuccia.morici@ospedaleniguarda.it

importantly, the filling defects of pulmonary vessels that were detected by CTA were, in most cases, more reminiscent of pulmonary thrombi than of emboli, because they were not fully occlusive. This observation is compatible with post-mortem descriptions of presence of thrombotic or thrombo-haemorrhagic microangiopathy in the pulmonary vessels, which likely developed locally as a consequence of a thrombo-inflammatory process that may not necessarily be counteracted by high-dose enoxaparin.

Indeed, too much remains unknown about this terrible disorder and more information is urgently needed. This can be achieved by rigorously conducted studies.

The Authors declare no conflicts of interest.

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