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## Scientific letter

### Incidence of heparin-induced thrombocytopenia in patients with 2019 coronavirus disease<sup>☆</sup>



#### *Incidencia de trombocitopenia inducida por heparina en pacientes con enfermedad por coronavirus 2019*

To the Editor:

Among patients with coronavirus disease 2019 (COVID-19), thrombocytopenia is a common abnormality. Due to this, the prophylactic application of low molecular weight heparin (LMWH) has been recommended by several expert consensus,<sup>1</sup> as one of its most serious complications is the well-known heparin-induced thrombocytopenia (HIT).<sup>2</sup>

Additionally, as recent publications have reported the presence of spontaneous HIT in critical patients affected by COVID-19 and *naïve* for heparin,<sup>3</sup> and that therefore a higher percentage and/or intensity than expected could lead to the presentation of said disorder, the objective of this study has been to quantify said incidence of HIT among patients affected by moderate or severe COVID-19.

For this, we have retrospectively analysed a cohort of COVID-19 patients (diagnosed by the polymerase chain reaction test or PCR), under prophylactic treatment with LMWH (bemiparin 2,500–3,500 IU Anti-Xa). They were consecutively admitted to the Hospital Real de Nuestra Señora de Gracia, internal medicine department, between 1st February and 16th March 2020, with a platelet count every 3–5 days and baseline between 100 and  $500 \times 10^3/\text{mm}^3$ .

The final study sample was 43 patients: 51% male, age 73.5 ( $\pm 16.9$ ), body mass index 27.4 ( $\pm 4.7$ ), procalcitonin 0.4 ( $\pm 1.5$ ) ng/mL, leukocytes 8.3 ( $\pm 4.5$ )  $10^3/\text{mm}^3$ , glomerular filtration (CDK-EPI) 70.2 ( $\pm 21.3$ ) mL/min, prothrombin time 12.7 ( $\pm 1.2$ ) s, Clauss fibrinogen 611 ( $\pm 151$ ), ferritin 814 ( $\pm 495$ ) ng/mL and D-dimer 3995 ( $\pm 7092$ ) ng/mL; of which 42% were being treated with hydroxychloroquine and 35% with hydroxychloroquine and lopinavir + ritonavir; 17 had associated risk factors: 35% DM2, 64.7% arterial hypertension and 17.6% renal failure.

The results identified 3 patients (6.9% of the sample), all male and aged 45, 71 and 90 years, whose risk quantification of iatrogenic thrombocytopenia obtained a value of 6, according to the 4Ts scoring system.<sup>2</sup> This meant they had a high probability of presenting HIT (Table 1). The incidence of HIT observed in our cohort (6.9%), although of moderate intensity (minimum platelet count reached  $> 100$ ), seems to suggest, as described by Xuan et al.,<sup>3</sup> that prior exposure to heparin is not absolutely necessary to induce HIT

**Table 1**

Value of the biochemical and hematological variables studied, baseline and at 5–10 corresponding to the 3 cases of patients with suspected heparin-induced thrombocytopenia.

Variable	Case 1		Case 2		Case 3	
	Baseline	5–10 d	Baseline	5–10 d	Baseline	5–10 d
Procalcitonin. ng/mL	1.0	0.9	0.198	0.065	0.136	1.81
Leukocytes $10^3/\text{mm}^3$	12.2	16.9	22	7.4	3.7	3.3
Glomerular filtration (CDK-EPI). mL/min	42	31	80	85	90	90
Prothrombin time. s	13.9	15.4	14.9	12.8	12.8	11.7
Clauss fibrinogen	559	434	152	128	613	450
Ferritin. ng/mL	211	136	1.339	1.014	839	1.088
D-dimer ng/mL	448	676	4.234	4.125	1.287	790
Platelets $10^3/\text{mm}^3$	239	111	182	90	385	186
Platelet decrease $\geq 50\%$	Yes		Yes		Yes	
Thrombosis	No		No		No	
Other causes thrombocytopenia	No		No		No	
4Ts score	6		6		6	

Values are presented as mean (standard deviation).  
d: days.

in COVID-19 patients, and that HIT can occur spontaneously as a result of SARS-CoV-2 infection.

Our results show a high occurrence of HIT (6.9%) among COVID-19 patients under prophylactic treatment with LMWH. However, the platelet decline was moderate and transitory, with recovery occurring during convalescence, either because the viral infection was less severe or because lower heparin doses were used. Therefore, although several authors have reported a protective effect of anticoagulation with heparin in severe COVID-19 patients,<sup>4</sup> the potential risk of HIT should be highlighted, especially when using high doses.

Regarding the limitations of this study, it should be noted that it is a retrospective design, and it focuses solely on the exploration of thrombocytopenia. The influence of other therapies (for example, hydroxychloroquine) has not been evaluated and additionally, it is possible that there has been a 'non-pharmacological change' in the patients' treatment, during the study period, in accordance with advancing knowledge of the COVID-19 pathophysiology. However, due to the lack of specific drugs against this infection, most of the patients received a similar treatment and, therefore, we believe that the results of the current study still have some clinical importance.

In conclusion, the incidence of HIT observed in patients with COVID-19, undergoing thromboprophylactic treatment with LMWH, is high (6.9%) although of moderate intensity. Therefore, in

<sup>☆</sup> Please cite this article as: Lozano R, Franco ME. Incidencia de trombocitopenia inducida por heparina en pacientes con enfermedad por coronavirus 2019. Med Clin (Barc). 2020;155:409–410.

patients with a strong suspicion of HIT, heparin treatment should be suspended and/or continued with an alternative anticoagulant treatment, to avoid the high risk of HIT-induced thrombosis.

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## Tocilizumab plus glucocorticoids in severe and critically COVID-19 patients. A single center experience



### Tocilizumab más glucocorticoides para tratar pacientes graves y en situación crítica infectados por COVID-19. Experiencia de un centro

Dear Editor:

The cytokine storms (CS) mediated by overproduction of proinflammatory cytokines have been observed in a large population of critically ill patients infected with COVID-19.<sup>1</sup>

In previous studies, severe patients that have been hospitalized for COVID-19 have had laboratory results that show an increased level of cytokines, specifically interleukin 6 (IL-6). Tocilizumab is a recombinant humanized monoclonal antibody that has an antagonist effect on the IL-6 receptor, and could play a role in treatment for severely ill patients with COVID-19.<sup>2</sup> Corticosteroids such as methylprednisolone (MP) are the conventional agents used to treat CS, but usually are related with risk of side effects, the most common the secondary bacterial superinfection. There are observational studies on the frontline in China and Italy that suggest the use of methylprednisolone was associated with better clinical outcomes in severe patients with COVID-19 pneumonia.<sup>3,4</sup>

This was a single centre observational study. We report the outcomes of patients treated with tocilizumab plus glucocorticoids in severe and critical severe COVID-19 patients between March 26 and April 17, 2020 in a Intensive Care Unit (ICU) Hospital in Barcelona, Spain. We included patients with high suspicion of CS (persisten fever, increase in inflammatory parameters (CPR, D-dimer, ferritine), and excluded patients with confirmed bacterial superinfection at the start of the treatment.

All patients enrolled met the severe or critical severe criteria defined by the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (6th interim edition) sponsored by National Health Commission of the People's Republic of China.<sup>5</sup>

The diagnose of severity was defined if any of the following conditions was met<sup>1</sup>: respiratory rate  $\geq 30$  breaths/min<sup>2</sup>; SpO<sub>2</sub>  $\leq 93\%$  while breathing room air<sup>3</sup>; PaO<sub>2</sub>/FiO<sub>2</sub>  $\leq 300$  mmHg. A critical case was diagnosed if any of<sup>1</sup>: respiratory failure which requiring mechanical ventilation<sup>2</sup>; shock<sup>3</sup>; combined with other organ failure, need to be admitted to ICU.

A single dose of tocilizumab was administered in 21 patients and two doses in 4 patients. Methylprednisolone were administered 1 mg/kg/day during the inflammatory phase. After that, decreasing doses were administered.

Twenty five patients (14 males and 11 females) with COVID-19 were included in this study. The characteristics of patients, status, laboratory and clinical outcomes are summarized in [Table 1](#). The media age of the patients was 62.4 years. Eight (32%) patients were severe ill, and 17 were critical severe ill (68%), 15 of them with invasive mechanical ventilation, 2 with non invasive ventilation and 8 with high doses of oxygen (O<sub>2</sub> mask more than 50% FiO<sub>2</sub>, or high flow oxygen) at the start of the treatment.

The body temperature of 19 patients (76%) returned to normal in the first 72 h after receiving the treatment. The total number of lymphocytes increases in 17 (68%) patients and CRP decreased significantly in 92% patients at 72 h after the start of treatment. At the same time this was related to a clinical improvement of most patients ([Appendix A](#)).

There were 8 (32%) patients with subsequent bacterial superinfection, all these patients with long ICU admission. The median of days of hospitalization was 25 (8–52) days.

At this time (May 31, 2020), 18 (72%) patients were discharged from hospitalization, 2 patients remain hospitalized, 1 patient in ICU, and 5 deaths (20%).

The time that the anti-inflammatory treatment with tocilizumab was started since the hospital admission was variable among patients, the treatment were started earlier in patients who survived than those who died ( $7.6 \pm 5$  vs.  $13.6 \pm 7.7$  days;  $p: 0.03$ ).

In our study we observed a significant decrease in fever, CPR, D-dimer, ferritine, and an increase in the total number of lymphocytes at 72 h after their start the anti-inflammatory treatment in critical COVID patients.