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RESEARCH LETTER

Heparin-Induced Thrombocytopenia in Severe COVID-19

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As the coronavirus disease 2019 (COVID-19) pandemic has spread throughout the world, important efforts have been made to describe its physiopathology and complications. In critically ill patients with COVID-19, a systemic inflammatory response associated with endothelial activation is observed.[1] A high rate of thrombotic complications has been described, including deep vein thrombosis.[2] Although the mechanisms of thrombosis are unclear, anticoagulation with high doses of heparin has been proposed for these patients.

Heparin-induced thrombocytopenia (HIT) is a severe, life-threatening drug reaction associated with a decrease in platelet count and a high risk of thrombosis caused by platelet-activating antibodies against PF4/heparin complexes.[3] The atypical clinical and therapeutic context of the COVID-19 pandemic, with a broader indication of curative anticoagulation, could lead to a higher prevalence of HIT.

In this context, we retrospectively reviewed all cases of HIT among patients presenting with COVID-19 acute respiratory distress syndrome (ARDS) in 2 intensive care units in southern France. We described 7 consecutive cases of HIT associated with COVID-19 ARDS between March 30 and April 18, 2020 (Table). Patients or their relatives received information and signed a nonopposition form, according to French law, to be enrolled in COAG-COVID (Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care). The study was approved by an ethics committee.

All patients presented antibodies to PF4/heparin, as detected by a quantitative chemiluminescent immunoassay (HemosIL AcuStar HIT immunoglobulin G, PF4-H, normal value <1 U/ml). Diagnosis was confirmed for the 7 patients using the heparin-induced platelet aggregation test. Six patients were male, with a median age of 57 years (interquartile range, 46–63 years). The median body mass index was 26 (interquartile range, 25–30). Most patients had severe ARDS, with a median Pao_2/Fio_2 ratio of 80 (interquartile range, 75–113). All but one were intubated and mechanically ventilated. Three were supported by venovenous extracorporeal membrane oxygenation for refractory hypoxemia. All patients were exposed to unfractionated heparin, including 5 after the administration of low-molecular-weight heparin for a median of 14 days (interquartile range, 11–16 days). All patients had curative anticoagulation objectives. The duration of heparin exposure before HIT diagnosis was >10 days for 6 patients. All patients presented a severe drop in platelet count. Five patients experienced at least 1 severe clinical thromboembolic event. Alternative anticoagulation was pursued with either danaparoid or argatroban. All platelet counts returned to normal values after the anticoagulation therapy was switched. At the observation period end point, 5 patients were discharged from the intensive care unit, including 3 from the hospital, and the remaining 2 were still in the intensive care unit.

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Key Words: COVID-19 ■ heparin ■ thrombocytopenia

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Table. Characteristics of 7 Patients With Severe COVID-19 Hospitalized in the ICU With HIT

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age, y	46	50	43	63	59	57	69
Sex	Male	Male	Female	Male	Male	Male	Male
Body mass index	27	25	47	21	33	26	27
Medical history	None	None	Severe obesity, asthma	None	Sleep apnea syndrome	Burnout	Diabetes type 2, hypertension
Medications	None	None	Bronchodilator	None	None	Paroxetine	Repaglinide, zofenopril
Delay between onset of symptoms of COVID-19 and admission to ICU, d	2	7	7	13	9	7	9
Invasive mechanical ventilation	Yes	Yes	Yes	Yes	Yes	No	Yes
Venovenous ECMO	Yes	Yes	Yes	No	No	No	No
Antiviral treatment	Hydroxychloroquine	Hydroxychloroquine	Lopinavir/ritonavir	Hydroxychloroquine	None	Hydroxychloroquine	Hydroxychloroquine
Heparin type during ICU stay	LMWH, then UH	LMWH, then UH	LMWH, then UH	LMWH, then UH	LMWH, then UH	UH	UH
Duration of heparin exposition before HIT diagnosis, d	16	13	15	14	9	11	16
4T score	6	6	6	4	5	5	4
Platelet count at admission, G/L	61	243	160	191	161	159	215
Platelet count at HIT diagnosis	33	73	48	56	62	39	107
Drop in platelet count, %	46	70	70	75	69	76	53
WBC count at diagnosis, G/L	8	7.2	9.4	8.6	10.4	4.49	15.5
Lymphocytes at diagnosis of HIT, G/L	0.69	0.64	0.78	0.71	0.69	0.75	0.76
CRP, mg/L	198	254	201	153	135	253	78
Anti-PF4 levels, URL/mL (normal value <1 U/ml)	46	11	39	60	4	21	2
Alternative anticoagulation after HIT diagnosis	Argatroban	Argatroban	Argatroban	Danaparoid	Danaparoid	Danaparoid	Danaparoid
Clinical thrombotic events	Multiple deep vein thrombosis	Intracardiac thrombosis, ECMO membrane thrombosis	Multiple deep vein thrombosis, ECMO pump thrombosis	Stroke	Deep vein thrombosis	None	None
Outcome status at day 28	Discharged from ICU	Still in ICU	Still in ICU	Discharged from hospital	Discharged from ICU	Discharged from hospital	Discharged from hospital

4T score indicates thrombocytopenia, timing of thrombocytopenia relative to heparin exposure, thrombosis or other sequelae of heparin-induced thrombocytopenia, likelihood of other causes of thrombocytopenia; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; LMWH, low-molecular-weight heparin; UH, unfractionated heparin; and WBC, white blood cell.

During the COVID-19 pandemic period, we admitted 86 patients with severe COVID-19 in 2 intensive care units, which represents an incidence of HIT of 8%. Although thrombocytopenia is frequent in critically ill patients, the incidence of HIT is relatively rare (<1%[3]; up to 3.7% in patients supported by extracorporeal membrane oxygenation).[4] In a previously published cohort of 105 patients supported by venovenous

extracorporeal membrane oxygenation, we reported an incidence of HIT of 2%[5] compared with 3 among 14 patients (21%) during the COVID-19 pandemic. We compared this cohort with a control cohort of patients in the intensive care units of our centers during a 6-month period from January 1 to June 1, 2019: 447 patients were admitted to our centers, with 58.8% of patients requiring mechanical ventilation and 13 patients (5%) supported by extracorporeal membrane oxygenation. During this period, 19 patients (4.2%) were tested for HIT, and 4 were ultimately positive, representing 0.89% of the cohort. The median rate of anti-PF4 among patients with HIT was 22.6, compared with 0.045 in HIT-negative patients. Regarding our results, we observed a nearly 10-fold higher occurrence of HIT during severe COVID-19 in our centers. This increased incidence could be explained by the higher doses of heparin used for treatment of patients with COVID-19 and by specific features of severe COVID-19 disease. Whereas obesity is associated with an increased risk of developing HIT, only 2 patients were obese in our observation.

The pathophysiology of an increased thrombosis risk or a potential increased HIT risk in the context of COVID-19 is not yet clearly understood. The higher prevalence of HIT in these patients could be explained by exacerbated immune reactions and probably by an increased release of PF4 linked to platelet activation.

Critically ill patients with COVID-19 develop life-threatening coagulopathy and thromboembolic complications that justify aggressive anticoagulation with close monitoring. However, the occurrence of HIT increases the risk of severe thrombotic events and could alter the risk–benefit balance of anticoagulation. In this context, clinicians should be aware of a possible higher incidence of HIT. Achieving a 4T score (thrombocytopenia, timing of thrombocytopenia relative to heparin exposure, thrombosis or other sequelae of HIT, likelihood of other causes of thrombocytopenia) in patients with COVID-19 is complex. Thrombocytopenia and thrombosis are commonly observed, and patients present with other causes of thrombocytopenia. Rapid detection of antibodies to PF4/heparin is necessary in patients with COVID-19 to avoid a misdiagnosis of HIT. Immune dysregulation observed during acute COVID-19 may contribute to HIT occurrence. Further larger investigations are warranted to confirm this increased incidence of HIT and to understand its physiopathology.

ARTICLE INFORMATION

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Disclosures

None.

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