Commentary

A rare disease

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See related research by Gettings *et al*., http://ccforum.com/content/10/6/R161

Abstract

Thrombocytopenia is a common finding in critically ill patients. Heparin-induced thrombocytopenia is an infrequent cause of a low platelet count. Intensivists should use the diagnostic classification system developed by the International Society on Thrombosis and Haemostasis to diagnose heparin-induced thrombocytopenia. The clinical relevance of the presence of anti-heparin/platelet factor 4 complex autoantibodies in the absence of clinical heparin-induced thrombocytopenia remains unknown.

Intensivists frequently encounter thrombocytopenia in the critically ill, which has an incidence of 30% to 50% in such patients. The low platelet count indicates the severity of disease in these patients and has prognostic significance. Most often, the thrombocytopenia is a transient phenomenon, and recovery of the platelet count often reflects clinical improvement. On the other hand, a persistent low platelet count or relapse of thrombocytopenia often portends clinical deterioration and death.

There are many potential aetiologies of thrombocytopenia in the critically ill, including loss, dilution, consumption, destruction and impaired production of platelets. Among the various types of thrombocytopenia, heparin-induced thrombocytopenia (HIT), in which anti-heparin/platelet factor 4 complex antibodies (the so-called HIT antibodies) play a central role, is regarded as the most common drug-induced immune-mediated thrombocytopenia. HIT, which involves a paradoxical association of a procoagulant state with an anticoagulant drug, is feared because of the possible occurrence of life-threatening and potentially fatal venous and arterial thromboembolic complications. It is implicated by the association of treatment with unfractionated heparin or low-molecular-weight heparin and development of thrombocytopenia, both of which are common in the ICU. HIT is actively diagnosed because of the preventability of its sequelae.

At the turn of the century the incidence of HIT in the critically ill was largely unknown. Seven investigations were begun at around that time, and slowly but surely the incidence of HIT in the critically ill has emerged. In the preceding issue of *Critical Care*, Gettings and coworkers [1] report their retrospective observations in surgical critically ill patients, in which they focus on the incidence of HIT antibody positivity, the incidence of HIT and the clinical relevance of HIT antibodies. Over 2 years a total of 2,046 patients were admitted, and there was suspicion of HIT in 210 of these. Nineteen patients tested positive for HIT antibodies, yielding an incidence of 0.9% of seroconversion and HIT. These patients were at increased risk for death or major thromboembolic complications and prolonged length of stay in the ICU in comparison with matched control individuals.

Two important comments can be made based on these findings. First, one can contest whether all 19 patients suffered from HIT, because seroconversion does not prove that HIT has developed. Stimulated by the peer review process, the authors used, retrospectively, the diagnostic classification system developed by the Scientific and Standardization Committee Subcommittee on Platelet Immunology of the International Society on Thrombosis and Haemostasis, which can be regarded as the current reference method [2]. Fifteen patients had an intermediate pretest probability and four patients had a high pretest probability of HIT. The diagnosis of HIT can be made if intermediate or high pretest probability is supported by the presence of HIT antibodies and proof of platelet aggregation. In other words, laboratory confirmation of HIT should consist of an antibody assay and a functional assay. In about half of cases in which there is a positive antibody test, the functional assay will be negative. Gettings and coworkers [1] did not use a functional test, and so the reported incidence of 0.9% is the incidence of seroconversion and not necessarily the incidence of HIT, which probably was lower.

HIT = heparin-induced thrombocytopenia; ICU = intensive care unit.

In the other six studies that investigated the incidence of HIT antibody positivity and HIT in general populations of critically ill patients [3-8], similar results were reported. In 261 patients in a medical-surgical ICU, no cases of HIT antibody positivity and no HIT were found [3]. In 267 patients treated in a combined intensive and coronary care unit, an incidence of 0.39% (95% confidence interval 0.01% to 2.1%) of HIT was reported [4]. In 55 patients treated in a general ICU, an incidence of 39.5% seroconversion was detected but no cases of HIT were identified [5]. In 233 patients in a medical ICU, an HIT incidence of 2.5% was found [6]. In 43 patients admitted for longer than 36 hours in a medical-surgical ICU, a seroconversion incidence of 16.3% and an incidence of HIT of 4.7% were demonstrated [7]. Finally, in 64 patients with multiple organ dysfunction syndrome in a surgical ICU, incidences of 4.7% for seroconversion and 4.7% for HIT were detected [8].

Second, the authors tried to analyze the clinical relevance of the presence of HIT antibodies, but they could have chosen their control group more carefully. The control group comprised a mixture of patients, most of whom were not suspected of having HIT and were therefore not tested. The authors could have drawn firmer conclusions if they had chosen the control group from among patients suspected of having HIT but who tested negative for HIT antibodies. Nevertheless, their results are in accord with those of a large study conducted in cardiac surgery patients in the critical care setting, of whom 6.6% were positive for HIT antibodies but who did not have HIT [9]. Patients with HIT antibodies required prolonged mechanical ventilation, developed acute renal failure necessitating haemodialysis, had a prolonged length of stay in the ICU, and consumed significant additional critical care resources.

The clinical relevance of the presence of HIT antibodies remains unknown. Other antiplatelet autoantibodies can be detected in patients with sepsis and in those undergoing cardiopulmonary bypass procedures [10]. These autoantibodies and HIT antibodies without platelet-aggregating properties may well represent important autoimmune mechanisms in severe disease, but they may be regarded as an epiphenomenon of severe disease as well. To date, no therapy directed against antiplatelet autoantibodies is of proven value in the critical care setting.

In conclusion, intensivists should be aware that HIT is a rare disease. Many critically ill patients will develop a low platelet count, but the likelihood that HIT is the cause is far less than that for many other causes. Intensivists should employ the tools provided by the International Society on Thrombosis and Haemostasis to diagnose HIT and should combine clinical data with sufficient laboratory data. The presence of HIT antibodies alone is not enough - a positive test is not necessarily a disease!

Competing interests

The author(s) declare that they have no competing interests.

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