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de Pont, Anne-Cornelie J. M.

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Heparin-Induced Thrombocytopenia: Finding the Needle in the Haystack*

Anne-Cornélie J. M. de Pont, MD, PhD
Department of Critical Care
University of Groningen
University Medical Center Groningen
Groningen, The Netherlands

Thrombocytopenia is a common laboratory finding among critically ill patients, occurring in at least 30–50% of the patients (1). Its cause is usually multifactorial and may include platelet consumption or aggregation, adherence to cells, splenic sequestration, decreased production, hemodilution, or destruction mediated by antibodies or complement (2). In heparin-induced thrombocytopenia (HIT), heparin-induced antibodies against platelet factor-4 trigger platelet activation and aggregation, which in the worst-case scenario may cause venous and arterial large vessel thrombosis, leading to death (3). Treatment of highly suspected or confirmed HIT consists of discontinuation of all forms of heparin and switching to another type of anticoagulation, preferably a direct thrombin inhibitor such as argatroban or bivalirudin or an indirect factor Xa inhibitor such as fondaparinux. Vitamin K antagonists are contraindicated in HIT because they enhance the prothrombotic state by inducing protein C deficiency (3).

Among critically ill patients exposed to heparin, HIT is a very rare cause of thrombocytopenia, the occurrence ranging from 0.02% to 0.45% among general ICU patients to 1–3% among cardiac ICU patients (3). Since this rare syndrome may have such devastating consequences, correct and timely diagnosis is of paramount importance. HIT is a clinical-pathologic diagnosis that requires both a clinical picture consistent with HIT and the presence of platelet-activating heparin-dependent antibodies (1, 3). The typical clinical picture consists of a more than 50% decline in platelet count starting 5–10 days after heparin exposure, in the absence of other causes of thrombocytopenia and typically associated with thrombosis. To quantitatively assess the possibility of the presence of HIT, the 4Ts score has been developed, assigning 0–2 points to each of these four clinical variables. A score of greater than or equal to 4 points indicates an intermediate (4, 5) to high (≥6) probability of HIT and warrants serological testing. For the detection of antibodies, a polyspecific enzyme-linked immunosorbent assay (ELISA) is commonly used. Although this test has a high sensitivity, its specificity is low. To increase the specificity of the test, it can be quantified by means of the optical density (OD). Every 0.5 increase in OD increases the likelihood of HIT by an odds ratio (OR) of 6.39 and every 1.0 increase in OD increases the likelihood by an OR of 40.81 (3). Nevertheless, in case of a positive ELISA, confirmation by means of a functional assay such as the serotonin release assay (SRA) is recommended (3). However, this test is technically difficult and expensive and obtaining the result may take up to 4 days.

In this issue of Critical Care Medicine, Gkalea et al (4) report the performance in critically ill patients of a rapid and easy to perform functional assay for HIT: heparin-induced multiple electrode aggregometry (HIMEA). In this technique, the attachment of platelets to the electrodes of the Multiplate analyzer (Roche Diagnostics, Mannheim, Germany) causes an increase of impedance, which can be transformed to arbitrary platelet aggregation units (AU) (5). In 87 critically ill patients with suspected HIT, the 4Ts score was performed, followed by three blood tests: ELISA immunoglobulin G, HIMEA, and SRA. In 12 patients, HIT was diagnosed. Twenty patients had a positive ELISA, 13 a positive SRA and 11 a positive HIMEA. Based on these results, sensitivity, specificity, positive and negative predictive value of HIMEA was 92%, 100%, 100%, and 98%, respectively. The authors conclude that HIMEA can improve the diagnostic procedure of HIT in critically ill patients. In addition, they propose a new algorithm for the diagnostic pathway.

In 2006, multiple electrode aggregometry was first described as a method to analyze platelet function in whole blood (6). Since this first publication, two groups have published about the use of this technique in the diagnosis of HIT, a Belgian group from Namur and the current French group from Paris. In their first publication, the French group compared HIMEA to both SRA and light transmission aggregometry (LTA) (7). They demonstrated that HIMEA and LTA had similar capacities to detect heparin-induced platelet aggregating antibodies. However, in 15 patients with a positive SRA and a negative LTA, HIMEA was also negative (7). In their second publication, the same group prospectively compared HIMEA and LTA to SRA as a gold standard among 200 consecutive patients suspected of HIT. In the study by Gkalea et al (8), HIMEA was positive in 17 of 21 positive SRA patients, coming down to a sensitivity of 81% with a specificity of 99%.

The Belgian group compared HIMEA to LTA, SRA, and the clinical diagnosis (9). In the study by Minet et al (9), HIMEA correctly identified six of eight patients with a clinical HIT

*See also p. 353.

Key Words: antibodies; heparin; low molecular weight heparin; platelet aggregation; platelet factor 4; thrombocytopenia

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diagnosis when a threshold of 183 AU was used (sensitivity 75%) and all eight when a threshold of 276 AU was used (sensitivity 100%). Interestingly, HIMEA was positive in three of the five SRA positive patients, regardless the threshold used. The authors emphasize that the SRA has to be validated and standardized before it can be used as a gold standard. In their study, one out of five patients with a clinical HIT diagnosis had a negative SRA (sensitivity 80%).

In 2009, Greinacher (10) proposed a diagnostic algorithm for HIT, consisting of a pretest probability test such as the 4Ts score, followed by an ELISA, and in case of an OD greater than 1.0 a functional assay such as the SRA. A similar algorithm was proposed in a recent review in “Chest” (3). Based on the results of their first study, the Belgian group tested another algorithm based on 4Ts score, ELISA, and HIMEA (11). One-hundred sixteen patients clinically suspected of HIT were prospectively tested. In only two patients HIT was clinically diagnosed. These two patients were both correctly identified by HIMEA using a threshold of 276 AU.

The question remains what HIMEA adds to the current diagnostic pathway. The great advantage of HIMEA is that it can be performed within 15 minutes (8). However, in order to perform the test, a Multiplate analyzer and the immediate availability of a healthy compatible blood group donor are required (11).

Across the different studies, the specificity of HIMEA in detecting clinical HIT ranges from 97% to 100%, which gives a positive result an acceptable reliability. However, the sensitivity of HIMEA ranges from 86% to 100%, which means that as much as 14% of the patients with a clinical HIT diagnosis might be missed in case of a negative HIMEA. Therefore, among patients with a high pretest probability, a positive ELISA and a negative HIMEA, an additional functional assay such as SRA or heparin-induced platelet activation has to be performed, as Gkalea et al (4) suggest in their proposed algorithm. In addition, the final diagnosis should always be confirmed by clinical reassessment (10).

So what is the advantage of incorporating HIMEA in the diagnostic algorithm? When we compare the “Chest” algorithm to the one by Gkalea et al (4), the only difference is that in true HIT patients, the diagnosis is confirmed more quickly by means of HIMEA. However, since both algorithms advocate that in all patients with a 4Ts score greater than or equal to 4, all heparins should be replaced by an alternative anticoagulant, speeding up the diagnostic pathway has no therapeutic consequence.

Taken together, HIMEA is a tool that can be beneficial in speeding up the diagnosis in HIT patients. Whether it is worth adopting to find this needle in a haystack, remains to be established.

REFERENCES