Thrombosis Research 158 (2017) 65–70

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Implementation of a rapid HIT immunoassay at a university hospital – Retrospective analysis of HIT laboratory orders in patients with thrombocytopenia☆,☆☆

Anne Black[a], Susanne Heimerl[a], Linnéa Oertli[b], Wolf Wilczek[c], Andreas Greinacher[e], Michael Spannagl[d], Wolfgang Herr[b], Christina Hart[b,*]

[a] Institute for Clinical Chemistry and Laboratory Medicine, University Hospital Regensburg, Regensburg, Germany
[b] Department of Hematology and Oncology, Internal Medicine III, University Hospital Regensburg, Regensburg, Germany
[c] Hospital Pharmacy, University Hospital Regensburg, Regensburg, Germany
[d] Department of Hemostasis and Transfusion Medicine, Ludwig-Maximilian-University of Munich, Munich, Germany
[e] Department of Immunology and Transfusion Medicine, Ernst-Moritz-Arndt-University, Greifswald, Germany

ARTICLE INFO

Keywords:
HIT
Thrombocytopenia
4Ts score

ABSTRACT

Background: Heparin-induced thrombocytopenia (HIT) is a rare cause of thrombocytopenia and a potentially life-threatening adverse drug reaction. Clinical overdiagnosis of HIT results in costly laboratory tests and anticoagulation. Criteria and algorithms for diagnosis are established, but their translation into clinical practice is still challenging.

Study design and methods: In a retrospective approach we studied all HIT related laboratory test requests within four years and evaluated data before (1st period, 24 month) and after (2nd period, 24 month) replacing particle gel immunoassay (PaGIA) and enzyme-linked immunosorbent assay (ELISA) by a chemiluminescent immunoassay (CLIA). HIT was confirmed by heparin-induced platelet activation (HIPA) test. Clinical pretest probability for HIT using an implemented simplified 4Ts score and platelet count were evaluated. Costs for laboratory tests and alternative anticoagulation were calculated.

Results: In 1850 patients with suspected HIT, 2327 laboratory orders were performed. In 87.2% of these orders an intermediate/high simplified 4Ts score was found. Thrombocytopenia was present in 87.1%. After replacing PaGIA and ELISA by CLIA the number of immunological and functional laboratory tests was reduced by 38.2%. The number of positive HIT immunoassays declined from 22.6% to 6.0%, while the number of positive HIPA tests among positive immunological tests increased by 19%. Altogether, acute HIT was confirmed in 59 patients. A decline in the use of alternative anticoagulants was observed in the 2nd period.

Conclusion: Our study shows that in a university hospital setting HIT is well-known, but diagnosis requires a precise laboratory confirmation. Replacing PaGIA and ELISA by CLIA did not influence laboratory order behavior but results in reduced overall costs for laboratory diagnostics and alternative anticoagulation.

1. Introduction

Heparin-induced thrombocytopenia (HIT) is a potentially life threatening, immunologically mediated adverse drug reaction to unfractionated heparin (UFH) or less common to low-molecular weight heparin (LMWH). Antibodies generated against platelet (PLT) factor 4 (PF4)/heparin complexes bind to PLT Fc receptors resulting in PLT activation, thrombocytopenia and thromboembolism [1]. Thrombocytopenia as the leading clinical symptom of HIT is common in hospitalized patients, especially in acutely ill patients, of whom about 50% will present with thrombocytopenia [2,3]. The frequency of HIT in heparin-exposed critically ill patients is only 0.3–0.5% [4]. Overdiagnosis and

Abbreviations: CLIA, chemiluminescent immunoassay; DTI, direct thrombin inhibitor; EDTA, ethylenediaminetetraacetic acid; ELISA, enzyme-linked immunosorbent assay; HIPA, heparin-induced platelet activation; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; IU, international unit; LMWH, low-molecular weight heparin; PaGIA, particle gel immunoassay; PF4, platelet factor 4; PLT(s), platelet(s); RI, rapid immunoassay; TAT, turnaround time; UFH, unfractionated heparin

☆ Source(s) of support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

☆☆ Conflict of Interest: There is no conflict of interest.

* Corresponding author at: Department of Hematology and Oncology, Internal Medicine III, University of Regensburg, Franz-Josef-Strauss-Allee 11, D-93053 Regensburg, Germany.
E-mail address: christina.hart@ukr.de (C. Hart).

http://dx.doi.org/10.1016/j.thromres.2017.08.008
Received 12 April 2017; Received in revised form 19 July 2017; Accepted 15 August 2017
Available online 15 August 2017

overtreatment of HIT are frequent and have major consequences as heparin is stopped and alternative anticoagulants such as the direct thrombin inhibitor (DTI) argatroban or the heparanoid danaparoid are started. These substances carry a higher risk of bleeding and are far more expensive than heparin [5]. The diagnosis of HIT is challenging and thus requires both careful clinical assessment and laboratory evaluation. The 4Ts score is widely used as a scoring system to estimate the clinical probability of HIT [6]. Laboratory tests for HIT include immunological assays and functional assays, for example the heparin-induced PLT activation (HIPA) test [7]. The widely used PF4/heparin enzyme-linked immunosorbent assays (ELISAs) have a high sensitivity, but limited specificity for clinically relevant antibodies due to detection of clinically insignificant anti-PF4-heparin antibodies. Furthermore, they are time consuming [8]. Recently, rapid immunoassays (RIs) with a short turnaround time (TAT) have been developed. Three RIs – the particle gel immunoassay (PaGIA), IgG-specific chemiluminescent assay (IgG-CLIA) and the lateral flow immunoassay were shown to improve specificity and thus accuracy of HIT diagnosis [9].

The trigger of our study was the apparently high number of HIT test orders at our hospital, especially in patients with thrombocytopenia. Based on this observation, we carried out a retrospective study focusing on the HIT laboratory ordering behavior of physicians in patients with suspected HIT over a period of 48 month. Additionally, we addressed the question if ordering behavior was influenced by changes of the test portfolio which was implemented independently by the central laboratory years before. We retrieved all available data of a two years period before (1st period) and after (2nd period) replacement of PaGIA and ELISA by CLIA, assessed the laboratory order behavior in patients with thrombocytopenia, and evaluated costs for laboratory diagnostics and alternative anticoagulation.

2. Materials and methods

2.1. Patients

In this retrospective analysis all orders for HIT-related laboratory tests (n = 2479) including PaGIA, ELISA, CLIA and HIPA between Jan 1, 2012 to Dec 31, 2015 were retrieved from the laboratory records as shown in Fig. 1. PLT count and information on clinical pretest probability were additionally obtained. Orders were excluded from the study if both criteria were missing (n = 152). A total of 1850 patients were included, for whom 2327 HIT-related laboratory tests were ordered. In 477 patients, HIT was suspected more than one time within a four-year period. Diagnosis of HIT was based on positive results in a HIT immunoassay(s) and the HIT functional assay. Clinical characteristics of patients with confirmed HIT were obtained by reviewing the patient chart. In all patients with suspected acute HIT, heparin was stopped and therapeutic-dose anticoagulation with either argatroban or danaparoid was initiated and HIT was mentioned in the patient report. The study was approved by the local Ethics Committee (number of ethical approval 14-101-0013).

2.2. Clinical pretest probability of HIT (4Ts)

When HIT laboratory tests were requested a “simplified 4Ts scoring system” had to be completed by the treating physician. Due to technical reasons our hospital IT system could not integrate the original 4 Ts score in the order entry laboratory system. Therefore a simplified version was created (Table 1) which includes the four parameters acute thrombocytopenia, timing of onset, thrombosis and other cause of thrombocytopenia as described before [6]. Symptoms for 4Ts could be answered with yes (2 points) or no (0 points) and the simplified clinical probability was calculated. A score 0–2 points indicated a low pretest probability whereas a score of 4–8 points indicated an intermediate/high pretest probability. Laboratory HIT testing was performed independently of the results of the simplified 4Ts score.

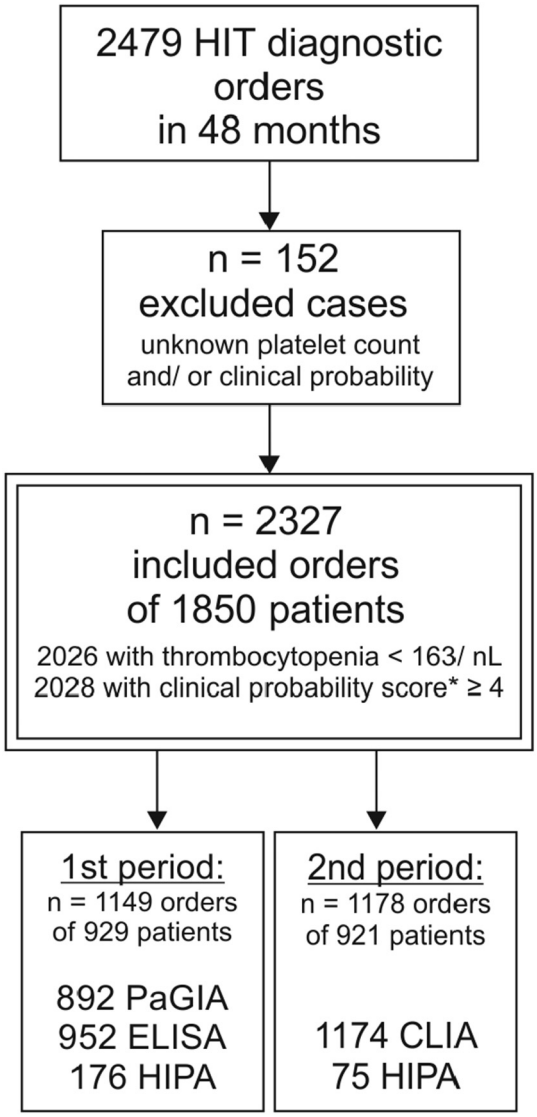

Fig. 1. Systematic search for HIT related laboratory tests in cases of suspected HIT. Within 48 months, the following criteria were retrieved from the laboratory records: platelet count (PLT), clinical probability (simplified 4 T-Score) and HIT laboratory tests (PaGIA: particle gel immunoassay, ELISA: enzyme-linked immunosorbent assay, CLIA: chemiluminescent immunoassay, HIPA: heparin induced PLT activation assay). 152 orders were excluded due to incomplete information on PLT count and/or clinical probability (* simplified 4Tscore). A total of 2237 cases were included for statistical analysis. After the 1st period, PaGIA and ELISA were replaced by HIT-CLIA (2nd period).

2.3. Blood sampling

For antibody assays, serum was obtained from whole blood in tubes filled with clotting activator coated beads (silicate; S-Monovette®, clotting activator, Sarstedt) by centrifugation for 10 min at 4000 × *g*. For analysis of PLT count, anticoagulated blood (tubes filled with ethylenediaminetetraacetic acid: 1.6 mg EDTA/1 mL blood; S-Monovette®, EDTA K_3, Sarstedt) were used not later than 6 h after sampling.

2.4. HIT assays

Until 2013 two different immunological assays were performed for HIT laboratory testing: a particle gel immunoassay (ID-PaGIA Heparin/PF4 Antibody Test, DiaMed) that detects all three major immunoglobulin classes (anti-PF4/heparin IgG/IgA/IgM) and an ELISA to detect anti-PF4/heparin-IgG antibodies (PF4-IgG, Immucor GTI