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ABSTRACT

Background: Accurate diagnosis of heparin-induced thrombocytopenia (HIT) is essential but remains challenging. We have previously demonstrated, in a retrospective study, the usefulness of the combination of the 4Ts score, AcuStar HIT and heparin-induced multiple electrode aggregometry (HIMEA) with optimized thresholds.
Objectives: We aimed at exploring prospectively the performances of our optimized diagnostic algorithm on suspected HIT patients. The secondary objective is to evaluate performances of AcuStar HIT-Ab (PF4-H) in comparison with the clinical outcome.
Methods: 116 inpatients with clinically suspected immune HIT were included. Our optimized diagnostic algorithm was applied to each patient. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) of the overall diagnostic strategy as well as AcuStar HIT-Ab (at manufacturer's thresholds and at our thresholds) were calculated using clinical diagnosis as the reference.
Results: Among 116 patients, 2 patients had clinically-diagnosed HIT. These 2 patients were positive on AcuStar HIT-Ab, AcuStar HIT-IgG and HIMEA. Using our optimized algorithm, all patients were correctly diagnosed. AcuStar HIT-Ab at our cut-off (>9.41 U/mL) and at manufacturer's cut-off (>1.00 U/mL) showed both a sensitivity of 100.0% and a specificity of 99.1% and 90.4%, respectively.
Conclusion: The combination of the 4Ts score, the HemosIL® AcuStar HIT and HIMEA with optimized thresholds may be useful for the rapid and accurate exclusion of the diagnosis of immune HIT.

Introduction

Immune heparin-induced thrombocytopenia (HIT) is a severe immunological adverse event of heparin therapy [1,2]. Early diagnosis is essential and both misdiagnosis and erroneous diagnosis should be avoided [3]. Indeed, a misdiagnosis may expose the patient to life-threatening thrombosis. Delays in the starting of treatment are associated with an initial 5%-10% daily risk of thrombosis, amputation, organ dysfunction or death [1]. An overdiagnosis may also lead to a discontinuation of the heparin treatment and a substitution by another more expensive anticoagulant which could be associated with an increased risk of bleeding without effective antidote [3,4]. The current diagnostic relies on the use of a clinical scoring algorithm ("4Ts score") together with immunological and functional assays (i.e. platelet activation assays) [1,2]. This combination improves HIT diagnosis compared to its components considered independently [5]. However, the scoring system has to be used carefully and may require some extensive documentation of the patient medical history [6]. Immunoassays are sensitive but poorly specific. The HemosIL® AcuStar HIT-IgG (PF4-H) and AcuStar HIT-Ab (PF4-H), two immunological assays, and the heparin-induced multiple electrode aggregometry (HIMEA), a functional assay, were recently proposed as new rapid methods for the diagnosis of HIT [7–9].

Previously, we performed a retrospective study on 106 patients with suspected HIT. We showed that a diagnostic algorithm based on 4Ts score, AcuStar HIT and HIMEA with optimized thresholds showed good performances for the rapid and accurate diagnosis of immune HIT (PPV: 88.9 % (95% CI: 51.7%-98.2%), NPV: 100.0 % (95% CI: 96.1%-100.0%)) [10].

In the present study, we explored prospectively the performances of our optimized diagnostic algorithm on HIT suspected patients in our academic tertiary hospital. Secondly, we evaluated performances of AcuStar HIT-Ab (PF4-H) in comparison with the clinical outcome.

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Materials and Methods

Patients

One hundred and sixteen inpatients (76 men and 40 women; 49 medical and 67 were surgical patients) suspected of developing HIT from 1st November 2011 to 31th January 2013 at the CHU Dinant Godinne - UCL Namur, Belgium, were included in the study, in accordance with the local ethics committee.

Healthy subjects

In order to perform HIMEA, whole blood samples from healthy volunteers are needed. Blood was collected with a 20 gauge needle via atraumatic antecubital venipuncture into polyethylene terephthalate tubes Venosafe® (Terumo Europe, Leuven, Belgium) containing 25 μg/mL of recombinant hirudin (Verum Diagnostica GmbH, Munich, Germany, 1:10 v/v). A discard tube was used to avoid tissue factor contamination. Blood was obtained from two O Rh +/− blood group donors. These donors did not take any medicine which could potentially affect their platelet function for 10 days before the blood sampling. Platelet donors were selected on the basis of a good reactivity with plasma of HIT patients. The platelet reactivity of the healthy donors was also assessed by HIMEA with the following reagents: adenosine diphosphate (ADP, final concentration: 6.5 μM), collagen (type 1, final concentration: 3.2 μg/mL), arachidonic acid (AA, final concentration: 0.5 mM) or thrombin receptor activating peptide (TRAP-6, final concentration 32 μM) (Dynabyte, Munich, Germany). Each volunteer presented normal aggregation.

Optimized diagnostic algorithm

Routine laboratory diagnosis was performed on HIT patients according to our optimized algorithm (Fig. 1) (except for AcuStar HIT-Ab which was performed on each patient). This flow chart is based on (1) 4Ts score, (2) AcuStar HIT (PFA-H) (immunological assay), and (3) HIMEA (functional assay).

4Ts score and clinical diagnosis

HIT was suspected because of a rapidly decreasing platelet count occurring in hospitalised patients under heparin therapy. Subsequently, the "4Ts score" was calculated (based on four criteria: the severity of the thrombocytopenia and its timing, the occurrence of a thrombosis and the exclusion of other causes of thrombocytopenia). Clinical data were recorded in real time in the hospital medical database. Clinical outcomes were retrospectively and independently confirmed by two investigators (VM and FM), not aware of the results of the laboratory assays. Clinical diagnoses made by these 2 local investigators were 100% concordant among them and with conclusions of the medical database. Several clinical criteria have to be fulfilled for the confirmation of clinical HIT diagnosis. Criteria from the ACCP (American College of Chest Physicians) guidelines were used to make the clinical diagnosis of HIT: (1) Thrombocytopenia, defined as at least a 30% decline in the platelet count, with a platelet count increase after heparin cessation; (2) Timing of platelet count fall after the initiation of heparin occurring between 4 and 14 days, or occurring within 24 to 48 hours (in case of prior heparin exposure within 30 days); and (3) lack of other, predominant causes of thrombocytopenia [11–13]. Other causes of thrombocytopenia analysed in this study were: neoplasia, current pregnancy or

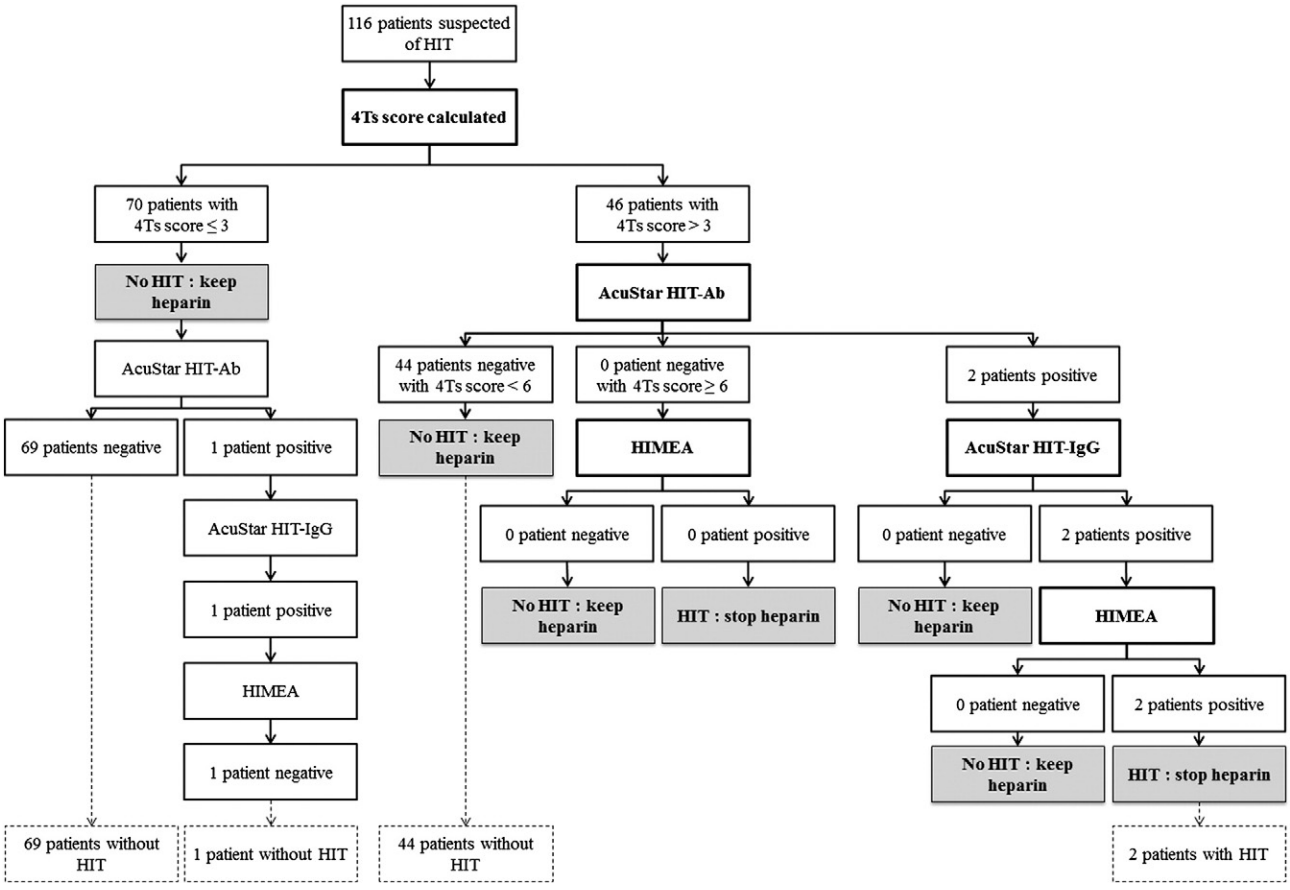

Fig. 1. Flow chart with results. Thresholds for AcuStar HIT-Ab, AcuStar HIT-IgG and HIMEA are, respectively, 9.41 U/mL, 2.89 U/mL and 276 U/mL at 1 IU/mL UFH and a reduction > 80% at 385 IU/mL UFH.

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postpartum, autoimmune disease, sepsis, disseminated intravascular coagulation, intra-aortic balloon pump counterpulsation, multitransfusion, multi-trauma, shock syndrome and drug-induced thrombocytopenia (quinolone, β-lactam, vancomycin, teicoplanin, rifampicin, isoniazid, amphotericin, fluconazole, chemotherapy, anti-GPIIb/IIIa; furosemide and proton pump inhibitors). All these 3 clinical criteria have to be fulfilled for the confirmation of clinical HIT diagnosis. The following information was taken into consideration: patient's medical history, types (fractionated vs. unfractionated) and doses of heparin administered, thrombotic complications, alternative diagnoses, therapeutic attitude, clinical and platelet count evolution, co-suspected medications, and physician's diagnoses [10,13].

Laboratory testing

Blood was collected with a 20 gauge needle via atraumatic antecubital venipuncture into polyethylene terephthalate tubes Venosafe® (Terumo Europe, Leuven, Belgium) containing buffered sodium citrate (109 mM, nine parts of blood to one part sodium citrate solution). Plasmas were tested prospectively in real time.

Immunological assay: AcuStar HIT-IgG (PF4-H) and AcuStar HIT-Ab (PF4-H)

The HemosIL® AcuStar HIT-IgG (PF4-H) and HIT-Ab (PF4-H) (Instrumentation Laboratory, Bedford, MA, USA) are two chemiluminescent two-step immunoassays detecting the presence of anti-PF4-heparin antibodies. The first one is specific for IgG, the second one is polyspecific (IgG, IgA and IgM). These assays have been described by Legnani et al. [7]. The immunological isotype mainly responsible for HIT is IgG [14]. IgM and IgA only play a minor role but we cannot rule out the possibility of these immunoglobulins to contribute to some degree of thrombocytopenia [15]. Consequently, in our algorithm, we decided to perform a first screening with AcuStar HIT-Ab (PF4-H). AcuStar HIT-IgG (PF4-H) is then applied in case of a positive result. AcuStar HIT-Ab (PF4-H) was performed for each patient regardless the 4Ts score. AcuStar HIT-IgG (PF4-H) was carried out on patients according to our flow chart (Fig. 1).

The threshold recommended by the manufacturer is 1.00 U/mL. We used the thresholds determined in our previous retrospective study, i.e. 2.89 U/mL and 9.41 U/mL for AcuStar HIT-IgG (PF4-H) and AcuStar HIT-Ab (PF4-H), respectively.

Functional assay: Heparin-induced multiple electrode aggregometry (HIMEA)

Multiple electrode aggregometry (MEA) is a method for the assessment of platelet function in whole blood (Multiplate® analyzer; Dynabyte, Munich, Germany) [16]. MEA is based on the principle of impedance aggregometry. Our protocol has already been described [10]. Each HIMEA assay is performed in real-time with the fresh blood of one of the two determined healthy donors. Results are expressed using the area under the aggregation curve (AUC) and the recording time is 30 minutes. The result is considered to be positive when the platelet aggregation occurred in the presence of low heparin concentration (1 IU/mL UFH) but is partially inhibited (reduction > 80%) by a high concentration of heparin (385 IU/mL UFH). The threshold determined in our retrospective study was 276 AU at 1 IU/mL UFH.

Data analysis

Data analysis was performed using Medcalc software (version 10.4.8) (*MedCalc Software bvba*, Ostend, Belgium). The sensitivity, the specificity, the negative predictive value (NPV) and the positive predictive value (PPV) of AcuStar HIT-Ab (PF4-H) were assessed using clinical diagnosis as reference.

Results

Out of the 116 patients included in this study, two (1.7%) were considered to have developed HIT based on our clinical diagnosis. The first one experienced a pulmonary embolism and the other one died during his hospitalisation following coronary thrombosis. Complete compression ultrasonography and multidetector spiral computed tomography were performed for suspected thrombosis.

Assessment of our optimized diagnostic algorithm (Fig. 1)

Among 116 patients included in this study, 70 patients (60.3 %), 44 patients (37.9%) and 2 patients (1.7%) presented a low (≤3), medium (4–6) and high (7–8) 4Ts score, respectively. No patient with a low PTP was diagnosed as having HIT.

Among 46 patients with a medium-high PTP score, HIT was excluded in 44 patients with AcuStar HIT-Ab (PF4-H) (threshold: 9.41 U/mL) (Fig. 1). The NPV and PPV of AcuStar HIT-Ab (PF4-H) was 100.0% (95% CI: 91.9%-100.0%) and 100.0% (95% CI: 19.3%-100.0%), respectively (Table 1). The 2 patients AcuStar HIT-Ab (PF4-H) positive were also positive on AcuStar HIT-IgG (PF4-H) (threshold: 2.89 U/mL) and on HIMEA (threshold: 276 AU at 1 IU of UFH). These two patients had clinically confirmed HIT. The sensitivity, specificity, PPV and NPV of this combination using our thresholds, for the 116 patients were 100.0 % (95% CI: 16.6%-100.0%), 100.0% (95% CI: 96.8%-100.0%), 100.0% (95% CI: 96.8%-100.0%) and 100.0% (95% CI: 16.6%-100.0%), respectively. (See Table 2.)

Comparison of performances of AcuStar HIT-Ab (PF4-H) at our threshold (9.41 U/mL) and at manufacturer's threshold (1.00 U/mL) (Table 1)

AcuStar HIT-Ab (PF4-H) was performed on each patient of the study regardless of the 4Ts score. For all patients (n = 116) at manufacturer's threshold, there were 11 false positives against 1 false positive at our threshold. The false positive result on AcuStar HIT-Ab (9.96 U/mL)

Table 1
Comparison of HemosIL® AcuStar HIT-IgG (PF4-H), HIT-Ab (PF4-H) and optimized diagnostic algorithm with the clinical diagnosis (n = 116: all patients suspected of HIT with clinical diagnosis available; n = 46: patients with medium-high pre-test probability; AU: arbitrary unit, NPV: negative predictive value, PPV: positive predictive value).

			Clinical diagnosis		Sensitivity % (95%CI)	Specificity % (95%CI)	NPV % (95%CI)	PPV % (95%CI)
			Negative	Positive				
AcuStar HIT-Ab (n = 116)	Threshold: >1.00 U/mL	Negative	103	0	100.0 (19.3-100.0)	90.4 (83.4-95.1)	100.0 (96.5-100.0)	15.4 (2.4-45.5)
		Positive	11	2				
AcuStar HIT-Ab (n = 116)	Threshold: >9.41 U/mL	Negative	113	0	100.0 (19.3-100,0)	99.1 (95.2-99.9)	100.0 (96.8-100.0)	66.7 (11.6-94.5)
		Positive	1	2				
AcuStar HIT-Ab (n = 46)	Threshold: >1.00 U/mL	Negative	40	0	100.0 (19.3-100.0)	90.9 (78.3-97.4)	100.0 (91.1-100.0)	33.3 (5.3-77.3)
		Positive	4	2				
AcuStar HIT-Ab (n = 46)	Threshold: >9.41 U/mL	Negative	44	0	100.0 (19.3-100.0)	100.0 (91.9-100.0)	100.0 (91.9-100.0)	100.0 (19.3-100.0)
		Positive	0	2				
Optimized diagnostic algorithm (n = 116)	Thresholds: >3; >9.41 U/mL; > 2.89 U/mL; >276 AU	Negative	114	0	100.0 (16.6-100.0)	100.0 (96.8-100.0)	100.0 (96.8-100.0)	100.0 (16.6-100.0)
		Positive	0	2				

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Table 2
Clinical and laboratory data for the 2 patients with a positive diagnosis of HIT.

	Laboratory assays			Clinical data							
	AcuStar		HIMEA	4Ts					Clinical evolution from the HIT suspicion to the discharge from hospital		HIT
	Ab (U/mL)	IgG (U/mL)	1 IU/mL (AUC)	Thrombocytopenia	Timing of thrombocytopenia	Thrombosis or other sequelae	Other causes for thrombocytopenia	4Ts score	Stop heparin	Platelet count increase	Clinical diagnosis
Patient 1	11.11	5.03	448	Platelet count fall > 50% and platelet nadir ≥ 20 (2 points)	Clear onset at day 7, no prior heparin exposure within 30 days (2 points)	Lung embolism and deep venous thrombosis (2 points)	Possible (1 point) (Tazocin®)	7	+	+	+
Patient 2	47.30	46.81	664	Platelet count fall > 50% and platelet nadir ≥ 20 (2 points)	Clear onset at day 7, no prior heparin exposure within 30 days (2 points)	Coronary thrombosis (2 points)	Possible (1 point) (Augmentin®, Nexiam®, dialysis)	7	+	ND (death)	+

was slightly above our threshold (9.41 U/mL). Specificity was significantly higher at our threshold, i.e. 99.1% (95% CI: 95.2%-99.9%) than at manufacturer's threshold, i.e. 90.4% (95% CI: 83.4%-95.1%). Among patients with a medium-high pre-test probability (n = 46), our threshold presented no false positives against the 4 false positive at manufacturer's threshold. Using our threshold, the specificity reached 100.0 % (95% CI: 91.9%-100.0%), and it was 90.9% (95% CI: 78.3%-97.4%) with the manufacturer's threshold.

Discussion

We performed the present study with the aim of assessing prospectively our immune HIT diagnostic algorithm with optimized thresholds (Fig. 1). Among 116 inpatients suspected of HIT, every patient was correctly diagnosed using our flow chart. Specificity was higher at our threshold (99.1% (95% CI: 95.2%-99.9%)) than at manufacturer's threshold (i.e. 90.4% (95% CI: 83.4%-95.1%)).

Applying our diagnostic algorithm, heparin therapy should be continued and no subsequent laboratory assay should be performed in patients with a 4Ts score ≤ 3 [1]. In this study, no patient with a low probability 4Ts score (≤3) (n = 70) was diagnosed as having HIT. It confirms the effectiveness of the 4Ts score to limit additional biological assays. Cuker *et al.* also concluded in a systematic review and meta-analysis that 4Ts score of patients with suspected HIT may reduce overtesting and overdiagnosis of suspected HIT patients and that a low probability 4Ts score was a robust tool to exclude HIT [17].

The HemosIL® AcuStar HIT-IgG (PF4-H) and AcuStar HIT-Ab (PF4-H) were proposed as chemiluminescent immunoassays. AcuStar can be run for single sample testing and it presents shorter running-time (30 minutes) than other commercially available immunologic assays (2–3 hours).

In our previous retrospective study, we demonstrated that the use of optimized thresholds markedly improved the specificity of AcuStar HIT-Ab (PF4-H) [10]. A recent study concluded that the diagnostic accuracy of the anti-PF4/heparin ELISA can be optimized by using a higher cut-off [18]. Using optimized thresholds in our algorithm should reduce overdiagnosis of HIT and the need to perform additional HIMEA. Actually, the manufacturers provided thresholds following a study on healthy subjects and not on a HIT suspected patient's population.

The HIMEA is a rapid functional assay. It can be performed within 15 minutes and does not require any preparation of patient's sample. However, the immediate availability of a healthy compatible blood group donor is required.

Our study suffers from some limitations. Firstly, it is a single-centre study, and therefore it does not allow inter-laboratory comparisons. Secondly, because of the intermediate size of our cohort the power of this study is limited. In a recent study, Althaus *et al.* defined lower cut-offs than in our study. Our cut-offs should be further validated or adjusted using larger sample size in a multicentre study to provide a sufficiently high NPV beside their excellent PPV [19]. However, it should be noted that due to the inter-instrument variation a fixed OD threshold of an assay depends of the instrument. Therefore, each laboratory should determine their cut-offs with a cohort of HIT suspected patients. Thirdly, our protocol may differ from other studies since no guideline on standardized HIMEA procedure is available [8,20]. The threshold depends on variables including volume of whole blood of the healthy subject, volume of sample of patients, volume and concentration of heparin, duration of the measurement and the platelet reactivity of the healthy donors. Finally, to ascertain the diagnosis of HIT as recommended by the consensus committee of the ISTH working group [21], it is necessary to perform a washed platelet activation assay. ^{14}C-Serotonin Release Assay (SRA) is still considered as one of the reference method but it has not been performed in this study. This assay is indeed not available in most routine hospital laboratories because of its well-known limitations (time-consuming, technically demanding and requires the use of radioactive material).

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Conclusion

In this study, we demonstrated that the combination of the 4Ts score, the HemosIL® AcuStar HIT and HIMEA with optimized thresholds may be useful for the rapid and accurate exclusion of the diagnosis of immune HIT among the 116 included patients. A large multicentre prospective study is needed to further validate our algorithm.

Authorship Contributions

Contribution: FM, BCH, MGO, JMD conceived the idea and designed the study protocol; VM, NB, JB, JD, SL, BD and FM collected, assembled data and interpreted the data; VM performed statistical analysis; VM and FM wrote the manuscript; and all authors reviewed and approved the manuscript.

Conflict of Interest Disclosures

The authors have no conflict of interest to disclose.

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