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HAEMATOLOGY

HIT or miss? A comprehensive contemporary investigation of laboratory tests for heparin induced thrombocytopenia

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Summary

Heparin induced thrombocytopenia (HIT) is a rare but potentially fatal complication of heparin therapy, which in a proportion of patients causes platelet activation and thrombosis. Initial clinical assessment of the likelihood of HIT is facilitated by laboratory testing to confirm or exclude HIT. This prospective investigation was performed over an 18-month period, and has involved testing of over 300 test samples from over 100 consecutive patients. Clinical assessment by 4T score was supplemented by laboratory tests that comprised both immunological [lateral flow ('STiC'), chemiluminescence (AcuStar; HIT-IgG$_{(PF4-H)}$), ELISA (Asserachrom HPIA IgG)] and functional assays [SRA, platelet aggregation using whole blood ('Multiplate') and platelet rich plasma ('LTA')]. We observed both false positive and false negative test findings with most assays. Overall, the whole blood aggregation method provided a reasonable alternative to SRA for identifying functional HIT. STiC, AcuStar and ELISA procedures were fairly comparable in terms of screening for HIT, although STiC and AcuStar both yielded false negatives, albeit also resulting in fewer false positives than ELISA. The 4T score had less utility in our patient cohort than we were expecting, although there was an association with the likelihood of HIT. Nevertheless, we accept that our observations are based on limited test numbers. In conclusion, no single approach (clinical or laboratory) was associated with optimal sensitivity or specificity of HIT exclusion or identification, and thus, a combination of clinical evaluation and laboratory testing will best ensure the accuracy of diagnosis.

Key words: Heparin induced thrombocytopenia; HIT; diagnosis; laboratory testing; clinical identification.

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INTRODUCTION

Heparin induced thrombocytopenia (HIT) represents a significant complication of heparin therapy, which in some patients causes platelet activation, thrombin generation, subsequent thrombosis and related morbidity.[1] Despite the recent introduction of direct oral anticoagulants,[2] use of heparin remains significant, especially within hospital settings, including the prophylaxis and initial treatment of venous thrombosis,[3] treatment of acute coronary syndromes and use in cardiac surgery and haemodialysis to ensure patency of blood circuits. HIT diagnosis or exclusion remains challenging for many reasons, and is facilitated by a combination of clinical assessment and laboratory testing.[1,4]

The most common clinical assessment approach is use of the 4T score (or 4Ts), which assesses Thrombocytopenia, the Timing of the platelet fall, the presence of Thrombosis, as well as oTher potential causes of the thrombocytopenia.[1,4,5] The 4Ts provides a pre-test probability score of the likelihood of HIT, with scores of 0–3, 4–5, and 6–8, respectively, identifying low, intermediate and high probability for HIT. The 4Ts reportedly has a high negative predictive value (NPV). In a meta-analysis of 13 studies, the NPV of a low probability 4Ts score was 99.8% [95% confidence interval (CI) 97.0–100.0%], and remained high irrespective of who undertook the score, the composition of the study population, or the prevalence of HIT.[5] The 4Ts, however, has low positive predictive value (PPV) of 9–17%, with differential PPV of 14% (95% CI 9–22%) for an intermediate and 64% (95% CI 40–82%) for high probability 4Ts score, respectively.[4,5] From a practical perspective, one can translate this background to simply: a low 4Ts usually excludes HIT (however, it does not always), and a high 4Ts does not categorically prove HIT (it is often something else).

Given patients with low 4Ts are considered unlikely to have HIT,[4,5] some believe that laboratory testing can be omitted in these cases, and the patient managed as if they do

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not have HIT. However, laboratory testing is generally suggested to further evaluate for pathological HIT in patients with intermediate and high 4Ts. In any case, results of laboratory testing are often not available in a timely enough manner to assist in making clinical decisions regarding management of HIT.

Laboratory tests comprise immunological assays, which are often more readily available, and are highly sensitive to HIT antibodies, albeit with low(er) specificity, versus functional assays, which tend to be more complex, less readily available, less sensitive to HIT, but with high(er) specificity for pathological HIT antibodies.[1,4] Indeed, a precise understanding of HIT pathogenesis[6] is key to the interpretation and understanding of HIT testing. The immunological assays will detect antibodies directed against platelet-factor 4-heparin (anti-PF4-heparin) complex, but only a portion of these 'immunologically-detected' antibodies will cause platelet activation, and hence pathological HIT; thus identifying the need to supplement immunological testing, when positive, with functional assays. In other words, immunological assays have an excellent NPV (98–99%), but a low PPV, owing to the detection of both clinically significant and clinically insignificant anti-PF4-heparin antibodies.[7] In systematic sero-surveillance studies,[8,9] clinically evident HIT developed in only a minority (2–15%) of heparin-treated patients who had immunologically detected anti-PF4-heparin antibodies, and this reflects a potentially high false positive rate using this 'screening' process. The emphasis on identifying pathological HIT therefore requires immunological screening of HIT to be followed by a confirmatory ('functional') test. Thus, screening tests must be highly sensitive and ensure that false negatives are minimised, whilst confirmatory tests must be specific and ensure that those false positives, identified by immunoassay screening, are then excluded from further consideration. False positives carry significant potential for patient harm should patients be treated as if they have HITs, when in fact they do not.[1]

In this paper, we report findings from an 18-month prospective study of HIT that has incorporated clinical assessment by 4Ts plus a battery of contemporary laboratory tests, comprising both immunological ('screening') and functional ('confirmatory') assays.

MATERIALS AND METHODS

Setting, patient population and study design

This study comprised a collaboration between several large centres within New South Wales (NSW) Health Pathology. The clinical assessments and the majority of laboratory tests were performed at the Institute of Clinical Pathology and Medical Research (ICPMR), located at Westmead Hospital. Additional laboratory HIT testing was performed by staff located at St George and Prince of Wales Hospitals. The patient samples derived from Westmead Hospital or from external referrals to the ICPMR laboratory. At the time of the study, the ICPMR was part of a network of laboratories called Pathology West, comprising 27 laboratories within the state of NSW, with most affiliated to rural hospital networks. The overall study design is summarised in Fig. 1. This prospective study was performed over an 18-month period, with a first phase comprising 8 months in which all samples from consecutive patients (n = 47) with a clinical suspicion of HIT were tested using both immunological and functional assays. One goal here (i.e., for 'Phase 1') was to help identify whether functional assays might identify samples that are negative by immunological assays. In other words, could the performance of functional assays be recommended, even if immunological assays were negative? The second phase ('Phase 2'), comprising the subsequent 10-month period, utilised 56 consecutive patients, where initial testing was performed by immunological assays, and functional assays only progressed if one or more immunological assay was positive; this strategy represents the more common HIT diagnosis approach. Thus, the main goal here was to test the 'common HIT diagnosis approach' and assess this for any weaknesses or failures with particular methodologies.

Clinical assessment

As mentioned, a formal clinical assessment was undertaken wherever possible using the 4Ts, as previously described.[1,4,5] As the samples/patients were derived from both local and remote/rural/referral sites, we were not able to perform 4Ts independently on all patients – in particular, there was limited access to clinical information from our remote referral sites; nevertheless, 4Ts was performed on the majority of patients (70/103; 68%). All 4Ts were performed blind to laboratory test results. As 4Ts was treated as one of the study parameters, not the gold standard to define cases of pathological HIT, we do not believe that the absence of 4Ts on a proportion of cases diminishes our study findings.

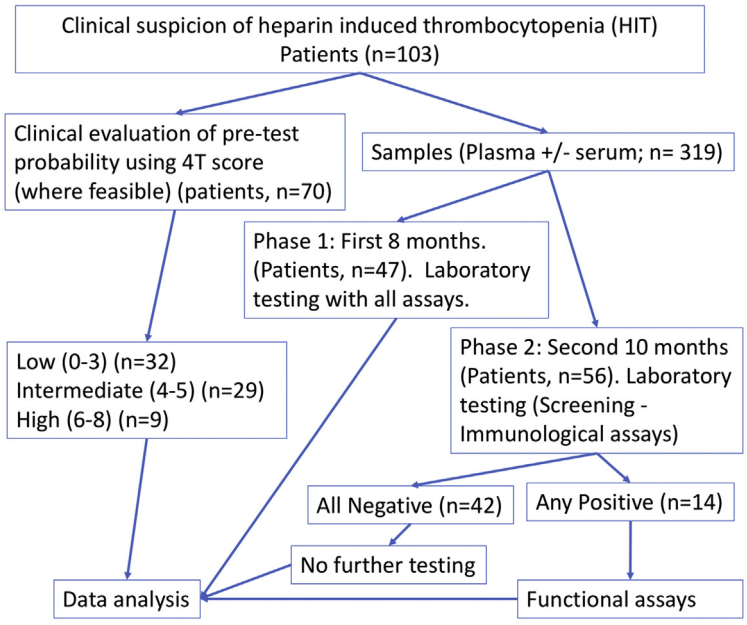

Fig. 1 A summary of the current study design, with summary of additional findings.

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