An Improved Definition of Immune Heparin-Induced Thrombocytopenia in Postoperative Orthopedic Patients

Theodore E. Warkentin, MD; Robin S. Roberts, MSc; Jack Hirsh, MD; John G. Kelton, MD

Background: Diagnosis of immune heparin-induced thrombocytopenia (HIT) is usually based on a fall in platelet count below $150 \times 10^9/L$ (standard definition of thrombocytopenia). However, this definition may be inappropriate for postoperative patients who often develop postoperative thrombocytosis. We sought to determine an improved definition of thrombocytopenia indicating HIT in postoperative orthopedic patients, including its impact on frequency and thrombotic risk of HIT.

Methods: We performed a secondary analysis of a clinical trial of 665 patients who received unfractionated or low-molecular-weight heparin following elective hip arthroplasty. Daily platelet counts and objective studies for deep vein thrombosis were performed in all patients. Laboratory detection of HIT antibodies from a 362-patient subgroup was used to define sensitivity and specificity of various definitions of thrombocytopenia to indicate HIT.

Results: The improved definition of HIT was a 50% or greater platelet count fall from the postoperative peak, as this definition had greater sensitivity (50% vs 25%) and similar high specificity (99.1% vs 99.4%) for detecting HIT-IgG compared with the standard definition. Patients with HIT who were identified using the improved definition had a higher frequency of thrombosis than patients without HIT (72.2% vs 17.3%; $P<.001$). The improved definition showed an even greater absolute difference in frequency of HIT between unfractionated and low-molecular-weight heparin (4.8% vs 0.6%; $P<.001$) compared with the standard definition (2.7% vs 0%; $P=.002$).

Conclusion: A 50% or greater fall in the platelet count from the postoperative peak is a sensitive definition indicating possible HIT that is associated with an increased risk of thrombosis.

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Immune heparin-induced thrombocytopenia (HIT) is an important and often serious complication of heparin therapy. The possibility of HIT is suspected when a patient has a fall in the platelet count while receiving heparin, and the diagnosis is supported by demonstrating heparin-dependent IgG antibodies (HIT-IgG). Unfortunately, results of HIT antibody assays are often not available in a timely manner, and initial management decisions are usually based on clinical suspicion. Thrombocytopenia is generally defined as a platelet count less than $150 \times 10^9/L$, a definition that is based on the frequency distribution of platelet counts in a normal population. However, this definition of thrombocytopenia may not be appropriate for postoperative patients who develop HIT. This is because HIT typically begins 5 to 10 days after starting heparin therapy, thus coinciding in postoperative patients who receive antithrombotic prophylaxis with heparin in the period in which the platelet count is rising to levels well above the preoperative values (postoperative thrombocytosis). Additionally, there are reports that thrombotic events can complicate HIT during a platelet count fall that does not necessarily attain thrombocytopenic levels, as conventionally defined.

In a previous article, we examined the frequency of HIT in a large randomized study that compared unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) for antithrombotic prophylaxis following orthopedic surgery (hip arthroplasty). In that study, we used the standard platelet count definition for thrombocytopenia (ie, a fall in the platelet count below $150 \times 10^9/L$). Because daily platelet counts were performed in that clinical trial and serial plasma samples were available in most study subjects irrespective of whether they developed a fall in the platelet count, this trial provided the opportunity to evaluate various definitions of thrombocytopenia.
nia for the diagnosis of HIT that might be more applicable to postoperative orthopedic patients than the standard definition.

**METHODS**

**CLINICAL TRIAL**

Figure 1 summarizes the study design. Analyses were performed using platelet count data from a clinical trial of UFH and LMWH.\(^{4,10}\) In brief, the clinical trial compared the use of a UFH preparation (Caliciparin; Anglo French Drug Company, Montreal, Quebec [given as 7500 U subcutaneously twice daily]) with an LMWH preparation (enoxaparin [Lovenox; Aventis Pharma, Laval, Quebec], given as 30 mg subcutaneously twice daily), both beginning on the first postoperative day. Venous thrombotic events were assessed by imaging studies, including contrast venography in 521 patients, with all venograms interpreted by a central committee that was blinded to patients’ assigned treatment.\(^{10}\)

HEPARIN-DEPENDENT, PLATELET-ACTIVATING HIT-IgG

We used the platelet \(^{14}\)C-serotonin release assay to determine the presence of platelet-activating HIT-IgG antibodies, as previously described.\(^{11,12}\) in a large subgroup of study patients. The subgroup consisted of 362 patients in whom serial plasma samples were available, with at least 1 that was obtained on postoperative day 7 or later (we excluded from analysis 25 patients from whom plasma samples were obtained earlier during the postoperative period and thus were noninformative regarding HIT-IgG antibody formation).\(^{2}\) The serotonin release assay result was considered positive if the sample caused greater than 20% serotonin release at 0.1 U/mL heparin, less than 20% serotonin release at 100 U/mL heparin, and less than 20% serotonin release at 0.1 U/mL heparin in the presence of Fc receptor blocking monoclonal antibody.\(^{11,12}\) We also used an enzyme immunoassay\(^{3,14}\) to confirm that antplatelet factor 4/heparin IgG antibodies were present in samples that tested positive in the platelet serotonin release assay (platelet factor 4/heparin is the antigen recognized by HIT-IgG). Hereafter, the term “HIT-IgG” indicates platelet-activating HIT antibodies of the IgG class detected using the platelet activation assay and confirmed by the IgG class–specific enzyme immunoassay.

**RECEIVER OPERATING CHARACTERISTIC CURVE ANALYSIS**

A diagnosis of immune HIT is usually considered when a platelet count fall occurs below a certain threshold (eg, a platelet count fall to \(<150 \times 10^9/L\)) and where there is a corresponding positive test result for HIT antibodies. However, as we sought to determine whether there might be a more appropriate definition for considering HIT relevant to this postoperative patient population, we performed receiver operating characteristic (ROC) curve analyses of the relationship between a variety of definitions of thrombocytopenia and the ability of these various definitions to correspond correctly to the presence of HIT-IgG. In brief, ROC curve analysis is an analytic tool that assesses the sensitivity–specificity trade-offs of various cutoffs between “negative” and “positive” test results in relation to a diagnostic end point. In our analyses, the diagnostic end point was the detection of HIT-IgG. Therefore, the “sensitivity” of a particular definition of thrombocytopenia refers to the fraction of the patients in whom HIT-IgG antibodies were detected (24 patients within the 362-patient subgroup), who met the definition for thrombocytopenia, whereas the “specificity” of the corresponding definition refers to the fraction of the remaining 338 patients who did not meet the definition of thrombocytopenia under examination.

Two different ROC curves were constructed: one for platelet count falls to less than an absolute platelet count threshold \(<300 \times 10^9/L, <275 \times 10^9/L\) and so forth in decrements of \(25 \times 10^9/L\), to \(<50 \times 10^9/L\) and (2) relative (proportional) platelet count falls \(>30\%, >40\%\), and so forth in increments of \(10\%\), to a platelet count fall of \(>90\%)\) from the postoperative peak.

**ANALYSIS OF THE 665-PATIENT STUDY POPULATION**

After determining an “improved” definition of thrombocytopenia using ROC curve analysis, we performed a second analysis whereby all 665 trial patients were evaluated using both the standard and the improved definition. This analysis allowed us to assess the impact of the improved definition on the frequency of HIT, including its relation to the heparin preparation used (UFH or LMWH).

For most of the patients (18/22) who developed a platelet count fall meeting the improved definition of thrombocytopenia, HIT-IgG test results were available, either because the patients were from the 362-patient subgroup that underwent systematic testing for HIT-IgG or because of testing during a diagnostic workup for thrombocytopenia (Table 1). In those remaining thrombocytopenic patients in whom blood was not available for testing, HIT was diagnosed if no other explanation for the platelet count fall was apparent and the platelet count recovered when heparin therapy was stopped.

**NORMAL POSTOPERATIVE PLATELET COUNT PROFILE**

We calculated a reference range for the platelet count in our patient population by determining the upper and lower 2 SD range for the preoperative and postoperative platelet counts (with...
correction

The area under each ROC curve was computed using a trapezoidal rule, and the SE of the area was estimated from log-transformed data) for the patients whose plasma tested negative for HIT-IgG.

### STATISTICAL ANALYSIS

We compared the proportions of patients who had outcome events between groups by the Fisher exact test\(^\text{15}\) and an associated method by Gart\(^\text{16}\) for computing confidence intervals around the odds ratio. Among patients who tested negative for HIT-IgG, we performed a \(x^2\) for linear trend test\(^\text{17}\) to evaluate whether the distribution of platelet count falls differed between patients with or without thrombosis. All quoted \(P\) values are 2-tailed.

Receiver operating characteristic curves for thrombocytopenia defined as a platelet fall to below an absolute threshold, indicating that the proportional representation of platelet count fall is more closely related to their sensitivity-specificity trade-offs for “detecting” the presence of HIT-IgG. In general, the ROC curve for the proportional platelet fall threshold was superior to that of the absolute threshold, enabling the comparison of the area under the ROC curve for the absolute threshold to that for the proportional threshold was also performed. Because both ROC curves were derived from the same group of patients, a formal test that allows for this pairing\(^\text{18}\) was used to compare the 2 ROC curve areas.

### RESULTS

The area under the ROC curve was not statistically significant (\(P=.38\)).

### ROC CURVE ANALYSIS OF THE 362-PATIENT SUBGROUP THAT UNDERWENT SYSTEMATIC TESTING FOR HIT-IgG

Of the 362 patients, 24 (6.6%) developed HIT-IgG antibodies that were detected using the platelet \(^{14}\)C-serotonin release assay; 20 of these samples generated greater than 50% serotonin release and 4 generated between 20% and 49% serotonin release. All 24 of these samples also tested positive in the platelet factor 4/heparin enzyme immunoassay. Figure 2 shows the results of the ROC curve analyses that examined a series of platelet count falls to below various absolute platelet count thresholds, as well as relative (proportional) platelet count declines in relation to their sensitivity-specificity trade-offs for “detecting” the presence of HIT-IgG. In general, the ROC curve for the proportional platelet fall threshold was superior to that of the absolute threshold, indicating that the proportional representation of platelet count fall is more closely related to HIT-IgG status. Although the observed results favored the proportional fall criterion, the difference in the 2 areas under the ROC curve was not statistically significant (\(P=.38\)).

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**Table 1. Patients Who Met the Standard or Improved Definition of Thrombocytopenia (or Both) Among All Study Patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Platelet Fall, % (Nadir, (\times 10^9/L))</th>
<th>Result of HIT-IgG Testing</th>
<th>HIT (by Improved Definition)</th>
<th>Type of Heparin Received</th>
<th>Thrombotic Events and Alternate Explanations for Thrombocytopenia (If Applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93.1 (22)</td>
<td>Positive</td>
<td>HIT</td>
<td>LMWH</td>
<td>Distal DVT; PE</td>
</tr>
<tr>
<td>2</td>
<td>90.1 (24)</td>
<td>Positive</td>
<td>HIT</td>
<td>UFH</td>
<td>Bilateral proximal DVT; PE</td>
</tr>
<tr>
<td>3</td>
<td>84.9 (28)</td>
<td>Positive</td>
<td>HIT</td>
<td>UFH</td>
<td>No thrombosis</td>
</tr>
<tr>
<td>4</td>
<td>81.3 (75)</td>
<td>Positive</td>
<td>HIT</td>
<td>UFH</td>
<td>Mesenteric artery thrombosis</td>
</tr>
<tr>
<td>5</td>
<td>79.5 (102)</td>
<td>Positive</td>
<td>HIT</td>
<td>UFH</td>
<td>Distal DVT</td>
</tr>
<tr>
<td>6</td>
<td>68.5 (182)</td>
<td>Positive</td>
<td>HIT</td>
<td>UFH</td>
<td>Proximal DVT</td>
</tr>
<tr>
<td>7</td>
<td>61.2 (133)</td>
<td>Positive</td>
<td>HIT</td>
<td>UFH</td>
<td>Bilateral (1 bilateral, 1 distal) DVT</td>
</tr>
<tr>
<td>8</td>
<td>61.1 (197)</td>
<td>Positive</td>
<td>HIT</td>
<td>UFH</td>
<td>Proximal DVT</td>
</tr>
<tr>
<td>9</td>
<td>58.4 (159)</td>
<td>Positive</td>
<td>HIT</td>
<td>UFH</td>
<td>No thrombosis</td>
</tr>
<tr>
<td>10</td>
<td>58.0 (161)</td>
<td>Positive</td>
<td>HIT</td>
<td>LMWH</td>
<td>Distal DVT</td>
</tr>
<tr>
<td>11</td>
<td>57.9 (297)</td>
<td>Positive</td>
<td>HIT</td>
<td>LMWH</td>
<td>No thrombosis</td>
</tr>
<tr>
<td>12</td>
<td>53.7 (329)</td>
<td>Positive</td>
<td>HIT</td>
<td>UFH</td>
<td>No thrombosis</td>
</tr>
<tr>
<td>13</td>
<td>87.8 (53)</td>
<td>Negative</td>
<td>Not HIT</td>
<td>UFH</td>
<td>No thrombosis; colon perforation, septicemia; platelet count rose to (260 \times 10^9/L) during further therapy with UFH</td>
</tr>
<tr>
<td>14</td>
<td>58.9 (159)</td>
<td>Negative</td>
<td>Not HIT</td>
<td>UFH</td>
<td>PE-associated DIC; platelet count rose to (300 \times 10^9/L) during further therapy with UFH</td>
</tr>
<tr>
<td>15</td>
<td>56.6 (206)</td>
<td>Negative</td>
<td>Not HIT</td>
<td>LMWH</td>
<td>Distal DVT; colon perforation, septicemia; platelet count rose to (224 \times 10^9/L) during further therapy with UFH</td>
</tr>
<tr>
<td>16</td>
<td>19.2 (143)</td>
<td>Negative</td>
<td>Not HIT</td>
<td>UFH</td>
<td>No thrombosis; marrow failure secondary to multiple myeloma</td>
</tr>
</tbody>
</table>

**Patients Within Remaining 362-Patient Population Who Did Not Undergo Systematic HIT-IgG Testing**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Platelet Fall, % (Nadir, (\times 10^9/L))</th>
<th>Result of HIT-IgG Testing</th>
<th>HIT (by Improved Definition)</th>
<th>Type of Heparin Received</th>
<th>Thrombotic Events and Alternate Explanations for Thrombocytopenia (If Applicable)</th>
</tr>
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<tbody>
<tr>
<td>17</td>
<td>93.2 (18)</td>
<td>Positive*</td>
<td>HIT</td>
<td>UFH</td>
<td>Proximal DVT</td>
</tr>
<tr>
<td>18</td>
<td>82.6 (79)</td>
<td>Positive*</td>
<td>HIT</td>
<td>UFH</td>
<td>Bilateral proximal DVT</td>
</tr>
<tr>
<td>19</td>
<td>69.1 (90)</td>
<td>Positive*</td>
<td>HIT</td>
<td>UFH</td>
<td>Proximal DVT</td>
</tr>
<tr>
<td>20</td>
<td>57.9 (231)</td>
<td>Not tested</td>
<td>HIT</td>
<td>UFH</td>
<td>Distal DVT; no other explanation for platelet count fall besides HIT</td>
</tr>
<tr>
<td>21</td>
<td>51.6 (275)</td>
<td>Not tested</td>
<td>HIT</td>
<td>UFH</td>
<td>No thrombosis; no other explanation for platelet count fall besides HIT</td>
</tr>
<tr>
<td>22</td>
<td>50.5 (192)</td>
<td>Not tested</td>
<td>HIT</td>
<td>UFH</td>
<td>Proximal DVT</td>
</tr>
<tr>
<td>23</td>
<td>73.0 (96)</td>
<td>Not tested</td>
<td>Not HIT</td>
<td>UFH</td>
<td>No thrombosis; isolated fall in platelet count considered to be spurious</td>
</tr>
</tbody>
</table>

**Patients Within 362-Patient Subgroup Who Underwent Systematic Testing for HIT-IgG**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Platelet Fall, % (Nadir, (\times 10^9/L))</th>
<th>Result of HIT-IgG Testing</th>
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<tr>
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<td>57.9 (297)</td>
<td>Positive</td>
<td>HIT</td>
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</tr>
</tbody>
</table>

Abbreviations: DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; HIT, immune heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin.

*Patients 17, 18, and 19 underwent testing for HIT-IgG during diagnosis workup of thrombocytopenia.
IMPROVED VS STANDARD DEFINITION OF THROMBOCYTOPENIA

Figure 2 shows that the sensitivity of the standard definition of thrombocytopenia for detecting HIT-IgG was 25% (ie, 6 of the 24 patients with HIT-IgG were “detected” by this definition). The specificity was high at 99.4% (ie, only 2 of the 338 patients who tested negative for HIT-IgG developed thrombocytopenia meeting the standard definition [these patients had clinical events such as sepsis or marrow failure that explained their thrombocytopenia]). Figure 2 further shows that a relative platelet count fall of 50% or greater had a sensitivity of 50% for detecting HIT-IgG (ie, 12 of the 24 patients with HIT-IgG were detected using this definition). Despite the greater sensitivity, the specificity remained high at 99.1% (ie, only 3 of the 338 patients who tested negative for HIT-IgG developed thrombocytopenia meeting this definition; further, these patients had clinical events such as sepsis that explained their platelet count declines). All 6 patients with HIT-IgG who met the standard definition of thrombocytopenia also met the improved definition of thrombocytopenia. Thus, a relative fall in the platelet count of at least 50% from the postoperative peak was selected as the “improved” definition for thrombocytopenia, since it identified twice as many patients who formed HIT-IgG (12 vs 6), but only identified 1 additional patient who did not form HIT-IgG (3 vs 2).

HIT AND RISK OF DVT IN THE 362-PATIENT SUBGROUP

To determine the association of thrombosis with the standard and improved definitions of thrombocytopenia, we compared the risk of thrombotic complications in patients with HIT diagnosed using either the standard or improved definition of thrombocytopenia with control patients who met neither definition for thrombocytopenia. Deep vein thrombosis (DVT) occurred in 57 (15.7%) patients who met neither definition for thrombocytopenia (including the “standard” definition of 150 × 10^9/L) and in 23 (6.6%) patients who met the improved definition of thrombocytopenia (including the “improved” definition of thrombocytopenia). Figure 2 further shows that a relative platelet count fall of 50% or greater had a sensitivity of 50% for detecting HIT-IgG (ie, 12 of the 24 patients with HIT-IgG were detected using this definition). Despite the greater sensitivity, the specificity remained high at 99.1% (ie, only 3 of the 338 patients who tested negative for HIT-IgG developed thrombocytopenia meeting this definition; further, these patients had clinical events such as sepsis that explained their platelet count declines). All 6 patients with HIT-IgG who met the standard definition of thrombocytopenia also met the improved definition of thrombocytopenia. Thus, a relative fall in the platelet count of at least 50% from the postoperative peak was selected as the “improved” definition for thrombocytopenia, since it identified twice as many patients who formed HIT-IgG (12 vs 6), but only identified 1 additional patient who did not form HIT-IgG (3 vs 2).

HIT AND RISK OF THROMBOSIS IN THE 665-PATIENT POPULATION

The available data set included 665 patients exposed to either UFH or LMWH who underwent daily platelet count testing and whose DVT status was known. In addition, 3 patients (1 with HIT) developed arterial thrombosis during the study. Overall, there were 23 patients who met either the improved or standard definition for thrombocytopenia (Table 1). However, 5 of these patients were judged not to have HIT, either because they tested negative for HIT-IgG and had alternate explanations for the thrombocytopenia (n=4) or because of a single low platelet count value believed to be spurious (n=1). Of the remaining 18 patients, 15 tested positive for HIT-IgG; the remaining 3 patients (in whom blood samples were not available for HIT-IgG testing) were considered to have HIT, since there was no other apparent explanation for the platelet count fall and the platelet count recovered after stopping heparin therapy.

Thus, 18 patients among the entire 665-patient population met the improved definition for HIT (9 of these 18 patients also met the standard definition). Among these 18 patients, the thrombotic event rate (venous or arterial thrombosis) was significantly higher than in the patients who did not have HIT: 13 (72.2%) of 18 vs 112 (17.3%) of 647; odds ratio, 12.4 (95% confidence interval, 4.0-45.1); P<.001 (Table 2).

Figure 3 shows the relationship between the onset of thrombocytopenia and occurrence of thrombosis for the 9 patients with HIT who met the improved, but
Heparin-induced thrombocytopenia is an important adverse drug reaction that is caused by heparin-dependent IgG antibodies (HIT-IgG) that cause platelet activation. The platelet activation is accompanied by formation of procoagulant, platelet-derived microparticles and increased thrombin generation, which could explain the strong association between HIT and thrombosis. Case reports and patient series have suggested that adverse clinical sequelae might occur in patients with detectable HIT-IgG but in whom no thrombocytopenia, as conventionally defined, occurred. However, previous studies have not examined the hypothesis that declines in the platelet count from the postoperative peak might correlate with formation of HIT antibodies and pose a risk for thrombosis, even when the platelet count nadir does not fall below the conventional platelet count threshold of 150 × 10^9/L.

Previously, we had compared the frequency and clinical impact of HIT in a large clinical trial (n=665 patients) that compared UFH and LMWH for antithrombotic prophylaxis after hip replacement surgery. We identified 9 patients with HIT, as defined using the standard definition of thrombocytopenia (platelet count fall to <150 × 10^9/L), all of whom had received UFH. This study included a large subgroup (n=362) of patients in which systematic testing for HIT-IgG was performed, which provided the opportunity to examine formally whether an “improved” definition of thrombocytopenia that increased the sensitivity for “detecting” formation of HIT-IgG could be identified. This seemed appropriate, since platelet counts typically rise in the second week following major surgery (postoperative thrombocytopenia), with the peak platelet count range reaching approximately 300 to 900 × 10^9/L by postoperative days 12 to 14 (Figure 3). Thus, a platelet count threshold of “only” 150 × 10^9/L (standard definition of thrombocytopenia) might underestimate the number of patients with clini-

Table 2. The Definition of HIT and the Risk for Thrombosis

<table>
<thead>
<tr>
<th>Definition of Thrombocytopenia</th>
<th>HIT</th>
<th>Controls</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIT diagnosed by standard definition (platelet count fall to ≤150 × 10^9/L)</td>
<td>8/9 (88.9)</td>
<td>117/656 (17.8)</td>
<td>36.9 (4.8-1638)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HIT diagnosed only by the improved definition (≥50% platelet count fall from the postoperative peak that never fell ≤150 × 10^9/L)</td>
<td>5/9 (55.6)</td>
<td>112/647 (17.3)</td>
<td>6.0 (1.3-30.5)</td>
<td>.01</td>
</tr>
<tr>
<td>HIT diagnosed by the improved definition (≥50% platelet count fall from the postoperative peak)</td>
<td>13/18 (72.2)</td>
<td>112/647 (17.3)</td>
<td>12.4 (4.0-45.1)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HIT, heparin-induced thrombocytopenia.
cally significant falls in the platelet count attributable to pathogenic HIT-IgG antibodies.

To perform these analyses, we used an objective indicator for HIT that was independent of the platelet count changes. For this purpose, we used the platelet serotonin release assay to detect the presence of platelet-activating HIT-IgG antibodies. The rationale for this approach is based on the high sensitivity of the platelet activation assay (90%) for detecting patients with clinically significant HIT, including patients who develop thrombotic complications associated with HIT.

Using ROC curve analysis, we identified an “improved” definition of thrombocytopenia indicating HIT based on a relative fall in the platelet count of 50% or greater from the postoperative peak. This definition increased the sensitivity of detecting HIT-IgG (through use of a change in platelet count as an indicator of HIT) from 25% to 50%, with similar specificity as the standard definition. Moreover, the improved definition identified patients that had an increased risk for thrombosis (13 [72.2%] of 18) compared with control patients (112 [17.3%] of 647) without HIT (Table 2). Further, all 9 patients who met the standard definition of HIT also met the improved definition (ie, those patients whose platelet count fell to <150 x 10^9/L also developed a ≥50% fall in the platelet count).

Our study indicates that the postoperative peak platelet count, rather than the preoperative peak platelet count, is the appropriate “baseline” for determining the proportional platelet count fall indicative of HIT. Although each of the 9 patients’ platelet count sequences shown in Figure 3 evinced a 50% or greater fall in the platelet count from the postoperative peak (median platelet count fall, 58.0%; range, 50.5%-68.5%) compared with their respective preoperative peak platelet count values, the relative platelet count declines were more modest (median, 28.3%; range, 2.0%-56.7%). The implication is that regular platelet count monitoring for HIT should begin as the platelets start to recover from the postoperative nadir to determine the postoperative platelet count peak that constitutes the appropriate patient-specific “baseline.”

When the improved definition of thrombocytopenia was applied to the entire 665-patient study population in a secondary analysis, we observed that the risk of HIT remained strongly associated with use of UFH compared with LMWH (odds ratio, 8.4 [95% confidence interval, 1.94-75.5]; P < .001). Using the improved definition, the frequency of HIT with UFH was 4.8% but only 0.6% with LMWH. Thus, even when using a more sensitive definition for HIT, a difference in the immune thrombocytopenic potential of these 2 heparin preparations remained evident. Further, this difference in HIT was clinically significant, since the frequency of HIT-associated thrombosis was also significantly greater in patients receiving UFH therapy compared with those receiving LMWH: 12/332 (3.6%) vs 1/333 (0.3%); odds ratio, 12.4 (95% CI, 1.82-533.8); P = .002. One patient who developed HIT-IgG during prophylaxis with LMWH, but who developed an abrupt platelet count fall of greater than 50% immediately after an intravenous UFH bolus, is classified according to the original allocated treatment (LMWH).

To our knowledge, our study is the first to investigate systematically the usefulness of a proportional platelet count fall to indicate HIT. Nevertheless, there is growing acceptance of this approach for defining HIT. For example, Pouplard and colleagues used a 40% or greater fall in platelet count during the second postoperative week (together with serological evidence of HIT antibodies) to define HIT following cardiac surgery. Wallis and coworkers used a 50% or greater fall in platelet count during heparin therapy (with serological evidence of HIT antibodies) to define HIT (predominantly postoperative patients). In a study of medical patients, Kappers-Klunne and colleagues also used a 50% or greater platelet count fall, although they accepted a 30% threshold if concomitant thrombosis occurred. Our study indicates (Figure 2) that whereas all of these proportional platelet count declines are more sensitive for detecting HIT than the standard definition, only a 50% fall is similarly specific as the standard definition for HIT. However, for a potentially serious disorder such as HIT, it may be reasonable to use a somewhat lower proportional platelet count fall, such as 30% or 40%, at least to prompt another platelet count measurement. Another consideration is that medical patients, unlike surgical patients, generally do not have a rising platelet count that begins a few days after admission, and so it remains uncertain whether the appropriate “baseline” for medical patients is the platelet count before heparin therapy is started or the highest platelet count from day 4 of heparin therapy onwards (ie, at a time when a fall in platelet count attributable to HIT is likely to begin).

Using the improved definition of HIT, 13 patients were identified who developed HIT-associated thrombosis (Table 2). Therefore, HIT “explained” only a minority (about 10%) of the 123 patients who developed thrombosis in this study of 665 postoperative orthope-
dic patients. Nevertheless, as HIT-associated thrombosis is often severe (eg, bilateral lower limb DVT, pulmonary embolism, or arterial thrombosis; Table 1) and requires specialized therapy (eg, avoidance of warfarin or substitution of heparin with a direct thrombin inhibitor), it is important to diagnose this complication of heparin therapy with platelet count monitoring.35

CONCLUSIONS

A 50% or greater fall in the platelet count from the postoperative peak (up to postoperative day 14) is a more accurate definition of thrombocytopenia indicating possible HIT in postoperative orthopedic patients. In our study, this improved definition had superior operating characteristics and led to twice as many patients being identified as having HIT, with a similar high specificity as observed with the standard definition of thrombocytopenia. The improved definition also was clinically relevant, since patients who met the optimal definition of HIT were also at increased risk for thrombotic events.

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