

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.

Arch Intern Med. 2003;163:2518-2524

From McMaster University (Drs Warkentin, Hirsh, and Kelton and Mr Roberts), the Henderson Research Centre (Dr Hirsh and Prof Roberts), and the Hamilton Regional Laboratory Medicine Program (Dr Warkentin), Hamilton, Ontario. The authors have no relevant financial interest in this article.

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).¹ 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,² 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).^{3,4} Additionally, there are reports⁵⁻⁹ 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,⁴ 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 (Calciparin; 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 ¹⁴C-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^{13,14} to confirm that antiplatelet 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

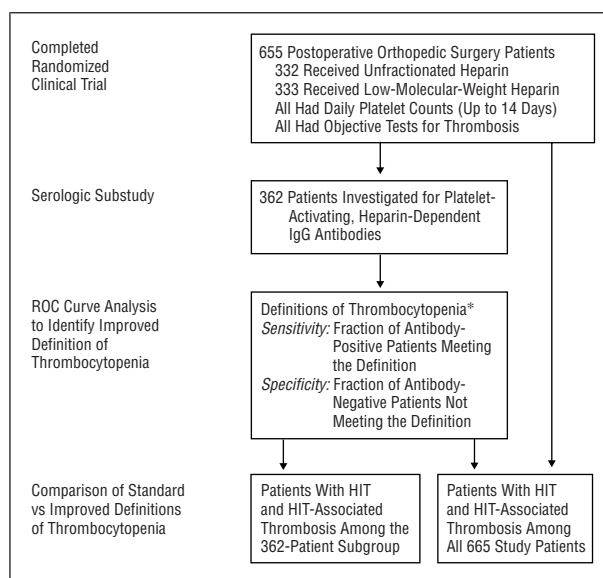


Figure 1. Study design. HIT indicates immune heparin-induced thrombocytopenia; ROC, receiver operating characteristic. The asterisk indicates that 2 series of definitions of thrombocytopenia were examined: (1) platelet count falls below an absolute threshold ($<300 \times 10^9/L$, $<275 \times 10^9/L$, 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.

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 the other for a relative (proportional) fall from the postoperative platelet count peak (platelet count fall $>30\%$, $>40\%$, and so forth in increments of 10%, to a platelet count fall of $>90\%$). Changes in the platelet count that began 5 or more days after beginning heparin therapy were studied. The peak postoperative platelet count represented the platelet count "baseline" in this study.

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

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

Patient No.	Platelet Fall, % (Nadir, $\times 10^9/L$)	Result of HIT-IgG Testing	HIT (by Improved Definition)	Type of Heparin Received	Thrombotic Events and Alternate Explanations for Thrombocytopenia (if Applicable)
Patients Within 362-Patient Subgroup Who Underwent Systematic Testing for HIT-IgG					
1	93.1 (22)	Positive	HIT	UFH	Bilateral proximal DVT; PE
2	90.1 (34)	Positive	HIT	UFH	Distal DVT; PE
3	84.9 (28)	Positive	HIT	UFH	No thrombosis
4	81.3 (75)	Positive	HIT	UFH	Mesenteric artery thrombosis
5	79.5 (102)	Positive	HIT	UFH	Distal DVT
6	68.5 (182)	Positive	HIT	UFH	Proximal DVT
7	61.2 (133)	Positive	HIT	UFH	Bilateral (1 bilateral, 1 distal) DVT
8	61.1 (197)	Positive	HIT	UFH	Proximal DVT
9	58.4 (159)	Positive	HIT	UFH	No thrombosis
10	58.0 (161)	Positive	HIT	LMWH	Distal DVT
11	57.9 (297)	Positive	HIT	LMWH	No thrombosis
12	53.7 (329)	Positive	HIT	UFH	No thrombosis
13	87.8 (53)	Negative	Not HIT	UFH	No thrombosis; colon perforation, septicemia; platelet count rose to $260 \times 10^9/L$ during further therapy with UFH
14	58.9 (159)	Negative	Not HIT	UFH	PE-associated DIC; platelet count rose to $300 \times 10^9/L$ during further therapy with UFH
15	56.6 (206)	Negative	Not HIT	LMWH	Distal DVT; colon perforation, septicemia; platelet count rose to $224 \times 10^9/L$ during further therapy with UFH
16	19.2 (143)	Negative	Not HIT	UFH	No thrombosis; marrow failure secondary to multiple myeloma
Patients Within Remaining 303-Patient Population Who Did Not Undergo Systematic HIT-IgG Testing					
17	93.2 (18)	Positive*	HIT	UFH	Proximal DVT
18	82.6 (79)	Positive*	HIT	UFH	Bilateral proximal DVT
19	69.1 (90)	Positive*	HIT	UFH	Proximal DVT
20	57.9 (231)	Not tested	HIT	UFH	Distal DVT; no other explanation for platelet count fall besides HIT
21	51.6 (275)	Not tested	HIT	UFH	No thrombosis; no other explanation for platelet count fall besides HIT
22	50.5 (192)	Not tested	HIT	UFH	Proximal DVT; no other explanation for platelet count fall besides HIT
23	73.0 (96)	Not tested	Not HIT	UFH	No thrombosis; isolated fall in platelet count considered to be spurious

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.

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 test¹⁵ and an associated method by Gart¹⁶ for computing confidence intervals around the odds ratio. Among patients who tested negative for HIT-IgG, we performed a χ^2 for linear trend test¹⁷ 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 and below a proportional threshold were calculated in the usual way.¹⁸ The area under each ROC curve was computed using a trapezoidal rule, and the SE of the area was estimated using the method of Hanley and McNeil.¹⁹ The area under the ROC curve represents a general measure of the diagnostic information conveyed by the test—in this case, the degree of platelet count reduction in relation to the presence or absence of HIT-IgG. A 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 pairing²⁰ was used to compare the 2 ROC curve areas.

RESULTS

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 ¹⁴C-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).

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%) of the 362 patients. The DVT rate was highest (4 [66.7%]) in the 6 patients who met the standard definition of thrombocytopenia indicating HIT, intermediate (3 [50.0%]) in the 6 patients identified only by the improved definition of thrombocytopenia indicating HIT, and lowest (50 [14.3%]) in the 350 remaining patients who met neither definition of HIT. Since the 6 patients who met the standard definition of thrombocytopenia also met the improved definition, the frequency of DVT in the 12 patients with HIT-IgG who developed thrombocytopenia meeting the improved definition was 58.3% (7 of 12), which was significantly greater than in the control patients (14.3% [50/350]; $P < .001$).

Further, of the 12 patients who tested positive for HIT-IgG but who did not meet the improved definition of thrombocytopenia, only 2 (16.7%) developed DVT, a frequency that did not differ significantly from the control patients who tested negative for HIT-IgG (14.2% [48/338]; $P = .68$). Among these 12 patients, only one exhibited a fall in platelet count that exceeded 20% (22.3% fall from 305 to 237 $\times 10^9/L$ between days 9 and 12), which was not complicated by DVT. Of the 2 patients who developed HIT-IgG and DVT, the platelet count fell slightly in one (by 15.0% from 414 to 352 $\times 10^9/L$ between post-

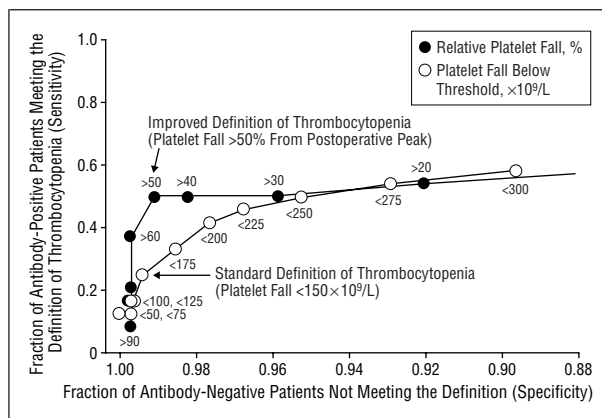


Figure 2. Receiver operating characteristic (ROC) curve analyses. Two different approaches for defining thrombocytopenia are compared: (1) platelet count falls below various platelet count thresholds defining thrombocytopenia (including the “standard” definition of $150 \times 10^9/L$) and (2) relative platelet count falls (by percentage) from the postoperative peak. A 50% fall in platelet count was designated as the “improved” definition of thrombocytopenia, since it was more sensitive than the standard definition for “detecting” heparin-dependent IgG antibodies (50% vs 25%), with similar high specificity (99.1% vs 99.4%).

operative days 9 and 13) and rose in the other (followed up to day 14).

Thrombocytopenia was not associated with thrombosis in the absence of HIT-IgG: among the 338 patients who tested negative for HIT-IgG (48 with DVT), we did not observe an association between DVT and greater relative falls in the platelet count (χ^2 for linear trend, $P = .91$).

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

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

Definition of Thrombocytopenia	Thrombotic Event Rate, No. of Patients Diagnosed/ Total Patients (%)		Odds Ratio (95% CI)	P Value
	HIT	Controls		
HIT diagnosed by standard definition (platelet count fall to $<150 \times 10^9/L$)	8/9 (88.9)	117/656 (17.8)	36.9 (4.8-1638)	$<.001$
HIT diagnosed only by the improved definition ($\geq 50\%$ platelet count fall from the postoperative peak that never fell $<150 \times 10^9/L$)	5/9 (55.6)	112/647 (17.3)	6.0 (1.3-30.5)	.01
HIT diagnosed by the improved definition ($\geq 50\%$ platelet fall from the postoperative peak)	13/18 (72.2)	112/647 (17.3)	12.4 (4.0-45.1)	$<.001$

Abbreviations: CI, confidence interval; HIT, heparin-induced thrombocytopenia.

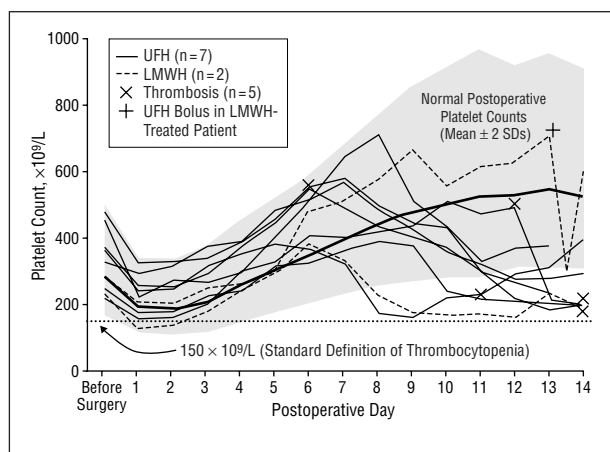


Figure 3. Serial platelet counts of 9 patients with immune heparin-induced thrombocytopenia (HIT) who met the optimal, but not the standard, definition for thrombocytopenia. The shaded area represents the normal postoperative platelet count range for this orthopedic patient population, since it was calculated from the patients who tested negative for HIT-IgG (see the “Methods” section). Of the 9 patients who received unfractionated heparin (UFH), 7 developed a 50% or greater fall in the platelet count; 2 of the 9 patients who received low-molecular-weight heparin (LMWH) developed a 50% or greater fall in the platelet count. However, 1 LMWH-treated patient developed the platelet count fall only after receiving a UFH bolus given for clinically suspected deep vein thrombosis (not confirmed by venography).

not the standard, definition of HIT. Five of these 9 patients developed DVT, with 3 occurring only after a substantial fall in the platelet count had occurred.

FREQUENCY OF HIT WITH UFH AND LMWH

As we had previously reported,⁴ a higher frequency of HIT was observed in the patients who received UFH compared with those who received LMWH when the standard definition of thrombocytopenia was used: all 9 patients identified with HIT had received UFH (**Table 3**). However, among the 9 additional patients with HIT who were identified using the improved definition of thrombocytopenia, we observed that 7 patients had received UFH and 2 patients had received LMWH. Thus, the predominance of HIT among patients receiving UFH was maintained, even when we included the additional 9 patients who met only the improved definition of thrombocytopenia. On analyzing all 18 patients who were di-

agnosed as having HIT using the improved definition of thrombocytopenia (including the 9 patients who also met the standard definition of thrombocytopenia), the frequency of HIT remained significantly greater in those patients who received UFH (4.8 vs 0.6%; $P < .001$).

COMMENT

Heparin-induced thrombocytopenia is an important adverse drug reaction that is caused by heparin-dependent IgG antibodies (HIT-IgG) that cause platelet activation.^{21,22} The platelet activation is accompanied by formation of procoagulant, platelet-derived microparticles^{23,24} and increased thrombin generation,^{25,26} which could explain the strong association between HIT and thrombosis. Case reports⁵⁻⁷ and patient series^{8,9} 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 $150 \times 10^9/L$.

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.⁴ We identified 9 patients with HIT, as defined using the standard definition of thrombocytopenia (platelet count fall to $<150 \times 10^9/L$), 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 thrombocytosis), with the peak platelet count range reaching approximately 300 to $900 \times 10^9/L$ by postoperative days 12 to 14 (Figure 3). Thus, a platelet count threshold of “only” $150 \times 10^9/L$ (standard definition of thrombocytopenia) might underestimate the number of patients with clini-

Table 3. Definition of Thrombocytopenia and the Frequency of HIT With UFH vs LMWH Therapy*

Definition of Thrombocytopenia	No. (%) of Patients		Odds Ratio (95% CI)	P Value
	UFH (n = 332)	LMWH (n = 333)		
Standard definition of HIT (platelet count fall to $<150 \times 10^9/L$)	9 (2.7)	0	∞ (2.01- ∞)	.002
Improved definition of HIT ($\geq 50\%$ platelet count fall from the postoperative peak)	16 (4.8)	2† (0.6)	8.4 (1.94-75.5)	<.001

Abbreviations: CI, confidence interval; HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

*There was a significantly higher frequency of HIT with UFH therapy compared with LMWH therapy, irrespective of whether the standard or improved definition of HIT was used. Using the improved definition of HIT, the frequency of HIT-associated thrombosis was also significantly greater in patients receiving UFH therapy compared with those receiving LMWH therapy: 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).

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^{11,12} 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.^{11-13,27-30}

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 $<150 \times 10^9/L$ also developed a $\geq 50\%$ fall in the platelet count).

Our study indicates that the postoperative peak platelet count, rather than the preoperative 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 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 defini-

tion, 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 who received UFH (12 [3.6%] of 332) compared with those who received LMWH (1 [0.3%] of 333) (odds ratio, 12.4 [95% confidence interval, 1.82-533.8]; $P < .001$).

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 colleagues²⁹ 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 co-workers³¹ 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 colleagues³² 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 125 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 warfarin²⁵ or substitution of heparin with a direct thrombin inhibitor¹), it is important to diagnose this complication of heparin therapy with platelet count monitoring.³³

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.

Accepted for publication June 27, 2003.

This study was supported by operating grants B-3763, T-4502, T-5207 (Dr Warkentin), and T-4404 (Dr Kelton) from the Heart and Stroke Foundation of Ontario, Toronto. Funding for the clinical trial was provided by Rhône Poulenc-Rorer (now Aventis Pharma, Laval, Quebec).

We had full access to all of the study data. The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

We thank Jo-Ann I. Sheppard, BSc(Hon) and Jane C. Moore, BSc, for technical assistance and Jo-Ann I. Sheppard for preparing the figures.

Corresponding author and reprints: Theodore E. Warkentin, MD, Hamilton Regional Laboratory Medicine Program, Hamilton Health Sciences, General Site, 237 Barton St E, Hamilton, Ontario, Canada L8L 2X2 (e-mail: twarken@mcmaster.ca).

REFERENCES

1. Warkentin TE, Chong BH, Greinacher A. Heparin-induced thrombocytopenia: towards consensus. *Thromb Haemost.* 1998;79:1-7.
2. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med.* 2001;344:1286-1292.
3. Bunting RW, Doppelt SH, Lavine LS. Extreme thrombocytosis after orthopaedic surgery. *J Bone Joint Surg Br.* 1991;73:687-688.
4. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med.* 1995;332:1330-1335.
5. Phelan BK. Heparin-associated thrombosis without thrombocytopenia. *Ann Intern Med.* 1983;99:637-638.
6. Hach-Wunderle V, Kainer K, Müller-Berghaus G, Pötsch B. Heparin-associated thrombosis despite normal platelet counts [letter]. *Lancet.* 1994;344:469-470.
7. Risch L, Pihan H, Zeller C, Huber AR. ET gets HIT-thrombotic heparin-induced thrombocytopenia in a patients with essential thrombocythemia (ET). *Blood Coagul Fibrinolysis.* 2000;11:663-667.
8. Klement D, Rammos S, von Kries R, Kirschke W, Kniemeyer HW, Greinacher A. Heparin as a cause of thrombus progression: heparin-associated thrombocytopenia is an important differential diagnosis in paediatric patients even with normal platelet counts. *Eur J Pediatr.* 1996;155:11-14.
9. Warkentin TE. Clinical presentation of heparin-induced thrombocytopenia. *Semin Hematol.* 1998;35(suppl 5):9-16.
10. Levine MN, Hirsh J, Gent M, et al. Prevention of deep vein thrombosis after elective hip surgery: a randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Ann Intern Med.* 1991;114:545-551.
11. Sheridan D, Carter C, Kelton JG. A diagnostic test for heparin-induced thrombocytopenia. *Blood.* 1986;67:27-30.
12. Warkentin TE, Hayward CPM, Smith CA, Kelly PM, Kelton JG. Determinants of donor platelet variability when testing for heparin-induced thrombocytopenia. *J Lab Clin Med.* 1992;120:371-379.
13. Warkentin TE, Sheppard JI, Horsewood P, Simpson PJ, Moore JC, Kelton JG. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood.* 2000;96:1703-1708.
14. Horsewood P, Warkentin TE, Hayward CPM, Kelton JG. The epitope specificity of heparin-induced thrombocytopenia. *Br J Haematol.* 1996;95:161-167.
15. Matthews DE, Farewell VT. *Using and Understanding Medical Statistics.* 2nd ed. New York, NY: Karger; 1988:20-26.
16. Thomas DG. Exact confidence limits for the odds ratio in a 2 x 2. *Appl Stat.* 1971;20:105-110.
17. Fleiss JL. *Statistical Methods for Rates and Proportions.* 2nd ed. New York, NY: John Wiley & Sons Inc; 1981:143-146.
18. Metz CF. Basic principles of ROC analysis. *Semin Nucl Med.* 1978;8:283-298.
19. Hanley JA, McNeil BJ. The meaning and use of the area under the receiver operating characteristic (ROC) curve. *Radiology.* 1982;143:29-36.
20. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology.* 1983;148:839-843.
21. Chong BH, Pitney WR, Castaldi PA. Heparin-induced thrombocytopenia: association of thrombotic complications with heparin-dependent IgG antibody that induces thromboxane synthesis in platelet aggregation. *Lancet.* 1982;2:1246-1249.
22. Kelton JG, Sheridan D, Santos A, et al. Heparin-induced thrombocytopenia: laboratory studies. *Blood.* 1988;72:925-230.
23. Warkentin TE, Hayward CPM, Boshkov LK, et al. Sera from patients with heparin-induced thrombocytopenia generate platelet-derived microparticles with procoagulant activity: an explanation for the thrombotic complications of heparin-induced thrombocytopenia. *Blood.* 1994;84:3691-3699.
24. Warkentin TE, Sheppard JI. Generation of platelet-derived microparticles and procoagulant activity by heparin-induced thrombocytopenia IgG/serum and other IgG platelet agonists: a comparison with standard platelet agonists. *Platelets.* 1999;10:319-326.
25. Warkentin TE, Elavathil LJ, Hayward CPM, Johnston MA, Russett JI, Kelton JG. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann Intern Med.* 1997;127:804-812.
26. Warkentin TE. Limitations of conventional treatment options for heparin-induced thrombocytopenia. *Semin Hematol.* 1998;35(suppl 5):17-25.
27. Greinacher A, Michels I, Kiefel V, Mueller-Eckhardt C. A rapid and sensitive test for diagnosing heparin-associated thrombocytopenia. *Thromb Haemost.* 1991;66:734-736.
28. Visentin GP, Ford SE, Scott JP, Aster RH. Antibodies from patients with heparin-induced thrombocytopenia/thrombosis are specific for platelet factor 4 complexed with heparin or bound to endothelial cells. *J Clin Invest.* 1994;93:81-88.
29. Poupard C, May MA, Lochmann S, et al. Antibodies to platelet factor 4-heparin after cardiopulmonary bypass in patients anticoagulated with unfractionated heparin or a low-molecular-weight heparin: clinical implications for heparin-induced thrombocytopenia. *Circulation.* 1999;99:2530-2536.
30. Warkentin TE, Greinacher A. Laboratory testing for heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-Induced Thrombocytopenia.* 2nd ed. New York, NY: Marcel Dekker Inc; 2001:231-269.
31. Wallis DE, Workman DL, Lewis BE, Steen L, Pifarre R, Moran JF. Failure of early heparin cessation as treatment for heparin-induced thrombocytopenia. *Am J Med.* 1999;106:629-635.
32. Kappers-Klunne MC, Boon DMS, Hop WCJ, et al. Heparin-induced thrombocytopenia and thrombosis: a prospective analysis of the incidence in patients with heart and cerebrovascular diseases. *Br J Haematol.* 1997;96:442-446.
33. Warkentin TE. Platelet count monitoring and laboratory testing for heparin-induced thrombocytopenia. *Arch Pathol Lab Med.* 2002;126:1415-1423.