HEPARIN-INDUCED THROMBOCYTOPENIA IN PATIENTS TREATED WITH LOW-MOLECULAR-WEIGHT HEPARIN OR UNFRACTIONATED HEPARIN

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Abstract *Background.* Heparin-induced thrombocytopenia, defined by the presence of heparin-dependent IgG antibodies, typically occurs five or more days after the start of heparin therapy and can be complicated by thrombotic events. The frequency of heparin-induced thrombocytopenia and of heparin-dependent IgG antibodies, as well as the relative risk of each in patients given low-molecular-weight heparin, is unknown.

Methods. We obtained daily platelet counts in 665 patients in a randomized, double-blind clinical trial comparing unfractionated heparin with low-molecular-weight heparin as prophylaxis after hip surgery. Heparin-induced thrombocytopenia was defined as a decrease in the platelet count below 150,000 per cubic millimeter that began five or more days after the start of heparin therapy, and a positive test for heparin-dependent IgG antibodies. We also tested a representative subgroup of 387 patients for heparin-dependent IgG antibodies regardless of their platelet counts.

Results. Heparin-induced thrombocytopenia occurred in 9 of 332 patients who received unfractionated heparin and in none of 333 patients who received low-molecular-weight heparin (2.7 percent vs. 0 percent; $P=0.0018$). Eight of the 9 patients with heparin-induced thrombocytopenia also had one or more thrombotic events (venous in 7 and arterial in 1), as compared with 117 of 656 patients without heparin-induced thrombocytopenia (88.9 percent vs. 17.8 percent; odds ratio, 36.9; 95 percent confidence interval, 4.8 to 1638; $P<0.001$). In the subgroup of 387 patients, the frequency of heparin-dependent IgG antibodies was higher among patients who received unfractionated heparin (7.8 percent, vs. 2.2 percent among patients who received low-molecular-weight heparin; $P=0.02$).

Conclusions. Heparin-induced thrombocytopenia, associated thrombotic events, and heparin-dependent IgG antibodies are more common in patients treated with unfractionated heparin than in those treated with low-molecular-weight heparin. (N Engl J Med 1995;332:1330-5.)

THROMBOCYTOPENIA induced by heparin typically appears five or more days after the start of heparin therapy.[1-3] The thrombocytopenia is caused by heparin-dependent IgG antibodies that activate platelets through their Fc receptors.[4-6] Recently, several laboratories have shown that these antibodies recognize a complex of heparin with platelet factor 4.[7-10] Paradoxically, thrombotic complications develop in some patients with heparin-induced thrombocytopenia,[1-3] possibly because of in vivo platelet activation.[11]

The frequency of heparin-induced thrombocytopenia and associated thrombotic complications is uncertain. Previous prospective studies have not usually confirmed the diagnosis with appropriate laboratory tests; other studies included patients with early thrombocytopenia, even though this transient and reversible event is not related to heparin-induced antibodies.[2,3]

In this article, we report our analysis of platelet counts and heparin-dependent IgG antibodies in a randomized, double-blind, controlled trial of 665 patients who received prophylaxis against venous thrombosis with either unfractionated heparin or low-molecular-weight heparin. We used a sensitive and specific assay for heparin-dependent IgG antibodies (the platelet ^{14}C-labeled serotonin-release assay[12,13]) to confirm the diagnosis of heparin-induced thrombocytopenia in all patients who had thrombocytopenia after receiving heparin for at least five days. We also tested a representative subgroup of 387 patients, regardless of their platelet counts, to determine the frequency of heparin-dependent IgG antibodies. We found that patients treated with unfractionated heparin had a higher frequency of heparin-induced thrombocytopenia and formation of heparin-dependent IgG antibodies than patients treated with low-molecular-weight heparin. We also found that heparin-induced thrombocytopenia is a risk factor for thrombotic complications, including venous thrombosis.

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Supported by grants from the Heart and Stroke Foundation of Ontario and Rhône–Poulenc Rorer. Dr. Warkentin is a Research Scholar of the Heart and Stroke Foundation of Canada. Dr. Levine is a Scientist of the Medical Research Council of Canada. Dr. Hirsh is a Distinguished Research Professor of the Heart and Stroke Foundation of Ontario. Dr. Kelton is a Career Investigator for the Heart and Stroke Foundation of Ontario.

METHODS

Randomized Clinical Trial

Platelet counts were obtained daily during a randomized trial in which a preparation of low-molecular-weight heparin, enoxaparin (Lovenox, Rhône–Poulenc Rorer, Montreal), was compared with a preparation of unfractionated calcium heparin (Calciparine, Laboratoires Anglo-French, Dorval, Quebec, Canada; prepared from porcine intestinal mucosa), for the prevention of thrombosis after elective hip surgery.[14] The preparations of both unfractionated and low-molecular-weight heparin were manufactured in France (Laboratoires Choay and Rhône–Poulenc Rorer, respectively). Low-molecular-weight heparin was given at a dose of 30 mg subcutaneously twice daily, and unfractionated heparin at 7500 units subcutaneously twice daily, beginning at 6 a.m. on the first day after the operation (day 1). The study drug was given for a mean ($\pm$SD) period of 10 ± 3 days (maximum, 14). Preoperative (base-line) and daily postoperative platelet counts were measured in all patients for 14 postoperative days or until discharge, if that occurred sooner (total, 8164 platelet counts; mean, 12 per patient).

Definition of Thrombocytopenia and Heparin-Induced Thrombocytopenia

Thrombocytopenia was defined as at least two consecutive platelet counts below 150,000 per cubic millimeter. Early thrombocytopenia was defined as thrombocytopenia occurring on postoperative days 1 through 5, inclusive, and late thrombocytopenia as that occurring

on or after postoperative day 6 (that is, after five days of receiving the study drug). Heparin-induced thrombocytopenia was defined as a decrease in the platelet count to below 150,000 per cubic millimeter after five days of treatment with the study drug (late thrombocytopenia) plus a positive test for heparin-dependent IgG antibodies.

Collection of Blood Samples to Test for Heparin-Dependent IgG Antibodies

Blood samples were obtained in one of two ways to test for heparin-dependent IgG antibodies. First, a test for heparin-dependent IgG antibodies was requested by some physicians throughout the clinical trial for eight patients who were thought to have heparin-induced thrombocytopenia. The identity of the study drug received by the patient was not known to any of the investigators at the time of such testing. Second, we also tested a large subgroup of 387 patients (58.2 percent of all study patients) for heparin-dependent IgG antibodies to determine the frequency of seroconversion independently of the platelet counts. These samples (total, 4308; mean, 11 per patient) were not selected from patients with thrombocytopenia, thrombosis, or other clinical events but were selected only on the basis of availability. Samples were not available from all 665 patients to be tested for heparin-dependent IgG antibodies because the decision to test blood systematically for these antibodies was made at the conclusion of the clinical trial. Because of the two methods of acquiring samples, tests for heparin-dependent IgG antibodies were performed in all study patients with late thrombocytopenia (12 patients, including 1 patient with early and sustained thrombocytopenia).

Serologic Assay for Heparin-Dependent IgG Antibodies

We used the platelet ^{14}C-labeled serotonin-release assay[12,13] to detect heparin-dependent IgG antibodies. At least two different samples, including the last sample obtained, were used for each patient in the subgroup of 387 patients. We also used stored serial samples to determine the date of seroconversion for patients who tested positive for heparin-dependent IgG antibodies. All laboratory testing was performed by personnel who were unaware of the platelet counts, clinical outcomes, or the type of heparin given.

Clinical Outcomes

Deep venous thrombosis, pulmonary embolism, and hemorrhage were diagnosed by objective tests and standard criteria.[14] We included all events that occurred before the patients' discharge from the hospital. Clinical events and radiologic studies were interpreted by a committee that was unaware of the assigned treatments.

Normal Range of Postoperative Platelet Counts

After orthopedic surgery, most patients have a transient decrease in the platelet count, followed by an increase above the preoperative count. We calculated a reference range for the platelet count in our population of patients by determining the mean ($\pm$2 SD) preoperative and postoperative platelet counts (with log-transformed data) for the patients whose plasma tested negative for heparin-dependent IgG antibodies (367 patients).

Statistical Analysis

The relevant outcomes in this study were all events that either occurred or did not occur in each patient. We compared the proportions of patients who had outcome events between groups by Fisher's exact test[15] and an associated method developed by Gart[16] for computing confidence intervals around the odds ratio. Confidence intervals for single binomial proportions were calculated by the "exact" approach.[17] The cumulative proportion of patients who had an event over time was estimated by the Kaplan–Meier method[18] to allow for variation in the length of time at risk. Cumulative-incidence curves were compared between groups by the Mantel–Haenszel test.[18] All P values are two-tailed.

Results

Late Thrombocytopenia

In the entire group of 665 patients, 12 patients had thrombocytopenia after receiving either unfractionated or low-molecular-weight heparin for five or more days. In 1 of these 12 patients thrombocytopenia developed on postoperative day 1 and persisted beyond day 5. All 12 patients had tests for heparin-dependent IgG antibodies, 8 because their physicians suspected that they had heparin-induced thrombocytopenia. Eight of the 12 were included (by chance) within the subgroup of 387 patients. Thus, four patients were tested twice because they were included in both groups from which samples were acquired.

Frequency of Heparin-Induced Thrombocytopenia

Nine of the 12 patients with thrombocytopenia had heparin-dependent IgG antibodies and therefore had heparin-induced thrombocytopenia. All of these nine had received unfractionated heparin (Table 1). Thus, of the 332 patients randomly assigned to receive unfractionated heparin, 2.7 percent (95 percent confidence interval, 1.3 to 5.1 percent) had heparin-induced thrombocytopenia. By contrast, none of the 333 patients who received low-molecular-weight heparin (0 percent, 95 percent confidence interval 0 to 1.1 percent) had heparin-induced thrombocytopenia ($P=0.0018$). Because some patients were discharged from the hospital before 14 days had passed, the cumulative proportion of patients who had heparin-induced thrombocytopenia at day 14 was 3.3 percent (Fig. 1). None of the nine patients with heparin-induced thrombocytopenia had major or minor hemorrhagic events.

Two patients with late thrombocytopenia tested negative for heparin-dependent IgG antibodies. Both had received unfractionated heparin. Alternative clinical factors could explain the thrombocytopenia in these two patients (multiple myeloma in one, and colon rupture with peritonitis and septicemia in the other). In both, the platelet count recovered to normal despite the continuation of heparin therapy. Neither patient had thrombosis.

A third patient who received low-molecular-weight heparin was found to have thrombocytopenia on postoperative day 1. It persisted until her death on postoperative day 29, despite the discontinuation of low-molecular-weight heparin on postoperative day 9. This patient had two negative tests for heparin-dependent IgG antibodies. She died with a leukoerythroblastic blood picture and metastatic adenocarcinoma in the bone marrow. No thrombotic event occurred.

Early Postoperative Thrombocytopenia

Thrombocytopenia occurred commonly (in 28.4 percent of patients) during the early postoperative period (postoperative days 1 through 5). There was no significant difference in the frequency of early thrombocytopenia between the group receiving unfractionated heparin and the group receiving low-molecular-weight heparin; thrombocytopenia occurred in 93 of 332 patients (28.0 percent; 95 percent confidence interval, 23.3 to 33.2 percent) receiving unfractionated heparin, as compared with 96 of 333 patients (28.8 percent; 95 percent confidence interval, 24.0 to 34.0 percent; $P=0.86$) receiving low-molecular-weight heparin. Fur-

Table 1. Clinical and Laboratory Findings in Nine Patients with Heparin-Induced Thrombocytopenia after Hip Surgery.*

Lowest Platelet Count	First Heparin-Dependent IgG Antibodies	First Decrease in Platelet Count	First Platelet Count Below 150,000/mm³	Occurrence of Thrombosis	Platelet Count on Day of Thrombosis	Location and Type of Thrombosis
per mm³		*postoperative day*			*per mm³*	
18,000	≤9†	6	6	10	20,000	Proximal lower-limb deep venous thrombosis
22,000	7	7	9	7	228,000‡	Bilateral proximal lower-limb deep venous thrombosis
				9	36,000	Pulmonary embolism
28,000	5	5	6	—	—	No thrombosis
34,000	7	7	8	11	34,000	Distal lower-limb deep venous thrombosis
				17	77,000	Pulmonary embolism
75,000	6	7	9	8	172,000§	Bowel infarction due to pathologically confirmed mesenteric-artery thrombosis
79,000	≤13†	6	8	8	140,000	Bilateral proximal lower-limb deep venous thrombosis
90,000	≤12†	7	9	13	106,000	Proximal lower-limb deep venous thrombosis
102,000	7	8	13	9	355,000¶	Distal lower-limb deep venous thrombosis
133,000	7	9	10	12	133,000	Bilateral lower-limb deep venous thrombosis (one proximal, one distal)

*All nine patients had received unfractionated heparin. Deep venous thrombi were confirmed by contrast venography, and pulmonary emboli were confirmed by high-probability ventilation–perfusion lung scans.

†Serial plasma samples were not available with which to determine the day of seroconversion, because this patient was not part of the 387-patient subgroup from which serial samples were obtained.

‡The first thrombosis in this patient occurred after seroconversion to heparin-dependent IgG antibodies and was associated with a decrease in the platelet count from 319,000 per cubic millimeter (on day 6) to 228,000 per cubic millimeter (on day 7); the second thrombosis (the pulmonary embolism) occurred when the platelet count was 36,000 per cubic millimeter.

§The mesenteric-artery thrombosis is presumed to have occurred on postoperative day 8 (the day of onset of abdominal pain) but was confirmed at laparotomy on day 10. The thrombosis occurred after seroconversion to heparin-dependent IgG antibodies and was associated with a decrease in the platelet count from 401,000 per cubic millimeter (on day 6) to 172,000 per cubic millimeter (on day 8).

¶The thrombosis occurred after seroconversion to heparin-dependent IgG antibodies and was associated with a decrease in the platelet count from 570,000 per cubic millimeter (on day 7) to 355,000 per cubic millimeter (on day 9).

thermore, the platelet count recovered within three days to more than 150,000 per cubic millimeter in 188 of 189 (99.5 percent) of these patients, despite the continuation of heparin. The one patient who did not have an increase in the platelet count had adenocarcinoma, as noted, and tested negative for heparin-dependent IgG antibodies. In the subgroup of 387 patients, tests for heparin-dependent IgG antibodies were negative in all 98 patients with early, reversible thrombocytopenia.

Thrombotic Events Complicating Heparin-Induced Thrombocytopenia

Table 1 shows the thrombotic events that occurred in the nine patients with heparin-induced thrombocytopenia. Seven patients had deep venous thrombosis, including five with proximal-vein thrombosis. Two patients had pulmonary embolism. One other patient had an arterial thrombosis (of the mesenteric artery). Heparin-induced thrombocytopenia was strongly associated with thrombotic events (odds ratio, 36.9; 95 percent confidence interval, 4.8 to 1638; $P<0.001$), in particular proximal deep venous thrombosis and pulmonary embolism (Table 2 and Fig. 2).

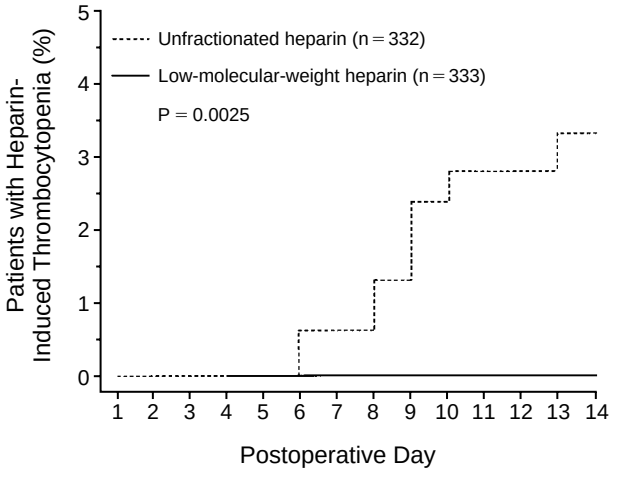

Figure 1. Cumulative Frequency of Heparin-Induced Thrombocytopenia in the Two Study Groups.

The postoperative day on which the platelet count fell below 150,000 per cubic millimeter is shown.

In five of the eight patients with thrombosis that complicated heparin-induced thrombocytopenia, the thrombosis began after the platelet count had fallen below 150,000 per cubic millimeter (Table 1 and Fig. 3). In three patients, however, the initial thrombotic event occurred when the platelet count was above 150,000 per cubic millimeter. However, in all these patients, seroconversion to heparin-dependent IgG antibodies had occurred, and the platelet count had begun to fall, before the onset of thrombosis or at the same time.

Laboratory and Clinical Analysis of Outcomes in the Subgroup of 387 Patients

Serial plasma samples from 387 patients were available to be tested for heparin-dependent IgG antibodies. By chance, this subgroup of patients included 8 of the 12 patients in the entire study population who had late thrombocytopenia ($P=0.77$) and 4 of the 8 patients who were tested because their physicians suspected heparin-induced thrombocytopenia ($P=0.73$).

Twenty of the 387 patients tested positive for heparin-dependent IgG antibodies. In all 20 samples, the tests were positive with both unfractionated heparin and low-molecular-weight heparin. Not all 20 patients had late thrombocytopenia, but a positive test for hep-

Table 2. Odds Ratio of Thrombotic Events in Patients with and Patients without Heparin-Induced Thrombocytopenia.*

Thrombotic Event	Patients with Thrombocytopenia (N = 9)	Patients without Thrombocytopenia (N = 656)	Odds Ratio (95 Percent Confidence Interval)	P Value
	no. of thrombotic events			
Distal deep venous thrombosis without proximal extension	2	84	1.9 (0.3–10.4)	0.74
Proximal deep venous thrombosis	5	29	27.0 (5.4–141)	<0.001
Pulmonary embolism	2†	2	93.4 (5.7–1374)	<0.001
Any venous thromboembolic event	7†	115	16.5 (3.1–163)	<0.001
Arterial thrombosis	1	2‡	40.9 (0.6–831)	0.040
Any thrombosis (venous or arterial)	8	117	36.9 (4.8–1638)	<0.001

*Patients with heparin-induced thrombocytopenia had a significantly increased frequency of thrombotic events, particularly venous thrombosis. All patients were followed to discharge in this analysis.

†Both patients with heparin-induced thrombocytopenia and pulmonary embolism also had venographically proved deep venous thrombi (one proximal and one distal).

‡One of these patients had a thrombotic (lacunar) cerebrovascular accident that was confirmed by a computed tomographic brain scan on postoperative day 17. The other died of cardiac arrest (due to ventricular fibrillation) on day 19 with no postmortem examination.

arin-dependent IgG antibodies was strongly associated with its development: 6 of the 20 patients had late thrombocytopenia as compared with 2 of the other 367 patients in the subgroup (odds ratio, 78.2; 95 percent confidence interval, 12.0 to 818.8; $P<0.001$).

We found a higher frequency of heparin-dependent IgG antibodies in patients who received unfractionated heparin than in those who received low-molecular-weight heparin: 16 of 205 patients (7.8 percent) as compared with 4 of 182 (2.2 percent), respectively ($P=0.02$). Tests of serial samples indicated that seroconversion had occurred in all 20 patients between postoperative days 5 and 10.

One or more thrombotic events occurred in 5 of the 6 patients (83.3 percent) in the 387-patient subgroup in whom heparin-induced thrombocytopenia developed. In contrast, thrombotic events occurred in 3 of 14 patients (21.4 percent) in whom heparin-dependent IgG antibodies formed without the development of thrombocytopenia, and in 63 of 367 patients (17.2 percent) who tested negative for heparin-dependent IgG antibodies. Heparin-induced thrombocytopenia was therefore associated with an increased risk of thrombosis, as compared with the risk in either the patients who had heparin-dependent IgG antibodies without thrombocytopenia (odds ratio, 18.3; 95 percent confidence interval, 1.1 to 943; $P=0.02$) or the patients who tested negative for heparin-dependent IgG antibodies (odds ratio, 24.1; 95 percent confidence interval, 2.6 to 1145; $P<0.001$). Patients in whom heparin-dependent IgG antibodies formed but who did not have thrombocytopenia were not more likely to have thrombosis than patients who did not form heparin-dependent IgG antibodies (odds ratio, 1.3; 95 percent confidence interval, 0.23 to 5.2; $P=0.72$).

The 387-patient subgroup was representative of the entire study population. There were no significant differences between this group and the remaining 278 study patients with respect to the study drug received ($P=0.07$), the frequency of heparin-induced thrombocytopenia ($P=0.74$), the occurrence of thrombotic events associated with heparin-induced thrombocytopenia ($P=1.0$), or the occurrence of any thrombotic event ($P=0.53$).

Discussion

In this study, we report the frequency of heparin-induced thrombocytopenia in 665 patients who received either unfractionated or low-molecular-weight heparin for antithrombotic prophylaxis after elective hip surgery. Daily platelet counts were obtained in all patients, and every patient who had thrombocytopenia after five days of heparin prophylaxis was tested for heparin-dependent IgG antibodies. We also tested a large, representative subgroup of 387 patients for heparin-dependent IgG antibodies regardless of their platelet counts.

We defined heparin-induced thrombocytopenia as a decrease in the platelet count to below 150,000 per cubic millimeter, beginning five or more days after the start of heparin therapy, and a positive test for heparin-dependent IgG antibodies. Our investigation was designed to avoid overestimating the frequency of heparin-induced thrombocytopenia, by excluding patients with early thrombocytopenia related to surgery or other factors.

We found heparin-induced thrombocytopenia in 2.7 percent of patients who received unfractionated heparin. By postoperative day 14, the cumulative risk of heparin-induced thrombocytopenia in this group reached 3.3 percent (Fig. 1). In contrast, no patient treated with low-molecular-weight heparin had heparin-induced thrombocytopenia. In eight of nine patients with heparin-induced thrombocytopenia, a thrombotic event occurred, giving an overall frequency of heparin-induced thrombocytopenia associated with thrombosis of 2.4 percent (95 percent confidence interval, 1.1 to 4.7 per-

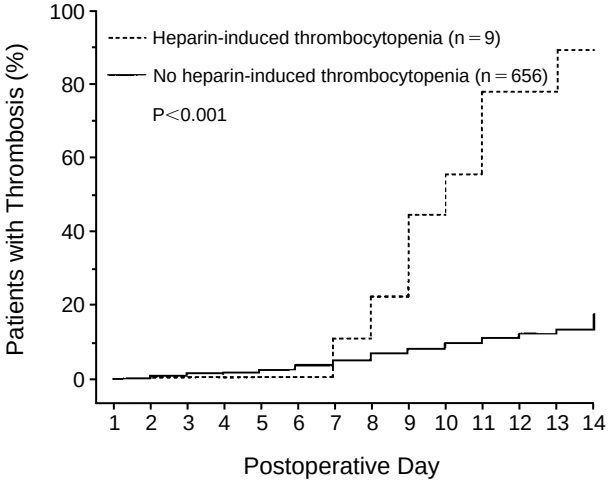

Figure 2. Cumulative Frequency of Thrombosis in Patients with and Patients without Heparin-Induced Thrombocytopenia.
All patients were followed to postoperative day 14 in this analysis.

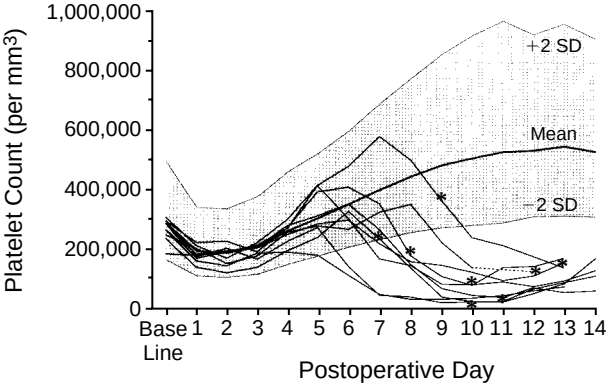

Figure 3. Serial Platelet Counts of Nine Patients with Heparin-Induced Thrombocytopenia.

The bold line and shaded area indicate the mean (±2 SD) platelet count in the reference population (367 patients negative for heparin-dependent IgG antibodies). In the reference population there was a uniform early postoperative decrease in the platelet count (with a maximal decrease at postoperative days 1 to 3), followed by a return to the base-line values (at approximately day 5), followed by platelet counts higher than those at base line (with maximal values at days 11 to 14). Asterisks indicate the occurrence of thrombotic complications in the patients with heparin-induced thrombocytopenia. A dotted line is shown for one patient because the platelet count was not available on the day that thrombosis developed.

cent) among the patients who received unfractionated heparin.

Tests of plasma samples from the subgroup of 387 patients allowed us to estimate the frequency of heparin-dependent IgG antibodies in patients receiving unfractionated or low-molecular-weight heparin. There was a significantly higher frequency of these antibodies in patients who received unfractionated heparin than in those who received low-molecular-weight heparin. Although a positive test for heparin-dependent IgG antibodies was strongly associated with thrombocytopenia, some patients did not have thrombocytopenia despite the presence of the antibodies in their plasma. This phenomenon may relate to the marked variability in the reactivity of platelets to heparin-dependent IgG antibodies.[13,19-21]

Heparin-induced thrombocytopenia was a strong risk factor for thrombotic events, particularly venous thrombosis (Table 2). Analysis of the 387-patient subgroup also showed a strong association between heparin-induced thrombocytopenia and thrombosis. The plasma samples from this subgroup were studied on the basis of availability alone; thus, bias in referral for laboratory testing does not explain the association between heparin-induced thrombocytopenia and thrombosis.

Previous reports of heparin-induced thrombocytopenia have emphasized its association with arterial thrombosis.[2,3] Although there was one patient in our series with arterial thrombosis (mesenteric-artery thrombosis resulting in bowel infarction), seven other patients with heparin-induced thrombocytopenia had venous thrombosis, including two with pulmonary embolism and five with proximal deep venous thrombosis. These observations are probably related to the high base-line risk of venous thrombosis in patients undergoing orthopedic surgery and to the systematic investigation for venous thrombosis we performed in all patients. Our previous retrospective study[22] indicated that the type of thrombotic complication (arterial or venous) is influenced by the clinical situation. We have recently postulated that the venous thrombotic complications that occur in some patients with heparin-induced thrombocytopenia might be related to the formation of procoagulant platelet-derived microparticles.[11]

Platelet counts have also been monitored in several large clinical trials that compared unfractionated with low-molecular-weight heparin as antithrombotic prophylaxis after hip surgery[23-27] or for the treatment of deep venous thrombosis.[28-35] However, in only one of these studies were tests for heparin-dependent IgG antibodies performed.[26] These investigators found heparin-induced thrombocytopenia in 2 of 199 patients (1.0 percent) who received unfractionated heparin after hip-replacement surgery, as compared with none of 198 patients who received low-molecular-weight heparin[26]; both patients with thrombocytopenia also had proximal deep venous thrombosis. In four other studies,[27-30] five additional patients had thrombocytopenia associated with thrombotic events (venous in four and arterial in one) that were thought to have been caused by heparin-induced thrombocytopenia, although confirmatory tests for heparin-dependent IgG antibodies were not reported; these five patients had also received unfractionated heparin.

Our study suggests that heparin-induced thrombocytopenia and associated thrombotic complications are relatively common adverse effects of heparin therapy. Moreover, heparin-induced thrombocytopenia is a strong risk factor for thrombotic events, including venous thromboembolism. We found that these complications were less likely to occur with low-molecular-weight heparin than with unfractionated heparin.

Low-molecular-weight heparin has certain advantages over unfractionated heparin, including the absence of a requirement for anticoagulant monitoring and a greater therapeutic index (less risk of bleeding for a given antithrombotic effect).[36,37] A disadvantage is the relatively high cost. In the United States, the preparation of low-molecular-weight heparin that we studied is about 10 times as expensive as unfractionated heparin when it is given as prophylaxis (approximately $20 per day vs. $2 per day). However, as more commercial preparations are approved for use, it is likely that the price difference will narrow, as it has in Europe.

It is important to emphasize that low-molecular-weight heparin is not indicated for the treatment of heparin-induced thrombocytopenia, because of the extensive cross-reactivity of the two forms of heparin.[2,3,38] However, the lower risk of immune sensitization and the correspondingly lower risk of heparin-induced thrombocytopenia and associated thrombotic events are important advantages of low-molecular-weight heparin over unfractionated heparin.

We are indebted to C.A. Smith and R.K. Sinha for assistance with laboratory studies and to Dr. J. Leclerc, Dr. J. Neemeh, Dr. P.J. Powers, Dr. R.M. Jay, Dr. A.G. Turpie, Ms. B. St. Jacques, Ms. L. Boulet, Ms. L.N. Klama, Mr. H. Nelson, and Dr. G. Foster for additional assistance with this study.

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