Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is caused by antibodies against a "self" protein—platelet factor 4—bound to heparin. We observed an overrepresentation of the female gender in 290 patients who developed HIT after cardiac or orthopedic surgery compared with the representation found in national databases (study 1). Therefore, we investigated gender imbalance in HIT by logistic regression analysis of a randomized controlled trial of unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) (study 2), and we analyzed individual patient data from 7 prospective studies comparing HIT frequency between UFH and LMWH, evaluating effects of gender, heparin (UFH vs LMWH), and patient type (surgical vs medical) (study 3). All 3 studies showed female overrepresentation, which for study 3 was a common odds ratio (OR) of 2.37 (95% confidence interval [95% CI], 1.37-4.09; $P = .0015$). Study 3 also showed an interaction between gender, heparin, and patient type. Although UFH was more likely than LMWH to cause HIT ($P < .0001$), this effect was predominantly seen in women compared with men (common OR, 9.22 vs 1.83; $P = .020$) and in surgical patients compared with medical patients (common OR, 13.93 vs 1.75; $P = .005$). We conclude that females are at greater risk for HIT and that using LMWH to prevent HIT may have greatest absolute benefit in females undergoing surgical thromboprophylaxis. (Blood. 2006;108:2937-2941)

Introduction

Heparin-induced thrombocytopenia (HIT) is a relatively common drug-induced immune reaction affecting platelets.[1] The immunologic basis of this disorder is the transient production[2] of platelet-activating antibodies of IgG class[3-5] that recognize multimolecular complexes of platelet factor 4 (PF4) and heparin.[6-8] An evolving concept is that HIT resembles an autoimmune disorder[9] because the pathogenic antibodies recognize one or more neoepitopes found on the "self" protein, PF4, rather than on heparin.[10,11] Indeed, in some patients, HIT strongly resembles an autoimmune process because heparin treatment initiates the anti–PF4/heparin antibody formation but then is no longer required for the development of thrombocytopenia.[12-14] To date, only a minor role for patient-specific risk factors for HIT has been reported. In particular, no association with human leukocyte antigen (HLA) genes is observed,[15] and the potential role of Fc receptor polymorphisms in HIT is debated.[16-18]

We previously observed in large retrospective studies that females constituted 56.4%[2] and 58.9%[19] of HIT patients, suggesting a possible gender imbalance. Together with the emerging concept of HIT as a drug-induced transient *autoimmune* disorder, we hypothesized that there might be a gender imbalance in risk for this adverse drug reaction, with a greater frequency among females, as observed in certain chronic autoimmune disorders.[20-22] We also examined whether the striking difference in risk for HIT between unfractionated heparin (UFH) and low-molecular–weight heparin (LMWH)[23] is consistent for both genders and in both surgical and medical patients.

Patients, materials, and methods

Study design

Hypothesis-generating study. We first investigated the gender distribution in a large database of patients with HIT (study 1). This database consisted of 2 well-defined patient subgroups (orthopedic and cardiac surgery) within a German database (n = 807) consisting of patients reported in a recent retrospective cohort study[19] and in 3 prospective treatment trials[24] of HIT. All these patients had clinical and serologic evidence for HIT, including either thrombocytopenia (defined as a platelet count decrease of 30% or greater) or thrombosis during or after heparin therapy, and all had positive results for HIT as determined by the heparin-induced platelet aggregation (HIPA) test. The gender distributions of these 2 subgroups were compared with those of national databases of orthopedic[25,26] and cardiac surgery[27] in Germany. The use

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of a nationwide comparison group was appropriate because the HIT database consisted of patients identified throughout Germany.

Approval for these studies was obtained from the McMaster University and the Ernst-Moritz-Arndt University Greifswald institutional review boards. Informed consent was provided according to the Declaration of Helsinki.

Analysis of a clinical trial. To corroborate the finding of a possible gender imbalance suggested by study 1, we performed an analysis of a clinical trial of 665 patients who had been randomly assigned to receive either UFH (n = 332) or LMWH (n = 333) after orthopedic (hip replacement) surgery (study 2).[28] This database was selected because a relatively large number (n = 18) of patients were identified as having acquired HIT and because (unlike the German HIT database) it included an intrastudy denominator of heparin-exposed female and male patients.[28] Furthermore, the designation as to whether the patients had HIT was based on studies of the effect of different definitions of platelet count decreases in HIT[28] and had been completed before the decision to analyze the database for effects of gender.

Systematic overview of data from patients. To further corroborate an effect of gender suggested by the previous studies and to examine whether a gender effect could interact with type of heparin (UFH vs LMWH) or type of patient population (surgical vs medical patients), we decided to analyze the gender distribution in all studies[28-35] that compared the frequency of HIT between UFH and LMWH, and for which laboratory testing for heparin-dependent antibodies was used to classify most or all patients in whom thrombocytopenia developed (study 3). For this analysis, we included either RCTs, nonrandomized comparisons, or before and after prospective cohort studies (in which prospective evaluation of UFH thromboprophylaxis was followed by prospective evaluation of LMWH thromboprophylaxis), provided that for the last group of studies, the clinical setting and laboratory methods used were similar during both study periods. We identified these studies from results of recent systematic reviews[23,36,37] and from our files. For 3 of the studies,[28,29,32] the data regarding HIT supplemented or supplanted those available from previously published studies[38-40] on the same (or nearly identical) patient groups. Gender information was not provided in the published reports of 4 of these studies[28-31]; to obtain this information for 2 of the studies,[28,29] we reviewed our study records, and for the other 2 studies,[30,31] we contacted the authors to obtain information on gender. One additional study[41] (which included only 2 patients with HIT) was excluded because the gender information was not available from the published report or from the authors. We used the numbers of HIT patients identified by the authors (according to the authors' definitions of HIT), except in the case of one study,[33] in which we excluded 3 patients who tested negative for anti–PF4/heparin antibodies by enzyme-immunoassay (a test considered to have high sensitivity for clinical HIT). All the studies used a proportional (relative) decline in the platelet count as the primary definition of thrombocytopenia. Usually the decline was 50% or greater,[28,30,32-35] though one study[31] used 40% and another[29] used 30% as relative platelet count fall thresholds to define thrombocytopenia.

Two studies[34,35] that reported the frequency of HIT occurring in 2 different cohorts of medical patients in Italy receiving either UFH[34] or LMWH[35] were included in our primary analysis. However, given that the before and after circumstances regarding the comparison of heparin types differed in important ways (including differences in participating hospital centers and different laboratories and somewhat different methods used to perform the testing for heparin-dependent antibodies) and because the Breslow-Day statistic (see "Statistical analysis") indicated that including these studies gave results that were now heterogeneous, we performed a secondary analysis excluding these 2 studies.

Because the RCT[28] analyzed in study 2 was also included in study 3, we performed an additional analysis within study 3 that excluded this RCT so as to be sure that any significant findings in study 3 were not driven by the results of this RCT.

Statistical analysis

Study 1 was analyzed by calculating the odds ratio (OR) with associated 95% confidence intervals (CIs) for the gender distribution among the HIT patient subgroups and comparing them with the corresponding national databases. Study 2 was analyzed by logistic regression to model the occurrence of HIT, with gender and heparin type (UFH vs LMWH) as factors. Fisher exact (2-sided) statistics were generated for categoric data analyses. *P* less than .05 was considered statistically significant.

For study 3, we used 2 different statistical approaches to perform systematic overviews of individual patient data obtained from 7 different comparison studies.[28-35] First, the analysis of these studies was performed using a fixed-effects approach to identify possible factors that influenced the incidence of HIT in UFH- and LMWH-treated patients. ORs were combined and reported separately and subsequently were compared for differences between groups defined by gender (female vs male) and patient type (surgical vs medical). The Mantel-Haenszel method was used for combining ORs.[42] The Breslow-Day heterogeneity test was used to test whether the ORs comparing the data of the individual studies were constant across studies. If the *P* value from the Breslow-Day test was more than .05, it was assumed that the ORs were homogeneous enough to be combined. The SAS System for Windows (version 8.2; SAS Institute, Cary, NC) was used to conduct the analysis.

In a second approach, we used a random-effects logistic model (using Stata 8.1 for Windows; Stata, College Station, TX) to analyze the influence of gender on the occurrence of HIT (controlling for patient type) and to analyze whether differences in risk for HIT between UFH and LMWH are affected by gender (controlling for patient type). This second statistical approach was used because it allows the simultaneous inclusion of several explanatory factors (gender, patient, and heparin type). In all analyses, a *P* value below .05 was considered statistically significant.

Results

Gender distribution in HIT compared with national databases (study 1)

Table 1 shows the gender distribution after orthopedic surgery and cardiac surgery in patients with HIT identified from the German database and compared with national databases for these patient populations. An overall female predominance was observed among the HIT patients (OR, 1.61; 95% CI, 1.24-2.08; $P = .0003$), with ORs for the subgroups of 1.51 (orthopedic) and 1.92 (cardiac) ($P = .009$ and $P = .006$, respectively). Although these results were statistically highly significant ($P = .0003$ for the combined patient groups), because of the absence of a precise denominator of overall heparin-exposed patients contributing to the HIT database and given the indirect nature of the comparison with the national databases, the results of this study were considered to be hypothesis generating.

Table 1. Gender distribution of HIT after orthopedic and cardiac surgery

Type of surgery, by sex	No. in Greifswald HIT patient database (%)	No. in German national database (%)
Orthopedic	219	219 663*
Female	166 (75.8)	148 355 (67.5)
Male	53 (24.2)	71 308 (32.5)
Cardiac	71	87 302†
Female	31 (43.7)	25 125 (28.8)
Male	40 (56.3)	62 177 (71.2)

Orthopedic surgery OR, 1.51 (95% CI, 1.10-2.05; $P = .009$). Cardiac surgery OR, 1.92 (95% CI, 1.20-3.07; $P = .005$). Combined surgery OR, 1.61 (95% CI, 1.24-2.08; $P = .0003$). Controlling for type of surgery (Breslow-Day test for homogeneity), $P = .396$.

*2002 data for trauma and elective hip replacement[25] and elective knee replacement[26] (data for the years preceding 2002 were unavailable).

†1997 data for cardiac surgery that included the use of cardiopulmonary bypass; data for patients with congenital heart disease were excluded.[27] When all available cardiac surgery data from the nationwide database were used for 1997 to 2002, the results (ratio of female to male) were 31:40 vs 176 500:400 200 (OR, 1.76; 95% CI, 1.10-2.81; $P = .017$).

Gender distribution in an RCT of postoperative thromboprophylaxis (study 2)

Study 2, which provided an intrastudy denominator of heparin-exposed female and male patients within an RCT of postoperative thromboprophylaxis (UFH vs LMWH) and in which 18 patients were identified with HIT,[28] also revealed a female predominance: 14 of 360 (3.9%) females and 4 of 305 (1.3%) males[28] (Table 2). For the subgroup of patients exposed to UFH, the frequency of HIT was 13 of 173 (7.5%; 95% CI, 4.1-12.5) females compared with 3 of 159 (1.9%; 95% CI, 0.4-5.4) males. Logistic regression showed that females had a significantly greater risk for HIT (OR = 3.31; 95% CI, 1.07-10.25; $P = .038$) and that patients receiving UFH had a greater risk for HIT than patients receiving LMWH (OR = 8.84; 95% CI, 2.01-38.84; $P = .004$).

Gender distribution in a systematic overview of data from individual patients (study 3)

Table 2 lists the gender distribution of HIT in 7 studies[28-35] comparing the frequency of HIT in patients administered UFH and LMWH. Four of these studies evaluated surgical patients,[28-31] and the other 3 studies evaluated medical patients.[32-35] Analysis of all 7 studies[28-35] using a fixed-effects statistical approach showed an overall greater frequency of HIT in females than in males (common OR = 2.37; 95% CI, 1.37-4.09; $P = .0015$).

Gender influences risk for HIT in surgical and medical patients treated with UFH. Among patients treated with UFH, females were significantly more likely than males to develop HIT (common OR, 4.53; 95% CI, 2.15-9.56; $P < .0001$), an effect that was similar in surgical (common OR, 4.55; 95% CI, 1.93-10.69; $P = .0002$) and medical patients (common OR, 4.47; 95% CI, 0.96-20.77; $P = .036$). However, among patients who received LMWH, no difference in risk for HIT was seen between females and males (common OR, 0.71; 95% CI, 0.26-1.90; $P = .498$). Except for one study,[35] the relatively low number of HIT cases among patients receiving LMWH makes it uncertain whether gender differences existed for LMWH.

When we analyzed the data using a logistic random-effects model, controlling for type of patient (surgical vs medical), we also found the odds for HIT to be much higher in females treated with UFH than in males, whereas in patients treated with LMWH, no significant effect of gender was seen (data not shown).

Greater risk for HIT from UFH than from LMWH primarily seen in females. It is known that there is a greater risk for HIT from UFH than from LMWH, at least in some patient populations.[23,28,36,38,39] Our analysis of the 7 studies (Table 2),[28-35] using a fixed-effects statistical approach, also indicated a greater risk for HIT from UFH than from LMWH (common OR, 5.29; 95% CI, 2.84-9.86; $P < .0001$). We next examined the 7 studies[28-35] with respect to whether this difference in risk for HIT between the 2 types of heparin is influenced by patient gender (female vs male) or by patient type (surgical vs medical). Table 3 shows the overall effects of these 3 factors (heparin type, patient type, gender), and it also shows the results of studies of the *interactions* of these 3 factors. We found the greater risk for HIT from UFH compared with LMWH to be especially marked in females (common OR, 9.22; 95% CI, 3.87-21.97; $P < .0001$), not in males (common OR, 1.83; 95% CI, 0.64-5.23; $P = .291$). This difference in the treatment effect (UFH vs LMWH) in females compared with the treatment effect in males was significant ($P = .020$).

The higher incidence of HIT from UFH in females observed using the fixed-effects analysis was confirmed by a logistic random-effects model that also confirmed that for males, no significant effect of type of heparin was seen (data not shown).

Greater risk for HIT from UFH compared with LMWH predominantly seen in surgical patients. The greater risk of UFH compared with LMWH was evident in surgical patients[28-31] but not in medical patients[32-35] (Table 3). Moreover, this difference in the treatment effect between surgical and medical patients was significant ($P = .005$) and thus unlikely to be explained by chance. Interestingly, the greater risk for UFH compared with LMWH was most evident in females undergoing surgery.

Secondary analysis suggests a possible greater risk for HIT in males treated with UFH than in those treated with LMWH. When we assessed for homogeneity among the 7 studies analyzed,[28-35] the Breslow-Day statistic ($P = .009$) indicated significant heterogeneity caused by inclusion of a before-and-after comparison of UFH and LMWH in medical patients.[34,35] Therefore, we performed a secondary analysis including the other 6 studies[28-33] that were homogeneous (Breslow-Day statistic; $P = .614$). In the secondary analysis, we also found that the risk for HIT was higher in females than in males (common OR, 4.00; 95% CI, 1.89-8.48; $P = .0001$). In addition, we found that UFH was associated with a higher risk for HIT than was LMWH (common OR, 15.63; 95% CI, 4.86-50.24; $P < .0001$). Compared with the primary analysis, the greater risk for HIT observed with UFH than with LMWH among females was even stronger (common OR, 19.99; 95% CI, 4.86-82.12; $P < .0001$). An important difference from the primary analysis, however, was that this analysis showed a significantly greater risk for HIT in males receiving UFH than in those receiving LMWH (common OR, 4.55; 95% CI, 1.17-12.75; $P = .025$).

Table 2. Studies evaluating the frequency of HIT between UFH and LMWH for which gender information was available

	Frequency of HIT (%)			
Study (LMWH), by setting	**Female, UFH**	**Male, UFH**	**Female, LMWH**	**Male, LMWH**
Surgery				
RCT[28] (enoxaparin)	13 of 173 (7.5)	3 of 159 (1.9)	1 of 187 (0.5)	1 of 146 (0.7)
PCS (B/A)[29] (enoxaparin)	10 of 131 (7.6)	2 of 100 (2.0)	0 of 171 (0.0)	0 of 100 (0.0)
PCS (B/A)[30] (enoxaparin)	5 of 182 (2.7)	0 of 70 (0.0)	1 of 171 (0.6)	0 of 81 (0.0)
PCS[31] (dalteparin)	4 of 55 (7.3)	2 of 102 (2.0)	0 of 39 (0.0)	0 of 132 (0.0)
Medical				
PCS (B/A)[32] (nadroparin)	4 of 93 (4.3)	1 of 107 (0.9)	0 of 75 (0.0)	0 of 36 (0.0)
RCT[33] (reviparin)	1 of 169 (0.6)	0 of 206 (0.0)	0 of 347 (0.0)	0 of 415 (0.0)
PCS[34,35] (several*)	4 of 332 (1.2)	1 of 266 (0.4)	5 of 830 (0.6)	9 of 935 (1.0)

Frequency of HIT is defined as number of patients with HIT out of number of total patients exposed.

B/A indicates before and after; PCS, prospective cohort study.

*LMWH preparations were nadroparin (n = 880 patients), enoxaparin (n = 700 patients), reviparin (n = 67 patients), dalteparin (n = 64 patients), and pamaparin (n = 43 patients).

Table 3. Factors influencing risk for HIT: type of heparin, patient population, and gender (fixed-effects statistical approach)

	Common OR for HIT	95% CI		*P*
		Lower	Upper	
Group (no. of studies)				
Overall effect of heparin type: UFH vs LMWH (7)	5.29	2.84	9.86	< .0001
Overall effect of patient type: surgical vs medical (7)*	3.25	1.98	5.35	< .0001
Overall effect of gender: female vs male	2.37	1.37	4.09	.0015
Interactions (no. of studies)†				
Female (7)	9.22	3.87	21.97	< .0001
Male (7)	1.83	0.64	5.23	.291
Females vs males	—	—	—	.020
Surgical (4)	13.93	4.33	44.76	< .0001
Medical (3)	1.75	0.73	4.22	.233
Surgical vs medical	—	—	—	.005
Female surgical (4)	17.39	4.22	71.70	< .0001
Female medical (3)	3.75	1.16	12.17	.025
Female surgical vs female medical	—	—	—	.103

All comparisons showed homogeneity among the respective studies (Breslow-Day, $P > .15$), except for overall effect of heparin type: UFH vs LMWH (7) (Breslow-Day, $P = .009$). The inhomogeneity resulted from inclusion of one prospective before-and-after cohort study.[34,35] When this study was removed from analysis, the resulting Breslow-Day statistic ($P = .614$) indicated homogeneity. Analysis of the remaining 6 studies[28-33] showed even greater overall risk for HIT with UFH than with LMWH (common OR, 15.63; 95% CI, 4.86-50.24; $P < .001$). In addition, the remaining studies showed even greater overall risk for HIT in females than in males (common OR, 4.00; 95% CI, 1.89-8.48; $P = .0001$). Similar results were seen when the randomized controlled trial[28] analyzed in study 2 was excluded from this analysis. For example, when analyzing only the remaining studies,[29-35] significant overall effects of heparin type (common OR, 4.56; 95% CI, 2.29-9.10; $P < .0001$), patient type (common OR, 2.77; 95% CI, 1.58-4.87; $P < .001$), and gender (common OR, 2.17; 95% CI, 1.16-4.07; $P = .013$) were seen. Similar results were observed in analyses for interactions in heparin type, patient type, and gender (data not shown).

*Studies were pooled across patient type to produce a simple 2 × 2 table. Surgical, 42 of 1999; medical, 25 of 3811. Fisher exact test (2-sided) *P* value.

†Male surgical and male medical comparisons were not considered because of lack of events. Interactions included all other parameters regarding risk for HIT comparing treatment with UFH and with LMWH.

Discussion

We performed 3 studies, each of which showed that females are at higher risk for HIT than males. The first analysis was a comparison of an HIT patient database with corresponding national databases (study 1). This led to our hypothesis of a potential gender imbalance in HIT because of the observed female predominance in HIT (Table 1).[25-27] Our hypothesis was further supported by an evaluation of an RCT of heparin-type thromboprophylaxis after orthopedic surgery (study 2),[28] in which female gender was significantly associated with risk for HIT. To provide additional evidence, we also performed a systematic overview of patient data obtained from 7 studies (Table 2), the RCT[28] examined in study 2 and 6 additional studies[29-35] (study 3). This analysis (Table 3) also indicated a female overrepresentation in HIT that was seen using 2 different statistical models. Overall, the increased risk for HIT in females (using a fixed-effects statistical approach), expressed as a common OR, was 2.37 (95% CI, 1.37-4.09; $P = .001$). This effect of gender on risk for HIT was robust—it was seen even if the RCT analyzed in study 2 was excluded from the analysis in study 3 or if the results of a before-and-after comparison[34,35] (which resulted in inhomogeneity by the Breslow-Day test) was excluded from analysis in study 3 (Table 3 footnote).

The increased frequency of HIT in females was observed most clearly in patients treated with UFH. Among patients treated with UFH, females were significantly more likely than males to develop HIT ($P < .001$). We did not see in our primary analysis a relationship between gender and risk for HIT among patients treated with LMWH ($P = .498$). Although we found significant gender differences regarding risk for HIT between patients receiving UFH and those receiving LMWH (Table 3), this might have been the result of a relatively low frequency of HIT among patients receiving LMWH, and it might have precluded detection of a true gender-related effect for this type of heparin. However, it is possible that the ultralarge multimolecular complexes formed between UFH and PF4 resulted in gender-dependent differences in the magnitude of the immune response toward these complexes or in the relative pathogenicity (platelet-activating properties) of the complexes formed. Fc receptor expression on platelets and Fc receptor–dependent platelet activation are considered gender independent,[43-45] though relatively small numbers of patients have been studied, and no information exists on gender dependence of PF4 binding to platelets, a variable that is relevant to HIT pathogenesis.[46] Further studies are needed to address these issues.

We confirmed and extended the findings of a recent meta-analysis by Martel et al,[23] who observed that the risk for HIT is greater in surgical patients receiving UFH than in those receiving LMWH. Consistent with that meta-analysis,[23] we found that the risk for HIT was much higher in surgical patients receiving thromboprophylaxis with UFH than in those receiving it with LMWH (common OR, 13.93; 95% CI, 4.33-44.76; $P < .001$) (Table 3). However, in medical patients, we did not observe a greater frequency of HIT with UFH or with LMWH (Table 3). Furthermore, a comparison of the effect of heparin type in surgical versus medical patients shows a significant difference ($P = .005$). Thus, based on current information, one should not necessarily assume that the markedly reduced risk for HIT reported in patients undergoing surgical thromboprophylaxis with LMWH applies to medical patients.

In conclusion, our studies indicate that females are at approximately twice the risk (by OR) for HIT as males. In addition, our study suggests there may be important interactions among gender, type of heparin, and type of patient that influence the frequency of HIT. In particular, it appears that the benefit of HIT reduction using LMWH might be especially pronounced in females undergoing surgical thromboprophylaxis (common OR, 17.39; 95% CI, 4.22-71.7; $P < .001$). Our study suggests that gender effects should be considered in future studies examining the frequency and the pathogenesis of HIT in different clinical situations and with different types of heparin.

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