Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis

A retrospective analysis of 408 patients

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Summary

Immune mediated heparin induced thrombocytopenia (HIT) is a prothrombotic adverse effect of heparin. However, only a subgroup of patients with HIT develops thromboembolic complications. We aimed to identify risk factors for developing HIT-associated thrombosis. We analyzed a registry of patients with clinical suspicion of HIT who tested positive using a sensitive functional assay. Patient information was obtained by a standardized questionnaire. By multivariate analysis the association of age, gender, type of patient population, and magnitude of the platelet count decline with the frequency, type (venous or arterial), and temporal pattern of thrombotic events was assessed. In 408 HIT patients we observed predominance of venous thrombosis (2.4:1), with 40% of patients developing a pulmonary embolism.

However, in the subgroup of post-cardiovascular surgery patients there was predominance of arterial thrombosis (1:8.5). The type of arterial thrombosis (limb artery thrombosis > thrombotic stroke > myocardial infarction) was the converse of that observed with typical atherothrombotic clots in non-HIT populations. In 59.8% of patients HIT-related thrombosis manifested either on the same day a platelet count decrease >50% was documented (26.3%) or before the decrease in platelet counts (33.5%). The most important risk factors for thrombosis were orthopedic/trauma surgery and the magnitude of platelet count decrease. HIT-associated thrombosis occurs in a considerable proportion of patients before platelet counts decrease by more than 50%.

Keywords

Heparin, heparin-induced thrombocytopenia, platelets, thrombosis

Introduction

Heparin-induced thrombocytopenia (HIT) is a clinicopathological prothrombotic syndrome caused by an immune response (1) usually to complexes of platelet factor 4 (PF4) bound to heparin (2). HIT antibodies can activate platelets, which results in procoagulant platelet membrane changes (3) that enhance thrombin generation in vivo (4). In patients who form high levels of platelet-activating HIT antibodies (5), the antibodies lead to thrombocytopenia, and a large proportion of these patients develop thromboembolic complications (TECs) (6).

Studies screening symptomatic as well as asymptomatic patients (7) showed that most patients who form anti-PF4/heparin antibodies do not develop clinical HIT, some develop a decrease of platelet counts only, and some patients develop associated thrombotic complications. The reasons for the differences in
clinical breakthrough of HIT are unknown. We used a large database of HIT patients to identify risk factors for the development of HIT-associated TECs.

Materials and methods

We identified all patients referred to our laboratories with clinically-suspected HIT who tested positive in a functional assay (heparin-induced platelet activation test, HIPA [8]) in one of two laboratories (Greifswald or Giessen). As the patients were identified between 1994 and 1997 the PF4-heparin ELISA was not available at that time for routine diagnosis. Clinical events prompting analysis of HIT-antibodies included a major decrease in platelet counts, or, if no preceding platelet count was available, an otherwise unexplained platelet count less than 100,000 platelets/μl; new thromboembolic complications (TECs) during heparin treatment; skin reactions at the heparin injection site (with or without platelet count fall); or systemic (anaphylactic) reactions following a heparin bolus was given. A positive HIPA test was defined as a positive reaction with platelets of at least 20 of 4 tests of HIT patients.

Table 1: Multiple logistic regression of age, gender, underlying disease, and platelet count decrease on thromboembolic complications (the number of evaluable patients for each parameter is given in parenthesis).¹

<table>
<thead>
<tr>
<th>Gender (406 patients)</th>
<th>Number of patients with TEC / number of evaluable patients (%)</th>
<th>Odds Ratio</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>80/167 (47.9%)</td>
<td>0.0</td>
<td>0.63–1.87</td>
<td>0.77</td>
</tr>
<tr>
<td>Female</td>
<td>146/239 (61.1%)</td>
<td>1.08</td>
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<table>
<thead>
<tr>
<th>Age (405 patients)</th>
<th>Number of patients with TEC / number of evaluable patients (%)</th>
<th>Odds Ratio</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–19 years</td>
<td>16/34 (47.1%)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–39 years</td>
<td>57/103 (55.3%)</td>
<td>2.71</td>
<td>0.96–7.61</td>
<td>0.06</td>
</tr>
<tr>
<td>40–59 years</td>
<td>134/232 (57.8%)</td>
<td>1.94</td>
<td>0.76–4.96</td>
<td>0.16</td>
</tr>
<tr>
<td>≥ 80 years</td>
<td>19/36 (52.8%)</td>
<td>0.98</td>
<td>0.29–3.29</td>
<td>0.98</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Underlying disease (400 patients)</th>
<th>Number of patients with TEC / number of evaluable patients (%)</th>
<th>Odds Ratio</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal medicine</td>
<td>62/143 (43.4%)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General surgery</td>
<td>20/53 (37.7%)</td>
<td>0.72</td>
<td>0.34–1.51</td>
<td>0.38</td>
</tr>
<tr>
<td>Cardio-vascular Surgery</td>
<td>12/31 (38.7%)</td>
<td>0.62</td>
<td>0.23–1.68</td>
<td>0.35</td>
</tr>
<tr>
<td>Orthopedic and trauma surgery</td>
<td>98/125 (78.4%)</td>
<td>5.34</td>
<td>2.67–10.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Others</td>
<td>30/48 (62.5%)</td>
<td>1.70</td>
<td>0.76–3.84</td>
<td>0.20</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Platelet count decrease (319 patients)</th>
<th>Number of patients with TEC / number of evaluable patients (%)</th>
<th>Odds Ratio</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 30%</td>
<td>5/19 (26.3%)</td>
<td>1.0</td>
<td></td>
<td></td>
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<tr>
<td>&gt; 30–50%</td>
<td>9/29 (31.0%)</td>
<td>1.72</td>
<td>0.40–7.47</td>
<td>0.47</td>
</tr>
<tr>
<td>&gt; 50–70%</td>
<td>27/57 (47.4%)</td>
<td>3.63</td>
<td>0.95–13.86</td>
<td>0.06</td>
</tr>
<tr>
<td>&gt; 70–90%</td>
<td>101/158 (63.9%)</td>
<td>8.11</td>
<td>2.29–28.64</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt; 90%</td>
<td>38/56 (67.9%)</td>
<td>8.79</td>
<td>2.16–34.17</td>
<td>0.002</td>
</tr>
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¹All predictors were simultaneously entered into the model. Hosmer-Lemeshow Chi-square=11.5 (8 df; p=0.18); Nagelkerke R Square=0.27.

The following parameters were obtained: gender; age (grouped as 0–19; 20–39; 40–59; 60–79; and ≥ 80 years); patient population (internal medicine, surgery [for subanalysis also grouped into orthopedic/trauma surgery; cardiovascular surgery; general/thoracic surgery], and others [e.g. neurology, urology, dermatology, gynecology, ear-nose-throat-surgery]); all available platelet counts; day of diagnosis of HIT, onset and location of thromboembolic complications, and start of heparin treatment (day of start of heparin was defined as day 0).

Platelet counts at diagnosis of HIT were compared to the highest available preceding platelet count, however, the frequencies of platelet count monitoring varied between patients. Only TECs occurring after at least 5 days of heparin were regarded as HIT-associated events for the purpose of this study, i.e., thromboses that led to heparin treatment were not considered HIT-associated TECs. The questionnaire required including only objectively confirmed TECs (methods differed according to the participating hospitals).

For discrete characteristics chi-square test was used, for continuous parameters the Wilcoxon test was applied. Using univariate and multiple logistic regression analysis, single and combined effects of gender, age group (due to small numbers age group 0–19 years and 20–39 years were combined), field of underlying disease, and relative decrease of platelet counts, on HIT associated TECs were assessed. Model fit was evaluated by the Hosmer-Lemeshow statistic and the Nagelkerke R Square index. For statistical analysis SAS (Version 6.12 and 8e) and SPSS (Version 12.0.1) were used. The level of significance was defined as 0.05 (two tailed).

Results

Gender and age
In 406/408 patients gender was documented (58.9% female and 41.2% male; >99% of caucasian origin), 66% were 60 years or older (mean age women 64.1 ± 15.4 SD years vs. men 60.7 ± 14.3 SD years); 0–19 years (1.5%); 20–39 years (6.9%); 40–59 years (25.4%); 60–79 years (57.3%); ≥ 80 years (8.9%).

Risk of TEC and underlying disease
In a multiple logistic regression analysis (Table 1) trauma/orthopedic surgery was an independent risk factor for developing HIT associated TECs (odds ratio 5.3 [95% CI 2.67 – 10.68; p<0.001]).

Platelet count decrease and risk of thrombosis
In 319 patients, platelet counts before occurrence of HIT were available. At the time of clinical diagnosis of HIT, a decrease in platelet counts of at least 50% occurred in 271/319 (84.9%) patients. Of the remaining 48 patients, HIT was suspected in 14 patients because of new thrombosis without platelet count fall > 30% (4.4%), in 20 patients (6.3%) due to a platelet count decrease between 30% and 50%; and in 14 (4.4%) because of one or more of the following: skin lesions at the heparin injection side, acute inflammatory reaction post intravenous heparin bolus, or an otherwise unexplained reported low platelet count during a previous intervention e.g. coronary angiography a week before without comparison value. The median platelet count
Of the 408 patients, 227 (55.6%) developed 434 TECs associated with HIT (1.91 TECs/patient). 101 patients had one TEC (44.5%); 69 patients had 2 TECs (30.4%); 41 patients had 3 TECs (18.1%); and 16 patients developed more than 3 TECs (7.1%). In 209 patients with one or more TECs, onset of thrombocytopenia and day of manifestation of TEC could be correlated. In 84 patients (40.2%) platelet counts decreased by more than 50% one or more days before the thrombosis manifested. The median time delay between platelet count decrease and manifestation of TEC was 3.5 days (25–75% quartile 1–7 days). In 55 patients (26.3%) thrombocytopenia was first documented on the same day of manifestation of thrombosis (Fig. 1). In 70 patients (33.5%) the thrombosis preceded a decrease of platelet counts. Among this last group of patients, the median time delay between thrombosis and onset of thrombocytopenia was 3 days (25–75% quartile 1–6 days) (Fig. 1). Thus, in almost 60% of patients, HIT-related thrombosis manifested either on the same day a platelet count decrease was documented or earlier.

Table 2 shows the localization of TECs in 225 patients (in 2 other patients information was missing regarding whether a limb TEC was arterial or venous). In 43.6% of patients, a pulmonary embolism occurred, and in 36.4% there was proximal deep vein thrombosis. The overall ratio of venous (n=306) to arterial (n=126) TECs was 2.4:1 (medical patients 2.3:1; general surgery patients 1.5:1; orthopedic/trauma surgery 2.9:1; all other patients 6.6:1). However in cardiovascular surgery patients, a marked predominance of arterial TECs was observed (ratio 1:8.5).

**Discussion**

The purpose of this study was to assess risk factors for thrombosis in serologically confirmed HIT. We used a retrospective approach due to the low frequency of HIT which makes it difficult to find sufficient numbers of patients with events in a prospective trial. We examined age, gender, type of platelet count decline in relation to the frequency, type, and temporal pattern of thrombosis.

As expected, we found HIT to be very prothrombotic (10), with 55.6% of patients developing one or more TECs (average 1.92 TECs/patient) and approximately 25% of patients developing three or more HIT related TECs. Our study underscores the predominance of venous TECs (71%) in HIT (10) and that a high percentage of these patients will develop pulmonary embolism (43.6%) (11). Interestingly, we also found a marked predominance of arterial TECs in patients undergoing cardiovascular surgery (12). Further, the rank of frequency of arterial occlusions was limb artery occlusions > stroke > MI, which is the opposite pattern as found in non-HIT patients with atherothrombosis.

Orthopedic/trauma surgery is shown to be an independent risk factor for the development of HIT associated thrombosis (13), with an odds ratio of 5.3 (95% CI 2.67–10.68; p<0.001).

We further confirm that the risk for HIT related TECs is related to the magnitude of the relative platelet count decrease (14). This further suggests that the degree of the platelet activating capacity of HIT antibodies is linked to the capability of these antibodies to induce HIT related complications. As HIT is so prothrombotic, and deep vein thrombosis and pulmonary embol-
ism are very frequent complications, the present study further corroborates that routine screening for thrombosis (e.g. by duplex sonography) should be performed in all patients with confirmed or strongly suspected HIT, even if the patient is asymptomatic for venous thromboembolism (15). As HIT occurs predominantly in elderly patients, potential renal impairment should be considered for dosing of alternative anticoagulants, especially for lepirudin (16) to avoid bleeding.

Perhaps the most surprising finding is that in almost 60% of patients with HIT associated thrombosis, the thrombosis either preceded or occurred on the same day that thrombocytopenia was first documented. In 33.5% of patients, thrombotic complications manifest before a major decrease in platelet counts occurred, with the diagnosis of HIT being made only when the platelet counts subsequently decreased over the next few days. Therefore it seems reasonable to include HIT in the differential diagnosis in all patients who develop a new TEC in the typical time window of HIT, i.e. after 5 or more days after starting heparin (17), whether or not a major drop in platelet count occurred.

It is interesting to note that in a prospective trial (11, 18) with daily platelet count monitoring in post-orthopedic surgery patients receiving heparin, in 4 of 13 HIT patients (30.7%), the thrombosis also occurred before platelet counts decreased by >50%, which is in line with our large retrospective study.

Therefore, even platelet count monitoring may not necessarily avoid all HIT related thrombosis. This underscores the importance of avoiding this complication by using the less HIT-inducing low-molecular-weight-heparin preparations, where otherwise clinically appropriate (18, 19).

Acknowledgement
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References