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Influence of the patient population on the risk of heparin-induced thrombocytopenia

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Abstract: **744 patients from 3 different clinical settings were evaluated as follows: unfractionated heparin (UFH) during or after cardiac surgery (n=100), UFH after orthopedic surgery (n=100, = 205) and molecular weight heparin (LMWH) after orthopedic surgery (n = 439). In the activation assay, the frequency of HIT-IgG formation varied from a minimum of 3.2% in orthopedic patients receiving LMWH to a maximum of 20% in cardiac patients receiving UFH; per antigen assay, the corresponding frequencies ranged from 7.5% to 50%.**

However, in patients who developed HIT-IgG and received UFH, the probability of HIT was higher in orthopedic patients than in cardiac patients (according to the activation assay: 52.6% vs. 5%; odds ratio 21.1). [95% CI, 2.2-962.8]; P = .001; nach Antigen-Assay: 34,5 % vs. 2,0 %; Odds Ratio, 25,8 [95 % KI, 3,2-1141]; P < 001). It is concluded that there is an unexpected dissociation between the frequency of HIT-IgG formation and the risk of HIT, which depends on the patient population.

Keywords: **cardiac patients, heparin-induced thrombocytopenia, patient population.**

I. INTRODUCTION

Heparin-brought about thrombocytopenia (HIT) is an unfavorable drug response due to heparin-established IgG (HIT-IgG) antibodies that spark off platelets.1-three The goal antigen includes multi-molecular complexes of platelet issue four and heparin.four-7 The frequency of HIT varies considerably, as noted through potential research.8,nine The motives for those versions are unknown however will be associated with exclusive heparin preparations,10 affected person populace-established factors, or maybe exclusive laboratory strategies used to locate the antibodies chargeable for HIT. Activation assays, which includes the platelet serotonin launch assay, locate HIT-IgG on the idea in their capacity to spark off platelets.11-thirteen Antigen assays, which includes a solid-section immunoassay, locate the binding of antibodies to immobilized platelet issue four–heparin complexes. four-7,14,15 Despite the growing use of those assays, few research has as compared their scientific usefulness in diagnosing HIT. Those studies14,16-18 evaluating activation and antigen assays generally had been confined to investigating affected person samples that have been referred with the scientific suspicion of HIT (excessive pretest probability). In this report, we describe the outcomes of laboratory checking out for HIT-IgG the use of each activation and antigen assays in 744 prospectively studied sufferers. The outcomes of this take a look at suggest that there may be a surprising dissociation among the formation of HIT-IgG and the threat for HIT amongst sufferers in whom antibodies shape this is affected person populace established.

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II. PATIENTS, MATERIALS, AND METHODS

Patient populations

The UFH and orthopedics group consisted of a group of 205 patients receiving porcine mucosal UFH (Calciparine; Laboratoires Anglo-French, Dorval, Quebec, Canada), 7500 IU every 12 hours by subcutaneous injection for up to 14 days or at upon discharge These patients had participated in a randomized clinical trial of UFH versus LMWH administered as antithrombotic prophylaxis following total hip arthroplasty (Study A). orthopedic surgery. The first group (Study A) consisted of 182 patients who received LMWH (Enoxaparin; Lovenox; Rhone-Poulenc Rorer, Montreal, Quebec, Canada) 30 mg every 12 hours by subcutaneous injection for up to 14 days or at discharge.

These patients had also participated in the study described above.10,19 The second orthopedic LMWH group (study B) consisted of 257 patients undergoing postoperative LMWH prophylaxis following orthopedic surgery (hip arthroplasty, n=105; knee arthroplasty, n = 152). These patients were receiving 1 of 3 LMWH preparations per current hospital practice at the time of study entry: enoxaparin (Lovenox; RhoÆne-Poulenc Rorer), 30 mg twice daily by subcutaneous injection, n= ,70; Tinzaparin (Innohep; Leo, Ajax, Ontario, Canada), 3000 U twice daily by subcutaneous injection, n=2; or dalteparin (Fragmin; Pharmacia, Mississaga, Ontario, Canada), 3000 U twice daily by subcutaneous injection, n = 185

Activation assay

The 744 patients underwent the platelet serotonin release assay as described11,12 using heat-inactivated citrated plasma or serum stored at -70°C prior to testing. Using a predetermined algorithm, samples were considered positive when all requirements were met. the following criteria were met: (1) 20% or more serotonin release at 0.1 U/ml heparin; (2) at least 50% inhibition of platelet activation by both an Fc-receptor blocking monoclonal antibody (IV.3) and a high concentration of heparin (100 U/ml); (3) Adequate activation profiles were observed with 3 positive controls (including 2 "weak" sera, i.e. with 20-50% serotonin release) and one negative control serum.

Antigen assay

Definitions

We defined possible HIT as a 50% or greater fall in the platelet count from the postoperative peak that occurred between days 5 to 14 after surgery, unless another cause for the thrombocytopenia was readily apparent (eg, culture-positive septicemia) or the platelet count recovered during continued heparin treatment. This definition of thrombocytopenia has the best correlation with the formation of HIT-IgG20 and is appropriate for a postoperative patient population in whom thrombocytosis commonly occurs between postoperative days 5 to 14. Heparin-induced thrombocytopenia (HIT) was defined when a patient with possible HIT also had positive results of at least one laboratory assay for HIT-IgG (by activation or antigen assay, or both).

Comparison of activation and antigen assays

Because both diagnostic assays are quantitative measurements, we used Receiver Operating Characteristic (ROC) curve analysis to compare the sensitivity-specificity trade-off at different diagnostic cut-offs that define negative and positive outcomes. The sensitivity of each assay was defined as the proportion (percentage) that tested positive in patients with possible HIT. The specificity of each assay was defined as the proportion (percentage) of patients who did not meet the study definition for possible HIT and tested negative for that assay. The ROC curve analysis was only performed for orthopedic patients as this patient group had a relatively large number of patients with possible HIT and additional patients with subclinical HIT IgG seroconversion (see 'Results').

To investigate whether further sample dilution would improve the balance between sensitivity and specificity of the antigen assay, we also ran the assay with the following sample dilutions: 1/50, 1/75, 1/100, 1/150 , 1/250 , 1/500, 1/750, 1/1000, 1/2500 and 1/5000. Following these preliminary studies, we systematically tested samples from orthopedic patients that tested positive in the antigen assay (at 1/50) at the following additional dilutions: 1/100, 1/250, 1/500 and 1/750.

III. STATISTICAL ANALYSIS

Comparisons of proportions between groups were performed using the Fisher exact test.21 An associated method developed by Gart22 was used for computing confidence intervals around the odds ratio. We performed logistic regression analysis23 to determine the impact of either heparin preparation (UFH compared with LMWH) and the type of patient population

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(cardiac compared with orthopedic patients) with respect to the frequency of HIT-IgG formation and the proportion of antibody-positive patients in whom possible HIT developed. Analyses were performed separately for activation and antigen test results. All quoted P values were 2-sided.

IV. RESULTS

Frequency of possible heparin-induced thrombocytopenia

Eighteen of the 744 prospectively studied sufferers had a 50% or more lower in platelet remember that commenced among postoperative days five and 14. Fifteen of those sufferers met the standards for viable HIT ,All 15 sufferers who have been recognized as likely having HIT additionally examined high quality for HIT-IgG the use of each the activation and the antigen assays. The frequency of HIT turned into highest (4.9%) with inside the orthopedic–UFH sufferers and turned into exceptionally low in each the orthopedic–LMWH sufferers (0.9%) and the cardiac–UFH sufferers (1%). One or extra thrombotic activities came about in 9 (60%) of those 15 sufferers; 7 sufferers had venous thromboembolism, 1 affected person had unilateral adrenal hemorrhagic infarction, and 1 affected person had arterial thrombosis. Three sufferers whose platelet counts fell with the aid of using 50% or extra among postoperative days five to fourteen did now no longer meet the standards for viable HIT. Thrombocytopenia advanced in affiliation with colon perforation and septicemia in orthopedic sufferers, one dealt with UFH and one dealt with LMWH. Both died. In each sufferer, however, platelet counts recovered for the duration of persevered heparin use. A 1/3 affected person had a 59% crease in platelet remember in affiliation with pulmonary embolism, however complete platelet remember healing for the duration of remedy with therapeutic-dose UFH came about. All three sufferers examined terrible for HIT-IgG with the aid of using activation and antigen assays.

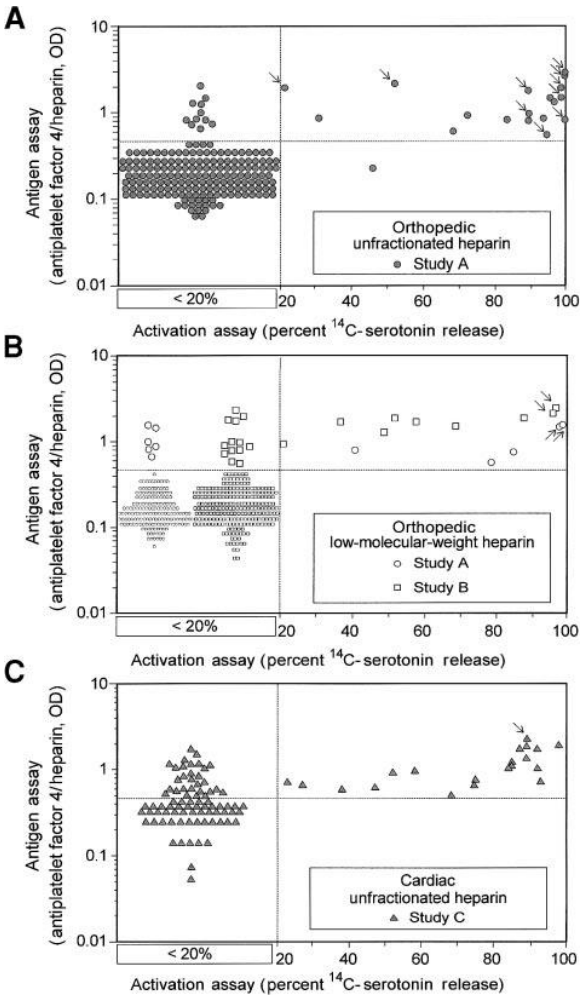

Figure 1. Comparison of activation and antigen assays for HIT-IgG antibodies in patients who have undergone cardiac and orthopedic surgery. Quantitative results of activation and antigen tests for HIT-IgG are shown for 3 clinical treatment settings: orthopedic–UFH (A), orthopedic–LMWH (B), and cardiac–UFH (C). Results are shown for all 744

patients. All antigen assay data are given quantitatively. For the activation assay results, samples that gave less than 20% serotonin release are as shown without reference to the actual quantitative result obtained (see box desig- nated < 20%); quantitative data are given when the percentage serotonin release was 20% or more. Arrows indicate the data points corresponding to the 15 patients with HIT identified in these prospective studies

Frequency of HIT-IgG antibody formation

Figure 1 summarizes the results of the laboratory assays for HIT-IgG among the 3 patient treatment groups studied.. Among sufferers who examined advantageous with the aid of using the activation assay and who obtained UFH, HIT advanced in 52.6% of orthopedic sufferers however most effective 5% of cardiac surgical procedure sufferers (odds ratio, 21.1 [95% CI, 2.2 to 962.8]; P = .001). Among sufferers who examined advantageous with the aid of using antigen assay and who obtained UFH, HIT advanced in 34.5% of orthopedic sufferers and most effective 2.0 % of cardiac surgical procedure sufferers (odds ratio, 25.8 [95% CI, 3.2 to 1141]; We investigated the period of heparin remedy as a motive fewer affected person with HIT-IgG with inside the cardiac organization had viable HIT. Figure 1 suggests that maximum sufferers with HIT (indicated with the aid of using arrows) had sturdy advantageous check outcomes for HIT-IgG the use of both assay: greater than 90% serotonin launch (activation assay) and more than 1.0 OD (antigen assay). Because activation and antigen assays had been advantageous at their traditional cutoff points (greater than 20% serotonin launch and more than 0.54 OD, respectively) for all 15 sufferers with viable HIT recognized with inside the potential studies, the sensitivity of every assay for HIT turned into high (100%). However, due to the fact the antigen assay turned into much more likely to be advantageous in sufferers in whom HIT did now no longer develop, the activation assay had advanced working characteristics (i.e., more diagnostic specificity) over all values of the diagnostic cutoff among advantageous and bad tests. For cardiac sufferers, the corresponding specificities had been most effective 81% and 51% use viable HIT advanced in fewer cardiac surgical procedure sufferers, despite the fact that HIT-IgG antibodies fashioned in greater.

V. DISCUSSION

For these reasons, we performed activation and antigen assays on blood samples from 744 patients prospectively evaluated for HIT and who were treated with UFH or LMWH after cardiac or orthopedic surgery. The highest frequency of HIT-IgG formation occurred after cardiac surgery: 50% of these patients had antibodies in the antigen assay and 20% had antibodies in the activation assay. In contrast, only 14.1% and 9.3% of patients received UFH after respectively, HIT-IgG has been detected in orthopedic surgery by antigen and activation assay. Activation assay (SRA, serotonin release assay, thick antibody-induced platelet activation in a heparin-dependent manner, 11-13 and the other recognizes HIT-IgG recognizing immobilized platelet factor 4: heparin antigen.4- 7,14,15 For example, is not known explain why HIT incidence differs among patients in prospective studies.8,9 Explanations include differences in the risk of formation and clinical effects posed by HIT-IgG antibodies, which depend on the patient population

For these reasons, we performed both activation and antigen assays on blood samples from 744 patients prospectively evaluated for HIT and who were treated with UFH or LMWH after cardiac or orthopedic surgery. The results of this study indicate a patient population dependent dissociation between the risk of HIT IgG development and the risk of HIT in patients in whom antibodies have developed. detected by activation assay. Instead only 14.

HIT-IgG was detected by antigen and activation assay in 1% and 9.3% of patients who received UFH after orthopedic surgery, respectively. Fewer orthopedic patients developed antibodies (7.5% and 3.2%, respectively) when receiving LMWH treatment.

Other investigators have also shown a high frequency of antibody development in cardiac surgery patients without associated thrombocytopenia.24-26 In 2 of these studies24,25 postoperative heparin prophylaxis was not administered, therefore the risk of HIT could have been reduced. Our study was not designed to determine the explanation for patient-population-dependent differences in the frequency and clinical significance of HIT-IgG formation. For both activation and antigen tests, a positive result in orthopedic patients may be more specific for clinical HIT.

Depending on the patient population, there are differences in the risk of HIT-IgG formation and in the thrombocytopenic potential of the antibodies.

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