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ORIGINAL ARTICLE

Heparin-induced thrombocytopenia: is it a graft-threatening complication?

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Summary

Heparin-induced thrombocytopenia (HIT), a prothrombotic complication of heparin therapy, can lead to serious thromboembolic events and cause significant morbidity and mortality. We aim to study the prevalence of HIT in the transplant population at our institute. This is a retrospective, single-center study which looked into the transplant database over a 25-year period. In patients with clinical suspicion of HIT, the 4T score was used, and laboratory tests such as ELISA HIT antibody and functional serotonin release assay, along with clinical manifestation of thromboembolic events were reviewed. Medical records of 2800 patients who underwent transplantation from January 1985 to December 2010 were reviewed. HIT antibody assay was performed in 262 patients from this group in which HIT was suspected. Of these, only 48 patients were HIT antibody positive along with moderate to high 4T score. The mean 4T score was 6.75 $\pm$ 1.4. Thrombotic complications were seen in 11 patients, with the highest in cardiac transplant recipients. Direct thrombin inhibitor (DTI) therapy was used in only eight patients who had thrombotic event. No other complications or mortality was reported in any of the HIT antibody-positive transplant patients. To our knowledge, this is the first study of its kind that has shown very low incidence of HIT in the transplant population except for in cardiac transplant recipients.

Introduction

Heparin-induced thrombocytopenia (HIT) is a well-recognized, prothromboticcomplication of heparin therapy [1,2]. Two types have been well described in the literature. Type I is an asymptomatic, transient, nonimmune-mediated reaction, which causes a mild degree of thrombocytopenia and spontaneously resolves even with the continuation of heparin therapy. It is not associated with any significant thrombosis or bleeding events. In contrast, Type II is a serious, immune-mediated condition, which causes significant morbidity and mortality. It results from the antibody formation provoked by the heparin and platelet factor-4 complex, causing platelet activation and leading to thrombin generation and eventual thrombosis or bleeding [3].

Early recognition and prompt discontinuation of any type of heparin product is recommended in situations where there is a high clinical suspicion of HIT [4]. To aid in the diagnosis, a 4T scoring system was developed to risk stratify patients who have an unexplained drop in the platelet count or any kind of thromboembolic events after heparin administration [5]. The 4T score includes thrombocytopenia, timing of platelet count fall, thrombosis and the absence of other causes of thrombocytopenia. Treatment includes cessation of all form of heparin and use of alternate forms of anticoagulants, such as lepirudin, bivalirudin, argatroban, fondaparinux, or danaparoid [6].

The incidence of HIT is studied in several different patient populations. It was found to be more prevalent in the surgical population, with the highest risk being in the neurosurgery, orthopedic surgery, and cardiac surgery patients [7–9]. Unprecedented use of heparin in hospitalized patients waiting to undergo transplant, at the time of the procedure and during the postoperative course is very common. Several small studies have reported the prevalence of HIT in specific transplant population. In a study

on liver transplant recipients by Huser *etal.* [10], the prevalence of HIT-antibody positive was found to be 30% when compared with 39% in a similar study carried out on cardiac transplant recipients [11]. However, its occurrence in the transplant community as a whole in a large cohort has not been reported.

Methods

This is a retrospective, cohort, single-center study carried out at Henry Ford Hospital (HFH), Detroit, Michigan, which is a tertiary teaching hospital. HFH is one of the largest transplant centers in the state of Michigan and is certified by the American Board of Transplantation to carry out multiorgan transplant.

Sample

A total of 2800 consecutive patients who have undergone various types of organ transplant during the years of 1985–2010 were identified from the hospital's administrative database using ICD-9 codes. The types of transplant included in the study were heart, lung, liver, kidney, pancreas, and bone marrow.

Inclusion criteria

A careful review of the patients' medical record was carried out to authenticate the type of transplant and history of heparin administration at some point before transplant. Those with incomplete medical records, diagnosis of HIT 1 year before transplant, and poor follow up were excluded from the study.

Outcomes

The primary outcome was the incidence of HIT in each transplant category. In patients with clinical suspicion of HIT, a pretest probability was calculated using the 4T scoring system (Table 1). The results were graded as low risk (0–3), intermediate risk (4–5), or high risk (6–8). Results of the laboratory test, such as the enzyme-linked immunosorbent assay (ELISA) HIT antibody test (detects IgG, IgM, and IgA antibodies against the PF4-heparin complex) and the functional serotonin release assay (SRA) test along with clinical manifestation of skin necrosis or thromboembolic events (both arterial and venous thrombosis), were reviewed. The 90 days mortality after transplantation related to HIT was also investigated.

Operational definition

Heparin-induced thrombocytopenia positivity was considered in those patients who had intermediate to high 4T score and were HIT antibody positive. HIT antibody positive patients with low 4T score were excluded from the final analysis.

Table 1. 4T scoring system.

4Ts		Score
1. Thrombocytopenia	(a) Fall in platelet count <30% from the baseline	0
	(b) Fall in platelet count 30–50% from the baseline	1
	(c) Fall in platelet count >50% from the baseline	2
2. Timing in platelet count fall	(a) Fall in platelet count <4 days with no previous heparin exposure	0
	(b) Fall in platelet count >10 days or fall $\leq$1 day with a history of prior heparin exposure between 30 and 100 days	1
	(c) Fall in platelet count between 5 and 10 days or fall $\leq$1 day with a history of prior heparin exposure <30 days	2
3. Thrombosis or other complications	(a) None	0
	(b) Suspected or recurrent thrombosis, erythematous skin lesion after initiation of heparin	1
	(c) Confirmed onset of new thrombosis, skin necrosis after initiation of heparin	2
4. Other causes of thrombocytopenia	(a) Definite causes	0
	(b) Possible causes	1
	(c) None	2

Statistical analysis

Categorical variables were expressed in absolute values and percentages, whereas the continuous variables expressed as mean $\pm$ standard deviation. Statistical analysis was carried out using the PASW v18 (Cary, NC, USA). The study protocol was approved by the Institutional Review Board of Henry Ford Health System.

Results

Between January 1985 to December 2010, 2800 patients underwent various types of transplant, among which 2587 patients met the inclusion criteria. Flow diagram of the study is provided (Fig. 1). Baseline characteristics of the transplant population are illustrated in (Table 2). Among the different types of transplant, kidney transplant accounted for the highest patient group (42%), followed by liver (34%), and then bone marrow (12%). The majority of

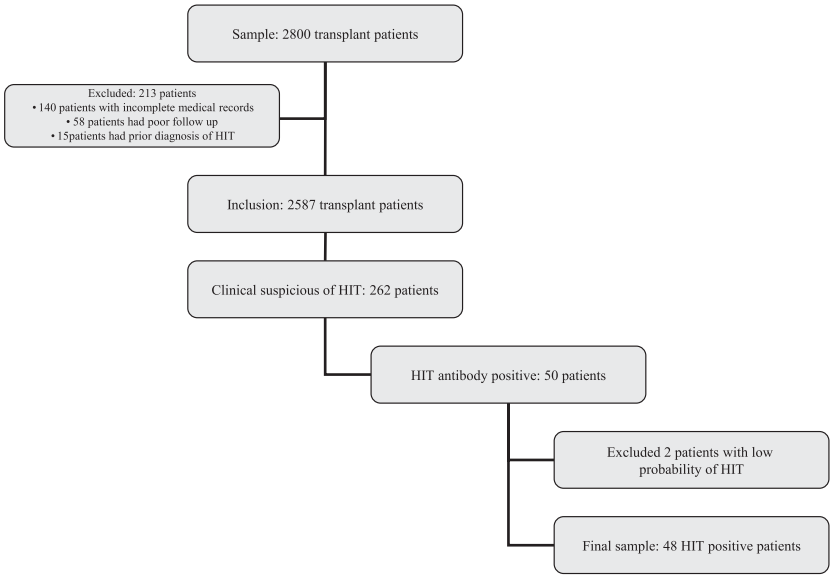

Figure 1 Flow diagram of the study population.

Table 2. Baseline characteristics of the transplant population.

	HIT-II-positive (n = 48)	HIT-II-negative (n = 2539)
Age (years ± SD)	57 ± 11 years	59 ± 7 years
Males, *n* (%)	34 (71)	1622 (64)
Caucasian, *n* (%)	38 (80)	1701 (67)
Type of transplant, *n* (%)		
Kidney (1068)	8 (0.75)	1060 (99.25)
Lung (107)	6 (5.6)	101 (94.3)
Liver (880)	11 (1.25)	869 (99.75)
Heart (165)	22 (13.3)	143 (86.6)
Bone marrow (305)	1 (0.3)	304 (99.67)
Pancreas (62)	0	62 (100)
Thrombosis caused by HIT, *n* (%)	11 (23)	–
90 days mortality, *n* (%)	2 (4)	56 (2.2)

the patients were male (1620, 63%). Unfractionated heparin (UFH) was the major form of heparin in our institute and was used in all the transplant patients at some point of time both before and after transplantation. In 53 (2%) cases, apart from the unfractionated form, low molecular weight heparin (LMWH) was also used.

Incidence of HIT antibody positive

Among the 2587 patients included in the study, HIT was clinically suspected in 262 (10%) patients. HIT ELISA antibody assay was performed in all the clinical suspected cases, of which 50 (1.9%) were positive. Of these, two patients had low 4T score and were thus considered as HIT-negative. Mean age was 57 ± 11 years and 71% were male patients. Baseline characteristics of the HIT-positive patients are illustrated in Table 2. The patients were predominantly Caucasian male. HIT antibody was positive in five patients before transplant and 43 patients after transplant. The initial indication for performing the test was an unexplained thrombocytopenia in all patients. A hematology consult was pursued prior to ordering the test in only eight (3%) of the cases. The mean 4T score was 6.75 ± 1.4. Median time to platelet fall is 8 (IQR: 7–9.25) days. Figure 2 demonstrates the drop in the platelet count over time.

Among the five patients who were HIT antibody positive within 5 months prior to transplantation, four patients were cardiac transplant recipients and were implanted using left ventricular assist device (LVAD) as a bridge to transplant. They either were on or had a history of UFH use. The remaining one patient was liver transplant recipient and received UFH for treatment of DVT in the past.

Occurrence of the thromboembolic events

Out of 262 patients with unexplained thrombocytopenia, 48/262 (18%) patients who were HIT antibody positive and had intermediate to high 4T score were included in the final analysis. Thrombosis was seen in 11 (23%) patients, with the highest occurrence seen in cardiac transplant population, four (8%). No thrombotic event was observed in patients with low 4T scores. Cases of venous thromboembolism included six cases of deep vein thrombosis, followed by five cases of pulmonary embolism and one each of

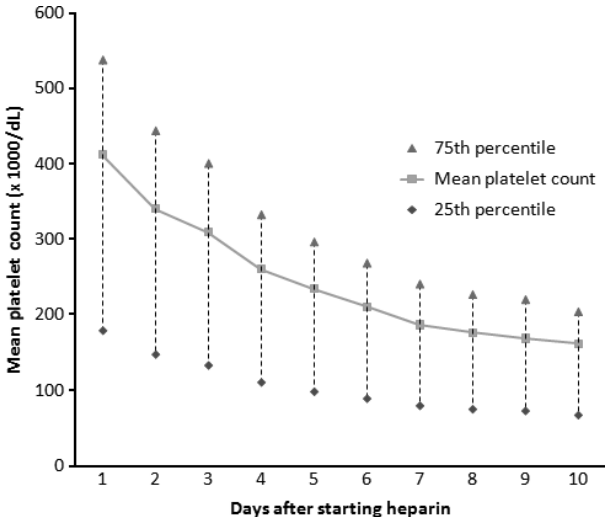

Figure 2 Time trend for drop in platelet count.

portal vein and splenic vein thrombosis. In four cases, simultaneous occurrence of deep vein thrombosis and pulmonary embolism was noted. Only two cases of arterial thrombosis (one case of left anterior descending artery occlusion causing a myocardial infarction and one case of left renal artery occlusion) were seen. None of the HIT antibody positive patients had any skin manifestations. SRA was performed in 14/48 (29%) of the patients with HIT antibody positive and 11/14 (78%) were positive. Baseline characteristics of the SRA-positive patients are described in Table 3.

Treatment

In all the HIT antibody positive patients, heparin was immediately discontinued. In some of the cases where there was an unexplained fall in platelet count and a high clinical suspicion of HIT, heparin was discontinued even before the test results of ELISA were available. Argatroban was used in 35/48 (73%) HIT antibody positive patients and in the remaining 13/48 (27%) with underlying liver dysfunction or abnormal liver function test lepirudin was used. Also among patients who suffered from thrombosis resulting from HIT, argatroban was initiated in six of the 11 patients and two patients with liver transplant received lepirudin. Two of the patients with DVT had inferior vena cava filters placed. The cardiac transplant patient with a coronary artery occlusion had a drug eluding stent placed. One of the liver transplant patients with splenic vein thrombosis received no intervention. There were no further events of thrombosis within 1 year post-transplant in patients that were treated with these medications. None of the patients on direct thrombin inhibitor had any complication from the therapy.

Table 3. Baseline characteristics of the SRA-positive patients.

Baseline characteristics	SRA-positive (n = 11)	SRA-negative (n = 3)
Age (years ± SD)	54 ± 11 years	56 ± 8 years
Males, *n* (%)	6 (54)	3 (100)
Caucasian, *n* (%)	7 (63)	3 (100)
Type of transplant, *n* (%)		
Kidney	3 (27)	1 (33)
Lung	1 (9)	0
Liver	1 (9)	1 (33)
Heart	6 (54)	1 (33)
Median time to platelet fall	7 days	8 days
Mean 4T score (±SD)	6.15 ± 1.4	5.85 ± 1.8
Thrombosis, *n* (%)	4 (36)	1 (33)
90 day mortality, *n* (%)	1 (9)	0

SRA, serotonin release assay test; SD, standard deviation.

Mortality

Out of the 48 HIT antibody positive patients, 90 days mortality was seen in two (4%) patients after transplantation. Both of them died because of sepsis related complications. There were no deaths reported because of HIT directly or indirectly.

Discussion

Heparin-induced thrombocytopenia occurrence in the general population is estimated to be around 1–3%, mostly attributable to unprecedented use of UFH in the hospital setting [12]. It is generally suspected in cases of unexplained acute thrombocytopenia; generally more than 50% fall in absolute platelet count from the baseline, in a patient that has been on heparin for 5–15 days. It is considered a clinicopathological diagnosis and has to be suspected in the right context. Thrombosis without thrombocytopenia or thrombocytopenia without positive HIT antibody test decreases the likelihood of HIT. The 4T scoring system aids in the clinical diagnosis of HIT [5]. Laboratory diagnosis is accomplished by detecting antibodies against the PF4-heparin complex using ELISA; this test has a high sensitivity but low specificity [13]. The gold standard test for diagnosing HIT is 14C-SRA test, which has both a high sensitivity and specificity; however, this test is not often used because of its high cost [14]. Once the diagnosis of HIT is made, or even merely in conditions of high clinical suspicion of HIT, the ACCP guidelines strongly recommend discontinuation of all forms of heparin and use of direct thrombin inhibitors instead [15].

In this study, the overall incidence of positive HIT antibody was 1.9%, which is similar to the occurrence in the general population, but low in comparison with the non-transplant surgical population. It should be noted that pre-

vious studies have shown that HIT is more common in female patients; however, our study population comprised predominantly of male patients, which was about 63% of the cohort [16]. This could underestimate the true incidence of HIT in transplant patients. Another possible explanation of this low incidence is center's implementation of strict screening criteria for HIT. Cuker in his article has rightly argued that HIT is being over-diagnosed and it is mostly because of the poor specificity of the ELISA test and the 4T scoring system [17].

Thrombosis was found in 23% of the HIT antibody positive patients in our transplant population. This is high in comparison to other studies. In a study of patients undergoing cardiac surgery, 25–50% of them tested positive for HIT antibody, but only 2.4% actually developed HIT [18]. Similarly, in a study of orthopedic patients, only 3% of the 15% HIT antibody positive patients developed HIT-Type II [9]. This again strengthens our argument that HIT is overdiagnosed. The high incidence of thrombosis among the HIT antibody positive patients in our population was owing to the fact that only patients with very high clinical suspicious and high probability of having HIT were screened for.

About two-thirds of the thrombotic complications were venous thrombosis, of which deep vein thrombosis accounted for six cases, followed by five cases of pulmonary embolism. Only two cases of arterial thrombosis were noted. All these cases were again reviewed to confirm that there received at least one dose of UFH. This increased incidence of venous thrombosis is consistent with previous studies [19,20].

Also, it should be noted that almost all the transplant patients in our study were exposed to UFH at some point of time, either before or after transplantation. It is mostly owing to the fact that UFH has shorter half-life and easy reversibility in cases of complications arising during procedures in the transplant population. However, LMWH as largely replaced UFH at most of the centers across the globe as the first line therapy. A recent published study in Cochrane database has shown that there is a lower incidence of HIT in postoperative patients undergoing venous thromboembolism prophylaxis prophylaxis with LMWH when compared to UFH [21].

The largest number of thrombosis was reported in the cardiac transplant patients, the least number in bone marrow transplant and no cases were seen in pancreatic transplant patients. Bone marrow transplant patients suffered from thrombocytopenia because of the conditioning phase where the host existing bone marrow is destroyed and replaced with stem cells. This could possibly explain why the incidence of HIT was 0.3% in this subgroup. In pancreatic transplant patients, no complications occurred. We attempted to review the literature regarding the presence of any possible theory, but could not find one. The only plausible theory we have, is the very low number of pancreatic transplant patients compared with other types of transplant in our cohort.

On the other hand, in the cardiac transplant patients, the incidence of HIT antibody positivity was close to 13% and thrombotic events were 2.4%; this is significantly higher than the general population. However, this number is smaller compared with the incidence rate of 24% and thrombotic events rate of 11% noted in a previously reported study carried out in orthotropic cardiac transplant population [11]. This discrepancy can be possibly explained by the different dosages and duration of UFH as well as the different number of exposures to UFH. In both the studies, it was difficult to obtain these values from retrospective chart review. Also, another possible explanation could be because of a smaller sample size of 46 patients in their study, compared with165 patients in our cohort. Still, in both studies, the incidence rate is at least three folds than that of the general population. This is owing to the fact that cardiac transplant recipients are exposed to large quantities of heparin in cases of acute coronary syndrome, use of support devices like intra-aortic balloon pump and even during cardiopulmonary bypass. Patients with a history of atrial fibrillation and those with high CHADS-2 score need heparin to be bridged to warfarin for stroke prevention.

Patients on LVAD have a higher incidence of HIT as seen in a previous studies were the incidence rate was as high as 26% [22,23]. This increased rate is owing to the fact that implantation and maintenance of LVAD require high doses of heparin anticoagulation therapy. Fortunately, none of these patients experienced thrombotic complications prior to transplant; this could simply be owing to the fact that they were anticoagulated.

In all the patients with suspected or diagnosed HIT, heparin therapy was immediately discontinued. Only in HIT antibody positive patients and those with thrombosis was the use of direct thrombin inhibitor reviewed. Eight of the eleven patients who suffered from thrombotic events received the alternate form of anticoagulation. Six of them were started on argatroban and two of the liver transplant patients received lepirudin. Also, it was decided never to restart the patients on any form of heparin therapy, with the possible exception of life-threatening conditions.

Limitations of the study lie mostly in the retrospective design and hence high likelihood of documentation error. It was difficult to obtain the doses, and duration of heparin therapy from the chart reviews because most of them had multiple hospitalizations and/or were transferred from outside facilities. Only 10% of the transplant population was tested for HIT antibody; hence, many of the possible HIT cases could have been missed leading to underestimation of the true incidence of HIT. Also, this was a single-center

study experience and hence it is difficult to generalize the results to the general transplant population.

In conclusion, this is the first largest observational study which looked into the incidence of HIT in transplant population. We believe that the transplant patients, with the exception of cardiac transplant recipients, can safely undergo any type of organ transplant, without having an increased incidence of peri- or postoperative complications or immediate mortality related to HIT as compared with patients undergoing other types of surgery. The increased incidence of HIT in cardiac transplant patients is most likely because of recurrent exposure to high amounts of UFH. We do not recommend routine screening of HIT antibody in this specific population as a result of increase in false-positive results, which lead to unnecessary changes in the anticoagulant therapy. However, until prospective, multicenter trials are completed, it is difficult to predict the true incidence of HIT in the transplant population.

Authorship

SH, WQ, SA, PK: designed the study, analyzed the results, and prepared the manuscript. AB, DK, CM: provided additional help with data collection. ZA: helped to edit the paper and write the discussion.

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