Heparin-Induced Thrombocytopenia and Cardiac Surgery

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Heparin-induced thrombocytopenia (HIT) is an immune-mediated condition characterized by thrombocytopenia with possible arterial and/or venous thrombosis. The overall incidence of HIT is low but ranges from 0.1% to 5%.[1,2] The incidence can be as high as 3% in patients undergoing cardiac surgery. The use of unfractionated heparin (UFH) is ubiquitous in patients who undergo cardiac procedures and carries a 10-fold higher incidence of HIT over low molecular weight heparin. Patients undergoing cardiac surgery thus form a unique group that warrants specific attention to this clinicopathologic entity considering the relatively high incidence and associated morbidity and mortality with a delay in diagnosis. In this article, we will discuss 5 clinical aspects pertinent to the diagnosis and management of HIT in cardiac surgery patients and review the current literature.

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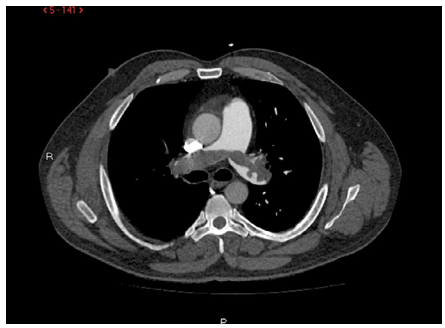
I. INCIDENCE AND OUTCOMES ASSOCIATED WITH THE DEVELOPMENT OF HIT IN PATIENTS WHO UNDERGO CARDIAC SURGERY

Central Message

The incidence of HIT in patients with cardiac surgery is about 0.3% and is associated with increased operative and postoperative complications. The development of HIT in this patient population results in up to 50% increase in mortality.



Saddle Pulmonary Embolism after Cardiac Surgery.

DISCUSSION

Seigerman et al in their multicenter, retrospective analysis of the National Inpatient Sample looked at the impact of heparin-induced thrombocytopenia (HIT) on postcardiac surgery outcomes.[3] Between 2009 and 2010, 186,771 patients in the Nationwide Inpatient Sample registry underwent cardiac surgery. Thrombocytopenia was identified in 17,315 patients (9.2%) undergoing cardiac surgery where 506 patients (0.3%) were diagnosed with HIT, and 16,809 patients (8.7%) with secondary thrombocytopenia. Female gender, renal failure, liver disease, congestive heart failure, atrial fibrillation, and cardiac insufficiency were independent predictors to the development of HIT in cardiac surgery patients. Operative mortality in patients with HIT was higher (11.1%) compared to patients with secondary thrombocytopenia (4.5%) or without thrombocytopenia (4%; Table 1). Stroke, amputation, acute renal failure, respiratory failure, and need for tracheostomy were significant adverse postoperative outcomes in patients with HIT. The presence of HIT was associated with a 50% increase in the perioperative mortality.

This study demonstrates the high morbidity and mortality associated with HIT post cardiac surgery.[3] Some of the limitations of this study include the lack of data on previous exposure to heparin, the ability to distinguish pre- and postoperative thrombocytopenia and variations in the coding practice. However, it reconfirms the current practice of keeping a low threshold of suspicion for HIT post cardiac surgery. Patients who present with thrombocytopenia or a new thrombotic event within 5–10 days of a cardiac surgery should raise a strong suspicion for HIT. Overall mortality associated with

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Table 1. Comparison of Thrombotic and Nonthrombotic Complications in Patients With HIT Relative to Patients With No Thrombocytopenia and Non-HIT Thrombocytopenia

Outcome	No Thrombocytopenia 169,962 (91%)	2^0 Thrombocytopenia 16,249 (8.7%)	HIT 560 (0.3%)	p Value
Any Complication (%)	10.2	10.4	29.0	<0.001
Mortality (%)	4.5	4.0	11.1	<0.001
Venous embolism (%)	1.3	1.7	6.4	<0.001
Pulmonary embolism (%)	2.3	2.0	4.1	<0.001
Deep venous thrombosis(%)	0.7	0.9	4.9	<0.001
Arterial embolus (%)	0.6	0.6	2.8	<0.001
Hepatic infarction (%)	0.0	0.0	0.2	<0.001
Mesenteric ischemia (%)	0.5	0.6	1.0	<0.001
Renal infarction (%)	0.1	0.1	0.2	0.086
Minor amputation (%)	0.1	0.1	0.3	<0.001
Major amputation (%)	0.0	0.0	0.4	<0.001
Tracheostomy (%)	1.6	2.0	6.6	<0.001
Respiratory failure (%)	17.9	28.3	39.1	<0.001
Acute renal failure (%)	13.4	20.4	36.2	<0.001
Mediastinitis (%)	0.1	0.1	0.6	<0.001
Postoperative stroke (%)	0.9	1.0	2.5	<0.001
Transfusion (%)	26.4	44.1	42.9	<0.001
Charges (thousands $)	139.2 ± 133	170.0 ± 130	261.5 ± 186	<0.001
Length of stay (days)	9.2 ± 11	10.6 ± 8.9	18.0 ± 15	<0.001
Nonroutine discharge (%)	16.8	24.5	32.9	<0.001

NOTE. The p value is provided for univariate comparison of patients without thrombocytopenia, to those with heparin-induced thrombocytopenia.

Abbreviations: HIT, heparin-induced thrombocytopenia.

Permission pending: Reference 3.

HIT is around 20–30%.[4,5] Mortality from HIT in post cardiac surgery was as high as 28% in another 10-year retrospective study.[6] Failure of prompt and early diagnosis often contributes to the morbidity and mortality associated with this condition. Thromboembolic complication, limb loss complication, as well as death, is estimated to be as high as 6.1% per day in this group of patients with undiagnosed HIT.[7]

The development of HIT is commonly noted in surgical patients especially cardiac, vascular particularly when there is a requirement for cardiopulmonary bypass (CPB) with exposure to UFH. The incidence in patients who undergo cardiac surgeries can be as high as 3%, and reports of up to 11% have been noted in patients who undergo cardiac transplantation. Most data are on patients who required coronary artery bypass surgery or valve replacement surgery with CPB. There is no precise epidemiologic data on HIT in other cardiac surgeries or with the use of extracorporeal membrane oxygenation.[8] The incidence of HIT in trauma and orthopedic patients has declined with the increasing use of low molecular weight heparin (LMWH) over UFH for venous thromboembolism prevention. Although thrombocytopenia is characteristic of HIT, patients with HIT have a low risk of bleeding and a high tendency to develop arterial and/or venous thrombosis. Overall, venous thrombotic complications are predominant in HIT with 40–75% of patients developing a thrombotic event.[9] However, in patients who undergo cardiac surgery, arterial thrombotic complications have noted to be 8.5 times more common than venous thrombosis.[10,11] Sites of arteriovenous cannulation are common sites for patients with HIT to develop thrombosis.[12] Deep vein thrombosis of proximal or distal lower extremity veins (44.5%) and pulmonary embolism (23.8%) are relatively more common than thrombosis of other venous sites.[4,13–15] Patients with arterial thrombosis are more likely to develop thrombosis of the upper or lower extremity arteries followed by a thrombotic stroke. Myocardial infarction is rare in patients who develop HIT after cardiac surgery, although thrombosis of the saphenous venous graft has been noted post coronary artery bypass surgery with the development of HIT.[16] Interestingly, this pattern of arterial thrombosis is a paradox to the sites of arterial thrombosis in noncardiac surgeries.[4] HIT post cardiac surgery can be further complicated with a clinical presentation consistent with disseminated intravascular coagulation.[17] Digital ischemia after cardiac surgery can be considered as a clinical sign of HIT after other causes such as complications from the use of vasopressors, hypotension, and peripheral artery disease have been ruled out.[18]

Key Points

- The overall incidence of HIT in patients who undergo cardiac surgery ranges from 0.1% to 3%. The National Inpatient Sample is the largest database of inpatient hospital care in the United States with a sample size of approximately 17,000 patients. The incidence of HIT was 0.3% while 8.7% of the population had other causes for thrombocytopenia.
- Female sex, atrial fibrillation, congestive heart failure, chronic kidney disease, chronic liver disease are patient characteristics strongly associated with the development of HIT.

- The development of HIT post cardiac surgery is associated with higher mortality of up to 11% compared to 4.5% in patients without HIT and 4% without any thrombocytopenia. HIT in post cardiac patients can thus result in more than 50% increase in mortality.
- Postoperative outcomes such as major amputation, acute renal failure, acute respiratory failure, need for tracheostomy, stroke, as well as prolonged hospital course are more common in patients who developed HIT after surgery.
- Arterial thrombosis is more common than venous thrombosis in cardiac patients with HIT.

II. THE UTILITY OF PREOPERATIVE TESTING OF ANTI-HEPARIN-PF4 ANTIBODIES IN PATIENTS WHO UNDERGO CARDIAC SURGERY

Central Message

In patients who undergo cardiac surgery, preoperative formation of anti-PF4/heparin antibodies is common. However, a positive antibody status does not predict the development of postoperative thromboembolic complications.

DISCUSSION

Yusuf et al in a systematic review sought to understand the prognostic significance of the preoperative presence of anti-PF4/heparin antibodies on postoperative outcomes, including thromboembolic events and mortality.[19] A total of 4 prospective and 1 retrospective cohort studies published between 1996 and 2010 that consisted of 2332 patients who underwent cardiac surgery were included in the analysis. These patients were not suspected of having HIT. All patients received preoperative bolus and intraoperative heparin in the form of UFH or LMWH. Five to twenty-two percent of patients had anti-PF4/heparin antibodies preoperatively; when assessed by antibody class 6−7% has IgG, 0−6% with IgA, and 13−18% with IgM anti-PF4 antibodies. There was no relationship between preformed antibodies with thromboembolic complications, myocardial infarction, and stroke in all but one of the studies. Kress et al reported an association between positive antibody status and the development of acute limb ischemia[20] (Table 2). Also, preoperative antibody status was not associated with increased mortality in any of the studies. Interestingly, there was an association between preoperative antibody positivity with nonthrombotic complications such as the requirement for hemodialysis, prolonged mechanical ventilation, gastrointestinal complications, as well as the length of hospital and ICU stay. When further assessed by the antibody subclass, patients with IgM antibodies subclasses were likely to have nonthrombotic complications. It is unclear if this relationship is truly causal, as the strongest association with the development of clinical HIT is in patients who have heparin-PF4 antibodies of the IgG subclass. Moreover, the IgM subclass is not associated with platelet activation and development of HIT.[21]

This systematic review was limited by the lack of an adjusted analysis, randomized trials as well as limitations in the data and outcomes captured in the individual studies. All studies included in this systematic review were cohort studies. The ELISA (enzyme-immunoassay [EIA]) test although sensitive lacks specificity in the diagnosis of HIT. Measurement of the optical density (OD) is a tool to augment the specificity, with some researchers quantifying this test as "weak positive" and a "strongly positive" test based on the values of OD. Values between 0.4 and 1.0 OD often corelate with a weakly positive serotonin release assay (SRA), and values >2.0 OD correlate with a 90% probability of a positive SRA. OD levels as a continuous variable and its association with thromboembolic complications were not looked into by 4 of the 5 trials that went into this systematic review. An OD of 0.5 and higher was considered positive. Selleng's analysis of OD as a continuous variable in Cox regression analysis failed to yield any significant association with postoperative thromboembolic outcomes. Patients with OD of 1 and higher in their preoperative testing had neither an adverse outcome nor a prolonged hospital course. Interestingly, the presence of IgM anti-PF4-heparin antibodies was associated with increased risk of nonthrombotic complications and prolonged hospitalization. Further criticism of this systematic review was the lack of a history of clinical HIT in the patients who had antibodies preoperatively. While the IgG class of antibodies appears to have the strongest association with thromboembolic events in confirmed HIT;[22,23] only 1 of the studies investigated the various subtypes of antibody classes.[24]

In conclusion, the utility of preoperative testing for anti-heparin-PF4 antibodies is limited to 2 groups of patients. The first group would be patients in whom there is a concern for HIT as evidenced by a drop in the platelet count or development of a new thrombotic event with a clear temporal association of heparin administration. The second group would be patients who have a history of HIT and will be undergoing cardiac surgery with plans for intraoperative use of UFH.

Key Points

- Preoperative anti-PF4/heparin antibodies are common in patients undergoing cardiac surgery, likely from the exposure to heparin during procedures such as coronary angiography. The incidence can be as high as 1 in every 5 patients going in for surgery.
- A positive antibody status does not translate to higher mortality or higher incidence of thromboembolic disease. Measurement of antibody titers with OD levels is more informative than the mere positive status.
- There is a statistical trend toward higher nonthrombotic complications in patients with preoperative positive antibody status. However, this does not justify preoperative anti-heparin-PF4 antibody testing in patients without a history of HIT.

Table 2. Clinical Outcomes by Preoperative Antibody Status

Study	Antibody class	Event category	Outcome	Ab+ events n (%)	Ab- events n (%)	P-value	OR/HR	95% CI
Visentin (8)	IgG/A/M	TE events	Thrombosis	0/11 (0)	0/40 (0)	--	--	--
Bauer (2)	IgG/A/M	TE events	Thrombosis	0/21 (0)	2/90 (2)	--	0.84*	--
		Death	Death, unspecified	1/21 (5)	2/90 (2)	--	2.2*	--
Bennett-Guerrero (3)	IgG/A/M	Death/LOS	Death (in-hosp) and/or LOS > 10 days	20/59 (34)	88/407 (22)	0.0284	1.98	1.06–3.62
Kress (9)†	IgG/A/M	TE events	MI	0/59 (0)	1/1054 (0)	>0.2	5.94*	--
			Stroke	4/59 (7)	37/1054 (4)	>0.2	2.00*	--
			Acute Limb Ischemia	3/59 (5)	10/1054 (1)	0.03	4.9	1.2–20.2
		Non-TE events	Renal/Dialysis	12/59 (20)	111/1054 (11)	0.03	2.2	1.1–4.3
			Ventilator > 96h	12/59 (20)	97/1054 (9)	0.02	1.9	0.92–4.1
			GI Complications	9/59 (15)	62/1054 (6)	0.01	2.9	1.3–6.6
		LOS	Post-op LOS	14.0 days	9.8 days	0.05	--	--
			ICU LOS	188.8 hrs	101.2 hrs	0.08	--	--
		Death	Mortality (in-hosp)	3/59 (5)	42/1054 (4)	>0.2	1.29*	--
Selleng (4)	IgG/A/M	TE events		5/128 (4)	25/463 (5)	--	0.72**	0.28–1.89
		Non-TE events		38/128 (30)	115/463 (25)	--	1.29**	0.90–1.87
		LOS		15.5 days	15.1 days	0.70	--	--
		Death, 30 days		3/128 (2)	17/463 (4)	--	0.64**	0.18–2.22
	IgG	TE Events		3/44 (7)	27/547 (5)	--	1.39**	0.42–4.60
		Non-TE Events		11/44 (25)	142/547 (26)	--	0.90**	0.49–1.64
		LOS		15.9 days	15.2 days	0.95	--	--
		Death, 30 days		3/44 (7)	17/547 (3)	--	1.49**	0.41–5.44
	IgA	TE complications		0/36 (0)	30/555 (5)	--	0.03**	0.00–2.27
		Non-TE complications		8/36 (2)	145/555 (26)	--	0.76**	0.36–1.64
		LOS		15.3 days	14.7 days	0.84	--	--
		Death, 30 days		1/36 (2)	19/555 (3)	--	0.91**	0.12–6.79
	IgM	TE complications		3/79 (4)	27/512 (5)	--	0.76**	0.23–2.50
		Non-TE complications		30/79 (38)	123/512 (24)	--	1.73**	1.15–2.61
		LOS		16.4 days	15.1 days	0.021	--	--
		Death, 30 days		0/79 (0)	20/512 (4)	0.09	--	--

Classification of Event Categories: 1) TE (Thromboembolic) Events: stroke, myocardial infarction, peripheral arterial thrombosis/embolism, deep vein thrombosis, pulmonary embolism. 2) Non-TE (non-thromboembolic) Events: post-operative infections, hemorrhagic/cardiogenic shock, psychosis, respiratory failure, renal failure/complications. Abbreviations: Ab, antibody; CI, Confidence Interval; GI, Gastrointestinal; HR, Hazard Ratio; Ig, Immunoglobin; ICU, Intensive Care Unit; LOS, Length-of-Stay; MI, Myocardial Infarction; OR, Odds Ratio; *, unadjusted/calculated odds ratio; **, hazard ratio. †NOTE: Within the 1114 patients analyzed in the Kress article HIT developed in 36 (3.2%) patients, of which 23 had preoperative anti-PF4/heparin antibodies and postoperative thrombocytopenia, and 13 seroconverted postoperatively with postoperative thrombocytopenia. Outcomes for patients with HIT could not be isolated from non-HIT patients.

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- The 2 groups of patients were preoperative testing for anti-heparin-PF4 antibodies should be considered would be patients in whom there is a preoperative concern for clinical HIT and in patients with previous HIT in who are to undergo cardiac surgery with plans for intraoperative use of heparin.
- The strongest association of anti-heparin-PF4 antibodies and venous thromboembolic events are in those who have positive IgG subclass of antibodies.

III. DIAGNOSIS OF HIT AFTER CARDIAC SURGERY

Central Message

Thrombocytopenia is common after cardiac surgeries requiring CPB. However, a biphasic pattern of thrombocytopenia in patients who required CPB for less than 2 hours, 5 days after their surgery was most consistent with a diagnosis of HIT.

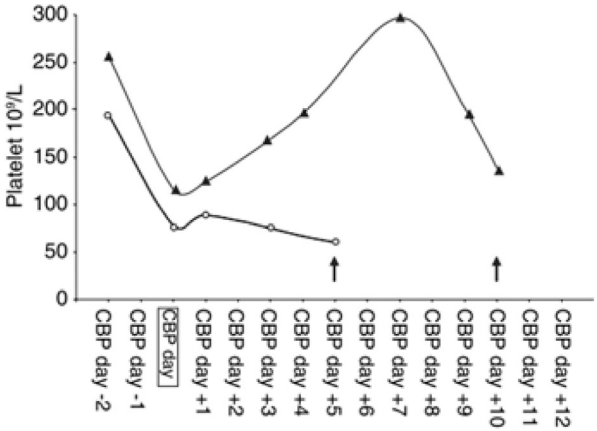

Figure 1. Example of biphasic pattern of thrombocytopenia as described by Lillo-Le Louet et al.
Example of platelet time courses from 2 distinct patients. Representation of one pattern A (biphasic pattern, solid triangles), characterized by a fall in the platelet count more than 4 days after CPB (the initial fall immediately after CPB is followed by a rise within 5 days and then by a further fall) and one pattern B (open circles), characterized by post-CPB thrombocytopenia persisting beyond day 4. Platelet counts are reported until the index date (first day of suspected HIT, arrows).

DISCUSSION

Lillo-le Louet et al in a single-center study evaluated 84 of 4500 patients who required CPB between 1997 and 2001 to assess for HIT and determine specific variables that may be helpful in early diagnosis of HIT after CPB.[25] All 84 patients received perioperative UFH or LMWH and developed thrombocytopenia. HIT was confirmed by the presence of antibodies to platelet factor 4 and heparin complexes (anti-PF4 antibodies), a rising platelet count after discontinuation of heparin with absence of other etiologies to explain the thrombocytopenia. In this group, 35 patients had confirmed HIT, and 49 patients were ruled out for HIT. Anti-PF4-heparin antibodies were positive in 100% of patients with HIT but were present in 26.5% of patients without HIT. SRA was positive in 94% of patients with HIT and negative in 100% of patients without HIT. Patients at risk of developing HIT included those that were on CPB for <2 hours, 5 or more days from CPB to when HIT was initially suspected and had a biphasic platelet count for the same timeframe. Most patients with HIT had a biphasic pattern of thrombocytopenia (Fig. 1). A post-CPB HIT probability score was designed from these variables that accurately identified 34 of the 35 patients with confirmed HIT (97%). These 34 patients had a minimum score of 2 (Fig. 2).

Variables	Score
Platelet count time course	
Pattern A	2
Pattern B	1
Time from CPB to index date	
≥ 5 days	2
< 5 days	0
CPB duration	
≤ 118 min	1
> 118 min	0
	Total score
Classification	
High probability of HIT	≥ 2
Low probability of HIT	< 2

Figure 2. Diagnostic score for HITin patients who undergo CPB.
New diagnostic score for HIT in patients with thrombocytopenia (<150 × 10^9 L^{-1} or fall exceeding 40%) after CPB.
Permission pending: Reference 25.

Twenty-eight of the 49 patients without HIT had scores of 1 or 0 (57%). Overall, this scoring system had a very high negative predictive value of 97% (ie, non-HIT patients with a score of 2 or less; 28/29 patients), and a positive predictive value of 62% (34/55 patients with a score of 2 or higher).

Some of the limitations of this study include the diagnostic criteria for HIT and the retrospective nature of the trial. Patients who had a negative SRA but had improvements in the platelet count with the discontinuation of heparin were included in the HIT arm of the study. Prospective trials with clear diagnostic criteria for HIT will be required to validate the results of this study. However, Lillo-le-Louet et al promptly recognized the need for precise clinical markers to identify HIT in this complex patient population. Their study also shows that the severity of thrombocytopenia did not correlate with prognosis or severity of HIT complications. There are several scoring systems to determine the possibility of HIT, most common of them are the 4—T score[26,27] and the HIT expert probability score.[28] Both these scoring systems unfortunately are not specific for the patients who have been on CPB.

Key Points

- 4—T score and other diagnostic commonly utilized in the diagnosis of HIT do not take into account patients who go through cardiac surgery. These patients are often critically ill and often require CPB that can cause hemodilution and platelet consumption to cause thrombocytopenia.
- Immunologic and functional assays to diagnose HIT are often not available immediately. Hence, recognizing the unique characteristics of HIT in cardiac patients is pivotal in prompt diagnosis.
- The duration of CPB, the pattern of thrombocytopenia, time from CPB to the index date of thrombocytopenia are the 3 most important characteristics to consider in the diagnosis of HIT in postcardiac surgery patients.
- The clinical criterion proposed by Lillo-le Louet et al is specific to patients who go on CPB and can be applied in the postoperative course when HIT is suspected.
- Patients undergoing cardiac surgery are often critically ill and have other reasons such as sepsis, medications, multiorgan failure as the etiology of the thrombocytopenia. A strong clinical suspicion with the available clinical tools is warranted to make the diagnosis of HIT.

IV. SAFETY AND EFFICACY OF BIVALIRUDIN IN THE MANAGEMENT OF HIT IN CARDIAC SURGERY PATIENTS

Central Message

When HIT is suspected, discontinue the use of all heparin-containing products and initiate a nonheparin anticoagulant. Bivalirudin, although not FDA approved for the treatment of HIT, is a safe and rapid-acting nonheparin anticoagulant with a short half-life that can be used in the management of HIT.

DISCUSSION

Joseph et al in a single-center, retrospective study of medical and surgical patients evaluated the efficacy of bivalirudin in patients suspected or confirmed for HIT, or had a past history of HIT.[29] Over a 9-year period between 2002 and 2010, 461 medical and surgical patients were identified who had received bivalirudin for HIT therapy. A total of 124 patients (26.9%) had confirmed HIT, while 75 (16.2%) had a history of HIT. The rest 262 (56.9%) had suspected HIT; the 4−T score was intermediate or high in 235 of the 262 patients in this cohort. Of those with confirmed or suspected HIT, 58% had a thrombus at the time of their HIT diagnosis. Despite therapeutic doses, 4.6% of patients developed a new thrombus on bivalirudin therapy. Patients were treated with bivalirudin for a median of 9 days. Adverse effects included major bleeding, which occurred in 35 of 461 patients (7.6%), but there was a statistically significant risk of major bleeding in the critically ill patients, which made up 23.2% of the population studied. Critically ill patients also had significantly higher 30-day mortality (P = 0.02). None of these patients managed with bivalirudin required HIT-related amputation (Table 3a, b). This study reported a male predominance for

Table 3. Outcomes of the Use of Bivalirudin in the Treatment of HIT

(a) Treatment results and outcomes

Characteristics	All patients (n = 461)	Previous history of HIT (n = 75)	Suspected HIT (n = 262)	Confirmed HIT (n = 124)	P-value for comparison between HIT groups
Bleeding, n (%)	46 (10.0)	10 (13.3)	29 (11.1)	7 (5.6)	0.134
Major bleeding	35 (7.6)	7 (9.3)	22 (8.4)	6 (4.8)	0.386
Fatal bleeding	7 (1.5)	2 (2.7)	5 (1.9)	0 (0)	0.242
Non-major clinically relevant bleeding	11 (2.4)	3 (4.0)	7 (2.7)	1 (0.8)	0.323
New thrombosis, n (%)	21 (4.6)	1 (1.3)	11 (4.2)	9 (7.3)	0.139
Amputation, n (%)	0 (0)	–	0 (0)	0 (0)	–
Transition to warfarin, n (%)	271 (58.8)	38 (50.7)	139 (53.1)	94 (75.8)	0.000
All-cause 30-day mortality, n (%)	67 (14.5)	10 (13.3)	45 (17.2)	12 (9.7)	0.138
Death resulting from HIT-related thrombosis, n (%)	1 (0.2)	–	–	1 (0.8)	–

HIT, heparin-induced thrombocytopenia.

(b) Predictors of the outcomes in patients with confirmed or suspected heparin induced thrombocytopenia treated with bivalirudin

		Major bleeding event		New thrombosis		30-day mortality	
	N	Yes	P	Yes	P	Yes	P
Critical care setting							
Yes	461	14 (13.1)	0.014	4 (3.7)	0.64	23 (21.7)	0.02
No		21 (5.9)		17 (4.8)		44 (12.6)	
Dialysis dependence							
Yes	461	13 (11.9)	0.06	7 (6.4)	0.21	32 (29.9)	0.000
No		19 (6.2)		11 (3.6)		33 (10.9)	
Chronic liver dysfunction							
Yes	461	3 (8.6)	0.82	3 (8.6)	0.24	8 (22.9)	0.16
No		32 (7.5)		18 (4.1)		59 (14.0)	
Platelet count nadir	386	50.6 ± 24.6 (vs. 67.6 ± 44.2 in the no-event group)	0.049	57.8 ± 33.4 (vs. 66.8 ± 43.7 in the no-event group)	0.36	55.7 ± 34.8 (vs. 68.4 ± 44.3 in the no-event group)	0.047

Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as n (%).

Permission pending: Reference 29.

HIT compared to most other studies reporting a female predominance. Interestingly, this study also found identical rates of HIT in medical and surgical patients whereas most of the literature points to a higher risk of HIT in surgical patients. The high rates of overall thromboembolic events discovered in this study could be secondary to the institutional practice at the centers where this study was conducted to aggressively screen for thrombosis in patients suspected to have HIT. Some of the limitations of the study include the retrospective nature of the study; the limited follow-up to 30 days. Also, importantly, only 32% of the population with intermediate to high suspicion received a definitive diagnosis of HIT. Despite these challenges, Joseph et al have the largest series in literature to evaluate the safety and effectiveness of bivalirudin in the management of HIT

Although, we have several nonheparin agents in the treatment of HIT; limited high-quality prospective data exist in comparing these agents. Moreover, these trials are limited by the lack of uniform diagnostic definition of HIT and have a small sample size. Skrupky et al found that patients on bivalirudin in comparison with argatroban had a twice the incidence of new thrombotic events, but had similar bleeding rates.[30] Dang et al in their study of 42 patients found that bivalirudin in comparison to argatroban and lepirudin achieved faster therapeutic anticoagulation. While there were no differences in bleeding rates between bivalirudin and argatroban, the overall cost of bivalirudin was lower than the other 2 agents.[31] Several other retrospective single-center studies have noted similar results.[32,33] In summary, bivalirudin is effective in the management of HIT, with and without thrombosis.

Bivalirudin is gaining popularity in the cardiac surgery literature and has been shown to be a promising alternative to UFH in patients without HIT requiring cardiac surgery in 5 clinical trials, without an increase in mortality or bleeding complications.[34–38] Some of the practical aspects of bivalirudin that warrant attention is the use of ecarin clotting time for intraoperative monitoring while on bivalirudin.[39] Activated clotting time (ACT), activated partial thromboplastin time are a reasonable alternative monitoring lab parameter. However, ACT can be less accurate with higher concentration of bivalirudin. It is critical to avoid pooling and stagnation of blood during CPB while on bivalirudin. The enzymatic metabolism of bivalirudin causes levels to drop in areas where blood stagnation and pooling is resulting in the formation of local thrombi. Surgeons have to be careful in misinterpreting this as insufficient anticoagulation.

Key Points

- Argatroban, bivalirudin, fondaparinux, lepirudin, danaparoid, and desirudin are nonheparin anticoagulants used in the treatment of HIT. Lepirudin was discontinued in 2012, while danaparoid is not available in the United States. Unfortunately, we do not have high-quality prospective head-to-head trials comparing these agents.
- Bivalirudin is a direct thrombin inhibitor used extensively during coronary interventions as well as cardiac surgeries in patients with and without HIT, although not FDA approved exclusively for HIT.
- The CHEST guidelines support the use of bivalirudin over argatroban in patients with HIT who need coronary interventions.
- Bivalirudin has a short half-life of 25 minutes and has enzymatic as well as renal clearance. Due to its moderate elevation of PT/INR compared to argatroban, bivalirudin offers an easier transition to an oral anticoagulant such as warfarin.
- Dose adjustments are required in patients with renal dysfunction. While on bivalirudin the recommended activated partial thromboplastin time is 1.5–2.5 times the patient's baseline and while on CPB the ACT is maintained at 2.5 times the baseline value.

V. INTRAOPERATIVE USE OF HEPARIN IN PATIENTS WITH A PREVIOUS HISTORY OF HIT

Central Message

In patients with a history of HIT, intraoperative use of UFH is safe provided their platelet-activating antibodies are undetectable preoperatively, and an alternate nonheparin anticoagulant is used in the postoperative period. Rechallenging with UFH does not expedite the production of platelet-anti-PF4 antibodies.

DISCUSSION

Heparin-dependent antibodies typically become undetectable anywhere between 50–85 days[9]; this raises the question on the use of UFH if clinically warranted after the antibody titres have become undetectable. The clinical conundrum on the intraoperative use of heparin in patients with previous HIT was evaluated in a single-center study by Warkentin et al.[40] They analyzed 20 patients with a history of HIT and the likelihood of developing recurrent HIT if re-exposed to heparin. Seventeen of the 20 patients were surgical, requiring cardiac, vascular surgeries or required CPB. Prior HIT diagnosis was confirmed based on either a 4–T score ≥4 points and positive platelet SRA or 4–T score ≥4 and positive EIA. On average, 4.4 years had elapsed between the initial diagnosis of HIT and heparin re-exposure. The primary outcome was either positive SRA seroconversion or increase in IgG, IgA, or IgM antibodies. Recurrent HIT was diagnosed based on having a positive EIA-IgG and SRA coinciding with a drop in the platelet count by more than 30% that could not be explained otherwise. Thrombocytopenia that developed prior SRA seroconversion was not attributed to HIT. Eleven of the 17 patients (64%) generated a positive immune response against

Table 4. Summary of Results for Heparin Challenge in Patients With Previous HIT

Anti PF4/heparin antibody responses after heparin re-exposure

Pt	Interval (weeks)	Rechallenge (postoperative antithrombotic therapy)	SRA pre/post	IgG pre/post	IgA pre/post	IgM pre/post	Seroconversion by SRA	Seroconversion by EIA
Reexposure in medical patients of a full anticoagulant course of treatment (n = 3)								
1	703	UFH × 11-day course	NA/–	NA/–	NA/–	NA/–	No	No
2	477	UFH × 17-day course	NA/–	NA/–	NA/–	NA/–	No	No
7	408	LMWH × 10-day course	–/–	+*/+*	–/–	–/–	No	No
Reexposure in surgical patients (post-cardiac/vascular surgery)—intraoperative UFH use only (n = 17)								
3	132	CPB UFH (danaparoid)	–/+++	–/+++	–/++	–/+	Yes	Yes
4	8	Vasc UFH (danaparoid)	–/–	–/–	–/–	–/–	No	No
5	8	CPB UFH (nil)	–/–	–/–	–/–	–/–	No	No
6	307	Vasc UFH (danaparoid)	–/–	–/–	–/–	–/–	No	No
8	180	CPB UFH (danaparoid)	–/+++	–/+++	–/++	–/+	Yes	Yes
9	21	Vasc UFH (clopid/ASA)	–/–	+/+	–/–	–/–	No	No
10	37	CPB UFH (danaparoid)	–/++	+/+++	+/++	–/–	Yes	Yes
11	47	Vasc UFH (clopid/ASA)	–/+++	+*/+++*	–/–	–/–	Yes	Yes*
12	62	Vasc UFH (danaparoid)	–/–	–/–	–/–	–/–	No	Nd
13	22	CPB UFH (danaparoid)	–/–	++/++	–/+*	–/–	No	Yes*
14	22	Vasc UFH (nil)	–/+++	+/+++	–/+++	–/–	Yes	Yes
15	515	CPB UFH (danaparoid)	–/+++	++/+++	–/+	+*/++*	Yes	Yes
16	422	Vasc UFH (danaparoid)	–/+++	+/+++	–/–	–/+	Yes	Yes
17	597	CPB UFH (fondaparinux)	–/+++	–/+++	–/–	–/+*	Yes†	Yes
18a	414	Vasc UFH (fondaparinux)	–/–	–/–	–/–	–/+	No	Yes
18b	+132	Vasc UFH (fondaparinux)	–/–	–/–	–/–	–/+	No	Yes
19	166	CPB UFH (warfarin)	–/–	++/++	–/–	–/–	No	No
20	20	CPB UFH (fondaparinux)	–/–	++/+++	–/+	–/–	No	Yes

*Positive anti-PF4/heparin EIA not inhibited by >30% in the presence of high heparin.
†Patient 17 developed HIT based upon both clinical picture and SRA+ status.
Yes* Any/all EIA seroconversion(s) for that patient were not inhibited >30% by high heparin.
Strength of assay results: EIA: –, negative; +, weak positive (0.40 [or 0.45] to 0.99 OD units), ++, moderate positive (1.00-1.99 OD units); +++, strong positive (≥2.00 OD units). SRA: –, negative (<20% serotonin release); +, weak positive (20.0-49.9% release); ++, moderate positive (50.0-79.9% release); +++, strong positive (≥80% release).
Clopid/ASA, clopidogrel/acetylsalicylic acid (aspirin); CPB, cardiopulmonary bypass; NA, not available; pre/post, test results of blood samples available shortly before heparin reexposure and after heparin reexposure, respectively; Pt, patient; Vasc, vascular surgery.

Permission pending: Reference 40.

PF4-dependent antigens. Nine of the 11 seroconversions were strongly positive with a reading of 2 OD units or higher. Eight of these 9 patients had a concomitant positive SRA. Subsequent antibodies did not develop any faster than the initial rate of development of antibodies with their first episode of HIT, nor any faster than the typical onset of HIT. Despite this high number of patients who had seroconversion, only 1 patient went on to develop clinical HIT in the absence of continued heparin use. This particular patients presentation is unique for what can be described as delayed onset HIT, which is a phenomenon where patients go on to develop clinical HIT despite the lack of a continued exposure to heparin. None of the other patients developed thrombosis or a drop in the platelet count at the time of seroconversion. This study shows that a heparin challenge in patients with prior HIT results in seroconversion no faster than typically seen with HIT and the overall risk of progression to clinical HIT is low. The authors suggest that intraoperative use of heparin is safe in these patients despite their prior history of HIT provided a nonheparin anticoagulant be used in the postoperative period (Table 4). Some of the limitations of this study include the small sample size and limitations of the data to a single center, which limits our ability to generalize this to a larger population. However, this study highlights that short course of heparin is probably safe in patients with a previous history of HIT, provided the use is limited to an intraoperative period, and the patient does not have platelet-activating antibodies.

Heparin is a preferred anticoagulant in cardiac surgery and CPB due to availability of a reversal agent, low cost and high operator familiarity with this drug. However, it is unsafe in patients with patients with previous HIT with detectable antibody titers. Under nonurgent situations, it is prudent to delay cardiac surgeries until the antibody titers become negative. However, in cases where surgery cannot be delayed, commonly used approaches include the use of a nonheparin anticoagulant such as bivalirudin, the use of UFH along with a platelet inhibitor such as iloprost or the use of plasmapheresis.[41] The idea of plasmapheresis is to seroconvert the patient or considerably reduce the antibody titers. If the episode of HIT has been greater than 100 days, intraoperative use of UFH can be justified under urgent circumstances provided all heparin products be avoided in the postoperative period.

Key Points

Patients with prior HIT who present for a cardiac or vascular surgery pose a unique challenge regarding the use of intraoperative and postoperative anticoagulation.

- HIT antibody formation does not reappear any faster in a patient with previous HIT when re-exposed to heparin.
- Intraoperative use of UFH is safe, provided the HIT antibodies are negative preoperatively, and a nonheparin anticoagulant is used in the postoperative phase. Also, it is prudent to avoid any heparin products in the preoperative period to prevent activation of the immune system.
- In patients with previous HIT in whom there is not sufficient time to test the antibody status and need urgent cardiac surgery. UFH could be used intraoperatively if the episode of HIT was more than 100 days ago.

- An alternate nonheparin anticoagulant such as bivalirudin can be initiated, provided the surgeon and the center have the expertise with these alternate agents.
- Intraoperative use of heparin along with a platelet inhibitor such as iloprost or the use of plasmapheresis to attempt seroconversion and to reduce the antibody burden are other options that have anecdotally been tried in managing these complex cases.

CONCLUSION

The preferential use of UFH, the high prevalence of anti-PF4/heparin antibodies, thrombocytopenia, and the lack of robust clinical diagnostic tools often results in a diagnostic and management dilemma of HIT in patients who undergo cardiac surgery. Hence surgeons have to familiarize with unique aspects of the management of HIT in such patients. Despite a reduction in the overall incidence of HIT due to increasing use of LMWH, HIT remains a viable concern in patients undergoing cardiac surgery and is associated with high postoperative complications and mortality.

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