REVIEW ARTICLE

Heparin-Induced Thrombocytopenia

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Hemorrhage is the most common and best-recognized complication of heparin treatment. However, a potentially more dangerous complication is the development of heparin-induced thrombocytopenia (HIT). All patients exposed to heparin, irrespective of the dose and route of administration, are at risk of developing HIT. It is due to the formation of antibodies against the heparin–platelet factor 4 complex, which cause secondary activation of platelets, coagulation and, finally, increased thrombin production. The main symptom is the sudden onset of thrombocytopenia involving a drop in the platelet count to less than 50% of the basal level, with or without the appearance of thrombotic complications some 5 to 14 days after the start of heparin therapy. Heparin-induced thrombocytopenia can be detected early in patients receiving heparin by monitoring the platelet count. Demonstration of heparin-dependent platelet activation using an antigen or functional assay confirms the clinical diagnosis. Once the diagnosis of HIT has been confirmed serologically or there is a high level of suspicion of HIT, heparin must be suspended and treatment with an alternative anticoagulant should be considered. This review contains a discussion of the diagnosis and treatment of this syndrome.

Key words: *Heparin-induced thrombocytopenia. Diagnosis. Treatment.*

Trombocitopenia inducida por heparina

La complicación más común y reconocida del tratamiento con heparina es la hemorragia, pero una complicación potencialmente más peligrosa es el desarrollo de la trombocitopenia inducida por heparina (TIH). Todos los pacientes expuestos a heparina de cualquier tipo y a cualquier dosis están en riesgo de TIH. Se debe a la formación de anticuerpos contra el complejo heparina-factor plaquetario 4, que secundariamente activa las plaquetas y la coagulación y finalmente produce un aumento en la formación de trombina. El síntoma principal es una trombocitopenia brusca, con una caída del 50% en el recuento plaquetario con respecto a los valores basales, y/o complicaciones trombóticas que aparecen 5 a 14 días tras el comienzo del tratamiento con heparina. La monitorización del recuento plaquetario en pacientes que reciben heparina permite el diagnóstico precoz de la TIH. La demostración de la activación plaquetaria dependiente de heparina con métodos antigénicos o funcionales confirma el diagnóstico. Una vez que se confirma serológicamente el diagnóstico de TIH o la sospecha es alta, se debe suspender el tratamiento con heparina y valorar el tratamiento con anticoagulantes alternativos. En esta revisión se discute los aspectos diagnósticos y el manejo de este síndrome.

Palabras clave: *Trombocitopenia inducida por heparina. Diagnóstico. Tratamiento.*

INTRODUCTION

Heparin is currently the most widely used anticoagulant. Although bleeding is the most commonly diagnosed complication associated with the use of any type of heparin, another potentially more serious complication is heparin-induced thrombocytopenia (HIT).

HIT is an autoimmune complication of treatment with heparins. Patients with HIT classically present absolute thrombocytopenia or a relative reduction in the number of platelets that is associated with an increase in the relative (odds ratio [OR], 20-40)[1-5] and absolute frequency (risk of thrombosis, 30%-75%) of thrombosis.[1-7]

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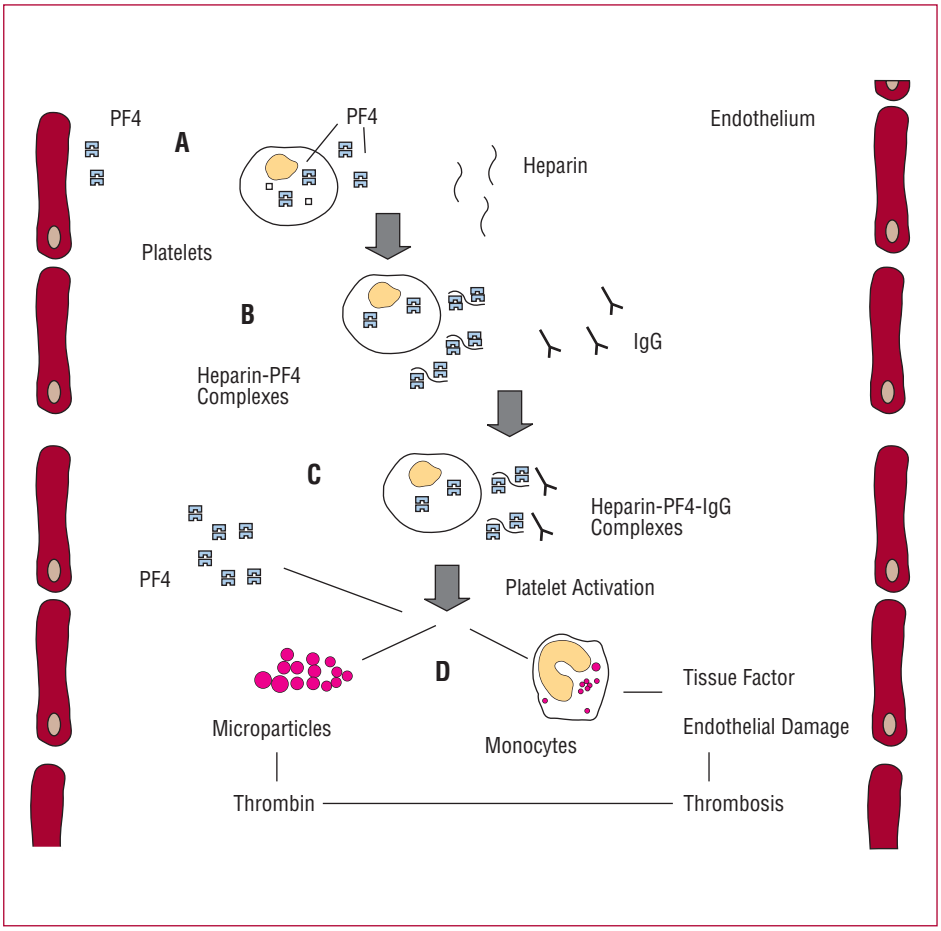

Figure 1. Pathogenesis of heparin-induced thrombocytopenia. A) Platelet factor 4 (PF4) is found in the alpha granules of platelets and on the surface of cells such as platelets and endothelial cells; B) when heparin binds to PF4 a complex is formed and new epitopes that act as immunogens are exposed; C) immunoglobulin (Ig) G antibodies bind to the heparin-PF4 complex; D) platelets are activated and microparticles and PF4 released; the heparin-PF4 complex also interacts with monocytes and causes production of tissue factor and endothelial damage; all these processes promote thrombosis.
IgG indicates immunoglobulin G.

It has been calculated that 1 in every 100 patients who receive unfractionated heparin for at least 5 days develop HIT associated with thrombosis[8]; however, up to 58% of critical patients admitted to hospital present thrombocytopenia not induced by heparin.[9] Consequently, the diagnosis of HIT is not straightforward and requires that other processes be ruled out; this has meant that despite its seriousness, HIT is underdiagnosed.

Given the importance of this complication and the widespread use of heparins, HIT should be suspected in all patients treated with heparin who develop thrombocytopenia with or without thrombosis.

PATHOGENESIS

Heparin has a high affinity for platelet factor 4 (PF4), a positively charged tetrameric protein found in the alpha granules of platelets and on the surface of cells such as endothelial cells and platelets. When heparin binds to PF4 a complex is formed that undergoes a conformational change and exposes new epitopes that act as immunogens.[10]

HIT occurs as a result of the binding of antibodies, typically immunoglobulin (Ig) G, to the heparin-PF4 complex. These anti-heparin–PF4 complex antibodies activate platelets via FcγIIa receptors and cause the release of prothrombotic microparticles, platelet consumption, and thrombocytopenia.[11,12] Platelet activation also leads to the release of PF4 from the granules, thereby perpetuating the cycle of complex formation and platelet activation. The released microparticles increase the production of thrombin, which is responsible for the thrombotic events.[12] The antigen-antibody complex also interacts with monocytes and leads to production of tissue factor and endothelial damage, both of which favor the development of thrombosis[13,14] (Figure 1). It has also been suggested that PF4 itself could neutralize the anticoagulant effects of heparin and promote a prothrombotic state.[15] Thus, all of these processes end paradoxically in the development of thrombosis in patients treated with heparin as an anticoagulant.

However, the appearance of anti-heparin–PF4 antibodies following exposure to heparin is highly variable[10,13,16-18] and predictive models have been described for specific clinical situations.[19] Although anti-heparin–PF4 antibodies are present in almost all patients with a diagnosis of HIT,[20,21] some patients with anti-heparin–PF4 antibodies do not develop HIT.[17] The reason why some patients with antibodies develop HIT and others do not is still not clear.[2,22-24]

TABLE 1. **Scoring System (4 T's) for Patients With Suspected Heparin-Induced Thrombocytopenia**[25,26]

	2 Points	1 Point	0 Points
Thrombocytopenia	Relative reduction >50% or nadir 20-100×10⁹/L	Relative reduction 30%-50% or nadir 10-19×10⁹/L	Relative reduction <30% or nadir <10×10⁹/L
Time between heparin exposure and thrombocytopenia	5-10 d or ≤1 day if exposed to heparin in the last 30 d	>10 d or ≤1 d if exposed to heparin in the last 30-100 d	≤1 d (without recent exposure to heparin) ≤
Thrombosis	Confirmed	Doubtful	No
Other causes of thrombocytopenia	No	Doubtful	Confirmed

The points obtained in each category are added and the pretest probability of heparin-induced thrombocytopenia is obtained as follows: 6-8, high probability; 4-5, intermediate probability; 0-3, low probability.

DEFINITION

HIT is an immune-mediated syndrome diagnosed on the basis of clinical and immunologic variables. The simple appearance of anti-heparin–PF4 antibodies is insufficient to establish a diagnosis of HIT. The typical presentation is that of a patient treated with heparin for at least 5 days who displays thrombocytopenia (relative reduction of ≥50%, even though the total platelet count may be >150×10⁹/L) or thrombosis associated with thrombocytopenia, and in whom other causes of thrombocytopenia have been ruled out and the presence of anti-heparin–PF4 antibodies confirmed.

When there is clinical suspicion of HIT, treatment should be initiated; a scoring system (the 4 T's)[25,26] has been described to establish the probability of HIT prior to testing for the presence of antibodies (Table 1).

INCIDENCE

In general, HIT occurs in between 0.5% and 5% of patients treated with heparin[10]; however, this is variable and essentially depends on the type of heparin used and the clinical presentation (Table 2).

Type of Heparin

HIT has been described in patients treated with all types of heparin and at any dose, including cases of patients with heparin-coated catheters and patients treated with small boluses of 250 units of heparin.[27,28] The incidence of HIT is up to 10 times higher in patients treated with intravenous heparin than in those treated with low-molecular-weight heparin.[29] An increased incidence of HIT has also been described in patients treated with heparin within 100 days of reexposure.[24] In patients treated with unfractionated heparin, a higher incidence of HIT has been reported in those treated with heparin of bovine origin than in those treated with porcine heparin.[1]

Clinical Presentation

The incidence of HIT is particularly high in patients receiving heart transplants (11%)[30] and those undergoing

TABLE 2. **Incidence of Heparin-Induced Thrombocytopenia According to Population Type and Recommendations on the Monitoring of Platelet Count According to the American College of Chest Physicians**[16]

Population Type	Examples	Frequency of Platelet Count
Recent exposure to heparin	Patients who have been treated with heparin in the last 100 days or those in whom it is unknown whether there has been exposure	Baseline and during the first 24 h
Acute systemic reaction	Patients presenting some form of systemic reaction in the first 30 min following administration of unfractionated heparin	Immediate and compared with previous counts
Risk of HIT >1%	Patients treated with unfractionated heparin at therapeutic doses or LMW heparin at antithrombotic doses	Baseline and at least every 2 d for 14 d following exposure or until discontinuation of heparin
Risk of HIT 0.1%-1%	Medical patients or pregnant women treated with unfractionated heparin at prophylactic doses or with LMW heparin following a bolus of unfractionated heparin; surgical patients treated with LMW heparin at prophylactic doses; patients treated with boluses of unfractionated heparin (intravascular catheter)	Baseline and every 2-3 d from day 4 to day 14 following exposure or until discontinuation of heparin
Risk of HIT <0.1%	Patients in treatment with LMW heparin at prophylactic doses	Unnecessary (according to presentation)

HIT indicates heparin-induced thrombocytopenia; LMW, low molecular weight.

orthopedic surgery,[22] and it is generally higher in surgical patients than in those receiving medical treatment.[23] HIT is rare in pediatric[31] and obstetric[32] patients, and in patients receiving hemodialysis.[33]

However, we should remember that despite the large variability in the incidence, patients of any age with any condition and receiving any type of heparin at any dose and via any administration route can develop HIT.

DIAGNOSIS

Presentation

Despite the thrombocytopenia characteristic of HIT, hemorrhage is uncommon; the fundamental clinical finding in HIT is thrombosis.[1,6] In these patients the relative rate of thrombosis (OR=20-40)[1-5] and the absolute rate of thrombosis (risk of thrombosis, 30%-75%)[1-7] are increased significantly. In patients diagnosed with HIT treated only by discontinuation of heparin, the rate of thrombosis is 38%-76%.[6,7,34,35] In patients diagnosed with HIT without thrombosis at the time of diagnosis, the risk of thrombosis in the days following discontinuation of heparin is 19%-52%[6,7,34,35]; this risk persists even when the platelet count returns to normal values.[34-36]

Thromboembolic complications can appear in arteries, veins, or both. Thrombosis in these patients is associated with high morbidity and mortality: up to 9%-11% require leg amputation[37,38] and mortality reaches 8%-20% despite treatment.[37,38] The reason that some patients with HIT develop thrombosis and others do not remains unclear. In cross-sectional studies it has been observed that thrombotic manifestations are correlated with biochemical markers of platelet activation and increased production of thrombin,[39] and in retrospective studies it has been reported that the risk of thrombosis is greater in patients with higher levels of anti-heparin–PF4 antibodies and in those with a relative thrombocytopenia greater than 70%.[40,41]

The following cardiological thrombotic complications have been described: occlusion of venous (not arterial) grafts, venous thrombosis in patients with central catheters, formation of atrial or ventricular thrombi, prosthetic thrombosis, myocardial infarction, and pulmonary embolism.[32,37,42-49] The presence of any of these complications in patients who have received heparin obliges that HIT be ruled out.

Other less common complications of HIT are cutaneous lesions and acute systemic reactions. Up to 20% of patients who develop antibodies display necrotic or erythematous lesions at the injection site of low-molecular-weight heparin.[50] Acute systemic reactions such as tachycardia, fever, rigors, hypertension, dyspnea, or chest pain occur following repeat intravenous administration of heparin in 25% of patients with circulating antibodies.[10]

Thrombocytopenia

Along with clinical suspicion, reduced platelet count is the deciding factor in the diagnosis of HIT in the majority of patients. In HIT, thrombocytopenia usually reaches absolute values of 50-80×10^9/L or reductions of ≥50%, and characteristically returns to normal a week after suspension of treatment with heparin. It is generally recommended to use the relative and not absolute reduction to assess thrombocytopenia.[16]

Thrombocytopenia typically appears 5 to 14 days after beginning treatment with heparin,[16,51] but earlier and later onset has also been described. In patients with anti-heparin–PF4 due to recent exposure to heparin, thrombocytopenia can even develop minutes after reexposure to heparin.[51,52] Thrombocytopenia has also been observed up to 3 weeks after cessation of treatment with heparin.[53,54] Monitoring of the platelet count would be indicated in all patients who receive heparin, but the frequency of the counts will depend on the risk.

Development of thrombocytopenia in patients receiving heparin is not exclusive to HIT and it is therefore necessary to undertake differential diagnosis with other entities (Table 3).

Nonimmune-mediated HIT (sometimes called type I HIT to differentiate it from the immune-mediated form, which was called type II, although this nomenclature is no longer in use) has been described, in which there are no clinical manifestations and in which thrombocytopenia usually appears 1 to 4 days after exposure to heparin, is less marked, and resolves spontaneously following discontinuation of heparin treatment.[10] It has been suggested that direct activation of platelets by heparin would be the mechanism responsible for this type of thrombocytopenia.[55,56]

Of particular importance from a cardiological perspective is the appearance of thrombocytopenia in patients treated with a combination of heparin and glycoprotein IIb/IIIa inhibitors, since both can cause thrombocytopenia, and in patients following heart surgery.

Glycoprotein IIb/IIIa inhibitors cause thrombocytopenia through the destruction of platelets by preformed antibodies against them.[57] In patients treated with glycoprotein IIb/IIIa inhibitors, the rate of moderate thrombocytopenia is 4.2% and of severe thrombocytopenia, 1%.[58] Unlike HIT, if thrombocytopenia has been caused by glycoprotein IIb/IIIa inhibitors, alternative anticoagulant therapy should not be used as it favors bleeding. Thrombocytopenia induced by glycoprotein IIb/IIIa inhibitors appears immediately (minutes to hours) following administration and the nadir tends to be lower (3-5×10^9/L).[57]

In patients who have undergone heart surgery the incidence of HIT is high, especially in transplant patients.[30] The thrombocytopenia associated with HIT in these patients usually appears between 5 and 10 days after surgery and it is recommended that a baseline platelet

TABLE 3. **Differential Diagnosis of Thrombocytopenia**[a]

	Comment
Pseudothrombocytopenia	
Dilution	Hemodilution, transfusion of packed cells, platelet sequestration in hypersplenism
Technical issues	Poor anticoagulation of the sample Subjects with EDTA-dependent pseudothrombocytopenia (see smear)
Reduced production (bone marrow)	
Viral infections	Human immunodeficiency virus, Epstein-Barr virus, rubeola, hepatitis C, etc
Chemotherapy and radiation therapy	
Acquired bone marrow aplasia or hypoplasia	Fanconi anemia
TAR syndrome	
B_{12} or folic acid deficiency	
Direct alcohol toxicity	
Increased platelet destruction	
Immune-mediated	Post-transfusion, neonatal, post-transplant
Infections or inflammation	Cytomegalovirus, infectious mononucleosis
Devices	Balloon pump, catheters, ventricular assist device, ventilators
Drugs	Heparin through a nonimmune-mediated mechanism
	Heparin through an autoimmune mechanism
	Glycoprotein IIb/IIIa inhibitors
	Others: quinine, quinidine, valproic acid
Others: antiphospholipid syndrome, HELLP syndrome, lupus, ITP, TTP, HUS, DIC	

[a]TAR indicates thrombocytopenia and absent radius; HELLP, hemolysis, elevated liver enzymes, and low platelets; ITP, idiopathic thrombocytopenic purpura; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; DIC, disseminated intravascular coagulation.

count be obtained followed by counts on alternate days between postsurgical days 4 and 14.[16] Any thrombotic event following surgery should lead to suspicion of HIT, particularly after postsurgical day 5.[42] The appearance of HIT in the first 4 days following surgery is rare, even in patients who receive heparin prior to surgery[42]; thrombocytopenia in the first few days following surgery should lead to suspicion of hemodilution or platelet consumption.[42]

Thrombocytopenia can also appear in other clinical situations, such as sepsis, disseminated intravascular coagulation, pulmonary thromboembolism, or bone marrow diseases, or in patients with intraaortic balloon pumps, or those undergoing hemofiltration[10,16] (Table 3).

In general, the differential diagnosis should be done based on clinical suspicion at the time of appearance of thrombocytopenia (HIT around day 5-14 following heparin treatment) and on the platelet count (typically around 50-80×10^9/L).

Detection of Antibodies

Systematic testing to detect antibodies in all patients treated with heparin is not recommended, since the sensitivity and specificity to predict the development of HIT is low.[16] Tests for the detection of antibodies should be based on clinical suspicion and should not delay the initiation of appropriate treatment when this is indicated according to the presentation.[59] Tests to detect anti-heparin–PF4 antibodies are recommended in all patients treated with heparin in whom HIT is suspected on the basis of the temporal profile of the reduction in platelet count or the appearance of thrombosis.[59]

Various tests exist for the detection of HIT antibodies, but there is no definitive test with a sensitivity and specificity of 100%. The immunologic methods that detect circulating IgG, IgA, and IgM have a sensitivity close to 97%, at the expense of a low specificity (74%-86%, higher in methods that only detect IgG), especially in patients receiving heart surgery,[21,22,60] leading to a high negative predictive value (>95%). Functional methods such as measurement of platelet aggregation or release of serotonin from activated platelets increase the specificity and positive predictive value (89%-100%)[60] (Table 4).

The use of both detection methods can be complementary; given the high negative predictive value, serologic testing is recommended in cases of intermediate or high suspicion, and if the result is negative, alternative diagnoses should be considered.[21,26] In patients with intermediate suspicion and positive serology, confirmation with a functional test is recommended if available.[60]

Figure 2 shows a proposed diagnostic and treatment algorithm for HIT.

TREATMENT

The objective in treatment of HIT is to reduce platelet activation and thrombin formation to reduce the risk of thrombosis. When there is intermediate or high suspicion of HIT, any form of treatment with heparin should be

TABLE 4. **Laboratory Tests to Detect Anti-Heparin–Platelet Factor 4**[a]

Methods	Technique	Advantages	Disadvantages
Functional			
Serotonin release	Quantification of serotonin released by platelet granules via radiolabeling or chemical detection	Higher sensitivity (>95%)	Requires platelet donors. Radioactive technique. Use restricted to research laboratories
Platelet activation	Direct visualization of platelet aggregation		
Adenosine triphosphate release	Detected through luminescence		
Platelet microparticles	Detection via flow cytometry		Use restricted to research laboratories
Aggregation test	Measurement of platelet aggregation with a conventional aggregometer	Availability	Limited sensitivity and specificity; requires platelet donors
Annexin V binding	Cytometric quantification of annexin V bound to activated platelets		
Immunologic			
PF4/polyanion electroimmunoassay	Detects PF4 polyvinyl sulfate	Availability; high sensitivity	Low specificity
PF4/heparin electroimmunoassay	Detects PF4-heparin-IgG complexes	High sensitivity and better specificity (only detects IgG)	Little availability (research laboratories)

[a]IgG indicates immunoglobulin G. Modified from Napolitano et al.[15]

discontinued, including low-molecular-weight heparin and heparin-coated catheters, and treatment with an alternative anticoagulant should be assessed. This recommendation applies both to patients with thrombotic phenomena and to those in whom HIT has only manifested with thrombocytopenia.[16]

In the absence of an alternative anticoagulant, the daily risk of thrombosis is 5% to 10% in the first few days following discontinuation of heparin treatment and the overall risk reaches 38% to 76% in the first month.[35] Low-molecular-weight heparin should not be considered as an alternative anticoagulant since it exhibits cross-reactivity with anti-heparin–PF4 antibodies.[16] Warfarin or acenocoumarol are also not valid alternatives since, paradoxically, they can worsen the thrombosis and cause gangrene of the extremities and cutaneous necrosis.[16,61,62] If a patient is being treated with warfarin or acenocoumarol when diagnosed with HIT, administration of vitamin K is recommended to reverse the effects of the drug.[16]

Two classes of anticoagulants can be used for the treatment of HIT: direct thrombin inhibitors and heparinoids. Direct thrombin inhibitors act to reduce the activity of thrombin, whereas heparinoids reduce its formation (Table 5).

There are no studies directly comparing the different types of alternative anticoagulants. The choice of an alternative anticoagulant should be based on availability, experience with its use, methods available for monitoring, and the clinical condition of the patient, especially in terms of renal and liver function.

Direct Thrombin Inhibitors

Lepirudin

Lepirudin is a recombinant derivative of hirudin obtained from yeast cells. It is a highly specific direct inhibitor of thrombin that blocks its thrombogenic activity by forming a complex with it. As a consequence, unlike heparin, it leads to direct inhibition of all the effects of both free and clot-bound thrombin.[38]

The anticoagulant effects of lepirudin are monitored with the activated partial thromboplastin time (aPTT), for which it is recommended to maintain concentrations 1.5 to 2.5 times baseline.[38] Lepirudin is eliminated renally. Its levels should be carefully monitored in patients with serum creatinine above 1.6 mg/dL and it should not be used in patients in hemodialysis programs or those with acute renal insufficiency.[63]

Three prospective multicenter studies with similar designs have evaluated the efficacy and safety of lepirudin for the treatment of patients with HIT.[31,47,48] Taken together, the 3 studies included 403 patients and 120 historical controls; patients with HIT and thrombosis received a loading dose of 0.4 mg/kg, followed by perfusion of 0.15 mg/kg/h, and patients with HIT without thrombosis were treated by perfusion at a dose of 0.1 mg/kg/h. The dosage was adjusted to achieve an aPTT 1.5 to 2.5 times the baseline value. The rate of death, amputation, and thrombosis at 35 days was less in patients who received lepirudin than in controls (29.7% and 52.1%, respectively; P=.0473). The rate of hemorrhage was higher in patients treated with lepirudin than in controls (29.4% and 9.1%;

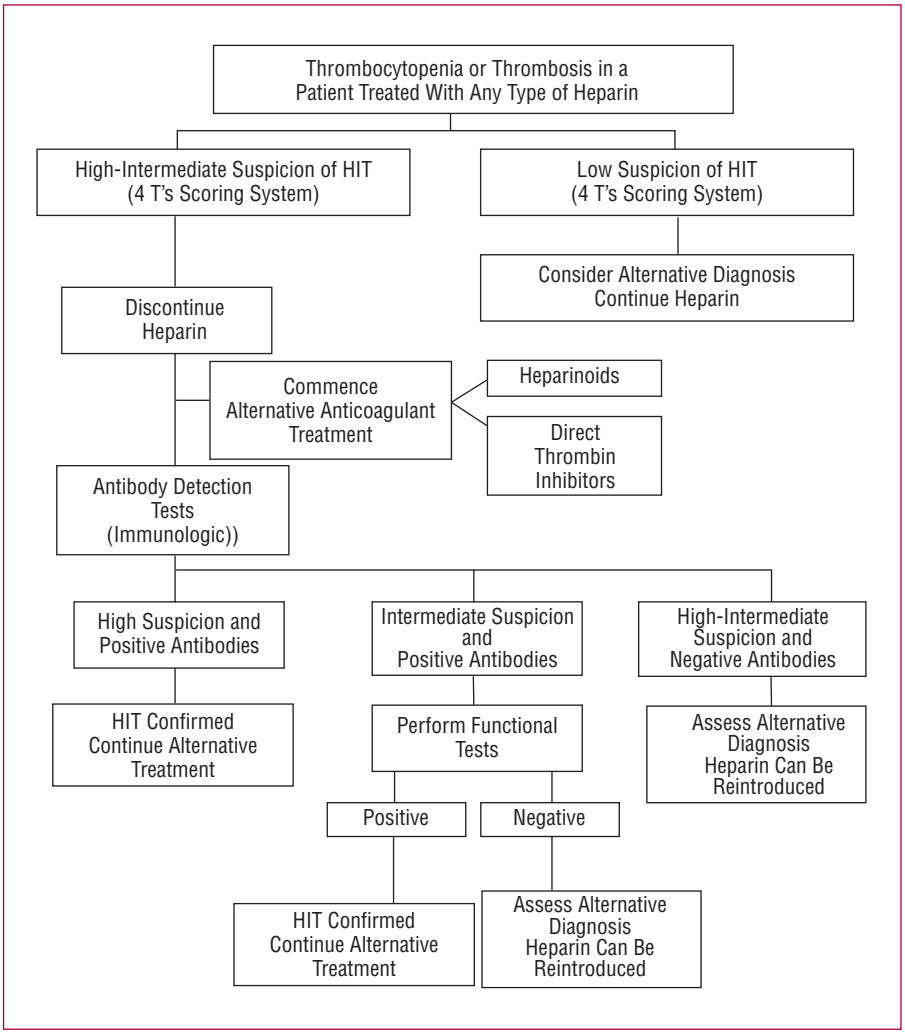

Figure 2. Diagnostic and treatment algorithm for heparin-induced thrombocytopenia (HIT).

P=.0148) and bleeding was the cause of death in 1.2% of patients treated with lepirudin.[38] The rate of hemorrhages observed in these studies has led to a recommendation that the initial dose be reduced to 0.1 mg/kg/h, especially in older patients or patients with renal insufficiency,[31,38] and some authors even recommend initial doses of 0.05-0.075 mg/kg/h.[64]

Antibodies are developed against lepirudin in 30% of patients treated for the first time with the drug, and this rate increases to 70% with reexposure. Fatal anaphylaxis has been described in patients sensitized to lepirudin, and consequently, it is not recommended that the drug be used on more than 1 occasion.[38,42]

Argatroban

Argatroban is a direct thrombin inhibitor derived from arginine that binds reversibly to the active site of thrombin. It does not require antithrombin III as a cofactor to exert its antithrombotic activity, since it acts as an anticoagulant by inhibiting the reactions induced or catalyzed by thrombin: fibrin formation; activation of coagulation factors V, VIII, and XIII; activation of protein C; and platelet aggregation. At therapeutic concentrations, argatroban does not have any effects on other serine proteases involved in blood clotting (trypsin, factor Xa, plasmin, and callicrein), but inhibits the action of free and bound thrombin without interfering with antibodies induced by heparin.[65,66]

Argatroban prolongs the prothrombin time (PT) and the anticoagulant effects of the drug should therefore be monitored through the aPTT.[66] The drug is eliminated by the liver.[66,67]

The efficacy and safety of argatroban was assessed in 2 prospective multicenter studies (Argatroban 911 and Argatroban 915) that included 722 patients with HIT.[34,37] The patients received a dose of argatroban of 3 µg/kg/min, adjusted for an aPTT 1.5 to 3 times the baseline value. In both studies, the results were compared with historical controls. The patients who had HIT without thrombosis treated with argatroban had a lower incidence of the combined event of death, amputation, and new thrombosis at 37 days (25.6% and 28%, compared with 38.8% in the controls; *P*<.04); in patients with HIT and thrombosis

TABLE 5. **Drugs for the Treatment of Heparin-Induced Thrombocytopenia**[a]

Drug	Dosage	Clearance	Monitoring	Comment
Direct thrombin inhibitors				
Lepirudin	Bolus, 0.4 mg/kg; perfusion, 0.15 mg/kg/h (reduce in case of renal insufficiency)	Renal	aPTT (adjust to 1.5-2.5)	Not to be used in case of acute renal insufficiency. Some authors recommend initial doses of 0.1 mg/kg/h[31,38] and 0.05-0.075 mg/kg/h[64]
Argatroban	2 µg/kg/min (maximum 10 µg/kg/min). PCA: 25 µg/kg/min (bolus 350 µg/kg)	Hepatic	aPTT (adjust to 1.5-3). In PCA, adjust ACT to 300-450 s	Can be used repeatedly. Tested in combination with glycoprotein IIb/IIIa inhibitors
Bivalirudin	PCA: bolus, 0.75 mg/kg; infusion, 1.75 mg/kg/h. Following the procedure, infusion at 1.75 mg/kg/h for 4 h or 0.2 mg/kg/h for 20 h.	Enzymatic (80%) and renal (20%)	ACT, aPTT	Experience with PCA
Heparinoids				
Danaparoid	Bolus, 2250 U; infusion, 400 U/h for 4 h, 300 U/h 4 h, and 150-200 U/h 5 days	Renal	Unnecessary. Factor Xa 0.5-0.8 U/mL	
Fondaparinux	2.5 mg/24 h subcutaneously	Renal	Unnecessary. Factor Xa 0.5-0.8 U/mL	Limited experience in HIT

[a]HIT indicates heparin-induced thrombocytopenia; ACT, activated clotting time; PCA, percutaneous coronary angioplasty; aPTT, activated partial thromboplastin time.

the rate of the combined event was 43.8% and 41.5% compared with 56.5% in the controls. The rates of bleeding were similar in the group of patients treated with argatroban and controls (6.9% and 5.7%, compared with 7% in controls).

The development of antibodies against argatroban has not been reported, even in patients subjected to repeated doses of the drug, nor have there been reports of anaphylactic reactions, meaning that the drug can be used repeatedly.[68]

Bivalirudin

Bivalirudin, an analog of hirudin, is a direct selective thrombin inhibitor. It acts as a reversible inhibitor of thrombin, neutralizing its effects, and also inhibits thrombin trapped in clots. It interferes with fibrin formation, platelet aggregation, factor XII activation, and other activities associated with blood clotting. Since it binds reversibly to thrombin, the anticoagulant effects of bivalirudin disappear soon after discontinuation of treatment. Elimination of bivalirudin occurs both renally and enzymatically. Although elimination is reduced by 80% in patients undergoing hemodialysis, it has been used effectively at low doses in patients with combined hepatic and renal insufficiency.[10,69]

Bivalirudin has been accepted for use in patients with suspicion of HIT undergoing angioplasty and its anticoagulant effects are monitored with the activated coagulation time (ACT); although little experience has been gained in the use of the drug in HIT outside of the context of percutaneous interventions, initial data are encouraging.[54,70-72]

Antihirudin antibodies are developed in 51% of patients treated with bivalirudin who previously received lepirudin, indicating cross-reactivity between the 2 thrombin inhibitors.[73]

Bleeding is the most important complication associated with alternative anticoagulant therapy with direct thrombin inhibitors. These drugs do not have a specific antidote. In the event of excessive anticoagulation, with or without associated bleeding, treatment with these drugs must be discontinued. The anticoagulant effects usually disappear in a matter of hours, depending on the half-life of the drug and its elimination pathway. The half-life of argatroban (39-51 minutes) is increased in cases of hepatic insufficiency[67] and the half-lives of lepirudin (1.7 hours) and bivalirudin (36 minutes) increase in cases of renal insufficiency.[37,63] A reduction in the concentration of lepirudin and bivalirudin with hemodialysis or hemofiltration has been described in some cases; however, the characteristics of this

elimination vary according to the filters used[74] and the elimination of argatroban with filtration is insignificant.[67] Little experience has been gained with the use of recombinant factor VIIa with a nonspecific antidote in patients with HIT and severe bleeding, although its usefulness has been suggested.[75,76]

Heparinoids

Danaparoid

Danaparoid is a synthetic mixture of heparan sulfate, dermatan sulfate, and chondroitin sulfate that acts in a similar way to heparin by inhibiting factor Xa. Anticoagulant therapy with danaparoid is monitored with the plasma concentration of antifactor Xa, since it does not affect aPTT or ACT. Danaparoid is renally eliminated.[36]

A clinical trial has been carried out in which patients were randomized to danaparoid plus warfarin or an antithrombotic agent (dextran sulfate) plus warfarin in patients with HIT and found that resolution of the thrombus was greater in patients treated with danaparoid.[36] No direct comparisons have been made with direct thrombin inhibitors, but a retrospective study comparing danaparoid at prophylactic doses with lepirudin at therapeutic doses found no difference in efficacy, although danaparoid was associated with a reduced risk of bleeding.[41]

Data have recently been published on 1418 patients treated with danaparoid for different reasons and at different doses, showing a rate of new thrombosis of 9.7% and a rate of hemorrhage of 8.1%.[36] The rate of cross-reactivity with heparin is around 3.2%.[36]

Fondaparinux

Fondaparinux is a synthetic inhibitor of factor Xa with greater specificity than unfractionated or low-molecular-weight heparin. The antithrombotic activity of fondaparinux is the consequence of selective inhibition of factor Xa by antithrombin III. Fondaparinux does not inactivate thrombin and it does not have any effects on platelets. It has a half-life of 15 hours, thereby allowing administration of a single daily dose. Its effect is reversible on treatment with factor VIIa. At the recommended doses, fondaparinux does not alter the aPTT, ACT, or PT. It is eliminated renally and should not be administered in patients with a creatinine clearance of less than 20 mL/min.[23]

Limited experience has been gained in the treatment of HIT with fondaparinux, but the published results do not show bleeding or thromboembolic events.[77-79] Cases of HIT have not been described in patients treated with fondaparinux, although anti-heparin–PF4 antibodies have been detected.[80] Fondaparinux does not show cross-reactivity with serum from patients with HIT.

OTHER CONSIDERATIONS RELATED TO TREATMENT

– Platelet transfusion should not be used prophylactically in HIT. HIT is an autoimmune phenomenon and an increase in the number of antigens can increase the state of hypercoagulability and cause thrombotic events[16]

– Glycoprotein IIb/IIIa inhibitors do not have a direct anticoagulant effect and do not inhibit activation of platelets by HIT antibodies; consequently, they are not effective for use in isolation in the treatment of HIT. However, the combination of glycoprotein IIb/IIIa inhibitors and alternative anticoagulants has been used effectively in the context of coronary angioplasty and has achieved an indirect reduction in thrombin formation and an inhibition of platelet aggregation,[81,82] indicating that they could be employed as a complementary treatment in selected cases

– Chronic anticoagulation: oral anticoagulation is recommended for at least 3 to 6 months in patients who have presented HIT and thrombosis.[10,13,16] In these cases, or in patients who require chronic anticoagulation for any other reason, the doubt arises as to when to reintroduce treatment with acenocoumarol or warfarin. Suspension of treatment with warfarin or acenocoumarol and reversal of its effects with vitamin K is recommended when there is suspicion of HIT. The patient should be treated with one of the alternative anticoagulants mentioned and treatment reinitiated with warfarin or acenocoumarol once the platelet count has returned to normal levels ($\geq 100\times10^9$/L or preferably 150×10^9/L).[16] Acenocoumarol or warfarin should be reintroduced without a loading dose and should overlap with alternative anticoagulant treatment for at least 5 days.[10,13,16] Patients treated with a direct thrombin inhibitor (bivalirudin, argatroban, or lepirudin) should be closely monitored, since these drugs can prolong PT.[83] During treatment with direct thrombin inhibitors, the relationship between PT and risk of bleeding is altered, and patients treated with these drugs in combination with warfarin often exhibit low PT without bleeding[10]

– Management of patients with a history of HIT. Patients with HIT do not always present HIT again upon reexposure to heparin,[51] although the risk is increased. Therefore, given the potentially serious complications associated with HIT, the use of alternative anticoagulants is recommended wherever possible in these patients[16,51,84]

CONCLUSIONS

HIT is a severe complication of a very common treatment. It is underdiagnosed and should be suspected in all patients treated with heparin who display thrombocytopenia or thrombosis. Other common causes of thrombocytopenia should be ruled out prior to diagnosis of HIT. When there is clinical suspicion of HIT, treatment with heparins should be immediately discontinued and

alternative anticoagulants such as direct thrombin inhibitors or heparinoids evaluated.

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