Heparin-induced thrombocytopenia in the cardiovascular patient: diagnostic and treatment guidelines

Ahmet Tayfun Gurbuz*, William G. Elliott, Ayhan A. Zia

Departments of Cardio-Thoracic Surgery and Cardiology, Tucson Medical Center, Tucson, AZ, USA

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Summary

Heparin-induced thrombocytopenia/thrombosis is an immunologic reaction to unfractionated heparin characterized by thrombocytopenia, platelet activation and thrombosis. A high index of suspicion is required for timely diagnosis and treatment. Treatment is complex and outcome may be less than satisfactory.

Keywords: Heparin; Thrombocytopenia; Thrombosis

1. Introduction

Heparin was introduced into clinical practice by McLean in 1916 [1]. Standard unfractionated heparin (UFH) is a mixture of sulfated mucopolysaccharides with molecular weights between 5000 and 30,000 Da. Heparin inhibits thrombin indirectly by binding to antithrombin III. It only binds to soluble thrombin and does not inhibit fibrin bound thrombin. The need for intravenous administration, close monitoring of coagulation parameters as well as association with several uncommon but serious side effects makes heparin less than an ideal anticoagulant.

The association of thrombocytopenia with heparin administration has been known for several decades. Weisman and Tobin [2] reported arterial embolization with fibrin platelet thrombi in patients on heparin therapy. Roberts postulated that platelet agglutination may be due to a reaction mediated by antibodies to heparin [3]. Rhodes identified the heparin dependent antibody as the cause of heparin-induced thrombocytopenia and thromboembolism [4].

Thrombocytopenia associated with UFH use occurs in two forms [5,6]. Type I thrombocytopenia is associated by reduction in the platelet count during the first 24-72 h of UFH therapy. This reaction occurs through a non-immunologic mechanism [7] and can be observed in as much as 10-20% of patients. Thrombocytopenia is always mild (>100 × 10^9/l), transient and is not associated with significant clinical findings. This abnormality is reversible and cessation of UFH is not required [8]. Type II thrombocytopenia is also known as HAT, HIT/T and white clot syndrome. This type differs from type I by its delayed onset, presence of marked thrombocytopenia (<100 × 10^9/l) and longer duration. Type II thrombocytopenia is an immunologically mediated reaction. It can be isolated to decreased platelet count (heparin-induced thrombocytopenia, HIT) or associated with thromboembolic complications (TEC) (heparin-induced thrombocytopenia thrombosis, HIT/T). The high incidence of subclinical thrombosis in patients presumed isolated HIT demonstrates that HIT and HIT/T represent different manifestations of the same pathological process. Type II heparin-induced thrombocytopenia (HIT/T) can result in life threatening complications and death despite treatment. This review will highlight the pathogenesis, clinical and laboratory manifestations, diagnosis and treatment of type II heparin-induced thrombocytopenia (HIT/T).

1.1. Definition

HIT/T is a clinical-pathological entity and is defined by the presence of three main factors: decreased platelet count, clinical symptoms (if any) and laboratory confirmation. Thrombocytopenia is the most commonly observed finding in HIT/T. The actual platelet count below which to suspect HIT/T varies however 100 × 10^9/l is the most commonly accepted number. A decrease in platelet count below 50% of the baseline maybe more accurate and should also be considered highly suspicious for diagnosis [9]. Although rare, full-blown HIT/T syndrome has been observed without thrombocytopenia [10-12]. Clinical manifestations are most commonly due to thrombosis in arterial and venous
circulation. Laboratory confirmation of HIT/T is essential to make the diagnosis.

1.2. Pathogenesis

Clinical and laboratory abnormalities result from an antibody that is produced against a complex of heparin and platelet factor 4 (PF4) [13]. PF4 is present in the platelet α granules and is released into the circulation following platelet activation. Binding of heparin to PF4 becomes antigenic in some patients and triggers immune response against which IgG antibodies are formed [14,15]. Antibody-PF4/heparin complex then binds to platelets and result in platelet activation, degranulation and aggregation [16]. Activated platelets also trigger other host systems including inflammatory cells, coagulation pathways and endothelial cells. This leads to generation of thrombin and intra-vascular coagulation. The initial reaction leads to aggregation and activation of more platelets followed by synthesis and release of more thromboxane A2 into the circulation [17]. A vicious cycle of more platelet activation as well as fibrin production and clot formation proceeds (Fig. 1). The end result is widespread platelet activation and formation of platelet thrombi causing occlusion of vasculature.

Antigenicity of the heparin-PF4 complex depends on the molecular weight and the degree of sulfation of the heparin molecule. Patients receiving low molecular weight heparin develop antibodies less frequently [18]. UFH preparations from bovine lung heparin are more commonly associated with HIT/T than porcine mucosal heparin [19].

Development of heparin dependent antibodies is not always associated with HIT/T syndrome however. Although HIT/T antibodies can be detected in up to 18% of patients who are exposed to UFH [20], only a fraction of these patients develop thrombocytopenia and still a few of those develop full-blown HIT/T (Fig. 1). This observation suggests that individual patient factors play an important role in the pathogenesis of HIT/T.

1.3. Incidence

Despite widespread use of UFH, HIT/T syndrome is not very common. The overall incidence was reported to be 3.4% in a meta-analysis of 14 prospective trials. Thrombotic
and embolic complications (TEC) were observed in 1% of all patients exposed to UFH [21].

Most large-scale reports however include a heterogeneous patient population with only a few cardiovascular patients pooled together with others [22]. This may be significant, since progression of HIT/T varies widely in different patient groups [23]. Cardiovascular patients are unique since a high percentage is exposed to UFH often on multiple occasions. Therefore, due to increased number of patients at risk, HIT/T is seen more frequently in cardiovascular practice and is associated with a disproportionately higher incidence of TEC. TEC are often multiple and may be initial presenting symptom in these patients [24]. The incidence of HIT/T following cardiac surgery is reported between 0.7 and 2% [9,25,26].

Widespread availability of heparin-associated antibody testing also brought out a subset of patients who develop immunologic reaction to heparin however never develop clinical HIT/T. Antibodies to heparin-PF4 are detected in 30–50% of patients after UFH exposure during cardiopulmonary bypass [27,28] however very few of these patients develop HIT/T. Finally, there is no difference in the incidence of heparin antibody development or HIT/T syndrome between ‘off pump’ and ‘on pump’ cardiac surgical patients [29].

1.4. Clinical presentation

Clinical presentation ranges from asymptomatic thrombocytopenia to a variety of intra-vascular thrombosis and embolism syndromes. Women are more commonly affected then men [30]. Onset of HIT/T following exposure to UFH has three defined patterns. If the subject has not been exposed to heparin in the previous 100 days, platelet count typically drops around the fifth day of UFH exposure. If patient has received heparin in the previous 100 days, thrombocytopenia occurs relatively rapidly (mean 10.5 h) after heparin administration [31]. This second scenario is seen in one third of the patients and observed more frequently in cardiovascular patients. Delayed onset of thrombocytopenia with full-blown HIT/T is rarely seen weeks after UFH exposure [32].

There is a general agreement that a 50% decrease in the count or an absolute platelet count of less then 100×10^9/l should be the first alarming sign of HIT/T. Other associated conditions in the critically ill patient i.e. intra-aortic balloon pumps, sepsis or DIC can result in thrombocytopenia also must be ruled out. Hemorrhage is an uncommon manifestation of HIT/T despite very low platelet counts [24,33] and is not considered to be one of the diagnostic criteria.

The most significant component of HIT/T is TEC. TEC are recognized in over 40% of HIT/T [34] and are more frequently observed in cardiovascular patients [9,26]. Thrombosis may be the first event leading to HIT/T diagnosis [26]. Although venous thromboses are overall more common [26], arterial thromboses are seen more frequently in the cardiovascular surgery patients. Subclinical extremity venous thrombosis has been demonstrated in a high proportion of patients with HIT/T [18], however, pulmonary embolism is the single most commonly reported embolic event [26]. Thrombosis of renal veins, upper limb veins as well as cerebral venous thrombosis is also reported [35].

Almost every arterial system can be affected by HIT/T. Mesenteric ischemia, upper extremity ischemia, renal artery thrombosis and renal shut down, aortic thrombosis, splenic artery thrombosis with splenic infarction as well as cardiac chamber thrombosis have been described [24]. There is also an increased incidence of graft closure following coronary artery bypass graft surgery [36]. A significant proportion of patients (33%) require limb amputation following thrombosis of extremity arteries [9,37,38]. These patients invariably have either an intra-vascular device in the vascular tree or have had a recent vascular intervention [39,40].

Renal failure requiring dialysis is common (30%) and associated with high mortality (83%) [24]. Incidence of cerebrovascular accidents is reported between 14 and 33% and is also frequently fatal.

TEC are observed most commonly after the diagnosis of HIT/T has been made but before initiation of alternative anticoagulant therapy and can be as high as 6.1% per patient day in the pre-treatment period. This decreases to 0.6% per patient day after institution of alternative anticoagulant therapy [24]. Therefore, it is critical to initiate alternative anticoagulant therapy as soon as HIT/T diagnosis is considered.

Several unusual clinical findings such as skin necrosis at the site of subcutaneous heparin administration [41] as well as resistance to UFH can precede the development of HIT/T. HIT/T is associated with high mortality rate (20-30%) in all series and more so in cardiovascular patients [42].

1.5. Diagnosis

Several clinical and laboratory criteria have been accepted for diagnosis.

1. Thrombocytopenia during heparin therapy
2. Resolution of thrombocytopenia after cessation of heparin
3. Exclusion of other causes of thrombocytopenia

HIT/T should be considered in every patient with a platelet count below 100×10^9/l or a decrease in the platelet count of more then 50% regardless of actual platelet count. In the typical patient, platelet count falls between 5 and 8 days after initiation of UFH. If thrombocytopenia occurs during the first 4 days of UFH exposure, it is either due to other reasons or patient has been exposed to UFH in the recent past (prior 3 months). Platelet count decreases within several hours (2.1–18.1 h) of exposure to UFH in the latter case [43]. Due to variations in the platelet count after cardiopulmonary bypass, the maximal post-operative platelet count should be considered as baseline platelet count in cardiac surgery patients.

The actual platelet count is usually in the range of 50-70×10^9/l and rarely below 15×10^9/l. One important diagnostic as well as therapeutic point is that platelet count recovers quickly after the discontinuation of heparin. Average time period for platelet count to reach 100×10^9/l is 4 days.

Due to the wide variation in clinical presentation and platelet counts, clinical suspicion is essential for diagnosis.
However, confirmation of diagnosis with pertinent laboratory tests is required to avoid unnecessary treatment. These tests also serve as guidance to future heparin usage if it becomes necessary.

There are two types of diagnostic tests HIT/T: platelet activation assays and immunoassays.

Platelet activation assays are serotonin release assay and heparin-induced platelet aggregation test (HIPA).

The most sensitive platelet activation/aggregation assay is the serotonin release test [44]. In this test, serum from patient with suspected HIT/T is incubated with radiolabeled platelets from normal donors and heparin is added to the mixture. Activation of platelets in the presence of heparin cause platelet degranulation and release of radioactive C14 labeled granules, which confirms HIT/T. This test is difficult and lengthy, therefore is currently limited to the reference laboratories. Platelet aggregation tests are based on the aggregation of platelets from normal donors in the presence of patient serum and heparin [45,46]. Platelets from normal donors are incubated with patient’s serum in the presence of heparin. Visual platelet aggregation, generation of platelet-derived microparticles with flow cytometry or release of radioactive serotonin is considered as end-points. This test can be performed on a large-scale basis for routine testing and results are rapidly available.

Immunossays are aimed to detect heparin-induced antibodies in the patient’s serum with suspected HIT/T. There are three types of commercially available immunossays. Solid phase anti-PF4/heparin enzyme linked immuno-sorbent assay ELISA (Asserachrom Stago, France), PF4-polyvinylsulfonate antigen ELISA (GTI, Brookfield, WI) and particle gel immunoassay (DiaMed, Cressier sur Monat, Switzerland) [47]. Although immunossays are very sensitive for detection of heparin-induced antibodies, they cannot demonstrate activation or aggregation of platelets due to antibody. Since anti-PF4 antibodies are detected in a large percentage of patients receiving heparin therapy without evidence of clinical HIT/T, this test is more commonly utilized as a screening assay. Diagnosis of HIT/T is then confirmed by one of the functional platelet activation assays (PAT, SRA).

Despite availability of multiple laboratory tests for the diagnosis of HIT/T, all lack specificity and sensitivity to a certain extent. A better approach is to obtain an immunoassay, which is rapid and available in most laboratories. A strongly positive immunoassay requires confirmation of diagnosis with a platelet activation assay. Clinical suspicion and correlation is again required prior to initiation of anti-thrombotic therapy.

1.6. Treatment

Management of HIT/T in a cardiovascular patient has to be considered in several steps.

First and most important is to discontinue all heparin as soon as HIT/T is suspected. This includes heparin-coated monitoring and intra-vascular access catheters. Platelet count usually begins to increase within 24-48 h after discontinuation of UFH and will increase above 100 \times 10^9/l in 4-5 days. Platelet transfusion therapy is not required and can result in increased incidence of thrombotic complications.

Although cessation of all heparin is an essential initial step, it does not decrease TEC or reduce mortality [26,42]. Furthermore, abrupt cessation of heparin results in a transient hypercoagulable/thrombotic state and may increase the incidence of TEC [48].

The association of high mortality with TEC (25-35%) has led clinicians to suggest prophylactic treatment with an alternative anticoagulant in all patients when there is a strong suspicion of HIT/T (second step) (see below).

The third step is laboratory confirmation of HIT/T. Since these tests are often sent to reference laboratories, results may not be available for several days. As mentioned above, the highest incidence of TEC in HIT/T patients occur in the period prior to initiation of alternative anticoagulants. The patient is therefore subjected to a hypercoagulable state both due to stopping UFH and due to increased possibility of developing TEC. Therefore, treatment with one of the alternative anticoagulant agents should be started without waiting for the results of confirmatory tests. The input from the consulting hematologist is invaluable when making this decision. If clinical condition improves and laboratory tests are negative for HIT/T, alternative anticoagulant can be stopped and platelet counts are observed carefully prior to re-starting UFH (if still necessary). If HIT/T is confirmed with one of the platelet activation assays, alternative anticoagulant is continued for the specified period of time (Table 3) and long-term anticoagulation with Warfarin is started (fourth step). Warfarin therapy should be initiated after platelet count has increased above \(100 \times 10^9/l\). An important point to keep in mind is to overlap alternative anticoagulant agents with Warfarin at least 5 days. Acute protein C deficiency is common in the first 3-4 days of initiation of Warfarin and can result in microvascular thrombosis leading to limb gangrene. Warfarin should be continued for at least 3 months since the risk for thrombosis remains high up to 6 weeks after discontinuation of heparin in HIT/T.

Treatment guidelines for specific clinical scenarios are summarized at the end of the text. There are two categories of alternative anticoagulant agents in clinical practice to treat HIT/T and related complications.

1. Non-thrombin inhibitors: low molecular weight heparin (LMWH), danaprod and ancrod
2. Direct thrombin inhibitors: hirudin and its recombinant derivative lepirudin as well as the synthetic direct thrombin inhibitors argatroban and bivalirudin.

2. Non-thrombin inhibitors

2.1. Low molecular weight heparin (LMWH)

These are a heterogeneous mixture of mucopolysaccharides prepared from chemical or enzymatic cleavage of UFH. LMWH maybe less likely to trigger formation of heparin-induced platelet antibodies and therefore is less likely to cause HIT/T.

However, LMWH is not recommended for treatment of HIT/T because heparin-induced platelet antibodies can...
activate platelets in the presence of LMWH. The incidence of cross-reactivity is high and approaches 100% [49]. In addition, further drop in platelet counts and recurrent thrombocytopenia has been reported in HIT/T during treatment with LMWH [50]. Despite these concerns, LMWH has been used in HIT/T patients requiring cardiopulmonary bypass [51]. A special set-up is necessary for monitoring since anticoagulant effect of this agent is measured using anti-factor Xa activity. There is no antidote and protamine partially reverses the anti-factor Xa activity of LMWH. This may result in increased incidence post-operative bleeding. Therefore, LMWH preparations should be avoided in patients with known or suspected HIT/T.

2.2. Danaproid

Danaproid (Orgaran™: Organon, Inc., West Orange, NJ) is a mixture of glycosaminoglycans derived from porcine intestinal mucosa [52]. It is similar to UFH and LMWH in structure and consists of heparan sulfate (84%), dermatan sulfate (12%) and chondroitin sulfate (4%). Its mechanism of action is via inhibition of factor Xa. The main route of excretion is through the kidney and half-life is 19-24 h.

Danaproid has been utilized as a substitution anticoagulant in patients with clinically suspected HIT/T [53]. It can be administered as intravenous infusion or subcutaneously. Danaproid has been withdrawn from the US market in April 2002 however it is available in Canada and Europe. In patients with HIT/T, danaproid is unique in inhibiting platelet aggregation in the presence of heparin-platelet antibody [54]. It can however cross-react with heparin-induced platelet antibodies (10-20%) and cross-reactivity should be ruled out prior to administration. This agent has been utilized successfully for the treatment of HIT/T patients (Table 2). In the largest clinical trial, danaproid was utilized in 666 HIT/T patients with high clinical response rate [55]. Danaproid has been used as an anticoagulant during cardiopulmonary bypass as well [56-61]. The drug is associated with a high incidence of intraoperative blood clots (one third of patients) as well as severe post-operative bleeding [59-62] when used during cardiac surgery. Danaproid anticoagulation requires anti-factor Xa level monitoring (Table 4). This test is not readily available in every institution. It takes up to 20-30 min to run an anti-factor Xa level. Re-infusion of pump blood post-operatively with cell saver devices is discouraged unless absolutely needed. Therefore, although there is some experience with this agent, danaproid should be used only when other antithrombin agents are not available.

2.3. Ancrod

Ancrod is a 17 amino acid proteinase obtained from Malayan pit viper venom (Ancrod™, Knoll Pharmaceuticals, Whippany, NJ). It acts by cleaving fibrinopeptide A from fibrinogen [63]. It has been used in patients with HIT/T including anticoagulation during cardiopulmonary bypass [64]. The drug’s activity is monitored using fibrinogen concentration. Therapeutic anticoagulation is obtained when the fibrinogen concentration decreases below 0.7 gm/l. Full dose is 1-2 U/kg body weight and administered in no less then 6 h. There is limited data regarding use of Ancrod for anticoagulation during cardiopulmonary bypass. The drug is administered at an intravenous infusion and has to be started at least 12 h prior to surgery. The rate of infusion is adjusted to the target fibrinogen concentration of 0.4-0.8 gm/l at the time of surgery. There is a significant increase in blood product transfusion with Ancrod utilization. The use of this agent has decreased considerably with introduction of newer alternative anticoagulants.

3. Direct thrombin inhibitors

These agents inhibit thrombin directly and have no structural similarity to heparin. They bind thrombin at a different site than heparin therefore all are able to inhibit thrombin bound to fibrin. This is of utmost clinical importance in patients with HIT/T since thrombin bound to fibrin is important in platelet activation. There is no cross-reactivity with heparin-induced antibodies. Hence, direct thrombin inhibitors maybe the ideal agents for management of patients with HIT/T.

There are currently three direct thrombin inhibitors available for use (Table 1).

3.1. Hirudin

Hirudin is a natural antithrombin produced by the salivary glands of medicinal leech (Hirudo Medicinalis). It is a 65 amino acid peptide and is the most potent and specific thrombin inhibitor known [65]. It has a high affinity for thrombin and irreversibly inactivates all enzymatic functions of thrombin. Hirudin can successfully inhibit thrombin bound to fibrin as well as soluble thrombin [66]. It differs structurally from heparin thus eliminating cross-reactivity. This drug is now produced in its pure form using recombinant technology: r-hirudin or lepirudin (Refudan™, Hoechst Marion Roussel, Kansas City, MO). r-Hirudin has stable and predictable pharmacokinetics. The drug is excreted through the kidneys and mean half-life is 0.8-2.0 h. Drug clearance is dependent on the creatinine clearance therefore dose reduction is recommended with renal insufficiency. r-Hirudin was found to decrease death, amputation and new TEC incidence over historical controls in HIT/T patients [67,68]. However, r-hirudin administration was associated with significantly higher incidence of bleeding and blood transfusion.

This drug has been utilized for treatment of HIT/T as well as for percutaneous coronary interventions (Tables 2 and 3). It has also been used as a sole anticoagulant during cardiac surgery [69,70]. The dosing regimen for r-hirudin during cardiopulmonary bypass is well established [71] (Table 4). Monitoring anticoagulation during cardiopulmonary bypass is achieved using ecarin-clotting time (ECT), which shows a linear correlation with plasma r-hirudin levels. Drug is cleared slowly from the circulation due to long half-life.

Development of antibodies against r-hirudin was observed in 44-75% of human subjects after 10 days of treatment [72]. There have been seven cases of severe anaphylactic
INR, international normalized ratio.

reactions to r-hirudin antibodies reported in Europe of which five were fatal. Therefore, it is important to rule out r-hirudin antibodies prior to re-exposing patients to this drug.

There is no known antagonist to r-hirudin. Partial reversal of anticoagulant effect can be accomplished with factor VII concentrates or prothrombin complex concentrates [73]. Some success with ultrafiltration or hemofiltration has been reported following cardiopulmonary bypass [74].

In summary, r-hirudin is an effective anti-thrombin and maybe useful for treatment of HIT/T. However, use of this drug during cardiovascular surgery can be associated with difficulty of monitoring the anticoagulant effect as well as increased incidence of post-operative bleeding and blood product transfusion.

3.2. Argatroban

Argatroban (Argatroban™, GlaxoSmithKline, Philadelphia, PA) is a relatively new thrombin inhibitor developed by modifications of L-arginine. It inhibits both free and fibrin bound thrombin in a reversible fashion. Its action is fast and reversible. Argatroban excretion is not impaired in renal failure due to hepatic metabolism. It has a short half-life (40-50 min) and anticoagulation can be monitored by aPTT or ACT (activated clotting time) [75]. It has been shown to have a lower hemorrhagic potential and higher affinity to fibrin bound thrombin compared to hirudin [76-78].

This drug decreased the incidence of death, amputation and new thrombosis in patients with HIT without complicating thrombosis [79,80]. Patients who received argatroban have faster recovery of platelet counts compared to the historical controls. Argatroban use does not result in increased incidence of bleeding.

The recommended dose for treating HIT/T is specified in Table 2. The duration of treatment is 5-7 days. Warfarin is started without a loading dose for long term anticoagulation after platelet count is above 100×10⁹/L. Argatroban, like other thrombin inhibitors, has been shown to prolong INR.

### Table 1
Alternative anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Structure</th>
<th>Action</th>
<th>Half-life</th>
<th>Elimination</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>r-Hirudin</td>
<td>65 Amino acid peptide</td>
<td>Direct thrombin inhibitor</td>
<td>40-120 min</td>
<td>Renal</td>
<td>Antibody formation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irreversible thrombin binding</td>
<td></td>
<td></td>
<td>Anaphylaxis with repeat administration</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dose adjustment in renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Excessive bleeding</td>
</tr>
<tr>
<td>Argatroban</td>
<td>L-Arginine derivative</td>
<td>Direct thrombin inhibitor</td>
<td>40-50 min</td>
<td>Hepatic</td>
<td>Dose adjustment in hepatic failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reversible thrombin binding</td>
<td></td>
<td></td>
<td>Prolongs INR when used concomitantly with Warfarin</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>20 Amino acid peptide</td>
<td>Direct thrombin inhibitor</td>
<td>25 min</td>
<td>Enzymatic</td>
<td>Limited experience for treatment of HIT/T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reversible thrombin binding</td>
<td></td>
<td>proteolysis</td>
<td>Intra-operative clot formation during cardiac surgery</td>
</tr>
<tr>
<td>Danaproid</td>
<td>Glycosaminoglycan mixture</td>
<td>Factor Xa inhibitor via antithrombin factor binding</td>
<td>19-25 h</td>
<td>Renal</td>
<td>Excessive bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dose adjustment in renal failure</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cross-reaction with HIT antibodies</td>
</tr>
</tbody>
</table>

INR, international normalized ratio.

### Table 2
Alternative anticoagulant therapy in HIT/T

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Monitoring</th>
<th>Duration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>r-Hirudin</td>
<td>0.4 mg/kg i.v. bolus then 0.15 mg/kg per h.i.v. infusion</td>
<td>Target aPTT 1.5-2.5×baseline or r-hirudin level 0.5-1.5 μg/ml</td>
<td>11-14 days</td>
<td>Greater efficacy</td>
<td>Higher incidence of bleeding</td>
</tr>
<tr>
<td></td>
<td>Initial bolus and infusion rate is reduced by 50% if used with thrombolytic therapy</td>
<td>Infusion rate adjusted in 20% increments to reach target aPTT</td>
<td></td>
<td></td>
<td>Antibody formation in 45-75% after 10 days i.v. infusion</td>
</tr>
<tr>
<td>Argatroban</td>
<td>2 μg/kg per min i.v. infusion</td>
<td>Target aPTT 2.3×baseline</td>
<td>5-9 days</td>
<td>No increased bleeding</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infusion rate adjusted in 1 μg/kg per min increments to reach target aPTT</td>
<td></td>
<td></td>
<td>No evidence of antibody formation</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>0.15-0.20 mg/kg per h.i.v. infusion</td>
<td>Target aPTT 1.5-3.0×baseline</td>
<td>7-10 days</td>
<td>No significant antibody formation</td>
<td>Prolongation of INR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infusion rate adjusted in 20% increments to reach target aPTT</td>
<td></td>
<td></td>
<td>Dose decreased in hepatic failure to 0.3 μg/kg per min</td>
</tr>
<tr>
<td>Danaproid</td>
<td>2500 U i.v. bolus then 400 U/h for 4 h then 300 U/h for 4 h then 150-200 U/h continuous infusion</td>
<td>Target plasma anti-Xa level 0.5-0.8 U/ml</td>
<td>&gt; 5 days</td>
<td>Can be administered s.q.</td>
<td>Mild prolongation of INR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No antibody formation</td>
<td>Can cross-react with anti-lepirudin antibodies</td>
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<td></td>
<td></td>
<td>Limited experience for treatment of HIT/T treatment</td>
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<td></td>
<td></td>
<td>Lower efficacy</td>
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<td></td>
<td></td>
<td>Cross-reaction with HIT antibodies</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Elevation of liver enzymes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not available in the US</td>
</tr>
</tbody>
</table>

aPTT, partial thromboplastin time.
 alters the antithrombin effect of r-hirudin rapidly clears following discontinuation of infusion. It is recommended that high dose infusion (5–10 μg/kg per min) should be utilized to provide adequate anti-coagulation and to prevent intra-operative clot formation during off pump surgical coronary revascularization [86].

This agent can be used effectively and safely for treatment of HIT/T. It can also be used during cardiac surgical procedures as an anti-coagulant. Anticoagulant effect can be monitored conveniently with ACT levels. The drug’s short half-life is an advantage to reduce bleeding and blood transfusion after discontinuation of infusion. Argatroban can also be used safely in patients with renal failure. There has been no incidence of antibody formation with this agent despite accumulating experience. Dose adjustment is required in patients with hepatic failure.

3.3. Bivalirudin

Bivalirudin (Angiomax™, The Medicines Company, Cambridge, MA) is a synthetic hirudin analog composed of 20 amino acids. Bivalirudin reversibly binds thrombin. Elimination is by enzymatic proteolysis (80%) as well as renal clearance (20%) [87]. Serum half-life is 25 min with normal renal function, however is longer in end stage renal disease (3.5 h). Antibody formation to bivalirudin is reported (< 1% after 5 day infusion). There is a potential risk of cross-reaction with preformed antibodies to r-hirudin. Therefore, caution should be practiced when administering bivalirudin to patients with prior r-hirudin exposure. ECT provides predictable measurement of anticoagulation especially during cardiac surgery.

Table 3
Alternative anticoagulants in percutaneous coronary intervention (PCI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Monitoring</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>r-Hirudin</td>
<td>0.4 mg/kg i.v. bolus followed by 0.10–0.24 mg/kg per h×24 h</td>
<td>Target aPTT 60–100 s</td>
<td>Cumbersome monitoring</td>
</tr>
<tr>
<td></td>
<td>followed by 0.04 mg/kg per h×24 h</td>
<td></td>
<td>Long half-life</td>
</tr>
<tr>
<td></td>
<td>350 μg/kg i.v. bolus followed by 25 μg/kg i.v.</td>
<td>Target ACT 300–400 s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>infusion Infusion stopped at the end of the procedure</td>
<td>Additional 150 μg/kg bolus to reach target ACT</td>
<td>Easy to monitor</td>
</tr>
<tr>
<td>Argatroban</td>
<td>0.75 mg/kg i.v. bolus followed by 1.75 mg/kg per h</td>
<td>Target ACT 350 s</td>
<td>Relatively short half-life</td>
</tr>
<tr>
<td></td>
<td>infusion Infusion stopped at the end of the procedure</td>
<td></td>
<td>Predictable anticoagulation</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>2250 U i.v. bolus followed by 150–200 U/h 1–2 days after PCI</td>
<td>Target anti-Xa level 0.5–1 U/ml</td>
<td>Limited experience</td>
</tr>
</tbody>
</table>

Table 4
Alternative anticoagulants for cardiac surgery

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Monitoring</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>r-Hirudin</td>
<td>0.25 mg/kg i.v. bolus, 0.20 mg/kg added to CPB prime (optional 0.</td>
<td>Target r-hirudin level 4 μg/ml</td>
<td>Cumbersome monitoring</td>
</tr>
<tr>
<td></td>
<td>5 mg/min (30 ml/h) i.v. infusion) additional 5 mg boluses added CPB</td>
<td>Target ECT between 400 and 500 s</td>
<td>Long half-life</td>
</tr>
<tr>
<td></td>
<td>to reach ECT 400 s</td>
<td>ECT monitoring every 15 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stop infusion 15 min prior to separation from CPB</td>
<td>while on CPB</td>
<td></td>
</tr>
<tr>
<td>Argatroban</td>
<td>0.1 mg/kg i.v. bolus followed by 5–10 μg/kg per min i.v. infusion</td>
<td>Target ACT between 200 and 400 s</td>
<td>Easy to monitor</td>
</tr>
<tr>
<td></td>
<td>(lower doses may result in clotting)</td>
<td>ACT monitoring every 15 min</td>
<td>Relatively short half-life</td>
</tr>
<tr>
<td></td>
<td>Stop infusion after completion of grafts or at separation from CPB</td>
<td>while on CPB</td>
<td>Predictable anticoagulation</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>0.75 mg/kg i.v. bolus followed by 1.75 mg/kg per h i.v. infusion</td>
<td>Target bivalirudin level 10 μg/ml</td>
<td>Limited experience</td>
</tr>
<tr>
<td></td>
<td>Stop infusion after completion of grafts or at separation from CPB</td>
<td>Target ECT between 400 and 500 s</td>
<td>Abnormal clotting</td>
</tr>
<tr>
<td>Danaproid</td>
<td>125 U/kg i.v. bolus after sternotomy and 3 U/ml in the pump prime solution</td>
<td>Target anti-Xa level 1.5 U/ml</td>
<td>Cumbersome monitoring</td>
</tr>
<tr>
<td></td>
<td>then 7 U/kg per h infusion</td>
<td></td>
<td>Increased blood transfusion</td>
</tr>
<tr>
<td></td>
<td>Stop infusion 45 min prior to separation from CPB</td>
<td></td>
<td>Abnormal clot formation</td>
</tr>
</tbody>
</table>

aPTT, partial thromboplastin time; ACT, activated clotting time.

CPB, cardiopulmonary bypass; ECT, ecarin clotting time; ACT, activated clotting time.
Bivalirudin is approved by the FDA to be used during percutaneous coronary interventions. The drug is safe and efficient compared to heparin in randomized trials for this purpose. Recommended dose for percutaneous coronary intervention is summarized in Table 3 [88].

Bivalirudin can be used for anticoagulation in treatment of patients with HIT/T. Monitoring is accomplished using aPTT (Table 2) [89]. Duration of treatment is similar to r-hirudin and is followed by long-term anticoagulation with Warfarin. As with other antithrombins, a 3-4 day overlap with Warfarin treatment is necessary prior to discontinuation of the drug.

Bivalirudin is also utilized for anticoagulation during cardiac surgery (Table 4) [90-92] and found to be a safe and effective anticoagulant compared to heparin [93]. The drug is administered as a 0.75 mg/kg bolus followed by 1.75 mg/kg per h infusion in off-pump coronary artery bypass graft surgery. The dose should be increased if cardiopulmonary bypass circuit is utilized (Table 4). ECT is used to monitor anticoagulation. The most important disadvantage is abnormal clot formation during the operation. Since the major mechanism of drug elimination is via enzymatic cleavage, thrombus has been observed where the blood is stagnant. Moreover, due to enzymatic elimination, a near normal body temperature has to be maintained for predictable dosing which is not always feasible during CPB. Some authors have recommended addition of 25 mg of the drug to the bypass circuit to prevent clotting at the end of cardiopulmonary bypass. Alternatively, all pump blood can be transferred to the cell saving device and re-infused to patient after processing. These steps can be somehow cumbersome for the operating team and may create difficulty if re-institution of cardiopulmonary bypass becomes necessary. Therefore, although bivalirudin is well established in percutaneous coronary interventions, more experience is required with this agent in cardiac surgery.

3.4. Intravenous gammaglobulin (i.v. IgG)

Intravenous gammaglobulin (i.v. IgG) has been shown to block activation of platelets by the heparin-associated antibody [94]. There are also clinical reports of increased platelet counts after administration of i.v. IgG in HIT/T patients [95,96]. The indications for this modality are limb threatening or life threatening thrombosis in patients who are already receiving one of the alternative anticoagulants. Recommended dose is 1 g/kg once a day for 2 days.

3.5. Plasmapheresis

Plasmapheresis has been used as an additional modality in patients with severe HIT/T complicated with TEC [97]. The mechanism of action is not clear however it may act by clearing the heparin-induced antibody from the circulation.

3.6. Platelet transfusions

Patients with HIT/T do not have spontaneous bleeding despite very low platelet counts. Moreover, there have been reports of increased thrombosis following platelet transfusions in patients with HIT/T. Therefore, platelet transfusion is contraindicated and should be avoided in known or suspected HIT/T patients [98].

3.7. Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIa/IIIb inhibitors (Tirofiban/Aggrastat and abciximab/ReoPro) are effective inhibitors of platelet aggregation. These agents have been used in combination with UFH for anticoagulation during CPB in HIT/T patients. Prior administration of short acting agent Tirofiban (Aggrastat) as a 10 µg/kg bolus and continuous infusion (0.15 µg/kg) followed by full dose UFH has provided effective anticoagulation during CPB without any TEC [99]. Tirofiban infusion is stopped 1 h prior to termination of CPB and UFH is reversed with Protamine in the usual fashion. Post-operative platelet transfusions are used if there is profound preoperative thrombocytopenia (<40,000/µL). Although this protocol has been successfully used in a number of patients, concerns over abnormal bleeding has prompted manufacturer to discourage Tirofiban use for this purpose.

3.8. Specific treatment protocols

3.8.1. Patients who develop thrombocytopenia during or following exposure to UFH

This represents the most common scenario in the cardiovascular patient population. The typical patient has received or is receiving UFH, is asymptomatic and platelet count is decreased below 50% of the baseline during a routine laboratory test. A systematic approach to these patients with an algorithm is necessary (Fig. 2). Thrombocytopenia should be confirmed with a peripheral smear and other causes should be ruled out. The next step is immediate discontinuation of all heparin. This step includes flush solutions for intravenous catheters, heparin-coated central venous and arterial monitoring lines as well as LMWH. ELISA is the most readily available and fastest test to detect presence of heparin-associated antibodies. Since ELISA has a rather high sensitivity for heparin-induced platelet antibodies, the likelihood of HIT/T is very low if ELISA is negative. Heparin can then be carefully resumed and platelet count is closely followed. If ELISA is positive, one of the platelet activation assays should follow to confirm HIT/T. One must realize that it may take several days before the results of these tests are available. One must also realize that at least half of the patients HIT/T will develop a TEC, which is associated with 20% mortality. Therefore, if there is a strong clinical suspicion of HIT/T, an alternative anticoagulant is started (preferably an antithrombin agent, Table 2) until the confirmatory test results are available. If the diagnosis of HIT/T is confirmed, alternative anticoagulant is continued until platelet count rises above 100×10^9/L. Warfarin is added at this point for long-term (3 months) anticoagulation. Argatroban is the preferred alternative anticoagulant at our institution due to its short half-life, ease of monitoring, safety in renal failure and low rate of bleeding complications. This agent does prolong INR, therefore specific instructions of the manufacturer should be followed during Warfarin administration.
3.8.2. Patients with known antibodies to heparin or history of HIT/T and require percutaneous coronary intervention (PCI)

All three antithrombin agents and danaproid have been successfully utilized during percutaneous coronary interventions (Table 3). Bivalirudin however has been used much more frequently and has proved to be safe and efficacious. Therefore, bivalirudin is the preferred antithrombin in patients who need PCI and have heparin-associated antibodies or history of HIT/T at our institution.

3.8.3. Patients with known antibodies to heparin or history of HIT/T and need cardiac or vascular surgical intervention that requires anticoagulation

The critical factor to determine the course of action in these patients is the period of time since the last exposure to UFH. Heparin-associated antibodies disappear from serum after 100 days (Fig. 3). Therefore, intra-operative heparin can be utilized in patients who need anticoagulation for cardiac or vascular surgery. It is however of utmost importance to avoid heparin before and after the procedure. This approach has been used by cardiac surgeons in the past and was found to be safe [100]. If patient has a history of HIT/T and last exposure to heparin was less then 100 days, an ELISA test is performed to detect heparin-associated antibodies. If ELISA is negative, UFH can be used during the intervention as outlined above. If ELISA is positive, an alternative anticoagulant is employed. Table 4 summarizes the three antithrombins as well as danaproid (not available in US) use during cardiac surgery. Among these, argatroban is again the anticoagulant of choice in our institution. This agent has a short half-life and is cleared from the circulation rapidly after discontinuation. Anticoagulation is conveniently monitored with ACT test intra-operatively therefore avoids complicated monitoring tests and decreases room for error. Risk of coagulopathy and excessive
post-operative bleeding is uncommon due to drug’s short half-life and rapid hepatic elimination. Antibody development is not reported. r-Hirudin, on the other hand, requires half-life and rapid hepatic elimination. Antibody development in the bypass grafts and stagnant areas, therefore surgery has been complicated with intra-operative clot reaction with re-exposure. Bivalirudin use during cardiac are also reports of antibody formation and fatal anaphylactic reaction with re-exposure. Bivalirudin use during cardiac surgery has been complicated with intra-operative clot formation in the bypass grafts and stagnant areas, therefore is not our first choice for this purpose.

References


