Thrombosis due to Heparin-induced Thrombocytopenia in Cardiac Surgery: is Fondaparinux an Effective Treatment?

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Keywords HIT; Cardiac surgery; Heparin; Thrombosis; Fondaparinux

Introduction

Thrombocytopenia after cardiac surgery may result from HIT, therefore it is included in differential diagnosis in all the patients with unexplained fall of platelet count.

HIT is defined as a fall of platelet count of about 50% occurring within 5 to 14 days after the start of heparin therapy that induces an intense prothrombotic state, due to an immune reaction against platelet factor 4 (PF4)-heparin complexes (Type 2 HIT), and resolves after stopping heparin [1,2]. Type 1 HIT is a mild thrombocytopenia that usually develops within 48 hours of initiating heparin. Only if the platelet count continues to fall in a non-bleeding patient, type 2 HIT should be considered and all heparins should be stopped [3]. HIT antibodies (H-IgG) occur more often in postsurgical than medical patients, and in those treated with unfractionated heparin (UFH) rather than low molecular weight heparin (LMWH) [3,4]. Overall, the absolute post-operative risk for HIT is higher with UFH (2% to 3%), compared to LMWH (0.2% to 0.6%) [2,5-7]. One hypothesis to explain why cardiopulmonary surgery patients have the highest prevalence of PF4/H-IgG is that extensive tissue injury causes widespread platelet activation releasing large quantity of PF4 that combines with heparin [8]. Furthermore, HIT is more likely to occur using high doses of UFH, although very small doses may also result in thrombocytopenia.

HIT can be seen with isolated thrombocytopenia (HIT) or concurrently with thrombotic complications (HITT). Combined clinical criteria and laboratory testing, are currently recommended for HIT diagnosis [9], but it remains a difficult condition to diagnose [10]. It is important to underline, in this regard, that many patients suspected of having HIT are finally proven to have different thrombotic disorders [11].

If HIT is suspected because of intermediate or high “4T score” (Thrombocytopenia, Timing, Thrombosis, and absence of oTher explanations) (Table 1) [5], all heparin products must be discontinued and non-heparin anticoagulant initiated. In the meantime, laboratory testing should be carried out [6,8,11,12]. Effective non-heparin anticoagulants include the FDA-approved direct thrombin inhibitors and the selective factor Xa inhibitors, such as fondaparinux [6,13]. Even if off-label for this condition, fondaparinux represents an attractive treatment for patients who develop HIT because it is not derived from heparin, has negligible to no cross-reactivity with HIT antibodies [6,13,14], and is an effective treatment in both HIT and non-HIT settings of thrombosis.
Platelet count was 210×10^9/L. Aortic cross clamp and cardiopulmonary bypass (CPB) times were respectively 70 and 94 minutes. (AVR) through ministernotomy. Before surgery, coronary angiography was performed and 5,000 IU UFH was given. On admission, her stenosis with no co-morbidities underwent aortic valve replacement (VKA) therapy was started. Thrombocytopenia (platelet count=27×10^9/L) was detected. Because of high probability of HITT (4T’s=7 points), VKA therapy was discontinued and LWMH was replaced with fondaparinux 5 mg, administered once daily, avoiding platelets transfusions. CT-scan revealed multiple thrombi occluding right pulmonary artery bifurcation and left subsegmentarier arteries. In addition, there was a venous thrombosis involving the superior cava at the axyous vein confluence as well as an inferior cava vein thrombosis extended for 5 cm above the iliac veins (Figure 1). Positive ELISA test for anti-heparin antibodies strengthened clinical suspicion of HITT.

Table 1: Estimating the pretest probability of HIT: the four Ts scoring system.

| Category                          | 2 points | 1 point | 0 points |
|-----------------------------------|----------|---------|----------|
| 1. Thrombocytopenia               | Platelet count fall>50% and platelet nadir ≥ 20×10^9 L^-1 | Platelet count fall 30%–50% or platelet nadir 10–19×10^9 L^-1 | Platelet count fall<30% or platelet nadir<10×10^9 L^-1 |
| 2. Timing of platelet count fall  | Clear onset between days 5 and 10 or platelet fall ≤ 1 day (prior heparin exposure within 30 days) | Consistent with days 5–10 fall, but not clear (e.g. missing platelet counts) or onset after day 10 or fall ≤ 1 day (prior heparin exposure 30–100 days ago) | Platelet count fall <4 days without recent heparin exposure |
| 3. Thrombosis or other sequelae   | New thrombosis (confirmed) or skin necrosis at heparin injection sites or acute systemic reaction after intravenous heparin bolus | Progressive or recurrent thrombosis or nonnecrotizing (erythematous) skin lesions or suspected thrombosis (not proven) | None |
| 4. Other causes for thrombocytopenia | None apparent | Possible | Definite |

Total score of ≥ 6 points, high probability of HIT; 4–5 points, intermediate probability of HIT; ≤ 3 points, low probability of HIT. CPB, cardiopulmonary bypass [5].

We reported three cases, among more than 4,000 cardiosurgical patients observed in the last 5 years, with HITT successfully treated with fondaparinux and withdrawal of all heparins.

**Case Report 1**

A 72-years old woman suffering from severe symptomatic aortic stenosis with no co-morbidities underwent aortic valve replacement (AVR) through ministernotomy. Before surgery, coronary angiography was performed and 5,000 IU UFH was given. On admission, her platelet count was 210×10^9/L. Aortic cross clamp and cardiopulmonary bypass (CPB) times were respectively 70 and 94 minutes. The patient experienced an uneventful recovery and anticoagulation therapy with nadroparin calcium was continued.

On day 8, patient presented right inferior limb oedema suggestive of deep venous thrombosis (DVT). Duplex Ultra Sound (DUS) confirmed a common femoral vein thrombosis; therefore, Vitamin K Antagonist (VKA) therapy was started. The day after, extreme thrombocytopenia (platelet count=27×10^9/L) was detected. Because of high probability of HITT (4T’s=7 points), VKA therapy was discontinued and LWMH was replaced with fondaparinux 5 mg administered once daily, avoiding platelets transfusions. CT-scan revealed multiple thrombi occluding right pulmonary artery bifurcation and left subsegmentarier arteries. In addition, there was a venous thrombosis involving the superior cava at the axyous vein confluence as well as an inferior cava vein thrombosis extended for 5 cm above the iliac veins (Figure 1). Positive ELISA test for anti-heparin antibodies strengthened clinical suspicion of HITT.

**Case Report 2**

Our second patient was an 83-years old woman suffering from symptomatic aortic stenosis with initial left ventricular dysfunction with moderate increase of systolic pulmonary artery pressure, and multiple co-morbidities: hypertension, history of arrhythmia, and chronic obstructive pulmonary disease (COPD). During the coronary angiography, standard dose of UFH (5,000 IU) was injected. We performed AVR in ministernotomy. CPB and cross clamp times were 95 and 75 minutes. After six days, the patient was dyspnoic and asthenic. CT-scan showed right atrial thrombosis and pulmonary embolism. Transoesaphageal echocardiography (TOE) suggested partial valve thrombosis (Figure 2). Platelet count was 40×10^9/L, associated with positive ELISA test for anti-heparin antibodies. Therefore, we suspended LWMH, and started fondaparinux 5 mg, administered once daily. After one week, platelet count reached 100×10^9/L and (VKA) therapy was given - together fondaparinux for the first 5 days - over the next 6 months. On transhoracic echocardiography, the bioprosthesis leaflets were completely thrombus free with medium gradient 8 mmHg, and CT-scan showed the complete recovery of pulmonary embolism. At 2-years follow-up, this...
patient is under monotherapy with acetylsalicylic acid (ASA) 100 mg daily, and currently is in NYHA class II.

Figure 2: Transesophageal echocardiography (TOE) shows partial valve thrombosis with a fix right cusp.

Case Report 3

The third case was a 70-years old female who underwent mitral-aortic replacement with a bioprosthesis. During angiography, she received 5,000 IU UFH. In post-operative day 3, during LWMH prophylactic treatment, she showed symptoms of transient ischemic attack (TIA), and therefore anticoagulant shift from LWMH to VKA was done. She was in sinus rhythm. Two days later, the patient had a stroke with partial hemiparesis. Cerebral CT scan confirmed the presence of recent ischemic lesion. In addition, TOE showed the presence of left atrial thrombus. At the same time, a dramatic decline of platelet count was observed, reaching 7×10⁹/L two days later (4T’s=7 points). Consequently, we stopped LWMH and started anticoagulant therapy with fondaparinux 5 mg/once daily, avoiding platelets transfusions. Subsequently, positive ELISA test for anti-heparin antibodies supported the clinical suspicion of HIT. We saw a gradual increase in platelet count, and started VKA therapy when platelet count improved to 100×10⁹/L. Overall, fondaparinux was administered for 10 days (including an overlap of 5 days of VKA therapy) without any side effects. Gradually we noted the patient recovery from the stroke with a residual slight hyposthenia. TOE showed the complete resolution of thrombosis. At 5-years follow-up, she was in good condition on ASA therapy.

Discussion

In cardiac surgery, UFH is largely used at very high doses to guarantee adequate anticoagulation during CPB mainly for its short half-life and the availability of protamine sulfate to reverse its effects [15]. After surgery, either UFH or LMWH are used. This wide use of UFH together with extensive tissue injury justifies the reported high risk of developing HIT (2-3%) in cardiac surgery patients [5]. Previously, a pooled analysis demonstrated that HIT incidence was 1.1% with porcine-intestine-derived UFH and 2.9% with bovine-lung-derived UFH [16], but just one of our patients received bovine, the other two porcine UFH.

One striking finding of our case series was that the point of heparin immunization occurred in the prooperative period, during the angiography when standard dose of UFH (5,000 IU) was administered. Notably, Foo et al. [17] reported positive test for anti-PF4/heparin antibodies in 10.1% of patients after cardiac catheterization.

Severe venous or arterial thrombosis in a patient on prophylactic or therapeutic doses of heparin combined with marked thrombocytopenia is the hallmark of HIT [18]. While thrombocytopenia is described in more than 20% of patients who underwent cardiac surgery, a typical clinical picture of HIT is observed only in 1-3%, with a 20-30% mortality rate [5,6,8,17]. Particularly, whereas fall in platelet count, which occurs in the first four postoperative days, is unlikely due to HIT, thrombocytopenia occurring between postoperative days 5 and 10 is highly predictive of HIT [19]. In our cases, platelet counts declined dramatically 5 to 10 days after the start of UFH (typical-onset HIT) [6]. Severe thrombosis, complicated by acute pulmonary thromboembolism or stroke, was documented in all our cases between days 5 and 8 post-CBP. This is no surprise since the risk for thrombosis correlates with the extent of decrease of platelets, with a greater fall in platelet counts associated with a high risk of thrombosis [19].

Other causes of thrombocytopenia were excluded in all cases. Thus, there was a high clinical suspicion (4T’s=7 points) of HIT, and while awaiting the results of laboratory tests all sources of heparin were removed. Anticoagulation with VKA was also discontinued as it can produce early hypercoagulability through depletion of protein C. VKA was immediately replaced with the non-heparin anticoagulant fondaparinux, avoiding platelets transfusions because they may further exacerbate the hypercoagulable state. Although there are a number of alternative anticoagulants that are recommended for a patient with HIT [18], our local approach to choose fondaparinux for patients who have normal renal function is based upon its subcutaneous administration, the no need for coagulation monitoring in routine practice, and the very low risk of major bleeding complications. As none of our cases had renal impairment or exacerbation of HIT [19]. In our cases, platelet counts declined dramatically 5 to 10 days post-CPB with a high risk of thrombosis [19].

Our clinical suspicion was subsequently strengthened by a positive ELISA test for anti-heparin antibodies, even if immunoassays can be positive in patients without clinical HIT (90% sensitivity, 30–70% specificity) [9,12,22] because they fail to discriminate platelet activating from nonpathogenic antibodies [9]. Unfortunately, the more specific functional tests were not feasible for our laboratory as for most clinical laboratories [22]. However, the detection of anti-heparin antibodies in patients with 4T’s>6 points have a posttest probability of HIT approaching 100% [9]. In addition, following our decision-making about anticoagulant therapy, the progressive rise of platelet count was noted in all the patients, and it was one of our clinical parameters for clear diagnosis of HIT.

Fondaparinux is an available and practice off-label therapy with a good anticoagulant action and a low haemorrhagic rate [6,14,21]. Like LMWH, it can be administered once or twice daily. However, experience with fondaparinux use for HIT is based on case series or retrospective studies [6,21,23]. Therefore this drug is suggested as a therapeutic option with a low recommendation level [18]. In addition, concern was expressed about the possibility of new
thrombotic events [11] as well as the occurrence of fondaparinux-induced thrombocytopenia [24].

Our series underscored safety and efficacy of fondaparinux in cardio-surgical patients with severe HIT complicated by thrombosis. Indeed, cardio-pulmonary thrombosis imaging resolution and platelet recovery were achieved in all cases. None developed new thromboses. In addition, even if post-cardiac surgery patients have an increased risk of bleeding due to both surgical and non-surgical causes, our approach seems to be a safe strategy because no patient exhibited clinically significant hemorrhage complications.

Our results should be seen in the context of the limited existing therapy options for HIT [20]. Other alternative drugs have been used in HIT, which have different characteristics that make them suitable in different situations [6,25]: the heparinoid with anti-factor Xa activity danaparoid (Orgaran) and the direct thrombin inhibitors, lepirudin, argatroban and bivalirudin. Unfortunately, given the absence of data from randomized trials, most recommendations for their use in HIT are supported by low-grade evidence, analogously to what happens for fondaparinux [18,20]. In addition, all of these alternative anticoagulants carry a significant risk of bleeding complications, are not available in all institutions (i.e. lepirudin and danaparoid are no longer available in the US) and/or require monitoring of anticoagulation. Despite their utility in HIT remains undefined because it is supported only by few clinical reports, other emerging attractive therapies are the new oral anticoagulants (rivaroxaban, dabigatran, and apixaban), which are approved for thromboprophylaxis as well thromboembolic conditions. They do not interact with anti-PF4/heparin antibodies and have rapid onset of action [26], although, for example, dabigatran can increase INR and, therefore, INR measurements should be interpreted cautiously when this drug is switched to VKA. Finally, plasmapheresis can be used as salvage therapy to reduce antibody burden in patients with refractory or progressive thromboses on alternative anticoagulation [27].

In conclusion, our data further support the observational evidence that fondaparinux is a safe and effective option in HIT-related thromboembolic complications. Different types of alternative anticoagulants can be useful in different clinical scenarios but it is more important to suspect HIT when there are suggestive clinical factors, because prompt therapeutic decisions are vital for prognosis and outcomes. Despite its off-label use, the lack of indication supported by prospective studies and the obvious limitations of our study, fondaparinux appears to us effective, low cost, practical and available therapy with a good anticoagulant action and low risk of bleeding events.

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