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Repetitive intraoperative use of recombinant hirudin (Lepirudin) in peripheral vascular surgery with HITT

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Summary

Heparin induced thrombocytopenia with thrombosis (HITT) is a rare but dangerous complication related to the application of unfractionated heparin or low molecular weight heparin. Due to an antibody dependent in vivo platelet activation, severe thromboembolic episodes may occur.

We present the case of a patient with HITT following implantation of an aorto-bifemoral graft secondary to bilateral common iliac artery stenoses. An arterial clot developed and led to a partial occlusion of the graft to the right external iliac artery. Heparin was replaced by Lepirudin, a recombinant hirudin. A bolus of 0.4 mg/kg body weight was given, thereafter 0.15 mg/kg body weight per hour was administered continuously i.v. to maintain the aPTT 2- to 2.5-fold above the baseline value. The platelet count (minimum 47 G/l) normalised within two days. During thrombectomy of the right common femoral artery we used Lepirudin intraoperatively (bolus injection of 0.2 mg/kg body weight) to prevent any further platelet and coagulation activation during the clamping phase.

Six months later the patient underwent two further bypass-operations due to severe stenoses of both superficial femoral arteries. Due to the high risk of thromboembolism if HITT recurred, a bolus of 0.2 mg/kg body weight of Lepirudin was given during each intervention. No bleeding complications occurred. In addition Lepirudin appeared to decrease platelet consumption in the absence of active thrombosis.

Direct thrombin inhibitors such as Lepirudin possess no heparin-like immunological properties and seem to have become the therapeutic "gold-standard" in patients with HITT. Our experience suggests that the repetitive intraoperative use of Lepirudin is safe and effective.

Key words: heparin induced thrombocytopenia; heparin; complication; recombinant hirudin; peripheral vascular surgery; clamping

Introduction

Heparin induced thrombocytopenia with thrombosis (HITT) is an infrequent but potentially fatal and thus much feared complication following the administration of unfractionated (UFH) or much less frequently low molecular weight heparin [1]. In this immunological phenomenon thrombocytopenia occurs due to antibody formation against complexes of heparin and platelet factor 4 (PF4). Binding of these antibodies to surface Fc-receptors of platelets and endothelial cells triggers a continuous platelet activation, which can lead to thromboembolism [1, 2].

Case report

We present a case of HITT following implantation of an aorto-bifemoral graft due to symptomatic stenoses of both common iliac arteries in a 53-year-old male patient with Fredrickson type IIb hyperlipoproteinaemia. Preoperative evaluation revealed no documented evidence of previous heparin exposure or thrombocytopenia. On examination, popliteal and pedal pulses were greatly reduced but no other pathology was noted. The platelet count was 208 G/l (normal range: 150–300 G/l) and the aPTT was 34 s (Dapttin® on BCS analyser, reference range: 28–41 s).

Postoperatively standard continuous i.v. anticoagulation with UFH was begun. The heparin dose was adjusted to maintain the aPTT at 2.5 times the baselin e value. After remaining in the normal range for the first eight days, the platelet count fell to 49 G/l on the ninth postoperative day and concomitantly a thrombotic occlusion of the right distal anastomosis of the bypass was detected. HITT was suspected and immunological testing using a heparin-PF4-ELISA (Asserachrom®; Stago®) confirmed the presence of heparin/PF4–antibodies. Heparin was immediately replaced with Lepirudin. An intravenous bolus of 0.4 mg/kg body weight was given followed by a continuous infusion of 0.15 mg/kg body weight per hour in order to maintain the aPTT at 2.0 to 2.5 times the baseline value. The platelet count rose to normal values within three days and reached a maximum value of 372 G/l under therapy with recombinant hirudin eight days later. Following the uneventful use of Lepirudin for eight days the thrombotic occlusion was successfully removed by thrombectomy. Before clamping a bolus of 0.2 mg/kg body weight (15 mg) Lepirudin was administered to prevent further thrombotic occlusion. There were no bleeding complications during surgery or the subsequent i.v. anticoagulation with Lepirudin. Very interestingly a much lower dose of Lepirudin was needed following removal of the thrombotic occlusion (fig. 1). Platelet aggregation inhibition with 100 mg Aspirin® per day was initiated before discharge.

Six months later the patient required two further bypass operations due to severe bilateral superficial femoral artery stenoses. Again he received repetitive Lepirudin boluses of 0.2 mg/kg body weight during surgery and postoperative thrombosis prophylaxis with i.v. Lepirudin. Between the first and the second hospitalisation, the platelet count had fallen to 187 G/l. During the second hospitalisation with prophylactic Lepirudin therapy we detected an increase in platelet concentration to a maximum of 346 G/l in the absence of any thromboembolic complications (see fig. 2). The further course was uneventful.

Discussion

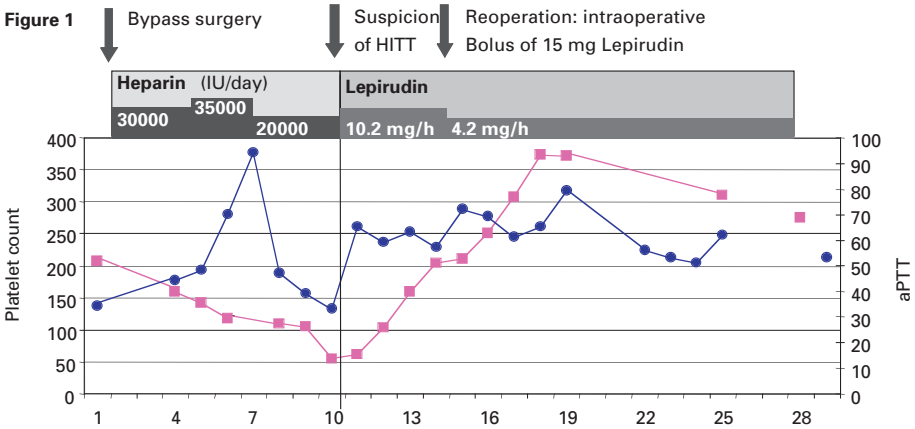
Decreasing platelet counts during heparin application in vascular surgery patients should raise the suspicion of heparin induced thrombocytopenia (HIT). Common causes of thrombocytopenia such as sepsis, disseminated intravascular coagulation or drug toxicity should be ruled out promptly. If suspicion of HIT persists or thromboembolism occurs (HITT), heparin should be withdrawn and replaced immediately [1, 2]. The observation of rising platelet counts during therapy with an alternative anticoagulant (e.g. Lepirudin) suggests the diagnosis of HITT. An immunological test (e.g. ELISA) should be performed to detect any circulating antibodies against heparin-PF4-complexes; we used the Asserachrom®-test (sensitivity ~ 85%, specificity ~ 90%).

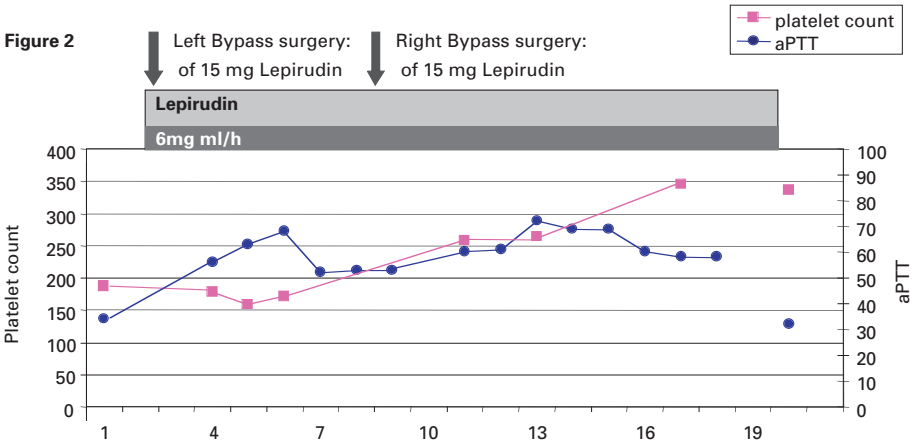
Direct thrombin inhibitors such as Lepirudin are considered to be the anticoagulants of choice in patients with HITT. This new group of anticoagulants has demonstrated high efficacy and low incidence of side effects [3]. As with UFH frequent monitoring is important to prevent bleeding complications. At present the aPTT is the most practical – albeit not the most accurate (especially with high concentrations) – means of monitoring therapy with Lepirudin. However new monitoring methods are being developed and may be on the market soon. For full dose anticoagulation one should attempt to prolong the patient's aPTT "baseline value" (measured before any form of anticoagulation is initiated) 1.5- to 2.5-fold [4]. There is a relatively linear dose effect relationship between hirudin concentration and aPTT up to approximately 70 to 80 s (depending on the reagent used). Caution is needed as higher hirudin concentrations do not induce a linear response with regard to aPTT prolongation. Attempting to achieve more pronounced aPTT prolongation (up to 3-fold "baseline value" as indicated by the manufacturer) could therefore lead to unexpectedly high hirudin concentrations with an accordingly increased bleeding risk.

In the patient we describe much higher doses of Lepirudin were required during acute episodes of thromboembolic complications (fig. 1). A probable explanation for this is a significantly increased concentration of thrombin during the presence of an intravascular thrombus.

Figure 1+2

Changes in the platelet count during the initial heparin therapy are displayed: an immediate improvement is seen after application of Lepirudin. Note the markedly reduced dose of Lepirudin needed to maintain the aPTT in the therapeutic range following removal of the thrombus (1). Note also the rapid and marked increase in the platelet count during administration of Lepirudin in the absence of active thromboembolism during the second hospitalisation (2).





Another striking aspect of this case is the increase in the platelet count during prophylactic therapy with Lepirudin in the absence of thromboembolic complications. This may be due to a decrease in vasculopathic platelet consumption in a patient with atherosclerotic disease and synthetic bypasses in place.

Given that patients with atherosclerotic disease often show impairment of renal function (creatinine clearance below 60 ml/min or serum creatinine above 1.5 mg/ dl), accumulation of hirudin – which is cleared through the kidney – is a potential problem [1]. The initial bolus dose as well as the later infusion dose and rate have to be reduced according to the degree of renal dysfunction (bolus doses as low as 0.005 mg/kg body weight have been advocated in anuric patients) and monitored closely (every 4 hours until the steady-state of aPTT is reached) to avoid accumulation and bleeding.

This case demonstrates that Lepirudin can be used safely and effectively as an alternative anticoagulant in peripheral vascular surgery and more specifically during the clamping phase to prevent intraoperative development of thrombosis [5]. In addition the repetitive use of Lepirudin proved to be effective and safe in the case we describe.

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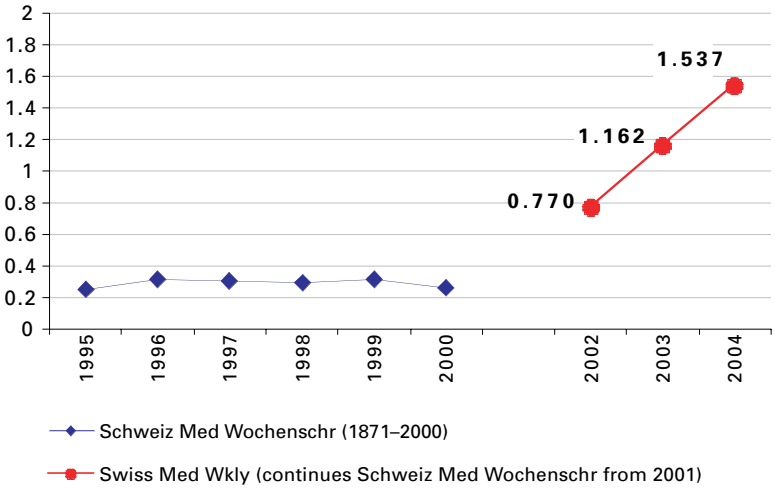

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