Thrombosis Research 146 (2016) 126–130

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Acute intraoperative heparin-induced thrombocytopenia (HIT) and thrombosis during coronary artery bypass grafting: Two case reports providing evidence for the role of preoperative LMWH in triggering sensitization

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ARTICLE INFO

Article history:
Received 26 November 2015
Received in revised form 17 August 2016
Accepted 18 August 2016
Available online 20 August 2016

Keywords:
CPB
Fondaparinux
HIT
Thrombocytopenia
Thromboembolism

ABSTRACT

Introduction: Systemic anticoagulation is necessary during cardiac surgery. To date, the only well established anticoagulation protocol involves the use of heparin. However, heparin can cause heparin-induced thrombocytopenia (HIT) a potentially life threatening immune-mediated thromboembolic syndrome. Until now, devastating consequences of HIT syndrome in patients undergoing heart surgery have been described, but only postoperatively. Here we report the development of HIT syndrome during cardiac revascularization by intra-operative heparin administration in two patients previously exposed to LMWH.

Patients/methods: We report on two patients who developed rapid and profound intravascular coagulation with severe thrombocytopenia (platelet count decreased from ≥250 × 10^9/L to 50 × 10^9/L) due to HIT development caused by heparin administration during coronary artery bypass graft surgery. In addition we report that fondaparinux, given intra-operatively in association with antithrombin, may be a suitable alternative anticoagulant for successfully preventing the devastating consequences of intra-operative HIT development.

Conclusion: To our knowledge, this is the first report describing the development of acute intra-operative HIT, secondary to high-dose UFH administered for coronary revascularization, in which the unexpected presence of platelet-activating anti-PF4/heparin antibodies at surgery was explained by preoperative administration of a one-week course of LMWH but without any preoperative evidence for HIT.

1. Introduction

Systemic anticoagulation is necessary during cardiac surgery. For the time being, the only well established anticoagulation protocol involves the use of heparin, which due to its predictability, rapid action, ease of monitoring by activated clotting time (ACT), ability to inhibit contact system-induced coagulation activation [1] and reversibility with protamine, becomes an integral part of cardiac operations performed with or without extracorporeal circulation. However, heparin can cause heparin-induced thrombocytopenia (HIT), a potentially life threatening immune-mediated thromboembolic complication. HIT occurs due to the formation of antibodies (mainly IgG) against platelet factor 4 (PF4)/heparin complexes that are able to induce activation and aggregation of platelets, massive thrombin generation and fibrin formation [2–4]. Usually, HIT antibodies are detectable 4–5 days after initiation of heparin (UFH) whereas thrombocytopenia starts 2 days later [5].

So far, in patients undergoing heart surgery, the devastating consequences of HIT syndrome have been described only postoperatively [6–8]. Here, we present evidence of severe intravascular coagulation due to HIT development caused by UFH administration during cardiac surgery in two patients who underwent coronary artery bypass graft surgery (CABG). The first patient underwent an 'on-pump' coronary

Abbreviations: HIT, heparin-induced thrombocytopenia; UFH, unfractionated heparin; LMWH, low molecular weight heparin; ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass; CPB, cardiopulmonary bypass; AT, antithrombin; ACT, activated clotting time; RαPTT, ratio activated partial thromboplastin time; AMI, acute myocardial infraction; ACCP, American College of Chest Physicians; HIPAG, heparin induced platelet aggregation test; O.D., optical density; IABP, intra-aortic balloon pump; CORO, cardiac catheterization.

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http://dx.doi.org/10.1016/j.thromres.2016.08.020
0049-3848/

artery bypass (ONCAB) graft surgery while in the second patient the heart surgery started as an 'off-pump' coronary artery bypass (OPCAB), but due to haemodynamic instability subsequent institution of CPB was required.

2. Patients/methods

The first patient, a 48 year old man, was treated with enoxoparin (LMWH) and nitroglycerin after an acute inferiolateral wall myocardial infarction (AMI). Cardiac catheterization revealed severe three-vessel coronary disease with depressed left ventricular ejection fraction (LVEF) of 25% that required coronary artery bypass grafting. In addition, the patient had hypercholesterolemia and he was a heavy smoker without however suffering from diabetes mellitus or showing clinical evidence of peripheral vascular disease or chronic obstructive pulmonary disease. Administration of LMWH (enoxoparin) was initiated (day 0) with the last dose administered on day 7 (i.e. 8th post AMI day), because of planned cardiac surgery, which was performed 12 h after the last dose of LMWH. There was no preoperative decrease in the platelet count, development of skin lesions at the LMWH injection sites, or any other indication pointing to a possible diagnosis of HIT (Fig. A1). Anesthesia and perioperative care were according to usual practice. Standard anticoagulation with UFH was used and the cardiopulmonary bypass (CPB) started when a target clotting activated time (ACT) of ≥480 s was achieved. However, 50 min later, the ACT was decreased to 350 s and increased no more than 400 s despite a further administration of UFH (10,000 U) and 1000 U of concentrated human antithrombin (AT) (Kybernin, CSL Behring). In addition, the patient's platelet count abruptly decreased from 260 × 10^9/L (preoperative value) to 50 × 10^9/L, clots were noted on the surgical field and blood flow appeared to decrease in all the three grafts. A possible diagnosis of acute intra-operative HIT ("rapid-onset HIT") secondary to intra-operative administration of UFH (initially 25,000 units and then 10,000 units administered to this point), was suspected, therefore the third coronary graft anastomosis was rapidly completed, and a blood sample was obtained for laboratory testing for HIT antibodies. UFH was stopped and the patient was given the direct thrombin inhibitor, lepirudin. Later the same day, laboratory tests confirmed the presence of high levels of platelet-activating anti-PF4/heparin antibodies (Table 1). Lepirudin was initially given by an intravenous (IV) bolus of 0.2 mg/kg body weight and then by an IV infusion. Due to haemodynamic instability, placement of an aortic balloon pump (IABP) was required. The patient remained haemodynamically stable allowing his IABP to be removed and his weaning started on the second postoperative day. On the third postoperative day however, an acute right brachial artery occlusion occurred requiring surgical thrombo-embolectomy. The infusion rate of lepirudin was increased targeting an aPTT at 2.3-times baseline aPTT value (range, 2.0–2.8) (RaPTT). Warfarin (coumadin) was started on the 9th postoperative day when the patient's platelet count rose to 150 × 10^9/L. Warfarin was given together with lepirudin for 11 days because we had difficulty in reaching a stable therapeutic INR value. Lepirudin was withdrawn after 2 therapeutic INR values were achieved. The postoperative course was further complicated by melena due to ischemic colitis that required right hemicolectomy. Lepirudin treatment was temporarily withheld for approximately 36 h in order for the patient to undergo hemicolectomy. The patient also developed thrombosis of the right femoral vein and left femoropopliteal artery. In addition the patient suffered from a pulmonary embolism, renal and respiratory failure, sepsis and wound breakdown. Finally the patient died on the 40th postoperative day from multiple organ failure (Fig. A1, 2).

The second patient, a 66-year-old man with a history of moderate renal decline (creatinine clearance 58 mL/min) and hypertension, but free from diabetes mellitus, was administered tinzaparin sodium (LMWH) for a newly diagnosed atrial flutter. Cardiac catheterization performed on the 5th day after initiation of LMWH demonstrated 4-coronary artery disease with preservation of ventricular function. Fifteen days later LMWH was stopped and the patient underwent cardiac surgery on beating heart. [9].

At the completion of distal grafts anastomoses though, instability occurred requiring institution of CPB. The CPB started 3 min after the administration of 10,000 IU of UFH and increment of ACT to 540 s while the proximal anastomoses on the ascending aorta (partially clamped) were performed. Thirty minutes after initiation of CPB, the grafts flow started to reduce whereas clots were noted in the surgical field and the platelet count decreased from what was 280 × 10^9/L the day before surgery to 35 × 10^9/L. HIT was suspected and therefore a blood sample was withdrawn for laboratory assessment and UFH was stopped immediately. An intravenous bolus of 7.5 mg fondaparinux was administered in association with 2.5 mg given subcutaneously. The patient was also given 1000 U of AT and 3 g hydrocortisone sodium succinate (Solu-Cortef). The CPB subsequently proceeded without any incident and the last proximal anastomosis on the ascending aorta was completed whereas the flow sufficiency in the bypass grafts was restored. The patient was promptly separated form CPB and remained haemodynamically stable. The following day fondaparinux was restarted at a daily dose 2.5 mg in association with 75 mg of clopidogrel. Laboratory evidence supporting the presence of high levels of platelet-activating anti-PF4/heparin antibodies was found (Table 1). Thrombocytopenia began to resolve (120 × 10^9/L) on the 6th postoperative day when warfarin was started and one day later the patient was discharged (Fig. B).

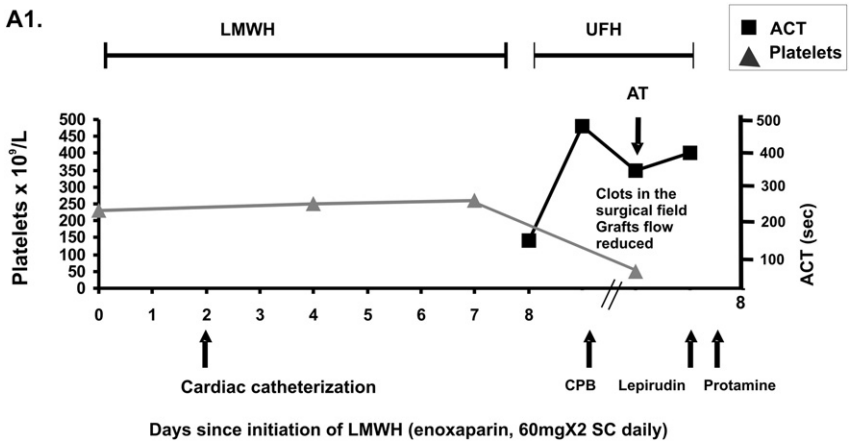

Fig. A. 1: The platelet count kinetics preoperatively and the profound thrombocytopenia in association with intravascular coagulation process intraoperatively; when the heart surgery and cardiac catheterization took place; the given anticoagulation preoperatively and during heart surgery; the serial ACT evaluation and its resistance to undergo prolongation despite excess of UFH (and AT) administration.