

Coronary arterial bypass surgery with beating heart in a patient with Heparin-induced thrombocytopenia: Usage of thrombin inhibitor (Lepirudin; r-hirudin)

Case Report

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Abstract: One of the most important adverse drug reactions that physicians encounter is the life-threatening prothrombotic syndrome known as heparin-induced thrombocytopenia (HIT). In patients with a history of heparin-induced thrombocytopenia and coronary arterial disease, alternative anticoagulatory regimens are needed during cardiac surgery for prevention of thrombosis. Treatment options for such patients now generally include the use of alternative anticoagulants such as lepirudin, bivalirudin, argatroban or danaparoid. In this article, we present a case where heparin-induced thrombocytopenia was properly performed coronary arterial bypass grafting by using lepirudin. (This sentence is confusing)

Keywords: Lepirudin • Heparin-induced thrombocytopenia • Coronary arterial bypass surgery • Heparin • Anticoagulation

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1. Introduction

Heparin-induced thrombocytopenia (HIT) is a relatively uncommon but not rare complication of heparin administration [1]. HIT is an immune-mediated drug reaction occurring in up to 3% of patients treated with heparin. It typically manifests 5 to 10 days after heparin therapy [2]. The pathogenesis involves the development of antibodies of the immunoglobulin G (IgG) that bind to platelet factor 4 (PF4)-heparin complexes [3,4].

This syndrome is more likely to occur during treatment with unfractionated heparin (UFH), but it can also be seen due to low molecular weight heparins (LMWHs). Administration of heparin causes platelet aggregation, thromboembolism, and thrombocytopenia. It is advisable that heparin not be administered in any form to patients with documented or suspected HIT. This situation, of course, elicits a problem for those

patients requiring cardiac surgery. In such patients, thrombin inhibitors can be used as lepirudin for systemic anticoagulation [5].

In this report, we submit our experience with lepirudin, which is a recombinant hirudin (r-hirudin) and an alternative to heparin for systemic anticoagulation. We use activate clotting time (ACT) and activated partial thromboplastin time (aPTT) for monitoring anticoagulation status during cardiac surgery with beating heart.

2. Case Report

We are presented with a 78-year-old male with anterior myocardial infarction admitted to the cardiology clinical. His electrocardiography had ST elevations in anterior derivations. In laboratory examination; thrombosit was 244,000/ml. In echocardiography, there was apical

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akinezia and ejection fraction was 50%. The patient was brought to the catheterization laboratory for both coronary angiography and insert temporary pace. After unfractional heparinization (UFH), the coronary angiography was made and determined two vessels disease including left anterior descending artery and right coronary artery. The operation decision was given for coronary arteries. Postcatheterization, the patient was hospitalized until his scheduled operation. The patient was treated with low molecular weight heparin (LMWH), a beta-blocker, and an angiotensin-converting enzyme inhibitor. After 3 days, laboratory examinations were repeated. The platelet count decreased from 244,000/ml to 58,000/ml. Due to this decrease in platelet count, the LMWH was discontinued and heparin-induced antibody tests were sent to the laboratory. The platelet count continued to decrease to 48,000/ml prior to surgery even after the heparin was discontinued. The heparin-induced antibody test (ELISA test) was positive, and a diagnosis of HIT was made. After heparin ceased, in 5th day, platelet count was determined as 92,000/ml. In operation, after induction of general anesthesia, anticoagulation was achieved with a bolus dose of 0.3 mg/kg lepirudin at 10 minutes. Then, lepirudin was continued by an infusion (0.15 mg/kg/hr). The ACT was used to monitor anticoagulation, and it was between 350 and 500 seconds during surgery. The aPTT was maintained between 1.5 to 2.5 times the normal values, and was greater than 200 seconds. Two coronary arterial bypass grafting was performed with beating heart by using two saphenous veins. The lepirudin infusion was discontinued after proximal anastomosis. The ACT returned to baseline after 40 minutes. Intravenous regimen transamine was used to minimize blood loss. No significant adverse effects were noted. The total blood product utilization during the surgery included red blood cell 300 ml, platelets 200 ml, and fresh-frozen plasma 400 ml. The total postoperative blood loss was 475 ml. The postoperative coagulation status was monitored using the aPTT, which returned to normal on postoperative in 2th day. The patient's platelet value was 140,000/ml on postoperative first day and 175,000/ml on postoperative in 5th day. Postoperative course was uneventfully. The patient was discharged on 10th day with acetylsalicylic acid therapy.

3. Discussion

Heparin is used for prophylaxis and/or therapy of thrombotic events, during cardiac surgery; immune-mediated HIT is the most severe adverse effect of heparin. It is an immune-mediated disorder resulting

when antibodies (typically IgG) are produced that bind to heparin complexed with a "self" protein, PF4 on the surface of platelets. The immune-mediated platelet activation of HIT leads to the paradoxical effect of an anticoagulant inducing coagulation as well as causing the loss of platelets from the circulation, and producing disseminated thrombosis, embolism, and profound thrombocytopenia [6].

HIT is diagnosed when there is substantial (> 30 to 50%) drops in platelet count within 5 to 10 days, thromboembolic events (venous and arterial thrombosis, skin lesions), and a positive PF4/heparin-ELISA and/or a positive heparin-induced platelet activation test (HIPA) [7,8]. The decrease in platelet counts occurred after day 3 from UFH and LMWH. The platelet count drop in HIT usually results in only moderately severe thrombocytopenia. It is between 20-150,000/ml (median, 60,000/ml) are seen in about 80% of patients [6] as our case. Platelet counts below 20,000 are only seen in approximately 10% of patients, but even then without concomitant bleeding. In the remaining 10% of patients, the platelet count does not fall below 150,000/ml. In our patient, there was no clinical sign except for platelet count drop and PF4/heparin-ELISA was positive.

The reported incidence of HIT varies from 1% to 30% of surgical patients. An incidence of approximately 1% has been reported in patients undergoing cardiac surgery [9]. When HIT is suspected, appropriate treatment begins with the immediate cessation of heparin exposure. All heparins, including LMWHs and even small doses of UFH, such as the residue from flushing invasive catheters, should be discontinued and, if possible, heparin-coated devices removed. Heparin's contraindication in patients with acute HIT necessitates the use of alternative agents when these patients require anticoagulation in association with cardiovascular surgery. Appropriate agents are either a direct thrombin inhibitor (DTI) such as lepirudin, argatroban, and bivalirudin, or the heparinoid factor Xa inhibitor, danaparoid [10,11].

Lepirudin (r-hirudin, Refludan®, Berlex Laboratories, Wayne, IN) is a recombinantly expressed variant form of hirudin, a single-chain, 65-amino acid polypeptide secreted by the salivary glands of the medicinal leech that is the most potent natural thrombin inhibitor yet identified. It is a highly specific direction inhibitor of thrombin [1,11]. Unlike heparin, its mechanism of action is independent of antithrombin III. R-hirudins are not inhibited by platelet factor 4. The initial dose for CPB is 0.25 mg/kg, followed by an infusion of 0.15 mg/kg/hr [7].

UFH is the anticoagulant of choice for cardiac surgery and has widespread use. Administration of

UFH is commonly continued after surgery to provide antithrombotic prophylaxis. In several prospective studies, the frequency of HIT in cardiac surgical patients who received UFH postoperatively was about 3%, which is consistent with the findings of retrospective reviews, in which the overall frequency was found to be about 2% [12]. Although less likely to cause HIT, LMWHs can induce HIT antibodies and clinical HIT can develop during LMWH administration [13]. There is emerging evidence that LMWHs cause HIT less often when compared with UFH [14]. These patients should therefore be anticoagulated with an alternative drug and they should be carefully assessed relation to thrombotic events. Recently, Farmer et al. [15] presented data suggesting that HIT patients without thrombosis still require therapeutic anticoagulation. Although our patient had only thrombocytopenia without thrombosis, we use also coronary arterial bypass with beating heart thrombin inhibitor due to risk of thrombotic events. Three different methods have been used to monitor anticoagulation by r-hirudin during anticoagulant therapy: ACT, aPTT, and ecarine clotting time (ECT) [16]. The ECT test allows for sensitive monitoring of high lepirudin concentrations. During cardiac surgery, lepirudin dosage is adjusted in conjunction with laboratory ECT monitoring, which can

be obtained rapidly using whole blood supplemented with normal human plasma [16]. Although recombinant hirudin combined with monitoring of ECT was a safe, effective, and easily managed anticoagulant technique, because ECT measurement was not made in our patient, we used ACT and aPTT levels during cardiac surgery. Lepirudin dosage adjustments was made to maintain the activated aPTT ratio at 1.5–2.5 times the patient's baseline [1]. ACT and aPTT were greater than 300 and 1.5–2.5 times, respectively. The embolic events were not determined after surgery in relation to lepirudin usage in our patient.

In conclusion, we consider that hirudin is an effective alternative anticoagulant for treatment of HIT patients with or without thrombosis during cardiac surgery. Also, HIT patients with isolated thrombocytopenia benefit from ACT and aPTT adjusted anticoagulation with lepirudin. Nonetheless, it is necessary and appropriate to monitor anticoagulant status during cardiac surgery and postoperatively term. Major hemorrhage, the main risk of lepirudin treatment, occurs in about 15% of patients. If activated clotting time and partial thromboplastin time age close monitored, the risk of bleeding might be reduced.

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