Case Reports

Anticoagulation with Bivalirudin during Deep Hypothermic Circulatory Arrest

in a Patient with Heparin-Induced Thrombocytopenia

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Heparin-induced thrombocytopenia is a well-recognized complication of anticoagulation with heparin. We present the case of a patient with recent heparin-induced thrombocytopenia who subsequently needed surgery on an emergency basis for acute type A aortic dissection. This article reports the successful use of bivalirudin, a direct thrombin inhibitor, as an alternative to heparin throughout cardiopulmonary bypass and deep hypothermic circulatory arrest. We contend that bivalirudin is a safe alternative to heparin when performing surgery for aortic dissection and should be considered as an option for use in patients who present with heparin-induced thrombocytopenia. ***(Tex Heart Inst J 2014;41(6):645-8)***

Key words: *Anticoagulants/adverse effects; aortic dissection; bivalirudin; blood coagulation; blood loss, surgical; cardiopulmonary bypass; circulatory arrest, deep hypothermia induced; hemofiltration; heparin/adverse effects; hirudins; thrombocytopenia/chemically induced/prevention & control*

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Heparin-induced thrombocytopenia (HIT) is a well recognized sequela of anticoagulation with heparin.[1] Unfractionated heparin (UFH) currently remains the gold standard for anticoagulation in cardiopulmonary bypass (CPB) because of its low cost, safety profile, ease of dosing, and effective reversibility with protamine. Nevertheless, it is estimated that about 17% of patients on UFH will develop an immune response through the generation of immunoglobulin-G (IgG) antibodies against the complex of heparin with platelet factor 4, which results in type II HIT in 1% to 3% of those patients.[2] The consequent immune complex induces platelet activation and consumption, causing a drastic fall in platelet count, arterial or venous thrombosis (or both), and eventual bleeding.[2,3] Patients with an established diagnosis of HIT—for whom surgery that necessitates anticoagulation is planned—should therefore be administered an alternative drug.[2] As a result of both blood stasis and alterations in enzymatic activity upon extreme temperature changes, deep hypothermic circulatory arrest (DHCA) further complicates the issues of anticoagulation, and increases the need for an alternative non-heparin-based anticoagulant. An alternative drug in such an instance is the bivalent, direct thrombin inhibitor bivalirudin, which achieves anticoagulation during CPB and DHCA.[4]

We report a case of type II HIT in a patient undergoing emergency surgery for an acute type A aortic dissection, requiring CPB and DHCA, in whom we successfully used bivalirudin as an anticoagulant.

Case Report

An 82-year-old man presented with chest pain and an inferior ST-elevation myocardial infarction. A computed tomographic (CT) angiogram also revealed a Stanford type A aortic dissection with a 6-cm ascending aortic aneurysm extending to the aortic arch and a large pericardial effusion with radiographic signs of tamponade. The patient also had severe aortic valve regurgitation, with a left ventricular ejection fraction of 0.62.

Heparin had been initiated for atrial fibrillation at another hospital, before acute aortic dissection was diagnosed. The patient developed HIT, which was confirmed via enzyme-linked immunosorbent assay for the presence of antibodies against heparin and platelet factor 4 complex. Heparin was subsequently discontinued.

The patient was taken to the operating room for repair of type A aortic dissection. Bivalirudin, a direct thrombin inhibitor, was used to achieve adequate anticoagulation

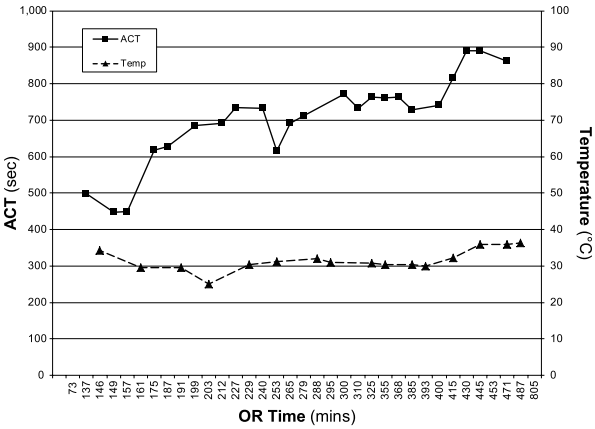

Fig. 1 *Intraoperative ACT levels. Intermittent doses of bivalirudin (0.5 mg/kg) were given during the procedure as needed, to maintain an ACT of more than 480 seconds.*

ACT = activated clotting time; OR = operating room

for CPB. Under a protocol similar to the one described by Koster and colleagues,[5] we primed the CPB circuit with 50 mg of bivalirudin and administered a loading dose of 1 mg/kg 15 minutes before cannulation. An infusion of 2.5 mg/kg/hr of bivalirudin was maintained for the duration of CPB. Intermittent doses (0.5 mg/kg) were given during the procedure as needed, to maintain an activated clotting time (ACT) of more than 480 seconds (Fig. 1). In addition, we diluted 100 mg of bivalirudin in 1,000 cc of sodium chloride solution and ran them into the cell-saver system. A bridge between the arterial and venous lines, close to the cannulation sites, was constructed in advance and was clamped.

We approached the aorta via a midline sternotomy and drained 300 to 450 mL of bloody effusive material. The right axillary artery and right atrium were cannulated, and immediate cooling was initiated. To avoid stagnation, the level of blood was maintained below 600 cc in the CPB reservoir.

The DHCA was initiated when the patient's bladder temperature reached 20 °C. The patient's head was packed with ice. Cardioplegic solution was infused retrogradely, both at initiation of DHCA and at 20-minute intervals thereafter. After each dose of cardioplegic solution, the line was flushed with Plasma-Lyte to remove residual blood. During DHCA, the venous and arterial lines were clamped distal to the bridge, and continuous circulation was established through the bridge in order to avoid blood stasis.

Selective antegrade cerebral perfusion was initiated via the right axillary cannula and via cannulation of the left carotid artery. The brachiocephalic artery was clamped in its mid portion, and the bridge between the arterial and venous lines was clamped again. The bridge was flushed periodically to avoid stagnation, and antegrade cerebral perfusion was maintained at a rate of 10 cc/kg. The temperature of the perfusate was 20 °C, the hematocrit was maintained at 30, and alpha-stat pH management was used.

The aortic arch was replaced with a 24-mm graft via the hemi-arch technique. Before completing the anastomosis, we removed the left carotid cannula, flushed the aorta via the right axillary artery, and carefully removed all the débris and air. The graft was cross-clamped and DHCA was discontinued. Rewarming was initiated.

The aortic root was replaced with a 21-mm Freestyle® bioprosthesis (Medtronic, Inc.; Minneapolis, Minn). The left main coronary artery was anastomosed to an 8-mm graft, which was then brought behind the Freestyle root and anastomosed to an opening on the root's right lateral surface. The dissected right coronary artery was bypassed with a saphenous vein graft.

The bivalirudin infusion was discontinued 15 minutes before weaning the patient from CPB, and decannulation was performed within 10 minutes after CPB. The bridge between the arterial and venous lines was reopened after decannulation (to prevent stagnation), and the CPB pump was once again primed with 50 mg of bivalirudin.

The patient was transfused with 23 units of packed red blood cells, 9 units of fresh frozen plasma, and 3 units of cryoprecipitate. He also needed 2 mg of NovoSeven RT recombinant coagulation factor VIIa (Novo Nordisk AS; Bagsvaerd, Denmark) intraoperatively. Continuous oozing of blood from the raw surface areas necessitated the placement of a vacuum dressing in an open chest.

Blood loss ceased on the 2nd postoperative day, and on day 5 the patient was taken back to surgery for chest closure. The patient had an uneventful postoperative course and was discharged from the hospital on postoperative day 8.

Discussion

Heparin-induced thrombocytopenia is a severe immune-mediated disorder resulting from IgG antibodies that are produced to counter a complex of heparin with platelet factor 4—which in turn leads to excessive platelet and thrombin activation.[5] If HIT is not diagnosed preoperatively, it can have devastating thromboembolic sequelae that include limb ischemia, myocardial infarction, stroke, pulmonary embolism, and even death.[6] Once HIT is diagnosed in patients who are receiving heparin, further administration of the drug should be discontinued immediately. After the discontinuation of heparin, the prothrombotic risk persists for days or even weeks.[3]

The main presentation of HIT after cardiac surgery is intravascular thrombosis, predominantly in arterial rather than venous sites: the mortality rates reported in large studies have been as high as 28%.[7] This cer-

tainly warrants an alternative non-heparin-containing anticoagulant. Although bivalirudin has become one of the most widely used antithrombotic agents in the United States for percutaneous coronary intervention, its use as an alternative to heparin during CPB has not been promoted because no antidote is available.[8] However, the CHOOSE-ON study,[6] the first to investigate bivalirudin's systematic use in HIT patients in need of CPB, confirmed that the direct thrombin inhibitor is a safe and effective drug for this indication.

Bivalirudin is semisynthetic, specific, and reversible. It directly inhibits thrombin by specifically binding to the catalytic site and to the anion-binding exosite of circulating and fibrin-bound thrombin.[9,10] It has a short half-life (25 min) and is primarily metabolized (80%) through proteolysis mediated by plasma proteases and thrombin. The other 20% is excreted by the kidneys. This makes the drug a safe alternative for patients with renal insufficiency.[2,11] Residual levels of the drug can also be cleared via hemofiltration, thus expanding the use of bivalirudin to include even those patients on hemodialysis.[2]

Ecarin clotting time has been recommended for intraoperative monitoring, but that test is not widely available and ACT can be used as a safe alternative.[2,6] In our patient, anticoagulation was maintained successfully above 480 seconds throughout the procedure. It is also important that ACT be monitored at regular intervals: after every additional bolus of 0.25 mg/kg and after adjustment of the infusion rate.

The sensitivity of bivalirudin to proteolysis is determined by the flow of blood. Blood stasis stimulates the activity of proteases and diminishes the effectiveness of bivalirudin.[4] The presence, therefore, of a visible thrombus in pooled blood, such as in the pericardial cavity, should not be interpreted as indicative of a need for additional anticoagulation—rather, it might be indicative of local bivalirudin metabolism, which does not correlate with intravascular levels. If blood cardioplegic solution is used, the blood should be drawn directly from the circuit, mixed with the cardioplegic solution, and immediately infused into the coronary system to avoid stasis.[12,13]

Deep hypothermia significantly reduces the proteolysis of bivalirudin.[4,5] This effect was observed in a patient with antiphospholipid syndrome that involved resection of right atrial thrombi: during DHCA, the ACT increased from 500 to 750 seconds, which suggested reduction of the proteolysis of bivalirudin.[4] In addition, ACT levels fell during rewarming, and a prophylactic bolus of bivalirudin was administered to keep the ACT over 450 seconds.

The risk of clot formation in the CPB circuit shortly after separation is high. To ensure the availability of the CPB circuit in case of hemodynamic instability, we created a bridge between the arterial and venous lines, reopened it, and primed the system with 50 mg bivalirudin after decannulation. Furthermore, active measures should be taken to maintain normothermia during the early postoperative period.

Our reported case is the 3rd in which successful anticoagulation with bivalirudin was achieved during CPB and DHCA[4,5] and the 2nd in which bivalirudin's use was validated in emergency cardiac surgery.[5] As with any other drug, bivalirudin has limitations. Because direct thrombin inhibitors lack a known antidote (unlike protamine for UFH), they should be strictly contraindicated in individuals who are actively bleeding.[2] Approximately 4 to 5 half-lives are needed for the effects of bivalirudin to be eliminated, unless their elimination is accelerated by hemodialysis.[4]

Despite these limitations, a non-heparin-containing anticoagulant is essential when heparin is contraindicated. Ideally, the safe and effective alternative should lack immunogenicity or cross-reactivity with heparin, have a short half-life, be quickly reversible, and be easy to monitor.[2] For these reasons, bivalirudin is a safe alternative to heparin in emergency (as well as elective) procedures that necessitate CPB and DHCA. It should be an attractive option in patients who present with HIT.[2] Nevertheless, larger studies are necessary to critically evaluate the safety profile and the effectiveness of bivalirudin in open-heart procedures.

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