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Original Research Paper

Cardiology

ANTICOAGULATION WITH BIVALIRUDIN IN CARDIAC SURGERY

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ABSTRACT The use of an alternative anticoagulant to heparin is required in patients undergoing on-pump cardiac surgery and who have been diagnosed with heparin hypersensitivity. Bivalirudin is an oligopeptide analogue of hirudin acting on thrombin through direct inhibition. It has a half-life of approximately 25 minutes, and is mostly cleared from the circulation by proteolytic enzymes. Its pharmacological properties make it an attractive alternative anticoagulant to heparin for patients presenting with heparin hypersensitivity requiring cardiac surgery. However, the normal surgical protocol needs adjusting to reflect these properties. These changes mostly affect the perfusion setup and conduct on bypass

KEYWORDS :

INTRODUCTION

We have successfully done off pump total arterial coronary surgery (CABG) using bivalirudin in a patient awaiting liver transplantation with history of variceal bleed and thrombocytopenia and also in another patient we used Bivalirudin for traumatic mitral regurgitation and heparin induced thrombocytopenia, who underwent mitral valve repair successfully.

Short case summary

First was a patient 46 yr old male awaiting liver transplantatio n at AIMS Cochin, diagnosed to have triple vessel disease, thrombocytopenia and bilateral severe varicose veins. He had history of multiple variceal bleed and anemia. Off pump (beating heart) total arterial revascularization, with fully skeletonized harvest of bilateral internal mammary arteries and bilateral radial arteries were done. Bivalirudin was used for the procedure. The following grafts were fashioned. LIMA – LAD, RIMA to PDA with extension of RIMA to reach distal PDA being done with EEA of right radial artery segment to RIMA. LIMA -LRA -Y (composite graft) was fashioned to D1, OMB1 and OMB2.Mid patch plasty after endarterectomy was done with radial artery segment.

The second was a young male 28 years old admitted with history of RTA at Nagercoil and blunt trauma. He was diagnosed to have superior mesenteric thrombosis. ECHO evaluation in ICU showed severe traumatic mitral regurgitation. He was diagnosed to have HIT. Successful repair of mitral valve was done with creation of artificial neo chordae using PTFE sutures, leaflet tear plication and reinforcement with CE annuloplasty ring. Bivalirudin was used in bypass.

TECHNIQUE

Bivalirudin was the anticoagulant during CPB. The extracorporeal circuit consisted of a roller pump, a Capiox SX oxygenator (Terumo Cardiovascular Systems, Ann Arbor, MI), and a hard plastic reservoir. No heparin was used. The pump priming solution consisted of 2000 mL of plasmalyte and 50 mEq of bicarbonate. Blood cardioplegia was given in antegrade and antegrade manner. OPCAB patients receive bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg/h infusion).Bivaliru din for ONCAB was administered intravenously as a 1.25 mg/kg bolus, followed by an initial continuous infusion at 2.75 $mg \cdot kg^{-1} \cdot h^{-1}$.Bivalirudin was added to the pump priming solution. The activated clotting time (ACT) was measured every 15 to 30 minutes. Additional boluses were given as needed, and the infusion rate was adjusted to obtain an ACT of 500 to 600 seconds.

DISCUSSION

During cardiac surgery the platelet count falls, primarily due to platelet damage and destruction in the bypass circuit and haemodilution. The platelet count falls after open-heart surgery by approximately 30% by the conclusion of surgery, reaching a nadir of 40 to 60% on the second or third postoperative day. In addition to drug-induced thrombocytope nia, the mechanical destruction of platelets and haemodilution in the bypass circuit play important roles in the occurrence of postoperative thrombocytopenia. Sepsis, intraaortic balloon pump and post transfusion purpura must also be considered in selected cases. Heparin is the standard agent used for systemic anticoagulation during cardiopulmon ary bypass. The early initiation of therapy with a direct thrombin inhibitor is recommended when HIT is suspected after PCI or open-heart surgery, or in patients with ACSs..

Heparin given to HIT type II can result in thromboembolic events, severe bleeding, and death.

Bivalirudin (Angiomax), a direct thrombin inhibitor, previously known as Hirulog, is a semi synthetic derivative of hirudin that inactivates both unbound and fibrin-bound thrombin, and rapidly induces anticoagulation. Primary elimination route is renal with a short duration of action, and can be used safely in patients with HIT type II. The cornerstone of therapy is discontinuation of heparin.Heparin -induced thrombocytope nia type II is an immune-mediated condition more common with the use of unfractionated heparins..Late recognition (i.e., postoperatively) is associated with a high frequency of bleeding (53%), arterial and venous thromboembolic complications (44%), and death (33%). The test result for HIT antibodies (polysaccharide-PF4complex) may be was negative. In up to 25% of cases, the antibody that causes HIT does not recognize the polysaccharide-PF4 complex, indicating that antigens other than PF4 are responsible for this condition.

HIT can be differentiated from thrombocytopenia due to GPIIb/IIIa inhibitor therapy by the time course and degree of thrombocytopenia. Thrombocytopenia due to HIT generally occurs between days 5 and 14 of heparin therapy. The exception to this rule is the patient who has been exposed to heparin in the previous 3 months in whom the fall is noted early after re exposure. The presence of petechiae or gingival hemorrhage, suggests a diagnosis other than HIT.

TIPS for thrombocytopenia for patients referred for cardiac surgery

- Most commonly associated with thrombocytopenia are the glycoprotein (GP) IIb/IIIa receptor inhibitors- abciximab, tirofiban, and eptifibatide and heparin.
- Pseudo thrombocytopenia occurs due to platelet clumping in tubes containing ethylendiaminetetraacetic acid as an anticoagulant.
- TTP associated with ticlopidine, occurs within 2 to 12 weeks of the initiation of therapy
- TTP related to clopidogrel occurs within the first 2 weeks of use
- For GPIIb/IIIa inhibitors the platelet count begins to fall very early after drug initiation, and so the platelet count should be checked 2 to 4 h after therapy with the agent has been started.
- GPIIb/IIIa inhibitor should be discontinued when a significant drop is noted early (unless pseudo thrombocytopenia is confirmed)
- Alternatives are needed when patients with heparin-inducedthrombocytopenia type II .Effective anticoagulatio n can be achieved with bivalirudin, a direct thrombin inhibitor.

We have now available the direct thrombin inhibitors, which include recombinant hirudin (lepirudin), argatroban, and bivalirudin (Angiomax). These compounds lack cross-reactivity with heparin antibodies. The disadvantages of their use include lack of an antidote, limited experience compared with heparin, and cost. Among the direct thrombin inhibitors, lepirudin has been the most frequently used during cardiac procedures. Unfortunately, it lacks an easy and standardized monitoring of anticoagulant activity during CPB. Its relatively long half-life (80 minutes) can increase the risk of postoperative bleeding. Argatroban has recently been used with success during CPB in Japan, but it is not available for use in the United States. It has a short half-life (30 minutes) and can be effectively followed with measurement of ACT during CPB.

Bivalirudin has specific advantages in special situations which include its short half-life (25 minutes),the ability to monitor its activity by measurement of ACT, the prothrombin time, activated partial thromboplastin time, thrombin time, and ACT all rise linearly with an increase in bivalirudin dose, bivalirudin is cleared by a combination of renal elimination and intravascular proteolysis, with renal elimination thought to be the major route of clearance, and the ability to adjust the dose of bivalirudin during CPB to keep the ACT between 500 and 600 seconds, using intravenous boluses in addition to the continuous infusion. During operation no clot formation was noted in the CPB circuit, tubing or operating field and the postoperative bleeding was acceptable as reflected by the chest tube output.

CONCLUSION

We conclude that bivalirudin is a safe alternative to heparin for anticoagulation during CPB in cardiac operations. For PCI Argatroban has been approved for use in patients with HIT. We would like to add that use off pump (beating heart technique) and of BIMA -of fully skeletonized internal mammary arteries bilaterally and radial arteries avoids the need for antiplatelet agents in the postoperative period and use of bivalirudin in these patients is safe and is extremely useful in the subset of patient awaiting liver transplant or those with HIT

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