**Bivalirudin, an Anticoagulation Alternative in Patients with Heparin Induced Thrombocytopenia during Cardiopulmonary Bypass**

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Heparin induced thrombocytopenia (HIT) is a relatively common adverse reaction in patients receiving heparin, occurring in up to 3% of heparinized patients undergoing cardiac surgery (1). It is the most common cause of drug related thrombocytopenia. 3 types of HIT exist: HIT 1, HIT 2, and HIT and thrombosis (HITT). While HIT 1 does not have any significant sequelae, HIT 2 and HITT result in platelet aggregation, thrombo-embolism, and thrombocytopenia. When thrombin is exposed to thrombogenic substances, platelets are activated and release platelet factor 4 (PF4). Heparin binds to PF4 creating a complex for IgG leading to further activation of platelets and release of thrombin (2). A HIT diagnosis, particularly HIT 2 and HITT, precludes the use of heparin. Patients with documented HIT requiring cardiopulmonary bypass (CPB) need alternatives to heparin.

A number of the alternatives to heparin therapy have been used over the years which include lepirudin, argatroban, and bivalirudin. Lepirudin, a recombinant form of hirudin derived from leech saliva, is a direct thrombin inhibitor with a long half-life and irreversible binding (3). Similarly, argatroban, a synthetic direct thrombin inhibitor, binds irreversibly and has a long half-life (4). Because of these properties, it makes the use of these alternatives to heparin more challenging. Bivalirudin, a synthetic 20 AA peptide analog of hirudin, is a direct thrombin inhibitor that works by binding to the catalytic and anion binding exosite sites. It is shorter acting with a half-life of 25 minutes and this makes it easier to use. Its elimination is dependant mostly on proteolytic cleavage and partly on renal clearance. The elimination profile is similar in healthy patients and in patients with mildly impaired renal function. Bivalirudin causes a dose-dependent increase in aPTT, PT, ECT, and ACT and does not have a reversal agent (5).

Currently bivalirudin is the most commonly used anticoagulant for patients with HIT who require CPB because of the shorter half-life. A baseline ACT value is checked before starting to give bivalirudin. The target of ACT for CPB is 2.5 times the baseline. A loading dose of 1mg/kg is given followed by an infusion of 2.5mg/kg/hour. 50mg of bivalirudin is added to the prime. If bank blood is used for the prime, bivalirudin is added as late as possible to ensure that enough is present in the prime. During CPB, a bolus of 0.2-0.5mg/kg of bivalirudin is given to maintain the ACT at 2.5 times the baseline. One of the major considerations is to avoid stagnation in the CPB circuit including the venous reservoir, surgical field (blood in the pleural space), and the vein grafts. Cardioplegia every 15 minutes, continuous use of a chest slinky, and using saline instead of blood in vein grafts helps to avoid blood stagnation. Bivalirudin infusion is discontinued approximately 15 minutes before coming off CPB. Bivalirudin should not be rebolused if CPB is resumed within 20-25 minutes. CPD instead of heparin is used for anticoagulation in cell saver (6). Bivalirudin is an effective alternative to heparin, especially for patients with HIT. Bivalirudin does not need to be reversed and its short half-life makes it easier to titrate. While there is no standard dosing for bivalirudin during CPB cases, most institutions use a similar dosing approach, described above. Dosing is based on clinical trials which compared bivalirudin to heparin for percutaneous coronary interventions (PCI). The primary endpoints for these studies included death, myocardial infarction, urgent target-vessel revascularization due to myocardial ischemia within 30 days, and major bleeding. Most studies had similar results for the primary endpoints except that major bleeding was more common in the groups that received heparin. One of the largest randomized double-blind multicenter studies was the REPLACE-2 trial. In this study, one group of patients undergoing PCI received bivalirudin with a platelet glycoprotein IIb/IIIa inhibitor (GPI) and the other group received heparin with a GPI. Bivalirudin was dosed at 0.75mg/kg and then infused at 1.75mg/kg/hour, values slightly less than what is being used for CPB cases (7). More recently, the New England Journal of Medicine released a study which compared bivalirudin (0.75mg/kg with 1.75mg/kg/hour infusion) and clopidogrel to unfractionated heparin and clopidogrel in patients undergoing PCI. This study also demonstrated increased bleeding complications with heparin use and found that in patients with stable and unstable angina who underwent PCI after pretreatment with clopidogrel, bivalirudin significantly reduced the incidence of major bleeding as compared with unfractionated heparin (8).

In summary, bivalirudin, with its short half-life, is an effective alternative to heparin in patients with HIT. While much of our information regarding bivalirudin is inferred, large double blinded studies comparing bivalirudin to heparin for CPB are lacking. With such studies, a more reliable and scientifically-based dosing guideline could be developed, particularly benefiting patients with HIT.