Fondaparinux as a Safe Alternative for Managing Heparin-Induced Thrombocytopenia in Postoperative Cardiac Surgery Patients

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Objective: **Heparin-induced thrombocytopenia (HIT) is a rare but severe prothrombotic disorder of heparin treatment that leads to a decline in platelet count and thrombotic complications. If HIT is suspected, then heparin should be stopped and an alternative anticoagulant started. Fondaparinux is a factor Xa-inhibitor that is not FDA-approved for this condition, but preliminary experience in HIT patients has been reported in the literature. The present study describes an experience of anticoagulation management with fondaparinux in postoperative cardiac surgery patients.**

Design: **Retrospective study.**

Setting: **Tertiary hospital.**

Participants: **Patients who had undergone cardiac surgery from October 2009 to June 2012.**

Interventions: **After HIT was suspected clinically, PaGIA and ELISA test were performed in all patients to diagnose HIT. In the patients included, anticoagulation was managed with a low dose of fondaparinux and daily monitoring of platelet count and anti-Xa level.**

Measurements and Main Results: **Of a total of 1,338 postoperative cardiac surgery patients, 15 patients were included (1.1%). Twelve of the 15 patients with HIT presented with renal failure and were under continuous renal replacement therapy. Two major bleeding events occurred during fondaparinux treatment, although platelet count and anti-Xa activity remained within the normal range. No thrombotic episodes were diagnosed.**

Conclusion: **With daily monitoring of anti-Xa activity, fondaparinux appeared to be a good alternative to heparin in the study group; however, randomized clinical trials are needed to establish the safety and efficacy of this drug in critically ill, previously HIT patients.**

KEY WORDS: heparin-induced thrombocytopenia, fondaparinux, cardiac surgery, HIT, HITT

THROMBOCYTOPENIA, defined as a decline in the platelet count by >50% from baseline, is frequent in patients who have undergone cardiopulmonary bypass and usually is due to hemodilution, mechanical destruction by intravascular catheters, antiplatelet agents, or infections. Less frequently, it may appear as a prothrombotic adverse drug reaction to heparin therapy known as heparin-induced thrombocytopenia (HIT).

HIT is defined as thrombocytopenia that occurs between 5 and 14 days after starting heparin, and its incidence in cardiothoracic surgical patients is 1% to 3%.[1–3] It is an immune-mediated disorder in which IgG antibodies against platelet factor 4/heparin complexes (PF4/H) develop. This leads to a decrease in platelet count and an increase in the risk of thromboembolic complications.[2]

Diagnosis of HIT should be based mainly on clinical criteria: Thrombocytopenia occurring during heparin administration, exclusion of other causes of thrombocytopenia, and recovery of platelet count after withdrawal of heparin. However, diagnosis may be confirmed by laboratory tests. The most widely available laboratory test is the enzyme-linked immunosorbent assay (ELISA). It has a sensitivity of 100% but its specificity is low, and this leads to a high rate of false positives and over-diagnosis of HIT.[4] The gold standard confirmatory test for diagnosing HIT, however, is the serotonin release assay (SRA), but its use is restricted to reference laboratories because specialized equipment is required.[5]

When HIT is suspected, heparin must be stopped and an alternative anticoagulant should be started. Direct thrombin inhibitors (DTI), such as bivalirudin, lepirudin, and argatroban, are recommended for this setting; however, such medications are not exempt from bleeding risk, and they are not available at all hospital centers.[1]

Fondaparinux is a possible alternative for patients with HIT, because it is not derived from heparin and has no cross-reactivity with HIT antibodies. Fondaparinux is not FDA-approved for this condition, but some case series have appeared in the literature.

Fondaparinux is a synthetic, specific inhibitor of activated factor X (Xa). Its use is controversial, and it has a low recommendation level (2C) in HIT patients;[1] however, the drug has its advantages, including a rapid onset of effect, a half-life of 17-21 hours, and lower cost and easier monitoring of anti-Xa activity than DTI. It also allows dose adjustment for therapeutic or prophylactic activity, and it does not prolong the international normalized ratio (INR). The main disadvantage is that it is predominantly cleared through the urine, so it is unsuitable for end-stage renal disease. Fondaparinux also has been found to induce or exacerbate HIT, but no reaction has yet been found between this drug and HIT sera.[6]

Over the past few years, several authors have published case series describing the use of fondaparinux in HIT patients.[7,8] They report a zero incidence of new thrombotic events and a

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lower rate of major bleeding complications than for lepirudin or argatroban.

Fondaparinux is the only drug available as a feasible alternative to heparin in this institution. A derivate of hirudin is available in the institution, but management has been unsuccessful, mainly because of the high rate of major and catastrophic bleeding events and the difficulty to monitoring them. Fondaparinux is, therefore, the first option in this setting despite its low quality of evidence, and it was prescribed off label in HIT diagnosed during postoperative cardiac surgery.

The aim of this observational study was to describe the authors' experience concerning the use of fondaparinux in postoperative cardiac surgery patients with suspected HIT.

METHODS

The study was approved by the Ethics Committee at this institution (code IIBSP-FON-2012-164) and conducted in accordance with the Declaration of Helsinki. Data were extracted retrospectively from a database that collects information concerning all postoperative cardiac surgery patients. From October 2009 to June 2012, all patients who presented severe thrombocytopenia within 5 to 10 days after starting systemic heparin therapy were analyzed. Thrombocytopenia was defined as a reduction in platelet count of more than 50% compared with the platelet count before starting heparin.

After cardiac surgery, systemic anticoagulation with unfractioned heparin (UFH) was started in patients with no risk of bleeding. Anticoagulation was monitored daily, measuring the aPTT ratio and the platelet count. The dose of UFH as anticoagulation treatment after heart valve replacement was 300-500 IU/kg/day. The aPTT target was a ratio between 2 and 2.5 for aortic valve replacements and between 2.5 and 3.0 for mitral valve replacements. The dose of UFH as a thromboprophylactic strategy after coronary array bypass graft (CABG) or heart transplantation was 100-200 IU/kg/day.

Patients with a moderate or high score in the 4Ts test were included. The 4Ts test rates the clinical probability of HIT as low, moderate, or high based on 4 features: (1) Thrombocytopenia (quantification of the platelet count drop), (2) timing (from heparin administration to appearance of thrombocytopenia), (3) thrombosis (arterial or venous), and (4) exclusion of other causes of thrombocytopenia.[9]

Although a low score has been related to a low pre-test possibility of HIT, its negative predictive value does not reach 100%.[7] Therefore, patients with a low score but severe thrombocytopenia lasting more than 72 hours, even though their thrombocytopenia could be attributable to other causes, were included.

After HIT was suspected, anti-platelet factor 4/heparin-antibodies were measured in 2 immunoassays: the ID-PaGIA heparin/*PF4* antibody test (DiaMed AG, 1785 Cressier s/Morat, Switzerland) and the enzyme-linked immunosorbent assays (*ELISA*) (Hologic Gen-Probe GTI Diagnostics, Inc., San Diego, CA) as a confirmatory test. If the ID-PaGIA was positive, heparin was withdrawn and fondaparinux was started. If ID-PaGIA was negative, heparin was continued until ELISA was confirmed (Fig 1).

Diagnosis of HIT included patients presenting (1) a moderate or high score in the 4T test and a positive ELISA immunoassay with an OD (optical density) >0.4 or (2) a low score in the 4T test but presence of severe thrombocytopenia (platelet count $<50 \times 10^9$/L lasting for at least 5 days), and positive ELISA with an OD > 0.4.

A low dose of fondaparinux initially was administered in view of the renal insufficiency, as in previous reports.[10] Subcutaneous administration was rejected because of unpredictable absorption in critically ill patients. The drug was injected intravenously daily at 8 PM. In patients receiving continuous venovenous hemodiafiltration (CVVHDF), fondaparinux was administered continuously by syringe.

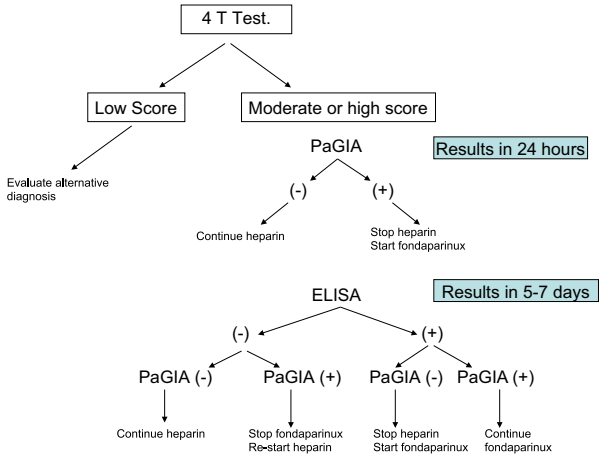

Fig 1. Diagnostic algorithm. (Color version of figure is available online.)

The therapeutic range of fondaparinux initially was adjusted to 0.4-0.6 IU/mL, as for low-molecular-weight heparin. However, given the lack of experience with fondaparinux and the different pharmacokinetics and pharmacodynamics between the drugs, the dose was adjusted to 0.4-1.0 IU/mL. To monitor fondaparinux activity, anti-Xa levels (IU/ml) were measured from the 6 AM routine blood draw. An initial dose of fondaparinux of 2.5 mg/24 hours was administered, adjusting this dose according to anti-Xa levels (IU/mL). The prophylactic dose was 1.25 mg/24 hours. Target values were 0.2-0.4 IU/mL for the prophylactic range. If the anti-Xa level was higher or lower than the range established, the next dose was halved or doubled, respectively.

If an invasive technique was needed during fondaparinux treatment, the drug was discontinued 24 to 36 hours before the procedure. It was restarted 6 to 8 hours later if there were no bleeding complications; the dose was adjusted in accordance with previous anti-Xa levels.

RESULTS

Of a total of 1,338 patients undergoing cardiac surgery, 15 patients (1.1%) met the inclusion criteria described above for HIT. Seven of the 15 patients were male (46%), and 8 were female (54%). Mean age was 64 years with a range of 30 to 77 years. Aortic valve replacement was performed in 5 of 15 (33%), mitral valve replacement or mitral annuloplasty in 5 of 15 (33%), and coronary artery bypass graft in 4 of 15 (26%), but only 2 of them combined with valve replacement. The interval from the start of heparin therapy to diagnosis of HIT ranged from 4 to 32 days. Mean time to recovery of platelet count after stopping heparin was 2.1 days (range: 1-5). Twelve patients had renal failure at the moment of diagnosis: 11 were under CVVHDF and 1 patient was receiving conventional dialysis (Table 1).

In the 4Ts test, 2 patients had a high score, 10 patients had a moderate score, and 3 patients had a low score. In the ELISA test, 7 patients had an OD >2 (2 patients in the high-score group in the 4Ts test, 4 patients in the moderate-score group, and 1 patient in the low-score group), and 7 patients had an OD between 0.4-1.0 (5 patients in the moderate-score group and 2 patients in the low-score group). The authors also included the patient who had an OD of 0.393 (weak positive). Platelet count at diagnosis varied from 5-51 $\times 10^9$/L.