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Plasmapheresis, intravenous immunoglobulin and fondaparinux treatment in heparin-induced thrombocytopenia after aortic and mitral valve replacement

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ABSTRACT

Heparin-induced thrombocytopenia is a complication associated with increased early mortality and major morbidity rates after open heart surgery. Herein, we present a case of heparin-induced thrombocytopenia with major hemodynamic deterioration following elective aortic and mitral valve replacement who was successfully treated with plasmapheresis, intravenous immunoglobulin, and fondaparinux.

Keywords: Heparin-induced thrombocytopenia; intravenous immunoglobulin; plasmapheresis; valve replacement.

Heparin-induced thrombocytopenia (HIT) is an uncommon complication with increased early mortality and major morbidity rates after open heart surgery.[1] Various treatment strategies, including intraoperative plasmapheresis, have been suggested in the treatment of HIT.[2] However, tailoring a treatment and management strategy for patients with postoperative HIT can be more challenging.

Herein, we present a case of HIT with major hemodynamic deterioration following elective aortic and mitral valve replacement who was successfully treated with plasmapheresis, intravenous immunoglobulin, and fondaparinux.

CASE REPORT

A 49-year-old female patient who was diagnosed with advanced mitral and aortic insufficiency was hospitalized for an elective procedure. Her medical history showed insulin-dependent diabetes, bipolar disorder with related medications, and prior use of immune suppressives and oral corticosteroids for rheumatoid arthritis. Angiography revealed normal coronary arteries. Preoperative laboratory values were as follows: urea 40 mg/dL, creatinine 0.97 mg/dL, hematocrit 40.6%, hemoglobin 13.1 g/dL, and platelets 311,000/μL. A written informed consent was obtained from the patient.

The patient underwent elective aortic and mitral valve replacement (21 mm and 29 mm, respectively; CarboMedics Inc, Austin, Texas, USA). Aortic cross-clamp time was 247 minutes, while total perfusion time was 282 minutes. Longer duration of cross-clamping was mainly due to challenging mitral exploration. In the operating room, the patient received a replacement of four units of erythrocyte suspension and three units of fresh frozen plasma solution. She was transferred to the intensive care unit (ICU) in stable condition under 10 μg/kg dobutamine, 4 μg/kg dopamine, and nitroglycerin with a temporary pacemaker in place due to bradycardia.

The patient developed signs of low output at sixth hours after surgery. Inotropic support was increased. Mechanical valve functions appeared to be normal on echocardiography. No localized bleeding or hematoma was identified. The patient underwent revision surgery. On her return to the ICU, the patient was oliguric to anuric with serum urea 57 mg/dL and creatinine 2.02 mg/dL. She underwent hemodialysis on the first postoperative day. In the ICU period, 450 mL fluid was drained on the day of surgery, 250 mL fluid was drained in the first postoperative day and 100 mL fluid was drained in the third postoperative day. Total amount of blood drainage from the chest tube was 800 mL. On the day of surgery, the patient was monitored in the ICU by routine blood gas parameters,

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hematocrit, hemoglobin levels, and drainage volumes. Neither concentrated erythrocyte suspension nor the fresh blood was necessary. Only two units of fresh frozen plasma were replaced. In the first and second postoperative days, one unit concentrated erythrocyte suspension was administered on each day.

The platelet count of the patient who was intubated and on daily hemodialysis with unfractionated heparin went into a rapid, progressive fall in the following days. Within the first four consecutive postoperative days, the platelet count was 48,000, 36,000, 16,000 and 10,000/μL, respectively. Diffuse ecchymotic rashes developed in the third or fourth day. These rashes were more prominent in the arms, neck around the catheter sites, and chest areas, which covered a relatively large area. Overall condition of the patient became worse. Blood hypoxia, aspiration of bloody fluid from the tracheal tube, hypotension, and ventricular tachycardia episodes were noted. Her clinical and laboratory findings under unfractionated heparin treatment made us suspect possible HIT condition due to dramatic fall in the platelet count, which was unable to be explained by any other means except the lack of massive bleeding or transfusions. Unfractionated heparin treatment was interrupted and substituted by low-molecular-weight heparin, fondaparinux (Arixtra® GlaxoSmithKline, Philadelphia, PA, USA), 2.5 mg subcutaneous administration at once. Upon the persisting hemodynamic deterioration, the patient was subjected to an emergency plasmapheresis (Prisma® TPE System, Gambro, IL, USA) in the fourth postoperative day. Plasmapheresis was repeated on the next day (in the fifth postoperative day). As recommended by the hematology consultant, intravenous immunoglobuline-IVIG (Pentaglobin® Biotest Pharma GmbH Dreieich Germany) was also administered as 50 mL on the sixth and seventh postoperative days. Following the treatment, the patient was hemodynamically stabilized with reduced hypoxia. The platelet count gradually increased, reaching 57,000, 66,000 and 71,000/μL in the sixth, seventh, and eighth postoperative days, respectively. The heparin-PF4 (platelet factor 4) antibody was found to be positive (STic Expert® HIT Diagnostica Stago SAS, Asnières sur Seine France) as assessed by the rapid lateral flow immunoassay (LFIA) method at a private laboratory.[3,4]

Renal functions also returned to normal after eight hemodialysis sessions. Fondaparinux treatment continued for a total of 17 days. Oral anticoagulant treatment, which was initiated when tracheostomy was practiced, continued afterwards. No bleeding complicated the fondaparinux treatment. Mechanical valve functions remained normal as confirmed by echocardiography. The tracheostomy cannula was removed in the 25th postoperative day. A slight, circumscribed, cutaneous, and subcutaneous seropurulent discharge from the sternal incision wound healed progressively with wound care and systemic antibiotherapy. The platelet count on the day preceding discharge from the hospital was 233.000/μL.

The patient was discharged in a stable condition in the 42nd postoperative day.

DISCUSSION

Heparin-induced thrombocytopenia occurs in 0.2 to 2% of cases of open heart surgery.[1,5,6] Suspecting HIT is the first step in diagnosis of the disease in cardiac surgical patients.[7] Taking into account for the other causes that may lead to drop in platelets, clinican should suspect for HIT in the findings which are unexplained thrombocytopenia, venous or arterial thrombosis in the presence of thrombocytopenia, necrotic skin lesions at heparin injection sites and acute anaphylactoid reactions after IV boluses of heparin.[7] Unlike cases with previous history of HIT, it can be more challenging to diagnose and establish a standard protocol for those with postoperative worsening of hemodynamic parameters.

In our case, HIT diagnosis was based on the clinical and laboratory findings. The 4Ts scoring system[8] was used in the clinical evaluation. The patient had a low-risk score of three, platelet nadir <10,000, 1 point; non-necrotizing widespread skin lesions, 1 point; and possible other causes of thrombocytopenia (rheumatoid arthritis), 1 point. The anti-PF4/heparine antibody was positive. Although pretest scores were low, clinical and routine laboratory findings with confirmed antibody positivity suggested HIT.

In addition, several conditions may cause or aggravate thrombocytopenia including extended total perfusion time, dialysis treatment, and history of rheumatoid arthritis requiring immunosuppressive treatment as in our patient. However, the decrease in the platelet counts during postoperative period was beyond expectations in our case who was on heparin treatment. The preoperative platelet count was 310,000/μL, whereas it was 48,000, 36,000, 16,000, and 10,000/μL in the

first, second, third, and fourth postoperative days, respectively. Simultaneously, ecchymotic eruptions appeared in the arms and neck around the catheter sites, which disseminated to the legs, chest, and abdomen over the next days. The patient's response to the treatment also supported the diagnosis of HIT. Following the discontinuation of heparin treatment, low-molecular-weight heparin treatment was initiated. Also, after plasmapheresis and intravenous immunoglobulin treatment, hemodynamic, laboratory, and clinical findings showed a rapid improvement. The amount of drainage was negligible and no massive blood transfusion was required. The thrombocyte count was 10,000/μL in the fourth postoperative day. However, after low-molecular-weight heparin was initiated, it increased to 57,000, 66,000, and 71,000 in the sixth, seventh, and eighth postoperative days, respectively. The clinical presentation of the patient and her responsiveness to the treatment, altogether, suggested HIT. Based on the anti-PF4/heparine antibody positivity, the condition was confirmed as HIT.

In the literature, some authors advocate that HIT diagnosis should not be eliminated in patients with low 4Ts scores[9,10] In a study in which surgical ICU patients were analyzed, the rate of HIT positivity was 8.6% in patients with a 4T score between 0 and 3, while the rate of HIT negativity was 57% among those with a score higher than 3[11] These results may raise a question on the reliability of the 4Ts scoring system.[11] Although both pretests and laboratory findings have some limitations, it is rare that both fail simultaneously.[9] In all patients with clinically suspected HIT, the detection of the anti-PF4/heparine antibody is required.[12]

In our case, we administered plasmapheresis in the fourth postoperative day, as the clinical worsening was apparent. Plasmapheresis was repeated on the following day. Treatment was followed by improved hemodynamic parameters and arrest of bleeding. In general, plasmapheresis recommendations for HIT following open heart surgery involve the postoperative period.[13] There is, however, no established treatment protocol. In a study, 11 patients with history of HIT underwent intraoperative plasmapheresis to reduce the antibody load.[2] Plasmapheresis was followed by the placement, under cardiopulmonary bypass, of a permanent left ventricular assist device in a patient with hemodynamic instability and acute viral myocarditis was reported in another case.[14] Therefore, we believe that the postoperative administration of plasmapheresis might play a critical role for the improved status of our case.

Furthermore, unfractionated heparin was substituted by fondaparinux in the fourth postoperative day due to worsened hemodynamic status and HIT-targeted treatment was, then, initiated. The platelet count increased within 17 days of treatment and no bleeding occurred. Bedside echocardiography showed no valvular problems. Current guidelines also indicate that fondaparinux may be used as an alternative agent in HIT treatment.[15] Fondaparinux doesn't enhance the platelet activation effect of HIT sera and could be used as a treatment for HIT.[16] In addition, a successful therapeutic use of fondaparinux was previously reported in a HIT case following the implantation of a left ventricular assist device.[17] We, therefore, suggest that fondaparinux may be used as an alternative intravenous anticoagulation agent in cases of HIT following mechanical valve replacement.

After consulting to a hematologist, we administered intravenous immunoglobulin in the sixth and seventh postoperative days. Intravenous immunoglobulin is often considered to be safe and effective, when used in open heart surgery cases with immune dysfunction accompanied by thrombocytopenia.[18] Similarly, we believe that the administration of intravenous immunoglobulin following plasmapheresis might contribute to the improved clinical status of our case.

In conclusion, the substitution of fondaparinux for unfractionated heparin and treatment with plasmapheresis and intravenous immunoglobulin may improve clinical and laboratory findings. Considering the long-term anticoagulant efficacy of fondaparinux and possible merits of plasmapheresis and intravenous immunoglobulin, the treatment which we used may be applicable for those with heparin-induced thrombocytopenia accompanied by compromised hemodynamics following mechanical heart valve replacement.

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