REPORT

Heparin-induced thrombocytopenia associated with cardiopulmonary bypass: Preliminary attempt with recombinant human thrombopoietin therapy

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Abstract: Recombinant human thrombopoietin (rhTPO) is popularly used for the treatment of chemotherapy-induced thrombocytopenia. However, rhTPO therapy for heparin-induced thrombocytopenia relating to cardiopulmonary bypass has not been previously described. A young patient developed heparin-induced thrombocytopenia during open-heart surgery. Postoperative rhTPO therapy (15000 units *injection hypodermatica* once daily for consecutive 3 days) made a quick platelet recovery without any side effects. Heparin-induced thrombocytopenia associated with cardiopulmonary bypass is more likely to be benign, and is curable to rhTPO therapy. The preliminary rhTPO administration of heparin-induced thrombocytopenia in association with cardiopulmonary bypass shows satisfactory pharmaceutical effects with lower dose, shorter duration treatment and shorter platelet increase time and recovery time in comparison with those for the treatment of chemotherapy-induced thrombocytopenia. rhTPO therapy does not produce any side effects and it could avoid or minimize necessary blood product infusions.

Keywords: Heparin; thrombocytopenia; thrombopoietin.

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is an immune-mediated disorder that frequently develops secondary to heparin therapy with a prevalence of 0.5-5% in general population (Jang and Hursting, 2005) and a prevalence of 3% in cardiac surgical patients with heparinization and cardiopulmonary bypass (Lillo-Le Louët *et al*., 2004). HIT is often present with moderate thrombocytopenia, whereas the platelet count may remain at 50-80×10^9/L. However, sometimes the platelet count, in spite of falling within the normal range, may show a 50% drop in comparison with the basic value (Franchini, 2005). The platelet count usually begins to increase 2-3 days after withdrawal of heparin therapy and recovers to the normal range in 4-10 days (Ahmed *et al*., 2007).

Recombinant human thrombopoietin (rhTPO) is popularly used for the promotion of megakaryocyte maturation and thrombocytopoiesis. Clinical observations illustrated safe and successful treatment of chemotherapy-induced thrombocytopenia with rhTPO. However, rhTPO therapy for heparin-induced thrombocytopenia relating to cardiopulmonary bypass has not been previously described. This article is to present the preliminary experience of rhTPO in the management of heparin-induced thrombocytopenia associated cardiopulmonary bypass.

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Clinical observation

A 35-year-old male was referred to our department due to intermittent chest distress and dyspnea for half a year. He was insignificant for a rheumatic history. On admission, physical examination revealed a heart rate of 112 beats/min and a diastolic cardiac murmur was audible at the apex. Electrocardiogram showed atrial fibrillation and echocardiography revealed severe mitral stenosis with a calculated mitral orifice area of 0.7 cm^2, a left atrial thrombus measuring 47×27×14 mm and a systolic pulmonary artery pressure of 43 mmHg. Mitral valve replacement and left atrial thrombectomy were performed with heparinization with 198 mg of heparin sodium injection (activated clotting time, 613 seconds). Before weaning from bypass, protamine 300 mg was infused for heparin reversal. But there was diffuse oozing of blood in the operative field without any active bleeding. Urgent blood test showed a severe decrease of the platelet count to 40×10^9/L. He was given fresh plasma 800 ml, cryoprecipitation 10 units and autotransfusion of 500 ml. Small amount of cryoprecipitation was also sprayed evenly onto the surgical field twice, but without showing persistent hemostatic effects. The activated clotting time was 129 seconds. During closure of the chest, it oozed severely and the pericardial and mediastinal spaces were quickly full of suffusion of blood each time after suction. Re-examination of the operative field precluded any active bleeding. Chest closed, the patient was sent back to the Intensive Care Unit. He was given 600ml of plasma

and rhTPO (Shenyang Sunshine Pharmaceutical Co. Ltd., Shenyang) 15000 units *injectio hypodermatica* once daily for consecutive 3 days. Drainage amount was up to 210 ml and 100 ml on postoperative days (PODs) 1 and 2, respectively. The platelet count gradually recovered. The patient was doing well since then.

A series of blood tests of the patient showed that the platelet count decreased to 40×10^9/L during the operation, remained low until POD 2, began to increase and approached to the normal value on POD 4, recovered to normal on POD 6, reached to a peak on POD 10 and then steadily decreased within normal ranges. Thrombocytocrit showed a same trend as the platelet count. The mean platelet volume, platelet volume distribution width and large platelet ratio displayed a contrary dynamics to those of the platelet count and thrombocytocrit, by increasing during operation until POD 2, decreasing since POD 4 and reaching to a nadir on POD 8. Between PODs 1 and 4, the mean platelet volume values were a little bit higher

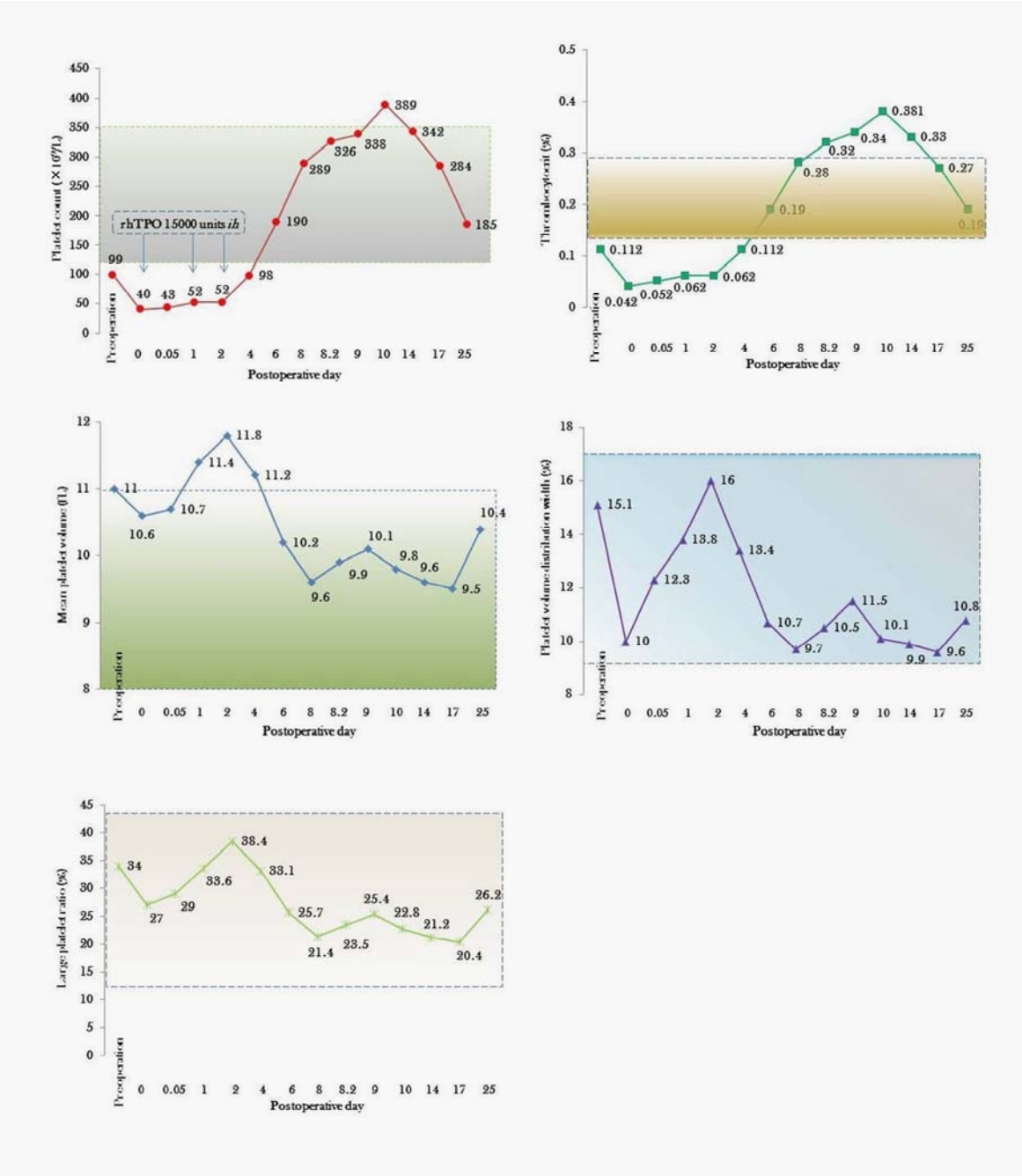

Fig. 1: Dynamic changes of (A) platelet count, (B) thrombocytocrit, (C) mean platelet volume, (D) platelet volume distribution width and (E) large platelet ratio. *ih*: *injectio hypodermatica*; rhTPO: Recombinant human thrombopoietin. The frames indicate normal value ranges.

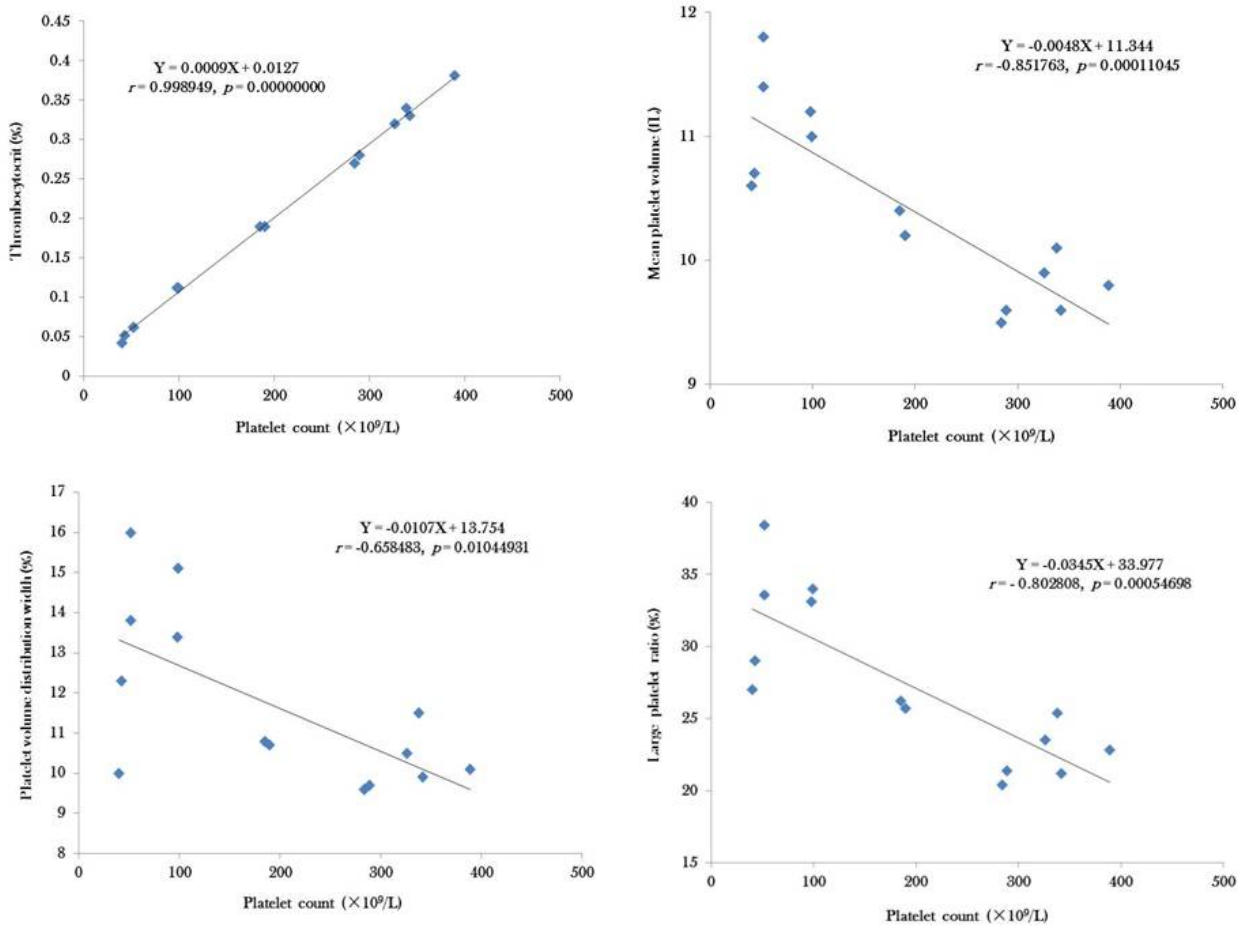

Fig. 2: Linear correlations between platelet count and thrombocytocrit, mean platelet volume, platelet volume distribution width and large platelet ratio

than normal range, while the platelet volume distribution width and large platelet ratio kept normal throughout the observation period (Fig. 1). The platelet count showed a significant positive correlation with thrombocytocrit, but significant negative correlations with the mean platelet volume, platelet volume distribution width and large platelet ratio (Fig. 2).

DISCUSSION

Heparin administration may induce thrombocytopenia and neo-thrombus formation (more in the veins than in the arteries). Alternative symptoms include chest pain, blush, headache, fever, chills and tachycardia, *etc*., which may appear within a few hours after heparin administration (Sun *et al*., 2011). When HIT occurs, immediate cessation of heparin and future re-exposure to heparin are mandatory. Oral warfarin therapy can be started as platelet count increases (Franchini, 2005). Direct thrombin inhibitors including lepirudin, argatroban and bivalirudin (Ortel, 2009), indirect factor Xa inhibitor danaparoid (Kodityal *et al*., 2003) and fondaparinux, a synthetic indirect factor Xa inhibitor (Samama and Gerotziafas, 2003) have been effectively applied in HIT patients. Other anticoagulants include low molecular weight heparin, orgaran (low molecular weight heparinoid) and ancrod (the defibrinogenating agent), have been safely and successfully administered in HIT patients (Brieger *et al*. 1998).

Thrombopoietin (TPO) is a 353-amino acid cytokine by hepatic synthesis. The primary bioactivity of TPO is to promote megakaryocyte maturation and thrombocytopoiesis. It often requires 4-5 days for the platelet count to rise after TPO therapy. Daily administration of rhTPO promotes megakaryocyte counts in the bone marrow, alleviates thrombocytopenia and attenuates anemia and leukopenia (Kuter and Begley, 2002).

Patients with solid cancer chemotherapy-induced thrombocytopenia treated with rhTPO (15000 units/day) took 6.18 days comparing to 10.46 days in those treated with interleukin-11 (1.5 mg/day) for the platelet count to increase to 100×10^9/L (Wang *et al*., 2010). rhTPO may shorten the platelet recover time to 9.8±4.2 and 12.8±3.6

days while it was 19.1±4.5 and 24.3±1.4 days in the control at the end of first chemotherapy circle to a platelet count of $\geq 75\times10^9$/L and $\geq 100\times10^9$/L, respectively (Wei *et al*., 2009). Chemotherapy-induced thrombocytopenia in leukemia showed a same response to rhTPO treatment with mild and tolerable side effects such as fever, knee arthralgia, dizziness, headache and chills (Pang *et al*., 2009). Gao *et al*. (2011) conducted a comparative study between rhTPO and intravenous immunoglobulin in patients with sepsis-associated thrombocytopenia. They found that the maximal platelet count, mean value of difference between minimal and maximal platelet counts, and average platelet counts on the second and third day after treatment were significantly higher in the rhTPO than that in the intravenous immunoglobulin group. The amounts of plasma and platelet transfusions were significantly reduced in the rhTPO group, showing a superior efficacy of rhTPO in the treatment of sepsis-associated thrombocytopenia. rhTPO Injection (commercial name, TPIAO) is an injectable product for the management of chemotherapy-induced thrombocy-topenia, and platelet deficiency and thrombocytopenia of alternative etiologies. It has two specifications 7500 units/1 ml and 15000 units/1 ml. rhTPO is recommended at a dose of 300 units/kg/day *injectio hypodermatica* for up to consecutive 14 days starting from 6-24 hours after chemotherapy. Clinical observations illustrated safe and successful treatment of chemotherapy-induced thrombocytopenia with rhTPO. But attempts of rhTPO in HIT in association with cardiopulmonary bypass have not been previously described.

The present study revealed HIT associated with cardiopulmonary bypass was relatively benign with attenuated platelet drop in terms of the absolute count and duration with the management of rhTPO. Short-term use of rhTPO for only consecutive 3 days could effectively withhold the HIT in relation to cardiopulmonary bypass. The platelet increase time and platelet recovery time were 4 and 6 days with the use of rhTPO in the present patient comparing with 6.18 and at least 19.1 days in the reported chemotherapy-induced thrombocytopenia. The contrary trends of the mean platelet volume, platelet volume distribution width and large platelet ratio illustrated a compensated mechanism in the condition of HIT.

CONCLUSIONS

rhTPO is rarely used in the management of benign HIT beyond chemotherapy-associated thrombocytopenia. Preliminary attempt of rhTPO in cardiopulmonary bypass related HIT has shown satisfactory pharmaceutical effects with lower dose, shorter duration treatment and shorter platelet increase time and recovery time in comparison with those for the treatment of chemotherapy-induced thrombocytopenia. rhTPO therapy might not generate any side effects and it might avoid or minimize necessary blood product infusions. Much work has to be done in the future in this regard.

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