Journal of Community Hospital Internal Medicine Perspectives

co-action PUBLISHING

CASE REPORT

Heparin-induced thrombocytopenia following coronary artery bypass grafting: a diagnostic dilemma

Raju Khanal, MD[1]*, Paras Karmacharya, MD[1] and Daniel A. Forman, DO[2]

[1]Department of Internal Medicine, Reading Health System, West Reading, PA, USA; [2]Hematology Oncology, Reading Health Physician Network, West Reading, PA, USA

The diagnosis of heparin-induced thrombocytopenia (HIT) is a challenge in post-cardiac surgery patients because of the high incidence of non-immune thrombocytopenia and heparin–platelet factor 4 antibodies in these groups. We present a case of HIT in a post coronary artery bypass surgery patient, which was successfully treated with prompt recognition and discontinuation of heparin products.

Keywords: *CABG*; *HIT*; *heparin-induced thrombocytopenia*; *serotonin release assay*

*Correspondence to: Raju Khanal, Department of Internal Medicine, Reading Health System, 6th Avenue, Spruce Street, West Reading, PA 19611, USA, Email: drraju34@gmail.com

Received: 2 June 2015; Revised: 26 July 2015; Accepted: 3 August 2015; Published: 19 October 2015

Heparin-induced thrombocytopenia (HIT) is a life-threatening, immune-mediated, pro-thrombotic disorder secondary to an idiosyncratic reaction to heparin and related molecules (1, 2). Prompt recognition of HIT is crucial to prevent progression to subsequent thrombotic complications, when it is then termed as HIT with thrombosis (HITT). Immediate cessation of all heparin products and holding the Vitamin K antagonist until the platelet counts recover, and starting alternative non-heparin anticoagulants such as direct thrombin inhibitors or fondaparinux, may halt this process (3, 4). The high incidence of thrombocytopenia and heparin–platelet factor 4 (heparin/PF4) antibodies in post-cardiac surgery patients makes HIT a diagnostic challenge in this population (5, 6). We here present a case of HIT in a post coronary artery bypass surgery (CABG) patient, which was successfully treated with prompt recognition and discontinuation of heparin products.

Case presentation

An 81-year-old white male was referred to the emergency department by his family doctor for chest pain and shortness of breath for 1 week. Past medical history was significant for hypertension, hyperlipidemia, diabetes mellitus type 2, gouty arthritis, and hypothyroidism. He was a non-smoker and did not have any history of coronary artery disease or heart failure. His medications included were aspirin, lisinopril, hydrochlorothiazide, atorvastatin, allopurinol and levothyroxine. His diabetes was under control with diet and exercise. He had not been exposed to heparin for at least a year.

On examination, blood pressure was 103/61 mmHg, heart rate was 97 beats per minute, respiratory rate was 16 breaths per minute, temperature was 37.1°C, and oxygen saturation was 94% on room air. Cardiovascular examination revealed jugular venous distension of 6 cm above the sternal angle, S3 gallop and a 2/6 holosystolic murmur at the apex, along with trace pitting pedal edema. Other examinations were unremarkable.

Electrocardiogram revealed ST segment depression in the anterolateral leads with elevation of cardiac enzymes: troponin I – 10.11 ng/ml (normal <0.06) and creatine kinase-MB – 12 ng/ml (normal 0–5). Other laboratory parameters were: white cell count $12.5 \times 10^3/\mu l$ (4.8–10.8), hemoglobin 11.6 g/dl (14–17.5) and platelet count $327 \times 10^3/\mu l$, creatinine 1.21 mg/dl (0.5–1.5). Electrolytes and liver functions were normal.

Emergent cardiac catheterization revealed severe multivessel coronary artery disease. An emergent CABG was done, which required cardiopulmonary bypass for hemodynamic instability. Considering low ejection fraction of 15% on echocardiogram done prior to the catheterization, an Impella device was placed for left ventricular support. At the time of presentation, intravenous heparin was started with bolus of 60 units/kg (maximum 4,000 units), followed by 12 units/kg/h (maximum 1,000 units/h), which was continued for 48 h, and subsequently changed to 8,000 units subcutaneous eight hourly for deep vein thrombosis prophylaxis. He also received heparin during CABG surgery and hemodialysis. He required multiple packed red blood cell transfusions (total 9 units) during hospitalization to account for blood loss during surgery.

Citation: Journal of Community Hospital Internal Medicine Perspectives 2015, **5**: 28745 - http://dx.doi.org/10.3402/jchimp.v5.28745

Temporary renal replacement therapy, initially continuous renal replacement therapy followed by hemodialysis was needed for initial 11 days following surgery for acute renal failure due to cardiogenic shock. The platelet count progressively dropped post-operatively (Fig. 1).

Initial thrombocytopenia was thought to be due to surgery, consumption during cardiopulmonary bypass, Impella and dilution. Coagulation profiles were normal (INR 1.1, PT 26 s [23–31], and fibrinogen 643 mg/dl [150–570]) and there were no schistocytes on peripheral smear.

Warkentin's 4T's score was 3 (decrease in platelet count by more than 50% in less than 4 days of heparin use, possible alternate cause of thrombocytopenia and no obvious thrombosis). Despite the low risk of HIT by 4Ts score, anti-heparin/PF4 antibodies enzyme-linked immunosorbent assay (ELISA) was sent because of continuous decrease in platelet counts even after 5 days following surgery. Heparin was stopped due to persistently decreasing platelet counts below $50 \times 10^3/\mu l$. The next day, ELISA turned positive with the titer of three optical density (OD; normal ≤ 0.30 OD). Considering the high titer of ELISA, argatroban was initiated immediately, and serotonin release assay (SRA) was sent for confirmation, which reported positive after 10 days. Ultrasound of lower extremities was negative for thrombosis. Platelet counts gradually increased 48 h after stopping the heparin.

Warfarin was started after the 13th post-operative day (POD) once the platelet count went up above $150 \times 10^3/\mu l$ (Fig. 1). On the 17th POD, anticoagulation was held and warfarin was reversed with 2 mg oral vitamin K due to concern for pericardial hematoma. The anticoagulation was resumed on the 20th POD. Subsequently, argatroban was switched to fondaparinux on the 23rd POD for bridging once the creatinine clearance remained persistently above 30 ml/min. He was discharged with warfarin to be continued for 6 weeks.

Discussion

HIT is a life-threatening, immune-mediated, prothrombotic disorder secondary to an idiosyncratic reaction to heparin and related molecules (1, 2). It is more common with unfractionated heparin (1–5%) than low molecular weight heparin ($<1\%$) (1, 4). It results from the development of autoantibodies to the heparin/PF4 complex, which stimulate platelets and trigger the coagulation pathway, leading to life-threatening arterial and venous thrombosis (HITT) in about 30–50% of the cases with a mortality of around 5% (1, 7). Mortality risk may increase up to 28% in cardiac surgery patients. Immediate discontinuation of heparin and initiation of non-heparin anticoagulants, especially direct thrombin inhibitors or fondaparinux, can decrease the risk of thrombosis by 50–70% (5).

Diagnosis of HIT can be a challenge in post-cardiac surgery patients, as non-immune-mediated, transient, asymptomatic thrombocytopenia can occur in 25% of these patients. A 40–60% drop in the platelet count, with lowest occurring in 1–4 days (2, 8), can occur due to dilution, consumption during cardiopulmonary bypass, or the direct agglutinating effect of heparin (2, 9, 10).

About 50% of patients with post-cardiac surgery seroconvert to HIT antibody positive, but only 1–2% develop clinical HIT, posing a further dilemma in diagnosis (9, 10). The drop in platelet counts by more than 30% or early thrombocytopenia with more than 30% superimposed drop after 5 days of surgery is more suggestive of HIT. Similarly, the decrease in platelet counts again after recovery from postoperative thrombocytopenia is also suggestive of HIT. However, early and persistent thrombocytopenia beyond 5 days of surgery without superimposed drop is rarely due to HIT (4, 6, 10). Our patient had more than 30% superimposed thrombocytopenia after the fourth POD.

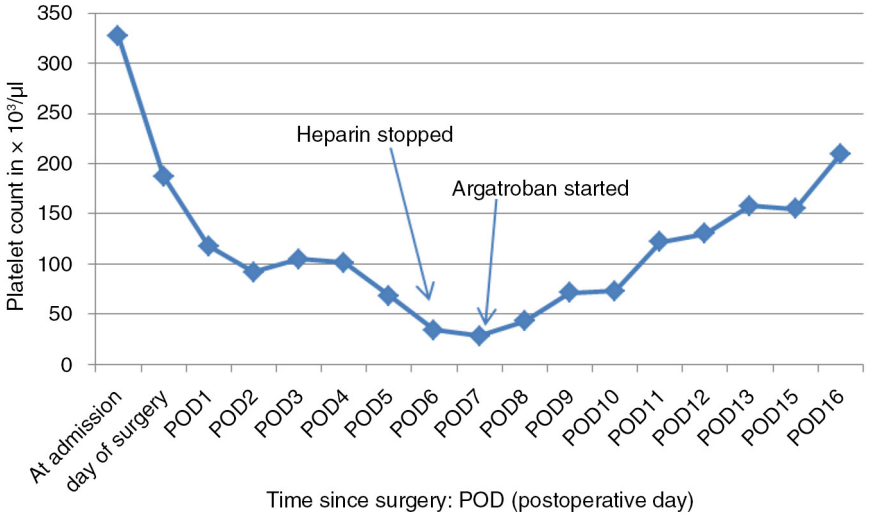

Fig. 1. Platelet trend after surgery.

Citation: Journal of Community Hospital Internal Medicine Perspectives 2015, **5**: 28745 - http://dx.doi.org/10.3402/jchimp.v5.28745

Table 1. Warkentin 4Ts clinical probability tool[a]

4Ts	2 points	1 point	0 point
Severity of thrombocytopenia	>50% fall in platelet counts with nadir $>20 \times 10^3/\mu l$	30–50% fall in platelet counts or platelet nadir $10–19 \times 10^3/\mu l$	<30% fall in platelet counts or platelet nadir counts $<10 \times 10^3/\mu l$
Timing of fall in platelet counts	5–10 days after starting heparin, or <1 day (prior to heparin exposure within 30 days)	10 days after starting heparin, or unclear timing, or <1 day (prior to heparin exposure (31–100 days)	<4 days after starting heparin without prior exposure to heparin
Thrombosis or other sequelae	Proved new thrombosis, or skin necrosis, or acute systemic reaction after intravenous heparin bolus	Progressive or recurrent thrombosis, or erythematous skin lesions at injection sites, or suspected thrombosis (not proven)	No thrombosis or other findings
Other causes of thrombocytopenia	None apparent	Possible	Definite

[a]Adapted from Ref. (1).

Warkentin's 4Ts score is a widely used and validated clinical pretest tool to predict HIT (Table 1). The total score describes the probability of HIT and is divided into low (0–3), intermediate (4, 5) and high risk (6–8), which represent an approximate probability of HIT of less than 1, 10, and 50%, respectively (1, 9). Patients with at least intermediate probability of HIT by 4T score should undergo testing for HIT antibody. Low probability scores should usually negate the need to perform HIT antibodies as it has a high negative predictive value (1). However, it may be reasonable to test for HIT antibody in patients like ours (4Ts score 3, 2 for severity of thrombocytopenia and 1 for possible alternative cause of thrombocytopenia), who have persistent drop in platelet counts even after the fifth POD without any identifiable cause.

HIT antibody testing (IgG ELISA and particle gel immunoassay), available in most of centers, have high sensitivity (>99%), but low specificity (74–86%). However, high titers of antibody improve specificity (4, 11). HIT is a clinicopathological diagnosis. Therefore, there is always a risk of overdiagnosis if we do not consider the clinical criteria. The diagnostic algorithm is shown in Fig. 2 (1, 12). Functional assays (SRA, heparin-induced platelet activation) are not readily available and take about a week to obtain the report. They are very sensitive (>95%) and specific (>95%) (1, 12).

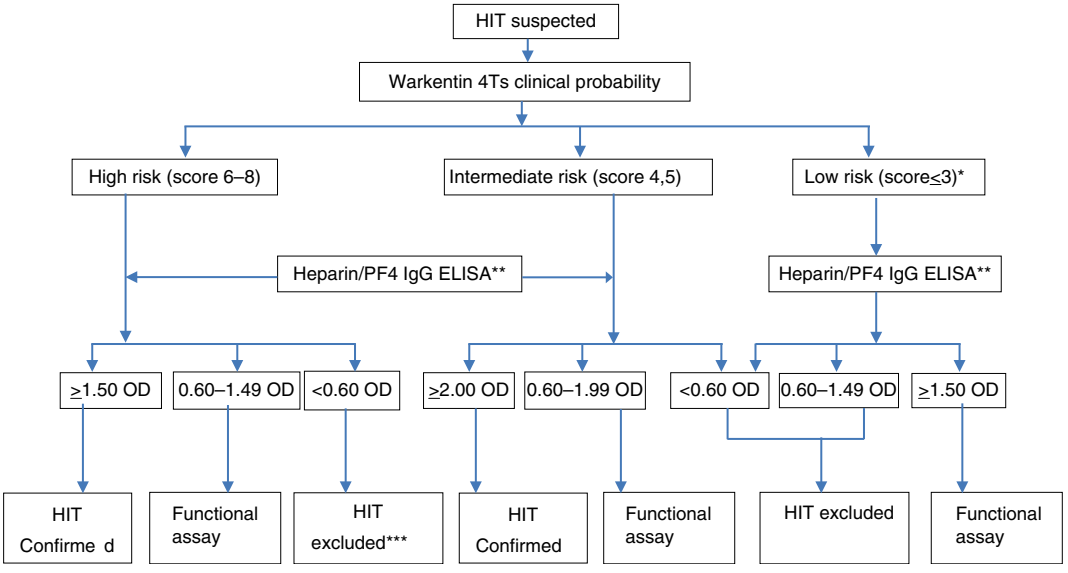

Fig. 2. Diagnostic algorithm for HIT (1).
*Low clinical risk has high negative predictive value. However, some physicians do heparin/PF4 IgG ELISA to avoid missing few true HIT cases.
**Positive titer ≥0.60 OD and negative titer <0.60.
***HIT is excluded, although some experts suggest a functional assay in high-risk clinical probability.

Treatment of HIT depends on pretest clinical probability. In patients with a pretest probability of intermediate risk (4Ts score of 4 or 5), all forms of heparin and related molecules must be stopped and alternative anticoagulation with non-heparin molecules including direct thrombin inhibitors, for example, argatroban, bivalirudin, and danaparoid, should be initiated (1). Argatroban is preferred in patients with renal failure (1, 7). Fondaparinux may be used although it has rarely been associated with disorders resembling HIT (13). Direct oral anticoagulants including rivaroxaban have been tried in few cases with positive outcomes and are still under study for the treatment of HIT (14).

Once the platelet count improves (more than $150 \times 10^3/\mu l$), alternative anticoagulants like warfarin should be instituted. Warfarin should be started at a low dose and overlapped with non-heparin anticoagulants for at least 5 days, until a therapeutic INR has been achieved. Although controversial, recommended duration of anticoagulation is 3 months for HITT and 4–6 weeks without thrombosis (4, 15). Platelet counts usually recover within 4 days of stopping heparin in about 50% of patients and within a week in 90% of patients. Sometimes it might take weeks, especially for aggressive cases of HIT (9). In our patient, the platelet count started rising after 2 days of stopping heparin and recovered within a week.

HIT antibodies usually disappear within 3 months. However, there is always a risk of recurrence upon re-exposure, although the risk is low especially with negative antibodies and short exposure to heparin during the intraoperative period (1, 16). Hence, alternative anticoagulation should be used until more data are available for reuse of heparin in these patients, and patients should use medical alert bracelets to avoid inadvertent use of heparin products in emergency situations.

Conclusion

More than 30% unexplained drop in platelet counts after 4 days of cardiac surgery is suggestive of HIT. Further evaluation even with low 4Ts score is mandated in these cases for early recognition and treatment to avoid catastrophic outcomes.

Conflict of interest and funding

The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

References

1. Linkins L-A. Heparin induced thrombocytopenia. BMJ 2015; 350: g7566.
2. Levy JH, Winkler AM. Heparin-induced thrombocytopenia and cardiac surgery. Curr Opin Anaesthesiol 2010; 23(1): 74–9. doi: 10.1097/ACO.0b013e328334dd2f.
3. Das P, Ziada K, Steinhubl SR, Moliterno DJ, Hamdalla H, Jozic J, et al. Heparin-induced thrombocytopenia and cardiovascular diseases. Am Heart J 2006; 152(1): 19–26. doi: 10.1016/j.ahj.2005.10.005.
4. Ortel TL. Heparin-induced thrombocytopenia: When a low platelet count is a mandate for anticoagulation. Hematol Am Soc Hematol Educ Program 2009; 225–32. doi: 10.1182/asheducation-2009.1.225.
5. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia and cardiac surgery. Ann Thorac Surg 2003; 76(6): 2121–31. doi: 10.1016/j.athoracsur.2003.09.034.
6. Selleng S, Malowsky B, Strobel U, Wessel A, Ittermann T, Wollert H-G, et al. Early-onset and persisting thrombocytopenia in post-cardiac surgery patients is rarely due to heparin-induced thrombocytopenia, even when antibody tests are positive. J Thromb Haemost 2010; 8(1): 30–6. doi: 10.1111/j.1538-7836.2009.03626.x.
7. Demma LJ, Paciullo CA, Levy JH. Recognition of heparin-induced thrombocytopenia and initiation of argatroban therapy after cardiothoracic surgery in the intensive care unit. J Thorac Cardiovasc Surg 2012; 143(5): 1213–18. doi: 10.1016/j.jtcvs.2011.07.068.
8. Warkentin TE. Heparin-induced thrombocytopenia in critically ill patients. Semin Thromb Hemost 2015; 41: 49–60. doi: 10.1055/s-0034-1398381.
9. Battistelli S, Genovese A, Gori T. Heparin-induced thrombocytopenia in surgical patients. Am J Surg 2010; 199(1): 43–51. doi: 10.1016/j.amjsurg.2009.01.029.
10. Selleng S, Selleng K, Wollert H-G, Muellejans B, Lietz T, Warkentin TE, et al. Heparin-induced thrombocytopenia in patients requiring prolonged intensive care unit treatment after cardiopulmonary bypass. J Thromb Haemost 2008; 6(3): 428–35. doi: 10.1111/j.1538-7836.2007.02870.x.
11. Lo GK, Sigouin CS, Warkentin TE. What is the potential for overdiagnosis of heparin-induced thrombocytopenia? Am J Hematol 2007; 82(12): 1037–43. doi: 10.1002/ajh.21032.
12. Raschke RA, Curry SC, Warkentin TE, Gerkin RD. Improving clinical interpretation of the anti-platelet factor 4/heparin enzyme-linked immunosorbent assay for the diagnosis of heparin-induced thrombocytopenia through the use of receiver operating characteristic analysis, stratum-specific likelihood ratios, and Bayes theorem. Chest 2013; 144(4): 1269–75. doi: 10.1378/chest.12-2712.
13. Warkentin TE. Fondaparinux: Does it cause HIT? Can it treat HIT? Expert Rev Hematol 2010; 3(5): 567–81. doi: 10.1586/ehm.10.54.
14. Linkins L-A, Warkentin TE. Rivaroxaban for treatment of HIT: A riveting first experience. Thromb Res 2015; 135(1): 1–2. doi: 10.1016/j.thromres.2014.10.019.
15. Linkins L-A, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th edn: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl): e495S–530S. doi: 10.1378/chest.11-2303.
16. Warkentin TE, Sheppard J-AI. Serological investigation of patients with a previous history of heparin-induced thrombocytopenia who are reexposed to heparin. Blood 2014; 123(16): 2485–93. doi: 10.1182/blood-2013-10-533083.