Transient Global Amnesia after Cardiac Surgery: The Presenting but Mostly Unrecognized Sign of Heparin-Induced Thrombocytopenia

Riccardo Cocchieri[1]; Iman Mousavi[2]*

[1]Cardiothoracic Surgeon, OLVG Hospital, Amsterdam, The Netherlands.

[2]Cardiothoracic Surgery Resident, OLVG Hospital, Amsterdam, The Netherlands.

Abstract

Benign heparin-induced thrombocytopenia (HIT) is common after cardiac surgery. HIT can be complicated with thromboembolic events. One of these rare and possibly underreported symptoms is transient global amnesia (TGA) which could cause higher morbidity in the short and midterm follow up.

Keywords: Cardiac surgery; Low-molecular-weight heparin; Heparin-induced thrombocytopenia; Transient global amnesia.

Abbreviations: HIT: heparin-induced thrombocytopenia; TGA: transient global amnesia; LMWH: Low-molecular-weight heparin; UFH: unfractionated heparin; Mini-MVP/R: minimally invasive mitral valve plasty/ replacement; POD: postoperative day; HIPAA: heparin induced platelet activation assay; ELISA: enzyme-linked immunosorbent assay; CT-scan: Computed tomography scan; MRI: Magnetic resonance imaging; TIA: transient ischemic attack; CVA: Cerebrovascular accident.

Introduction

Heparin-induced thrombocytopenia (HIT) is one of the well-known drug reactions after administration of different forms of heparins. It is associated with significant morbidity if unrecognized. Non-immunologic heparin-associated thrombocytopenia (type I) is characterized by mild and transient thrombocytopenia without an increased risk of thrombosis and the immune-mediated thrombocytopenia (type II) is associated with a hypercoagulable state [1]. Thromboembolic complications develop in 30-50% of patients with a predominance of arterial thromboembolism in cardiac surgery patients [2,3]. One of the rare and under-reported thromboembolic events of type II HIT after cardiac surgery is transient global amnesia (TGA) which is related to ischemic or metabolic disturbances in the cerebral arteries [4]. Because of the journal word restrictions we describe only 4 of the 11 cases (observed in one year) of TGA and positive HIT diagnosis in the postoperative course after cardiac surgery.

Case presentations

Case 1

A 57-year-old man was admitted to our hospital with mitral valve insufficiency without relevant medical history. He underwent minimally invasive mitral valve plasty (mini-MVP). The postoperative course was uneventful with discharge on postoperative day (POD) seven. A few hours later he was readmitted with amnesia and paresthesia of lips and tong. Patient was disoriented and exhibited severe anterograde amnesia, as well as retrograde amnesia for recent events. The CT brain showed no detectable abnormalities nor echocardiography showed signs of endocarditis. He was discharged with diagnosis of transient ischemic attack (TIA) without any change of the medications. Three days later he presented with paresthesia and weakness of both legs. The thrombocyte count dropped from 232 x 10^9/L to 90 x 10^9/L. The suspicion of HIT led us to stop tinzaparin and continue with warfarin as monotherapy. Two days later thrombocyte count raised to 210 x 10^9/L. Both the heparin induced platelet activation assay (HIPAA) and the enzyme-linked immunosorbent assay (ELISA) were positive for HIT. At the two week follow-up the patient was fully recovered with the exception of minor residual memory problems.

Case 2

A 66-year-old man was admitted to our hospital with aortic valve stenosis. He underwent minimally invasive aortic valve replacement with a Perceval valve (Livanova, Saluggia, Italy) through right anterior thoracotomy. The postoperative course was complicated by atrial fibrillation. Heparin was initially started and switched to tinzaparin on the next day. On POD seven the patient became disoriented and exhibited severe anterograde and retrograde amnesia which dissolved within an hour. The thrombocyte count decreased from 205 x 10^9/L to 82 x 10^9/L. HIT laboratory tests were requested and tinzaparin was switched to fondaparinux. Two days later he experienced another episode of TGA with recovery within an hour. The thrombocyte amount decreased to a minimum of 49 x 10^9/L and recovered 11 days later to 164x109/L. The HIPAA was negative but the ELISA was strongly positive. The patient was fully recovered at follow-up.

Case 3

A 66-year old man was admitted to our hospital with dyspnea due to bicuspid valve-associated aortopathy. He underwent a biological Bentall procedure with Perimount Magna Ease valve (Edwards, Lifesciences Corp, Irvine, CA) and Gelweave Valsalva prosthesis (Terumo-Vascutek, Renfrewshire, Scotland, UK). The postoperative course was complicated by atrial fibrillation. Nadroparin was started and the patient was discharged on POD seven. Three days later he was readmitted with global amnesia without other neurological signs. Patient asked questions repetitively and exhibited severe retrograde amnesia for recent events. The thrombocyte count was 240 x 10^9/L but the suspicion of HIT led us to switch fraxiparin to fondaparinux. Both the HIPAA and the ELISA were positive. Three days later the thrombocyte count raised tot 468 x 10^9/L and no residual symptoms were observed.

Case 4

A 54-year old women was admitted to our hospital with mitral valve insufficiency and atrial fibrillation. She underwent a mini-

MVR with ST. Jude – Epic valve (Abbott Medical, Minneapolis, USA) and MAZE procedure. The postoperative course went uneventful and the patient was discharged on POD four. Five days later the patient was readmitted with 2 short episodes of TGA. During this episodes the patient became fully disoriented, exhibited severe anterograde and retrograde amnesia and asked questions repetitively. The laboratory test showed a thrombocyte count of 273 x 10^9/L. HIT laboratory tests were requested and nadroparin was switched to fondaparinux. The HIPAA was negative but the ELISA was strongly positive. There were no recurrence of complains in the following days.

Discussion

TGA is a clinical syndrome characterized by the sudden onset of mainly anterograde but also retrograde amnesia, accompanied by repetitive questioning without compromise of other neurological functions. It mostly lasts for 1-10 hours and typically less than 24 hours after withdrawal of heparin. Initial fast recovery with sudden onset of global amnesia was characteristic in our patients and lasted mostly only a few hours after therapeutic switch. Only a few patients experienced recurrence of TGA shortly after the first episode. We observed full rapid remission of neurological signs in all patients but two. There is a correlation between the moment of the diagnosis and residual complains. In our first patients the confirmation of HIT and therapeutic switch was relatively late and therefore minor residual complains were observed in the short and midterm follow up which is probably due to small white matter lesions which are most probably caused by micro thromboembolism as a result of HIT [1,5].

The immune-mediated thrombocytopenia is caused by the formation of antibodies that activate platelets. The principal antigen is a complex of heparin and platelet factor 4 (PF4) and its affinity depends on the molecular weight, chain length and degree of sulfation [1]. The higher molecular weight of unfractionated heparin (UFH) compared with low molecular weight heparins (LMWH) explains the higher incidence of complicated HIT in patients treated with UFH. This difference is especially seen in post-surgical patients and mainly patients who receive heparin of bovine origin [1,6].

The incidence of HIT and related thromboembolic complications is probably higher than reported [1]. The short administration of LMWH heparins post cardiac surgery could be a cause of spontaneous recovery and underreporting of such side effects. The first exposure to heparin molecules and sensitization is an important factor for developing HIT. The incidence of HIT is higher if heparin is used more than 4 days and typically starts after 5-10 days [1]. The symptoms in our case series occurred between day 5-10 postoperative as described earlier in the literature [4,7]. A positive history of heparin use in the last 100 days could lead to earlier onset of symptom presentation. Therefore, medical history plays an important role in the diagnosis.

Benign thrombocytopenia post cardiac surgery especially with use of cardiopulmonary bypass and specific valve prosthesis is frequently seen [3,8]. Early differentiation between benign thrombocytopenia and type II HIT on the other side can sometimes be challenging. A biphasic platelet count profile with first fall in the first 48-72 hours followed by second fall between postoperative day 5-10 is highly suspicious for type II HIT. The thrombocyte count characteristically declines with 50% but in some patients

it doesn't fall below 150 x 10^9/L. In addition some of patients develop thromboembolic complications shortly before or concomitant with the thrombocyte count decrease [2] as was also seen in 5 of our patients. Therefore we recommend combination of a good clinical assessment and lower threshold for laboratory tests.

Different risk-scoring systems like the 4 T's of HIT [1] with the timing and magnitude of the thrombocyte decline, new thromboembolic events and the likelihood of other reasons for thrombocytopenia is helpful in estimating the probability of HIT. The knowledge and awareness about possible thromboembolic events like TGA are of great importance. Awareness in our team resulted in good differentiation and early diagnosis of these patients. This is especially important in older patients after cardiac surgery where amnesia is sometimes directly linked to delirium, anxiety or CVA which is one of the important reasons for treatment delay and higher morbidity in the follow up. Early clinical confirmatory laboratory tests are available on the market. Our hospital adopted the HIPAA with a sensitivity of 35-85% and the ELISA with sensitivity of 80-100% but a low specificity [1]. In few cases HIPAA was negative but ELISA was strongly positive (values > 1.5); HIT couldn't be ruled out and it is advisable to repeat the HIPAA test if the clinical suspicion persists [9]. Both test results are available after a few days but we suggest early treatment to prevent midterm complications in suspected cases.

The therapeutic goal is to remove all sources of heparin and initiate alternative anticoagulation. It is not advisable to switch UFH to LMWH because of the strong cross reactivity of HIT antibody with the LMWH-PF4 complex [1]. A few alternative treatments (e.g. fondaparinux) have shown promising results in HIT patients. The thrombocyte amount normally rises in 2-3 days and usually returns to normal within 4-10 days after the cessation of heparin. It takes normally 2-3 months to get a complete clearance of the antibodies during which period alternative anticoagulation is recommended [1].

Conclusion

Thrombocytopenia is a common, mostly innocent, phenomenon after cardiac surgery. Therefore the immune-mediated thrombocytopenia with ischemic complications could be underdiagnosed resulting in high midterm morbidity. Although lower extremity deep vein thrombosis and distal arterial micro embolization of the extremities are often described as presenting symptoms, our clinical experience showed that TGA could be the most frequently presentation symptom. When HIT is suspected, a switch from heparin to alternative anticoagulation should be directly applied, considering the test results normally takes a few days.

References

1. Ahmed I, Majeed A, Powell R. Heparin induced thrombocytopenia: diagnosis and management update. Postgrad Med J. 2007; 83: 575-82.

2. Greinacher A. Clinical Practice. Heparin-Induced Thrombocytopenia. N Engl J Med. 2015; 373: 252-61.

3. Pishko AM, Cuker A. Heparin-Induced Thrombocytopenia in Cardiac Surgery Patients. Semin Thromb Hemost. 2017; 43: 691-8.

4. Warkentin TE, Hirte HW, Anderson DR, Wilson WEC, O'Connell GJ, Lo RC. Transient Global Amnesia Associated With Acute Heparin-Induced Thrombocytopenia. The American Journal of Medicine. 1994; 97: 489-91.

5. Filley CM, Fields RD. White matter and cognition: making the connection. J Neurophysiol. 2016; 116: 2093-104.

6. Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev. 2017; 4: CD007557.

7. Teh CH, Robertson MN, Warkentin TE, Hendriksen PA, Backenbury ET, Anderson JAM. Transient Global Amnesia as the Presenting Feature of Heparin-Induced Thrombocytopenia. J Card Surg. 2010; 25: 300-2.

8. Wollersheim LW, Li WW, Bouma BJ, Repossini A, van der Meulen J, de Mol BA. Aortic Valve Replacement With the Stentless Freedom SOLO Bioprosthesis: A Systematic Review. Ann Thorac Surg. 2015; 100: 1496-504.

9. Greinacher A, Ittermann T, Bagemuhl J, Althaus K, Furll B, et al. Heparin-induced thrombocytopenia: towards standardization of platelet factor 4/heparin antigen tests. J Thromb Haemost. 2010; 8: 2025-31.