

## WHERE HAVE THE PLATELETS GONE? TIROFIBAN INDUCED THROMBOCYTOPENIA

Fahad Shamsi<sup>1</sup>, Javed Tai<sup>2</sup>

<sup>1,2</sup> Department of Interventional Cardiology Aga Khan University Hospital, Karachi-Pakistan

**Address for Correspondence:**

**Dr. Fahad Shamsi,**

Department of Interventional Cardiology Aga Khan University Hospital, Karachi-Pakistan

Email: drfahadshamsi@gmail.com

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### ABSTRACT

Glycoprotein IIb/IIIa inhibitors (GP IIb/IIIa) prevent platelet aggregation by blocking fibrinogen binding to GP IIb/IIIa receptors on platelets. GP IIb/IIIa inhibitors have shown to improve clinical outcomes. They are widely used in patients with acute coronary syndrome and following percutaneous intervention (PCI). Thrombocytopenia associated with this class of agents is a well-known complication. Drug dependent antibodies are the cause of thrombocytopenia in this condition. However, severe thrombocytopenia is rare.

Here we report a case of acute severe thrombocytopenia following treatment with tirofiban, a GP IIb/IIIa inhibitor in a patient who underwent PCI for ST-elevation myocardial infarction (STEMI).

**Key Words:** Thrombocytopenia, Glycoprotein IIb/IIIa inhibitors, Tirofiban

### INTRODUCTION

Drug induced thrombocytopenia (DIPT) is often missed in the course of patient's medical management. Many physiological factors aid in masking this phenomenon. Globally reported incidences of severe drug induced thrombocytopenia are few in numbers. Studies conducted in the west propose that drug induced thrombocytopenia affects about 10 persons per million annually and puts the elderly and hospitalized persons at a higher risk as they are more exposed to medications.<sup>1</sup> However, recent evidence has implicated certain drugs including heparin, quinine and antibiotics especially sulfonamides, vancomycin and rifampicin. Tirofiban is also reported to cause thrombocytopenia.<sup>2</sup> It is a glycoprotein IIb/IIIa inhibitor and is prescribed to patients with acute coronary syndrome and myocardial infarction. This case report aims to highlight the occurrence of severe drug induced thrombocytopenia caused by Tirofiban.

## CASE REPORT

A 55 years old man, visited the emergency department with complain of central chest pain for two and a half hours. He was a known case of hypertension and chronic smoker. He had a history of Non- ST elevation myocardial infarction 10 months ago for which he underwent coronary angiography. At that time, PCI of right coronary artery was performed with two bare metal stents. At presentation, his vital signs revealed a heart rate of 108 beats per minute and a blood pressure of 130/80 mm Hg. On examination, chest was clear. First and second heart sounds were audible with no added sounds. Other findings were insignificant. Electrocardiogram showed ST elevation in lead V2 to V6. Diagnosis of anterior wall MI was made. Baseline laboratory investigations revealed hemoglobin of 15.1mg/dl, platelet count of 208,000, prothrombin time (PT) of 11.1 sec, activated partial thromboplastintime (APTT) 30.0 sec, INR of 1.06 and serum creatinine of 1.0mg/dl. The patient recieved 5000 IU of intravenous heparin, 300 mg aspirin and 600mg clopidogrel. An informed consent was obtained for coronary angiography and primary PCI and then patient was immediately transferred to cardiac catheterization laboratory.

Coronary angiography revealed an occluded mid Left anterior descending artery (LAD). Left circumflex artery had mild plaquing with moderate stenosis (60-70%) in first obtuse marginal branch. The right coronary artery (RCA) had mild instent restenosis and mild disease in distal vessel. PCI to LAD was performed with thrombus aspiration and direct stenting with 3.0 x 30 mm BMS. Thrombolysis in Myocardial Infarction (TIMI) grade III flow was achieved post PCI with no residual lesion. Tirofiban was administered in a PCI bolus dose and continued as an infusion for 12 hours post PCI. The next day, patient's routine labs reports showed marked decrease in platelets, went to  $23 \times 10^9/L$ . The possible causes of severe thrombocytopenia which were considered included heparin induced thrombocytopenia (HIT) and Tirofiban induced thrombocytopenia. The platelet counts were closely monitored and serum platelet factor- 4 (PF4) was also sent. Aspirin and clopidogrel were discontinued and platelets were arranged in case patient require transfusion.

Platelet count further decreased to  $13 \times 10^9/L$  over next 24 hours. PF4 was found to be negative which excluded the possibility of HIT. On the third day, thrombocytes increased to  $44 \times 10^9/L$ . Once the platelets count increased up to  $50 \times 10^9/L$  on day 4, aspirin was restarted. The following day platelets rose to  $84 \times 10^9/L$  and clopidogrel was also restarted. Patient was kept under observation for another 48 hours in the hospital. The counts increased to  $108 \times 10^9/L$  and the patient was discharged from the hospital with a follow up after 7 days.

## DISCUSSION

Drug-induced thrombocytopenia (DIPT) is described as sudden decrease in platelet count to less than  $20 \times 10^9/L$ .<sup>3</sup> Due to its rapid onset; it remains a point to ponder for many clinicians in order to demarcate it from other physiological factors. DIPT is often not detected initially in many hospitalized patients as it may be subjected to complications such as sepsis.

DIPT characteristically is an immune-mediated reaction. Certain classifications of drugs are sensitive to glycoproteins on platelet surface. Due to their high affinity, drug-dependent antiplatelet antibodies bind firmly to the receptors on platelet in their presence.<sup>4</sup> Drug-dependent anti platelet antibodies classically generate upon exposure to a new drug for 1 to 2 weeks. It may also form following intermittent use of a drug for a long time.

Glycoprotein (GP) IIb/IIIa inhibitors, a class of effective blood thinners, block the attachment of fibrinogen to activated GPIIb/IIIa receptors, thus restricting platelet-platelet interaction and thrombus formation.<sup>5</sup> Unlike other drugs, an exceptional feature of GP IIb/IIIa inhibitor-induced thrombocytopenia is that the platelet count substantially decreases within 24 hours of initial administration of the drug.<sup>6</sup> For rest of the drug categories, it requires a longer period of time post administration so as to sensitize and mediate antibody formation.<sup>7</sup> Three GPIIb/IIIa inhibitors namely; abciximab, tirofiban, and eptifibatide are approved for clinical use by FDA. In our case study, we present evidence to tirofiban induced thrombocytopenia.

Tirofiban is an antithrombotic agent which inhibits platelet aggregation by binding to the receptor glycoprotein IIb/IIIa on platelet's surface. It is prescribed for patients with acute coronary syndrome (unstable angina/non-Q-wave or elevated ST segment myocardial infarction) before, during and after PCI. A bolus of 25 mcg/kg/min followed by a continuous infusion of 0.15 mcg/kg/min for 12 to 18 hours is recommended after PCI.<sup>8</sup>

Another cause of thrombocytopenia is heparin. There are two types of heparin-induced thrombocytopenia (HIT). HIT type I occurs within two days after initiation of treatment and is usually characterized by slight thrombocytopenia. The mechanism is non-immune. Thrombocytopenia that developed early during the course of treatment in our patient was ruled out to be HIT type I. HIT type II is a more serious form and is an immune mediated disorder. It is characterized as antibodies against the heparin-platelet factor 4 complex (PF4). The heparin-PF4 complex binds to an activated platelet surface and is recognized by the Fab region of HIT antibody, forming a heparin-PF4-antibody complex on the platelet. Activated platelets with the heparin-PF4-antibody complex attached to their surface undergo aggregation and

are removed prematurely from the circulation leading to thrombocytopenia (HIT). It occurs usually 5 days after initiation of heparin, or less when there is prior exposure to heparin. As our patient had prior exposure to heparin, it was considered as a possible cause in our case. However absence of heparin-dependent antibodies, ruled out the possibility. So the GP inhibitor (tirofiban) was considered as the most likely cause of thrombocytopenia in this case.

The patient in the case mentioned above received a tirofiban bolus during PCI and followed by an infusion. Platelet count decreased within 24 hours of tirofiban administration and improved over the next 3-4 days. Thus, the decline in the platelet count was attributed to tirofiban.

## CONCLUSION

To Conclude, tirofiban may induce severe thrombocytopenia. It can only be detected by careful monitoring. Platelet count should be monitored during the treatment with GP inhibitors to avoid unexplained bleeding complication.

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