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TIROFIBAN INDUCED THROMBOCYTOPENIA: A CASE REPORT OF A RARE SIDE EFFECT

Yusuf Savran[1*], Kutlay Aydin[2], Suleyman Men[3]

[1]Department of Internal Medicine, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey.
[2] Department of Intensive Care Medicine, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey.
[3]Department of Radiology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey.

Corresponding Author:- **Yusuf Savran**
E-mail: yusuf.savran@deu.edu.tr

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ABSTRACT
Glycoprotein IIb/IIIa inhibitors are commonly used in treating patients with acute coronary syndromes in combination with angioplasty. Tirofiban is a nonpeptide inhibitor of the platelet glycoprotein IIb/IIIa receptor which interferes with platelet aggregation and may lead to severe thrombocytopenia with an incidence of 0.5% . In this report, we describe a case of acute serious thrombocytopenia during 24 hours of Tirofiban administration in a patient in whom primary percutaneous cerebral embolization and stent implantation was performed for subarachnoid hemorrhage caused by cerebral artery aneurism.

INTRODUCTION

Glycoprotein (GP) IIb/IIIa inhibitors prevent platelet aggregation and thrombus formation and are used in patients with acute coronary syndromes and percutaneous coronary interventions as antiplatelet agents [1,2]. There is a clear association between the use of GP IIb/IIIa inhibitors and thrombocytopenia. GP IIb/IIIa inhibitor-induced thrombocytopenia typically occurs within 24 hours of initial drug administration, and occasionally within 30 minutes to several hours [3]. Tirofiban-induced thrombocytopenia ($<100x10^9$/L) is reported to be 1.1% to 1.3% and severe thrombocytopenia ($<50x10^9$/L) is reported to be 0.4% to 0.5% in literature [3,4]. We report severe trombocytopenia($16X10^9$/L) following prophylactic Tirofiban infusion after cerebral embolization and stent implantation in a case with subarachnoid hemorrhage originating from a cerebral aneurism.

Case presentation

54-year-old man was found unconscious at home and brought to emergency service. On first evaluation he was comatous(Glasgow coma score : E1M1V1) and physical examination detected; blood pressure: 172/112 mmHg, pulse:102/m rythmic, pupils miotic but light reactive, respiratory rate: 28/min and remaining systemic examination findings were normal. Laboratory investigation displayed normal glucose, renal and liver functions and electrolytes. Hemogram findings were in normal limits excluding leukocytes (WBC: $18.9X10^9$/L ,hemoglobin: 16.8 g/dL,Plt: $164x10^9$/L)(Table 1). Brain computerized tomography (CT) displayed diffuse subarachnoid hemorrhage in bilateral sulci, basal cisterns and ventricules. A Neuroangiography CT reported an aneurism with dimensions of 10x9.5x13 mm at the level of anterior communicating artery. The patient was consultated with Neurosurgeons and they applied an external ventricular drainage catheter. The patient was intubated due to low Glasgow coma score. He was admitted to Intensive Care Unit for mechanical ventilation support and close hemodynamic monitorization. Neurosurgeons did not

plan an emergent operation. A diagnostic cerebral angiography was performed by Radiology Department. A saccular type aneurism was detected at the level of anterior communicating artery and embolization via metal coils and stent implantation was done. A heparin bolus of 5000 U and Tirofiban at a dose of 0.4 mcg/kg was applied in 30 minutes to prevent occlusion during the procedure and Tirofiban was continued at a dose of 0.1 mcg/kg/min for 24 hours after he was transferred back to the Intensive Care Unit. The hemogram findings after the procedure showed progressive decline in both hemoglobin and platelet values but especially profound trombocytopenia ($16x10^9$/L) developped at the 16th hour of Tirofiban infusion (Table 1). Fortunately the patient had no clinical signs of trombocytopenia and a control brain CT reported no acute pathology. The patient was consultated with Hematology consultant specialist. Thrombocytopenia was also confirmed by a peripheral blood smear. Checkup on the peripheral smear of a blood sample validated the extensive lack of platelets with no clustering. Tirofiban was immediately stopped and diagnostic evaluation for the etiology of trombocytopenia was started. Hematologic disease states including disseminated intravascular coagulation (DIC) were excluded by laboratory determinations such as serum fibrinogen level, D-dimer, fibrin degradation products, prothrombin time, and activated partial thromboplastin time. We were not able to exclude heparin-induced thrombocytopenia with the enzyme-linked immunosorbent assay for antibodies to platelet factor 4/heparin because it was not in use in our hospital. The onset of thrombocytopenia was sudden and without a thrombotic complication, which is more likely with heparin, thus tirofiban seemed to be the most likely causative agent. The patient was transfused with 8 units of platelets. Control hemogram reported a platelet count of $75x10^9$/L . After cessation of Tirofiban control hemogram values progressively started to ameliorate with a platelet count of $137x10^9$/L on the third day (Table 1)

	Baseline	Pretreatment	8th hour of infusion	16th hour of infusion	72 hours postinfusion
WBC (10^9/L)	**18,9**	**19**	**7,8**	**9,5**	**9,6**
Hemoglobin (g/dL)	**16,8**	**14,6**	**11,9**	**11,7**	**9,4**
Plt (10^9/L)	**164**	**119**	**75**	**16**	**137**

WBC: White blood cells; Plt: platelets

DISCUSSION

Thrombocytopenia, at times profound, has been observed within 24 hours, and occasionally within several hours, of the initial dose of GP IIb/IIIa inhibitors [3,5,6]. Randomized trials have documented significantly increased rates of thrombocytopenia with eptifibatide or tirofiban [6-8]. Thrombocytopenia following GP IIb/IIIa inhibitors is hypothesised to occur due to antibodies against platelet neoepitopes that are exposed by alteration of the conformation of the GP IIb/IIIa complex during normal platelet aggregation [9,10].

Treatment with GP IIb/IIIa inhibitors has also been associated with pseudothrombocytopenia [11]. The "gold standard" for evaluation of thrombocytopenia of any cause is examination of the peripheral blood smear. Peripheral blood smear of our patient confirmed true trombocytopenia.

The differential diagnosis for some other drug-induced thrombocytopenias should be punctiliously made. Heparin-induced thrombocytopenia (HIT) type I tends to occur within minutes to hours of postexposure in those who have received heparin therapy within the past 6 months and is usually mild and asymptomatic [12]. In HIT type II, the mechanism is immunologic in origin, and thrombocytopenia typically occurs approximately 5 days after initiation of treatment in patients without prior exposure to heparin [12]. Although we did not search for heparin-dependent antibodies, we consider that the acute severe thrombocytopenia observed in our case was very unlikely to be heparin induced, because our patient had no prior exposure to heparin. The coagulation parameters were found to be all normal excluding DIC and any other hematologic disease.

In conclusion our case reports highlights the importance of mild to severe trombocytopenia that may be experienced during treatment with GP IIb/IIIa inhibitors. Because of the possibility of sudden and severe drug-induced thrombocytopenia, the platelet count should be monitored frequently in patients receiving GP IIb/IIIa inhibitors. A reasonable plan for patients about to be treated with these agents is to obtain a platelet count prior to treatment, within two to four hours following the intravenous bolus, daily during therapy, and again prior to the patient's discharge [13]. If the platelet count falls to $<100x10^9$/L or decreases by 25 percent or more from its pretreatment level, additional platelet counts should be obtained and an evaluation should be started first of all to rule out pseudothrombocytopenia. If pseudothrombocytopenia is ruled out the GP IIb/IIIa inhibitor should be discontinued. Platelet transfusion should be used if the platelet count is $<20x10^9$/L, if there is overt bleeding, or if an emergency invasive procedure is required.

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REFERENCES

1. King S, Short M, Harmon C. (2016). Glycoprotein IIb/IIIa inhibitors: The resurgence of tirofiban. *Vascul Pharmacol*, 78, 10-6.
2. Sabatine MS, Jang IK. (2000). The use of glycoprotein IIb/IIIa inhibitors in patients with coronary artery disease. *Am J Med*, 109(3), 224-37.
3. Dasgupta H, Blankenship JC, Wood GC et al. (2000). Thrombocytopenia complicating treatment with intravenous glycoprotein IIb/IIIa receptor inhibitors: a pooled analysis. *Am Heart J*, 140(2), 206-11.
4. Huynh T, Piazza N, DiBattiste PM, et al. (2005). Analysis of bleeding complications associated with glycoprotein IIb/IIIa receptors blockade in patients with high-risk acute coronary syndromes: insights form the PRISM-PLUS study. *Int J Cardiol*, 100(1), 73-8.
5. Merlini PA, Rossi M, Menozzi A, et al. (2004). Thrombocytopenia caused by abciximab or tirofiban and its association with clinical outcome in patients undergoing coronary stenting. *Circulation*, 109(18), 2203-6.
6. Brener SJ, Zeymer U, Adgey AA, et al. (2002). Eptifibatide and low-dose tissue plasminogen activator in acute myocardial infarction: the integrilin and low-dose thrombolysis in acute myocardial infarction (INTRO AMI) trial. *J Am Coll Cardiol*, 39(3), 377-86.
7. (1998). Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med*, 339(7), 436-43.
8. (1998). A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med*, 338(21), 1498-505.
9. Bougie DW, Wilker PR, Wuitschick ED et al. (2002). Acute thrombocytopenia after treatment with tirofiban or eptifibatide is associated with antibodies specific for ligand-occupied GPIIb/IIIa. *Blood*, 2002, 100(6), 2071-6.
10. Billheimer JT, Dicker IB, Wynn R et al. (2002). Evidence that thrombocytopenia observed in humans treated with orally bioavailable glycoprotein IIb/IIIa antagonists is immune mediated. *Blood*, 99(10), 3540-6.
11. Sane DC, Damaraju LV, Topol EJ, et al. (2000). Occurrence and clinical significance of pseudothrombocytopenia during abciximab therapy. *J Am Coll Cardiol*, 36(1), 75-83.
12. T. E. Warkentin and A. Greinacher. (2004). Heparin-induced thrombocytopenia: recognition, treatment, and prevention—the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy, *Chest*, vol. 126, supplement 3, 311S–337S.
13. Arnold DM, Nazi I, Warkentin TE et al. (2013). Approach to the diagnosis and management of drug-induced immune thrombocytopenia. *Transfus Med Rev*, 27(3), 137-45.