# Extreme Thrombocytopenia Following Abciximab Therapy

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Antagonists of the glycoprotein IIb/IIIa receptor block the binding of fibrinogen and von Willebrand factor to the platelet receptor. This effect can lead to bleeding and thrombocytopenia. We analyzed the incidence and clinical repercussions of severe thrombocytopenia (<20 000 /μL) secondary to abciximab treatment in a prospective study of 375 patients (74% men) who underwent percutaneous coronary revascularization and received abciximab at our hospital. We recorded clinical and demographic characteristics, angiographic findings, laboratory results and platelet counts (before, 4 hours after and 12 hours after the procedure) and hematocrit. The incidence of severe acute thrombocytopenia was 1.1%. All patients were men, and none had relevant bleeding complications. Management consisted of monitoring the bleeding, discontinuing the drug and transfusing platelets. Clinicians should be alert to this complication during the initial hours after the administration of abciximab.

**Key words:** *Abciximab. Thrombocytopenia. Angioplasty.*

**Trombocitopenia extrema secundaria a abciximab**

Los antiagregantes antiglucoproteína IIb/IIIa bloquean la unión del fibrinógeno y el factor de Von Willebrand a sus receptores. Pueden causar hemorragia y trombocitopenia. Se ha analizado la incidencia y la repercusión clínica de la trombocitopenia extrema severa (< 20.000 por μl) secundaria a abciximab en un estudio prospectivo de 375 pacientes (el 74%, varones) sometidos a cateterismo cardíaco percutáneo y tratados con abciximab en nuestro hospital. Se registraron las características clínicas, demográficas, del procedimiento y los datos analíticos, así como el recuento plaquetario (antes del procedimiento y a las 4 y 12 h de éste) y el hematocrito.

La incidencia de trombocitopenia aguda extrema en los 375 pacientes fue del 1,1%. Todos fueron varones y no presentaron complicaciones hemorrágicas relevantes. Debe considerarse esta complicación en las primeras horas posteriores a la administración del fármaco. Su manejo consistió en vigilancia del sangrado, suspensión del fármaco y transfusión plaquetaria.

**Palabras clave:** *Abciximab. Trombocitopenia. Angioplastia.*

## INTRODUCTION

The role of glycoprotein IIb/IIIa receptor blockers in the treatment of the acute coronary syndrome is becoming increasingly important. Abciximab, tirofiban, and eptifibatide have all shown good clinical results.[1] Abciximab, the Fab fragment of the chimeric monoclonal antibody 7E3, inhibits platelet aggregation, preventing binding of the Von Willebrand factor, fibrinogen and other adhesive molecules to the glycoprotein IIb/IIIa receptor of activated platelets. Abciximab also blocks the generation of thrombin which follows platelet activation.[2]

The main indication for abciximab is prevention of the acute coronary syndrome, especially in patients scheduled to undergo interventional coronary procedures.[3] The most important adverse side effects of abciximab are hemorrhage and thrombocytopenia,[4] which Berkowitz et al[5] classified into four progressive groups depending on the reduction in the platelet count. Severe acute thrombocytopenia shows a platelet count below 20 000/μL and its incidence

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ranges from 2.4% to 4%, according to the series.[6] The origin of severe acute thrombocytopenia is unknown, although a possible mechanism involves the appearance of specific monoclonal glycoprotein IIb/IIIa antibodies or IgG antibodies against the murine sequences of activated platelets after a second administration of the drug.[7,8] The aim of this study was to determine and analyze the incidence of complications of severe acute thrombocytopenia secondary to the administration of abciximab in our hospital.

## PATIENTS AND METHODS

A prospective study was undertaken from January 1997 to January 2002 of 375 consecutive patients who underwent percutaneous coronary intervention (PCI) for 436 lesions and who were treated with abciximab according to the hospital protocol. Measurements were made of demographic, clinical, and angiographic variables, as well as of the platelet count 4 hours after and 12 hours after starting treatment with abciximab. The qualitative variables were expressed as percentages and the quantitative variables as the mean ± standard deviation or the median. The Kruskal-Wallis test was used to analyze the difference between groups in hematocrit count. The data were processed statistically with SPSS, version 9.0.

A patient was considered to have severe acute thrombocytopenia when the platelet count was below 20 000 /μL. For the diagnosis of thrombocytopenia, additional platelet counts were made using 2 separator tubes which contained ethylenediaminetetraacetic acid (EDTA) and citrate, respectively. A manual count was also done to rule out the possibility of pseudothrombocytopenia.

The indications for the use of abciximab were established according to the hospital protocol:

– Percutaneous coronary intervention in the clear presence of a thrombus or unstable plaque, or closure of the artery during angioplasty.

– Diabetic patients undergoing angioplasty in the context of stable or unstable angina.[9,10]

– Short-term reduction of the risk for acute myocardial infarction in patients with unstable angina who fail to respond to conventional medical therapy and who are due for early PCI.

The abciximab dose was 0.25 mg/kg given in an intravenous bolus 10-60 min before the operation, followed by continuous intravenous infusion of 0.125 μg/kg/min for 12 hours (up to a maximum of 10 μg/kg/min).

Besides abciximab, all the patients were treated with 300 mg of acetyl salicylic acid (ASA) 2 hours before the intervention and daily thereafter. Clopidogrel was also used in 99% of the patients (300 mg loading dose, followed by 75 mg daily after the intervention for 1 month) or ticlopidine (500 mg loading dose, followed by 250 mg/12 h) in the unusual case of intolerance to clopidogrel. Heparin was given to all patients, and the dose adjusted according to body weight, with an initial bolus of 70 U/kg, to maintain an activated coagulation time of 200-300 seconds.

## RESULTS

The mean age of the 375 patients, 74% of whom were men, was 60.5±8.2 years (median, 64 years). A stent was implanted in 97% of the patients (mean, 1.25 stents per patient). Table 1 shows the demographic variables, the history and the angiographic data of the patients. The mean ejection fraction was 56.3±6.8%.

The mean platelet count after the administration of abciximab was 231 466±47 000/μL. The mean overall hematocrit was 35.7% (42% in the patients without thrombocytopenia). The accumulated overall incidence of thrombocytopenia was 11.5%. Table 2 shows the accumulated incidences in the different thrombocytopenia groups, as well as the mean hematocrit value in each group. No significant differences were detected between the groups in hematocrit values.

In the whole series there were just 4 cases of severe acute thrombocytopenia, which represented an incidence of 1.1%. All 4 cases were in men with a platelet count prior to administration of abciximab within the normal range. The course, concentrated platelet needs and recovery times from the thrombocytopenia are shown in Table 3. Hemorrhagic complications were not important: 2 patients had a mild inguinal

TABLE 1. **Personal History and Angiographic Data***

| | n | % |
|---|---|---|
| Diabetes | 145 | 38.7[a] |
| Hypertension | 191 | 50.9 |
| Hypercholesterolemia | 166 | 44.3 |
| Prior smoker | 229 | 61 |
| Active smoker | 139 | 37 |
| Family history | 45 | 12 |
| Previous AMI | 94 | 25 |
| Previous bypass | 34 | 9 |
| Previous PTCA | 34 | 9.9 |
| Unstable angina | 255 | 68 |
| AMI in previous 30 days | 157 | 42 |
| Primary or rescue PTCA | 50 | 13.3 |
| Disease | | |
| 1 vessel | 165 | 44 |
| 2 vessels | 127 | 34 |
| 3 vessels | 82 | 22 |

*PTCA indicates percutaneous transluminal coronary angioplasty; AMI, acute myocardial infarction; n, absolute frequency.
[a]81% of these patients had type 2 diabetes mellitus.

hematoma, 1 of whom also had occasional epistaxis. Only 1 patient required a blood transfusion, of 2 units of concentrated red cells. No patient presented hemodynamic instability or needed vasoactive drugs.

## DISCUSSION

Thrombocytopenia secondary to treatment with abciximab is an uncommon side-effect and related with the risk of hemorrhage. A recent meta-analysis showed the incidence of severe thrombocytopenia to be 1%.[11] The incidence of severe acute thrombocytopenia in the different series ranges around 0.7%,[4,5,12-14] which approximates to the 1.1% found in our study. Risk factors for thrombocytopenia secondary to abciximab include age >65 years, weight <90 kg, and a platelet count before intervention of <200 000/μL.[11] The only one of these factors in our study was weight, which is of little importance.

Several studies show that important hemorrhagic complications are unusual in this type of severe acute thrombocytopenia.[11,15] In our patients only 2 had mild inguinal hernias, one of these accompanied by epistaxis. Thus, hemorrhagic complications were mild and with no clinical consequences, except for the requirement for closer follow-up for signs of bleeding and a longer stay in our unit than the mean stay for scheduled PCI. Special care was taken to prevent increasing the risk of hemorrhage, with avoidance of intramuscular injections and venous lines. Arterial introducers were withdrawn accompanied by manual compression and weights.

Other studies have shown increased requirements for transfusion of platelets and other blood-derived products according to the bleeding, the period of resolution and the degree of thrombocytopenia.[5,11,14,16] Following these indications, 3 of our patients needed an important supply of concentrated platelets (Table 3). The remaining patient presented no obvious bleeding or fall in hematocrit, and therefore received no platelet transfusion despite the degree of thrombocytopenia. A case of massive cerebral hemorrhage in association with severe acute thrombocytopenia (4000/μl), 90 minutes after starting treatment with abciximab, has recently been reported in a patient who underwent angioplasty because of acute myocardial infarction.[13]

TABLE 2. **Accumulated Incidence of Thrombocytopenia and Hematocrit**

| Thrombocytopenia Groups | Frequency | Percentage | Hematocrit (%) |
|---|---|---|---|
| 1 150 000-100 000 | 33 | 8.8 | 34.4 |
| 2 100 000-50 000 | 6 | 1.6 | 32.8 |
| 3 50 000-20 000 | 0 | 0 | – |
| 4 <20 000 | 4 | 1.1 | 30.25 |

The management of thrombocytopenia secondary to abciximab is controversial. Platelet transfusion and immediate cessation of treatment appear to be the most effective measures[15]; whether other antiplatelet therapies should also be suspended is unclear. Studies are under way of the administration of corticoids[17] together with the platelet transfusion, which would enable either abciximab to be restarted or another glycoprotein IIb/IIIa receptor blocker to be used.

Our experience suggests that platelet transfusion and cessation of abciximab, as well as of other drugs with the potential to cause bleeding (heparin, ASA, ticlopidine, and clopidogrel), have reduced and lessened the hemorrhagic complications, and the resolution phase was no greater than previously reported, from 3 days to 1 week.[12,15] Accordingly, we closely monitor the platelet count and the hematocrit until the resolution phase.

Pseudothrombocytopenia, which is responsible for more than one third (36%) of the reduction in platelet count in patients who undergo PCI,[18] differed from true thrombocytopenia, as mentioned in the section on Patients and Methods.

Types I and II thrombocytopenia induced by heparin should be borne in mind when giving this drug concomitantly with abciximab. However, these types of

TABLE 3. **Description of the Patients With Severe Acute Thrombocytopenia***

| | Age, Years | Platelet Count on Admission | Thrombocytopenia and Time to Onset From Administration of Abciximab | Platelet Transfusions Given | Time to Recovery From Thrombocytopenia |
|---|---|---|---|---|---|
| 1 | 66 | 193 000/μL | 3000/μL at 7 h | 9 U (day 1)<br>8 U (day 2)<br>9 U (day 3) | 70 000/μL (day 4)<br>83 000/μL (day 5)<br>246 000/μL (day 9) |
| 2 | 55 | 145 000/μL | 2000/μL at 7 h<br>600/μL at 12 h | 16 U (day 1)<br>15 U (day 2) | 45 000/μL (day 4)<br>60 000/μL (day 6)<br>46 000/μL (day 4) |
| 3 | 47 | 270 000/μL | 6000/μL at 6 h | 8 U (day 1) | 159 000/μL (day 7) |
| 4 | 65 | 235 000/μL | 13 000/μL at 6 h | 0 | 21 000/μL (day 2) |

*U indicates units of concentrated pLatelets transfused.

thrombocytopenia rarely occur until at least 24 hours after exposure, they favor the onset of thrombosis, specific anti-heparin antibodies appear and the resolution of the symptoms takes longer.[19,20]

The incidence of thrombocytopenia following the combined administration of abciximab, ticlopidine, and clopidogrel has not yet been sufficiently examined. Whereas ticlopidine does not increase the incidence of thrombocytopenia, clopidogrel appears to do so.[21]

Replacement of abciximab by eptifibatide[22] or tirofiban[23] seems to be safe in patients who have thrombocytopenia secondary to abciximab and who still require glycoprotein IIb/IIIa receptor blockers.[22,23]

The 4 patients were reported to the hospital pharmacovigilance committee in order to obtain a truer reflection of the incidence of thrombocytopenia in daily clinical practice. Our protocol now includes a blood test 2 hours after starting abciximab therapy in order to enable the early detection of thrombocytopenia.

## REFERENCES


1. Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. Lancet 1999;353:227-31.
2. Coller BS. Blockade of platelet GPIIb/IIIa receptors as an antithrombotic strategy. Circulation 1995;92:2373-80.
3. The EPIC investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994;330:956-61.
4. Makoni SN. Acute profound thrombocytopenia following angioplasty: the dilemma in the management and review of the literature. Heart 2001;86:E18.
5. Berkowitz SD, Harrington RA, Rund MM, Tcheng JE. Acute profound thrombocytopenia after c7E3 Fab (abciximab) therapy. Circulation 1997;95:809-13.
6. Tcheng JE, Keriakes DJ, Lincoff AM, George BS, Kleiman NS, Sane DC. Abciximab readministration: results of the Reopro Readministration Registry. Circulation 2001;104:870-5.
7. Peter K, Straub A, Kohler B, Volkmann M, Scharz M, Kubler W, et al. Platelet activation as a potential mechanism of GP IIb/IIIa inhibitor-induced thrombocytopenia. Am J Cardiol 1999;84:519-24.
8. Curtis BR, Swyers J, Divgi A, Mcfarland JG, Aster RH. Thrombocytopenia after second exposure to abciximab is caused by antibodies that recognize abciximab-coated platelets. Blood 2000; 99:2054-9.
9. The EPISTENT Investigators. Randomized placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998;352:87-92.
10. Hernández García JM, Domínguez Franco A, Jiménez-Navarro MF, Alonso Briales JH, Curiel Balsera E, Gómez Doblas JJ, et al. ¿El abciximab mejora el pronóstico de los diabéticos tras la intervención coronaria percutánea? Rev Esp Cardiol 2002;55: 810-5.
11. Keriakes DJ, Berkowitz SD, Lincoff AM, Tcheng JE, Wolski K, Achenbach R, et al. Clinical correlates and course of thrombocytopenia during percutaneous coronary intervention in the era of abciximab platelet glycoprotein IIb/IIIa blockade. Am Heart J 2000;140:74-80.
12. Reddy MS, Carmody TJ, Keriakes DJ. Severe delayed thrombocytopenia associated with abciximab (Reopro) therapy. Catheter Cardiovasc Interv 2001;52:486-8.
13. Vahdat B, Canavy I, Fourcade L, García E, Quilici J, Bonnet JL, et al. Fatal cerebral hemorraghe and severe thrombocytopenia during abciximab treatment. Catheter Cardiovasc Interv 2000;49: 177-80.
14. Jubelirer SJ, Koenig BA, Bates MC. Acute profound thrombocytopenia following c/E3 Fab (abciximab) therapy: case reports, review of the literature and implications for therapy. Am J Hematol 1999;61:205-8.
15. Dasgupta H, Blankenship J, Wood GC, Frey CM, Demko SL, Menapace FJ. Thrombocytopenia complicating treatment with intravenous glycoprotein IIb/IIIa receptor inhibitors: a pooled analysis. Am Heart J 2000;140:206-11.
16. Kereiakes DJ, Essell JH, Abbottsmith CW, Broderick TM, Runyon JP. Abciximab-associated profound thrombocytopenia: therapy with immunoglobulin and platelet transfusion. Am J Cardiol 1996;78:1161-3.
17. Nguyen N, Salib H, Mascarenhas DA. Acute profound thrombocytopenia without bleeding complications after re-administration of abciximab. J Invasive Cardiol 2001;94:245-51.
18. Sane DC, Damaraju LV, Topol EJ, Cabot CF, Mascelli MA, Harrington RA, et al. Occurrence and clinical significance of pseudothrombocytopenia during abciximab therapy. J Am Coll Cardiol 2000;36:75-83.
19. Schmitt BP, Adelman B. Heparin-associated thrombocytopenia: a critical review and pooled analysis. Am J Med Sci 1993;305: 208-15.
20. Galeote G, Hussein M, Sobrino N, Calvo L, Sánchez-Recalde A, Sobrino JA. Utilización de enoxaparina o heparina no fraccionada en combinación con abciximab durante la intervención coronaria percutánea: estudio piloto aleatorizado. Rev Esp Cardiol 2002;55: 1261-6.
21. Coto H. Platelet receptor glycoprotein IIb/IIIa inhibition with eptifibatide in a patient with thrombocytopenia after treatment with abciximab. J Invasive Cardiol 2000;12:528-31.
22. Tcheng JE, Keriakes DJ, Braden GA, Jordan RE, Mascelli MA, Langrall MA, et al. Readministration of abciximab: interim report of the Reopro readministration registry. Am Heart J 1999;138: S33-8.
23. Arjomand H, Magsi ZM, Chang KS, Mascarenhas DA. Abciximab readministration: a single-operator community-hospital experience. Catheter Cardiovasc Interv 1999;47:294-6.