Administration of a Glycoprotein IIb/IIIa Receptor Blocker with a Thienopyridine Derivative Does Not Increase the Risk of Thrombocytopenia[1]

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ABSTRACT. The combination of aspirin, a thienopyridine derivative, and a glycoprotein IIb/IIIa receptor inhibitor has become standard therapy for patients undergoing percutaneous coronary intervention (PCI). Recent studies have shown an increased incidence of thrombocytopenia in those patients receiving a high loading dose of clopidogrel (thienopyridine) with abciximab (IIb/IIIa receptor inhibitor) prior to coronary intervention. We reviewed the records of 504 patients who underwent PCI at a large tertiary care hospital and noted an incidence of thrombocytopenia of 4.8%, comparable to published historical controls who received abciximab without clopidogrel. In patients undergoing PCI, there was no difference in thrombocytopenia or bleeding complications between patients receiving a high or a low dose of a thienopyridine. We conclude that a high loading dose of a thienopyridine derivative prior to PCI may be administered safely and efficaciously in the setting of concomitant administration of abciximab without an undue risk of thrombocytopenia.

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INTRODUCTION

Platelet mediated acute and subacute thromboses are serious complications of intracoronary stent placement. Data from the late 1990s demonstrated the efficacy and safety of combined therapy with aspirin and a thienopyridine derivative for reducing stent subacute thrombosis rates from 2% to as low as 0.5% (Moussa and others 1999; Bage and others 1998; Leon and others 1998; CAPRIE 1996). Additionally, recent data has demonstrated a reduction in subacute thrombosis in patients receiving a loading dose of a thienopyridine derivative prior to percutaneous coronary intervention (PCI) (Steinhubl and others 1998). Higher loading doses of clopidogrel or ticlopidine result in more rapid platelet inhibition, which translates into a lower total major adverse cardiac event rate (Pache and others 2002; Bhatt and others 2001; Gawaz and others 2001). More recent data has shown the utility of also administering glycoprotein (Gp) IIb/IIIa antagonists in patients undergoing PCI to further reduce major adverse cardiac events (EPIC 1994).

Glycoprotein IIb/IIIa inhibitors themselves may induce thrombocytopenia (Berkowitz and others 1997, 1998). Recent observational data has suggested that triple antiplatelet therapy with aspirin, a thienopyridine derivative, and a Gp IIb/IIIa antagonist for PCI may be associated with an unacceptably high incidence of thrombocytopenia measured at 24% with a 300 mg loading dose of clopidogrel (Dillon and others 2000). This antiplatelet combination is currently administered in up to 60% of patients undergoing PCI in the United States, and therefore has important implications (Dillon and others 2000). However, in our clinical experience, we have not observed excessive thrombocytopenia with this combination of medications. We therefore sought to evaluate this important clinical issue by analyzing our prospectively collected data over a one-year period at a tertiary care community hospital.

MATERIALS AND METHODS

We reviewed the medical records and catheterization reports from 520 patients who underwent PCI between 1 January 1999 and 31 December 1999 at Akron City Hospital (part of the Summa Health System), a 530-bed tertiary care community hospital in Akron, OH. Patients were excluded from the study if emergent reversal of antiplatelet therapy was required; data was incomplete; or aspirin, a thienopyridine derivative, or a Gp IIb/IIIa receptor blocker was not administered.

Patients who underwent PCI received either abciximab (a chimeric Fab Gp IIb/IIIa receptor blocker) bolus and infusion at the time of and beyond PCI, or tirofiban (a synthetic peptide Gp IIb/IIIa receptor blocker) infusion prior to and beyond PCI per FDA guidelines (PDR 2002).

The particular thienopyridine derivative (clopidogrel or ticlopidine) and dosage was at the interventionalist's discretion. Patients receiving 75 mg to 150 mg of clopidogrel on the day prior to the procedure or the morning of the procedure were classified as the Low Loading Dose Clopidogrel group (LLDC). Patients who received 300 mg to 375 mg were classified as the High Loading Dose Clopidogrel group (HLDC). Patients who received 250 mg to 500 mg of ticlopidine were classified as the Low Loading Dose Ticlopidine group (LLDT). Patients who received 1000 mg were classified as the High Loading Dose Ticlopidine group (HLDT).

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Platelet counts obtained prior to PCI were compared with platelet counts at 2 to 4 hours, 18 to 24 hours, and 48 to 72 hours following PCI. Thrombocytopenia was defined as a platelet count less than 100,000 platelets/mm^3. Severe thrombocytopenia was defined as a platelet count less than 20,000 platelets/mm^3. Hemoglobin levels were obtained before PCI and at the documented nadir up to 72 hours following PCI.

Other patient data assessed included age, sex, weight, serum creatinine, diagnosis of hypertension, diabetes mellitus, hyperlipidemia, tobacco abuse, bleeding complications, requirement for transfusion of blood products, and the length of stay after PCI. Medical information such as treated or untreated hypertension, diabetes mellitus, hyperlipidemia, and renal function were obtained by chart review of initial history and physical, initial nursing assessment and vital signs, and laboratory data. Bleeding complications and transfusion requirements were obtained through chart review of the entire length of stay. Length of hospital stay was defined as date of intervention until the day of hospital discharge.

Statistical Analysis

The analysis performed used both descriptive and inferential statistics. The inferential statistics used both Chi Squares and *F* tests. The Pearson correlation and analysis of covariance were also employed. A power analysis was run to determine the likelihood of making a Type II error. Confidence intervals were also calculated. The *F* test is also very robust; that is, the assumptions that the variance of the criterion measures is the same for each of the treatment populations and that the criterion measures for each treatment population are normally distributed "can be violated in most cases without seriously distorting the stated alpha level" (McNeil and others 1996). The *F* calculation was performed using the formula presented by McNeil and others (1996):

$$F = \frac{(R^2f - R^2r)/df_n}{(1 - R^2f)/df_d}$$

Where:

R^2f = the proportion of observed variance (of the dependent variable) accounted for by the full linear regression model.

R^2r = the proportion of observed variance (of the dependent variable) accounted for by the restricted linear regression model.

df_n = the number of linearly independent vectors in the full linear regression model minus the number of linearly independent vectors in the restricted linear regression model.

df_d = the number of participants minus the number of linearly independent vectors in the full linear regression model.

A power analysis (McNeil and others 1996) calculation was performed using the following formulas:

$$L = f^2 * df_2$$

Where:

L = a function of power (needed to enter power tables)

f^2 = effect size

$df_2 = N - m_1$

N = number of participants

m_1 = number of independent vectors in the restricted regression equation

m_2 = number of independent vectors in the restricted model

$df_1 = m_1 - m_2$

The next test was performed on the general linear model test to determine if the variables of interest were significant while holding constant the covariants.

RESULTS

Study Groups

Of the 520 patient charts reviewed, 16 were excluded for the following reasons: 6 patients died unrelated to thrombocytopenia within 24 hours of PCI resulting in incomplete data; 4 coronary artery perforations required immediate cessation and reversal of platelet inhibition; 3 patients did not receive a Gp IIb/IIIa receptor blocker; 1 patient did not receive a thienopyridine derivative; 1 patient had an ascending aortic aneurysm requiring surgical intervention, and 1 patient had a pulmonary artery rupture secondary to pulmonary artery catheter insertion requiring immediate cessation and reversal of platelet inhibition. After the above exclusions, 504 patients were included in data interpretation (Table 1). Of the 504 patients, 490 received the Gp IIb/IIIa inhibitor abciximab and 14 received tirofiban. Two hundred fifty-four patients received a low loading dose of clopidogrel (LLDC) and 145 received a high loading dose of clopidogrel (HLDC). One hundred two patients received a low loading dose of ticlopidine (LLDT) and 3 patients received a high loading dose of ticlopidine (HLDT).

TABLE 1

Number of patients receiving each combination of medication.

	Abciximab	Tirofiban	Total
LLDC *	245	9	254
HLDC **	141	4	145
LLDT ‡	101	1	102
HLDT ‡‡	3	0	3
Total	490	14	504

* LLDC = Low Loading Dose Clopidogrel (75-150 mg).
** HLDC = High Loading Dose Clopidogrel (300-375 mg).
‡ LLDT = Low Loading Dose Ticlopidine (250-500 mg).
‡‡ HLDT = High Loading Dose Ticlopidine (1000 mg).

Demographics

Demographic characteristics are shown in Table 2. There were 318 males and 186 females with ages ranging from 27-93 years, with an average age of 63 years old. Of the 504 patients, 167 had diabetes mellitus; 319 had hypertension; 153 had current tobacco abuse, and 135 patients had a history of remote tobacco abuse; 284 had hyperlipidemia. Serum creatinine ranged from 0.1-9.8 mg/dl, with an average of 1.1 mg/dl. Forty-seven patients had a serum creatinine >1.5 mg/dl.

TABLE 2

Patient demographics and risk factors.

Variables	
Patients	504
Males	318
Age	Mean 63 y (27-93)
Diabetes	167
Hypertension	319
Current Smoker	153
Remote Smoker	135
Hyperlipidemia	284
Creatinine	Mean 1.1 mg/dL (0.1-9.8)
Creatinine >1.5	47

Incidence of Thrombocytopenia

Of the 504 patients who underwent PCI and received both a thienopyridine derivative and a GP IIb/IIIa receptor blocker, 24 (4.8%) developed thrombocytopenia. Only one patient had severe profound thrombocytopenia with a platelet count nadir of 3000 platelets/mm^3. No other patients had platelet counts below 52,000 platelets/mm^3. Table 3 demonstrates the incidence of thrombocytopenia for each group. Two of the patients developed pseudothrombocytopenia related to EDTA clumping and did not have thrombocytopenia on repeat analysis of heparinized samples.

Nine (3.7%) of the 245 patients who received LLDC and abciximab had documented thrombocytopenia. Two of the patients had low platelets (116,000 platelets/mm^3 and 128,000 platelets/mm^3, respectively) prior to administration of LLDC, resulting in nadir platelet counts of 77,000 platelets/mm^3 and 82,000 platelets/mm^3, respectively. One (11%) of the 9 patients who received LLDC and tirofiban had thrombocytopenia. Bleeding complications among the LLDC group included 10 vascular access site hematomas, 3 gastrointestinal bleeds, 3 patients with hematuria, 2 retropertinoneal hemorrhages, 1 pulmonary hemorrhage, 1 vitreous hemorrhage, and 1 subconjunctival hemorrhage.

TABLE 3

Incidence of thrombocytopenia for each combination of medication.

	Abciximab	Tirofiban	Total
LLDC	9/245 (3.7%)$^{*\#\ddagger}$	1/9 (11%)*	10/254 (3.9%)
HLDC	6/141 (4.2%)$^{\#}$	0/4	6/145 (4.1%)
LLDT	8/101 (7.9%)†‡	0/1	8/102 (7.8%)
HLDT	0/3†	0/0	0/3
Total	23/490 (4.7%)	1/14(7.1%)	24/504 (4.8%)

Incidence of thrombocytopenia (platelet count <100,000 platelets/mm^3) among patients receiving different dosages of a thienopyridine and a Gp IIb/IIIa derivative.

* (abciximab-LLDC vs tirofiban-LLDC) $c^2 = 6.4$ {significant, *N* very small. One needs to question the stability of this result.}

$^{\#}$ (abciximab-LLDC vs abciximab-HLDC) $c^2 = 0.6$ {NS}.

† (abciximab-LLDT vs abciximab-HLDT) $c^2 = 4$ {significant, *N* very small. One needs to question the stability of this result.}

‡ (abciximab-LLDC vs abciximab-LLDT) $c^2 = 0.029$ {NS}.

Only 1 of the patients with gastrointestinal blood loss had documented thrombocytopenia.

Six of 141 (4.2%) patients who received HLDC and abciximab had documented thrombocytopenia during the 2-72 hour window after PCI. None of the 4 patients who received HLDC and tirofiban had documented thrombocytopenia. Eight patients in the HLDC group suffered from a vascular access site hematoma; three of these had thrombocytopenia. Four patients in the HLDC group had gastrointestinal blood loss; only one of these had thrombocytopenia. Three other patients in the HLDC group had a bleeding complication from hematuria, intracranial hemorrhage, or epistaxis; none had documented thrombocytopenia.

Eight (7.9%) of the 101 patients who received LLDT and abciximab had thrombocytopenia. One patient received LLDT and tirofiban without documented thrombocytopenia. There were 8 bleeding complications in patients who received LLDT, including 5 groin hematomas, 2 patients with gastrointestinal blood loss, and 1 patient with hemoptysis. None of these patients had documented thrombocytopenia.

None of the 3 patients who received HLDT and abciximab had thrombocytopenia. Two of the 3 patients in the HLDT group had a bleeding complication: one patient had a vascular access site hematoma and the other had a retroperitoneal hemorrhage. No patients received HLDT and tirofiban.

Comparison of Study Groups

There was a significant increase in the percentage of patients who developed thrombocytopenia and received LLDC/tirofiban compared with LLDC/abciximab (Table 3). However, the *N* was very small and the

statistical stability of this result was questionable. There was no percentage difference in thrombocytopenia between patients receiving LLDC/abciximab and HLDC/abciximab, with 93.5% confidence. More patients in the LLDT/abciximab group developed thrombocytopenia than in the HLDT/abciximab group; however, again *N* was small and the statistical stability of this comparison was questionable. Lastly, there was no significant difference in thrombocytopenia incidence between patients receiving LLDC/abciximab and LLDT/abciximab.

Bleeding Complications

Fifty-one patients received blood transfusions during their hospital stay. Vascular access site hematoma and catheterization site oozing were the most common reasons for blood transfusion. This was followed by "no identifiable source of blood loss," GI blood loss, preexisting anemia with renal failure, preexisting anemia without renal failure, retroperitoneal hemorrhage, pulmonary hemorrhage, hematuria, and intracranial hemorrhage.

Eight patients received platelet transfusions: 5 patients were given platelets for vascular access site hematoma or catheterization site ooze requiring blood transfusion, 1 patient for retroperitoneal hemorrhage, 1 patient for pulmonary hemorrhage, and 1 patient who developed severe profound thrombocytopenia was transfused with platelets for a nadir platelet count of 3,000 but had no bleeding complications.

The length of stay ranged from 1-29 days with an average of 3 days. One hundred eight-two patients had a 1 day stay; 124 patients were discharged on day 2; 70 patients were discharged on day 3; and 128 patients had a length of stay >3 days.

With a sample of 504 subjects, and an incidence rate of 4.8% of thrombocytopenia, the researchers are 95% confident that the upper limit of incidence of thrombocytopenia would not exceed 8.8% with any combination of thienopyridine derivative and Gp IIb/IIIa antagonist. We are also 99% confident that the upper limit of thrombocytopenia will not exceed 9.8%. (If the assumption of distribution normality was extremely violated, we would still be 75% confident that the rate of incidence would not exceed 9.8%.) These are considered very conservative confidence estimates.

DISCUSSION

Using the general linear model (McNeil and others 1996), we found the overall incidence of thrombocytopenia in patients who received a combination of a high loading dose thienopyridine derivative with infusion of a Gp IIb/IIIa receptor blocker to be 4.8%. This is similar to the 2.5-5.2% incidence of thrombocytopenia observed with aspirin and a Gp IIb/IIIa receptor blocker without a thienopyridine in prior studies (EPIC 1994). In patients receiving aspirin and a Gp IIb/IIIa inhibitor, there was no statistically significant difference in thrombocytopenia between patients receiving the high or low loading dose of either thienopyridine derivative. Furthermore, there was no statistically significant difference in the incidence of thrombocytopenia between patients receiving either clopidogrel or ticlopidine (whether high or low loading dose). Despite the low numbers of patients receiving tirofiban, we detected no difference in thrombocytopenia between patients receiving either abciximab or tirofiban regardless of the thienopyridine or dose administered. Lastly, there was no significant correlation between the high loading dose thienopyridine group and an increased incidence of bleeding complications or transfusion of blood products.

Subacute thrombosis following stent placement has been dramatically reduced since the introduction of aggressive platelet inhibition directed at multiple sites of platelet activation. First the introduction of the thienopyridine derivatives against the platelet ADP receptor in conjunction with aspirin dramatically reduced the incidence of subacute thrombosis. The more favorable side effect profile offered by clopidogrel over ticlopidine has made ADP receptor blockade safer and better tolerated (Pache and others 2002; Taniuchi and others 2001; Mishkel and others 1999; Moussa and others 1999). With the addition of chimeric antibody fragments and small molecules directed against the platelet glycoprotein IIb/IIIa receptor, major adverse cardiac events have been further reduced.

Concerns have mounted that platelet inhibition, particularly with the use of a high loading dose of clopidogrel in combination with a Gp IIb/IIIa receptor inhibitor may cause excessively high rates of druginduced thrombocytopenia (Dillon and others 2000). Additionally, the concomitant use of three antiplatelet agents has raised the concern about potential bleeding complications, particularly in those receiving a high loading dose of a thienopyridine derivative (Pache and others 2002; Bertrand and others 2000). Our results, however, support the safety of the use of a high loading dose of a thienopyridine derivative prior to PCI.

The strength of this study relies upon the use of power analysis (McNeil and others 1996) (0.90 for detecting small effect sizes, $f^2 = 0.02$, a = 0.05, $N = 504$) and very conservative confidence estimates. Potential limitations include the fact that the patients were treated in a non-randomized fashion at the interventionalist's discretion, which may incorporate an unknown or undetected clinical bias in treatment decisions. Furthermore, there were only 14 patients treated with the small molecule tirofiban as opposed to the antibody fragment abciximab. Fewer patients received ticlopidine than clopidogrel and there were only three patients who received a high loading dose of ticlopidine.

Therefore, the use of a high initial loading dose of clopidogrel or ticlopidine to maximize platelet inhibition combined with aspirin and a Gp IIb/IIIa receptor blocker prior to PCI is both beneficial and safe. We advocate appropriate clinical monitoring for thrombocytopenia, blood loss, and other rare but potentially serious side effects of thienopyridine derivatives. We conclude that a high loading dose of clopidogrel or ticlopidine should be part of routine therapeutics. Due to the better side effect profile, clopidogrel may be the preferred agent.

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