Safety and Efficacy of Ticlopidine for Only 2 Weeks After Successful Intracoronary Stent Placement

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Background—In patients receiving intracoronary stents, stent thrombosis is reduced when ticlopidine therapy is combined with aspirin after the procedure. However, ticlopidine causes neutropenia in 1% of patients when administered for ≥2 weeks, and little is known about the duration that ticlopidine needs be administered to prevent stent thrombosis.

Methods and Results—We analyzed 827 patients undergoing successful stent placement in 1061 coronary segments at Mayo Clinic who were treated between May 1, 1996, and October 31, 1997. Chronic warfarin therapy, cardiogenic shock, and enrollment in research protocols requiring 4 weeks of ticlopidine were exclusion criteria; ticlopidine was discontinued after 14 days in all remaining patients. The mean age of the study population was 64±11 years; 49% had suffered a prior infarction, 20% had undergone coronary artery bypass surgery, and 65% had multivessel disease. The indication for stent placement was dissection or abrupt closure in 31% of patients and suboptimal results from balloon angioplasty in 18%. Placement was elective in 51% of patients, and 10.3% of patients were treated within 12 hours of an acute myocardial infarction. Mean nominal stent size was 3.3±0.5 mm. High-pressure inflations (≥12 atm) were performed in all patients (mean, 17±4 atm). Intravascular ultrasound was used to facilitate stent placement in 8.8% of patients. Abciximab was administered to 38% of patients; 11% of patients who were at increased risk of stent thrombosis were treated with enoxaparin for 10 to 14 days. Adverse cardiovascular events in the 14 days after stent placement occurred in 11 patients (1.3%). Two patients died of nonischemic causes (sepsis and renal failure) in the 15th through 30th days after ticlopidine was stopped. However, there were no cardiovascular deaths, myocardial infarctions, coronary artery bypass operations, or repeat angioplasty procedures between the 15th and 30th days; stent thrombosis did not occur in any patient after ticlopidine had been stopped. No patient developed neutropenia, although 1.8% of the first 489 patients who were closely monitored for side effects from ticlopidine developed side effects requiring its discontinuation, and milder side effects occurred in 4.7%.

Conclusions—In patients receiving intracoronary stents, the discontinuation of ticlopidine therapy 14 days after stent placement is associated with a very low frequency of stent thrombosis and other adverse events. (Circulation. 1999;99:248-253.)

Key Words: stents ■ angioplasty ■ thrombosis ■ platelet aggregation inhibitors ■ ticlopidine

The frequency of acute and subacute thrombosis of coronary stents has been dramatically reduced by advances in stent deployment techniques and modification of the anticoagulant regimen after the procedure.1 Although aspirin, low-molecular-weight dextran, dipyridamole, intravenous heparin, and warfarin were initially administered to all patients receiving intracoronary stents in an attempt to prevent stent thrombosis, subsequent studies have shown that antiplatelet therapy with aspirin and ticlopidine alone is associated with a <2% frequency of stent thrombosis,2,3 far less than was associated with the more intensive anticoagulant therapy used in previous studies.4–8 However, ticlopidine is frequently associated with side effects, the most serious of which is neutropenia, which can be life threatening.9 In view of this, white blood cell counts need to be measured serially, generally every 2 weeks, in patients treated with ticlopidine for ≥4 weeks. Ticlopidine-induced neutropenia occurs in ≈1% of patients treated for ≥2 weeks; it has not been described in patients treated for ≤2 weeks.10–12

Because we observed 3 cases of severe neutropenia (<0.5×10⁹ cells/L) in 417 patients (0.7%) treated with ticlopidine for 30 days after stent placement but did not observe any cases of stent thrombosis between 2 and 4 weeks

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after stent placement in these patients, we hypothesized that the risk of life-threatening neutropenia in the 15th through 30th days after stent placement may exceed the risk of stent thrombosis during this time interval and that discontinuation of ticlopidine after 14 days might reduce the frequency of serious complications associated with stent placement.

Therefore, we performed this prospective study to determine the risk of stent thrombosis and other adverse events, as well as the frequency of side effects from ticlopidine, in patients receiving intracoronary stents in whom ticlopidine was stopped 14 days after stent placement.

Methods

Between May 1, 1996, and October 31, 1997, 1406 patients underwent successful intracoronary stent implantation at Mayo Clinic. Seventy-two patients (5.1%) required warfarin therapy for reasons unrelated to the stent procedure and were excluded from the present study. Patients receiving unapproved stents in research protocols requiring 4 weeks of ticlopidine (n=230, 16.4%), those not receiving high-pressure inflations after deployment (n=57, 4.1%), those not treated with ticlopidine or aspirin because of contraindications to these medications (n=89, 4.3%), those with cardiogenic shock (n=27, 1.9%), those refusing access to their medical records for research purposes (n=18, 1.3%), and 86 patients with incomplete follow-up (6.1%) were also excluded. All of the remaining 827 patients (58.8%) who underwent successful elective or bail-out stent implantation at the Mayo Clinic were enrolled in the present study and were prescribed ticlopidine for only 14 days after stent placement; these 827 patients form the study population in this report. The present study was approved by the Institutional Review Board of the Mayo Clinic.

Stent-Implantation Procedure

All patients received ≥325 mg of aspirin before or during the procedure; an initial dose of 500 mg of ticlopidine was generally administered in the catheterization laboratory immediately before the stent-implantation procedure. A second dose of 250 mg of ticlopidine was generally administered the evening of the procedure. During the procedure, patients generally received a weight-adjusted bolus of heparin (100 U/kg) and additional heparin during the procedure as needed to maintain an activated clotting time of 250 to 350 seconds. At the discretion of the interventional cardiologist, abciximab (0.25 mg/kg bolus, followed by a 0.10 μg/min continuous infusion for 12 hours) was administered to 312 patients (38%) believed to be at high risk for thromboembolic complications. In patients to whom abciximab was given, a lower target activated clotting time of 200 to 300 seconds was used.

Stents were implanted according to standard percutaneous techniques. The stents used in the present study were either Palmaz-Schatz coronary stents, Palmaz or Palmaz-Schatz biliary stents (Johnson & Johnson, Interventional System Co), or the Gianturco-Roubin Flex-Stent (Cook Inc). After stent implantation, high-pressure balloon inflation to ≥12 atm was performed after deployment in all patients with minimally compliant balloon catheters.

Intravascular Ultrasound

Intravascular ultrasound was not required by protocol but was performed for clinical or angiographic indications at the discretion of the interventional cardiologist. When intravascular ultrasound was performed, either a 2.9F monorail system with a 30-MHz transducer-tipped catheter (Micro View; Cardiovascular Imaging Systems Inc) or a 3.5F Sonicath monorail system with a 30-MHz transducer-tipped catheter (Boston Scientific Corporation/Sci-Med Life Systems Inc) was used. The ultrasound catheter was advanced distal to the stent, and images were recorded while the imaging catheter was manually withdrawn through the stented segment. Images were stored on Super VHS videotape. Qualitative analyses and quantitative measurements were generally performed during the procedure.

On the basis of results of intravascular ultrasound, further expansion of the stent was performed if any of the following were observed: incomplete stent expansion (a cross-sectional area within the stent <90% of the cross-sectional area of the distal reference segment), incomplete apposition of the stent struts or loops to the vessel wall, uncovered dissections, >50% obstruction of the vessel lumen immediately adjacent to the stent, or inflow or outflow obstruction of >60% of the cross-sectional area relative to the reference segment proximal or distal to the stented segment.

Angiographic Analysis

Angiography was performed in orthogonal views in all cases. Sublingual nitroglycerin (0.4 mg) was given before the initial and final angiographic assessments. Visual analysis of the angiograms was used to guide the procedure. Lesions were characterized according to a modification of the American College of Cardiology/American Heart Association scoring system by the interventional cardiologist immediately before the procedure.

Medication After Discharge

After the procedure, additional heparin was generally not administered, and sheaths were removed when the activated clotting time was <160 seconds. Patients were treated with 80 to 325 mg/d aspirin indefinitely and 250 mg of ticlopidine twice daily for 14 days. A complete blood count was obtained before the procedure, after 2 weeks of ticlopidine, and 2 weeks after ticlopidine had been discontinued. Some patients believed to be at increased risk of stent thrombosis, such as those with acute myocardial infarction, those receiving stents ≤3 mm in diameter, those with a residual stenosis after stent placement of ≥20% by visual estimate, those with diffuse proximal or distal disease that could not be dilated, those in whom angiographic evidence of coronary dissection persisted after stent placement, and those with angiographic evidence of a large burden of intracoronary thrombus before the procedure or any thrombus after the procedure were also administered subcutaneous injections of low-molecular-weight heparin (enoxaparin) in doses of 30 to 60 mg twice a day for 10 to 14 days at the discretion of their interventional cardiologist beginning 4 to 6 hours after sheath removal. Additional medical therapy was administered by the patient’s physician if necessary.

Follow-Up

The first 489 patients were telephoned by the nurse stent coordinator 2 and 4 weeks after the procedure. Subsequently, patients in the study population were contacted 6 months after the procedure, and 30-day events were analyzed. The case records of all patients followed up at this institution were examined. Documentation of adverse events that occurred at other institutions during follow-up was obtained from the attending physicians at those institutions.

Definitions

Successful stent placement was defined as delivery of the stent to the treatment site with reduction in the residual stenosis to <50% without the in-laboratory occurrence of death, myocardial infarction, or a complication requiring immediate coronary artery bypass surgery. Multivessel disease was defined as the presence of a ≥70% lesion in a major coronary artery or its major branches and a ≥50% lesion in a second coronary artery or its major branches. Pseudoocclusive myocardial infarction was considered to have occurred when a patient developed prolonged chest pain thought to be the result of myocardial ischemia by the patient’s physician or had a rise in serum creatine phosphokinase elevation to 2 times normal or an elevated MB isoenzyme and developed new Q waves on the ECG. Myocardial infarction after discharge was considered to have occurred when any 2 of the following 3 criteria were met: (1) prolonged chest pain thought to be the result of myocardial ischemia by the patient’s physician, (2) serum creatine phosphokinase elevation to 2 times normal or elevated MB isoenzyme, or (3) development of new Q waves or significant ST-T wave changes on the ECG. Severe neutropenia was defined as <0.5 × 10⁹ cells/L.
Follow-Up Events
Major clinical events after discharge included death, myocardial infarction (Q-wave and non–Q-wave), stent thrombosis, coronary artery bypass surgery, and repeat angioplasty of the stented segment. Stent thrombosis was considered to have occurred in all patients in whom a follow-up angiogram revealed evidence of thrombus within the stent, in whom a myocardial infarction occurred without proof that the infarct artery was not the stented vessel, or in whom death occurred that was believed to possibly be cardiac in origin. The frequency of side effects from ticlopidine was also analyzed. Follow-up angiography was generally only performed for clinical indications, such as the recurrence of severe angina or a markedly abnormal functional test, at the discretion of the attending physician. Results are presented as either a percent of the total or as mean ± 1SD.

Results
Baseline Characteristics
The baseline clinical characteristics and indication for stent placement are shown in Table 1. The mean age of the study population was 64 ± 11 years. Diabetes mellitus was present in 18% of patients. Prior myocardial infarction had occurred in 49% of patients; prior coronary artery bypass surgery had been performed in 20% of patients. The indication for stent placement was treatment of dissection or abrupt closure in 31% of patients and suboptimal results from balloon angioplasty in 18%; placement was elective in 51% of patients. Eighty-five patients (10.3%) were treated within 24 hours of an acute myocardial infarction.

Angiographic and Procedural Characteristics
The angiographic and procedural characteristics of the study population are displayed in Table 2. There were 1061 segments treated in the 827 patients; 1253 stents (1.5 stents per patient) were placed. The number of stents placed per patient was 1 in 525 patients, 2 in 210 patients, 3 in 62 patients, 4 in 25 patients, 5 in 2 patients, and 6 in 2 patients. Stents placed include the Palmaz-Schatz (78%), the Gianturco-Roubin (19%), and Johnson & Johnson biliary stents (3%). Several patients received >1 stent design; a Palmaz-Schatz stent was placed in 84% of patients, a FlexStent was placed in 21% of patients, and a biliary stent was placed in 3% of patients. Mean nominal stent size was 3.3 ± 0.5 mm. High-pressure inflation (≥12 atm) was performed in all patients (mean, 17 ± 4 atm). The mean postprocedural residual stenosis within the stents was 4 ± 7%.

Frequency of Intravascular Ultrasound
Intravascular ultrasound was performed in 73 (8.8%) of the 827 patients on the basis of physician preference or the angiographic appearance of the treated vessel and led to
additional treatment (such as additional balloon inflations or placement of additional stents) in 49% of these patients.

Adverse Cardiovascular Events During the Initial Hospitalization
Of the 827 patients in whom angiographic success had been achieved, 5 (0.6%) died during the initial hospitalization. One patient might have suffered stent thrombosis. She had received 600 mL of contrast, had only 1 kidney, and refused renal dialysis and other life-prolonging measures. The last ECG before her death on the third day after stent placement suggested ischemia without ST-segment elevation; no autopsy was performed. One patient died of a pulmonary hemorrhage shortly after the procedure; abciximab had been given. The stent was patent without thrombus on autopsy. One patient died of a pulmonary embolus shortly after the procedure; there was no evidence that stent thrombosis had occurred. One patient with thrombocytopenia secondary to cirrhosis and lung cancer died of a retroperitoneal hemorrhage that occurred 14 hours after the procedure; the stent was widely patent without thrombus on autopsy. One patient died of multiorgan system failure and a possible pulmonary embolism. On autopsy, the stent was widely patent without thrombus. Four patients (0.5%) required repeat procedures. One suffered a non-Q-wave infarction within several hours of stent placement. Repeat angiography revealed a severe dissection distal to the stent without evident thrombus, and an additional stent was placed. The other 3 patients suffered stent thrombosis and underwent urgent repeat angioplasty; all 3 suffered non-Q-wave myocardial infarction and survived. One had been receiving enoxaparin. In all, 9 patients (1.1%) suffered 1 of these adverse events—death, myocardial infarction, repeat angioplasty or bypass surgery—during their initial hospitalizations.

Adverse Cardiovascular Events Between Hospital Discharge and 14 Days After the Procedure
Two additional patients suffered adverse events after discharge during the 2 weeks of ticlopidine therapy. Both patients died suddenly, and stent thrombosis may have been the cause. Neither patient underwent autopsy. There were no other adverse cardiovascular events after discharge.

Therefore, a total of 11 patients (1.3%) suffered an adverse event in the 14 days after stent placement, during the administration of ticlopidine. Six events (0.7%) were definitely or possibly the result of stent thrombosis.

Among patients in whom a suboptimal stent result was achieved (defined as a residual stenosis >20%, any dissection or thrombus evident after completion of the case, or less than Thrombolysis In Myocardial Infarction [TIMI] grade 3 flow), 2.7% (5 of 188) died or suffered stent thrombosis within 14 days compared with 0.9% (4 of 424) in whom a stent was placed electively (*P*<0.07). In patients in whom a stent was placed nonselectively (defined as stent placement for a suboptimal balloon angioplasty result or for threatened or acute closure), 1.7% (7 of 403) died or suffered stent thrombosis within 14 days compared with 0.9% (4 of 424) in whom a stent was placed electively (*P*<0.32).

Adverse Cardiovascular Events Between 15 and 30 Days
Two patients died in the 15th through 30th days, after ticlopidine had been discontinued. One died on day 23 of overwhelming systemic infection after abdominal surgery for a colonic abscess. A second patient died on day 17 of a ventricular tachyarrhythmia while suffering from acute renal failure and hyperkalemia. She had had a myocardial infarction shortly before stent placement and had chronic congestive heart failure and a prior stroke. The patient had insisted that dialysis not be performed and declined other life-prolonging measures. However, there were no ischemia-related deaths and no myocardial infarctions, repeat angioplasty procedures, or coronary artery bypass operations between the 15th and 30th days; stent thrombosis did not occur in any patient.

Adverse Reactions to Ticlopidine
Adverse reactions to ticlopidine were not uncommon. Among the first 489 patients who were contacted at 2 and 4 weeks after the procedure and carefully questioned regarding side effects to medications, ticlopidine was discontinued in 9 patients (1.8%) due to a skin rash in 6, diarrhea in 2, and nausea in 1. One of these patients developed stent thrombosis 2 days after cessation of ticlopidine and died. Milder side effects believed to be due to ticlopidine but not requiring its discontinuation occurred in 23 patients (4.7%), including rash in 7, diarrhea in 8, and nausea in 9. Neutropenia did not occur in any patient.

Discussion
The most important findings in the present study are that in patients in whom intracoronary stents are implanted by use of high-pressure balloon inflations, ticlopidine can be safely discontinued after 2 weeks with no apparent increase in the risk of stent thrombosis. This appears to have been true for patients believed to be at increased risk for stent thrombosis in whom abciximab was administered during the stent procedure or in whom low-molecular-weight heparin was administered for 10 to 14 days, and for patients believed to be at low risk of stent thrombosis treated with aspirin and ticlopidine alone. After discontinuation of ticlopidine following 14 days of therapy, stent thrombosis did not occur.

Time Course of Stent Endothelialization
Studies in which serial angioscopy was performed after successful coronary stent implantation suggest that complete endothelialization did not occur in at least some patients until 4 to 6 weeks after stent placement. Animal studies have also revealed that endothelialization of the stent may not be complete at 2 weeks. These studies would suggest that the risk of stent thrombosis may persist for ≤12 weeks.
Absence of Late Stent Thrombosis in Patients Treated With Aspirin and Ticlopidine

Stent thrombosis occurring >14 days after stent deployment appears to be very rare in patients treated with aspirin and ticlopidine. A randomized study comparing the use of aspirin and ticlopidine with aspirin and warfarin in 517 patients treated with Palmaz-Schatz stents, in whom an excellent angiographic result was achieved, revealed a significantly lower frequency of adverse cardiovascular events at 30 days in the aspirin and ticlopidine–treated patients (1.6% versus 6.2%; P=0.01). No patient in the aspirin and ticlopidine group had stent thrombosis >4 days after stent placement; ticlopidine was continued for 30 days in the present study. In another study, patients receiving Palmaz-Schatz stents in whom an excellent angiographic result was achieved were randomized to receive either aspirin, aspirin and warfarin, or aspirin and ticlopidine for 4 weeks. Clinically evident stent closure (a hierarchical composite end point that included death, emergency bypass surgery, and Q-wave myocardial infarction and repeat revascularization) within 30 days occurred in 3.6%, 2.4%, and 0.6% of patients, respectively. Stent thrombosis did not occur in any patient >14 days after stent placement. We have previously noted that in the first 761 patients who had intracoronary stents placed at Mayo Clinic with the use of high-pressure balloon inflations after stent deployment, in whom aspirin and ticlopidine were administered for ≥4 weeks, stent thrombosis did not occur in any patient >14 days after the stent procedure. The 95% CIs associated with our observation of no cases of late stent thrombosis in 827 patients are 0% to 0.5%. It is therefore very likely that the 1% risk of neutropenia associated with >2 weeks of ticlopidine therapy is more than twice the risk of stent thrombosis when ticlopidine is discontinued after 2 weeks. Larger studies are needed to confirm that the risk of stent thrombosis is as low as it appears to be in the present study.

Ticlopidine

Although the exact mechanism of action of ticlopidine remains unknown, it is known that ticlopidine interferes with ADP-induced platelet-fibrinogen binding and platelet–platelet interactions. The effect on platelet function is irreversible for the life of the platelet. Ticlopidine has been shown to reduce acute closure during balloon angioplasty in placebo-controlled trials and to reduce coronary stent thrombosis compared with treatment with aspirin alone and aspirin with warfarin,2,3,17,18 Side effects from ticlopidine are relatively common, the most serious of which is neutropenia, which occurs in 1% of patients treated for >2 weeks.10–12 Neutropenia has not been reported in a patient treated with ticlopidine for only 2 weeks. In the present study, white blood cell counts were measured 2 and 4 weeks after stent placement; however, because ticlopidine-induced neutropenia usually resolves quickly after ticlopidine is discontinued, it is not clear whether there is sufficient risk to monitor the white blood cell count in patients in whom only 2 weeks of ticlopidine therapy is planned.

Risk-Benefit Analysis of Discontinuing Ticlopidine Therapy After 2 Weeks

Even if stent thrombosis is found in larger studies to occur occasionally in patients in whom ticlopidine is stopped after 2 weeks, it is likely to occur in <1% of patients, which is the reported incidence of ticlopidine-induced neutropenia. An additional benefit of discontinuing ticlopidine therapy after 2 weeks is that the practice will reduce patient discomfort and the expense associated with the need to monitor the white blood cell count in patients treated for longer periods, as well as the expense of the medication itself.

Limitations of the Study

It is possible that subclinical stent thrombosis may have occurred in some patients; angiography was not performed in patients without symptoms or signs of coronary ischemia. Therefore, it is possible, although unlikely, that the reported frequency of stent thrombosis may be an underestimate if any subclinical cases of stent thrombosis occurred.

Summary

The results of the present study suggest that ticlopidine can be safely discontinued 14 days after coronary stent implantation. The risk of stent thrombosis in the 15th through 30th days after stent placement when ticlopidine is discontinued after 14 days (0% in the present study) appears to be less than the 1% risk of ticlopidine-induced neutropenia when ticlopidine is continued for >2 weeks.

References


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