Effectiveness of Clopidogrel and Aspirin Versus Ticlopidine and Aspirin in Preventing Stent Thrombosis After Coronary Stent Implantation

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Background—Ticlopidine has been shown to reduce the incidence of stent thrombosis compared with warfarin, but it may cause serious hematological side effects. Clopidogrel, a new thienopyridine derivative, may be a safe alternative to ticlopidine. The aim of this study was to compare the safety and efficacy of clopidogrel and aspirin with those of ticlopidine and aspirin in patients undergoing coronary stent implantation.

Methods and Results—The population of this study consisted of 2 groups: patients who underwent coronary stenting and were treated with ticlopidine and aspirin (TA group, n = 1406), and patients who underwent coronary stenting followed by treatment with clopidogrel and aspirin (CA group, n = 283). At 1-month follow-up, there was no difference in stent thrombosis (1.5% versus 1.4%, P = 1.0) or major adverse cardiac events (3.1% versus 2.4%, P = 0.85) between the TA and CA groups, respectively. The probability of any side effect (neutropenia, diarrhea, rash) was significantly higher in the TA group (10.6% versus 5.3%, P = 0.006; relative risk, 0.53; CI, 0.32 to 0.86).

Conclusions—These data suggest that clopidogrel may be an effective pharmacological regimen after coronary stent implantation. Furthermore, the simpler dosing regimen, the absence of neutropenia, and the lower frequency of other side effects make it a safe alternative to ticlopidine. (Circulation. 1999;99:2364-2366.)

Key Words: clopidogrel n ticlopidine n stents

Coronary stent implantation has become the dominant form of catheter-based coronary interventions on the basis of data demonstrating the efficacy and safety of coronary stenting when appropriate technique and postprocedure antiplatelet therapy are used.1,2 The combination of ticlopidine and aspirin has been confirmed to be superior to aspirin alone or aspirin and coumarin in randomized trials.3,4 Despite the effectiveness of ticlopidine, a small incidence of side effects remains,5 in particular hematological side effects that may occasionally be fatal.6

Clopidogrel, a new thienopyridine derivative, was recently approved for use in patients with atherosclerotic vascular disease to reduce the incidence of ischemic events.7 This antiplatelet agent may potentially be of use after stent implantation to reduce stent thrombosis without the added risks of hematological toxicity. As of this writing, few data are available as to the effectiveness of this agent in preventing thrombosis after stenting. The purpose of this study was to compare the safety and effectiveness of clopidogrel and aspirin with those of ticlopidine and aspirin in a consecutive series of patients undergoing coronary stent implantation.

Methods

Patient Population, Stent Implantation, and Pharmacological Regimen

Between September 1996 and June 1998, 2057 patients underwent stent implantation for obstructive coronary artery disease. Of these, 368 were excluded from this study because of (1) requirement for oral anticoagulation (57 patients); (2) administration of abciximab (280 patients); (3) procedural failure: less than TIMI 3 flow (8 patients), residual diameter stenosis >50% (4 patients), emergency bypass surgery (3 patients), or intracerebral hemorrhage (1 patient); and (4) patients who received aspirin alone (14 patients) or ticlopidine alone (1 patient) because of known allergy to the other agent. The final study population consisted of patients who underwent coronary stenting between September 1996 and February 1998 and were treated with ticlopidine and aspirin (TA group: 1406 patients, 1763 lesions) and patients who underwent coronary stenting between March 1998 and June 1998 and were treated with clopidogrel and aspirin (CA group: 283 patients, 376 lesions). Stent implantation was performed by use of techniques previously described,2 and quantitative angiographic analysis was performed with a computer-based system (CMS version 3.0, MEDIS). Ticlopidine was administered as a loading dose of 500 mg followed by 250 mg PO twice a day for 2 weeks.8 Clopidogrel was administered as a loading dose of 300 mg followed by 75 mg PO once a day for 4 weeks. Aspirin was administered as 325 mg PO

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TABLE 1. Patient Clinical and Angiographic Characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>TA Group (n=1406)</th>
<th>CA Group (n=283)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±12</td>
<td>64±12</td>
<td>0.20</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>951 (68)</td>
<td>193 (68)</td>
<td>0.89</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>301 (21)</td>
<td>63 (22)</td>
<td>0.75</td>
</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>490 (35)</td>
<td>97 (34)</td>
<td>0.89</td>
</tr>
<tr>
<td>Lesions (n=1763)</td>
<td>(n=376)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion complexity,* n (%)</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>190 (11)</td>
<td>24 (6)</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>438 (25)</td>
<td>96 (25)</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>586 (33)</td>
<td>130 (35)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>549 (31)</td>
<td>126 (34)</td>
<td></td>
</tr>
</tbody>
</table>

Quantitative angiography

<table>
<thead>
<tr>
<th>Preprocedure</th>
<th>Reference diameter, mm</th>
<th>Minimum lumen diameter, mm</th>
<th>Lesion length, mm</th>
<th>Postprocedure</th>
<th>Minimum lumen diameter, mm</th>
<th>Diameter stenosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.83±0.67</td>
<td>0.84±0.47</td>
<td>10.93±5.59</td>
<td></td>
<td>3.13±0.55</td>
<td>10±15</td>
</tr>
</tbody>
</table>

A value of P<0.05 is considered significant.

*AHA/ACC classification.

Once a day to both groups. All patients were instructed to follow up with their referring physician in 2 weeks for clinical assessment and blood count analysis. In addition, a dedicated nurse practitioner (R.M.) was performing telephonic follow-up evaluation at 1 month on an ongoing basis.

Statistics

Statistical analysis was performed with StatView software. Continuous normally distributed data were expressed as mean±SD and were compared by unpaired Student’s t test. Categorical variables were expressed as numbers and percentages and compared by the χ² test. Differences were considered statistically significant at a value of P<0.05.

Results

Patient Characteristics and Procedural Data

Patient characteristics and angiographic measurements are shown in Table 1. Similar numbers (1.3+0.6 versus 1.3+0.5, P=1.0) and types (slotted tube, 87% versus 88%; coil, 12% versus 12%; and Wallstent, 1% versus 0%, P=0.49) of stents were implanted in the TA and CA groups, respectively. Bailout stenting was performed with similar frequency in both groups (6% versus 7%, P=0.57).

Medication Side Effects and Clinical Outcome

During the period of this study, 16 patients in the TA group (1.1%) and 2 patients in the CA group (0.7%) were lost to follow-up. Of the study population, 46 patients (3.3%) in the TA group and 8 patients (2.8%) in the CA group (P=0.85) discontinued the study drug early for reasons other than the occurrence of an outcome event. Reasons for stopping ticlopidine were rash in 30 patients, diarrhea in 6 patients, rash and diarrhea in 5 patients, neutropenia in 4 patients, and noncompliance in 1 patient. Reasons for stopping clopidogrel were rash in 4 patients, diarrhea in 3 patients, and noncompliance in 1 patient. The incidence of stent thrombosis, cardiac events, and medication side effects at 1-month follow-up is shown in Table 2.

Discussion

Rationale for Use of Clopidogrel After Stent Implantation

Clopidogrel is a thienopyridine derivative that inhibits platelet aggregation by inhibiting the binding of ADP to its platelet receptor, which leads to direct inhibition of the binding of fibrinogen to the glycoprotein IIb/IIa complex. Although both ticlopidine and clopidogrel prevent platelet aggregation evoked by shear stress, experimental studies suggest that clopidogrel is more effective than either aspirin or ticlopidine in preventing the high-shear-stress-dependent coronary stent thrombosis. Furthermore, clopidogrel has a favorable safety profile compared with ticlopidine, for which routine hematological monitoring is mandatory to ensure early detection of potentially lethal hematological events. The incidence of neutropenia with ticlopidine is proportional to the duration of treatment (up to 2.4%), and it may resolve with drug cessation in most but not all cases. Another serious side effect of ticlopidine is thrombotic thrombocytopenic purpura (TTP). A recent review documented 60 cases of TTP among patients treated with ticlopidine, with an associated mortality rate of 33%. In this review, 12 patients developed TTP after receiving ticlopidine for ≥3 weeks after stent implantation. Other common but less morbid adverse effects reported to accompany ticlopidine use are gastrointestinal symptoms. Clopidogrel was developed because it did not show bone marrow toxicity in tissue culture and animal models. In the large CAPRIE trial, the incidence of severe neutropenia with long-term use was only 0.05%, which was similar to the rate seen with aspirin (0.04%). In addition, the proportions of patients with severe rash and diarrhea while on clopidogrel in this trial were less than those reported with ticlopidine but twice as high as with aspirin. Therefore, the combination of a favorable safety profile and a proven experimental and
clinical antiplatelet effect make clopidogrel an attractive alternative to ticlopidine after coronary stent implantation.

**Clopidogrel: Administration and Clinical Impact**
The inhibition of platelet aggregation by clopidogrel is concentration dependent. In this study, clopidogrel was administered as a loading dose of 300 mg, a dose that provides 80% platelet inhibition in 5 hours, followed by 75 mg PO daily for 4 weeks. Aspirin was added to clopidogrel because this drug has no effect on the cyclooxygenase pathway, and therefore, both agents may work synergistically, as is the case with ticlopidine. In this study, stent thrombosis occurred with similar frequency in the ticlopidine and clopidogrel groups (1.5% versus 1.4%, P=NS). Similarly, there was no difference between the 2 groups in incidence of major adverse cardiac events at 1-month follow-up (3.1% versus 2.4%, P=NS).

With respect to side effects, neutropenia occurred in 4 patients (0.3%) in the ticlopidine group but none of the patients in the clopidogrel group (0%). This rate of neutropenia is similar to those in other stent trials in which ticlopidine was used for 4 weeks. In this study, rash occurred significantly more often in the ticlopidine group despite the short duration of administration. The incidence of diarrhea was also slightly higher, but not statistically significant. Overall, patients in the ticlopidine group were at twice the risk of having any side effect compared with patients receiving clopidogrel.

**Study Limitations**
First, this is a nonrandomized comparison between the 2 pharmacological regimens. However, these regimens were used in a chronologically consecutive manner, an approach that eliminates the potential for operator bias in selecting one specific regimen over the other. Second, because the incidence of stent thrombosis with antiplatelet therapy is very low, a higher number of patients is necessary to establish equivalence between clopidogrel and ticlopidine. Therefore, a large randomized trial is needed to establish the validity of these data.

**Conclusions**
These data suggest that clopidogrel may be an effective pharmacological regimen after coronary stent implantation. Furthermore, the simpler dosing regimen and the absence of hematological toxicity make it a potential safe alternative to ticlopidine.

**References**
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