Effect of perioperative platelet inhibition on postcarotid endarterectomy mural thrombus formation

Results of a prospective randomized controlled trial using aspirin and dipyridamole in humans

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A prospective randomized double-blind trial was conducted to study the effect of platelet-inhibiting drugs on mural thrombus formation after carotid endarterectomy. Twenty-two patients undergoing carotid endarterectomy were randomly assigned to perioperative administration of an aspirin/dipyridamole combination or a placebo, and the postoperative results were compared. Autologous indium-111-labeled platelets were injected postoperatively, and platelet deposition was measured at the endarterectomy site. It was found that the treated group had a significant reduction in platelet accumulation compared with the placebo group. The results suggest that the perioperative use of aspirin/dipyridamole may reduce the risk of operative stroke and the long-term risk of repeat carotid stenosis.

Key Words: carotid endarterectomy • mural thrombus formation • aspirin • dipyridamole • autologous indium-111-labeled platelets

Opinions are divided as to whether platelet inhibitors should be used in the perioperative period in carotid endarterectomy patients. The unproven but potential benefit of their use would be a reduction in platelet deposition at the endarterectomy site after surgery and, consequently, a decreased incidence of postoperative thromboembolic stroke; in the longer term, a lower recurrence of carotid stenosis would be achieved. The administration of autologous indium-111 (111In)-labeled platelets followed by nuclear imaging can be used to monitor semi-quantitatively platelet deposition and the effect of platelet inhibitor therapy on this deposition in man. We employed this method to study the effect of aspirin and dipyridamole therapy on mural thrombus formation after carotid endarterectomy in a prospective randomized placebo-controlled double-blind trial.

Clinical Material and Methods

Study Design

Informed consent was obtained from 22 patients scheduled for carotid endarterectomy who were then assigned a previously randomized study number and medication. The patient, treating physician, and trial investigators remained blind to the nature of the study medication, which consisted of either a combination of aspirin (330 mg) and dipyridamole (75 mg) in a single preparation three times daily or identical placebo capsules. Patients with a history of a bleeding disorder or a drug allergy to aspirin or dipyridamole were excluded from entry into the study. If patients were already receiving antiplatelet medications, the drugs were discontinued at least 10 days before operation so that they would not influence platelet function at the time of surgery.

The study medication was begun at least 5 days prior to the operation and was continued right up to the evening prior to surgery. Carotid endarterectomy was carried out by one of the three surgeons (W.M.L., F.G., or P.M.W.). Intraoperative heparinization with full protamine reversal after arteriotomy closure was used in every case. The study medication was resumed orally the following day and continued for 5 additional days.
postoperatively. On the morning of the 1st postoperative
day, an aliquot of the patient's blood was with-
drawn for platelet harvesting and $^{111}$In labeling. The
labeled platelets were then returned to the patient
through a peripheral vein. Twenty-four hours following
this, a nuclear scan of the carotid area was obtained for
platelet imaging. After the platelet study, 15 mCi of
technetium-99m-labeled human serum albumin ($^{99m}$Tc
HSA) was injected intravenously into the patient, and
a blood-pool scintigram of the head, neck, and upper
thorax was obtained 15 minutes later. Patients were
carefully monitored for postoperative neurological def-
cits and hemorrhagic wound complications.

**Patients Studied**

Twenty-two patients, 12 in the control group and 10
Treated with aspirin and dipyridamole, were studied.
Their characteristics are listed in Table 1. Of the 12
patients in the control group, eight were male and four
were female, and their mean age was 65 years. End-
arterectomy was performed in eight of these patients
for transient ischemic attacks (TIA's), in two for partial
strokes, and in two for asymptomatic stenoses opposite
previously corrected symptomatic carotid artery steno-
ses. Of the 10 patients in the treatment group, four
were male and six were female, and the mean age was 64
years. Eight of these patients underwent end-
arterectomy for TIA's, one for partial stroke, and one
for a reversible ischemic neurological deficit. Many
patients in both groups were taking cardiac and anti-
hypertensive medications, but none in either group took
anticoagulant or platelet-inhibiting drugs (other than
the study medication) within 10 days of surgery.

**Platelet and Blood-Pool Labeling, Imaging, and
Quantification**

On the morning following surgery, approximately
50 cc of blood was collected from each patient and
the platelets were separated and labeled with $^{111}$In ox-
ine according to the method of Welch and Mathias. It
has been shown previously that indium labeling
does not alter platelet function. The platelets were
resuspended in several cubic centimeters of plasma
and infused back into the patient through a peripheral
vein. The mean labeling efficiency was 50% (range
30% to 71%) and the mean injected dose of $^{111}$In
was 391 μCi (range 240 to 529 μCi). The mean number
of platelets injected was $1.8 \times 10^{10}$ (range $3.5 \times 10^{10}$
to $4.33 \times 10^{10}$).

Twenty-four hours following platelet reinjection a
scintigram of the neck was obtained with a Seimen's
ZLC 3700 gamma camera with a computer interface.
A medium-energy collimator was used and a gamma
ray spectrometer was adjusted to include the 174 and
247 kV peaks of $^{111}$In radionuclide. In a preliminary
study, we found that, if platelet labeling was performed
on the morning of surgery with reinfusion immediately
postoperatively, it became difficult to distinguish
wound hematoma from mural thrombus. This has been

![Image](https://via.placeholder.com/150)

**TABLE 1**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control Group</th>
<th>Treated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>sex (M:F)</td>
<td>8:4</td>
<td>4:6</td>
</tr>
<tr>
<td>mean range</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>range 54-77</td>
<td>52-76</td>
</tr>
<tr>
<td>standard deviation</td>
<td>7.68</td>
<td>6.43</td>
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<tr>
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<td></td>
</tr>
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<td>9</td>
</tr>
<tr>
<td>atherosclerotic heart disease</td>
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<td>2</td>
</tr>
<tr>
<td>diabetes</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>indication for surgery*</td>
<td>TIA 8</td>
<td>8</td>
</tr>
<tr>
<td>RIND 0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>partial stroke 2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>asymptomatic 2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* TIA (transient ischemic attack) refers to an ischemic deficit that lasts less than 24 hours. RIND (reversible ischemic neurological deficit) refers to a deficit that persists beyond 24 hours but completely resolves within 1 week. Partial stroke refers to a partial deficit that persists beyond 1 week.
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TABLE 2
Results of 99mTc blood-pool imaging*

<table>
<thead>
<tr>
<th>Area Studied</th>
<th>Control Group</th>
<th>Treated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>operative site</td>
<td>221.87</td>
<td>36.93</td>
</tr>
<tr>
<td>contralateral carotid artery</td>
<td>208.12</td>
<td>47.61</td>
</tr>
<tr>
<td>aortic arch</td>
<td>414.14</td>
<td>112.85</td>
</tr>
</tbody>
</table>

* Results expressed as counts/100 pixels/µCi. None of the differences between groups were significant. SD = standard deviation.

TABLE 3
Operative data in treated and control patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Control Group</th>
<th>Treated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>vein patch used</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>postoperative stroke*</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>wound hematoma</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>adverse reaction to medication</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* See text for details.

the endarterectomy site would correspond to a difference in 111In.

Results

There was a significant reduction in labeled platelet accumulation at the endarterectomy site in the aspirin/dipyridamole-treated group compared to the control placebo group. The mean radioactive platelet accumulation in the placebo group was 4.60 counts/100 pixels/µCi compared to a mean of 2.64 counts/100 pixels/µCi in the treated group (p < 0.005, unpaired two-tailed Student's t-test) (see Fig. 1 for these values, and standard deviations).

Analysis of the 99mTc HSA blood-pool images showed that there were no significant differences between the two groups in mean 99mTc HSA activity at the operative site, the contralateral carotid artery, or at the aortic arch site (Table 2). Since the blood-pool fraction of 111In-labeled platelets should have a distribution similar to that of 99mTc HSA, these results indicate that treatment did not affect the circulating blood-pool contribution of 111In-labeled platelets at the operative site and that the observed difference between groups was due to a difference in platelet accumulation. Supporting this was the finding that there were no significant differences between the two groups in mean platelet activity at either the nonoperated carotid bifurcation (3.71 counts/100 pixels/µCi control, 3.12 counts/100 pixels/µCi treated) or the aortic arch (9.21 counts/100 pixels/µCi control, 9.44 counts/100 pixels/µCi treated). Activity at these sites must reflect blood-pool activity and platelet deposition on the atherosclerotic vessel wall.

Table 3 describes the course of the treated and control patients. One patient in the control group and none in the treated group had a vein patch inserted at endarterectomy. There were two postoperative strokes, both occurring in the control group in patients whose indication for surgery was a TIA. The first patient developed a paretic right hand shortly after awakening from a left carotid endarterectomy. She was immediately taken back to the operating room where a thick "white" mural thrombus was found at the endarterectomy site, but the carotid artery was still patent. The thrombus was removed and she then had a vein patch inserted since some narrowing of the lumen at the endarterectomy site was thought to have contributed to the thrombosis. Her deficit improved but had not entirely resolved at her 6-month postoperative follow-up examination. The other postoperative deficit occurred several hours after right carotid endarterectomy and consisted of apraxia and cortical sensory loss in the left upper extremity. A postoperative angiogram confirmed that the vessel was patent, but there was some irregularity and mild narrowing at the endarterectomy site. A subsequent computerized tomography scan showed a small right parietal cortex infarction. The patient's deficit had improved considerably by the time of discharge, 14 days later. There were no postoperative wound hematomas in any of the patients in the study.

Discussion

The reported risk of stroke following carotid endarterectomy varies greatly from series to series, with
operative stroke rates ranging from 2% to 24% of patients found in a limited review of the literature. A number of factors appear to influence the frequency of stroke complicating carotid endarterectomy. In general, experienced surgeons in specialized centers achieve lower operative stroke rates. From a detailed analysis of their patients, Sundt and colleagues were able to correlate surgical risk with the patient’s neurological and medical condition. The high-velocity flow state existing in the arterial system as well as the establishment of laminar blood flow with good surgical technique are major factors discouraging thrombosis and ensuring patency after arterial reconstruction. Finally, in addition to the expertise of the surgeon, the condition of the patient, and the special hemodynamic conditions at the time of arterial repair, there is little question that the thrombogenic endarterectomy site itself, which is vulnerable to mural thrombosis and embolization, is another major determinant of operative outcome. When an atherosclerotic plaque is removed from the carotid artery and then blood flow is restored, the exposed media, and in some instances adventitia, induces platelet aggregation and mural thrombus formation; it can take up to 30 days before reendothelialization occurs across the entire endarterectomy site. If the mural thrombus is excessive, cerebral embolism or carotid occlusion can occur. In addition, excessive mural thrombus after surgery may lead to repeat carotid stenosis. Dirrenberger and Sundt stated their belief that some recurrent plaques are in fact semi-organized thrombi still present from the first operation. After aggregation, platelets degranulate and release factors that stimulate smooth muscle and fibroblast mitogenesis and migration to the underlying neointima. In some patients this response may be abnormally exuberant and lead to repeat stenosis of the lumen by a process known as “neointimal fibro-muscular hyperplasia,” which some consider a form of immature atherosclerotic plaque. Excessive mural thrombus formation might, therefore, through several different mechanisms, cause restenosis of the carotid artery.

Realizing the importance of postoperative mural thrombus formation in the genesis of postoperative stroke and repeat carotid artery stenosis, some surgeons have recommended anticoagulation or platelet-inhibitor therapy after endarterectomy. Gross, et al., described the routine use of a postoperative heparin infusion, but it is recognized that this practice is attended by a higher risk of potentially dangerous wound hematoma, and there is also a suggestion that it is associated with an increased risk of postoperative cerebral hemorrhage. Based upon their work in a canine model of carotid endarterectomy, Dirrenberger and Sundt recommended not reversing heparin administered in a controlled trial in humans. Almost 20 years ago, Lougheed, et al., recommended oral administration of an anticoagulant drug (dicumarol) before and after carotid endarterectomy; however, the high rate of postoperative neck hematomas led them to abandon this practice several years later.

Several authors state that they institute a course of aspirin in the early postoperative period to deter platelet aggregation at the endarterectomy site but this would likely be too late to inhibit thrombus formation effectively. Animal studies indicate that platelet inhibition before endarterectomy can significantly reduce mural thrombus formation. Deen and Sundt showed that perioperative intake of aspirin and dipyridamole significantly reduced thrombus formation after carotid endarterectomy in dogs; this treatment was even superior to brief perioperative heparinization as described by Dirrenberger and Sundt. Ercius, et al., showed that aspirin in a dose of 10 mg/kg given 18 hours before carotid endarterectomy in dogs significantly reduced thrombus formation at the endarterectomy site. Another antiplatelet agent, ibuprofen, when started preoperatively, was shown to markedly reduce mural thrombus formation and neointimal thickness in endarterectomized canine aortas. Other work in animals suggests that platelet-inhibiting agents prevent neointima formation in vascular grafts. In humans, a perioperative aspirin/dipyridamole combination has been shown to reduce platelet deposition in vascular prostheses and to improve early and late vein-graft patency after coronary bypass operations.

In this study, a series of patients undergoing carotid endarterectomy were randomly assigned to receive either aspirin/dipyridamole combination or placebo for at least 5 days before surgery and again after surgery. Employing platelet-imaging methods, we labeled patients’ platelets with ~ and measured indium accumulation at the endarterectomy site 24 hours later with a gamma camera. We observed significantly less platelet accumulation during this period in the platelet-inhibited patients, and we believe this suppression in platelet deposition exists from the time of endarterectomy until reendothelialization occurs, as has been observed in animal experiments.

The dose of aspirin (300 mg/8 hrs) and dipyridamole (75 mg/8 hrs) was chosen because it has been shown to improve both early and long-term patency of vein-grafts in coronary bypass operations in man. The pharmacology of these two drugs and the rationale for their combination has been reviewed in detail elsewhere. It appears that each inhibits platelet function through separate mechanisms: aspirin by blocking cyclo-oxygenase, and dipyridamole by inhibiting platelet phosphodiesterase and raising cyclic adenosine monophosphate levels. Thus, it is postulated that in combination they may potentiate each other’s antithrombotic activity.

Our numbers are too few to answer these questions...
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directly, but it seems that an aspirin/dipyridamole combination, by reducing mural thrombus formation on the thrombogenic endarterectomy surface, could reduce the risk of operative stroke and repeat carotid stenosis. While we did not observe any hemorrhagic complications in our small series, we acknowledge that there is a mild increased bleeding tendency with this treatment and, indeed, others have noted an association with wound hematomas. We believe that this risk is far less than with heparin infusions or oral anticoagulant drugs, however, and can be overcome with good surgical hemostasis. We recommend the use of an aspirin/dipyridamole combination perioperatively in carotid endarterectomy.

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References


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