A Randomized Trial of Aspirin or Heparin In Hospitalized Patients With Recent Transient Ischemic Attacks
A Pilot Study
Jose Biller, MD, Askiel Bruno, MD, Harold P. Adams Jr., MD, John C. Godersky, MD, Christopher M. Loftus, MD, Victoria L. Mitchell, RN, NC I, Karla J. Banwart, RN, NC I, and Michael P. Jones, PhD

In a randomized pilot study we compared the efficacy of temporary anticoagulation with intravenous heparin sodium to the efficacy of aspirin in preventing cerebral infarction in hospitalized patients with recent (<7 days) transient ischemic attacks (TIAs). Fifty-five patients (33 men, 22 women) aged 36–81 (mean 62.7) years met entry criteria and agreed to participate. Symptoms prompting hospitalization were referable to the carotid distribution in 43 patients (34 hemispheric, nine retinal); 12 patients had vertebrobasilar distribution TIAs. Twenty-seven patients received heparin and 28 received aspirin. Patients were treated until surgery or until long-term medical therapy was instituted, 3–9 (mean 5.5) days in the heparin group and 3–15 (mean 5.8) days in the aspirin group. Recurrent TIAs occurred in eight patients given heparin and in seven treated with aspirin. Infarction occurred in one patient in the heparin group and in four patients in the aspirin group (three brain, one retinal infarction). Initial symptoms in these five patients were referable to the carotid distribution in two and to the vertebrobasilar distribution in three. All patients but the one with a retinal infarction had recurrent TIAs prior to stroke. Our pilot study suggests that hospitalized patients with recent TIAs are at high risk for recurrent TIAs (15 of 55, 27%) and brain infarction (five of 55, 9%) and that patients with recent vertebrobasilar distribution TIAs have a marginally significantly higher risk (odds ratio 6.83, 95% confidence interval 0.65–88.66) of infarction than patients with recent carotid distribution TIAs. (Stroke 1989;20:441–447)
distribution included unilateral or bilateral weakness or paresthesias, ataxia, imbalance or clumsiness not associated with vertigo, or binocular visual complaints. Patients with isolated transient vertigo, diplopia, dysphagia, and dysarthria were included only if these symptoms accompanied one or more of the previously described complaints. Arterial hypertension was defined as consistently elevated blood pressure of $\geq 140/90$ mm Hg or a history of elevated blood pressure treated with antihypertensive agents. Diabetes mellitus was defined according to the 1979 report of the National Diabetes Data Group. Hypercholesterolemia was defined as a fasting cholesterol concentration greater than the 75th percentile for the adult US population. We entered patients with TIsAs presumed to be secondary to thrombotic or embolic occlusions of large arteries as well as patients with TIsAs possibly due to small-vessel disease or from a probable cardiac source. Informed consent was obtained from all patients. The study protocol was reviewed by the ethical committee, and institutional review board approval regarding human subjects was obtained.

We excluded patients with focal deficits lasting >24 hours, those with intracranial hemorrhages or active bleeding (i.e., gross hematuria, active gastrointestinal bleeding, or heme-positive stools), those with intracranial aneurysms visualized on baseline computed tomography (CT), and those with sustained calculated mean arterial blood pressures of >140 mmHg. We also excluded patients with elevated partial thromboplastin times (PTTs), elevated prothrombin times (PTs), platelet counts of <125,000/mm³, and those with renal insufficiency (blood urea nitrogen concentration [BUN] of >50 mg/100 ml, creatinine concentration of >3 mg/100 ml) or active hepatic disease (PT of >15 seconds). We also excluded pregnant women, patients with active collagen-vascular disease, and those with known hypersensitivity or other adverse reaction to heparin or aspirin.

On admission, all patients were interviewed and had complete physical and neurologic examinations by the three participating neurologists. Patients were seen daily during hospitalization. Baseline diagnostic studies included chest roentgenogram, 12-lead electrocardiogram (ECG), complete blood cell count with differential and platelet count, PT, PTT, blood glucose level, blood chemistries, serum electrolytes, erythrocyte sedimentation rate, urinalysis, hemocult testing, and unenhanced brain CT.

Echocardiography, ultrasound and Doppler studies of the carotid arteries, ultrafast (cine) CT of the heart, cerebral angiography, and magnetic resonance imaging (MRI) of the brain were optional. Noninvasive grading of carotid artery stenosis was made by the Doppler velocities and spectral broadening (when performed) as follows: 0–15% diameter stenosis, peak systolic velocity of <120 cm/sec, no spectral broadening; 16–49% diameter stenosis, peak systolic velocity of <120 cm/sec, spectral broadening throughout systole; 50–79% diameter stenosis, peak systolic velocity of >120 cm/sec, increased diastolic flow, marked spectral broadening; 80–99% diameter stenosis, internal carotid artery end-diastolic peak velocity of >120 cm/sec, and total occlusion, unilateral flow of 0 or reversed flow in the common carotid artery and no signal in the internal carotid artery.

Randomization was achieved by blind selection of cards that listed either heparin or aspirin as treatment. No stratification variables were used. Patients randomized to heparin treatment were given an intravenous bolus injection of 5,000 units heparin sodium (porcine intestinal mucosa) followed by a constant maintenance infusion. The hourly dose of heparin was started at 1,000 units and was adjusted to maintain a PTT of 1.5–2.0 times the baseline value. Every effort was made to maintain a satisfactory degree of anticoagulation. If the PTT was less than desired, the dose of heparin was increased by 2,000–4,000 units for 24 hours; a second bolus injection of heparin was avoided. If the PTT was greater than desired, the dose of heparin was reduced by 2,000–4,000 units for 24 hours. Heparin therapy was continued for a minimum of 3 and a maximum of 9 (mean 5.5) days. Heparin was discontinued at the time of cerebrovascular surgery or when maintenance therapy was begun. Patients randomized to aspirin treatment were given two 325-mg tablets b.i.d. (1,300 mg/day) for a minimum of 3 and a maximum of 15 (mean 5.8) days. Both investigators and patients were aware of the treatment given to each patient.

An intention-to-treat analysis was used to measure response to treatment. Differences in proportions were assessed using Fisher’s exact test. The principal outcomes for the assessment of efficacy were fatal or nonfatal cerebral infarction and recurrent TIAs occurring during hospitalization. Occurrence of events was determined by any of the three participating neurologists. Cerebral infarction was diagnosed when a patient had signs and symptoms persisting for >24 hours and when ancillary investigations (CT and/or MRI) corroborated a new stroke.

Results

Patient Characteristics

From June 1, 1986, through July 1, 1988, 62 patients were eligible for the study. Seven were excluded; four refused to participate, one was taking warfarin for another medical condition and had a baseline PT of 26 seconds, one had a baseline BUN of >50 mg/100 ml, and another had an intracranial aneurysm visualized on baseline CT and MRI. Therefore, the study group comprised 55 patients, 33 men and 22 women, aged 36–81 (mean 62.7) years. Twenty patients had a history of a single TIA, 21 patients had sustained more than one but fewer than five TIAs, and 14 patients had
TABLE 1. Doppler Carotid Studies in 35 Patients With Transient Ischemic Attacks

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>Group</th>
<th>Heparin</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-15%</td>
<td>37</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>16-49%</td>
<td>11</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>50-79%</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>80-99%</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>100%</td>
<td>6</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

n, number of arteries.

five or more TIAs prior to admission. The time from the last TIA to initiation of treatment was 0 day in 22 patients, 1 day in nine, 2 days in 11, 3 days in six, 4 days in four, 5 days in two, and 6 days in one. Thirty-one patients had a history of arterial hypertension, 22 had a history of heart disease, 28 were cigarette smokers, 16 had hypercholesterolemia, and seven had diabetes mellitus. Forty-three patients experienced a TIA in the carotid distribution (34 hemispheric, nine retinal), while 12 had vertebrobasilar distribution TIAs. Carotid bruits were heard in 17 patients (unilateral in 10, bilateral in seven), while 12 had vertebrobasilar distribution TIAs. Carotid bruits were heard in 17 patients (unilateral in 10, bilateral in seven), two patients had supraventricular bruits, and one had vertebral bruits; cervical bruits were absent in the remaining 36 patients (65%).

Of the 55 patients, eight had ECG changes compatible with remote myocardial infarction and one had atrial fibrillation. Baseline CT was normal in 42 patients; 12 had hypodense areas (consistent with old infarcts in 10 and with possible new infarcts in two) and one patient had unrelated abnormalities. Echocardiography was normal in 23 of 41 patients; eight (20%) had left atrial enlargement, four (10%) had mild mitral regurgitation by Doppler echocardiography, four (10%) had mild aortic valve calcification, two (5%) had mitral annulus calcification, two (5%) had left ventricular hypertrophy, one (2%) with Ebstein's anomaly had a possible atrial septal aneurysm not visualized by ultrafast CT of the heart, and one (2%) had a possible left ventricular thrombus not documented by ultrafast CT of the heart. B-mode ultrasound and Doppler studies of the cervical carotid arteries were performed in 35 patients (70 arteries); of the 22 arteries with $\geq 50\%$ diameter stenosis, 10 were in the heparin group and 12 in the aspirin group, and of the 48 arteries with $<50\%$ diameter stenosis, 25 were in the heparin group and 23 in the aspirin group (Table 1). Of the 43 patients who had TIAs in the carotid distribution, 32 had duplex studies of the cervical carotid arteries; 14 (44%) had $\geq 50\%$ diameter stenosis. Cerebral arteriography was performed in 45 patients (23 in the heparin group and 22 in the aspirin group). The frequency of patients with carotid distribution TIAs and $\geq 50\%$ stenosis on angiography was equal in the two groups (Table 2). MRI was performed in seven patients; in two, it demonstrated a posterior fossa infarction not visualized on sequential CT and in another, it demonstrated a discrete hemorrhagic transformation of cerebral infarction not visualized on CT (in a patient receiving aspirin).

Treatment lasted 3–15 (mean 5.9) days. Mean length of hospital stay was 6.1 days for patients receiving only medical therapy and 11.8 days for those who also had carotid endarterectomy.

TABLE 2. Distribution of Angiographic Lesions in Patients With Transient Ischemic Attacks

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Carotid distribution (n=39)*</th>
<th>Vertebrobasilar distribution (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arteries</td>
<td>Heparin</td>
</tr>
<tr>
<td>Unilateral occlusion</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq 80%$</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Unilateral</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Bilateral</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>50–80%</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Unilateral</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bilateral</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Unilateral</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Bilateral</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Ulcer</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Normal angiogram</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

*Not all had bilateral studies, >1 abnormality in some; 2 had associated intracranial atherosclerosis, 2 had associated intracranial saccular aneurysms, 2 had tortuous vessels without stenosis, 1 had carotid dolichoectasia. Intracranial vertebrobasilar artery.

†Basilar artery.

‡Bilateral internal carotid artery stenosis of $>80\%$ plus bilateral vertebral artery origin stenosis of $<50\%$.
Treatment Outcome

Twenty-seven patients received heparin and 28 received aspirin. The randomization scheme we used accomplished a balanced number of patients with potential risk factors in the two groups: there were 10 patients with heart disease in the heparin group and 12 in the aspirin group, 15 patients with hypertension in the heparin group and 16 in the aspirin group, and 12 tobacco users in the heparin group and nine in the aspirin group. The average age was 63.2 years in the heparin group and 62.2 years in the aspirin group.

Following initiation of treatment in the heparin group, eight of 27 patients had recurrent TIAs (single in four and multiple in four; mean 1.9 events) and one had a cerebral infarction (Figure 1). After initiation of treatment in the aspirin group, seven of 28 patients had recurrent TIAs (single in two and multiple in five; mean 2.1 events) and four had infarctions (three a cerebral infarction and one a retinal infarction). The proportion of patients experiencing recurrent TIAs did not differ significantly between groups (p=0.467).

Among the 43 patients with carotid distribution TIAs, seven of 23 receiving heparin and four of 20 receiving aspirin had recurrent TIAs (p=0.335). Among the 12 patients with vertebrobasilar distribution TIAs, one of four receiving heparin and three of eight given aspirin had recurrent TIAs (p=0.594). Infarction during medical treatment...
occurred in two (one cerebral and one retinal) patients with carotid distribution TIAs (4.6%) and in three patients with vertebrobasilar distribution TIAs (25%) (Figure 2); this gives an odds ratio of 6.83 (95% confidence interval 0.65-88.66), which is only marginally significantly different from 1 (p=0.063). Among the patients with carotid distribution TIAs, one of 23 receiving heparin and one of 20 patients given aspirin experienced an infarction (p=0.720). However, among the patients with vertebrobasilar distribution TIAs, zero of four on heparin and three of eight on aspirin experienced an infarction (p=0.254). All brain infarctions were anteplaced by recurrent TIAs. Cerebral/retinal infarction developed mainly among patients with high-grade arterial stenosis or occlusion. Correlation of TIAs, angiography results, and subsequent stroke risk is illustrated in Table 3.

Because a recurrent TIA or brain infarction was interpreted as failure of the study drug, three patients in the aspirin group (one with carotid distribution TIAs and two with vertebrobasilar distribution TIAs) had the aspirin withdrawn and heparin started upon the decision of the attending physician.

Adequate anticoagulation was achieved in all but two patients at some time during treatment (mean PTT of 64 seconds). The only cerebral infarction in the heparin group occurred when the PTT was 60 seconds.

No hemorrhagic complications occurred. No patient in the heparin group developed thrombocytopenia; one patient in the aspirin group had evidence of hemorrhagic transformation of a cerebral infarct without clinical deterioration. One patient in the heparin group had a groin hematoma after completion of angiography; no treatment was required. Sixteen carotid endarterectomies (10 in the heparin group and six in the aspirin group) were performed without mortality. One patient (in the heparin group) (6.3%) had a single recurrent TIA following surgery, and one patient (in the aspirin group) (6.3%) had a postoperative cerebral infarction.

### Discussion

Considerable controversy remains about the proper management of patients with recent TIAs. Immediate intravenous administration of heparin has been recommended for high-risk patients with recent TIAs. Heparin has been used in high-risk patients, those with TIAs of increasing severity, frequency, or duration, and as an interim medical measure while patients are evaluated before surgery or initiation of maintenance medical therapy. However, there is a natural reluctance among physicians to accept the risk of heparin in TIA patients. No prospective randomized data are available to support the use of heparin in patients with recent TIAs.

Aspirin is the most commonly prescribed drug for long-term treatment in patients with TIAs. Several large, carefully performed, clinical trials have demonstrated reduction in the incidence of stroke and stroke-related mortality with the use of aspirin. However, it must be recognized that these long-term prophylactic studies with aspirin did not include many patients with recent (<7 days) TIAs; no data are available on the efficacy of aspirin in this situation. Our study confirms that the interval since the most recent TIA is an important factor in forecasting the risk of brain infarction. We found a 27% (15 of 55) frequency of recurrent TIAs and an overall 9% (five of 55) frequency of infarction during medical treatment.

Our study suggests that patients with recent episodes of transient monocular blindness have a substantial risk of retinal infarction. Marshall and Meadows studied the natural history of 80 patients with amaurosis fugax and found an only 16.2% incidence of stroke or permanent visual loss in 4 years of follow-up. However, the impression that recent retinal TIAs may be more benign than hemispheric carotid distribution ischemic events may derive in part from the inclusion by these authors of young patients free of atherosclerotic disease and patients treated with carotid endarterectomy. Paffenbach and Hollenhorst evaluated 24 patients with amaurosis fugax and cholesterol retinal emboli.

### Table 3. Correlation of TIAs, Angiography Results, and Subsequent Stroke

<table>
<thead>
<tr>
<th>Pt/sex</th>
<th>Group</th>
<th>Site</th>
<th>Before randomization</th>
<th>Recurrent</th>
<th>Angiography results</th>
<th>Stroke site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F</td>
<td>Heparin</td>
<td>Carotid hemispheric</td>
<td>2</td>
<td>3</td>
<td>50-80% L ICA stenosis</td>
<td>L frontal</td>
</tr>
<tr>
<td>2/F</td>
<td>Aspirin</td>
<td>Vertebralbasilar</td>
<td>3</td>
<td>2</td>
<td>Not done</td>
<td>Occipital/cerebellar</td>
</tr>
<tr>
<td>3/F</td>
<td>Aspirin</td>
<td>Vertebralbasilar</td>
<td>8</td>
<td>2</td>
<td>50% R vertebral stenosis</td>
<td>Pontine</td>
</tr>
<tr>
<td>4/M</td>
<td>Aspirin</td>
<td>Retinal</td>
<td>3</td>
<td>0</td>
<td>R ICA occlusion</td>
<td>R retina (BRAO)</td>
</tr>
<tr>
<td>5/M</td>
<td>Aspirin</td>
<td>Vertebralbasilar</td>
<td>3</td>
<td>5</td>
<td>Not done (in previous angiogram &gt;80% stenosis of basilar artery)</td>
<td>Occipital, cerebellar, brainstem, thalamic</td>
</tr>
</tbody>
</table>

Pt, patient number; F, female; M, male; TIA, transient ischemic attack; L, left; R, right; ICA, internal carotid artery; BRAO, branch retinal artery occlusion.
followed them for 6–10 years, and found a 37.5% incidence of stroke or permanent visual loss. We found a 22% (two of nine) frequency of recurrent retinal ischemia and an 11% (one of nine) frequency of retinal infarction during medical therapy.

Vertebrobasilar distribution TIAs have been thought to have a more benign prognosis than carotid distribution ischemic events, although this impression may derive in part from the inclusion of patients with nonfocal, nonspecific symptoms. Because the etiology, pathogenesis, size, and location of vessel involvement is rather heterogeneous in patients with vertebrobasilar ischemia, our findings in so few patients should be considered preliminary. Nonetheless, contrary to expectation, our data demonstrate a 33.3% (four of 12) frequency of recurrent vertebrobasilar ischemic events and a 25% (three of 12) frequency of vertebrobasilar artery territory infarction during treatment. We believe that they may reflect a subset of patients with vertebrobasilar ischemia. All cases of vertebrobasilar artery territory infarction occurred in patients treated with aspirin. However, there was an over-representation of patients in the aspirin compared with the heparin arm (eight versus four) among those with TIAs in the vertebrobasilar distribution. This makes definitive interpretation of the results difficult. The notion that anticoagulant as opposed to antiplatelet drugs might act differently in patients with vertebrobasilar TIAs can be entertained since all five major cerebral infarctions reported by Putman and Adams in 74 patients treated with heparin occurred in patients with carotid distribution TIAs; none occurred in the 14 patients with ischemic disease of the vertebrobasilar system.

We believe there are methodologic weaknesses in our pilot study. Our sample size, despite 2 years of recruitment, is small and may be responsible for the nonsignificance of some of our results. This should not detract from the marginally significant difference between the carotid and vertebrobasilar groups concerning cerebral infarction. Trends similar to those in this pilot study based on a much larger study population would be highly statistically significant. A much larger study population will require approximately >20 years of recruitment at a single institution or, more likely, a large, multicenter, clinical trial of emergency medical therapy for patients with recent TIAs.

In addition, we did not exclude nonatheromatous vascular diseases and potential cardiac sources of embolism. However, rapid differentiation of these etiologies from the most common atherothromboembolic etiology of TIAs can be difficult. Nonetheless, we found only two patients with potential nonatheromatous causes for TIAs. One patient with hypercholesterolemia, recurrent bouts of amaurosis fugax, and severe bilateral carotid stenosis had chronic atrial fibrillation; we believed that her stereotypical retinal ischemic episodes were secondary to carotid atheromatosis. A second patient with vertebrobasilar TIAs and atheromatous unilateral occlusion of the intracranial vertebral artery had an "asymptomatic" Ebstein's anomaly and a probable atrial septal aneurysm on echocardiography (not confirmed on ultrafast CT of the heart); she also had an atrial septal defect on cardiac catheterization. The underlying cause for her TIAs was uncertain, and she had no recurrence with medical therapy only. No hematologic abnormality was found in any of our patients to explain their TIAs.

Although we were unable to demonstrate a significant difference between aspirin and heparin treatment in preventing recurrent TIAs or cerebral infarction, our results should not be interpreted as discouraging. Although on a percentage basis we have not demonstrated any major difference between our treatment and the natural history of untreated TIAs, among our medically treated patients there was only one major cerebral infarction, which is consistent with the report of Grotta et al, who found that the severity of the ischemic event appears to be lessened by the use of aspirin.

Our preliminary findings cannot provide absolute recommendations for the clinician caring for patients with recent TIAs. A large, multicenter, prospective, randomized, clinical trial with an adequate number of patients should be carried out to determine whether there is a difference between aspirin and heparin in the management of patients with recent TIAs.

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References


KEY WORDS: aspirin · cerebral ischemia, transient · clinical trials · heparin
A randomized trial of aspirin or heparin in hospitalized patients with recent transient ischemic attacks. A pilot study.

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