Lack of Association Between Carotid Plaque Hematoma and Ischemic Cerebral Symptoms

Laura Lennihan, MD, William J. Kupsky, MD, J.P. Mohr, MD, W. Allen Hauser, MD, James W. Correll, MD, and Donald O. Quest, MD

To investigate the association between carotid plaque hematoma and symptoms of cerebral ischemia a retrospective review of 200 consecutive carotid endarterectomies at the Neurological Institute of New York was carried out. Data analyzed included cerebral ischemic symptoms, angiographic findings, preoperative use of antithrombotic agents, and microscopic pathology of endarterectomy specimens. No association was found between ischemic symptoms ipsilateral to the endarterectomy and presence, size, or age of plaque hematomas. Plaque hematomas were less common among patients who took antithrombotic agents preoperatively than among those who did not. The presence of plaque hematoma was associated with angiographic carotid cross-sectional area stenosis of >75%. Patients with stenosis of <75% were more likely than those with stenosis of >75% to have ischemic symptoms ipsilateral to the endarterectomy, suggesting that criteria for surgical treatment of carotid atherosclerosis differ for those who are symptomatic vs. those who are asymptomatic. These results demonstrate the limitation of using a surgical series to extend causal inferences about the relation between plaque hematoma and cerebral ischemic symptoms to the general population of people with carotid atherosclerosis. (Stroke 1987;18:879–881)

Subjects and Methods

During the period under study, 200 carotid endarterectomies were performed. The study included those 198 endarterectomies about which clinical information could be found. Ninety-three men and 84 women with a mean age of 66 years comprised the study population; 156 had unilateral and 21 had bilateral endarterectomies. Clinical information was obtained by chart review to determine whether symptoms of focal cerebral ischemia in the territory of the treated carotid artery had occurred prior to surgery. The number of days before surgery of the initial and all subsequent neurologic symptoms was recorded, whether the symptoms were in the carotid territory of interest or not. In addition, data on timing and duration of the use of antithrombotic agents, both antiplatelet agents and anticoagulants, were obtained. The chart reviewer was blinded to the histologic characteristics of the surgical specimen and the angiographic findings.

Characterization of the pathology of endarterectomy specimens was based on microscopic examination of hematoxylin and eosin stained cross-sections. The pathologist had no knowledge of the clinical data on any patient. Plaque hematomas were recognized by the presence of degenerating blood or hemosiderin, and the age of the hematoma was estimated using standard histologic criteria of reaction to tissue injury to categorize the hemorrhages as acute, recent, of intermediate age, or old. An acute hematoma, estimated to be <1 week old, showed intact and degenerating red cells, many polymorphonuclear leukocytes and a few mononuclear cells, and little or no evidence of organization. A recent hematoma, estimated to be 1–4 weeks old, showed degenerating red cells, pigment-laden and foamy macrophages, developing organization tissue, and a predominance of mononuclear inflammatory
cells. A hematoma of intermediate age, estimated to be >4 weeks old, showed only residual degenerating blood, maturation of organization tissue with enlargement of vascular spaces, and loss of inflammatory cells except macrophages and a few plasma cells. An old hematoma, estimated to be months or years old, showed vascular, loose myxoid or collagenous tissue on hematoxylin and eosin stain and varying numbers of hemosiderin-laden macrophages, confirmed on a Prussian blue stain for iron. Large hematomas were defined as those occupying ≥50% of the plaque cross-sectional area and contributing to high-grade stenosis or near-occlusion.

Angiograms were examined for 135 of the 198 endarterectomies. Determination of the degree of stenosis was made by measuring the minimal residual lumen and estimating the normal lumen diameter at that site in 2 planes. Severity of the stenosis was assessed based on a calculated percent reduction in cross-sectional area, with ≥75% reduction considered a critical or hemodynamically significant stenosis. The angiograms were reviewed without knowledge of the clinical or pathologic data.

Statistical analysis was performed using the $\chi^2$ and Mantel-Haenszel $\chi^2$ methods.

**Results**

Symptoms of cerebral ischemia occurred in the territory of 122 (62%) of the treated carotid arteries, 38 (19%) had symptoms in some other vascular territory, 26 (13%) had nonlocalizing symptoms, and 12 (6%) had no neurologic symptoms. Of those 122 cases with ipsilateral symptoms, i.e., in the territory of the treated carotid artery, the timing of preoperative occurrence was 1–7 days in 8 (7%), 1–4 weeks in 32 (26%), 1–6 months in 57 (47%), and >6 months in 25 (20%).

All endarterectomy specimens had 1 or more histologic features of atherosclerosis. Ninety-six of the 198 specimens (48%) had evidence of plaque hematoma: 35 acute, 11 recent, 23 intermediate, and 27 old; 21 specimens (48%) had evidence of plaque hematoma: 35 acute, 11 recent, 23 intermediate, and 27 old; 21 cases classified as having large hematomas, 32 of 38 cases without critical stenosis (84%) had ipsilateral symptoms. These data document that, of the 198 endarterectomies, 5 were done in patients with both a large hematoma <4 weeks old and ipsilateral symptoms during the 4 weeks prior to surgery.

Of the 135 cases for which angiograms were reviewed, angiographically 97 (71.8%) had a critical stenosis. In the group with plaque hematoma, 83.3% had a critical stenosis on angiogram, while in the group with no plaque hematoma, only 58.7% had this degree of stenosis, showing an association between plaque hematoma and critical stenosis ($\chi^2 = 10.06, p<0.01$). Of the 21 cases classified as having large hematomas pathologically, 17 angiograms were reviewed and all showed stenosis of ≥75%. Fifty-one of 97 cases with critical stenosis (53%) had ipsilateral symptoms, and 32 of 38 cases without critical stenosis (84%) had ipsilateral symptoms. These proportions are significantly different ($\chi^2 = 15.66, p<0.001$), indicating an association between ipsilateral symptoms and the absence of critical stenosis. Since some authors have suggested that a plaque hematoma may disrupt the intimal surface and predispose to embolism from a nonstenotic artery, we did a stratified analysis based on the presence or absence of plaque hematoma. The stratified analysis demonstrated that the association between ipsilateral symptoms and noncritical stenosis was not explained by the presence of a plaque hematoma (Mantel-Haenszel $\chi^2 = 0.002, p>0.25$).

Concern has been raised that the use of antiplatelet agents or anticoagulants may increase the occurrence of plaque hematoma, thereby putting patients with atherosclerotic plaques at increased risk for ischemic events. To investigate this point, patients were classified as to whether they made daily use of an antithrombotic agent during the month prior to surgery. Data were obtained on use of antithrombotic agents for 148 of the 198 endarterectomies. Among the 97 users of antithrombotic agents, 25% had a plaque hematoma <4 weeks old, whereas among the 51 nonusers, 43% had a plaque hematoma <4 weeks old, a significant difference indicating no increased risk of plaque hematoma in users of antithrombotic agents ($\chi^2 = 5.28, p<0.025$).
Discussion

An important aspect of prevention of cerebral infarction is elucidating the pathogenesis of atherosclerosis of the carotid bifurcation. Both perfusion failure distal to a critical stenosis and embolism due to ulceration of an atherosclerotic plaque have been claimed as causes of cerebral infarction. Some investigators who have studied gross and microscopic pathologic specimens of carotid plaques have concluded that hemorrhage within the plaque contributes to the development of both stenosis and ulceration. They have also reported that plaque hematoma is found more often in symptomatic compared with asymptomatic patients undergoing endarterectomy and concluded that plaque hematoma has an important role in causing cerebral infarction. Others have not found carotid plaque hematoma to be associated with cerebral ischemic symptoms.

In agreement with these studies, we found that hematoma is a common pathologic feature of carotid plaques. However, we did not find an association between symptoms and hematomas, ipsilateral symptoms being as common among those with as those without plaque hematoma. Among those patients with large hematomas, that type presumed to be most likely to cause symptoms because of a sudden and significant reduction in lumen diameter, only 5 had onset of symptoms ipsilateral to the hematoma, and within the same period that the hematoma occurred. Thus, in only 5 of 198 cases can it be postulated that the hematoma precipitated cerebral ischemia by causing a critical stenosis. Among the remaining cases with ipsilateral symptoms, plaque hematoma may have contributed to the development of stenosis or ulceration but, given the lack of a temporal association between hematoma and symptoms, plaque hematoma cannot be identified as a direct cause of cerebral ischemia. It is possible that failure to recognize an association between the time of occurrence of hemorrhage and the onset of symptoms occurred because of inaccuracies in methods for determining the age of the hematoma. While our dating criteria are based on standard histologic criteria including the presence of degenerating blood, type of inflammatory response, and degree of organization, these criteria define only the general sequence of events, which may be altered by a variety of factors. For example, because the atherosclerotic plaque is rather avascular, the usual reaction to hemorrhage may be delayed and slowed. In this study, an attempt was made to compensate for such discrepancies by using broadly defined time periods.

In the present study, plaque hematoma was positively associated with angiographically demonstrated critical stenosis. Plaque hematoma is one of several features of atherosclerosis contributing to the complexity and thickness of the plaque. Our study found it to be a marker of the severity of atherosclerosis. What is perhaps surprising is that ipsilateral symptoms were no more common among those with critical stenosis. Rather, the noncritical stenosis group had the greater proportion with ipsilateral symptoms. This result seems to suggest that criteria for selecting patients for surgery at our institution are different for those who have ipsilateral symptoms than for those who do not. A patient with TIA may have an endarterectomy on the ipsilateral carotid for a noncritical stenosis, while a patient who has no ipsilateral symptoms will not be referred for endarterectomy unless the stenosis compromises flow. Since plaque hematoma is a marker for stenosis severity, it is not surprising that hematoma does not correlate with ipsilateral symptoms. These results demonstrate the limitation of using a surgical series to extend causal inferences about the relation between plaque hematoma and cerebral ischemic symptoms to the general population of people with carotid atherosclerosis. Based on our results, the risk of plaque hemorrhage causing an infarct due to embolism or reduced flow in an asymptomatic person with an atherosclerotic plaque is not a justification for prophylactic endarterectomy.

Concern has been raised that antithrombotic agents may increase the chance of intraplaque hemorrhage and cause cerebral infarction or TIA. We demonstrated no increased risk of plaque hematoma among those patients taking antithrombotic medications during the month before surgery.

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References


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