Editorial

Carotid Endarterectomy Clinical Trials

Carotid endarterectomy is done to prevent stroke. Although risks are associated with the procedure and its financial cost is high, strokes cause major disability and death. Faced with the possibility of stroke, many patients who have stenotic lesions of the carotid artery have decided that the cost and risk of the procedure are preferable to the alternative. The basic mechanics of the procedure are easily described, and the atherosclerotic plaques that are removed have an obvious intuitive relationship to future possible strokes. As many as 80,000 carotid endarterectomies are performed annually in the United States. Through the years, surgeons have improved the operative techniques in an effort to reduce the number of complications from the procedure. Methods for confirming the presence of stenosis of the carotid artery have likewise improved. Many physicians are confident that the procedure reduces the subsequent incidence of stroke. Yet, carotid endarterectomy has never been subjected to the rigorous scientific testing that has become the standard for new pharmacologic and surgical treatments. Because of the lack of proof that the procedure is effective, no convincing answer is available for those who are increasingly concerned that the outcome after endarterectomy is not well known and may, in fact, not be good enough to justify the risks and the cost of the procedure.

In recent years, changes in several circumstances have increased the doubt about the value of carotid endarterectomy. Several reports have described unexpectedly high variability in the rate of perioperative morbidity and mortality.[1,2] Even if the related surgical morbidity is low, other changing factors are influential—for example, a decline in the overall incidence of stroke and the unmeasured benefit presumed to result from improved medical care to prevent stroke, especially the use of aspirin and the management of hypertension.[3] Noninvasive testing methods have been developed that facilitate identification of patients who have carotid stenosis, especially those who are asymptomatic. A substantial disparity has developed between those physicians with confidence that endarterectomy has some benefit, at least in some subset of patients,[4] and those physicians who assert that any benefit may be outweighed by unacceptably high risks.[5] This disparity needs to be resolved.

In the analysis of reports in the literature, some investigators questioning the benefit of carotid endarterectomy have been so convincing that one might possibly conclude that the issue has already been resolved.[6,7] Nevertheless, few physicians would disagree that well-designed clinical trials would provide the best data for making decisions. With the currently available data, we are not making decisions based on objective information; we are simply guessing. Is it surprising that patients are being offered contradictory opinions and widely different treatment modalities for a relatively simple clinical problem?

The results of the Extracranial-Intracranial Bypass Trial may have created the impression that all surgical procedures to prevent stroke are ineffective.[8] This trial showed no benefit from extracranial-intracranial bypass procedures in patients with transient ischemic attack or stroke, but the patients selected for that trial were those with atherosclerotic lesions inaccessible to carotid endarterectomy or those with carotid occlusions. The purpose of endarterectomy is to prevent distal embolization and progressive stenosis leading to occlusion, something far different from the redistribution of blood flow sought through bypass procedures. Because adequate clinical studies have not been done, questioning the effectiveness of endarterectomy in some situations may be reason-

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able, but the available data are insufficient to conclude that it is ineffective in either symptomatic or asymptomatic patients. If ample data had been accumulated, the variability in the use of the procedure would be far less.

In the current situation, no one can be comfortable. Patients who have carotid stenosis but have not undergone endarterectomy may have serious and disabling strokes that might have been prevented by surgical intervention. In contradistinction, a patient who dies as a result of a surgical complication might never have had a stroke. Each physician has had to determine an individual response to this dilemma.

The National Institute of Neurological Disorders and Stroke (NINDS) is supporting three clinical trials to determine the effectiveness of carotid endarterectomy in various patient populations, and patients are already being recruited for these three trials. With the widespread support of the medical and surgical community by referral of patients to these important trials, they will be completed quickly. One of the trials—the Mayo Asymptomatic Carotid Endarterectomy (MACE) Study—is described by David O. Wiebers, M.D., and his colleagues in this issue of the *Proceedings* (pages 897 to 904). The purpose of this trial is to investigate the effectiveness of endarterectomy in patients who have no symptoms but who have well-substantiated hemodynamically significant carotid stenosis. Patients with asymptomatic arterial stenoses selected by various noninvasive testing and angiographic criteria are being enrolled in the Asymptomatic Carotid Atherosclerosis Study (ACAS); the principal investigator is James F. Toole, M.D., at the Bowman Gray School of Medicine. Henry J. M. Barnett, M.D., at the University of Western Ontario, is the principal investigator in the North American Symptomatic Carotid Endarterectomy Trial (NASCET). Patients who have had transient ischemic attacks or minor strokes are being enrolled in this trial. Both the ACAS and the NASCET are large multi-institutional randomized trials. In all three trials, patients are screened very selectively. Consequently, these trials are highly dependent on a large number of referrals.

In none of these ongoing trials is the outcome apparent or easy to predict. Any benefit from surgical treatment is dependent on three important interacting variables—the rate of occurrence of stroke without endarterectomy, the rate of occurrence of stroke after endarterectomy, and the surgical morbidity and mortality. These rates can be estimated from previous descriptive epidemiologic studies, but the precision of such estimates is questionable. Different groups of patients are likely to have different rates of occurrence of stroke. For instance, a patient with no history of transient ischemic attack and a pressure-significant lesion detected on ocular pneumoplethysmography is less likely to have a stroke than a patient with a similar lesion and a history of several transient ischemic attacks. The potential benefit of endarterectomy, however, may not be reduced in the asymptomatic patient, inasmuch as that patient may also be less likely to have a stroke or die as a result of the surgical intervention. The rate of occurrence of stroke is not necessarily constant; after an initial reduction in the stroke rate subsequent to endarterectomy, the rate could change. The rate of occurrence of stroke in patients without endarterectomy may not change the same as the rate after endarterectomy.

In these NINDS trials, the eligible patients selected on the basis of specific criteria all undergo assessment as if they were scheduled for a surgical procedure. The patients agree to randomization before the mode of treatment is revealed. After the decision is made, the treatment group is not changed even if, for some reason, the operation is delayed or never performed. The purpose for this formal procedure is to ensure that the two groups of patients being compared are as similar as possible.

Surgeons are carefully reviewed before being approved to participate in such a trial. Documentation of surgical experience and a low rate of surgical morbidity and mortality must be obtained. Monitoring of the surgical morbidity and mortality continues during the trials.

In the MACE trial, patients must have evidence of a pressure-significant lesion on ocular pneumoplethysmography in association with

confirmatory ultrasound studies and a neurologic history and examination that exclude the possibility of prior symptoms. In this group of patients, the investigators predict that the rate of occurrence of stroke in patients without endarterectomy given 80 mg of aspirin daily will be about 5% per year. In the patients who undergo endarterectomy, the surgical morbidity and mortality are predicted to be 1% or less and the rate of occurrence of stroke after endarterectomy to be less than 2% per year. Even if these assumed rates are accurate, the difference between the two treatments will be extremely difficult to detect. It is easy to understand how clinical intuition can lead to vastly different therapeutic strategies for two patients with similar cerebrovascular disease.

When a physician is contemplating whether to refer a patient for possible participation in a clinical trial, the many positive aspects of participation in such a trial should be considered. In a clinical trial, the uncertainty is stated clearly from the beginning. Initially, it may seem that the patient has a 50% probability of receiving a treatment that will later be proved ineffective. Is this scenario, however, any different from the usual clinical practice? In fact, the patient in a clinical trial may have several advantages. Because of the close monitoring of the quality of care through telephone calls and regular return visits for reevaluation, the outcome may be better than usual for all patients, whatever treatment they receive. Whenever any obvious difference between treatment groups is detected, the trial can be stopped early; thus, any actual differences in outcome that would seriously affect more than a few patients are unlikely. An additional advantage is the knowledge that any surgical procedure will be done by a surgeon whose record has been carefully evaluated, whose complication rate is proved to be within the highest standards, and who is part of a team that is committed to ensuring good follow-up care for any participating patient. Through the news media, many patients are aware of the uncertainty of the treatment for carotid artery disease. They may be frustrated by receiving contradictory advice from various clinicians. Although clinical trials do not offer a definite answer in the short term, they do offer a straightforward approach to the problem with well-defined risks and benefits and the promise of definite answers in the long term.

The most satisfying answers to the problem of optimal treatment for carotid artery disease will be provided by clinical trials. Without the support from clinicians in these trials, the answers would have to be based on the conflicting information that is already present. Increasing medical costs are necessitating a reevaluation of therapeutic strategies, particularly those that are more expensive and controversial. Unless a clearly defined benefit is derived from a procedure, the current trend is to restrict therapeutic options in order to reduce variability in the quality and cost of medical care. The burden is shifting to the practitioner to justify the selection of a specific treatment.[9] Until that justification is available, cost-containment efforts will certainly restrict the practicing physician's choices in the diagnosis and treatment of carotid stenosis.

Participation in clinical trials is one of the few ways that physicians can demonstrate their concern for the quality of medical care and can continue to make accurate medical decisions. The best way to contribute to the success of a clinical trial is for physicians to participate in the process that will determine the answer. Leaders in the fields of vascular surgery, neurologic surgery, and neurology are participating in the ongoing NINDS trials. Despite individual opinions about what treatment will prove to be best, these physicians realize the necessity of obtaining definite answers. In any given physician's practice, the number of patients who will meet the selection criteria for a trial are few. Therefore, the success of these endarterectomy trials will depend on referral of patients by a large number of physicians.

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