EC/IC Bypass Study

IN 1967 Donaghy and Yasargil both reported a new surgical procedure designed to circumvent an occluded internal carotid artery. The introduction of extracranial/intracranial arterial bypass surgery was heralded as a significant advance in the treatment of cerebrovascular disease. Because of the inherent logic of the operation, the creation of an anastomosis between the superficial temporal artery and a branch of the middle cerebral artery quickly appealed to the neurosurgical community. For the first time a surgical procedure seemed to be available for those patients with symptomatic atherosclerotic lesions of the internal carotid or middle cerebral arteries that could not be dealt with by direct endarterectomy.

In the first decade after the introduction of intracranial/extracranial bypass procedures many reports appeared to indicate that the operation could be performed with relatively low morbidity and mortality, and the techniques could be improved to ensure a high degree of patency of the anastomoses. This was followed by anecdotal reports of improvement in patients undergoing the procedure. The indications for the operation proved a somewhat more difficult question to answer. There was widespread acceptance of the procedure as a prophylactic measure in patients with TIAs or small strokes to prevent progression to major cerebral infarction. A smaller group of neurosurgeons went so far as to claim that the operation was of benefit to patients with major completed strokes.

In an effort to avoid the problems that had evolved in the use and evaluation of carotid endarterectomy for TIAs, asymptomatic bruits and strokes, a cooperative study to test the hypothesis that intracranial/extracranial bypass procedures could reduce the incidence of stroke and death in a well-defined population was organized in 1977 under the leadership of Dr. Henry J.M. Barnett. When the study was started, neurosurgeons with demonstrated interest and established expertise in performing intracranial/extracranial bypass procedures were recruited widely in the U.S. and Canada to contribute patients. The response was disappointing as many surgical groups had concluded that the operation was both useful and effective and therefore did not need to be studied in a randomized fashion. Because of the inability to persuade enough surgeons in North America to enter the study, additional centers were sought in Europe and Asia. This created concern among both the organizers of the study as well as its critics since such an approach might be incapable of testing the hypothesis because more centers would each be contributing small numbers of patients. This development increased the need for careful selection of centers, surveillance of patient selection, surgical technique and follow-up assessment. It was essential that so diversified a study did not distort the results and render the study unreliable because of wide variation in neurosurgical and medical care.

The report of the International Cooperative Study of Intracranial/Extracranial Arterial Anastomosis (EC/IC Bypass Study) has now been published. It is a landmark study because of its size, duration, and careful attention to the details. In contrast to earlier cooperative studies on the surgical treatment of stroke, it seems to provide some definitive answers to the original question. This question, could intracranial/extracranial bypass surgery reduce the risk of subsequent stroke and stroke-related death in patients with transient ischemic attacks and mild stroke by 33%, formed the central hypothesis of the study. The patients selected for the study were those with TIAs or mild stroke who had angiographic evidence of occlusion or stenosis in the internal carotid or in the initial segment of the middle cerebral artery that were not amenable to direct approaches. To obtain a satisfactory answer, a randomized study was proposed. An estimated fourteen hundred patients were needed with 700 in both the surgically and medically treated groups to be able to achieve statistical validity. The initial report of the study outlined the methodology used and reported on the success of the random allocation of patients to each group. The two groups were almost identical for age, sex, race, occurrence of TIAs, severity of stroke, and other medical problems.

By September 1982 the required number of patients had been entered and the follow-up assessments were well underway. To the great credit of the principal investigator and his colleagues no patient who entered the study was lost to follow-up. Follow-up was equally good from centers that contributed large numbers of patients and those that contributed smaller numbers. Ninety-eight percent of those allocated to surgical treatment had the bypass performed. The overall bypass patency rate was 96% and did not differ significantly between centers or by location in North America, Asia or Europe.

The data obtained from follow-up has been analyzed, and it is clear that extracranial/intracranial arterial bypass surgery utilizing an anastomosis of the su-
peripheral temporal artery to the middle cerebral artery does not provide protection in preventing subsequent stroke or stroke-related death. This result has been carefully analyzed and does not appear to be influenced by a number of factors including the type of arterial lesion found on cerebral angiography, whether occlusion or stenosis, the presence of complicating medical diseases, the side of the ischemic event, the age or sex of the patient, or the size or location of the participating center. The number of single strokes that occurred during follow-up was almost identical in the two groups, 18% of the medically treated and 20% of the surgically treated patients; more than one stroke occurred in 10% of the medical group and in 11% of those assigned to surgery.

Analysis of several subgroups of patients in whom a benefit might have been anticipated also failed to reveal any significant benefit of extracranial/intracranial arterial bypass surgery. Those situations in which bypass surgery was most likely to provide benefit such as internal carotid artery occlusion, severe distal (siphon) stenosis, and recent onset of TIAs were analyzed separately. No evidence of benefit from surgery was found. The concept that improving cerebral blood flow to an area which has become ischemic or has marginal flow might improve the outcome was investigated. The functional status of both groups of patients during follow-up was compared; there was no difference in the number of medically or surgically treated patients who improved, remained the same or died. The effect of surgery on recurrence of TIAs in those patients who originally presented with these events was evaluated, and no difference was observed in the frequency of TIAs between the two treatment groups. Identical percentages of patients in each group experienced a minimum of a 50% reduction of TIAs.

In patients with middle cerebral artery stenosis or in those with internal carotid artery occlusion and continuing TIAs, extracranial/intracranial arterial bypass surgery was found to have a higher incidence of stroke and stroke-related deaths than nonsurgical treatment. Of even greater interest was the finding that those patients who developed a stroke after a patent EC/IC bypass had been established did not fare better than the group of medically treated patients who sustained cerebral infarctions during the course of the study. Benefit from surgery in these two categories of patients might have been expected by even the most skeptical physician.

Another striking negative outcome was the comparison of those patients with poor angiographic appearance of the bypass with those with excellent bypasses on the post-operative studies. Outcome was no better in those patients with the best angiographic flow through the bypass than in those with the poorest flow.

An important part of the study was the meticulous follow-up. Not a single patient was lost to follow-up and patient assessment was excellent. Fortunately the results leave little doubt about the value of extracranial/intracranial arterial bypass surgery. Too often studies of this sort leave the medical community uncertain as to whether surgical procedures are useful or not because of poor study design, inadequate follow-up or indefinite results. This often leads to misuse of the procedure usually in the form of too frequent use. The conclusion that fatal and non-fatal stroke are not prevented by extracranial/intracranial arterial bypass surgery in the overall study or in the subgroups examined is strengthened by the size and care of the study, the evenness of the randomization and the uniformity of the population studied. The high percentage of patency and the low surgical morbidity and mortality, as good as reported in any of the non-controlled studies in the literature, leave no room to fault the design of the study. Many centers were involved, but all measured up to the high standards set by the investigators.

Several "internal controls" add strength to the lack of support for the central hypothesis. There was no benefit seen in those patients with excellent bypasses when compared with the poor anastomoses as analyzed by post operative angiography. There was no difference in the degree of reduction of TIAs in the medically or surgically treated patients. Finally the outcome of those patients who sustained a stroke after randomization was no different in the medical or surgical group.

Is this a "negative" study? The answer to this question is emphatically "no". For the first time a rigorous study with "state of the art" methods for clinical trials has looked at a widely accepted surgical procedure. The first reaction of neurosurgeons and neurologists must be one of disappointment since a logical operation with low morbidity and mortality is not effective. More importantly though the study should point the way for future investigation. Why is increased CBF ineffective in preventing stroke or mitigating the extent of the infarct once the bypass is established? Perhaps the approach to stroke has been too simplistic. In recent years most attention has been focused on large vessel disease as the primary etiologic factor. Platelets and the larger vessels supplying the brain may not be the only cause of stroke. It may lie at the microvascular level in the endothelium or systemically in the blood perfusing the brain. Undoubtedly some will try to rescue the procedure. It may still have applications but not for the prevention of stroke due to atherosclerosis.

Fletcher McDowell, M.D.
White Plains, New York
Eugene S. Flamm, M.D.
New York, New York

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F McDowell and E S Flamm

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