Stroke: The Way Things Really Are

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Summary of Review

This review summarizes the evidence for many of the modalities used to prevent stroke in high-risk patients, including antiplatelet drugs, anticoagulants, and endarterectomy, and the limitations of each. Controversial therapeutic modalities for which no scientific proof exists, such as anticoagulation of progressing stroke, are also discussed. The term "standard of care" should apply to modalities proven to be effective by scientifically controlled studies, not because they are used by many physicians.

Background

To comply with governmental requirements regarding the validity of therapeutic modalities and for medico-legal purposes, it is important to distinguish between what has been scientifically proven and what is anecdotal in the prevention and management of stroke.

The time has come when health care reform and good medical practice will require physicians to act on statistically verified information in the management of their patients. The concept of "outcome research" has already begun to influence whether or not a specific diagnostic or therapeutic modality is reimbursable. It is no longer acceptable to use such statements as "certain authorities believe" or "the literature suggests" regarding a therapeutic modality as a means of recommending its use. Nowhere is this problem more evident than in the management of cerebrovascular diseases. In this context it is pertinent to review briefly what is known and what is not, with the understanding that this review is not intended to be encyclopedic or to cover the entirety of cerebrovascular disease, but rather to address some of the more controversial issues.

Happily, there has been some progress in reducing the incidence of and/or mortality from stroke. Although the reasons for this decline are not yet totally clear, the identification and modification of risk factors for stroke are almost certainly responsible. Control of hypertension, dietary and activity modification, and abstinence from smoking or excessive alcohol ingestion can be achieved through physician and patient education. The public health process that promotes this education should target the young and healthy and receive the priority it deserves. The concept of prevention of disease, with the exception of vaccines for infectious disease prophylaxis, has never achieved the status it merits in clinical medicine, at least partially because physicians are trained to react to problems rather than anticipate and prevent them. A further major investment in the concept of disease prophylaxis, directing the message to all segments of our population, would pay huge dividends in stroke prevention.

The identification of risk factors is, of course, insufficient in itself to prevent stroke, but it is obviously the requisite first step. Cerebral transient ischemic attacks (TIAs) were early identified as a significant risk factor for both stroke and myocardial infarction, but the management of patients with TIAs was dominated for at least 20 years by empirical, unproven modalities, including endarterectomy and anticoagulation. We are indebted to those clinical investigators who insisted on the scientific method of prospective, controlled, randomized clinical trials as a means of identifying the value or lack thereof of presumed therapeutic agents, whether they were aspirin, other antiplatelet agents, carotid endarterectomy, or extracranial/intracranial anasto-

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Treatment of acute stroke is still disappointing despite the development of many promising pharmacological strategies in experimental animals. An important part of the reason may be that the window of therapeutic opportunity is much shorter than the usual entry time of patients in most clinical trials. This logistic problem merits serious attention.

Conclusions

Numerous controlled, randomized, multicenter clinical trials have demonstrated that the efficacy of various therapies directed at preventing or treating stroke can be determined and that anecdotal data may be misleading and harmful. At the least we should be aware of what we know and what we do not. (Stroke. 1994;25:1290-1294.)

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Because aspirin therapy occasionally induces gastric ulceration and hemorrhage, numerous controlled studies have been undertaken to determine the lowest effective dosage.\textsuperscript{5-7} Despite evidence that a low dose (75 mg) is better than placebo, there is still substantial disagreement as to whether low-dose aspirin therapy is as effective in reducing stroke as 975 mg daily, even though gastrointestinal complications are fewer with low-dose therapy; the treating physician must take these unsettled issues into account when prescribing aspirin dosage. Enteric-coated aspirin causes less gastrointestinal disease than regular aspirin, and absorption appears to be reliable.\textsuperscript{8} In the United States many physicians prescribe Ecotrin, which is reported to produce similar salicylate blood levels as comparable doses of regular aspirin.

Ticlopidine hydrochloride (500 mg daily) has been reported to be significantly more effective than aspirin in reducing stroke in men and women with a history of TIAs or minor stroke, with a 47% risk reduction compared with placebo; it also significantly reduces the incidence of vascular death and myocardial infarction in patients with unstable angina.\textsuperscript{9-11} The side effects of ticlopidine include rash, diarrhea, and neutropenia, which are usually reversible on discontinuation of the drug. Thus, ticlopidine would appear to be a more effective drug than aspirin in the prevention of stroke if patients can be closely monitored. It is often prescribed for patients who have an intolerance to aspirin or who have had ischemic symptoms while taking aspirin.

The identification of nonvalvular atrial fibrillation as a major risk factor for stroke was followed by a series of controlled, prospective, randomized trials that have finally identified that long-term anticoagulation with warfarin (international normalized ratio, 1.5 to 3.5) is effective in reducing stroke incidence by 67% compared with placebo.\textsuperscript{12-17} Two of these studies\textsuperscript{12,14} also evaluated aspirin. In one,\textsuperscript{14} aspirin dosage of 75 mg daily was not effective in reducing stroke, whereas in the other,\textsuperscript{12} 325 mg aspirin daily reduced stroke incidence significantly as compared with control treatment. The European Atrial Fibrillation Stroke Prevention Study demonstrated that in patients with nonvalvular atrial fibrillation who had suffered a recent TIA or minor stroke, anticoagulation for 1 year prevented 90 vascular events (mainly strokes) in 1000 patients, whereas 300 mg aspirin daily prevented 40 vascular events each year for every 1000 treated patients. Major bleeding complications from anticoagulants were 2.8% per year and 0.9% per year on aspirin.\textsuperscript{18} The relative effectiveness of larger doses of aspirin or of ticlopidine has not yet been investigated, but on the basis of extant data, both drugs should at least be considered if warfarin is contraindicated. There is no current justification for the use of long-term anticoagulants in patients with lone atrial fibrillation (that is, patients with atrial fibrillation but no other cardiac or pulmonary disease)\textsuperscript{13,17,19} because the incidence of cerebral infarction in that group of patients is too small to warrant the risk.

Although long-term anticoagulant therapy is routinely used to prevent cerebral embolism in patients with recent myocardial infarction and individuals with mitral valve disease, most of the studies supporting this practice have compared the effects of treatment with results anticipated from the natural history of the process, and further randomized studies would be helpful.\textsuperscript{20-24} Nevertheless, given existing data, the use of long-term anticoagulant therapy in the setting of valvular disease or recent myocardial infarction seems indicated.

The criteria for how soon to anticoagulate a patient with a cerebral embolism from a cardiac source have not yet been scientifically established, so recommendations for management of that problem are still based on anecdotal data. The issue is to prevent additional embolism but avoid bleeding into the cerebral infarction, and there are conflicting views in the literature\textsuperscript{25-29} that make a scientific judgment in any given case impossible at this time. Although the risk of recurrent embolism is about 10% during the first 2 weeks, a spontaneous hemorrhagic transformation of an infarct may not be evident by computed tomography for 48 to 72 hours; it is also generally acknowledged that the larger the infarct, the greater the likelihood that it will become hemorrhagic.

Despite the fact that there are no controlled studies that evaluate the risk-to-benefit ratio of heparin in progressing stroke, it is still widely used based on what can only be considered anecdotal data.\textsuperscript{30-34} The presumed physiological basis for heparin therapy is that a progressing stroke is the result of a propagating thrombus in either the carotid or vertebral-basilar circulation. In fact, there are no convincing clinical or pathological data to support that concept. A progressing carotid-circulation stroke may be the result of progressing edema around the infarct. Certainly there are no valid data that would mandate the use of heparin in progressing stroke of either the anterior or posterior circulation.

The fact that there is no other treatment available for such patients does not justify the use of a hazardous drug. Controlled studies may eventually settle this important issue. In the meanwhile, the physician who chooses to use heparin in that setting should at least be aware of the lack of scientific evidence that it is beneficial and of the potential hazards of heparin administration. By no stretch of the imagination should a physician prescribe any drug for management of that problem are still based on anecdotal data. The issue is to prevent additional embolism but avoid bleeding into the cerebral infarction, and there are conflicting views in the literature\textsuperscript{25-29} that make a scientific judgment in any given case impossible at this time. Although the risk of recurrent embolism is about 10% during the first 2 weeks, a spontaneous hemorrhagic transformation of an infarct may not be evident by computed tomography for 48 to 72 hours; it is also generally acknowledged that the larger the infarct, the greater the likelihood that it will become hemorrhagic.

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is a candidate for endarterectomy. However, it is not enough to recommend endarterectomy based on degree of carotid stenosis alone. The fine print of the study, specifically the impressive list of reasons for exclusion from that study, must also be read and considered and included in any decision to operate. Along with the degree of carotid stenosis, the age of the patient, presence of symptomatic coronary artery disease, bilaterality of carotid disease, and presence of intracranial arterial disease must also be factored into that decision; so must be the prior audited surgical record for carotid endarterectomy of the operating surgeon, whose skill must equal that of the trial surgeons lest the benefit of surgery compared with medical care alone be lost. The availability of such data should be mandated for every surgeon who undertakes this procedure. In fact, it rarely is.

The study continues for patients with carotid stenosis of less than 70%, but at this time there are no definite indications for or against surgery in that group. It must be remembered that none of these studies addressed the issue of emergency or immediate carotid endarterectomy for TIAs, acute stroke, progressing stroke, or crescendo TIAs. Nor has there ever been a study that evaluated those problems in a randomized, controlled fashion. Endarterectomy or even anticoagulants in those circumstances have no scientifically proven value, and the risk of complications from surgery is substantial. The correct management for asymptomatic carotid bruit remains uncertain despite the publication of the three studies. The study that has entered the largest number of patients has not yet reported its results. A brief critique of these studies by Barnett and Haines points out the discrepancies among them and the reasons for doubting conclusions based on reported data. Before the initiation of these prospective studies, other studies had concluded that there were no proven indications for endarterectomy in these patients and that the natural history was better than the results of surgery, including its complications. At the present time, even though the existing data suggest that the stroke rate is higher in patients with severe asymptomatic stenosis, there are no proven indications for carotid endarterectomy in any patient with asymptomatic stenosis. The prior studies demonstrated that asymptomatic carotid bruits are associated with a high incidence of coronary artery disease. By extrapolation one would reason that these patients should be treated with aspirin or ticlopidine and that they should all have careful cardiological investigations and management. In the meantime, it can only be hoped that the present ongoing study will provide definitive answers as to which of these lesions should be treated surgically or medically and the influence on outcome of the degree of stenosis and other clinical features.

The need-to-treat syndrome is a major factor in determining how physicians react to disease in general and specifically cerebral vascular disease. The sordid early history of carotid endarterectomy for TIAs, partial or complete carotid artery occlusion, or asymptomatic carotid bruits is a case in point, as is the continued use of heparin in progressing stroke, anticoagulation for the prevention of thrombotic stroke, or the administration of steroids in acute stroke. It appears that appropriate data are finally emerging in regard to carotid endarterectomy. It can only be hoped that these data will be properly used in clinical practice. As for the other therapeutic modalities mentioned, responsible physicians must be prepared to accept what is actually known from scientific data when recommending a potentially hazardous therapeutic modality, rather than rely on instinct, clinical impression, or the need to do something rather than nothing. For example, there has never been a controlled study that addresses scientifically how to treat dissections of the carotid artery, yet statements in textbooks and review articles advocate anticoagulant therapy, a treatment not without its own hazards. If we cannot be effective, we can at least be honest in how we approach such problems and hope for an eventual scientific resolution of most of them. By the same token, it is not scientifically or morally justifiable to assert that an unproven and even potentially hazardous therapeutic modality is the "standard of care" in a malpractice action.

It is, of course, disheartening to admit that we still cannot effectively treat an acute stroke. There have been improvements in the medical management of patients with acute stroke that might reduce the mortality from such complications as deep vein thrombosis or aspiration pneumonitis, but it is still not possible to prevent the progression of a cerebral ischemic process to infarction in humans. It is my position that the detailed studies of biochemical, physiological, and pathological changes that occur sequentially and predictably in cerebral ischemia induced in experimental animals have already resulted in therapeutic strategies that have been proven to be variably effective in modifying the ischemic process and protecting the brain. The various modalities used have included increasing cerebral perfusion by pharmacological means, including intra-arterial clot lysis, decreasing cerebral energy requirements, use of Ca+ ion channel blockers, antagonism of excitatory neurotransmitters, and administration of free-radical quenchers among others. Several reviews have outlined these modalities and the results of their use in animal experimentation and trials in human subjects, and there are now rigorous criteria for the ways in which trials in human subjects should be conducted in the future. The failure of these modalities in human trials until now may well be a factor of the duration of time between the onset of ischemia and initiation of treatment. Practically all clinical studies have had a hiatus of at least 4 hours, and many as long as 12 to 24 hours, from onset of the ictus to treatment. It has been known for many years that brain cell dysfunction occurs within seconds of onset of ischemia and that permanent neuronal injury occurs within 6 to 8 minutes. That is certainly true for the center of an area of ischemic tissue, and although the periphery of the ischemic zone, termed penumbra, may remain metabolically impaired but still viable for somewhat longer, its rescue will also depend on relatively early pharmacologic intervention. The window of therapeutic opportunity for effective therapeutic intervention is, therefore, quite small; our attention must now be directed toward devising means to begin treatment of stroke patients much earlier than has ever been attempted in the past. There is evidence that this can be accomplished by appropriate education of all principals involved and streamlining the systems involved in getting patients to
the hospital and through triage and evaluation.54 Numerous drug trials for treatment of acute stroke are currently being conducted or planned. These trials should aim at the earliest possible entry of patients if they are to answer the question of effectiveness. The logistic processes involved in treating stroke must be addressed as vigorously as has the development of logical, scientifically valid, pharmacologic interventions in experimental cerebral ischemia if effective treatment of stroke in humans is ever to be achieved.

In view of the current intense debate concerning health care reform and presumed excessive costs of medical care, physicians concerned with the management of patients with strokes ought also to look objectively at the cost-effectiveness of rehabilitation. Appropriate prospective controlled studies are needed to identify which patients will benefit, the timing and duration of treatment, the specific beneficial treatment modalities, and other identifiable factors.55 The current criteria for the prescriptions of rehabilitation after stroke are frequently arbitrary and sometimes influenced by the perceived desires of the patient and the patient’s family.

Clinicians who face problems for which no statistically valid solutions exist should consider sharing that fact with the patient or family before instituting unproven treatment modalities, in particular those which have significant inherent risks. Certainly no physician should be criticized for not doing what is not known to be helpful, nor should he be criticized for using an unproven therapeutic modality so long as the patient or family are aware of the risks involved.

References

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