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STROKE: PREVENTION STILL THE BEST TREATMENT

Although exciting new strategies may make it possible to minimize the damage in an acute stroke, the best treatment is still to prevent it in the first place.

The incidence of stroke has been declining in the United States for the last 30 years, probably due to improved detection and treatment of high blood pressure. The major risk factors for stroke that can be modified are hypertension, cardiac disease, and transient ischemic attacks. Approximately 80% of strokes are ischemic in nature (65% related to atherosclerosis, 15% cardioembolism), and hemorrhage accounts for 20%.

PREVENTION

Endarterectomy

Carotid endarterectomy prevents stroke 17% better than medical therapy alone in patients with symptomatic carotid stenosis > 70%. Surgery is of no benefit in patients with symptomatic stenosis of less than 30%. Whether surgery provides benefit in the middle range of 30% to 70% stenosis is the topic of ongoing research. Patients at higher risk benefit more from surgery than patients at lower risk.

Warfarin

Several recent studies have shown that warfarin reduces the risk of stroke by up to two thirds in patients with nonvalvular atrial fibrillation. Debate now centers on whether subgroups of patients with atrial fibrillation, such as those with left atrial enlargement, would benefit more from warfarin therapy, and whether aspirin is of any use in patients with atrial fibrillation. There is some evidence that aspirin lowers the risk of stroke in atrial fibrillation, but probably not as effectively as warfarin, especially in patients over age 70.

In a young patient with lone atrial fibrillation, most physicians would use aspirin and not warfarin. For most elderly patients with chronic atrial fibrillation, low-dose (international normalized ratio 2.0 to 3.0) warfarin is now recommended. There is no proof that warfarin is of any use in atherosclerosis-related stroke, but a large study is underway to find out.

Aspirin

Aspirin has supplanted warfarin as the standard medication for stroke prevention. A meta-analysis showed aspirin works best for preventing heart attack, lowering the risk of heart attack by approximately one third. It is slightly less effective for stroke prevention, reducing risk by approximately one fourth.

The best dose of aspirin for stroke prevention is still a topic of debate. Higher doses probably work better than lower doses, although the difference is not dramatic, and higher doses produce more side effects. Most neurologists start with one or two adult (325-mg) aspirin tablets per day. If a patient continues to have transient ischemic attacks while taking one aspirin, the dose can be increased to four aspirin per day for a few months and then reduced if the patient does well.

Ticlopidine

Ticlopidine is now the drug of choice for patients who continue to have strokes or transient ischemic attacks while taking aspirin. It is also indicated for patients who have had a major cerebral infarct. This new antiplatelet agent does not affect the arachidonic acid cascade; instead, it blocks the fibrinogen receptor on the platelet membrane. Because there could be a severe synergistic antiplatelet effect between aspirin and ticlopidine, they should not be given together.

In controlled trials comparing ticlopidine with aspirin, ticlopidine was 47% more effective than as-

pirin for stroke prevention in the first year of therapy. Ticlopidine also has the advantage of not aggravating peptic ulcer disease, unlike aspirin.

Ticlopidine causes one gastrointestinal problem: diarrhea. However, this often goes away if the dose is lowered or if the drug is stopped for a few days and then restarted. Ticlopidine causes serious neutropenia in 0.8% of patients, almost always within the first 3 months of therapy. Therefore, patients taking ticlopidine should have a complete blood count every 2 weeks for the first 3 months of therapy.

Ticlopidine costs approximately $1,000 a year, much more than aspirin. Some physicians advocate using ticlopidine for 1 year instead of aspirin in all patients who have had a mild stroke or transient ischemic attack, and then switching to aspirin. It may also be considered instead of aspirin in patients with combined coronary and cerebrovascular disease.

TREATING ACUTE STROKE

There is no proven treatment for acute stroke, but investigators now realize the value of early intervention. This is difficult since on the average 36 hours elapse after onset of stroke before patients come to the emergency room. In all current stroke therapy trials, patients must be treated within 6 hours, and in the ongoing National Institutes of Health (NIH) trial of tissue plasminogen activator, they must be treated within 90 minutes.

Ischemia is a graded phenomenon, and infarction depends on the duration and severity of ischemia. The brain can survive focal ischemia for 6 hours, on the average. The normal blood flow in the brain is approximately 50 mL/100g/minute. The ischemic threshold is approximately 20 mL/100g/minute, and the infarction threshold is approximately 10 mL/100g/minute.

A blocked artery produces a core of dead tissue (an infarct) in the brain. Surrounding the infarct is a "penumbra" or "shadow zone," where cells survive but do not work well. It is these cells that we want to save.

Optimizing circulation

The central strategy is to keep blood flow above 10 mL/100g/minute and preferably above 20 mL/100g/minute. Proper blood pressure management usually means *not* lowering the blood pressure, as the autoregulation curve is often "shifted to the right," and lowering the blood pressure precipitously can extend the infarct. Algorithms can help guide how to manage blood pressure in acute stroke.

Heparin therapy

No study before 1980 on the value of heparin in stroke in evolution had sufficient power, and studies since then have failed to show any benefit. I use heparin in patients who have had a minor stroke which is definitely not due to hemorrhage and which is most likely a large-vessel atherothrombotic stroke, not a lacunar stroke.

Thrombolytic therapy

The Cleveland Clinic has helped pioneer this exciting field, but many questions remain unanswered. The ongoing NIH study and other studies use intravenous tissue plasminogen activator. However, intra-arterial therapy is probably much more effective than intravenous therapy. Therefore, we have undertaken perhaps the most ambitious and aggressive trial of acute stroke therapy ever attempted. Patients in this study undergo angiography followed by injection of prourokinase directly into the thrombus. Hemorrhage, either during the procedure or several hours after the vessel is opened, is a definite risk with this therapy.

Finding the occlusion

A neurologic examination cannot locate the occlusion in an acute stroke, or even determine whether there is an occlusion. Angiographic studies may be normal in as many as 20% of patients who would otherwise seem to be candidates for thrombolysis. Nevertheless, if thrombolytic therapy is to help, the occlusion must be diagnosed and located quickly.

Currently, patients with acute stroke undergo computed tomography (CT) to rule out hemorrhage. A hyperdense middle cerebral artery on the CT scan is very specific for occlusion but is not very sensitive. In fact, most patients with middle cerebral artery occlusion do not show this sign. Magnetic resonance imaging, although costly and cumbersome, provides more information. Magnetic resonance angiography can demonstrate an occlusion with more sensitivity than CT. The gold standard is still angiography. In addition, magnetic resonance diffusion provides information about tissue perfusion and the therapeutic window at a lower cost than positron-emission tomography.

Preventing metabolic consequences of ischemia

Tissue acidosis due to accumulated lactate, a major cause of delayed neuronal injury, results when ischemia precludes aerobic metabolism of glucose. Therefore, intravenous solutions should not contain glucose, glucose levels should be monitored frequently, and hyperglycemia should be controlled aggressively.

Calcium homeostasis is disturbed during ischemia, leading to increased calcium influx, membrane degradation, release of arachidonic acid, vasoconstriction, and platelet aggregation. Free radicals are also released, producing additional membrane damage. Therapeutic interventions at this level would include antagonists of the excitatory neurotransmitters, calcium-channel antagonists, membrane-stabilizing agents, free-radical scavengers, prostacyclin, platelet antiaggregants, and vasodilators that selectively affect the arterioles.

Cerebral edema due to cellular swelling and fluid extravasation across a disrupted blood-brain barrier further impedes cerebral blood flow and clearance of lactate. This is an ominous sign, best treated in an intensive care unit with intracranial pressure monitoring and osmotic dehydration.

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SUGGESTED READING

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HEALTH EFFECTS OF MAN-MADE MINERAL FIBERS

Man-made vitreous fibers, used everywhere in modern society as insulation, filters, and reinforcers for plastic, have only recently been subjected to studies in animals and man to determine their safety. Fortunately, their health risk appears to be low and can be minimized by controlling airborne exposure through ventilation (the recommended exposure limit is one fiber per cm^3) and proper work practices (eg, use of respiratory protection).

What is the pathogenic potential of these fibers? What are the short-term and long-term occupational risks associated with their manufacture? What are the clinical signs of exposure? The following brief update for clinicians addresses the key concerns about these widely used materials.

FIBER TOXICOLOGY

Man-made vitreous fibers can be divided into three general groups: glass fiber, mineral wool, and ceramic fiber. They have played an increasingly important role in recent years as asbestos substitutes.

Three main factors determine the pathogenic potential of a fiber: the dose delivered to the target organ, the dimensions of the fiber, and its durability in biologic systems. The chemical composition and surface properties of the fiber may also contribute to its disease-producing potential. Dose is related to airborne exposure to respirable fibers, measured in fibers per cm^3. Some fibers clear the mucociliary mechanism, while others are translocated to respiratory or terminal bronchioles, the interstitium, and the lymphatic system.

According to the Stanton hypothesis, long, thin fibers (≤ 0.25 μm in diameter and > 8 μm in length) are more carcinogenic than shorter, thicker fibers. Asbestos fibers tend to fracture lengthwise, making them more dangerous than man-made vitreous fibers, which fracture crosswise. The probability of disease increases the longer a biologically active fiber remains unaltered. Fibers fracture and dissolve in biologic systems; in vitro testing with Gamble's solution reveals that, among man-made fibers, refractory ceramic fiber is the most durable, followed by mineral wool and glass fiber.

HEALTH EFFECTS

Concerns about the possible health effects of man-made vitreous fibers are based on previous experience with asbestos, a well-established cause of mesothelioma, lung cancer, and both interstitial and pleural fibrosis.

Animal studies

Except for refractory ceramic fiber, most man-made mineral fibers have not caused cancer in animal studies. However, mesotheliomas can be induced