Medical Staff Conference

Controversies in the Medical Management of Stroke

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chair of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *One of the neglected areas in internal medicine is that of cerebrovascular accidents. A patient with a stroke is often considered to be on the frontier between medicine and neurology, with neither discipline directing the attention to this group of patients that the seriousness of the illness warrants. For this Medical Staff Conference, Dr Michael E. Charness from the Department of Neurology will discuss this topic for us.*

DR CHARNESS:† I would like to examine some currently controversial areas in the medical management of patients with stroke, with an emphasis on the still-confusing issue of anticoagulation.[1] I will focus on the role and timing of anticoagulation in cases of cardiac embolic stroke, stroke in evolution, transient ischemic attacks (TIAs) and completed stroke. I will not deal extensively with the overall medical and surgical management of cases of TIA, which have been reviewed recently.[2]

Cardiac-Cerebral Embolism

Cardiac-cerebral embolism is increasingly recognized as an important cause of stroke. Thirty years ago, emboli arising from the heart were felt to account for just 3% of all strokes; in current series, with better diagnosis of predisposing cardiac conditions, this estimate has risen to around 20%.[3] For the purpose of this discussion, the term "embolic stroke" will refer to strokes caused by nonseptic emboli arising from the heart but not from the carotid artery.

The diagnosis of cardiac-cerebral embolism is largely clinical. In most patients a sudden neurologic deficit develops that is maximal at onset. Transient ischemic attacks precede few of these strokes.[4] The carotid circulation of the brain, which receives the highest percentage of cerebral blood flow, is affected in most cases; hence, in most patients a mixed sensorimotor deficit will develop, accompanied at times by aphasia and homonymous hemianopia. Seizures accompany between 10% and 15% of cases of embolic stroke and less than 3% of cases of nonembolic ischemic cerebral infarction. Clinical or radiologic evidence of infarction in several cerebrovascular territories and computed tomographic (CT) evidence of hemorrhagic infarction, while uncommon, are highly indicative of embolic stroke or vasculitis.

The "smoking gun" that most implicates the heart in cerebral infarction is, of course, the presence of an appropriate predisposing cardiac lesion. In Table 1 are summarized many of the presently recognized cardiac lesions associated with embolic stroke.[3] Arrhythmias, including atrial fibrillation of both ischemic and rheumatic causes, are especially important. Embolization after myocardial infarction generally occurs within six weeks and is more likely with large infarcts, transseptal infarcts, ventricular aneurysms or accompanying congestive heart failure.[3,4] Mitral valve prolapse has been identified in 40% of stroke patients younger than age 45; however, stroke in this age group is itself relatively uncommon.[5]

Anticoagulation is of unquestionable benefit in a variety of disorders associated with embolization from the heart or veins. However, the prompt use of anticoagulation for cardiac-cerebral embolism has been restrained by certain clinical concerns. That is, 44 years ago, Fisher and Adams found microscopic petechial hemorrhage dotting the region of cerebral infarction in numerous autopsy specimens from cases of embolic stroke.[4] There has therefore been legitimate concern that prompt anticoagulation could harm patients who have cardiac-cerebral embolism by converting an ischemic infarct into a hemorrhagic infarct. Four considerations dominate this area of controversy: (1) the risk of recurrent embolization after an initial embolic stroke, (2) the timing of recurrence, (3) the efficacy of anticoagulation in preventing both short-term and long-term recurrences and (4) the risks of anticoagulation. The information governing these issues is less complete than one would hope. Nevertheless, I will

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ABBREVIATIONS USED IN TEXT
CT = computed tomography
TIA = transient ischemic attack

briefly synthesize the available data, with suggestions for patient management.

Risk and Timing of Recurrent Cerebral Embolism

Older studies, based largely on patients with rheumatic heart disease, indicate that among patients with an initial cerebral embolism, about 40% will have a recurrent event within ten years, most of these within six months.[4] Darling and co-workers found an equal risk of recurrence among patients who had rheumatic heart disease or nonrheumatic atrial fibrillation and following myocardial infarction.[6] In several recent studies, cerebral embolism recurred within just one to two weeks of an initial cardiac embolic event in between 10% and 20% of patients.[7-10] Hence, patients with cardiac-cerebral embolism of various causes have a significant (10% to 20%) risk of recurrent embolism within a short (7 to 14 days) period of time.

Efficacy of Anticoagulation in Preventing Recurrent Embolism

The efficacy of anticoagulation in preventing cerebral embolism must also be discerned mostly from older, suboptimal clinical studies. Anticoagulation with sodium warfarin appears to reduce the long-term risk of recurrent embolization by as much as 80% to 90%.[3,11] This benefit has been best shown for patients with rheumatic heart disease, but appears likely for patients with nonrheumatic atrial fibrillation and in patients after a myocardial infarction.

The effect of prompt anticoagulation on early recurrent cerebral embolism has been the subject of a number of recent nonprospective investigations. For cases of cardiac-cerebral embolism of various causes, anticoagulation within 48 hours reduced the incidence of reembolization during the subsequent two weeks from 13% to less than 5%.[7-10] A randomized prospective study found similar results, though the number of patients and events was small.[10]

Anticoagulation, therefore, appears to be effective in preventing late recurrent embolism due to cardiac disease and, when begun promptly, may also reduce the early risk of recurrent embolic stroke.

Risk of Anticoagulation in Patients With Cardiac-Cerebral Embolism

The next area of controversy concerns the risk of anticoagulation in patients with cardiac-cerebral embolism. Whether or not effective in reducing the risk of early recurrent embolism, prompt anticoagulation could be justified only if the benefits outweighed the risks. Of special concern is the potential for immediate anticoagulation to cause clinically significant intracerebral hemorrhage.

Although microscopic hemorrhage is frequently identified in postmortem specimens from cases of embolic stroke, CT evidence of macroscopic hemorrhage during life is actually quite rare. Hart and colleagues, in a retrospective study, found CT evidence of hemorrhagic infarction in just 4/147 (3%) patients with embolic stroke.[12] Koller and associates reported similar results.[7]

Furlan and co-workers prospectively examined the brain CT scan of 54 consecutive patients with cardiac-cerebral embolism, including 35 patients who had a second CT scan after adequate anticoagulation was achieved.[8] They found CT evidence of hemorrhage in just one (2%) patient. Although heparin therapy was continued in this patient, there was no subsequent deterioration either clinically or radiographically. Reembolization occurred in 5/25 (20%) patients in whom anticoagulation was delayed by more than 24 hours and in 0/23 patients who were anticoagulated within 24 hours.

The possible benefit and the safety of prompt anticoagulation were recently evaluated in a prospective cooperative study.[10] Anticoagulation was carried out safely in 24 patients with embolic stroke; in fact, hemorrhagic transformation of lesions occurred in only two patients, neither of whom had been anticoagulated. The risk of hemorrhagic infarction appeared to be related to the size of the initial embolic infarction. Early recurrent embolic stroke occurred only among nonanticoagulated patients. This study, which showed a trend toward reduction of early recurrent embolic stroke by heparin, was unfortunately terminated before statistical significance could be determined.

The overall safety of continuous intravenous heparin therapy was examined in 510 patients with strokes of different causes.[13] The risk of central nervous system hemorrhage was only 0.8%. In all, five deaths were associated with hemorrhagic complications of therapy. Heparin therapy had to be discontinued in 3.1% due to overt systemic hemorrhage,

TABLE 1.—*Cardiac Lesions Producing Cerebral Embolic Events* *

Cardiac Condition	*Nature of Embolus*
Myocardial infarction	Mural thrombi
Postinfarction aneurysms and akinetic segments	Stasis thrombi
Postinfarction atrial fibrillation	Atrial thrombi
Mitral stenosis with or without fibrillation	Atrial or auricular thrombi
Atrial fibrillation of any cause	Atrial thrombi
Mitral regurgitation with atrial mural 'jet lesions'	Small mural thrombi
Bacterial endocarditis	Valvular mycotic thrombi
Nonbacterial thrombotic endocarditis	Valvular thrombi
Prolapsing mitral valve	Valvular thrombi, atrial thrombi
Mitral annulus calcification	(?) Degenerate valve fragments
Calcific aortic stenosis	(?) Degenerate valve fragments
Atrial myxoma	Neoplastic fragments, (?) attached thrombi
Prosthetic heart valve	Attached thrombi

*From Barnett et al.[3]

1.8% due to occult hemorrhage and 1.4% due to heparin-associated thrombocytopenia. The major risk for systemic hemorrhage was age 60 years or older. Intracerebral hemorrhage complicated heparin therapy in 2 of 152 patients with a known cardiac source for embolization. While infrequent overall, intracerebral hemorrhage occurred more often in patients with large cerebral infarcts.

Not all investigators advocate prompt anticoagulation. In a retrospective study, Shields and associates found anticoagulant-related cerebral hemorrhage in five patients; four had been anticoagulated within 36 hours of the embolic event, two had been anticoagulated excessively and all had large initial cerebral infarcts.[14] They reviewed an additional nine similar cases culled from the literature and proposed a three- to four-day waiting period before anticoagulating patients with embolic infarction.

Summary of Risks and Benefits of Prompt Anticoagulation in Embolic Stroke

Recurrent cerebral embolism will occur within two weeks in 10% to 20% of patients with embolic stroke. The risk of reembolization appears to be similar in patients with rheumatic heart disease, myocardial infarction and nonrheumatic atrial fibrillation. Prompt anticoagulation with heparin may reduce the rate of early recurrent stroke from at least 13% to less than 5%. Hemorrhagic transformation of embolic infarcts occurs infrequently during heparin anticoagulation, develops spontaneously in some untreated patients and is not always clinically significant. The risks of systemic and central nervous system complications due to prompt heparin therapy appear to be outweighed by the possible benefits of therapy.

Management of Patients With Embolic Stroke

All patients admitted with cerebral infarction should have a CT brain scan to rule out hemorrhagic or mass lesions.[15] The possibility of embolic stroke should be considered if an appropriate underlying cardiac lesion is suggested from history, examination and electrocardiogram. If a lumbar puncture was part of the diagnostic evaluation, administration of heparin should be delayed two to four hours to avoid a small risk of spinal epidural hematoma[15]; otherwise, continuous intravenous heparin therapy should be started immediately. Long-term warfarin therapy will be required in patients whose underlying cardiac conditions pose a continued threat to recurrent embolization. The recommendation to anticoagulate promptly should be tempered in patients with very large infarcts, severe neurologic deficits, uncontrolled hypertension, CT evidence of hemorrhagic infarction or systemic lesions predisposing to hemorrhage. I would not recommend anticoagulating patients with the clinical appearance of embolic stroke in whom no underlying cardiac lesion can be found.

These recommendations are based on personal experience and assessment of the literature. As always, insufficient data foster controversy and differing opinions are abundant; nevertheless, early anticoagulation is being endorsed by an increasing number of neurologists.[3,4,7,8,10,12,16]

Stroke in Evolution

Stroke in evolution is a progressive clinical deterioration that shortly follows new symptoms of cerebral ischemia. The initial deficits may worsen or new deficits appropriate to the initially involved vascular distribution may appear. Progressive symptoms due to carotid thrombosis usually evolve within 24 hours—less than 4% of these patients will accumulate new deficits after 48 hours.[17] When basilar thrombosis underlies an evolving stroke, symptoms develop over a longer period of time—from 72 hours to as long as a week. Careful observation of patients with new cerebral infarcts should reflect these time courses.

The syndrome of stroke in evolution may, of course, be produced by lesions other than progressive vascular thrombosis. In one study, 42% of patients with stroke in evolution had nonischemic lesions, including hemorrhagic infarction, hemorrhage, tumor, subdural hematoma, aneurysm and arteriovenous malformation.[15] Lacunar infarction may also present in a stepwise, progressive fashion. These various causes must be excluded before starting anticoagulation; with the exception of subarachnoid hemorrhage, CT brain scan is more sensitive than lumbar puncture in their detection.[15]

The recommendation to anticoagulate patients who have evolving stroke derives from a small number of suboptimal studies. In some, stroke in evolution is not clearly defined or includes the progressive lethargy and worsening deficits that accompany postinfarction cerebral edema. Nevertheless, the data available suggest that anticoagulation may prevent progression of cerebral infarction; in the best designed study, progression was observed in 26/67 untreated and 9/61 treated patients.[18] These data are not so overwhelming that anticoagulation should be vigorously pursued in high-risk or questionable cases. For example, I would not anticoagulate a patient with progressive stroke if brain CT scan were not available. Lumbar puncture is too insensitive to exclude most hemorrhagic lesions, and, in this instance, the risks of anticoagulation might outweigh any possible benefits.

Anticoagulation in Cases of Transient Ischemic Attacks and Completed Stroke

In patients who have transient ischemic attacks, anticoagulation may possibly decrease the incidence of further attacks; however, anticoagulation does not appear to reduce the subsequent incidence of stroke.[19] Patients with vertebrobasilar TIAs may benefit from a brief course of anticoagulation, but after a year of therapy, the risks of hemorrhagic complications exceed the potential benefits.[20]

Before diagnostic angiography, anticoagulation is cur-

TABLE 2.—*Treatment of Cerebral Infarction*

Limit infarct size
Increase blood flow to ischemic zones
Decrease neuronal metabolism
Prevent new infarction
Anticoagulation
Antiplatelet agents
Surgery
Risk factor management
Prevent and treat complications
Phlebothrombosis in the hemiplegic leg
Pneumonia
Fluid and electrolyte disorders
Ischemic ulcers and contracture
Peripheral nerve pressure palsies
Late epilepsy
Depression

TABLE 3.—*Limiting Infarct Size*

Increase blood flow to ischemic zones
Vasodilators
Papaverine hydrochloride
Prostacyclin
Hypercapnia
Hypocapnia
Steal from normal to ischemic zones
Permit or induce hypertension
Streptokinase
Naloxone hydrochloride
Hyperbaric oxygen
Phlebotomy
Reduction of brain edema
Decrease neuronal metabolism
Barbiturate coma

rently used in the initial management of patients with frequent and recent TIAs. This practice is not based on clinical data, and aspirin may be a viable alternative when a preocclusive vascular lesion is not suggested clinically. There are theoretical reasons for preferring aspirin over heparin in these patients. First, heparin can increase platelet aggregation, an undesirable effect in patients with carotid artery TIA.[1] Second, some carotid artery TIA may be precipitated by plaque hemorrhage—a condition that heparin could conceivably aggravate.[21] Clinical studies are clearly needed to address these theoretical concerns.

Anticoagulation is of no proven benefit in patients with completed strokes of noncardiac cause.[11]

Management of Cases of Completed Stroke

There are three major goals in treating patients with completed stroke: limiting infarct size, preventing new infarction and preventing and treating complications. These are summarized in Table 2.

Limiting Infarct Size

A lesion resulting from cerebral infarction comprises two pools of neurons: dead cells, which are truly a lost cause, and ischemic cells, which may recover, remain ischemic and dysfunctional or go on to die. There are two general strategies for preserving and resuscitating this ischemic pool: to increase nutrient supply and to decrease metabolic demand (Table 3).[22]

Nutrient supply could be increased by augmenting blood flow to the ischemic region. This logical notion has two possible drawbacks. First, reperfusing a region of cerebral infarction can result in cerebral hemorrhage, as was discovered in the early attempts to revascularize occluded carotid arteries.[19] Second, ischemic zones may lose the brain's normal capacity for autoregulation of cerebral blood flow; hence, general cerebral vasodilators may steal blood from the passive ischemic regions while increasing perfusion of normal regions.[19,22,23]

The use of papaverine hydrochloride and hypercapnia as vasodilators has produced conflicting results in studies that are generally too small to allow definite conclusions.[19,22,23] Prostacyclin has been administered intravenously to small numbers of patients in open trials with encouraging results.[24] Inducing hypertension has transiently benefited a few patients, but is not generally recommended. Maintaining an adequate systemic blood pressure, however, would appear to be vital for the passive, pressure-dependent ischemic brain regions. In this regard, some degree of hypertension should be allowed in patients with chronic hypertension who would normally require a higher systemic blood pressure to maintain adequate cerebral perfusion.[25] Thrombolytic therapy using streptokinase and urokinase was not efficacious in several double-blind trials conducted in the 1960s.[11] Intracerebral hemorrhage developed in a number of treated patients, perhaps as a consequence of reperfusing ischemic or infarcted tissue. Administration of hyperbaric oxygen can increase function in ischemic regions but risks decreasing cerebral blood flow diffusely by reflex cerebral vasoconstriction.[19,22]

Considerable controversy surrounds the use of naloxone hydrochloride in patients with stroke. In a report from this institution, intravenous administration of naloxone transiently reversed the neurologic deficits of three patients with rather complicated neurosurgically related ischemic events.[26] In contrast, naloxone produced no improvement in a mixed group of 19 stroke patients at San Francisco General Hospital Medical Center.[27] It remains to be determined whether higher doses of this or other opiate antagonists will be beneficial for any subgroup of stroke patients.[28]

A hematocrit in excess of 45% is a risk factor for stroke.[3,29] Cerebral blood flow declines over a range of rising normal hematocrits and can increase in individual patients following phlebotomy. Phlebotomy may, therefore, be beneficial for those stroke patients with hematocrits in the mid to high 40s,[3,29] though this practice remains to be validated by controlled clinical trials.

Few measures are available to reduce neuronal metabolism. Hypothermia might be effective but has worsened ischemic infarction in animals, possibly by increasing blood viscosity.[22] Barbiturate coma can decrease neuronal metabolism and has been beneficial in several stroke models when induced before the ischemic lesion.[30] The results of small trials in cases of human ischemic infarction have been disappointing. Barbiturate coma prevents monitoring of the neurologic state and has adverse cardiovascular effects. Further studies will have to show benefits that outweigh these potential disadvantages.

Preventing New Strokes

Stroke is a significant risk factor for the development of further strokes.[2,3] One gram of aspirin per day significantly

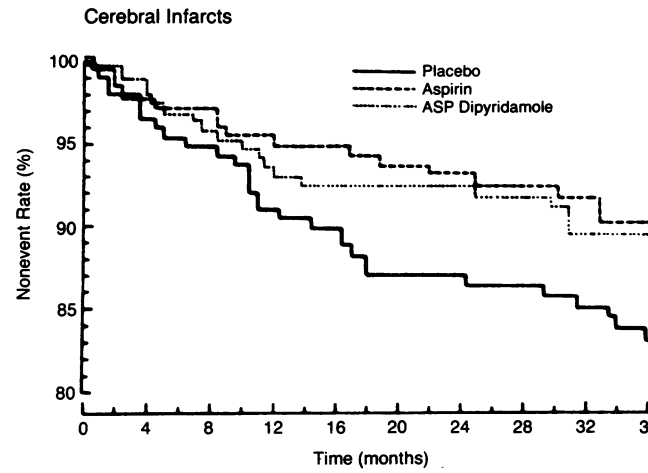

Figure 1.—AICLA (Accidents, Ischemiques Cerebraux Lies à l'Atherosclerose) study results: Distribution of fatal and nonfatal cerebral infarction (from Bousser et al[31]).

reduced the risk of subsequent stroke in both men and women with a recent stroke or TIA (Figure 1).[31] The benefits of lower aspirin dosages remain undetermined.[3] As mentioned earlier, anticoagulation can decrease recurrent embolic stroke. Risk factor management should never be overlooked in a stroke patient[3]; in particular, systolic hypertension should be treated, though, as already emphasized, this is most safely done after the acute phase of a stroke.

Preventing and Treating Complications

Cerebral edema arises within hours of cerebral infarction, peaks at between two and four days and resolves within two weeks.[22,32] An initial cytotoxic component occurs when ischemic and infarcted cells lose the capacity to maintain their functional and structural integrity. A vasogenic component arises subsequently. Cerebral edema can progress to brain herniation and death and, in milder forms, can extend the area of infarction by impairing cerebral microvascular flow.[19,22]

The treatment of ischemic cerebral edema is unsatisfactory. Steroids would not be expected to affect cytotoxic edema. Several prospective, double-blind studies have failed to show any benefit of steroids in stroke, and, in some instances, complications were higher in the steroid-treated patients.[32] Osmotic agents have also been disappointing. Mannitol is either ineffective or only briefly useful and may cause rebound intracranial hypertension following its withdrawal. Glycerol is metabolized by brain cells and may improve cerebral metabolism; however, clinical studies of its use in cases of ischemic cerebral edema have provided only equivocal evidence of benefit.[19,23,32]

Thrombophlebitis is an often-neglected stroke complication. Between 33% and 59% of stroke patients may have deep venous thrombosis that in most cases affects the hemiplegic leg.[19] Prophylactic minidose heparin therapy can reduce this high incidence fivefold without hemorrhagic complications[33,34]; clinical trials are warranted to see if aspirin can do as well.

Pneumonia is a common stroke complication that may be prevented by meticulous airway care and prophylactic intubation when a neurologic deficit compromises airway protection. For example, I would electively insert an endotracheal tube in a patient with a brain-stem stroke in whom cranial nerve dysfunction leads to pooling of secretions in the hypopharyngeal region.

Epilepsy arises in 6% to 15% of all stroke patients.[19,23] Seizures occurring within the first two weeks have a low likelihood of becoming recurrent; hence, long-term treatment with anticonvulsants is often unnecessary.[19,35] Seizures arising after the first two weeks, however, tend to be recurrent and should be treated over the long term with anticonvulsants.

Limb contractures and ischemic ulcers can be avoided by assiduous nursing care and physical therapy. Preventable peripheral nerve injuries occur when partially paralyzed limbs are left hanging or in contact with sharp or rigid objects—wheelchairs are notorious offenders here.

Finally, depression complicates the recovery from stroke in as many as 50% of patients. Although this depression is, in part, an appropriate response to a sudden loss of function, it is likely that cerebral ischemia also directly alters the level of important neurotransmitters. The early use of antidepressant medications may be beneficial for patients with severe depression.

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