Anticoagulation: Is There Still a Role in Atherothrombotic Stroke?

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The title suggests that anticoagulation may no longer have a role in the treatment of atherothrombotic cerebrovascular disease. While evidence from recent studies has not shown a distinct benefit of anticoagulation following acute stroke, the designs of these studies may not have distinguished important differences in stroke types adequately. Before judging anticoagulation, we will review the pathogenesis of atherothrombotic stroke and consider the historical role of anticoagulation in its treatment by analyzing early and recent treatment trials. Although questions remain about timing and duration of treatment, the effectiveness of anticoagulation in preventing recurrent cardiac source cerebral embolism has generally been accepted and therefore will not be discussed.1

The use of anticoagulants in atherothrombotic cerebrovascular disease is based on their ability to interfere with thrombus formation. Thrombosis superimposed on vessels narrowed by atherosclerotic plaque is a critical feature of the atherosclerotic process. Inhibition of thrombosis allows continued blood flow in the primary vessels causing ischemia, as well as in vessels arising from the parent trunk threatened by obstruction from advancing clot. This may provide time for the formation of important collateral blood channels to ameliorate the ischemic process.

Anticoagulants

Heparin

The anticoagulant activity of heparin is by inhibition of coagulation factors interfering with fibrin formation and thrombus propagation. Administered intravenously, heparin has an almost immediate anticoagulant effect which operates through the cofactor antithrombin III. Antithrombin III, on binding heparin, undergoes structural changes that neutralize coagulation factors XIIa, Xla, XAa, IIa, and kallikrein. Heparin also has a slight direct fibrinolytic action.

Hemorrhage is the most common and serious complication of heparin treatment. The risk of central nervous system hemorrhage varies, but in most studies it has been between 1 and 7%.2-6 Several randomized controlled trials have shown that an excessively prolonged activated partial thromboplastin time (aPTT) and other coexisting factors, such as hypertension, large infarct size, and advanced age, contribute to bleeding complications.7 However, others have not found that bleeding correlates with the aPTT.2-7 Severe thrombocytopenia (platelets less than 100,000/mm3), mediated by heparin-induced antibodies, may contribute to bleeding and occurs in up to 15% of patients.

Warfarin

Warfarin inhibits the coagulation cascade by interfering with the hepatic synthesis of vitamin K-dependent factors X, IX, VII, and II. Warfarin limits formation of the amino acid gamma-carboxyglutamate, which is necessary for the normal synthesis of these factors. The kinetics of the warfarin anticoagulant effect depend on the half-lives of the inhibited clotting factors which range from 6 to 60 hours and account for the 1–3 day delay between peak plasma concentration and maximal effect.

Hemorrhage is the main complication of warfarin. The prothrombin time (PT) is usually maintained at 1.2–1.5 times control to achieve effective anticoagulation and minimize bleeding complications.

Pathogenesis of Cerebral Ischemia

The effectiveness of therapy depends to a significant extent on the underlying vascular mechanisms, which are diverse. Important factors to consider include the size (large vs. small arteries) and location (extracranial, intracranial, deep penetrators) of affected vessels, as well as the extent of the atherosclerotic process (occlusion, stenosis, or patent with smooth or irregular plaque characteristics). Along with these anatomic and vascular factors, the type of clinical presentation (transient, evolving, or permanent) may also be important but does not necessarily predict the underlying vascular condition or extent of brain injury.

Cerebral ischemia related to atheromatous disease involves atherosclerotic narrowing or occlusion of large extracranial and intracranial vessels. The pathophysiology of cerebral ischemia related to large artery atherothrombotic disease involves 1) hemody
namic changes (low-flow state), 2) distal propagation of thrombus, and 3) local (arterial-to-arterial) embolism. The hemodynamic mechanism requires a significant reduction in lumen size or actual occlusion from atherosclerotic plaque and blocks the collateral circulation usually corresponds to the suprasylvian region of the hemisphere. The second mechanism, distal propagation of thrombus, also involves a severe obstructive process with accumulation of thrombus due to slow blood flow. The thrombus may enlarge and extend distally into the circle of Willis and block the collateral pathways from the opposite carotid or vertebrobasilar systems. Local embolism, the third mechanism, occurs when thrombus dislodges from an atherosclerotic plaque and blocks the distal circula-

tion. These three mechanisms, operating singly or together, are the major consequences of the atherothrombotic process, producing transient symptoms and permanent neurologic signs.

The pathology of small penetrating arterial disease caused by chronic hypertension differs from large vessel atherothrombosis. An occlusive process, lipohyalinosis or microatheroma, obstructs the lumen or origin of these arterioles supplying deep brain structures. While both atherosclerotic large artery disease and small vessel microatheroma are obstructive to blood flow and may present with similar clinical features, they differ in the size and location of resulting infarcts, availability of collateral circulation, and the propensity for large artery disease to lead to distal thrombus propagation and local embolism. These differences may affect response to therapy.

Most therapeutic trials have grouped patients by the temporal features of cerebral ischemia, such as transient ischemic attacks (TIA), stroke-in-evolution, and acute but partial stroke, even though these features may not reflect the underlying vascular mechanism. In assessing the efficacy of anticoagulation, a precise diagnosis should be established by identifying subgroups of patients according to the underlying vascular and brain pathology. Such shortcomings in the design of anticoagulation trials may have obscured potential benefits. In this review we will assess early and recent studies on anticoagulation in cerebrovascular disease before offering an opinion concerning the role of anticoagulation in the treatment of atherothrombotic stroke.

Early Studies (1940–1980)

Enthusiasm for the use of anticoagulation in atherothrombotic cerebrovascular disease was generated by several favorable clinical observations which prompted formal studies to assess the effects of anticoagulants on specific cerebrovascular conditions.

Almost 50 years ago, Hedenius reported “favorable” results in five of 18 patients treated with heparin for cerebral thrombosis. From 1953 to 1956, several investigators reported a decrease in the number of TIAs in patients with the clinical diagnosis of basilar artery thrombosis treated with heparin. Fisher treated 58 patients with anticoagulants who had TIA and signs of cerebral thrombosis. The TIA ceased (except for an occasional attack) in 28 of 29 treated patients, and symptoms recurred in 12 of 20 patients on stopping anticoagulation. Eleven of 14 patients with stroke-in-evolution had satisfactory results. Among 37 patients who were not treated, 17 had a stroke, and four had recurrent TIA. Fisher concluded that “the data suggest that anticoagulant therapy abolishes transient ischemic attacks and prevents or postpones the arrival of the threatening stroke.”

The Veterans Administration Cooperative Study reported that one of 22 patients randomized to treatment with oral anticoagulants had a stroke compared with nine of the controls. Four fatal and six major hemorrhages occurred in the treated group. Siekert et al reported recurrent TIA in four of 115 treated patients. In a later study they found that seven of 175 (4%) patients treated with anticoagulation had new cerebral infarction compared with 51 of 160 (32%) controls. Baker et al, in a randomized study of anticoagulant therapy, reported new cerebral ischemic events in 12 of 30 (40%) treated patients and 18 of 30 (60%) controls. All patients were males, only 10 had angiography, and no major hemorrhagic complications occurred.

The National Cooperative Study reported 443 randomized patients divided into five diagnostic categories. Five of 24 treated patients had recurrence in a 4-month follow-up compared with 23 events in 20 controls. Of 61 patients treated for thrombosis-in-evolution, nine had progression of infarction compared with 26 of 67 patients in the control group. Finally, of 72 treated patients with completed stroke, 12 showed progressive infaracts compared with only five of 16 in the control group. Twelve fatal hemorrhages occurred in the treated group. The authors concluded that “from the standpoint of mortality, long-term anticoagulation therapy plays no beneficial role in the treatment of thrombotic cerebral vascular disease and may be harmful.” However, they believed that short-term (4–6 months) anticoagulation might be worth while in the subcategories of TIA and thrombosis-in-evolution.

Friedman et al reported that of 22 treated patients none had cerebral infarcts compared with seven of 22 patients in the control group.

During this early period several studies of anticoagulation in stroke showed no benefit. Rose found no improvement in three patients with hemiplegia who were anticoagulated with heparin and/or dicumarol. Fisher reported a decrease in the number of TIA in 17 patients treated with anticoagulants compared with 15 controls. However, two of the controls accounted for most of the 500 TIA. Pearce et al studied 37 patients with TIA (17 received high-dose oral anticoagulants and 20 controls received a low, ineffective dose) and
found no differences between the two groups. Toole et al. found that six of 21 (29%) patients receiving anticoagulation had a cerebral infarction compared with seven of 56 (13%) controls.

Recent Studies (1980s)

Several advantages distinguish the current decade of studies from the past: a larger number of patients with multiple variable analyses, emphasis on acute stroke, comparison of heparin to aspirin, and better angiographic documentation.

Putnam and Adams, in an uncontrolled study, treated 74 patients who had recent TIA (carotid or vertebralbasilar) with short-term heparin and found that TIA continued in 12 patients (16.2%) and cerebral infarction occurred in five patients (6.8%). The infarcts occurred primarily among 23 patients found to have 80% or greater stenosis or occlusion of the internal carotid artery among a group of 61 patients having angiograms. Systemic bleeding complications (not CNS) were noted in nine patients (12.2%).

Duke et al. in a double-blind, randomized, placebo control trial studied 225 patients with acute, partial, stable thrombotic stroke. They found no significant difference between treatment and control groups in degree of neurologic changes, incidence of stroke progression, and functional activity level at follow-up. Angiography was not performed, and small vessel disease was not excluded. No significant bleeding complications were reported.

Haley et al. studied 36 patients treated with heparin for progressive ischemic infarctions involving several stroke mechanisms, including lacunes; 18 patients (50%) had continued neurologic worsening despite anticoagulation.

Biller et al. conducted a randomized pilot study comparing the efficacy of heparin anticoagulation to aspirin in the prevention of cerebral infarction in 55 patients with recent TIA (carotid 43, vertebralbasilar 12). No statistical difference between the treatment groups was found for recurrent TIA, but patients with vertebralbasilar TIA had a higher risk of infarction than those with carotid TIA regardless of treatment. Forty-five patients had angiography, approximately equally distributed between the two treatment groups, but the details of the angiographic lesions and their effects on outcome were not clearly delineated. There were no hemorrhagic complications.

Ramirez-Lassepas et al. studied 136 patients treated with heparin for acute ischemic infarction related to several stroke mechanisms including lacunes and cardiac source embolism. No angiograms were performed. A good to excellent recovery in 81% of patients led the authors to conclude that "intravenous heparin may be beneficial in reducing the incidence of fluctuation and late deterioration in patients with acute ischemic stroke." In six patients heparin was discontinued because of bleeding complications including two with intracerebral hemorrhage.

Critique of Studies

Brust critically reviewed anticoagulation reports up to 1977, highlighting the diversity of 27 studies and their complexity of interpretation. Many of the same problems have recurred in the present decade of studies. The standard problems have been lack of randomized control designs, small numbers of patients entered, variable clinical definitions for TIA, no information on past TIA and stroke, inclusion of cerebral embolism patients, undefined exclusion criteria or elimination of patients because of surgical treatment such as carotid endarterectomy, and lack of information concerning bleeding complications. Additional deficiencies include unblinded trials, overrepresentation of male patients, and overlapping of the combined effects from heparin and warfarin which could have led to misinterpretation of drug efficacy.

Perhaps the most critical shortcoming of these trials has been the failure to delineate subgroups of stroke patients based on the underlying vascular mechanisms of cerebral ischemia. The characterization of patient groups by clinical features, such as TIA, stroke-in-evolution, and acute partial infarction, fails to distinguish between different vascular pathologies. It is unreasonable to presume that anticoagulation benefits all of these different vascular mechanisms, and lumping patients together may obscure potential benefits. While it is difficult to distinguish between major stroke mechanisms on clinical grounds alone, this is no excuse for continued failure to document underlying vascular mechanisms.

Because of these shortcomings in study design, we agree with Caplan that the value of anticoagulation in atherothrombotic stroke remains an unsettled issue awaiting further clarification. Disregarding these shortcomings and proposing that heparin carries significant risks and offers no benefits, others have argued against its continued use.

Current Therapeutic Strategy

Despite the absence of proven benefit and considering the inherent shortcomings of prior treatment trials, we believe that there is still a theoretic and empiric role for anticoagulation in atherothrombotic cerebrovascular disease. It is important that properly designed trials be undertaken to provide more answers. Until then, based on the pathogenesis of atherothrombotic cerebral ischemia, we use anticoagulation in a few very specific circumstances once the mechanism of the underlying vascular disease has been established by cerebral angiography or noninvasive techniques.

We use anticoagulation in the setting of an acute occlusion of a large extracranial or intracranial artery, such as the internal carotid or vertebral artery, provided the patient has sustained only a mild-moderate neurologic deficit and not a major debilitating stroke. In individual case reports and pathologic studies, acute occlusion of the extracra-
nial internal carotid or distal vertebral artery can represent an unstable condition in which local embolism or distal propagation of thrombus may place the patient at further risk for infarction. Until the thrombus organizes and becomes adherent to the vessel wall, we use heparin initially and then warfarin for a few weeks to two months after the acute event. Long-term anticoagulation is usually not necessary once the acute situation has stabilized.

Our second indication for use of anticoagulation involves patients with TIA or mild-moderate neurologic deficits with proven stenosis of a major intracranial artery such as the middle cerebral artery, the basilar artery, or, if surgery is not being considered, the extracranial internal carotid artery. Heparin is used initially, especially if patients are unstable, followed by long-term warfarin anticoagulation, keeping the prothrombin time no more than 1.5 times the control value. The arterial stenosis may be followed serially with duplex scans and transcranial Doppler sonography without subjecting the patient to the risk of cerebral angiography. If the vessel occludes and the patient remains stable, then warfarin may be discontinued.

From our own practice we analyzed the course of patients treated with warfarin anticoagulation for symptomatic atherothrombotic disease, excluding patients with cardiac source embolism. Twenty-five patients with angiographically documented large artery disease of the carotid and vertebrobasilar circulations have been followed on warfarin for 5 months to 8 years, 22 of these patients for 1 year or more and 18 for 2 years or more. The vascular lesions included bilateral vertebral artery disease in seven patients (five stenoses, two occlusions), basilar artery stenosis in five patients, middle cerebral artery stenosis in four patients (two also involved the distal internal carotid artery), carotid siphon stenosis in three patients, diffuse atheroma of the vertebrobasilar and carotid systems in three patients, and one patient each with isolated stenosis of the anterior cerebral artery, posterior cerebral artery, and posterior inferior cerebellar artery.

All patients presented with symptoms or signs appropriate to their large artery disease: 14 patients had only TIA, five had TIA followed by a mild-moderate stroke, and six had stroke alone. Acutely ill or unstable patients were usually given heparin followed by warfarin for the long term, but some stable patients with only TIA were started immediately on warfarin without the use of heparin.

During follow-up at least two thirds of the patients remained neurologically stable. Seventeen patients had no further ischemic events (transient or permanent) while eight had some recurrence of symptoms. In four this involved single, minor spells. The remaining four patients had continuation of their original ischemic events, and one of them had progressive brain stem infarction leading to death from presumed basilar artery occlusion while on heparin. There were no differences in outcome in patients with carotid or vertebrobasilar disease. The only important bleeding complication was a colonic wall hematoma in one patient who recovered fully on conservative therapy.

These uncontrolled observations do not provide proof of anticoagulation efficacy. Rather, they suggest it is safe and that further study in patients with known vascular lesions may provide the necessary data for accurately assessing anticoagulation treatment in atherothrombotic stroke.

References


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