Review article

Anticoagulant therapy for ischemic stroke: A review of literature

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For many years, anticoagulants have been used in the emergent treatment of patients with acute ischemic stroke. Anticoagulants are prescribed in an effort to prevent first or recurrent stroke, especially among patients with cardioembolism due to arterial fibrillation and large-artery atherosclerotic disease. Despite the widespread use, efficacy and safety of anticoagulants are controversial. Experts have given a broad spectrum of opinions. Surveys of practitioners have also demonstrated a lack of consensus on the use of anticoagulants for ischemic stroke. The uncertainty is due, in large part, to the lack of definitive clinical data. A review by the panel of the Stroke Council of the American Heart Association found no strong evidence for effectiveness of anticoagulants in treating acute ischemic stroke. Several clinical trials have suggested that utility of emergent anticoagulation has no significant effect in improving clinical outcomes for patients with acute ischemic stroke. In the present review, we have attempted to provide a framework for the emergent use of anticoagulants in acute ischemic stroke patients.

Key words: Ischemic Stroke, Anticoagulants, Significant effect

INTRODUCTION

Stroke is the leading cause of disability and the third leading cause of death in the United States with an estimated annual total cost of 57.9 billion dollars.[1] Each year, 5 million people die as a consequence of stroke, and at least 1 in 6 patients who survive a stroke will suffer another stroke within 5 years. There are about 600,000 new strokes each year in the European Union (EUSI 2003) and over 700,000 new strokes each year in the USA (AHA 2006). Two-thirds of all strokes occur in developing countries and over 80% of all stroke-related deaths occur in developing countries.[2] Although data on the epidemiology of stroke, its pattern and risk factors from Iran is scarce, the available data suggests relatively low incidence of stroke. This may reflect a similarity toward neighboring countries and a contrast with Western countries.[3]

Physicians have used anticoagulants to treat patients with acute ischemic stroke for 50 years. These medications continue to be prescribed commonly. Despite their widespread use, the usefulness of emergency anticoagulation is a subject of debate.[4] Disagreements exist about the best agent to administer, the route of administration, the use of a bolus dose to start treatment, the level of anticoagulation required, and the duration of treatment. Heparin and low molecular weight (LMW) heparin have been evaluated for the treatment of acute ischemic stroke. However, clinical trials have not adequately evaluated adjusted-dose intravenous anticoagulation in patients with selected stroke subtypes, and only one trial has evaluated the role of very early anticoagulation after stroke onset.[5] Beside uncertainty regarding efficacy, a safety concern that urgent anticoagulation may lead to symptomatic intracranial hemorrhage exists as well. Physicians have been uncertain about the severity of neurological impairments or the initial CT findings that would contraindicate the early use of heparin. Anticoagulants often are prescribed to patients with recent stroke in an effort to prevent early recurrent stroke and to improve neurological outcomes. The Cerebral Embolism Study Group estimated that the risk of early recurrent embolism was 12% among untreated patients with embolic stroke.[6,7] A Norwegian trial testing urgent anticoagulation among patients with recent stroke and atrial fibrillation found the risk of recurrent stroke to be 8% in 1 week.[8] Other trials testing anticoagulants in stroke have found the rates of early recurrent stroke to be much lower (in the range of 0.3%/d to 0.5%/d).[9-11] These relatively low rates mean that detection of a therapeutic effect in prevention of early recurrent stroke by anticoagulation will be difficult.

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There is substantial variability in the acute management of stroke within and between countries. Stroke clinicians are interested in studying variations in management, because this may help them choose better treatments that could improve outcomes.[12]

Pathophysiology of Ischemic Stroke

Approximately 45% of ischemic strokes are caused by small or large artery thrombus, 20% are embolic in origin, and others have an unknown cause.[13] Thrombosis is the basic process in atherothrombotic ischemic stroke, and it can form in the extracranial and intracranial arteries when the intima is roughened and plaque forms along the injured vessel. The endothelial injury initiates platelet adhesion and aggregation, which is responsible for thrombus formation at the site of plaque. During an embolic stroke, a clot travels from a distant source and lodges in cerebral vessels. Microemboli can break away from sclerosed plaque in the artery or from cardiac sources such as atrial fibrillation, patent foramen ovale, or a hypokinetic left ventricle.[13] Emboli in the form of blood, fat, or air can occur during surgical procedures, most commonly during cardiac surgery, but also after long bone surgeries.[14] Less common causes of ischemic stroke include carotid dissection and the presence of coagulopathies.[15] Other causes include arteritis, infection, and drug abuse, such as the use of cocaine.[13,16] As a thrombosis or emboli cause a decrease in blood supply to the brain tissue, events occur at the cellular level, referred to as the ischemic cascade.[17] Understanding the ischemic cascade has led to the concept of therapeutic time window for treatment possibilities.[18]

Anticoagulants Therapy for Stroke Subtypes

As noted above, clinical trials have not adequately evaluated adjusted intravenous anticoagulation in patients with selected stroke subtypes. Therefore, there are conflicting data regarding the benefit of intravenous unfractionated heparin or LMW heparin in the subgroup of patients with large vessel atherosclerotic disease. The TOAST trial evaluated the efficacy of the LMW heparinoid danaparoid administered as an intravenous bolus within 24 h of symptom onset and continued for seven days in 1281 patients with acute ischemic stroke.[9] Compared to placebo, danaparoid was associated with no improvement in overall outcome at three months (75% and 74%). However, subgroup analysis suggested a higher rate of favorable outcomes in patients treated with danaparoid who had a large artery atherosclerotic stroke (68% vs. 55% with placebo). A subsequent analysis of this study suggested that acute performance of carotid duplex imaging to identify patients with carotid occlusion or severe stenosis may improve selection of patients who could benefit from use of this agent.[19]

The FISS-tris trial evaluated the LMW heparin nadroparin (3800 anti-factor Xa international units, 0.4 ml subcutaneously twice daily) versus aspirin (160 mg once daily) started within 48 h of acute ischemic stroke onset and continued for 10 days.[20] The main study population was 353 patients with confirmed large artery occlusive disease, consisting of 300 with intracranial, 11 with extracranial, and 42 with both intracranial and extracranial disease. The mean time to treatment was about 30 h. There was no significant difference between treatment with nadroparin or aspirin for the proportion of patients with good outcome at six months (73% vs. 69% absolute risk reduction 4%; 95% CI -5 to 13).

In a trial of unfractionated heparin in hyperacute stroke, a single center randomly assigned 418 patients with nonlacunar hemispheric infarction (with cardioembolic, atherothrombotic, or unknown/ undetermined etiology) to receive either intravenous heparin or saline within 3 h of stroke onset for five days.[21] The primary endpoint (a favorable outcome at 90 days) was observed significantly more frequent in patients in heparin group as compared with those in saline group (38.9% vs. 28.6%, respectively, $P = 0.025$). Heparin use was associated with an increased risk of intracranial and extracranial hemorrhage, with no significant increase in mortality. Other studies of heparin therapy in acute stroke did not consider the etiology of stroke and yielded mixed results.[21-23]

Atrial Fibrillation and Cardioembolic Stroke

A subject of intense debate is the role of immediate anticoagulation with heparin in stroke patients with atrial fibrillation (AF). It appears that early treatment with heparin in patients with AF who have an acute stroke may result in unfavorable clinical outcomes, although a careful assessment of risk for thromboembolism and serious bleeding in individual patients is essential. Further evidence comes from a 2007 meta-analysis that examined seven trials involving 4624 patients and compared heparin with LMW heparins started within 48 h of acute cardioembolic stroke with other treatments (aspirin or placebo).[24] The following observations were reported: 1) Anticoagulants were associated with a statistically insignificant reduction in recurrent ischemic stroke within 7 to 14 days (3.0% vs.

4.9%, OR: 0.68, 95% CI: 0.44-1.06). 2) Anticoagulants were associated with a statistically significant increase in symptomatic intracranial hemorrhage (2.5% vs. 0.7%, OR: 2.89, 95% CI: 1.19-7.01). 3. Anticoagulants and other treatments had a similar rate of death or disability at 3 to 6 months of follow up. Thus, the published results do not support early anticoagulant treatment of acute cardioembolic stroke.[24] However, the use of warfarin is strongly recommended for patients with left ventricular dysfunction and atrial fibrillation as it has been shown that atrial fibrillation is associated with relatively high incidence of cardioembolic events including stroke.[25] Warfarin can reduce the risk of stroke in patients with atrial fibrillation. On the other hand, the use of warfarin in patients with left ventricular dysfunction and sinus rhythm is still a matter of debate. The comparison between warfarin and aspirin in the patients with reduced cardiac ejection fraction (WARCEF) is currently underway.[26]

Progressing Stroke

Heparin is often prescribed for patients who continue to have neurologic deterioration in the first hours or days after stroke (i.e., "progressing stroke", also referred to as "stroke in evolution"). Studies performed in the 1950s and 1960s suggested that IV heparin therapy may be beneficial for patients with unstable ischemic stroke with as much as a 50% reduction in the likelihood of further worsening.[27,28] These studies, however, were either not randomized or blinded, had poorly defined inclusion and exclusion criteria, or did not use standardized assessments for outcomes. Other nonrandomized studies of consecutive patients with unstable stroke who received IV heparin have shown high rates (27% to 50%) of further progression despite treatment.[29,30] The TOAST trial did not find an improvement in outcomes with danaparoid treatment in such patients, nor did a nonrandomized study of heparin therapy.[9] These findings do not support a role for heparin in halting neurologic worsening after stroke. So the 8th edition of American College of Chest Physicians (ACCP) Evidence Based Clinical Practice Guidelines for Antithrombotic and Thrombolytic Therapy for Ischemic Stroke recommend against full dose anticoagulation for these patients.[31]

Cervical Artery Dissection

Cervical dissection is an important cause of stroke in the young. In a systematic review and meta-analysis, the effectiveness of different treatment approaches such as antithrombotic medications, thrombolysis and stenting in management of cervical arteries dissection were assessed with sufficient data for comparison of antiplatelet versus anticoagulation therapy.[32] In this assessment, no randomized trials were identified, but 34 non-randomized studies including 762 patients were evaluated. There was no significant difference in risk of death [antiplatelet 5/268 (1.8%), anticoagulation 9/494 (1.8%), P = 0.88)]; stroke [(antiplatelet 5/268 (1.9%), anticoagulant 10/494 (2.0%), P = 0.66)], or stroke and death between antiplatelet and anticoagulatant therapy. There are no data to support the therapeutic superiority of anticoagulants over antiplatelet agents on treatment of cervical artery dissection.

Venous Thrombus

Dural sinus and/or cerebral veins thrombosis (CVT) is an uncommon form of stroke, usually affecting young individuals.[33,34] Anticoagulation therapy in CVT is used for prevention of thrombus growth, to facilitate recanalization, and to prevent DVT or PE. Controversy has ensued because cerebral infarction with hemorrhagic transformation or ICH is commonly present at the time of diagnosis of CVT, and it may also complicate treatment.[35] Despite using anticoagulation in treatment of patients with CVT there are controversies due to complications such as hemorrhage conversion after ischemic stroke or ICH that may further complicate the treatment plan.[35] Data from a meta-analysis that examined two trials revealed a statistically insignificant relative risk of death or dependency with anticoagulation (RR: 0.46, 95% CI: 0.16-1.31), with a risk difference in favor of anticoagulation of 13% (95% CI: 30%-3%). The RR for death was 0.33 (95% CI: 0.08-1.21).[36-38] Another randomized trial included 57 women with puerperal CVT confirmed by CT imaging. Treatment was with subcutaneous heparin 5000 IU every 6 h, dose-adjusted to an activated partial thromboplastin time 1.5 times baseline for at least 30 days after delivery. Outcome assessment was not blinded. Three patients in the control group either died or had residual paresis compared with none in the heparin group.[39] Other studies have suggested low rates of cerebral hemorrhage after anticoagulation for CVT.[36,40] The largest observational study was the ISCVT, which included 624 patients at 89 centers in 21 countries. Nearly all patients were treated with anticoagulation initially, and mortality was 8.3% over 16 months; 79% had complete recovery (modified Rankin scale [mRS] score of 0 to 1), 10.4% had mild to moderate disability (mRS score 2 to 3), and 2.2% remained severely disabled (mRS score 4 to 5).[41] Data from other observational studies suggest a range of risks for ICH after anticoagulation for CVT from zero to 5.4%.[36,42-44]

Although there is limited data from randomized controlled clinical trials, these findings, in combination with observational data on outcomes and bleeding complications of anticoagulation, support a role for anticoagulation in treatment of CVT, regardless of the presence of pretreatment ICH, and anticoagulation appears safe and effective in CVT. Also, if anticoagulation is given, there are no data supporting differences in outcome with the use of UFH in adjusted doses or LMWH in CVT patients.

Heparin, LMW Heparin, and Warfarin

There are scant clinical data directly comparing unfractionated heparin with low molecular weight (LMW) heparin for ischemic stroke treatment. One randomized, open-label study of acute ischemic stroke patients found no significant difference between treatment with intravenous heparin as compared with subcutaneous enoxaparin twice daily.[45] Systemic and cerebral embolic events, bleeding complications, and outcome at three months were similar in both groups. Another trial found that subcutaneous enoxaparin was as safe and effective as unfractionated heparin for prevention of venous thrombosis in acute ischemic stroke patients.[46]

The largest randomized controlled trial, which was performed in England and studied two doses of subcutaneous heparin in undefined stroke patients, showed no significant benefit with heparin.[10] LMW heparins have several potential advantages over unfractionated heparin including ease of administration, more rapid achievement of therapeutic effect, decreased requirements for blood testing (LMW heparins do not require PTT monitoring in patients who are not pregnant), and lower rates of thrombocytopenia. One disadvantage is that LMW heparins are more expensive, although this may be outweighed by reduced administration and monitoring costs.

A systematic review published in 2008 examined the effect of anticoagulant therapy versus control in the early treatment of patients with acute ischemic stroke.[47] This review included 24 trials involving 23,748 subjects. The quality of the trials varied considerably. The anticoagulants tested were standard unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors. The following were the major findings: 1) Based upon 11 trials (22,776 patients), anticoagulant therapy did not reduce the odds of death from all causes (odds ratio 1.05, 95% CI 0.98-1.12). 2) Based upon eight trials (22,125 patients), anticoagulants did not reduce the odds of being dead or dependent at the end of follow-up (odds ratio 0.99, 95% CI 0.93-1.04). 3) Although full anticoagulant therapy was associated with about nine fewer recurrent ischemic strokes per 1000 patients treated, it was also associated with a nine per 1000 increase in symptomatic intracranial hemorrhages. Similarly, anticoagulants avoided about four pulmonary emboli per 1000, but this benefit was offset by an extra nine major extracranial hemorrhages per 1000. 4) Sensitivity analyses did not identify a particular type of anticoagulant regimen or patient characteristic associated with net benefit.

A 2002 systematic review assessed the effectiveness of anticoagulants compared with antiplatelet agents in acute ischemic stroke.[48] The reviewers concluded that anticoagulants offer no net advantages over antiplatelet agents and they recommended that antiplatelet agents be the antithrombotic agents of first choice. However, this conclusion was driven in part by the lack of randomized trials comparing anticoagulation with antiplatelet therapy in the high-risk settings where we believe anticoagulation should be considered.

Contraindications

Anticoagulant therapy for acute stroke may only be considered after a brain imaging study has excluded hemorrhage and estimated the size of the infarct. Early anticoagulation should be avoided when potential contraindications to anticoagulation are present, such as a large infarction (based upon clinical syndrome or brain imaging findings), uncontrolled hypertension, or other bleeding conditions. Although there is no standard definition, many stroke experts consider large infarcts to be those that involve more than one-third of the middle cerebral artery territory or more than one-half of the posterior cerebral artery territory based on neuroimaging with CT or MRI.[49] Infarct size can also be clinically defined, but this process can result in underestimation of the true infarct volume when the so-called silent areas of the association cortex are involved. Clinical estimation of infarct size should be considered in conjunction with the National Institutes of Health Stroke Scale (NIHSS) score. One study found that an NIHSS score greater than 15 was associated with a median infarct volume of 55.8 cm^3 and worse outcome than NIHSS scores of 1 to 7 (median volume of 7.9 cm^3) or 8 to 15 (median volume of 31.4 cm^3).[50] Thus, patients with an NIHSS score >15 generally have a large infarct. However, it should be recognized that,

in the early hours of an acute stroke, part of the clinical deficit may be attributed to the penumbra, where the brain is ischemic but not infarcted.

CONCLUSION

Guidelines issued in 2007 by the American Heart Association/American Stroke Association state that urgent anticoagulation is not recommended for the treatment of patients with acute ischemic stroke. Similarly, guidelines from the American College of Chest Physicians (ACCP) 8th edition issued in 2008 recommend against full-dose anticoagulation for patients with acute ischemic stroke. While many specialists believe it has no role at all in the early acute phase of ischemic stroke, the ACCP noted that some experts recommend early anticoagulation for various ischemic stroke subtypes, including cardioembolic stroke and stroke with documented intraluminal thrombus or arterial dissection. However, there is no true consensus, and there are data suggesting that recurrent stroke risk after dissection is similar whether treated with antiplatelet or anticoagulants. In agreement with the national guidelines, there is no recommendation and efficacy for using full-dose anticoagulation for treatment of patients with acute ischemic stroke because of limited efficacy and an increased risk of bleeding complications.

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