An Alternative View of Heparin Anticoagulation in Acute Focal Brain Ischemia

Stephen J. Phillips, MBBS, FRCP(C)

Despite the lack of evidence of its efficacy, heparin therapy has been recommended for selected patients with ischemic stroke syndromes. However, heparin has procoagulant effects on platelet function and a propensity to produce serious side effects. When these factors are considered, heparin loses its appeal as a therapeutic agent for patients with acute focal cerebral ischemia. (Stroke 1989;20:295-298)

Miller and Hart recently reviewed the role of heparin in the treatment of acute focal cerebral ischemia and concede that the benefits of heparin are unproven; nonetheless, they provide recommendations for its use in selected patients with acute ischemic stroke syndromes. In the absence of evidence that heparin is beneficial in this setting, justification of its use depends on evaluation of its mechanism of action and its unwanted side effects. All these factors considered, I propose that heparin loses its appeal as a therapeutic agent.

Mechanism of Action

Heparin markedly accelerates the rate of neutralization of factors XIIa, XIa, IXa, and Xa and thrombin by antithrombin III. Heparin also inhibits the activation of prothrombin by factor Xa in the absence of antithrombin III and at high concentrations catalyzes the inactivation of thrombin by heparin cofactor II. Heparin has no direct thrombolytic action; therefore, its administration cannot be assumed to lower the risk of recurrent embolism from intracardiac or intra-arterial thrombi.

These effects of heparin on fibrin formation are important in the treatment of venous thromboembolism. However, they are less relevant to a discussion of arterial thromboembolic disease since platelets, not fibrin, are the main components of arterial thrombi. Platelets play a key role in thrombogenesis, and heparin has a number of important effects on platelet function.

The addition of heparin to platelet-rich plasma anticoagulated with citrate results in a variable degree of platelet aggregation. Other in vitro studies have shown that heparin neutralizes prostacyclin's inhibitory effect on platelet aggregation, enhances platelet aggregation in response to adenosine diphosphate and epinephrine, and potentiates platelet synthesis of thromboxane A2. Clinically, acute transient thrombocytopenia and prolongation of the bleeding time have been observed following heparin infusion.

Heparin-induced thrombocytopenia can also occur several days after heparin therapy is initiated. The true frequency of this phenomenon is difficult to establish since it depends on how thrombocytopenia is defined. In a prospective study of 137 patients treated with heparin for symptomatic ischemic cerebrovascular disease, a decrease in platelet count was observed in 86% of the patients. Severe (<100,000 platelets/µl) heparin-induced thrombocytopenia probably occurs in 5-10% of patients and is thought to be immunologically mediated. However, unlike other drug-induced autoimmune thrombocytopenias that are associated with bleeding, delayed heparin-induced thrombocytopenia is associated with arterial thrombosis. This suggests that platelets become activated and are consumed, not simply removed from the circulation. In the prospective study of heparin therapy for symptomatic ischemic cerebrovascular disease by Ramirez-Lassèp, nine of 14 new ischemic events and three of six deaths occurred among patients whose platelet count decreased by ≥40%.

To help prevent thrombotic complications, it has been suggested that all patients receiving heparin have serial platelet counts. However, this approach is not only very costly but also unlikely to succeed because heparin-associated thrombosis can occur...
without thrombocytopenia. This latter observation suggests that qualitative changes in platelet function (which are not routinely assessed in hospital laboratories) are important in the genesis of heparin-associated thrombosis.

Although many questions regarding a heparin-platelet interaction remain unanswered, available evidence indicates that the effects of heparin on platelet function tend to promote arterial thrombosis. Experimental evidence suggests that rational antithrombotic therapy consists of both a platelet inhibitor and an anticoagulant. However, the combination of aspirin and heparin is associated with an increased risk of hemorrhagic complications. Low-molecular-weight heparin derivatives (heparinoids) may be less likely to induce thrombocytopenia, but data concerning their use in stroke patients are preliminary only.

Lack of Evidence of Benefit

In an attempt to prevent subsequent thromboembolic stroke, anticoagulant therapy is administered to patients who have had one or more transient ischemic attacks (TIAs). Heparin is considered rational therapy for patients who come to medical attention soon after a TIA because there is evidence that the risk of stroke is highest in the month following the first TIA. However, in a population-based study of the initial management of TIs of recent onset, patients treated with heparin fared the same (in terms of the probability of death, stroke, and either stroke or TIA during the 30 days after the initial examination) as those who did not receive heparin. As indicated by the authors, this result requires cautious interpretation because of the retrospective, nonrandomized design of the study. On the other hand, it is unusual for a nonrandomized study to show no benefit from the therapeutic agent under consideration; most bias in this type of study tends to favor the treatment. Furthermore, this study came from the Mayo Clinic, which has much experience in the use of heparin for patients with recent TIs. Keith et al. also estimated that approximately 1,200 patients would have to be randomized in a trial designed to detect, with a power of 90%, a 50% reduction in the risk of stroke during the first month after a TIA. For two reasons 1,200 patients is almost certainly an underestimate of the required sample size: first, it is probably more realistic to look for a 25-33% reduction in stroke risk, and second, to confine the study to an examination of the effects of heparin alone, the analysis would be restricted to a period of approximately 5 days, during which very few end points would occur. It is doubtful that such a trial will ever be undertaken, especially in view of the increasing competition for funding from newer, more promising therapeutic agents.

In patients who have had a cardioembolic stroke, anticoagulants are used to prevent recurrent embolism. There has been only one randomized trial of heparin therapy in patients with presumed cardioembolic stroke. Unfortunately, the trial was stopped prematurely "because of the apparent safety of immediate anticoagulation." Meaningful statistical analysis was impossible because insufficient end points occurred. Furthermore, there is evidence that immediate heparin therapy is not safe because of the risk of hemorrhage into an area of cerebral infarction. The risks and benefits of heparin for cardioembolic stroke patients have not been defined precisely enough to allow comfortable clinical decision making.

Stroke in progression is not always due to progressing thrombosis. In fact, it is not certain how often progressing thrombosis underlies neurologic deterioration in patients with an acute focal cerebral ischemic insult. Lacunar infarctions frequently develop over a period of up to 36 hours. However, heparin does not seem to be effective against lacunar stroke in progression. Anticoagulant therapy may be particularly hazardous in lacunar stroke since hypertension-associated intracerebral hemorrhage and lacunar infarction appear to be due to the same arteriopathy.

All studies that have examined the effect of anticoagulant therapy in patients with progressing stroke are flawed because of nonrandomized design, inadequate sample size, inadequate investigation into the cause of the deterioration, and/or a tendency to analyze the combined effects of heparin and warfarin. The latter approach is open to question since heparin and warfarin have different mechanisms of action. Consequently, it is unknown whether heparin therapy is beneficial to patients with progressing stroke.

A recent double-blind, placebo-controlled trial in patients with acute partial stable stroke of presumed thrombotic mechanism demonstrated no benefit from the intravenous administration of heparin to prevent progression of stroke. This trial has provided the first evidence of heparin's ineffectiveness in patients with acute focal cerebral ischemia; other studies merely failed to provide evidence of any benefit.

Complications

In their review, Miller and Hart indicate that hemorrhagic complications of heparin therapy occur in 1-4% of patients with acute brain ischemia (they do not address the problem of heparin-induced thrombocytopenia and thrombosis). A complication rate even this low would be unacceptable if, in fact, heparin is of no benefit. Complications of heparin therapy can be devastating and may not be predictable, preventable, or reversible. They include death, intracerebral hemorrhage, retroperitoneal hemorrhage, adrenal hemorrhage, carotid occlusion after endarterectomy, cerebral infarction, and myocardial infarction.
Hemorrhagic complications may or may not be associated with an excessively prolonged activated partial thromboplastin time (>2.5x normal). “Standard” doses of heparin produce much interpatient variation in the anticoagulant effect. Major fluctuations in anticoagulation intensity are common even when heparin is administered by continuous intravenous infusion. Thrombotic complications are not always associated with thrombocytopenia.

Conclusion
It is natural that physicians feel compelled to intervene when faced with a patient who has a threatened or progressing stroke. However, lack of apparent benefit, a propensity to produce serious side effects, and procoagulant effects on platelet function make heparin an unattractive choice of therapy for patients with acute focal cerebral ischemia. Furthermore, excluding heparin from clinical trials of new treatments for ischemic stroke would seem to be ethical and scientifically desirable.

References
20. Walker AM, Jick H: Predictors of bleeding during heparin therapy. JAMA 1980;244:1209-1212
Diagnosis and Management. New York, Raven Press Publishers (in press)

42. Haley EC Jr, Kassell NF, Tourner JC: Failure of heparin to prevent progression in progressing ischemic infarction. Stroke 1988;19:10-14


47. Putman SF, Adams HP: Usefulness of heparin in initial management of patients with recent transient ischemic attacks. Arch Neurol 1985;42:960—962


KEY WORDS • anticoagulants • cerebrovascular disorders • heparin
An alternative view of heparin anticoagulation in acute focal brain ischemia.

S J Phillips

*Stroke*. 1989;20:295-298
doi: 10.1161/01.STR.20.2.295

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/20/2/295

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in
*Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click Request
Permissions in the middle column of the Web page under Services. Further information about this process is
available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/