**Immediate Anticoagulation in Acute Focal Brain Ischemia Revisited**

**Gathering the Evidence**

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"Immediate" Heparin Anticoagulation in Acute Ischemic Stroke: Gathering the Evidence

Several large randomized clinical trials (RCTs) have recently evaluated the efficacy and safety of "immediate" administration of low-fixed-dose subcutaneous unfractionated heparin (UFH), medium-fixed-dose subcutaneous UFH, dalteparin, nadroparin, certoparin, tinzaparin, or danaparoid in patients with presumed acute ischemic stroke. A systematic review of 23,427 patients anticoagulated within 2 weeks from the onset of symptoms disclosed that treatment was associated with about 9 fewer recurrent ischemic strokes per 1000 patients treated, but it was also associated with a similar sized 9 per 1000 increase in symptomatic intracranial hemorrhages.1 Disclaiming theoretical biological disadvantages of UFH, the highest bleeding rate was found in patients treated with low-molecular-weight heparin (LMWH) or heparinoids. Nevertheless, some clinical guidelines recommend immediate anticoagulation for patients at higher risk of stroke recurrence, whereas delaying anticoagulation for several days is preferred for patients at low risk for early recurrence.2 Case-by-case consideration of anticoagulation is advocated by others, depending on the underlying vascular mechanism, the size and location of the affected vessel, and extent of the atherosclerotic process. Finally, the Cochrane Investigators disregard any type of anticoagulant in acute ischemic stroke.1

The evidence favoring or discouraging the administration of adjusted-dose UFH to patients with ischemic stroke is scanty.3–5 Available data on "immediate" anticoagulation is also inadequate, especially if we concur that a 2-week delay outlasts the concept of treatment immediacy in ischemic stroke. Clashing with the main conclusion of the systematic review, a few studies emphasized the relevance of dose-adjusted UFH6 and treatment expeditiousness.7 Thus, recovery was greater in patients treated within 6 hours of symptom onset, and stroke recurrence and serious bleeding were associated with abnormal coagulation test results.6,7 While the nature of these studies makes it difficult to completely overcome the effects of confounding, they represent the largest series of patients "immediately" anticoagulated with adjusted-dose UFH. In the IST, 800, 3000, and 7000 patients were randomized to treatment within 3, 6, and 12 hours, respectively, and there was no heterogeneity of effect with decreasing time to randomization. However, UFH was administered subcutaneously, and at least 24 additional hours have to be added before stable anticoagulant effects were accomplished.

The Anti-Inflammatory Properties of UFH Might Not Be Shared by Other Antithrombotics

During the past years, major advances have taken place to increase the understanding of inflammatory-mediated damage after ischemic stroke. The participation of cytokines, adhesion factors, and leukocytes occurs rapidly, because most molecules are upregulated at 1 hour after ischemia and have a peak response at 6 to 12 hours.8 Inhibition of inflammation could be a part of the beneficial effects of UFH in coronary heart disease.9 Anti-inflammatory effects include binding to Mac-1, inhibition of leukocyte rolling, blocking of selectins, or attenuation of iNOS and NO release.10,11 In murine brain ischemia, higher anticoagulant doses12 and shorter anticoagulation delays13 were the most effective. UFH showed better results than equivalent anticoagulant doses of LMWH.12 Total leukocyte count14 and plasma levels of proinflammatory cytokines15 were also lower in patients anticoagulated than in those antiaggregated, and these effects were associated with greater recovery and less risk of worsening.14,15 Recovery was also associated with a lower increase of VCAM-1 in patients treated with UFH but not with aspirin.16

A Testable Hypothesis

VCAM-1 is an adhesion factor intensely expressed by human astrocytes and endothelial cells from infarcted tissue17 that induces tissue factor (TF) expression.18 Following the release of cytokines, TF is the primary cellular initiator of the coagulation cascade in vivo and represents a hemostatic envelope diffusely expressed in human cortex and cerebral vessels.19 UFH abrogates the endotoxin-induced increase in TF-positive monocytes in vivo and increases plasma levels of TF pathway inhibitor.20 UFH decreases high TF plasma levels...
and monocyte procoagulant activity in unstable angina and perhaps in acute ischemic stroke. Whether VCAM-1 participates in this mechanism remains to be elucidated. In the coronary circulation, coagulation is initiated by exposure of blood to TF located in ruptured plaques, damaged subendothelium, and activated leukocytes. Given the rich and widespread expression of TF on the cerebral cortex and intracerebral vessels, any acute ischemic injury could initiate the coagulation cascade, regardless of the cause of stroke. Theoretically, UFH would be useful in most patients if the drug prevents the proinflammatory mechanisms previously described. Obviously, close monitoring of the agent would be mandatory to avoid dose-related complications.

In summary, the evidence gathered in LMWH trials or in trials in which UFH was given subcutaneously at low or medium doses should not be applied to adjusted-dose UFH. Recent observational studies have provided encouraging results, although with the potential effect of confounding. Therefore, a new heparin RCT is necessary that gives appropriate credit to the importance of the therapeutic window (anti-inflammatory), adjusted dose (anti thrombotic), intravenous administration (expeditiousness), and close monitoring (safety). To palliate the current non-evidenced-based situation, the Rapid Anticoagulation Prevents Ischemic Damage (RAPID) Trial was designed. In RAPID, a total of 1400 patients from several European centers will be allocated within 12 hours from clinical onset to weight-adjusted intravenous UFH or aspirin. Participants will be requested to calibrate aPTT local ratios to determine the therapeutic range in ratios equivalent to heparin levels of 0.3 to 0.5 U/mL. Control of UFH will be made by using frequent aPTT ratios. The completion of this academic study is due in 2002. Meanwhile, doctors willing to prescribe adjusted-dose UFH to their patients should not be deterred by the evidence gathered in antithrombotic trials that explored other anti-thrombotic modalities.

References

Key Words: cerebrovascular disorders  heparin  inflammation
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Stroke. 2001;32:577-578
doi: 10.1161/01.STR.32.2.577

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/32/2/577

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