Theoretical Utility of Heparins
Heparin reduces development of erythrocyte-fibrin thrombi that form in regions of vascular stasis especially within the heart, in severely stenosed arteries sometimes engrafted on white thrombi, in acute arterial occlusions as fresh tails on existing thrombi, and within extremity and pelvic veins. Unfortunately, heparin use can be associated with severe bleeding, especially if not closely monitored.

Optimal Testing of Heparin Effectiveness and Safety
Heparin should not be indiscriminately used in all brain ischemia patients. Bleeding complications will outweigh therapeutic benefit. Unfortunately, randomized trials have not adequately studied heparins in patients with conditions likely to respond to treatment. Reported trials lumped patients with brain ischemia together without diagnostic investigations defining etiology, stroke subtypes, or vascular lesions.

Worsening and new neurologic deficits can develop when thrombi form, propagate, and embolize. Stroke worsening, even when thrombi are present, occurs in only 20% to 33% of ischemic strokes. Even when anticoagulants are stopped because of hemorrhage in prosthetic heart valve patients, recurrent embolism rarely occurred during the next 10 days. Most cardioembolic recurrences do not occur during the first week after an embolus. Worsening in patients with atherothrombotic large artery occlusive disease is due to perfusion failure often unrelated to changes in occlusive thrombi. Randomized trials to effectively determine heparin utility must be (1) eclectic and include only patients in whom brain and cardiac and vascular imaging show high-risk cardiac and artery-to-artery embolic brain infarcts and in patients with documented severe extracranial or intracranial large artery occlusive disease; (2) powered to account for clinical worsening and/or new brain infarcts in less than one third of patients; and (3) closely monitored to ensure infrequent bleeding. No available trials even remotely meet these criteria. In the International Stroke Trial (IST), the largest heparin trial, vascular and cardiac imaging were not reported, some patients had no brain imaging before treatment, heparin was given subcutaneously while elsewhere heparins are usually given intravenously, and levels of anticoagulation were not always closely monitored. Heparin effectively prevented pulmonary embolism.

Available Data

Acute Ischemic Stroke
In the TOAST trial, a low-molecular-weight heparinoid was given within 24 hours of acute ischemic strokes, by continuous intravenous infusion for 7 days with dose adjustments after 24 hours according to anti–Xa factor activity. Danaparoid treatment was effective in patients diagnosed clinically as having large artery atherosclerosis in whom heparinoid reduced recurrent strokes during the 7 days of infusion, and rates of favorable and very favorable outcomes were significantly higher in patients given heparinoid compared with placebo. Danaparoid was effective in patients with large artery atherosclerosis who had severe cerebral internal carotid artery (ICA) stenosis. Heparinoid-treated patients with ICA stenosis had significantly more favorable and very favorable outcomes. A study of heparin given within 5 hours after anterior circulation strokes showed that heparin could be given safely with minimal bleeding.

Cardiogenic Embolism
Early anticoagulation of patients with atrial fibrillation–related strokes can be safe and effective. Chamorro et al treated patients with atrial fibrillation–related cardioembolic strokes with intravenous or subcutaneous heparin as soon as CT excluded brain hemorrhage. The 74 patients treated within 6 hours had better recovery than the 157 treated between 6 and 48 hours. Patients with recurrent strokes had lower mean APTT ratios than those without recurrence.

Dural Sinus and Cerebral Venous Thrombosis (CVT)
Case reports and reviews showed that patients did not worsen or develop new hemorrhages after heparin. Among 82 heparin-treated patients, there were no deaths, and 77% of patients recovered completely. Among 79 patients given anticoagulants, 94% improved and survived while only half of 157 patients not given anticoagulants survived. Meta-analysis of 2 trials showed an absolute risk reduction in mortality of 14% and a relative risk reduction of 70% in heparin-treated patients. Einhaupl et al planned a 60-patient study, but interim analysis after the first 20 was so positive for heparin that the study was terminated. Severity scores in the heparin-treated group were much improved over placebo. Among 102 patients with CVT (43 with intracerebral hemorrhages), those not treated with heparin fared worse and had higher mortality. In a double-blind, placebo-
controlled multicenter trial, CVT patients treated with low-molecular-weight heparin had better outcomes than those given placebo.\textsuperscript{15} No new symptomatic brain hemorrhages occurred.

Conclusions

(1) Heparins should not be indiscriminately given to all acute brain ischemia patients. (2) The efficacy of heparins has been inadequately tested in patients with defined stroke subtypes and occlusive vascular lesions. (3) More trials are needed testing heparins in patients whose cardio-cerebrovascular lesions are clarified by modern brain and vascular imaging. (4) Heparins effectively prevent venous thrombosis and pulmonary embolism. (5) Knowledge of thromboembolism pathophysiology and clinical experience leads to the \textit{theory} that heparins will prevent red thrombus development, propagation, and embolism. (6) Until more definitive trials are performed, I use heparins in patients with: large artery occlusions and severe stenosis; cardiogenic embolism with a high acute recurrence risk; dural sinus and cerebral venous thrombosis.

References


\textbf{Key Words:} heparin \textbullet{} ischemia \textbullet{} stroke \textbullet{} ischemic \textbullet{} thrombosis

\section*{Full Heparin Anticoagulation Should Not Be Used in Acute Ischemic Stroke}

Peter Sandercock, MA, DM, FRCP, FMedSci

Unfractionated heparin was first used in clinical practice more than 50 years ago, at a time when medicinal products did not require a license.\textsuperscript{1} Have the randomized trials performed since then reliably shown that full anticoagulation with intravenous (IV) unfractionated heparin (UFH) or IV heparinoid does more good than harm? No. If the available evidence on IV heparin in acute ischemic stroke were submitted to the FDA today, would it get a license for acute stroke? I think not.

Some experts recommend full-dose IV UFH for acute cardioembolic stroke, stroke due to carotid dissection, progressing stroke, and basilar thrombosis. What evidence is there for each of these? There have been 2 small randomized trials of full-dose IV UFH versus control (with a total of 270 patients); 1 in cardioembolic stroke and 1 in stable partial noncardioembolic ischemic stroke.\textsuperscript{2-4} The data from the trials did not provide evidence of net benefit either separately or combined in a meta-analysis.\textsuperscript{2-4} A Cochrane systematic review of the studies in carotid dissection found no randomized trials and concluded that the nonrandomized studies did not show any clear advantage of anticoagulants over aspirin.\textsuperscript{5} No randomized trials have been conducted in patients with basilar thrombosis.\textsuperscript{2} There are 2 additional small trials comparing full-dose IV unfractionated heparin with other agents: 1 compared full-dose IV UFH with aspirin (the interim results were inconclusive and the trial continues); another compared subcutaneous low-molecular-weight heparin with IV UFH and was also inconclusive, with no evidence of an effect on stroke progression.\textsuperscript{7}

The TOAST trial has been the largest study of IV anticoagulation in acute ischemic stroke to date.\textsuperscript{8} It tested a regimen of intravenous
heparinoid that was very carefully designed to achieve full anticoagulation as quickly as possible. It included 1281 patients within 24 hours of onset of ischemic stroke. It was placebo controlled, very well conducted, and yet found no evidence of net benefit overall or in cardioembolic stroke.8 The suggestion from a post-hoc subgroup analysis of benefit in patients with large-artery stroke needs to be confirmed by an additional trial.

The safety of full-dose IV heparin regimens has not been reliably established by the trials to date. The 95% CIs for the effects on the odds of death during the treatment period were wide and could not exclude the possibility of a substantial excess of deaths (for IV UFH, an 89% reduction to 271% increase, and for IV heparinoid, a 45% reduction to 211% increase in the odds of death).2 The trial data on symptomatic intracranial hemorrhages (SICH) were sparse (there were no data from the trials of UFH, and, in the TOAST trial, the CIs stretched from a 2% reduction to a 769% increase in the odds of SICH).2

I believe the available data would not be sufficient to support a product license for IV UFH in acute ischemic stroke, yet it is still widely used in this setting.9 Heparinoid administered intravenously remains unlicensed for acute stroke. I would be very interested to know how, given the lack of evidence, the clinicians who use IV heparin in acute stroke justify this unproven treatment to their patients. If one were to give a potent antithrombotic regimen like full-dose IV UFH to a stroke patient in the context of a randomized controlled trial, one would have to do many things; give the patient (and his or her family) an information leaflet detailing the risks and benefits quite clearly; ensure that the patient had understood there were definite risks and that the trial treatment was unproven; then obtain the patient’s written informed consent. I imagine that clinicians who administer intravenous UFH in their routine clinical practice rarely follow such procedures. The doctor merely writes the prescription for IV heparin and the patient receives it gratefully, ignorant of the lack of evidence of benefit and the potential risks.

The RAPID trial of IV UFH seeks to provide reliable evidence on the effects of intravenous UFH in acute ischemic stroke.10 No trials of IV heparinoid are in progress. Until the results of RAPID are available, full-dose intravenous unfractionated heparin should be regarded as an unproven, experimental treatment.11 If a clinician insists on using it in routine clinical practice, outside a clinical trial, he or she should obtain fully informed consent before starting treatment.

Heparin in Stroke: Not for Most, but the Controversy Lingers

Geoffrey A. Donnan, MD, FRACP; Stephen M. Davis, MD, FRACP

Few issues in stroke management ignite as much passion as the role of heparin. As outlined by both authors, we are now in the more fortunate position of having more evidence than ever before on its usefulness and hazards. As indicated by Sandrock, much of this evidence suggests that a small reduction in recurrent stroke is outweighed by an increased risk of cerebral hemorrhage. Further, the risk of early recurrent embolism in atrial fibrillation (one of the most common former indications for intravenous heparin) appears to be lower than was originally believed. While there have been major contributions to the evidence base by trials such as IST, TOAST, and others, there is still no large published trial of monitored intravenous, unfractionated heparin in acute ischemic stroke.

Pleasingly, the recent increase in the total evidence base has most likely reduced the somewhat indiscriminate use of intravenous heparin worldwide after onset of ischemic stroke.

References


Key Words: anticoagulants, heparin, stroke, ischemic

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To reinforce this trend, we agree with both Sandercock and Caplan that indiscriminate use of heparin should certainly be discouraged.

However, there are still important gaps in the evidence base. These include the role of anticoagulation in patients with high-grade large artery stenosis and repeated events, or minor established strokes. Similarly, there is uncertainty about the role of acute anticoagulation in patients with high-risk cardiac lesions (e.g., atrial or ventricular thrombus on echocardiography). There is also unlikely to be trial evidence in the foreseeable future for rarer stroke subtypes such as large artery dissection and cerebral vein thrombosis. For the latter, there is consensus among most clinicians that heparin should be used, although this is based on small trials and indirect evidence.

What to do in these less certain areas where evidence is lacking? Perhaps, fortunately, the art of medicine is not dead and decisions need to be made on an individual basis. Hence, we would generally agree with Caplan that heparin is reasonable to use in some circumstances and that further trial evidence is needed. One stark fact remains: in our own practice, we have become far more selective in the use of heparin, and this is a direct result of accumulated evidence to date. We look forward to more.

KEY WORDS: heparin stroke, acute stroke, ischemic
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