Full Heparin Anticoagulation Should Not Be Used in Acute Ischemic Stroke

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Unfractionated heparin was first used in clinical practice more than 50 years ago, at a time when medicinal products did not require a license. 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. The data from the trials did not provide evidence of an effect on stroke progression. 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. No randomized trials have been conducted in patients with basilar thrombosis. There are 2 additional small trials comparing full-dose UFH 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.

The TOAST trial has been the largest study of IV anticoagulation in acute ischemic stroke to date. 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. 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). 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).

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. 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. 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. 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.

References


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