Intravenous Unfractionated Heparin in Patients With Acute Ischemic Stroke: A Treatment to Be Used in the Context of Randomized Trials Only

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There is no reliable evidence from randomized controlled trials to support the routine use of intravenous unfractionated heparin in acute ischemic stroke, yet this treatment is very widely used in the United States and elsewhere. The Collaborative Embolism Study Group trial included just 45 patients within 48 hours of stroke onset, and a study by Duke et al in 1986 included 225 patients with stable ischemic stroke. Neither of these trials showed clear evidence of benefit. It seems quite extraordinary that clinicians continue to use this treatment in the absence of reliable data from randomized trial evidence: a triumph of opinion over evidence. A systematic review of the 21 completed randomized trials comparing different heparin regimes with control in acute ischemic stroke, including a total 23,427 patients, again failed to provide evidence of net benefit from unfractionated heparin, low-molecular-weight heparin, or heparinoid (the latter given either subcutaneously or intravenously). There is also good evidence that the more intensive the heparin regime, the higher the bleeding risk.

This does not look promising as an evidence base for a new randomized controlled trial! On the other hand, there are thousands of clinicians worldwide who strongly believe in the benefit of intravenous heparin regimens in acute ischemic stroke; there are many more who do not. Dr Chamorro’s proposal for the RAPID randomized trial comparing intravenous heparin with aspirin may help to settle this therapeutic debate. The proposed trial is relatively small; for such a potentially important question it would ideally be an order of magnitude larger if it is to produce really reliable results. However, it is notoriously difficult to raise funding for randomized trials of interventions with limited or no commercial potential. Furthermore, the RAPID trial will be competing with other pharmaceutical stroke trials that may offer investigators substantial rewards for including patients. Thus, clinicians who wish to participate in the RAPID trial may, on occasion, face a scientific and ethical dilemma: put the patient into RAPID (and address an important scientific question but receive little if any financial reward) or put them into a pharmaceutical trial with substantial rewards.

The trial should go ahead, and struggle against the many barriers that will be placed in its way. Of course, if the trial is unequivocally positive, then stroke physicians around the world will be delighted and intravenous heparin will become more widely used. If, on the other hand, it provides really reliable evidence that intravenous heparin is hazardous, then I hope many centers will abandon the routine use of this treatment. At present, it should be used only in the context of a randomized controlled trial. If we restricted its use to randomized controlled trials, recruitment in the trials would be completed much more quickly and we would get an answer to this vexing question, which has remained unanswered since heparin was first used in an inconclusive stroke trial over 40 years ago.

References
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