Clot Retrieval for Stroke Should Be Restricted to Clinical Trials

No

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Intra-arterial (IA) stroke thrombolysis using clot retrieval devices is currently being done routinely at most comprehensive stroke centers worldwide. In the United States, the MERCI retriever was used in 2300 ischemic stroke interventions in 2006 and total IA ischemic stroke interventions were estimated to be 3500 to 7200. Estimates of the potential annual number of IA stroke interventions in the United States alone range from 10 400 to 41 500, and comprehensive stroke centers use a clot retrieval device in approximately 65% of IA interventions. Importantly, although IA stroke intervention typically begins with mechanical clot retrieval, it frequently incorporates thrombolytic agents, antithrombotics, and platelet inhibition. As a result, there are no standard IA protocols or even standard criteria for device selection and it is routine to make interventional decisions “on the table.” This reflects the complex technical heterogeneity of acute stroke arterial recanalization and further complicates the design of any potential randomized clinical trial (RCT).

There is a long history of surgical procedures being done without any RCT data whatsoever. At least for IA stroke thrombolysis, we have one Phase III RCT demonstrating proof of principle and clinical efficacy. Of course, the irony is that Prolyse in Acute Cerebral Thromboembolism (PROACT) II used an unapproved drug (r-prourokinase) and specifically prohibited mechanical clot manipulation. The evolution of interventional neuroradiology has now introduced a new “twilight zone” of “approved” but “unproven” stroke clot retrieval devices. Both the MERCI and PENUMBRA devices were Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services approved without a RCT or definitive evidence of clinical efficacy. Although some may disagree with these FDA and Centers for Medicare and Medicaid Services decisions, this is akin to disagreeing with the Supreme Court.

The ethics of performing IA thrombolysis both outside and inside of a clinical trial have recently been extensively debated. Considering that the criteria for FDA approval were “safety and efficacy” and for Centers for Medicare and Medicaid Services reimbursement “reasonable and necessary,” the use of stroke clot retrieval devices (in the United States) is not only legal but ethical outside of a RCT. A compelling case can also be made that universal collective equipoise does not exist regarding IA thrombolysis. US Institutional Review Boards have required the inclusion of the availability of stroke clot retrieval devices in informed consents. This further complicates recruitment into RCT; the subtleties of clot retrieval versus an improved modified Rankin score at 90 days are likely to be lost on patients and families in the throes of an acute stroke.

In the United States, ethics are conflated by Centers for Medicare and Medicaid Services hospital reimbursement policies for IA stroke thrombolysis. Centers for Medicare and Medicaid Services policies and off-label use of devices have posed tremendous recruitment barriers for RCT. Another controversy relates to who should perform acute ischemic stroke interventions. Training and credentialing criteria have recently been published, which have implications for vetting in RCT. Certainly clot retrieval devices have different technical training requirements than “simple” IA thrombolysis.

The need for more data is a separate issue from whether use of clot retrieval devices or IA thrombolysis should be restricted to clinical trials. The painfully slow recruitment in (MR and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) and Interventional Management of Stroke (IMS3) indicates how difficult such RCTs are to complete. Recruitment enthusiasm may depend on the clinical trial. For example, IMS3 has no competing trials and avoids the contentious issue of a “placebo.” Ten years after PROACT II, what question do we really want to answer? Is it simply “does IA thrombolysis work” or has it evolved to “in which patients does it work”? It is not widely known that 10 years ago, the FDA approved a protocol for PROACT III with a sample size of 450; why was it not done? The issues became cost, the ethics of a “placebo” control, recruitment, and ultimately feasibility. Indeed, the task became so daunting that Abbott eventually abandoned the entire arena of stroke thrombolysis. In negotiations with Concentric over the MERCI retriever, at least one source reports the FDA admitted another RCT like PROACT II was not feasible. At a minimum, this suggests

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194
that any additional IA RCT will require international academic–industry collaboration and a novel design.

In addition to recruitment, a major challenge for any new IA RCT will be to tackle not only the technical, but also the physiological heterogeneity of acute ischemic stroke. Recent mismatch imaging-based RCT such as Desmoteplase in Acute Ischemic Stroke Trial (DIAS) 2, Diffusion and Perfusion Imaging for Understanding Stroke Evolution (DEFUSE), and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) highlight that acute ischemic stroke is even more physiologically heterogeneous than we thought.\(^\text{11,12}\) Unfortunately, from industry’s perspective, this reduces the potential market and increases the cost of the RCT. Nonetheless, in my view and the placebo issue aside, an IA RCT that does not adequately account for stroke heterogeneity (both technical and physiological) will either require a huge (and therefore not feasible) sample size or will be doomed to failure.

Should we therefore put a moratorium on stroke clot retrieval devices and IA thrombolysis and restrict use to clinical trials? Aside from the bald fact that in the United States such restricted use would not be legal (and we can debate the logistics of revising the FDA Modernization Act another time), a “yes” answer exposes the conflict between academic altruism and a certain stroke realpolitik. So my answer is “no, but . . .” “No, but” we need new data to move beyond old questions. Simply repeating PROACT II but with clot retrieval devices and relying on traditional randomization to account for stroke heterogeneity (both technical and physiological) has a low probability of successful completion. The catheter tip is out of the barn.

Disclosures

A.J.F. is Principal Investigator for PROACT II and North American Principal Investigator DIAS 2.

References


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