Recanalization Devices Should Be Restricted to Clinical Trials

Pro (kind of)

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Yes, they work (sometimes)!

However, “caveat emptor”—let the buyer beware.

Both authors have encountered astonishing success stories with interventional recanalizations using them alone or in combination intravenous (IV) and intra-arterial (IA) lytics and devices. One of the authors (W.H.) did the ward rounds on their intensive care unit last Monday (first week of August); he found 2 patients next to each other, who, over the weekend, sustained a severe stroke with a M1/carotid T-occlusion. They both came within a 3-hour time window and presented with National Institutes of Health Stroke Scale (NIHSS) scores of 18 (right hemispheric) and 21 (left hemispheric). The initial CT showed a hyperdense middle cerebral artery sign in one and a T-occlusion (CTA) in the other case. Both were treated with IA devices after bridging lysis in one. One of them was included in a prospective clinical trial (Percutaneous Recanalization in Ischemic Stroke Management (Mindframe) [PRIISM] study); the other one could not be entered into the trial and was not treated with IV recombinant tissue plasminogen activator because of recent cardiac surgery and an international normalized ratio of 2.4. Following up with the patients on intensive care unit rounds, they were both on their way to the stroke unit. The 62 year old with the left middle cerebral artery occlusion presented with a NIHSS score of 4 (he was the one in the randomized trial); the other right hemispheric patient was down to a NIHSS of 2. The CT and MRI lesions were restricted to a central infarct pattern involving the basal ganglia and the insular ribbon, but not the internal capsule or cortical areas. One of the authors (P.D.S.) vividly remembers a 45-year-old patient with a proximal right-sided middle cerebral artery occlusion and a full-blown middle cerebral artery syndrome treated in the spring of this year with the penumbra device after full-dose IV thrombolysis to which neither clot nor patient had responded 1.5 hours later when the microcatheter was in place.1

The clot was out in 5 minutes, the patient was up and walking the next day, and after standard 90 day follow-up a few weeks ago, he had a mild fine motor disturbance on the left (NIHSS score 0, modified Rankin Scale score 1). So, yes, devices work. However, both authors can also remember many patients in whom interventional therapy did not work—or—even worse—caused severe bleedings, dissections, and other major damage that had a negative impact on outcome. So, are devices ready for prime time yet?

In the recent issues of Stroke, several publications and comments have addressed this topic2–5; however, for the sake of length, we do not discuss intracranial stenting “devices” used for secondary prophylaxis in symptomatic intracranial stenoses, where also more and more critical voices are raised.6,7 Let us review the evidence behind transvascular approaches and the way they are usually applied. After all, thrombolysis started with IA treatment.8 It was the advent of recombinant thrombolytics and the interest of the industry in this market that made us move to intravenous therapies being tested in randomized clinical trials. IV thrombolysis worked: the National Institute of Neurological Disorders and Stroke study9 and the recent European Cooperative Acute Stroke Study (ECASS) 3 study10 both were clearly positive in their primary end points. Even ECASS I and II had very clear signals toward improved outcome. However, the patients included in those studies only rarely correspond to patients that we currently consider to be candidates for IA approaches, be it IA thrombolysis or device-assisted recanalization.

We do not have evidence for the 2 most important questions: is IA therapy superior to IV treatment and is the device-assisted transvascular approach superior to IA or IV thrombolysis? Furthermore, as recently demonstrated in a secondary analysis of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) data, is recanalization the issue or is it reperfusion, the former not necessarily also leading to the latter?11 We know from Prolyse in Acute Cerebral

Received and accepted October 7, 2009.

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(Stroke. 2010;41:191-193.)

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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.109.569905

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Thromboembolism (PROACT II) that IA infusion of pro-urokinase close to or into the clot of an M1 occlusion is superior to intravenous sham infusion of low-dose heparin. This difference could be due to an actual worsening in the control subjects caused by heparin. Nevertheless, PROACT II was the third ever positive clinical trial in acute stroke, which, however, was not accepted by the Food and Drug Administration authorities.

All devices that have been developed later were approved according to the rules and regulations of the device branch of the Food and Drug Administration, that is, Merci, EKOS, and, most recently, penumbra. Of importance is the fact that, unlike for the development of therapies, for the approval of devices, no clinical benefit needs to be shown. Thus, the label typically reads “can be used for reopening arteries.” Feasibility and safety have to be shown, and this does not require randomization or other controls. A recanalization device that succeeds in recanalizing a vessel indicates that the procedure is feasible. On first look, that seems easy and logical. The problem is that varying definitions of recanalization (up to 7 variants of TIMI grading) and the use of target vessel recanalization as an end point for feasibility may be irrelevant. When the clot is successfully moved or pushed from the very proximal middle cerebral artery 3 mm distally into the mid-middle cerebral artery, does this recanalization of the “target vessel” mean anything for the patient or imply true feasibility? At least it may (in part) explain why the trial with the highest recanalization rates and the comparatively lowest baseline NIHSS scores had the poorest rate of independent outcomes (modified Rankin Scale score 0 to 2).

Assessing safety is more difficult. How can we judge safety when there is no control group? If mortality and intracerebral hemorrhages were zero, that would be excellently safe and we would happily agree that the device is safe. However, that is not the case. How do the published safety data of device studies look? We see mortality rates of approximately 30%, and we see bleeding rates on the order of ≈10%. Not necessarily safe, but also not necessarily a reason for concern, because most patients in those registries have much more severe strokes than the ones we consider for IV thrombolysis. However, we do not know because there is no comparator. It may be a characteristic feature of these patients that they have a high mortality and a higher bleeding rate. The same is true for outcome; we know that the chances for good outcome (modified Rankin Scale score 0 and 1 or 0 to 2) is defined by the initial stroke severity and age. If the median baseline NIHSS score is approximately 10, 50% of the patients will experience an independent outcome without any specific treatment. If the median NIHSS score is 18, the rate may be as low as 10% to 15%. From all (uncontrolled) device trials, we cannot derive whether an observed 20% or 30% independent outcome rate is a good result because the control group is missing.

Finally, there is also something about the way clinical trials and procedures with devices are performed. Unlike IV thrombolysis with a standard operating procedure and thus a standardized treatment mode and dose, devices are used together with IA thrombolytics, GP2b/3a inhibitors, a little bit of heparin, maybe other platelet inhibitors alone, or in combination. In most instances, not one, but several, devices are used in sequence. Some of our colleagues in interventional neuroradiology report that they use on average 2 to 3 devices plus drugs before the vessel is opened, which also implies time delays. As said before, tissue reperfusion being a more relevant surrogate parameter than recanalization is not assessed at all. Also, there may be substantial time delays toward recanalization.

Currently, we sense a clear line between clinical practice in an individual patient and the recommendation of certain procedures for wider use. Although we use IA therapies in selected patients (like described previously in this article), we hesitate to recommend them for routine use. What we need is undisputed evidence for the principle that IA devices improve clinical outcome compared with standard therapy. Although we are hoping that Interventional Management of Stroke study 3 (IMS3), the future phases of the PRIISM program, or the upcoming IA thrombolysis trials with plasmin render this evidence, it may be difficult to succeed. Even if recruitment is successful, it will be difficult to define which of the multiple possible interventions is best suited for a given patient. The IMS3 investigators have difficulty recruiting patients, because interventionalists in many centers consider IA treatment state of the art and do not want to randomize patients. Moreover, financial incentives have been addressed before; altering current reimbursement strategies would be an invaluable facilitator for trial recruitment and also modified trial statistics and weighted randomization with all their backdraws may help to get our proactive interventional colleagues on board.

Here is fact instead of fiction. We do not know whether devices with or without IA drugs are superior (there are good reasons to believe that they may be), but our colleagues— exactly those whom we need to finally get us valid data—seem already convinced that they are better. They do not have different data to look at; they rather extrapolate from personal experience, which is good, but not scientifically robust. The evolving stories around carotid stenting should flash an alarm about the robustness of personal experience and uncontrolled registry data.

Before we can recommend the use IA devices for treatment of certain patient groups, we need to establish the evidence. We are not anti-innovative and we are absolute protagonists for aggressive treatments of a potentially devastating disease. Although we are convinced that devices and interventional therapies (may) have merit, we need to show for whom.

Therefore, we need the randomized controlled trials of devices against standard therapy, but we fear that we will never get them.

Disclosures

None.

References


**Key Words:** clinical trials ■ controversies ■ recanalization devices