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COMMENTARY

Reperfusion Therapy for Acute Ischemic Stroke: How Should We React to the Third Interventional Management of Stroke (IMS III) Trial?

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Much of the risk of stroke is modifiable. In the United States, stroke ranks as the fourth leading cause of death.[1] For survivors, stroke can result in neurologic impairment and functional disability. Regrettably, stroke prevention tends to be underdelivered or not delivered with optimal intensity. On a population basis, many individuals report symptoms consistent with transient ischemic attack but go undiagnosed. Undiagnosed transient ischemic attack is serious because patients are at high risk of early recurrence and benefit from intensive early treatment.[2]

Stroke care changed forever with the approval of recombinant tissue plasminogen activator (rtPA) for acute ischemic stroke shortly after publication of the results of the National Institute of Neurological Disorders and Stroke (NINDS) rtPA trial in 1995.[3] Adoption of the therapy has taken time, in large part because rtPA trials and trials of other intravenous (IV) thrombolytic therapies compellingly showed that thrombolytic agents carry risk of intracranial hemorrhage. Intravenous rtPA is the paradigmatic high-risk—high-yield therapy. The stroke care system has had to adapt accordingly.

Acute recanalization of arterial occlusions in ischemic stroke has been associated with improved clinical outcomes.[4] A limitation of rtPA therapy is the low rate of recanalization in occluded cerebral arteries. There have been attempts to improve recanalization rates by using novel thrombolytic agents such as tenecteplase (TNK). Compared with rtPA, TNK has a longer half-life (allowing bolus infusion), has greater fibrin specificity, and is more resistant to plasminogen activator inhibitor. Two randomized clinical trials of IV TNK vs IV rtPA have been performed[5,6]; however, a definitive phase 3 trial comparing TNK to rtPA is lacking. Combinations of thrombolytic and antiplatelet agents have also been tested. The CLEAR (Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke) and CLEAR-ER (Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke — Enhanced Regimen) trials demonstrated that the glycoprotein IIb/IIIa inhibitor eptifibatide may be safely combined with medium-dose IV rtPA administered within 3 hours of symptom onset.[7,8]

An alternative approach to improving recanalization rates in acute ischemic stroke is endovascular therapy with local delivery of a thrombolytic agent into the clot or mechanical thrombectomy. The first substantive test of intra-arterial thrombolytic therapy was the PROACT (Prolyse in Acute Cerebral Thromboembolism) II trial.[9] Although the trial showed significant positive results for the primary end point of modified Rankin score (mRS) of 0 to 2 at 90 days (40% vs 25%), only 180 patients were randomized, and none of the secondary end points were significantly favorable. This is in stark contrast to the NINDS rtPA trial, in which 624 patients were randomized and all secondary end points were consistently favorable at 90 days.

In 2004, the Merci catheter (Concentric Medical, Inc) was the first mechanical device approved by the US Food and Drug Administration to remove clot from cerebral arteries. At the time of approval, there was no published evidence of superiority of the device over IV rtPA with regard to recanalization or clinical outcomes. Initial use demonstrated a remarkably high 90-day fatality rate of 34%.[10] By comparison, the 90-day mortality rate for IV rtPA was 17% in the NINDS trial.[3] Subsequently, there have been technical advances in mechanical

thrombectomy. Suction-aspiration catheters such as the Penumbra system (Penumbra, Inc) and self-expanding retrievable stents were introduced as newer-generation devices for mechanical clot retrieval. The Solitaire stent retriever (Covidien) achieved significantly higher rates of recanalization than the Merci device (61% vs 24%; $P<.0001$) in a randomized trial that directly compared the 2 devices.[11] The Trevo stent retriever (Concentric Medical, Inc) also demonstrated significantly higher rates of recanalization (86% vs 60%; $P<.0001$) when compared with the Merci device.[12]

Time is brain. Randomized trials of IV thrombolysis have consistently shown that the shorter the onset to treatment time, the more likely patients will have a favorable outcome. This relationship was suggested in the National Institutes of Health rtPA pilot trials[13,14] and then demonstrated in the NINDS rtPA trial.[3] A subsequent meta-analysis confirmed the relationship between time to treatment and clinical outcome.[15] The latest time point beyond which tissue plasminogen activator is no longer beneficial is not precisely defined. Intravenous rtPA is licensed for use in the United States within 3 hours of stroke onset but did not receive Food and Drug Administration approval for use beyond 3 hours. The American Stroke Association has concluded that the efficacy of IV rtPA between 3 and 4.5 hours is not well established and recommends further study.[16]

Not every patient with a given onset-to-treatment time has the same degree of salvageable brain tissue, or penumbra. Conceptually, the penumbra is the oligemic tissue that surrounds the core of an infarct, which remains viable for a period of time due to collateral arterial flow. Both computed tomographic and magnetic resonance imaging (MRI) techniques have been developed in an attempt to measure penumbra. The MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy) trial did not demonstrate the utility of multimodal MRI in identifying a patient population that responds to reperfusion beyond the IV rtPA window.[17] Of interest, MR RESCUE did demonstrate that patients with an identifiable penumbra had smaller strokes measured by tissue volume and better clinical outcomes than patients without a penumbra regardless of treatment. It may be that the penumbra seen on MRI identifies patients with better cerebral arterial collaterals. Whatever the mechanism(s) of the penumbra, it is not clear how comparable MRI and computed tomographic perfusion imaging techniques improve treatment selection or outcomes in patients presenting with acute stroke.

Third Interventional Management of Stroke Trial

Higher recanalization rates and delays in treatment initiation associated with endovascular therapy provided the rationale for combining IV rtPA with endovascular therapy.[18] The Third Interventional Management of Stroke (IMS III) trial compared combined IV rtPA and endovascular therapy to IV rtPA alone.[19] The study was designed to randomize 900 patients in a 2:1 ratio to combination therapy or IV rtPA alone. Key eligibility criteria included age 18 to 82 years, administration of IV rtPA within 3 hours of symptom onset, and National Institutes of Health Stroke Scale (NIHSS) score higher than 10 or NIHSS score of 8 to 9 with computed tomographic angiographic evidence of proximal vascular occlusion. Endovascular treatment options included the use of intra-arterial rtPA with or without EKOS (EKOS Corporation), Merci, Penumbra, or Solitaire devices at the discretion of the operator. The study protocol allowed use of newer mechanical thrombectomy devices as they received regulatory approval.

Following randomization of 656 subjects at a planned interim analysis, the study was stopped by recommendation of the Data and Safety Monitoring Board in April 2012 after crossing a predefined futility boundary. A total of 434 patients had been randomized to combination therapy, with 334 patients receiving endovascular therapy. The majority of patients (266 of 334) treated with endovascular therapy received intra-arterial rtPA alone or in combination with mechanical thrombectomy. Stent retrievers were infrequently used, with only 12 patients treated with the Solitaire device and 2 patients with the Trevo device. Time to endovascular therapy was significantly longer (mean, 249 minutes) than had been achieved in preliminary studies.[20] No significant difference in functional independence as measured by an mRS of 0 to 2 at 90 days was seen between combination therapy and IV rtPA (40.8% vs 38.7%). No significant safety concerns were identified at the

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time of trial cessation by the Data Safety and Monitoring Board. Rates of symptomatic intracranial hemorrhage at 30 hours were similar (6.2% vs 5.9%; P=.83), but the rate of asymptomatic intracranial hemorrhage was higher in the combination therapy cohort (27.4% vs 18.9%; P=.01).

Before randomization, 47% of patients had baseline computed tomographic angiography or magnetic resonance angiography. Recanalization rates at 24 hours were significantly higher in the endovascular arm (85.7% vs 60.8%).[19] Notably, the recanalization rates for IV rtPA in IMS III were higher than historically achieved in the middle cerebral artery.[4] The strongest signal of efficacy for endovascular therapy was in terminal internal carotid artery occlusions with baseline NIHSS scores of 20 or higher and early initiation of therapy.

Implications for the Practitioner

The role of endovascular treatment of acute ischemic stroke remains undefined. In current clinical practice, endovascular treatment has been considered for symptom onset less than 4.5 hours in those ineligible for rtPA, rescue therapy for nonresponders following rtPA, and as primary therapy more than 4.5 hours from symptom onset. Recently published American Heart Association guidelines for the early management of acute ischemic stroke endorse the use of intra-arterial rtPA for major stroke syndromes with symptom onset less than 6 hours when IV rtPA cannot be administered (Class I, Level of Evidence B).[16] Mechanical thrombectomy with the Merci, Penumbra system, Solitaire, or Trevo device is endorsed in carefully selected patients to achieve recanalization (Class IIa, Level of Evidence B). We interpret the sum of the current evidence to suggest that endovascular treatments should be utilized within the setting of a clinical trial whenever possible. We recognize that ongoing reimbursement for use of mechanical thrombectomy devices poses a challenge to enrollment into clinical trials. The IMS III limits routine consideration of combined IV/intra-arterial therapy.

Primary endovascular therapy in IV rtPA–eligible patients has received consideration as a potential alternative reperfusion strategy for acute ischemic stroke. The SYNTHESIS Expansion trial randomized 362 patients to treatment with IV rtPA within 4.5 hours or less from symptom onset (n=181) or endovascular therapy (intra-arterial rtPA or mechanical thrombectomy at the operator's discretion; n=181) within 6 hours or less from symptom onset.[21] Time from stroke onset to treatment was 1 hour longer in the endovascular arm (3.75 vs 2.75 hours; P<.001). The proportion of patients achieving an mRS of 0 to 1 at 90 days did not differ between the IV rtPA group and the endovascular group (34.8% vs 30.4%; −4.4% absolute risk difference, P=.37). Primary endovascular therapy did not achieve outcomes superior to IV rtPA.

Guidelines and recently published results from clinical trials continue to support rtPA as the only established therapy for acute ischemic stroke. Intravenous rtPA should be administered to eligible patients even if they are being considered for intra-arterial therapy (Class I, Level of Evidence A).[16]

Implications for Future Research

If patients with stroke can benefit from endovascular therapy, how can they be identified? The mechanism by which an occluded cerebral artery is recanalized is likely to be much less important than the speed at which blood flow can be restored to ischemic brain. Therefore, improving time to treatment with endovascular therapy must remain a priority. Time to treatment for endovascular therapy was progressively longer in the pilot and phase 2 studies that predated IMS III (Figure). Experienced and highly motivated centers may more efficiently deliver endovascular therapy with an increase in time to treatment as more centers participate in larger phase 3 studies. In IMS III, endovascular therapy performed best in the cohort receiving IV rtPA within 120 minutes or less from symptom onset with an rtPA-to-groin puncture time of 120 minutes or less (relative risk, 1.29; 95% CI, 0.90-1.86). Best practices and benchmarks for mobilization of interventional and neuroanesthesia teams, securing angiography suites, and optimal sedation techniques should be developed. A "lead-in" paradigm in which endovascular teams demonstrate minimum time standards for resource deployment could be used to select sites for future trials.

Clinical equipoise must be maintained for unproven therapies. Bias favoring interventional approaches for stroke treatment existed before

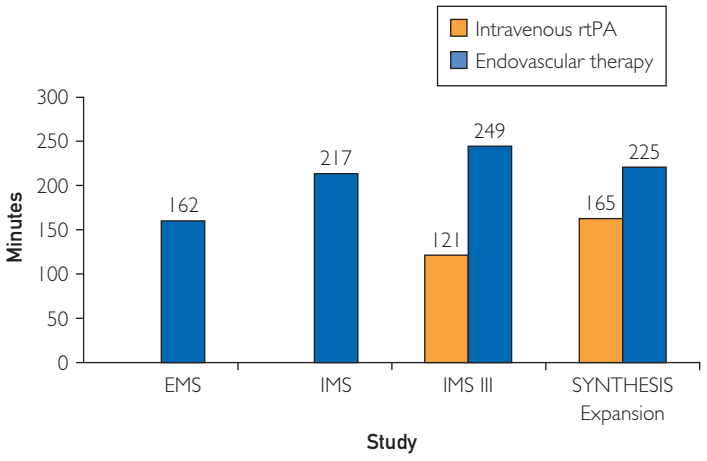

FIGURE. Time from stroke onset to treatment in 4 studies of endovascular therapy and intravenous (IV) recombinant tissue plasminogen activator (rtPA). The Emergency Management of Stroke (EMS) and Interventional Management of Stroke (IMS) trials were preliminary single-arm designs of combined IV rtPA and endovascular therapy. The Interventional Management of Stroke (IMS) III trial was a comparative study of combined IV rtPA and endovascular therapy vs IV rtPA alone. The SYNTHESIS Expansion trial was a comparative study of primary endovascular therapy vs IV rtPA. Numbers above bars indicate mean time from symptom onset to treatment.

the organization of randomized comparative trials[22] and likely still exists despite the negative results of IMS III and SYNTHESIS Expansion. In a parallel comparison, randomized trial, unbalanced randomization did not appreciably reduce power until the randomization ratio exceeded 3:1.[23] It has been argued that in some instances, unbalanced randomization can be seen as having ethical advantages over balanced randomization.[24] However, the 2:1 randomization scheme used in IMS III suggests that investigators had a biased assumption that the endovascular group would do substantially better than their IV rtPA counterparts. Future clinical trials should carefully consider the rationale for use of unbalanced randomization schemes.

In future trials, historically low recruitment rates could be offset by careful site selection and fostering international collaboration. The SWIFT PRIME (Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke) trial[25] has yet to begin recruiting but will use a multicenter, international design to compare IV rtPA with combination therapy with IV rtPA and the Solitaire device. Potential predictors of clinical outcomes such as site of occlusion, clot length, and use of general anesthesia may be used to select patients most likely to benefit from endovascular therapy.

Conclusion

Despite early trial termination and a negative result, IMS III has informed contemporary acute ischemic stroke therapy. In hopes of establishing evidence of clinical efficacy with endovascular treatment, future comparative studies will need to be performed in an environment of equipoise between endovascular and medical reperfusion strategies. Improving time to treatment with endovascular therapy and identifying responder populations should remain priorities.

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