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Trials of endovascular therapies or collaterals?

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Abstract

Several landmark clinical trials of endovascular therapy for acute ischemic stroke have recently jolted the concerted multidisciplinary efforts to develop effective revascularization strategies. Further consideration of these four endovascular stroke trials published in the last year suggests a more fundamental question: are these trials of specific treatments or have the results simply reflected the importance of underlying pathophysiology? Data from IMS III, MR RESCUE, SWIFT and TREVO2 consistently demonstrate the dramatic impact of collateral perfusion in acute ischemic stroke. Such collateral, or parallel, trials of the underlying pathophysiology in stroke reveal that diagnosis or selection of optimal candidates may be paramount to the specific drug or device therapy. Future trials of endovascular therapies may harness the influential role of collaterals as critical selection criteria for intervention, with triage based on imaging rather than time alone. Treating the optimal patient may be more important than chasing an elusive magical therapy.

Keywords

acute ischemia; collateral circulation; endovascular; hemodynamics; stroke

Several landmark clinical trials of endovascular therapy for acute ischemic stroke have recently jolted the concerted multidisciplinary efforts to develop effective revascularization strategies. After waiting up to eight-years for the completion of two simultaneous randomized controlled trials (RCTs), both studies failed to demonstrate the benefit of endovascular therapy (1,2). In the International Management of Stroke (IMS) III trial, various intra-arterial drug and device approaches yielded no advantage over standard intravenous thrombolysis (2). Similarly, the MR RESCUE trial showed no benefit of mechanical thrombectomy compared to medical management (1). These potentially pivotal results follow the recent publication of two other trials establishing the dramatic superiority of stent retriever devices over the standard device used for mechanical thrombectomy (3,4). Trial-ists have promulgated that these novel stent retriever devices have dramatically modernized therapy, outpacing the arduous six- to eight-year task of completing two RCTs. Others simply concluded that the outdated device protocols allowed too much time to lapse before treatment. Before we embark on another round of trials and invest considerable

resources to such research, one must question these explanations for such recent results. Prompt implementation of therapy has always been a priority, and future device developments will undoubtedly evolve during successor trials. Further consideration of these four endovascular stroke trials published in the last year suggests a more fundamental question: are these trials of specific treatments or have the results simply reflected the importance of underlying pathophysiology?

Data from IMS III, MR RESCUE, SWIFT and TREVO2 consistently demonstrate the dramatic impact of collateral perfusion in acute ischemic stroke. In the endovascular arm of IMS III, 331 cases were prospectively evaluated for collateral grade immediately prior to intra-arterial treatment, including 278/331 (84%) with adequate collateral views. Collaterals were associated with successful recanalization, reperfusion, and good clinical outcome [modified Rankin score (mRS) 0–2 at day 90] (5). In MR RESCUE, collateral perfusion or a penumbral pattern was predictive of good clinical outcome, irrespective of therapeutic approach (1). SWIFT was one of the earliest trials of endovascular therapy ever performed (4). Better collaterals were linked with Thrombolysis in Cerebral Infarction (TICI) 2b or 3 reperfusion ($P = 0.019$), better median National Institutes of Health Stroke Scale at day 7/dischARGE ($P < 0.001$) and better day 90 mRS ($P < 0.001$) (6). Similarly, more robust collateral grade (odds ratio 1.85, $P = 0.003$) was predictive of good clinical outcome at day 90 in the TREVO2 trial (7).

Such collateral, or parallel, trials of the underlying pathophysiology in stroke reveal that diagnosis or selection of optimal candidates may be paramount to the specific drug or device therapy. During the earliest hours, after stroke symptom onset, a wide variation in the degree or adequacy of collateral perfusion across a population may underscore the importance of time. Many individuals with poor collaterals and relatively severe neurological deficits may be helped only via rapid use of revascularization to offset evolving ischemic injury. At later stages, such individuals are no longer considered for intervention and only those individuals with relatively more robust collaterals have survived. Imaging may therefore be used to select ideal candidates with less extensive injury due to collateral compensation. This survival bias of endovascular therapy at later hours after stroke symptom onset may paradoxically ensure that these individuals with vigorous collaterals achieve better revascularization results and resultant good clinical outcomes. In sum, the impact of time varies from early to later stages in acute ischemic stroke, ranging from decisive to less influential, based on time to presentation of any individual patient. Future trials of endovascular therapies may harness the influential role of collaterals as critical selection criteria for intervention, with triage based on imaging rather than time alone. Treating the optimal patient may be more important than chasing an elusive magical therapy.

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