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Cost-Effectiveness of Mechanical Clot Removal in Acute Ischemic Stroke: Too Much, Too Young, Too Fast

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COMMENTARY

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Airbourne, Runnin' Wild, 2009

In their article "Is Mechanical Clot Removal or Disruption a Cost-Effective Treatment for Acute Stroke?" Drs Nguyen-Huynh and Johnston put forward an analysis comparing intra-arterial (IA)/mechanical therapy with the best medical therapy beyond the 3-hour time window regarding cost-effectiveness, applying a Markov model. The model came up with 84% recanalization and 6.3% symptomatic hemorrhage rates after intervention versus 24% and 2% in the best medical treatment. This translated into 7718 US dollars (US$) net cost as opposed to 0.82 quality adjusted life years (QALYs) and a net gain of 9386US$/QALY. The authors correctly qualified their results and concluded that the results were not derived from randomized controlled trials and, therefore, were sensitive to several assumptions.

First, we firmly believe that IA/mechanical treatment for selected patients is not only a valid therapeutic option but also the best option. After all, thrombolysis started with IA treatment.[1] Furthermore, we, as do others, believe that with ever-improving technology and experience in the coming years, IA therapy may be shown to be not only superior to intravenous (IV) therapy beyond, but also within, 3 or 4.5 hours, in selected patients. We fear, however, that many proactive readers of this article, including health care administrators, may not be as critical as the authors themselves were with regard to the conclusions.

Several recent publications and comments have addressed the topic of developing acute stroke therapies.[2-6] With the advent of recombinant thrombolytics and the interest of the industry in this market, IV thrombolytics were tested in randomized clinical trials, and IV thrombolysis worked. The National Institute of Neurological Disorders and Stroke study[7] and the recent European Cooperative Acute Stroke Study (ECASS) III study[8] were clearly positive in their primary end points, with very clear signals in ECASS I and II. The newest pooled analysis confirms this.[9] Currently we do not have evidence for the most important questions: 1) Is IA therapy superior to IV treatment, and 2) is the device-assisted transvascular approach superior to IA or IV thrombolysis? Furthermore, it is unclear which thrombolytic (recombinant tissue plasminogen activator, urokinase, reteplase, and so forth), which sedation technique (awake anesthesia versus analgosedation/intubation), which protocol (too numerous to write them down), or which adjuvant treatment (dose and substance of platelet inhibitors, heparin flush, glycoprotein IIb/IIIa antagonist, and so forth) should be used for IA therapy.

This problem of treatment variations has hampered thorough clinical evaluation of IA treatment during the past decade. In fact, to date, device-assisted IA treatment appears to be the most nonstandardized procedure in the treatment of acute stroke. In addition, outcome definition is as heterogeneous as the procedure itself, with varying definitions of recanalization ($\leq$7 variants of Thrombolysis in Myocardial Infarction grading),[5] the use of target-vessel recanalization as an end point, and the consistent neglect of the admittedly overused dogma of "time is brain." This confusion may, in part, explain why the trial with the highest recanalization rates and the comparatively lowest baseline National Institutes of Health Stoke Scale scores had the poorest rate of independent neurologic outcomes.[6] Concerning cost and time delays, interventional neuroradiologists frequently report that they use, on average, 2–3 devices plus drugs before the vessel is opened during $>$1 or 2 hours. With regard to patient selection, we recommend reading the recent article by Riedel et al,[10] which reports a simple selection tool regardless of the time window. Finally, how can we judge safety when there is no control group? Mortality rates around 30% and bleeding rates on the order of 10% or higher (6.3% in the authors' analysis appears to be very optimistic in the face of differing numbers in the literature) are not good but may, on the other hand, be no reason for concern, taking stroke severity of the treated patients into account. This open question cannot be solved without a concurrent control group in a randomized trial.

We know from Prolyse in Acute Cerebral Thromboembolism II (PROACT II) that IA infusion of prourokinase close to or into the clot of an M1 occlusion is superior to IV infusion of low-dose heparin. This difference could be due to an artificially poor outcome in the PROACT II control patients.[11] Nevertheless, PROACT II was the third-ever positive clinical trial in acute stroke, which, however, was not accepted by the US Food and Drug Administration (FDA) authorities. The data from PROACT II are not directly clinically applicable anyway, because prourokinase, to the best of our knowledge, is not commercially available anywhere. All IA mechanical approaches that have been developed later (ie, the Merci retriever, Concentric Medical, Mountain View, California; MicroLysUS, EKOS, Bothell, Washington; and, most recently, the Penumbra System, Penumbra, Alameda, California) were approved according to the rules and regulations of the device branch of the FDA,[2] implying that no clinical benefit needed to be shown. Thus, the label typically reads "can be used for reopening arteries." The feasibility and safety can be shown without requiring randomization or other controls. The strong beliefs of many interventionalists, industry-driven interests, and interests of hospital administrations (cost-effectiveness from a business point of view) inhibit recruitment into well-designed interventional trials such as the Interventional Management of Stroke Trial 3 (www.strokecenter.org/trials).

What we need is undisputed evidence for the principle that IA devices improve clinical outcome compared with standard therapy. Altering current reimbursement strategies would be an invaluable facilitator for trial recruitment as would modified trial statistical methods.[5] Such changes might be helpful to get our interventional colleagues on board to settle this issue once and for all, with hard data, rather than personal experience (which is good, but not scientifically robust).[2]

The established sequence of implementing a novel therapy is the following: 1) prove feasibility; 2) show preliminary safety; 3) establish safety and gather first data regarding effect size

(efficacy); 4) perform an adequately powered and well-designed study to firmly establish the safety and clearly show efficacy; 5) once efficacy is established but the evidence is somehow equivocal, establish efficacy by repeat performance in a confirmatory trial; 6) perform a meta-analyses and design registers; 7) enter guidelines; and 8) perform cost-effectiveness analyses.

The analysis by Nguyen-Huynh and Johnston is too much (regarding interpretation), too young (immature regarding the data used), and too fast (too early in the sense of the above-formulated sequence of events). This article has been drafted at a time point when we are still somewhere between points 1 and 3 of the sequence of implementing the novel therapy above. There may be political consequences that hamper the finalization of a rigorous controlled randomized trial the authors themselves are calling for. Therein, we see the danger that it will not do us any ethical service or the patient any medical service.

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