Editorial

Intracranial Stenosis – The Need for a Randomized Clinical Trial

Worldwide, intracranial stenosis represents the single most common etiology of stroke [1]. Influenced by atherosclerotic risk factors as well as race-ethnic differences, the condition may grow in prevalence in many developing nations. The study of intracranial stenosis has been propelled in recent years by heightened diagnostic surveillance, improved vascular imaging, expanding endovascular techniques and devices, and groundbreaking clinical trials.

Despite improvements in diagnosis, patients with symptomatic intracranial stenosis face staggering risks of recurrent stroke. Those in the highest risk category include patients with 70-99% stenosis and recent symptoms [2]. In this subset, the risk of stroke has been estimated to be 22.9% at 1 year, with much of the risk concentrated early after the initial event. Not only is the condition the most common case of stroke but one associated with the highest risks of recurrent stroke.

Advances in medical management have a pivotal role in stroke risk reduction. Recent randomized controlled trials and the data from the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial suggest that aggressive blood pressure lowering and lipid-lowering therapies may lower the recurrent stroke risk [3-5]. Therefore, every effort should be made to use antiplatelet medications and achieve optimal targets for blood pressure and lipid lowering.

However, the most exciting development in recent years is the possibility of endovascular revascularization. Akin to the impact of carotid endarterectomy on the risk of stroke in patients with symptomatic high-grade extracranial internal carotid artery stenosis, an interventional treatment for the treatment of symptomatic high-grade intracranial stenosis hold the promise of revolutionizing the field.

With the explosion of endovascular therapies for intracranial stenosis, much has been learned; even more needs to be understood. Based on the available registries and published data on the most commonly used and appealing device for treatment of intracranial stenosis, the Gateway Wingspan System, the 30-day rate of peri-procedural complication including stroke and death is approximated to be 6% [6-8]. While this rate is similar to that observed in the symptomatic carotid endarterectomy trials, the long-term stent-related restenosis and thrombosis risk, as high as 30% at 6-12 months, may further increase subsequent stroke risk. Indeed, the cumulative 1-year risk of stroke is estimated to be 15%, much higher than that seen following endarterectomy for symptomatic high–grade carotid artery stenosis [8, 9].

These initial data with self-expanding stents raise concerns about the durability of the stent, and whether stroke risk will actually be lower than medical management alone. In fact, symptomatic in-stent stenosis can become as challenging to manage as the original atherosclerotic stenosis. Primary angioplasty without stenting and drug eluting stents can theoretically address the problem of delayed in-stent stenosis. Unfortunately, they are limited by fact that only case series have thusfar been published and also are associated with other equally important concerns related such as duration of antiplatelet therapy.

The available data suggest that the stroke risk with maximal medical management and the procedural stroke and death risks plus long-term ipsilateral stroke risk combined following stent placement are both approximately 20% in the first year. An equipoise regarding best management is therefore clearly evident. Besides scientific uncertainty, there is also a concern that endovascular procedures, having gained Food and Drug Administration approval given its safety profile and technical success, will outstrip any chance of a proper assessment of its clinical efficacy to prevent strokes. At present, there are no data supporting the superiority of either medical treatment or intervention.

Thus, there will never be a better time to test interventional management of symptomatic intracranial stenosis. With many different endovascular options, the challenge of assuring homogeneous treatment in a trial comparing intervention to medical management is great. However, given the published prospective data with the Wingspan stent and its entrance into most interventionalists' armamentarium, and the marketplace, this device seems to be the most logical option to test in a clinical trial. Thus, the comparison of best medical therapy versus best medical therapy plus stenting remains a viable question in need of urgent answering.

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) is an investigator-initiated, phase III randomized clinical trial testing the hypothesis that angioplasty with Wingspan stent placement plus aggressive medical therapy is superior to aggressive medical therapy alone (NCT00576693). It will enroll 764 patients with recent non-disabling ischemic stroke or transient ischemic attack within the first 30 days after the event in whom angiography confirms stenosis of 70-99% of major intracranial artery. Medical therapy will include aspirin and clopidogrel for 90 days in both arms following aspirin alone, blood pressure lowering to < 140/90 mmHg (<130/80 mmHg in diabetics), and lipid lowering to a goal of LDL < 70 mg/dL. The primary outcome is any stroke or death within 30 days after enrollment or an ischemic stroke in the territory of the symptomatic intracranial artery from day 31 to the end of follow-up (mean 2 years).

Intracranial stenosis represents the stroke subtype associated with the highest and earliest risk of recurrent stroke. Although antiplatelet therapy alone does not seem to alter natural history significantly, aggressive multimodal medical therapy may

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afford some additional risk reduction. While stenting is a promising treatment for intracranial stenosis, its use without proof that it provides additional benefit over medical therapy would bypass the scientific process necessary to develop an evidence-based approach for treatment. We hope that the ongoing SAMMPRIS trial will answer this very important clinical question and help determine the best management for this grave disease. The stroke community should support, participate in, and, most importantly, accept the results of well-designed clinical trials.

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