Management of Symptomatic Intracranial Arterial Stenosis: Endovascular Therapy

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Patients with symptomatic intracranial stenosis are at high risk of subsequent stroke despite the use of antithrombotic agents or surgical management. Although endovascular therapy appears to promise therapeutic solutions, the reported high peri-procedural adverse event rate limits the widespread use of this technique. In the past few years, the morbidity and mortality associated with intracranial angioplasty and stenting have decreased with the development of new intracranial specific devices. The most recent prospective studies on intracranial stenting have been nothing more than registries of patients with symptomatic intracranial stenosis of 50% or greater who have failed medical therapy. However, no randomized controlled data exist on the comparison between endovascular therapy and medical treatment. There are new data identifying factors associated with a higher risk of stroke in medically treated patients. These findings will help to define a high-risk patient population on whom the initial controlled trials will be conducted.

Introduction

Endovascular therapy is increasing in popularity in the treatment of symptomatic intracranial atherosclerosis. This enthusiasm is supported by the fact that this disease causes a significant number of ischemic strokes and is associated with a severe prognosis, as underscored by the annual 8% to 24% stroke rate in patients with intracranial atherosclerosis [1–3,4•,5•]. The optimal medical management of this disease is still under investigation, and to date the Warfarin-Aspirin for Symptomatic Intracranial Disease (WASID) trial [4•] is the only study to have investigated antithrombotic therapy in symptomatic intracranial stenosis. WASID compared warfarin with aspirin and was stopped prematurely because of safety concerns in the warfarin-treated group. No consensus exists regarding the optimal medical therapy, and numerous patients will experience recurrent symptoms despite multiple antithrombotic medications [5•]. The surgical option with extracranial-to-intracranial bypass procedures was abandoned due to the lack of benefit over medical therapy and in the subset of patients with middle cerebral artery (MCA) stenosis due to a worse outcome [1]. In this context, endovascular therapy (ie, angioplasty and stenting) appears to promise therapeutic solutions in patients failing medical treatment. Several centers have been reporting their experience with endovascular interventions in intracranial atherosclerosis; however, no prospective randomized study of endovascular intervention versus medical therapy has been performed. For some groups of patients (eg, those requiring urgent intervention), these procedures remain controversial mainly due to their high morbidity and mortality rate [6•]. Endovascular therapy has also been used for acute ischemic stroke treatment, but the present review focuses on secondary prevention only.

Eligible Patients

Determining which patient is eligible for endovascular treatment is critical. Currently, the most common indication for endovascular intervention is recurrent symptoms in the territory of an arterial stenosis of 50% or greater in severity despite medical therapy [7]. The risk-to-benefit ratio has to be considered thoughtfully; these procedures remain high risk even in the best of hands and the natural history of intracranial stenosis may be different from one patient to another. For asymptomatic intracranial atherosclerotic lesions, the annual risk of stroke is not clearly defined because most of the studies excluded these asymptomatic patients. However, as in extracranial carotid stenosis, a difference in the therapeutic management should be considered between symptomatic and asymptomatic
stenoses. In MCA disease, asymptomatic stenoses are usually associated with a benign prognosis [8]. In fact, asymptomatic MCA disease is associated with an annual 2.8% (ipsilateral: 1.4%) risk of new cerebrovascular events compared with a 12.5% (ipsilateral: 9.1%) risk in patients with symptomatic MCA stenosis [9].

The recent prospective WASID study is the most important source of natural history data on this patient population. WASID was the largest study of symptomatic intracranial stenosis to date and included patients with angiographically defined stenoses of 50% to 99% of the major intracranial vessels, namely the internal carotid artery, MCA, basilar artery, and vertebral artery. Patients were randomly assigned to receive warfarin to achieve an International Normalized Ratio of 2.0 to 3.0 or to receive aspirin (1300 mg/d). After randomization of 569 patients, enrollment was stopped due to concerns about the safety of the patients who received warfarin. Within a mean follow-up of 1.8 years, significantly more adverse events were documented in patients receiving warfarin versus aspirin (9.7% vs 4.3% for death and 8.3% vs 3.2% for major hemorrhage, respectively). Moreover, no difference was observed for the primary endpoint (ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke) between the two groups [4•]. Recurrent stroke occurred in 19% of patients; 73% of these ischemic strokes were in the territory of the stenotic artery. WASID also showed that some patients are at higher risk for stroke recurrence than others. For example, patients with stenoses of 70% to 99% had significantly higher annual stroke rates of up to 22.5%, whereas patients with 50% to 69% had an 8.2% rate [10].

The risk of stroke increases linearly with percent stenosis, and these findings confirm the results of the retrospective WASID pilot study [11••]. The risk of stroke in the territory of the stenotic artery was also higher in patients enrolled 17 days or less after the qualifying event, confirming that recurrent events tend to occur very soon after initial presentation. Thus the presence of recent symptoms suggests that all interventions, whether medical or endovascular, should be initiated very soon after clinical presentation. Additional variables, the National Institutes of Health Stroke Scale score (NIHSS), and the type of qualifying event (transient ischemic attack [TIA] or stroke) were identified as possibly associated with an increased risk of stroke in the territory of an intracranial stenosis. The association of the NIHSS with increased risk of subsequent stroke suggests that patients with stroke-related deficits seem to be at higher risk of recurrent event than patients presenting with TIA. The reason is unclear and these data should be considered cautiously as they were derived from subgroup analyses. The qualifying event was not an independent predictor of recurrent stroke by itself, but patients with stroke and stenosis of 70% to 99% were at high risk, whereas patients with TIA and stenosis of 50% to 69% stenosis were at lower risk. Other parameters such as female gender, diabetes, or hemodynamic stenosis may also be associated with ischemic recurrent strokes [10,11••,12,13]. On the other hand, the location of the stenosis and the use of antithrombotic agent at the time of a qualifying event were not predictors of stroke in the territory of the stenotic artery. Patients with stenosis located in the posterior circulation were not at higher risk of stroke than those with anterior circulation stenoses as previously described [3,14]. Retrospective data from the WASID pilot study and conventional teaching had suggested that patients with posterior circulation stenosis had worse outcome compared with those with anterior circulation stenosis [3]. Although lesion location is not by itself a predictor of event recurrence, other lesion characteristics (which were not studied in the WASID trial), such as the presence of collateral blood flow, lesion ulceration or irregularity, and the presence of tandem lesions, are factors that should be considered in the evaluation of patients with intracranial stenoses. Overall, the results of the WASID trial are of importance as they define a high-risk group of patients that should be aggressively treated. Patients with stenosis of 70% to 99% with recent symptoms represent a subset of patients that may benefit from endovascular therapy, particularly if they have failed a medical antithrombotic regimen.

Procedure and Medical Management

Antithrombotic therapy and sedation are decisive issues in these patients. Specific data in intracranial atherosclerotic disease are scarce and most of the antithrombotic strategies have been taken from the large quantity of data on coronary interventional techniques (eg, pre-procedural aspirin and clopidogrel administration has been empirically applied to intracranial stenting) [15]. Based on the weight of evidence showing significantly improved acute and long-term outcomes, pretreatment of patients with aspirin and clopidogrel has become a standard practice in intracranial angioplasty and stent patients [16]. These procedures should not be performed without dual antiplatelet therapy. The role of platelet glycoprotein IIb/IIIa receptor antagonists in the setting of intracranial endovascular stenting procedures is unclear; there are limited data supporting a beneficial effect but there are some reports showing a potentially increased risk of intracranial hemorrhage. Therefore, the routine use of such agents for elective intracranial procedures is not warranted and their use should be reserved for patients not adequately pretreated with oral antiplatelet agents or in thrombotic procedural complications. However, some operators do use abciximab during intracranial intervention [17,18]. For intracranial interventions, as with all endovascular interventions, heparin remains the anticoagulant of choice, and an adequate level of anticoagulation as measured by the activated clotting time is essential in all cases; however, there is no consensus on the optimal regimen [19].