Management of Intracranial Cerebral Arterial Stenosis

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Introduction

Intracranial arterial stenosis is used to be thought of as an uncommon cause of ischaemic stroke in Western literatures, accounting for about 10% in whites. Wong in 2006 reported that larger artery intracranial stenosis affecting the middle cerebral artery, intracranial portion of the internal carotid artery, vertebrobasilar artery and posterior and anterior cerebral artery is more common in Asian patients. In fact, it is estimated to account for 33-50% of strokes and 50% of transient ischaemic attacks in the Chinese population; it was also found in 47% of patients with stroke in Thailand; and it was significant in approximately 48% of patients with stroke in Singapore.

Natural History

There are several important clinical trials that would give a clearer picture of the risks of strokes in patients having a large intracranial artery stenosis. The Extracranial-Intracranial (EC-IC) Bypass Study provides prospective data on the risk of stroke in patients with symptomatic carotid siphon or middle cerebral artery (MCA) stenosis. In this trial, patients with carotid siphon or MCA stenosis who were treated medically (management of risk factors and 1300 mg/d aspirin) had an annual stroke rate of 8% to 10%.

Patients with symptomatic intracranial vertebral artery or basilar stenosis are at a higher risk of stroke, MI, or sudden death. Upon following up of 68 patients with 50-99% stenosis in the vertebrobasilar arteries for a median period of 13.8 months, 15 patients (22%) had an ischaemic stroke (4 fatal), 3 patients (4.5%) had a fatal myocardial infarction (MI) or sudden death. Overall, the estimated stroke risk of patients having a severe degree of arterial stenosis ranged from 10-20% yearly.

Medical treatment of Atherosclerotic Intracranial Arterial Stenosis

Antiplatelet vs. Anticoagulant

Calpan proposed a pathophysiological rationale for anticoagulation to suggest warfarin is a common treatment choice for symptomatic intracranial stenosis. However, the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial showed that aspirin was safer and as effective as warfarin for stroke prevention in patients with symptomatic intracranial stenosis. WASID was stopped early after a mean follow-up of 1.8 years because of higher rates of death and major haemorrhage in the warfarin arm. The primary end point of ischaemic stroke, brain haemorrhage or vascular death, occurred in 22.1% of patients assigned aspirin and 21.8% of those in the warfarin group. The rates of myocardial infarction or sudden death were also higher in the warfarin arm. Even in the vertebrobasilar arterial stenosis with a higher risk of stroke, there is no clear evidence of any benefit of warfarin over aspirin. Other antiplatelet agents (e.g., clopidogrel and combination of dipyridamole/aspirin) have been shown to have similar stroke recurrence rates in patients with various underlying causes of stroke and in a subset of patients with large artery atherosclerosis in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) Study. In summary, aspirin should be the drug of choice unless not tolerated by the patient.

Endovascular Therapy

Angioplasty and stenting have emerged as therapeutic options for symptomatic intracranial stenosis over the past few decades. Initially the risk of angioplasty was very high by borrowing the hardware from the cardiologists. Since that time, advances in microcatheter and balloon technology, the high risk of recurrent strokes in patients with intracranial stenosis despite medical management in WASID, and the success of endovascular treatments for other intracranial diseases have led to a renewed interest in intracranial angioplasty and stenting.

Angioplasty alone

Retrospective angioplasty studies reported high technical success rates with reduction of stenosis to <50%, but the 30-day rate of stroke or death has varied widely (4-40%). Restenosis rates after angioplasty have been reported between 24-50%.

Overall, available data on intracranial angioplasty suggest that it can be performed relatively safely in stable patients, but the long-term outcome after angioplasty has not been prospectively studied. Moreover, there are numerous technical drawbacks to angioplasty including immediate elastic recoil of the artery, dissection, acute vessel closure, residual stenosis after the procedure, and high restenosis rates.
**Angioplasty plus Stenting**

The Wingspan system is currently the only FDA-approved device for treating symptomatic intracranial stenosis. In 2005, the Wingspan Stenting System (Boston Scientific) was approved by the FDA for use under an HDE (humanitarian device exemption) in patients with symptomatic intracranial stenosis who are refractory to medical therapy. Hong Kong was also one of the study sites. It was a prospective multicentre international Phase I trial which included 45 patients with symptomatic 50% to 99% intracranial stenosis who had recurrent strokes despite antithrombotic therapy. The technical success rate was 97.7% and the 30-day stroke or death rate was 4.5%. The 1-year rate of ipsilateral stroke was 9.3%. The restenosis rate was 7.5% at 6 months and none was symptomatic.\(^5\)

In WASID the most important baseline predictors of stroke in the territory were severity of stenosis and time from qualifying event to enrollment. The rate of stroke in the territory in patients with >70% stenosis was 18% at 1 year (95% CI = 13% to 24%) vs. 7% at 1 year (95% CI = 5% to 10%) in patients with <70% stenosis. The National Institute of Health (NIH) recruited patients from sixteen medical centres enrolled consecutive patients being treated with a Wingspan stent in this registry between November 2005 and October 2006. A total of 129 patients with symptomatic 70-99% intracranial stenosis were enrolled. The technical success rate was 96.7%. The frequency of any stroke, intracerebral haemorrhage, or death within 30 days or ipsilateral stroke beyond 30 days was 14.0% at 6 months. The frequency of >50% restenosis on follow-up angiography was 13/52 (25%). The results indicate that the observed rates of any stroke or death within 30 days or stroke in the territory beyond 30 days are similar in the two groups up to 3 months but diverge afterwards (lower in the stented patients).

Comparison of the event rates in high-risk patients in WASID vs. this registry does not rule out either that stenting could be associated with a substantial relative risk reduction (e.g., 50%) or has no advantage compared with medical therapy. Further randomised control study is required.

**Future Directions**

The best treatment for prevention of another stroke or TIA in patients with narrowing of one of the arteries in the brain is uncertain. There are several aspects that clinicians should be focused and require further research.

**Aggressive management of risk factors**

In WASID, elevated blood pressure was significantly associated with an increased risk of ischaemic stroke.\(^6\)

Raised low density lipoprotein (LDL) was also strongly associated with poor outcomes in patients, because 25.0% of patients with LDL >115 mg/dL had the primary end point compared with 18.5% of patients with a mean LDL <115 mg/dL. Among the mere 10% of patients with mean LDL <70 mg/dL only 7% had a primary end point compared to 23% of the patients with LDL >70 mg/dL (P<0.09).

Recent research has also indicated a benefit in the prevention of recurrent strokes by Intensive Medical Therapy, which is defined as treating risk factors for stroke like high blood pressure, elevated LDL (low density lipids - the “bad” form of cholesterol) and diabetes.\(^10\)

**Clinical trial**

The Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) Trial is a NIH sponsored, on-going randomised trial at 60 US sites designed to determine whether angioplasty and stenting plus aggressive medical management is superior to aggressive medical management alone for the prevention of recurrent stroke in patients with 70% to 99% stenosis of a major intracranial artery.\(^11\)

Patients will be randomised 1:1 to either arm. Aggressive medical management in SAMMPRIS will consist of dual antiplatelet therapy (aspirin+clopidogrel) for 90 days in all patients. All patients will also receive protocol driven risk factor management targeting a LDL <70 mg/dL and systolic blood pressure <140 mm Hg (<130 if diabetic) and a comprehensive lifestyle modification programme to assist with weight reduction, exercises, smoking cessation, and nutrition.

**Summary**

Symptomatic atherosclerotic intracranial stenosis is a high-risk condition. WASID showed that aspirin is safer and as effective as warfarin for preventing recurrent strokes. Angioplasty and stenting cannot be justified in patients with <70% stenosis, given the low risk of stroke in the territory of a stenotic artery (6% at 1 year) and the inherent risk of current technology. Patients with severe stenosis, recent ischaemic symptoms and an NIH stroke scale score of > 1, and females are at the highest risk for strokes, and therefore have the greatest likelihood of benefiting from angioplasty and stenting.\(^12\)

The linear relationship between the degree of stenosis and stroke risks with medical therapy also supports a mechanical approach to revascularisation. At present, however, there is no level 1 evidence to support angioplasty and stenting for patients with symptomatic intracranial atherosclerotic disease. A randomised controlled trial is needed to prove the efficacy of this therapy. It should also be noted that these patients as a group have frequent vascular risk factors and will require aggressive medical management. In addition, rates of restenosis and the clinical consequences of restenosis will need to be closely monitored in future studies.
References


