LARGE ARTERY ATHEROSCLEROSIS: ASYMPTOMATIC INTERNAL CAROTID ARTERY STENOSIS

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Atherosclerosis of the large arteries is responsible for about 15 % of all ischemic strokes. Within the last decade, there has been significant progress in the medical management of atherosclerosis. Blood pressure lowering and control of dyslipidemia have improved, resulting in enhanced secondary stroke prevention. Even with the availability of surgical and endovascular therapies for some large artery atherosclerotic lesions, specifically carotid disease, the importance of intensive medical management cannot be overemphasized. In this presentation, I shall discuss contemporary management principles for patients with asymptomatic carotid stenosis.

Cervical Carotid Atherosclerosis

Carotid atherosclerosis accounts for about 7% of ischemic strokes. In the Framingham Heart study, the degree of stenosis was predicted by common baseline atherosclerotic risk factors such as older age, cigarette smoking, systolic blood pressure and total cholesterol[1]. In studies from the pre-statin era, patients with an asymptomatic carotid stenosis less than 75% had an annual stroke risk of 1.3%; and with a stenosis greater than 75% the annual risk of stroke was 2-2.5%. On the other hand, using 1990's medical therapy, symptomatic carotid stenosis over 70% carries an annual stroke risk of 10-15%. Intensive medical therapy and carotid revascularization procedures reduce these risks.

An important study in recent years is the Carotid Revascularization Endarterectomy versus Stenting trial (CREST). The trial originally focused only on symptomatic carotid stenosis patients [2]. In 2005, recruitment was extended to asymptomatic patients in order to reflect the real-world scenario, where the majority of revascularization procedures are performed among asymptomatic patients. The primary outcome was stroke, myocardial infarction (MI) or death during the periprocedural period or any ipsilateral stroke within 4 years.

After 4 years of follow-up, the primary outcome occurred in 7.2% of the 1262 patients in the CAS group and 6.8% of the 1240 CEA patients, p=0.51[2]. There was no difference in the primary outcome between the procedures throughout the duration of follow-up. However, upon review of the individual components of the outcome, important differences emerged. In comparison to the CEA group, patients in the CAS group had significantly higher perioperative strokes (4.1% CAS versus 2.3% CEA, p=0.01) and perioperative minor ipsilateral strokes (2.9% CAS versus 1.4% CEA, p= 0.009)[2]. Perioperative MI was significantly higher among the CEA patients (1.1% CAS versus 2.3% CEA, p= 0.03). The significant increase in strokes among the CAS patients was noted up to 4 years (6.2% CAS versus 4.7% CEA, p= 0.049)[2].

The traditionally accepted endpoint of stroke and death in the perioperative period, and stroke up to 4 years of follow-up (excluding MI) was significantly higher in the CAS arm (6.4% with CAS and 4.7% with CEA, p= 0.03)[2]. A noteworthy feature about the assessment of outcomes in CREST was the regular screening for MIs with EKGs and cardiac enzymes before and after the procedure [2]. Some critics question the inclusion of MI within the primary outcome while evaluating procedures intended for stroke prevention [3]. As outcomes go, does a stroke or an MI have greater impact? The physical component of the SF 36 questionnaire for health related quality of life, was significantly worse at one year among stroke patients, but showed an uncertain effect among MI patients. The mental component was also significantly worse among stroke patients at one year [2]. On the other hand, long-term mortality rates were higher among patients who suffered an MI in the perioperative period, even after adjustment of baseline co-morbid factors [4]. Whether the perioperative MI event is causally linked with later mortality or whether it is a marker of patients with a greater atherosclerotic disease burden is unclear.

Asymptomatic Carotid stenosis:

Case 2: An 80 year old man was referred for left carotid stenosis which was detected by his internist after a carotid bruit was heard. Carotid duplex revealed 80-99% stenosis. CTA was interpreted as showing 70-80% stenosis. The patient was on aspirin 325 mg per day, atorvastatin 80 mg per day, ramipril 10 mg per day, and a diuretic. Blood pressure was 136/78. Low density lipoprotein was 51 mg/dl.

The risks of stroke in patients with asymptomatic stenosis are lower than those with symptomatic stenosis, as mentioned above. Therefore, the management of this condition is more controversial. There is increasing evidence to show that intensive medical therapy only, without revascularization, can reduce the

ischemic stroke risk dramatically. Over the last decade, the intensity of medical therapy has improved significantly. In NASCET only 16% of patients assigned to the medical arm and 13% of patients assigned to the CEA arm were on lipid lowering medications [5]. In the Asymptomatic Carotid Surgery Trial-1 (ACST-1), a trial that randomized patients with asymptomatic carotid stenosis to medical therapy versus CEA, the use of lipid lowering medications improved from 7-11% in the early 1990s at the start of the trial, to 80-82% in the late 2000s towards the end of long term follow up [12]. The use of antihypertensive drugs similarly improved, corresponding to a drop in mean diastolic blood pressures over time [12].

Abbott analyzed 11 asymptomatic carotid intervention studies between 1985 and 2007[13]. Raw data from these trials were used to calculate rates of ipsilateral stroke, ipsilateral stroke/TIA, any territory stroke and any territory stroke/TIA in the medical therapy arm. There was a significant reduction in the rate of each outcome during this time period [13]. The outcome rates from medical therapy in the more contemporary studies were quite similar, if not better than the CEA arm in the asymptomatic carotid artery surgery (ACAS) trial [13]. In conclusion, extremely low stroke rates (1% per year or less) can be achieved by intensive medical therapy among patients with asymptomatic carotid stenosis.

In the CREST study, about 47% of the overall population was asymptomatic [2]. The rate of the primary outcome was similar: 5.6% with CAS and 4.9% with CEA [10]. None of the secondary outcomes were different in the asymptomatic subset. However, the stroke and death rate by four years was 4.5% in the CAS arm and 2.7% in the CEA arm (p=0.07) [10]. While not statistically significant, this difference may be clinically important. CREST was not designed for asymptomatic patients initially. The study methods did not provide enough power to identify significant differences in the asymptomatic subgroup. A similar trial designed with sufficient power in the asymptomatic subgroup could plausibly have found the above difference in stroke and death rate to be significant [3].

In view of the extremely low event rates noted with contemporary medical therapy among asymptomatic patients, a carotid intervention study (CREST2), comparing optimal medical therapy alone vs. optimal medical therapy plus revascularization, for patients with asymptomatic carotid stenosis of 70-99% has received funding and started enrolling patients in late 2014. Over 500 patients have been enrolled thus far (www.crest2trial.org).

Case 2 comment: The patient was counseled regarding the uncertain benefit of revascularization in his age group. He continued on aggressive medical therapy and has been symptom-free for three years. This type of patient could be considered for enrollment in a clinical trial such as CREST 2.

Conclusion:

Large artery atherosclerosis is an important, medically treatable, cause of ischemic stroke. Strict control of atherosclerotic risk factors is essential. Surgical and endovascular options benefit patients with symptomatic, moderate to severe carotid stenosis, although the benefit is not as robust in women. Any future endovascular or surgical interventions for asymptomatic cervical carotid stenosis or intracranial atherosclerosis will be held to stringent safety standards, given the low stroke rates achieved by contemporary intensive medical therapy. New clinical trials will examine the merits of carotid revascularization versus contemporary medical therapy in asymptomatic patients (CREST 2). Aggressive medical therapy is also beneficial for symptomatic intracranial atherosclerosis and will serve as a benchmark for any future comparisons of endovascular treatment.

Table 1: Patients at high surgical risk for Carotid Endarterectomy, where Carotid artery Stenting may be considered as an option.

Anatomical factors (surgically inaccessible carotid stenosis)*:*
Obesity
High carotid bifurcation
Severe cervical spine arthritis
Clinical factors:
Clinically significant cardiac disease (Congestive heart failure, abnormal stress test, need for open heart surgery)
Severe lung disease
Contralateral Carotid Occlusion
Contralateral laryngeal nerve palsy
Previous radical neck surgery
Previous radiation to the neck
Recurrent stenosis after carotid endarterectomy

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