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Short Communication

Asymptomatic carotid artery disease – What is the evidence for intervention?

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ABSTRACT

Strong evidence exists in favor of revascularization in symptomatic carotid artery stenosis. Contrarily, no unified consensus exits on the best management strategy in asymptomatic carotid artery disease. Early trials on carotid revascularization in asymptomatic stenosis suggested an absolute benefit in favor of intervention. However, with the advent in aggressive medical therapy, rate of stroke/TIA in the territory of asymptomatic stenosis is small and has dropped to approximately 1% per annum. Similarly, complication rate with carotid revascularization has reduced with gain in operator experience. This is evident from the lead-in phase analysis of the Carotid Revascularization Endarterectomy Versus Stenting Trial and the interim results of the asymptomatic carotid surgery (ACST) 2 trial. Therefore, it is crucial to determine the patient group at 'high' risk of future stroke on medical therapy. Plaque morphology, collateral status and cerebrovascular reserve, microembolic signals on Transcranial Doppler assessment, history of contralateral stroke/TIA, and severity and progression of stenosis are the key predictors of future stroke risk. We discuss the evidence in support of revascularization in severe 'high risk' asymptomatic stenosis based on review of published literature.

1. Introduction

Early carotid revascularization in symptomatic severe carotid stenosis offers significant absolute and relative risk reduction in ipsilateral stroke and TIA.[1] To the contrary, it is not clear as to what the best management strategy should be in incidentally discovered carotid artery stenosis. Asymptomatic carotid disease is commoner in men and the prevalence of >50% carotid stenosis ranged from 0.2% (age <50 years) to 7.5% (age ≥80 years). Among women aged ≥80 years the prevalence was 5%.[2] Long-term risk of stroke, myocardial infarction and non-stroke vascular deaths is significantly higher in patients with asymptomatic carotid stenosis of >50%.[3] Henceforth, the need to determine the salient indicators that would favor revascularization as opposed to best medical therapy in asymptomatic carotid stenosis. An early trial (asymptomatic carotid artery stenting trial) on endarterectomy for asymptomatic carotid artery disease with stenosis of >60% showed an absolute risk reduction in 5-year aggregate risk of ipsilateral stroke and any perioperative stroke or death of 5.9% in favor of the interventional arm.[4] Similarly, there was risk reduction in favor of intervention for stroke and perioperative events at 5 and 10 years in the asymptomatic carotid surgery trial (ACST) 1

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trial.[5] The criticism, however, is that there has been a marked change in aggressive medical therapy, and that these patients may be best managed medically. Annual ipsilateral stroke rates have progressively dropped with aggressive medical therapy since 1985; the annual ipsilateral stroke rate was 1.3%, 1.2% and 0.6% in the ACSRS, ASED and the SMART studies respectively.[6–8] Nonetheless, evolution in technology and growth in operator experience is evident from the decline in the rates of periprocedural events over time. For instance, periprocedural stroke or death rate with carotid artery stenting (CAS) has declined from 2.5% in CREST trial to 1% in the preliminary data published from the ongoing ACST 2 trial.[9,10] Therefore, it is of prime importance to select the ideal candidate likely to benefit from the intervention. Additional factors other than stenosis alone are likely to play an important role in determining the best management strategy in patients with asymptomatic stenosis. We will be discussing the factors that determine 'high' risk patient group.

2. Determinants for 'high' risk

2.1. *Plaque morphology*

Echolucent plaques are lipid rich, and therefore are prone to rupture. In patients with a carotid stenosis of >70%, the presence of an echolucent plaque predicted a higher ipsilateral stroke rate with a hazard ratio of 6.43.[11] Interestingly, the risk of ipsilateral stroke doubled, when microembolic signals (MES) were present in addition to echolucent plaques. Similarly, Kakkos et al. noted that the presence of a large juxtaluminal black (hypoechoic area) area predisposed to a higher ipsilateral stroke rate.[12]

Neovascularity and intra-plaque hemorrhage are other key morphological attributes that predisposes to ipsilateral stroke. Rupture of the friable new vessels results in plaque hemorrhage which in-turn leads to the formation of the lipid rich core. The risk of ipsilateral stroke was 3.5 times more likely, when intra-plaque hemorrhage was noted on MRI.[13] Similar results were observed by Qiao et al.; adventitial neovascularity and plaque hemorrhage were associated with a significantly higher risk of ipsilateral stroke (OR – 10.1%).[14]

Finally, presence of plaque ulcers on 3D ultrasound served to be an important radiological parameter that predicted ipsilateral stroke risk. The relative risk for an ipsilateral stroke was 8.6 when ≥3 ulcers were present.[15] Therefore, determining plaque morphology either on ultrasound or on MRI allows us to quantify the stroke risk in the ipsilateral carotid territory.

2.2. *Transcranial Doppler (TCD) microemboli*

MES are a reflection of unstable vulnerable plaque morphology. In a large prospective study that enrolled 482 patients with >70% carotid stenosis, the hazard ratio for the development of ipsilateral stroke in the presence of TCD microemboli was 6.9, and this was statistically significant.[16] Similar, high relative risk of 11.7 for stroke or death at 3 years was noted in the group with at least 2 MES in a 1 h recording.[15] In another report, Spence et al. noted that the stroke rate in the first year in MES + patients was high (15.6%) in comparison to MES – patients (1%).[17] They concluded that the morbidity and mortality related to CAS or carotid endarterctomy should be <1% in order to consider offering interventional treatment in the MES – patient group. Therefore, MES on TCD monitoring are predictive of higher ipsilateral stroke rate.

2.3. *Cerebrovascular reserve and collaterals*

Change in mean flow velocity with hypercapnia on TCD allows for the evaluation of the cerebrovascular reserve. A breath holding index of <0.69 indicates poor reserve. A more than 3-fold risk of ipsilateral stroke was observe in patients with impaired cerebrovascular reserve.[18] Cerebrovascular reserve is in turn dependent on the extent of willisian, external carotid – ophthalmic and leptomeningeal collaterals. A lone anterior communicating artery collateral serves to least affect the cerebrovascular reserve. The breath holding index is lower when more than one willisian or a combination of willisian and external carotid–ophthalmic collateral are noted. Cerebrovascular reserve is most impaired, when leptomeningeal collaterals alone are noted.[19] Therefore, assessment of collateral type and extent provides an indirect assessment of the cerebrovascular reserve. In conclusion, impaired cerebrovascular reserve is a strong predictor of ipsilateral stroke.

Most importantly, well trained operators with adequate experience alone can reliably determine MES on TCD and also evaluate the cerebrovascular reserve.

2.4. *Silent infarcts*

In clinically asymptomatic patients, Kakkos et al. noted that the annual stroke rate was high (3.6%) when embolic infarct was present when compared to absence of silent infarcts (1%).[20] Similarly, an 8.5-fold higher risk for ipsilateral stroke or TIA was noted in the patient group with silent infarct.[21] In essence, the risk of ipsilateral stroke was higher in the patient group with clinically asymptomatic infarcts.

2.5. *Extent and progression of stenosis*

The stroke rates increased with the degree of stenosis. De Weerd et al. noted a higher annual ipsilateral stroke rate in patients with stenosis >90% (4.8%) as compared to the patient group with stenosis of <80% (1%).[2] Similarly progression of stenosis on interval imaging was a strong predictor of ipsilateral stroke and TIA. The stroke and TIA rates were 27.1% and 17% in patients with progression of stenosis. This was significantly higher to the reported 0.8% stroke rate in patients without progression.[22] Contrary to this, in a large study the risk of annual ipsilateral stroke jumped from 1.5% in the absence of progression to 2.6% when there was progression in the stenosis; a <2-fold increase in stoke risk. Nonetheless, progression in stenosis indicates a higher annual ipsilateral stroke rate.

2.6. *Combined parameters*

Combination of clinical and radiological parameters appear to predict ischemic stroke with higher sensitivity and specificity. Evidence is from the ACSRS study; the area under receiver