A Need for Tailored Approach for Patients with Symptomatic Intracranial Atherosclerotic Stenosis

Symptomatic intracranial atherosclerotic stenosis (ICAS) is associated with a risk of recurrent stroke in approximately 14% of patients in first 90 days of index event despite best medical management.[1] The risk appears to be particularly high in certain ethnic groups like African-American, Asian, Hispanic and South-Asian heritage. Baseline stroke severity, diffuse atherosclerosis and multiple diffusion-weighted lesions may be associated with unfavorable outcome and recurrent stroke.[2] In this issue of the journal the authors demonstrate in a retrospective study an increased risk of recurrent stroke in patients with ICAS from the US (21%) compared with the India (2%). Patients from the US were older, one-third had a prior stroke, one-fifth had coronary artery disease, 44% were on anti-platelet medication and 47% were on statin medication prior to admission. Where as patients from India were younger, more likely to have diabetes and have severe stroke at admission. Furthermore, only 60% patients from the US were on dual antiplatelet therapy at discharge compared with 90% from the India. However, this additional 30% difference in the dual antiplatelet therapy alone may not explain the 20% increase in recurrent stroke rate.

Patients with ICAS have a diverse spectrum of vascular phenotype, with variable degree of stenosis (presence of sub-clinical perfusion deficits), focal and diffuse atherosclerosis pattern, collateral artery distribution and plaque enhancement suggestive of inflammation, hemorrhage and vascularity.[3] These patients with ICAS may also have variable amount of aspirin and clopidogrel resistance.[4] Stringent control of blood pressure (<130 mmHg) with antihypertensive agents or a drop in BP because of autonomic nervous system dysfunction associated with diabetes may also cause worsening of the symptoms or lead to a hemodynamic stroke in patients with ICAS.

SAMMPRIS study conclusively demonstrated that aggressive medical management including dual antiplatelet (aspirin 325 mg and clopidogrel 75 mg) for 90 days, strict control of primary risk factors; systolic BP <140 mmHg and LDL <70 mg/dl and control of secondary risk factors diabetes, increase exercise and smoking cessation is better than intracranial stenting for preventing recurrent stroke in patients with ICAS.[5] Nonetheless, this uniform strategy of best medical management may not be sufficient in a proportion of patients with ICAS. It may be imperative to identify high-risk group in this cohort and employ individually tailored approach.

Patients with high degree of stenosis and/or having cerebral hypoperfusion without ischemia identified on computed tomography perfusion or perfusion-weighted magnetic resonance imaging may be at a high risk for a hemodynamic stroke. A recent study in non-cardioembolic stroke patients ineligible for revascularization therapy and progressive stroke, showed promising results with therapeutic induced hypertension.[6] In that study the odds for neurological improvement (NIHSS > 2) was 2.5 times and odds for functional independence (Modified Rankin scale 0-2) was 3 times in intervention arm (n = 77) compared with standard care arm (n = 76); however, this needs further confirmation in patients with ICAS. A less rigorous control of BP may be needed in this group of patient.

Remote ischemic conditioning (RIC) is feasible in acute stroke patients in the first 24 hours and may help to prevent infarct growth and recurrent stroke.[7] RIC has been tested in a phase 2 study in patients with ICAS and shown to reduce the annual incidence of recurrent stroke and improvement in cerebral blood flow.[8] RIC was given in both upper limbs, two times a day for 300 days with an automated device. RIC was useful in older patients as well. Larger pivotal study is underway.

It may be important to test presence of clopidogrel resistance acutely in high-risk patients with ICAS (Severe stenosis, diffuse atherosclerosis, cerebral perfusion deficits, multiple vascular co-morbidities, multiple diffusion-weighted lesions and severe neurological deficits). The choice of agent to be used in patients with clopidogrel resistance and their efficacy remains to be studied. Ticagrelor, prasugrel, rivaroxaban (2.5 mg) in combination with aspirin and cilostazol all are potential agents in patients with clopidogrel resistance. Intracranial stenting is not recommended in most patients acutely because of peri-procedural stroke risk.[5] However, patients with high-risk for recurrent stroke or patients with recurrent in-hospital stroke or stroke after first few weeks of index events; intracranial vessel stenting remains an option.

Patients with symptomatic ICAS have a more aggressive natural history. It is important that an individually tailored approach be considered consisting of dual antiplatelet therapy and vascular risk factor management in combination with additional investigation and novel therapies. It may be appropriate to identify a high-risk group using vessel wall imaging, antiplatelet therapy resistance and perfusion imaging. Novel strategy like RIC, newer antiplatelet agents and therapeutic induced hypertension could be investigated in patients with ICAS to determine if these therapies can improve outcome in this aggressive disease.

Mahesh P. Kate, Ashfaq Shuaib[1]

Division of Neurology, Department of Medicine, Alberta Health Services, University of Alberta Hospital, Edmonton, [1]Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Canada

Address for correspondence: Dr. Mahesh P. Kate, Neurologist, 1T1-14, OPR, University of Alberta Hospital, 8440, 112 St NW, Edmonton - T6G2B7, AB, Canada.
E-mail: mahesh@ualberta.ca

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Submitted: 25-Nov-2019 **Revised:** 02-Dec-2019
Accepted: 26-Nov-2019 **Published:** 07-Feb-2020

DOI: 10.4103/aian.AIAN_623_19