

Mini-Review

The Latest Information on Intracranial Atherosclerosis: Diagnosis and Treatment

Jaseong Koo

Department of Neurology, Stroke Center at Cardio-Cerebro-Vascular Center, Seoul St. Mary's Hospital, Catholic University of Korea, Seoul, Korea

Key Words

Ischemic stroke · Intracranial atherosclerosis · Treatment

Abstract

Intracranial atherosclerotic stenosis (ICAS) is the most common cause of ischemic stroke in the world. ICAS is especially common in the Asian population accounting for 30–50% of all ischemic strokes. The risk of recurrent stroke in patients with symptomatic ICAS is the highest among the stroke subtypes. Two major factors associated with recurrent stroke are high degree (>70%) of stenosis and progression of ICAS. Transcranial Doppler ultrasound, CT angiography, MR angiography, and conventional catheter angiography are used for the diagnosis of ICAS. Today, high-resolution MRI can provide important information to improve the understanding of pathophysiology and diagnosis of ICAS. For prevention of recurrent stroke in patients with ICAS, surgery and endovascular intervention failed to show benefit over best medical treatment. Best medical treatment includes intensive risk factor control and antiplatelet therapy. Various antiplatelet drugs or their combination can be used for prevention of recurrent stroke in patients with ICAS. Cilostazol with or without aspirin is effective in preventing progression of symptomatic ICAS. Cilostazol is also safer than aspirin in terms of bleeding complications.

© 2015 S. Karger AG, Basel

Prevalence of Intracranial Atherosclerotic Stenosis

Ischemic stroke is a clinical syndrome caused by various etiologies. The vascular mechanisms in the pathogenesis of ischemic stroke can be classified into small vessel occlusion, large artery atherosclerosis, cardioembolism, and other miscellaneous conditions. Among

The content of this paper was presented at the 11th International Stroke Summit, Nanjing, 2015.

Jaseong Koo
Department of Neurology, Stroke Center at Cardio-Cerebro-Vascular Center
Seoul St. Mary's Hospital, Catholic University of Korea
222 Banpo-daero, Seochogu, Seoul 06591 (Korea)
E-Mail nrkoomh@chol.com

the various mechanisms, intracranial atherosclerotic stenosis (ICAS) is particularly prevalent in the Asian population and accounts for 5–10% of stroke in white people, 15–30% in black people, and up to 30–50% in Asian people, which suggest that ICAS is the most important cause of ischemic stroke in the world, and its global burden as a cause of stroke is likely to increase further. The suggested explanations for the racial difference in the prevalence of ICAS are genetic susceptibility, difference in lifestyle and risk factor profiles. Risk factors for ICAS include advanced age, hypertension, diabetes, hyperlipidemia, and metabolic syndrome.

Prognosis and Diagnosis of ICAS

The risk of recurrent stroke in patients with symptomatic ICAS is the highest among the stroke subtypes. According to the results of a recent study, Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS), the risk of any recurrent stroke or death was 17.5% at 1 year and 19.8% at 2 years despite best medical management. Two major factors associated with recurrent stroke are high degree (>70%) of stenosis and progression of atherosclerosis [1].

Diagnostic evaluations of ICAS include transcranial Doppler (TCD) ultrasound, CT angiography (CTA), MR angiography (MRA), and conventional catheter angiography. Although catheter angiography is the gold standard for diagnosis and evaluation of ICAS, it is not used as a routine method due to risk of periprocedural complications. TCD, CTA, and MRA are noninvasive methods and provide safer and less expensive ways to assess ICAS than conventional catheter angiography, but the accuracy of these methods is less clearly established. In the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial, TCD and MRA had high negative predictive values (86–91%) but low positive predictive values (36–59%) [2]. These data suggest that TCD and MRA are useful in screening for exclusion of ICAS, but unreliable to establish the diagnosis of ICAS. CTA is more accurate than MRA for the diagnosis of ICAS and has a high sensitivity and specificity for detection of $\geq 50\%$ ICAS. However, neither CTA nor any of the other noninvasive diagnostic tests accurately measure the degree (or percentage) of stenosis. Currently, high-resolution MRI can provide important information to improve the understanding of pathophysiology and diagnosis of ICAS by enabling imaging of intracranial plaque and the adjacent arterial wall.

Stroke Mechanism and Management of ICAS

There are three main mechanisms of stroke related to ICAS: hypoperfusion, artery-to-artery embolism, and in-situ thrombosis. Although stroke is caused by combinations of these mechanisms in most cases, identifying the major contributing mechanism is important to choose an optimal method for acute management and long-term prevention of recurrent stroke. If hypoperfusion is a main mechanism, methods to improve perfusion should be emphasized during the acute period, and revascularization can be considered for prevention of recurrent stroke. If artery-to-artery embolism and/or in-situ thrombosis are important pathophysiology, a more intensive antiplatelet therapy can be considered.

Because of a high risk for recurrent stroke with antithrombotic therapy such as high-dose aspirin or warfarin anticoagulation, revascularization such as bypass surgery or an endovascular procedure was used. Two large prospective randomized trials (EC-IC Bypass Surgery Study and Carotid Occlusion Surgery Study) which evaluated the efficacy and safety of bypass surgery compared with medical treatment failed to show any benefit of surgery over medical

treatment [3, 4]. SAMMPRIS is the only prospective randomized controlled study to compare endovascular stenting with medical treatment. The results showed that stenting was associated with high early morbidity and was no more effective than medical treatment. Long-term outcome was equally unfavorable in the stenting group. Based on these trials, although there are still some arguments, stenting and bypass surgery are not considered optimal for treatment of ICAS. Various antiplatelet drugs or their combination can be used for prevention of recurrent stroke in patients with ICAS. During acute period, especially when artery-to-artery embolism or in situ thrombosis is a major pathophysiology, intensive antiplatelet therapy with dual antiplatelets can be useful. Long-term therapy with dual antiplatelets is not recommended because of the significantly increased risk of bleeding complications. For the long-term prevention of recurrent stroke, cilostazol with or without aspirin is useful. Cilostazol shows antiplatelet activity by inhibiting phosphodiesterase which increases cAMP concentrations. In addition to antiplatelet activity, cilostazol also has vasodilatory activity, inhibits vascular smooth muscle proliferation, and protects the endothelium. In 2 prospective randomized studies in Asian patients, cilostazol was effective in the prevention of ICAS progression. In a study which compared aspirin plus cilostazol with aspirin alone in Japanese patients with ICAS, the rates of progression of ICAS were similar between the two groups, and the combined secondary endpoint (stroke and silent brain infarcts) was lower in the cilostazol group. In another study of Korean patients with lacunar infarct, cilostazol significantly improved vasomotor reactivity measured as pulsatility index by TCD. Moreover, it seems quite clear that cilostazol is safer than aspirin and probably safer than other antiplatelets in terms of reducing bleeding complications, especially hemorrhagic strokes.

Conclusion

ICAS is the most important cause of stroke, especially in the Asian population. Surgical or endovascular treatment failed to show benefit over antiplatelet therapy. Available evidence suggests that cilostazol is the best choice among the various antiplatelets in terms of safety as well as efficacy.

Disclosure Statement

Jaseong Koo has received honoraria and a grant from Otsuka International Asia Arab.

References

- 1 Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, et al: Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011;365:993–1003.
- 2 Feldmann E, Wilterdink JL, Kosinski A, Lynn M, Chimowitz MI, Sarafin J, Smith HH, Nichols F, Rogg J, Cloft HJ, Wechsler L, Saver J, Levine SR, Tegeler C, Adams R, Sloan M; Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) Trial Investigators: The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial. *Neurology* 2007;68:2099–2106.
- 3 The EC/IC Bypass Study Group: Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. *N Engl J Med* 1985;313:1191–1200.
- 4 Powers WJ, Clarke WR, Grubb RL Jr, Videen TO, Adams HP Jr, Derdeyn CP; COSS Investigators: Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: the Carotid Occlusion Surgery Study randomized trial. *JAMA* 2011;306:1983–1992.