39th Mihara Award Memorial Lecture

Title

Establishment of remote ischemic conditioning as a new therapeutic strategy for acute ischemic stroke

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Background and purpose

Therapy in acute ischemic stroke has made big progress in terms of thrombolysis and thrombectomy. However, less than 10% of patients with acute ischemic stroke can receive recirculation therapy due to time window and sever tissue injury. Therefore, new strategy to mitigate ischemic injury itself is expected to come out. Previous all clinical trial employing free radical scavenger, glutamate receptor antagonist and neurotrophic factors have failed in acute ischemic stroke. Important factors determining functional outcome in ischemic stroke are both ischemic severity as expressed as residual blood flow and ischemic period until recirculation. Leptomeningeal anastomosis could be one of the most important factors determining ischemic severity during major vessel occlusion.

The purpose of this study is (1) to elucidate the effect of remote

ischemic conditioning (RIC) on collateral development, infarct lesion, and functional outcome, and clarify the mechanisms underlying RIC on brain protection, and (2) to apply RIC in patients with acute ischemic stroke focusing collateral development as a therapeutic target.

Methods

Basic Research: Effect of RIC on leptomeningeal anastomosis, early ischemic lesion in MRI diffusion weighted imaging, and infarct size in murine permanent occlusion model of middle cerebral artery

For experimental ischemia, C57BL/6 mice are subjected to permanent occlusion of left middle cerebral artery (MCA) under isoflurane anesthesia. Hind limb ischemia is accomplished by tightening a cuff around the upper thigh to achieve limb pallor for 4 cycles with each occlusion or release phase lasting 5 min. After RIC or sham procedure, MRI is performed using a 1T small animal MRI scanner to visualize early ischemic lesion in DWI. In one set of experimental groups, after MRI examination, the right atrium of the heart was incised under euthanization with 4.0% isoflurane, then white latex compound is injected into the left ventricule to visualize collateral circulation. In other groups, mice receive RIC once a day, neurologic signs are examined and after sacrifice, TTC staining is performed to measure infarct volume.

In order to see the effect of RIC on ischemia-reperfusion model,

left MCAO occlusion is induced by an intraluminal occlusion for 45 min using a nylon filament suture, and after recirculation MRI DWI is performed using a 1T small animal MRI scanner. In order to evaluate neuron damage and breakdown of blood-brain barrier, we examine immunohistochemical findings for microtuble associated protein 2 (MAP2), glial fibrillary acidic protein (GFAP), fibrinogen and IgG.

Clinical Research: Randomized controlled trial of RIC on acute ischemic stroke

We focused on acute ischemic stroke without recirculation of major vessel. We enroll 100 patients within 48 hours since onset of stroke in 5 stroke centers including our hospital. Major inclusion criteria are age 20-85 years old, NIHSS 8-22, MRI examination within one hour before randomization. We divide RIC and SHAM procedure groups. In RIC group, four cycles of unilateral lower limb ischemia without paresis for 5 minutes followed by reperfusion for another 5 minutes are performed once a day for a total of seven days. NIHSS score is measured every day, and MRI examination is again scheduled a week later. Primary outcome is modified Rankin scale at 90 days after stroke and MRI lesion volume change between entry and 7 days later.