Remote Ischemic Conditioning for Secondary Stroke Prevention: Time for Clinical Trial?

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Remote ischemic conditioning (RIC) is a form of cytoprotection in which small doses of an injurious agent including ischemia, activate protective pathways that prevent from subsequent larger injuries (1). Hypoxic conditioning of the brain was first reported in the 1960s in a study that showed that exposure of rats to brief anoxia improved survival under anoxic conditions (2).

RIC involves repetitive inflation and deflation of a cuff around a limb to pressures above systolic blood pressure, with the intention of protecting distant organs such as the heart, kidney or brain. The mechanism by which the signal is transferred from the peripheral limb to the brain remains unclear. Transient occlusion with a tourniquet or blood pressure cuff on the arm can stimulate the release of autacoids that activate an afferent neural pathway that result the release of nitric oxide from blood vessels indicting that nitrite is a major mediator of RIC (3). In areas of hypoxia, nitrite is reduced to nitric oxide, which mediates hypoxic vasodilatation and inflammatory gene expression, with subsequent benefit on enhancing cerebral blood flow (4). However, multiple candidate messengers have been associated with a remote conditioning stimulus, including

adenosine, opioids, exosomes and microRNAs (1,5). Neural pathways are also implicated with RIC effects abolished in preclinical models through transection of the femoral nerve or cholinergic ganglionic blockade (6).

The proposed multimodal mechanisms lend RIC to potential therapeutic benefit in the acute phase of stroke (per-conditioning) through cytoprotection and mediating the inflammatory response. However, further interest in chronic RIC suggests that improvements in vascular health may occur with repeated cycles of RIC over many days-to-months (termed post-conditioning if initiated after a vascular event), with recent proof-of-concept trials in managing hypertension (7), and the possibility of reducing recurrent cerebrovascular events after recent TIA or ischemic stroke (8).

Several clinical trials have tested proof-of-concept, feasibility, tolerability and efficacy of RIC in the treatment of ischemic stroke with differing results. Similar to natural history studies of TIA prior to stroke as a model of RIC, clinical efficacy of RIC in the treatment of acute ischemic stroke (AIS) remains controversial. To address this, Li et al conducted a meta-analysis of randomized clinical trials in both per- and post-conditioning, which is reported in this issue of Neurology (9).

In this systematic review and meta-analysis, the authors evaluated the efficacy and safety of RIC in ischemic stroke patients. The authors identified 22 randomized clinical trials with n =7657 patients. The authors found that RIC did not improve functional outcomes measured using the modified Rankin score (mRS), regardless of whether they received medical management (mRS 0-1: RR 1.61, 95% CI 0.94-2.76, P=0.08) or reperfusion therapy with intravenous thrombolysis or mechanical thrombectomy (RR 1.02, 95% CI 0.91-1.14, P = 0.74). In the medical management group, patients who received RIC had 1.7 points lower follow-up NIHSS compared

to the control group (P<0.00001). In addition, RIC was associated with 18% lower risk of stroke recurrence (RR 0.82, 95%CI 0.71-0.95, P=0.008) while long-term RIC significantly reduced the long-term recurrence of stroke events by 51% (RR 0.49, 95%CI: 0.25 – 0.95, P = 0.04).

These findings are interesting and raise some questions. Although the decrease of NIHSS by 1.7 point was statistically significant, average baseline NIHSS in these studies decreased from 11.3 to 9.6. Is this decrease clinically meaningful? Probably not. As the authors stated in the discussion, RIC has limited effectiveness in improving functional outcome in patients with stroke, though analyses may be underpowered. A significant limitation in interpreting these data is the heterogeneity between trials in terms of timing of RIC application, RIC dose and RIC site of application. Further, one of the three phase III trials included in the analyses has not yet been published and the data are based on a conference presentation only.

The meta-analysis results appear to be largely driven by three phase III RCTs and the differences in trial methodology should be explored further to help interpret the findings. RICAMIS, a Chinese trial (n=1776) used bilateral upper limb RIC for 14 days after AIS within 48 hours, excluding those receiving reperfusion therapy, was positive in improving day 90 mRS.(10). RESIST (unpublished) applied single limb RIC (for seven days in 80% of strokes) in the ambulance to 1500 participants, about 50% were AIS, 11% intracerebral hemorrhage and the remainder TIA or stroke mimic; the results were neutral for the primary outcome, day 90 mRS. Finally, the RICA trial (n=3033) assessed 12 months of daily bilateral upper limb post conditioning up to 15 TIA) and 30 (AIS) days post event in Chinese patients with intracranial stenosis and showed a reduction in the composite secondary outcome of stroke, TIA and myocardial infarction (9). Therefore, uncertainty remains on the effect of remote ischemic per-conditioning in AIS, with higher doses for a more sustained period of time potentially effective.

The efficacy of RIC in secondary stroke prevention is an interesting finding of the meta-analysis and both the neuroprotective effect on stroke outcome and the potential to induce an ischemic tolerance to reduce future vascular events warrants further research, though the absence of a reliable surrogate biomarker to help determine unknowns regarding optimal RIC dose and time of administration remain a challenge.

Secondary stroke prevention efficacy of RIC has significant clinical implications. In the reported meta-analysis 13 out of 22 clinical trials were conducted in China and as the authors mentioned may not be generalizable to other populations. Therefore, more clinical trials with large and diverse population are required to confirm findings of this meta-analysis as RIC is a promising intervention for secondary stroke prevention.

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