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Remote ischemic conditioning for stroke prevention in symptomatic intracranial atherosclerotic disease

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Stroke caused by atherosclerotic intracranial arterial stenosis (ICAS) is one of the most frequent causes of stroke worldwide (Gutierrez et al., 2022). It is associated with a high risk of stroke recurrence, despite best medical management with dual antiplatelet treatment and aggressive treatment of other vascular risk factors (Hurford et al., 2020; Gutierrez et al., 2022). Interventional strategies with angioplasty and stenting have not been effective in reducing stroke recurrence (Chimowitz et al., 2011). Additional add-on treatments are needed to reduce the burden of ICAS related stroke.

Remote ischemic conditioning (RIC) using transient limb ischemia/reperfusion cycles has recently been shown to be safe, feasible, and to have potentially beneficial effect on long term recovery in acute ischemic stroke (Chen et al., 2022; Hess et al., 2022). The exact mechanisms of signal transmission and brain protection are unknown, and the optimal dosing of RIC (unilateral vs bilateral, arm vs leg, number of cycles and duration of each cycle etc.) is yet unknown (Hess et al., 2015).

Long-term RIC treatment in patients with symptomatic ICAS has been tested in two prior small randomized controlled trials (Meng et al., 2012; 2015). Here, daily RIC treatment was associated with improved cerebral perfusion, reduced inflammatory markers, improved functional outcome, and decreased stroke recurrence.

In The Lancet Neurology, Dr. Hou and colleagues (2022) report findings from a large, randomized sham-controlled trial (RICA trial), assessing the effects of daily remote ischemic conditioning as a secondary preventive against new ischemic events in 3,033 patients with ICAS related stroke or transient ischemic attack (TIA). The study was conducted at 84 Chinese centers, and eligible patients had a 50-99% intracranial arterial stenosis and a recent qualifying ischemic event (AIS/TIA)

Patients were randomized 1:1 to RIC (using 200 mmHg cuff occlusion pressure for 5 minutes and 5 minutes reperfusion for 5 cycles on both upper extremities once daily for one year) or Sham RIC (60 mmHg of occlusion pressure but otherwise identical to RIC) in addition to standard care. The primary endpoint was time to first occurrence of ischemic stroke (non-fatal and fatal). In the intention-to-treat analysis no significant difference was found (hazard ratio (HR) 0.87, 95% confidence interval (CI) 0.74-1.03; p = 0.12). In the predefined secondary endpoint, RIC treatment was associated with a significant reduced risk of the composite endpoint of stroke, TIA, or myocardial infarction (HR 0.82, 95% CI 0.71-0.95; p = 0.009). Only 1,409 out of 3,033 patients (46%) had a predefined acceptable treatment adherence of 50% of assigned treatments completed (per-protocol). In the per-protocol analysis, RIC treatment reduced the occurrence of AIS, and the composite endpoint of AIS, TIA, and MI. Treatment adherence did not differ between RIC and Sham-RIC, and there was no difference in the number of serious adverse events between treatment arms. Overall, the trial result was neutral, but with a signal of effect in patients with a good treatment adherence.

Together with previous studies including the newly published RICAMIS trial in JAMA, it seems likely that RIC has beneficial effects in acute stroke, perhaps in stroke prevention, and may be the first cerebroprotective agent to prove translatable to humans (Chen et al., 2022). However, there are some obstacles to overcome. Treatment adherence and the optimal dosing of RIC are currently unknown. Data from clinical studies will be needed to provide answers on how much, how often, and how these choices affect adherence. In line with this, identification of RIC biomarkers may be of great value to move the field forward.

Adherence and dosing are likely connected, and in the current trial, a large drop in adherence occurred after one month of treatment for both RIC and Sham-RIC. It would be very interesting to know the specific reasons for discontinuing the treatment. Was the reason discomfort, too time consuming, or impractical to perform? To accommodate this, Dr. Hou

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and colleagues (2022) describe the development of a future wearable RIC device. Additional aids such as electronic reminders, telephone calls, and health status self-monitoring apps/"gamification" on smartphone may be needed to increase adherence in future studies.

In the current trial, only patient with ICAS were included. The findings need confirmation in other large, preferrable multinational RCTs, with clinical meaningful effects on the primary endpoint measure. Future trials should include different ethnic groups and explore the effect of RIC in different stroke etiologies.

The potential effects of RIC are encouraging while we wait for results from ongoing and future studies.

Conflict of interest

Authors RAB and GA report no conflict of interest.

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