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[Intervention Review]

# Remote ischaemic conditioning for preventing and treating ischaemic stroke

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## ABSTRACT

### Background

Remote ischaemic conditioning (RIC) has been developed as a neuroprotective strategy to prevent and treat ischaemic stroke. It usually involves restricting blood flow to limbs and then releasing the ischaemic blood to promote a neuroprotective effect. Preclinical studies have suggested that RIC may have beneficial effects in ischaemic stroke patients and those at risk of ischaemic stroke. However, existing evidence is insufficient to demonstrate the efficacy and safety of RIC in preventing and treating ischaemic stroke.

### Objectives

To assess the benefits and harms of RIC for preventing ischaemic stroke and for treating people with ischaemic stroke and those at risk for ischaemic stroke.

### Search methods

We searched the Cochrane Stroke Group Trials Register (16 January 2018), the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 12) in the *Cochrane Library* (January 2018), MEDLINE Ovid (1946 to January 2018), Embase Ovid (1974 to January 2018), Web of Science Core Collection (1950 to January 2018) and three Chinese databases (January 2018). We also searched four ongoing trials registers, reference lists, and conference proceedings.

### Selection criteria

We included randomised controlled trials (RCTs) comparing RIC with sham RIC or medical management in people with ischaemic stroke or at risk of ischaemic stroke.

### Data collection and analysis

Two review authors independently selected studies, assessed trial quality and risk of bias, and extracted data. We used the GRADE approach to assess the quality of the evidence.

### Main results

We included seven trials, involving 735 participants, in this review. We analysed the effects of RIC on preventing and treating ischaemic stroke respectively.

We evaluated risk of bias and judged it to be low for generation of allocation sequence in six studies and unclear in one study; unclear for allocation concealment in four studies and low in three studies; high for incomplete outcome data (attrition bias) in five studies and low in two studies; high for blinding in three studies and low in four studies; low for selective reporting; and high for other sources of bias in six studies and low in one study.

We included three trials (involving 371 participants) in the analysis of the effects of RIC on ischaemic stroke prevention. In people with symptomatic intracerebral artery stenosis, recurrent stroke was significantly reduced by RIC (risk ratio (RR) 0.32, 95% confidence interval (CI) 0.12 to 0.83; 2 trials, 182 participants, low-quality evidence). In people with carotid stenosis undergoing carotid stenting, there was no significant difference in the incidence of ischaemic stroke between participants treated with RIC and non-RIC (RR 0.22, 95% CI 0.01 to 4.03; 1 trial, 189 participants, low-quality evidence); however the stroke severity (assessed by infarct volume) was significantly lower in participants treated with RIC (mean difference (MD) -0.17 mL, 95% CI -0.23 to -0.11; 1 trial, 189 participants, low-quality evidence). Adverse events associated with RIC were significantly higher in participants treated with RIC (RR 10.91; 95% CI 2.01 to 59.28; 3 trials, 371 participants, low-quality evidence), but no severe adverse event was attributable to RIC treatment. No participants experienced death or cardiovascular events during the period of the studies; and no trial reported haemorrhagic stroke or improvement in neurological, psychological or cognitive impairment.

We included four trials (involving 364 participants) in the analysis of the effects of RIC on ischaemic stroke treatment. In acute ischaemic stroke, for people receiving intravenous thrombolysis, the rate of death or dependency was significantly increased by RIC treatment compared with non-RIC treatment (RR 2.34; 95% CI 1.19 to 4.61; 1 trial, 285 participants, low-quality evidence). In people with acute ischaemic stroke, there was no significant difference between RIC and non-RIC for reducing stroke severity as assessed by the National Institutes of Health Stroke Scale score and the final infarct volume (standardised mean difference (SMD) -0.24 mL, 95% CI -1.02 to 0.54; 2 trials, 175 participants, very low quality evidence). There was no significant difference between RIC and non-RIC for improving the psychological impairment (SMD -0.37 points, 95% CI -1.15 to 0.41; 1 trial, 26 participants, very low quality evidence) and the cognitive impairment (SMD -0.26 points; 95% CI -0.72 to 0.21; 3 trials, 79 participants, low-quality evidence) in people with acute ischaemic stroke and cerebral small vessel disease. No trial reported ischaemic stroke, recurrent ischaemic stroke, improvement in neurological impairment, hemorrhagic stroke, cardiovascular events, and RIC associated adverse events.

### Authors' conclusions

We found low-quality evidence that RIC may reduce the risk of recurrent stroke in participants with intracerebral artery stenosis and reduce stroke severity in participants undergoing carotid stenting, but it may increase death or dependence in participants with acute ischaemic stroke who are undergoing intravenous thrombolysis. However, there is considerable uncertainty about these conclusions because of the small number of studies and low quality of the evidence.

## PLAIN LANGUAGE SUMMARY

### Remote ischaemic conditioning for preventing and treating stroke caused by low blood flow

#### Review question

What are the benefits of using remote ischaemic conditioning (a noninvasive physical therapy that involves inflating blood pressure cuffs to reduce blood flow in arms and legs, and then releasing the affected blood around the body) in people with stroke or those at risk of stroke caused by low blood flow?

#### Background

Stroke is the leading cause of adult disability globally, and ischaemic stroke (caused by reduced blood flow) accounts for most strokes. Nearly a quarter of individuals with ischaemic stroke will experience further events (recurrent stroke). Remote ischaemic conditioning (RIC) is a strategy to protect and prevent damage to brain tissue by improving its ability to tolerate reduced blood flow. Studies have suggested that RIC may have beneficial effects for preventing and treating ischaemic stroke.

#### Study characteristics

This review included seven studies (specifically randomised controlled trials), involving 735 people. The studies compared RIC with sham RIC or medical management in people with ischaemic stroke or at risk of ischaemic stroke. Three trials (involving 371 people) were eligible for our analysis of RIC for preventing ischaemic stroke, and another four trials (involving 364 people) were eligible for our analysis of RIC for treating ischaemic stroke. The included trials were carried out in China, Denmark, and the UK.

#### Key results

The results of this review are current up to January 2018. In people with narrowing of arteries in the brain, RIC may reduce the risk of recurrent stroke. In people being treated with stenting (the insertion of a metal or plastic tube) for narrowed arteries in the neck, RIC may reduce the size of new brain injuries caused by reduced blood flow. However, its effect on clinical outcomes (stroke and death) was unclear. Adverse events were significantly more common in the RIC group but were not reported to be severe.

Among people with acute ischaemic stroke (where it had only been several hours from symptom onset) who received clot-dissolving medicines, we found that RIC may increase the risk of death or dependency (needing help from others). We found no significant differences in the size of the final stroke. In people with acute ischaemic stroke and chronic blood vessel disease of the brain, RIC did not affect measures of nerve function, mood, or thinking ability.

**Quality of evidence**

There is low-quality evidence which suggests that RIC may help prevent recurrent stroke in people with narrowed arteries in the brain, and may increase death or dependency in people with acute ischaemic stroke who received clot dissolving medication. The evidence is less clear for reducing the volume of the stroke (size of brain lesion caused by low blood flow). Further research is likely to have an important impact on our confidence in these findings.