Self- or caregiver-delivered manual remote ischemic conditioning therapy in acute ischemic stroke is feasible: the Early Remote Ischemic Conditioning in Stroke (ERICS) trial [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

**Background:** Infarct growth and recurrent stroke may be responsible for early morbidity and mortality in patients with acute ischemic stroke. Remote ischemic conditioning (RIC) may reduce infarct growth and prevent recurrent stroke; however, the exact dose remains to be investigated. We hypothesized that self- or caregiver-delivered six cycles of RIC intervention in acute ischemic stroke for the first 12 weeks is feasible and safe compared to the four cycles RIC intervention.

**Methods:** Adult ischemic stroke patients presenting within the first 48 h of symptom onset were screened. Patients with magnetic resonance imaging (MRI) evidence of acute infarct were randomized (1:1) to receive either four or six cycles of RIC therapy sessions two times daily in both arms for 12 weeks. All patients underwent MRI for infarct volume assessment and endothelial-dependent flow-mediated dilation (EDFMD) testing at baseline, 7 days and 12 weeks.

**Results:** A total of 57 patients with mean±SD age of 59.4±12.4 years and median National Institute of Stroke Scale, 4 (IQR, 3-7) were randomised at a median of 23 h 30 min (IQR, 10 h 20 min to 30 h) after symptom onset to either the four-cycle (n=27) or six-cycle group (n=30). A total of 18 (66%) patients completed ≥50% sessions in 12 weeks in the four-cycles group; 21 (69.7%) patients completed ≥50% sessions in 12 weeks in the six-cycle group (p=0.4). There was no between-group differences in infarct growth, early neurological deterioration, recurrent stroke, and EDFMD at 7 days and 90 days.

**Conclusion:** Both four and six cycles of short-term self- or caregiver-delivered RIC therapy is safe and may be feasible in acute
ischaemic stroke patients. Randomised clinical trials are needed to assess efficacy to decrease infarct growth and prevent early neurological deterioration.

**Registration**: Clinical Trial Registry - India: CTRI/2016/11/007495; registered on 25/11/2016.

**Keywords**
Stroke, Cerebral Infarction, Remote Ischaemic Conditioning, Diffusion Magnetic Resonance Imaging

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Introduction

Early neurological deterioration (END) can occur in 14–34% of patients with acute ischemic stroke within the first few days and is associated with worse clinical outcomes. END is attributed to progression of stroke in one third of patients, this proportion increases further in patients with single subcortical stroke. Progression of stroke may be due to infarct growth due to persistent and progression of cerebral ischemia. Infarct growth within the first seven days independently predicts poor outcome in patients with ischemic stroke and is directly proportional to increased functional disability at 3 months as assessed by modified Rankin scale (mRS). Other mechanisms of END are re-occlusion post-recanalization, which may-occur in one-third of patients post-intravenous thrombolysis, hemorrhagic transformation, clot propagation, recurrent stroke and cerebral edema. Furthermore, patients with large artery atherosclerosis and current smokers are more likely to have END.

Currently, strategies targeting prevention of END and recurrent stroke are early revascularization, antithrombotics, risk factor control and stroke unit management. Even in patients undergoing endovascular therapy there is increased incidence of END. Patients with persistent occlusion after endovascular therapy may have an infarct growth of up to 50 ml. Furthermore, risk of recurrent stroke is between 4 and 8% with best medical management in the first 12 weeks. Any new strategy will have to involve both the acute phase in first 7 days and up to 12 weeks post-stroke.

Remote ischemic conditioning (RIC) involves brief cyclic ischemia (5 minutes) and reperfusion (5 minutes) of a distant organ (limb muscles) to protect at-risk (cerebral tissue) organ tissue by increasing ischemia tolerance. In experimental stroke RIC alone or in combination with existing revascularization therapy may have additive effect and reduce infarct size. Human clinical trials in acute ischemic stroke have been promising so far. However, the exact mechanism of action of RIC, duration of therapy, dose of intervention, and feasibility of multiple sessions for multiple weeks in acute ischemic stroke patients are not clear. We hypothesized that self or caregiver delivered six cycles of RIC intervention in acute ischemic stroke for the first 12 weeks is feasible and safe compared to the four-cycle RIC intervention.

Methods

Early Remote Ischemic Conditioning in Stroke (ERICS) was a prospective randomised open-label blinded-endpoint trial conducted in the Emergency and Neurology departments of a tertiary care hospital in Northwest India. The study was conducted between July 2016 and March 2018. The trial stopped after completing 3 months of follow up for all enrolled patients. The Christian Medical College and Hospital, Ludhiana Institutional Ethics Committee approved the study. A written informed consent was obtained from all individual participants included in the study. Patients with acute transient ischaemic attack (TIA) and ischaemic stroke were block-randomised (using Research Randomizer) 1:1 to treatment with 4 or 6 cycles of RIC therapy twice daily for 12 weeks in addition to standard of care management.

Study patients

Patients presenting with first-ever ischemic stroke within first 48 h of the index event were screened. All patients ≥18 years of age, with transient ischemic attack (TIA) or mild to moderate neurological deficits (National Institute of Health Stroke Scale (NIHSS), 0–15) with magnetic resonance imaging (MRI) showing evidence of acute diffusion restriction suggestive of acute infarct and having at least one vascular risk factor (hypertension, diabetes mellitus, dyslipidemia, current smoking, coronary artery disease, symptomatic intracranial or extracranial atherosclerosis and valvular heart disease) were included. Patients with acute infarct volume >70 ml on MRI, premorbidity disability (mRS>2), unstable blood pressure, symptomatic arrhythmia, upper limb injury, history of upper limb arterial atherosclerosis, increased bleeding risk, pregnant and lactating women, stroke due to vasculitis syndrome, patients with history of non-compliance, and patients with easy bruising tendencies were excluded.

The study coordinator/lead investigator delivered RIC therapy while in hospital. Family members were trained for at least three consecutive days for a total of five to six sessions by the study nurse/lead investigator. All patient were given three manual aneroid BP machines for home-therapy. After discharge, the trained family members delivered the RIC therapy at home. The caregiver maintained a daily therapy diary and the study coordinator made a weekly telephone call to the family to assess any fidelity and instrument issues.

Study procedures

All patients received standard of care management. At baseline symptom onset, NIHSS, vital signs, stroke risk factors and past medical history was recorded in a case record form. In addition, patients underwent MRI and measurement for endothelial dependent flow mediated dilation (EDFMD) at baseline, day 7 and day 90. Ankle brachial index (ABI) was measured at baseline and day 90. All patients completed a qualitative feedback to assess intervention non-compliance at the end of study (available as Extended data). The study coordinator...
administered the questionnaire. It had a total of six questions and took less than 3–4 minutes to complete.

**MRI acquisition and analyses.** Patients were imaged on 1.5-T whole-body Signa Excite GE Medical Systems MRI scanner. MRI acquisition protocol consisted of axial T1-, T2- weighted images, fluid attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) and MR angiography with time-of-flight (MRA-TOF). All imaging data was anonymized and assigned a study number for the purpose of blinding researchers analyzing images. All planimetric analyses were performed using AnalyzePro v.1.0 software (AnalyzeDirect, Overland Park, KS, USA). Infarct volumes were measured using semiautomatic threshold-based segmentation techniques by two blinded raters (MK and SB; interclass correlation coefficient, 0.95). All sequential images were co-registered before assessment. Change in infarct volume was defined as the difference between baseline DWI lesion volume and day 7 FLAIR lesion volumes. Infarct growth was defined as increase in infarct volume of ≥0.2 ml. MRA-TOF images were assessed for occlusion and stenosis of the cerebral arteries.

**Endothelial dependent-flow mediated dilation (ED-FMD).** Endothelial function was assessed with ED-FMD with high-resolution Philips ultrasound with L12-3 linear array transducer probe. A longitudinal section of brachial artery was assessed for peak velocity and arterial diameter. A cuff was placed above the observed arterial segment. The cuff was inflated 60 mmHg above the systolic blood pressure for a continuous period of 5 minutes. The post-deflation observation period began 30 seconds before deflation. The ultrasound probe is placed in the same brachial artery region as pre inflation. The total observation period was 150 seconds, 30 seconds prior to deflation and 2 minutes after deflation. All measurements were made for both arms. The baseline assessment was done after the first RIC therapy session. ED-FMD was calculated as the percentage difference (pre inflation and post-deflation) in the arterial diameter and baseline arterial diameter.

**Resting ankle brachial index (ABI).** After the first RIC therapy session resting ABI was assessed with vascular Doppler ultrasound with 8-MHz probe (VD-320, Vcomin, Shenzhen, China). Systolic BP was measured in the arm and followed by

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**Figure 1. Remote ischemic conditioning therapy, 4-Cycles and 6-Cycles.**
the same side leg. The measurements were done on both sides. The probe was placed over the brachial artery in the arm and dorsalis pedis artery in the foot. RABI was calculated as ratio of arm and foot systolic BP.

Outcome measures
The primary outcome measure was safety and feasibility of the 12 weeks of self/care-giver delivered RIC therapy in patients with high-risk acute ischemic stroke within 48 h of symptom onset. The feasibility was assessed on the basis of discontinuation of therapy (defined as stopping of study intervention for >3 consecutive days), completion rates of therapy (100%, 50–99% and <50%) and fidelity of the therapy. Qualitative feedback was taken from all patients to assess the reasons for continuation and discontinuation for therapy.

The secondary imaging outcome measures was absolute infarct volume change ≥0.2 ml at day 7 and silent infarcts on follow-up MRI. The secondary endothelial function outcome measure was percentage difference in the affected side ED-FMD at day 7 and day 90, and absolute difference between the four- and six-cycle group. The secondary clinical outcome was occurrence of early neurological deterioration (NIHSS ≥ 2) at day 7, recurrent stroke within 90 days and mRS at 90 days.

Sample size and statistical analysis
As this was a safety and feasibility study a convenience sample size of n = 50 was planned. Furthermore, a 15% drop rate was estimated, thus an additional seven patients were enrolled.

Variables with continuous data were assessed for normality using the Kolmogorov-Smirnov test. Symptom onsets to intervention duration, NIHSS, Infarct volume, mRS ED-FMD values and therapy sessions completed at 12 weeks were not normally distributed. The between-group differences were assessed using Mann-Whitney U-test. Age, BP, body mass index, and resting ABI was normally distributed and between groups differences for these was assessed using Student’s t-test. The between group differences for the nominal variables was assessed with Chi-square test with Yates correction. Completion rates were expressed as percentages. The qualitative feedback was tabulated as absolute numbers. All analysis was done using SPSS version 24 (IBM, Armonk, USA).

Results
Patient characteristics
A total of 57 patients with mean±SD age of 59.4±12.4 years and median NIHSS score of 4 (IQR, 3-7) were randomised at a median of 23 h 30 min (IQR, 10 h 20 min to 30 h) after symptom onset to either the four-cycle (n=27) or six-cycle (n=30) group (Figure 2). The baseline demographic, clinical and imaging patient characteristics were well matched in both groups (Table 1).

Safety and feasibility
None of the patients developed any serious adverse events related to the study intervention during the 12 weeks study. A total of 19 (33.3%) patients discontinued the study intervention during the study period (Table 2). In total, five (8.8%) patients felt the study intervention duration was too long, three (5.2%) patients developed transient petechial rash over the fore-arm distal to the compression due to capillary fragility and two (3.5%) patients stopped due to pain in the arm during intervention. A further five (8.8%) patients were not able to take therapy for two times daily in both hands in each group. Three (5.2%) patients had thrombophlebitis in the cubital vein and in two patients the post stroke-paresis worsened during the therapy in both the groups. None of the patients discontinued the therapy in the first week, except for those who developed transient petechial rash. There were ten (17.5%) patients lost-to follow-up.

Completion rates and fidelity
The median sessions completed at the end of 12 weeks was 95 (IQR, 52-122) in the four-cycle group and in the six-cycle group was 86 (37.5-122, p=0.5). In the four-cycle group, nine (33%) patients completed 100% of sessions, nine (33%) completed between 50 and 99% of sessions and nine (33%) patients completed <50% sessions in 12 weeks. In the six-cycle group, 10 (33%) patients completed 100% sessions, 11 (36.7%) completed between 50 and 99% of sessions and nine (30%, p=0.9) completed <50% sessions in 12 weeks.

Infarct volume and clinical outcomes
There was no difference in the infarct volume change between groups at day 7 and day 90 (Table 3). Nine (33.3%) patients in the four-cycle group and 13 (43.3%) in the six-cycle group developed infarct growth by day 7. An additional five (18.5%) patients in the four-cycle group and two (6.7%) patients in the six-cycle group developed infarct growth by day 90. There was no significant difference between groups.

In the four-cycle group, two (7.4%) patients developed END and three (11.1%) patients developed silent infarcts. In the six-cycle group, three (10%) patients developed END and two (6.7%) patients developed recurrent stroke, whereas three (10%) more patients developed silent infarcts. There was no between-group difference in the END and silent infarcts. The mRS score at 90 days was similar in both the four- and six-cycle group (2 (IQR, 0-3) vs. 1 (IQR, 0-2.5), respectively; p=0.6).

ED-FMD and ABI
The median ED-FMD in the affected and un-affected sides was similar between groups at the baseline, day 7 and day 90 (Table 3). Also on repeated measures of ANOVA as well there was no between group difference at different time points. The baseline ABI in right and left side was similar in both groups. The ABI at 90 days in right and left side was similar in both groups (Table 3).

Discussion
Our study shows that self or caregiver delivered therapy is feasible and safe in both the four- and six-cycle groups in patients with mild to moderate acute ischemic stroke patients.
Two-thirds of patients completed at least 60 intervention sessions in 6 weeks in both the groups. The primary reason for discontinuation of therapy in both groups was longer duration of intervention. The END and infarct growth was similar in both groups. There was also no between-group difference in the ED-FMD and ABI.

To our knowledge, four studies have assessed safety and feasibility of RIC therapy (1-14 sessions) in acute ischemic stroke patients. Hougaard et al. delivered one session of four cycles in a single arm in the ambulance manually during transportation in a pragmatic study in 247 patients. There was trend of reduced tissue risk of infarction in patients who received intervention. England et al. safely delivered one session of four cycles manually in the single arm in the first 16 hours of symptom onset in 13 patients. Zhao et al. delivered nine sessions of four cycles with an automated machine in single arm in patients undergoing mechanical thrombectomy. The study team could safely deliver 78% of the sessions in the first seven days after thrombectomy. Li et al. delivered 14 sessions of four cycles with an manual machine in single arm within 72 hours of symptom onset. The completed therapy could be delivered in >95% of patients. The longest duration of successful RIC therapy has delivered by Meng et al. for 300 days in both arms two times daily with five cycles session in patients with intracranial atherosclerosis with an automated machine. Self/caregiver delivered manual RIC therapy in both arms may be feasible for a shorter duration (6 weeks) to prevent recurrent stroke and...
Table 1. Baseline demographic, clinical and imaging patient characteristics in the two intervention groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Four-cycle group (n=27)</th>
<th>Six-cycle group (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean±SD)</td>
<td>58.3±12.7</td>
<td>60.1±12.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>14:13</td>
<td>22:8</td>
<td>0.2</td>
</tr>
<tr>
<td>Median symptom onset to intervention, hh:mm (IQR)</td>
<td>24:30 (10:20-34:00)</td>
<td>23:10 (27:30-12:30)</td>
<td>0.4</td>
</tr>
<tr>
<td>NIHSS, median</td>
<td>4 (2-6)</td>
<td>4 (3-7.5)</td>
<td>0.4</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>147.2±22.9</td>
<td>141.1±17.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>85.6±10</td>
<td>85.3±8.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>25 (92.5)</td>
<td>26 (86.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>10 (37)</td>
<td>15 (50)</td>
<td>0.5</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>9 (33.3)</td>
<td>8 (26.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>8 (29.7)</td>
<td>6 (20)</td>
<td>0.5</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>8 (29.6)</td>
<td>12 (40)</td>
<td>0.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.9±3.9</td>
<td>25.7±5.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Anterior circulation stroke, n (%)</td>
<td>18 (66.7)</td>
<td>24 (80)</td>
<td>0.4</td>
</tr>
<tr>
<td>Arterial stenosis or occlusion, n (%)</td>
<td>6 (28.6)</td>
<td>12 (40)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

NIHSS: National Institute Health Stroke Scale; BP, blood pressure.

Table 2. Reasons for discontinuation of study intervention.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Four-cycle group (n=10)</th>
<th>Six-cycle group (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Factors</td>
<td>Felt better, n=1 Death, n=2</td>
<td>Alternative Therapy, n=1</td>
</tr>
<tr>
<td>Caregiver factors</td>
<td>Illness of Caregiver, n=1</td>
<td>Re-hospitalized for Abdominal Surgery, n=1 Death, n=1</td>
</tr>
<tr>
<td>Intervention Related Factor</td>
<td>Transient Petechial Rash, n=1 Pain during Intervention, n=2</td>
<td>Transient Petechial Rash, n=2 Longer duration of Intervention, n=3</td>
</tr>
<tr>
<td></td>
<td>Longer duration of Intervention, n=2 Treatment associated Anxiety, n=1</td>
<td></td>
</tr>
</tbody>
</table>

Infarct growth. It is possible that longer compliance could be achieved with automated device compared to the manual device.

Results using experimental animal models for acute ischemic stroke have suggested that even single five-cycle session may reduce infarct size and improve cerebral perfusion. This effect may be additive to thrombolysis as well. In a single human trial, a five-cycle session twice daily in both upper limbs was able to reduce the risk of recurrent stroke and improve cerebral perfusion. However, it is not known if the benefit would additive if we increase the number of cycles per session. We tested both four- and six-cycle sessions in our study. Though the study was not powered to assess difference in infarct volumes and recurrent stroke, there was no trend of difference in both groups. Furthermore, there was no difference in endothelial function as well given that RIC is an systemic protection strategy. This may indicate that six cycles gives similar results to four cycles.

Ongoing clinical trials with RIC therapy in acute ischemic stroke are delivering therapy for one session in three studies and for 3 to 7 days in three other studies. In our study, 12% of patients had infarct growth even after 7 days and 10% of patients developed silent brain infarcts during the 12-week period. Silent brain infarcts may be associated with increased risk of recurrent stroke and cognitive decline. Furthermore, risk of recurrent stroke is high in the first 90 days after stroke, and risk is persistent even at 1 year. RIC therapy may have to be given for >7 days after acute ischemic stroke in a high risk population.

Our study has several limitations. We enrolled patients at a median of 24 h after symptom onset, it is possible that the infarct growth may be less during this period. A total of 10 (16%) patients were lost to follow-up during the study. The reason for this could be out-pocket expense involved in the standard
treatment of stroke. We relied on the patient/caregiver-completed diaries for the completion rates of RIC therapy. This step was taken to make it easily implementable and generalizable. We used a manual device to deliver RIC therapy, which may reduce the treatment fidelity; however, all patients were given timers and adequate training during hospital stay. We also had no sham group so we could not compare the two different intensities of RIC to a sham control group.

**Conclusion**

Short-term self- or caregiver-delivered manual RIC therapy is safe and feasible in acute ischaemic stroke patients. A larger randomised controlled trial is needed to prove the efficacy of RIC therapy to reduce infarct growth and recurrent stroke.

**Data availability**

**Underlying data**

Harvard Dataverse: Replication Data for: Self or caregiver delivered manual remote ischemic conditioning therapy in acute ischemic stroke is feasible: the Early Remote Ischemic Conditioning in Stroke (ERICS) trial. [https://doi.org/10.7910/DVN/8G01IK](https://doi.org/10.7910/DVN/8G01IK).

This project contains the following underlying data:

- ERICS_Master_Final (all data collected for each patient).

**Extended data**

Harvard Dataverse: Replication Data for: Self or caregiver delivered manual remote ischemic conditioning therapy in acute ischemic stroke is feasible: the Early Remote Ischemic Conditioning in Stroke (ERICS) trial. [https://doi.org/10.7910/DVN/8G01IK](https://doi.org/10.7910/DVN/8G01IK).

This project contains the following extended data:

- INTERVENTION NON COMPLIANCE ASSESSMENT_V2_MK (non-compliance questionnaire)

**Reporting guidelines**


Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

**Acknowledgements**

We acknowledge the work of study coordinator Mr. Naushad Akhtar.

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**Table 3. Outcome measures in the intervention groups.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Four-cycle group (n=27)</th>
<th>Six-cycle group (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median infarct volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.3 (1.2-21.1)</td>
<td>8.3 (1.7-32.1)</td>
<td>0.6</td>
</tr>
<tr>
<td>Day 7</td>
<td>2.9 (1.2-58)</td>
<td>10.7 (1.9-33.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Day 90</td>
<td>3.8 (1.6-39.2)</td>
<td>13.8 (2.4-34.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>% ED-FMD affected side, median (IQR)</td>
<td>Baseline</td>
<td>13 (11-18)</td>
<td>0.3</td>
</tr>
<tr>
<td>Day 7</td>
<td>10 (6-17)</td>
<td>12 (6-20)</td>
<td>0.5</td>
</tr>
<tr>
<td>Day 90</td>
<td>11 (4-18)</td>
<td>11 (7-25)</td>
<td>0.6</td>
</tr>
<tr>
<td>% ED-FMD un-affected side, median (IQR)</td>
<td>Baseline</td>
<td>16.5 (6-25)</td>
<td>0.7</td>
</tr>
<tr>
<td>Day 7</td>
<td>11 (4-29)</td>
<td>11 (5-15)</td>
<td>0.8</td>
</tr>
<tr>
<td>Day 90</td>
<td>12 (6-28)</td>
<td>16 (7-22)</td>
<td>0.6</td>
</tr>
<tr>
<td>Right ankle-brachial index, mean±SD</td>
<td>Day 7</td>
<td>0.95±0.12</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Day 90</td>
<td>0.95±0.13</td>
<td>0.9</td>
</tr>
<tr>
<td>Left ankle-brachial index, mean±SD</td>
<td>Day 7</td>
<td>0.95±0.14</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Day 90</td>
<td>0.96±0.13</td>
<td>0.6</td>
</tr>
</tbody>
</table>

ED-FMD, endothelial dependent flow mediated dilation.
References


Open Peer Review

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Version 1

Reviewer Report 14 February 2020

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This pilot study (Early Remote Ischemic Conditioning in Stroke (ERICS) trial) assessed the feasibility and safety of two remote ischemic conditioning (RIC) therapy regimens in patients after mild to moderate acute ischemic stroke or transient ischemic attack. Patients were randomized to self-administer or receive by a caregiver twice daily sessions of either 4 or 6 bilateral upper arm ischemia-reperfusion cycles. About one-third of patients discontinued therapy over the 12-week follow-up, which was similar between the 4- and 6-cycle groups. Further, no “serious adverse events” were reported in either group. This is timely work in that RIC is currently being considered and investigated as a neuroprotective therapy for ischemic stroke.

I suggest the following to make the article scientifically sound and maximize the study's impact on the field:

1. I believe the most important contribution of this study is its findings on the feasibility of patients manually receiving RIC at home and their compliance to the regimen. Although only a small sample of patients (n=57) were randomized and received the intervention, there appear to be sufficient data to report informative frequencies of discontinuation and qualitative findings on reasons for non-compliance. This is useful information for planning a full-scale RCT to test the efficacy and safety of RIC in acute ischemic stroke patients.

2. Data on the primary outcome measure of discontinuation of therapy should be presented under “Results” --> “Completion rates and fidelity”. I gleaned from the rest of the text that the frequency of discontinuation was 10/27 in the 4-cycle group and 9/30 in the 6-cycle group. These proportions should be compared statistically with a chi square test or presented with confidence intervals.

3. Under "Methods" --> "Outcome measures", how was fidelity of the therapy defined or operationalized for data collection and analysis?
4. Even though no serious adverse events were observed, I do not believe the conclusion about the safety of RIC is appropriate for this study design (i.e., two intervention groups) and small sample size. The safety data should be interpreted as exploratory.

5. Under "Methods" --> "Outcome measures", there are no specific definitions of safety measures. The results mention "serious adverse events" but there is no apparent list of what were considered and measured as SAEs.

6. The interpretation of differences between secondary outcomes appear to heavily rely on statistical differences. As the authors noted, this was a small study and not adequately powered to statistically detect meaningful differences. I suggest the authors revise their interpretation of secondary outcome results to focus on clinical significance and state as exploratory conclusions for replication in larger studies.

7. Were data collected on who was providing the intervention (self and caregiver)? Perhaps in the daily diary or weekly calls? A comparison of compliance between self and caregiver administration would be very informative for planning a full-scale RCT.

8. More discussion of the RIC regimen used in this study (i.e., bilateral, upper arm) in comparison to previous and ongoing studies is important. Some stroke studies administer RIC in only one (nonparetic) arm. Others administer RIC with thigh cuff inflations. How might the feasibility and compliance observed in this study depend on the regimen used and translate to others?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** I am the PI of a pilot study of the feasibility of prehospital delivery of remote ischemic conditioning by emergency medical services in chest pain patients (clinicaltrials.gov NCT03400579). This study is funded by the North Carolina Translational and Clinical Sciences Institute, University of North Carolina at Chapel Hill, which is supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Award Number UL1TR001111.

**Reviewer Expertise:** emergency medicine, stroke, statistics
I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 05 November 2019

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The authors report the results of a small phase 2 study of the adherence to twice daily remote ischemic conditioning with two different intensities (4 cycles or 6 cycles) for 12 weeks (with treatment 5 days or more per week) in patients with recent ischemic stroke (enrolled about 24 hours after stroke). In total, there were 57 patients randomized (27 to 4 cycles, 30 to 6 cycles per treatment). The trial was conducted at a single site in India.

The main finding was that there was no difference between the randomized groups in adherence. Ten were lost to follow up and 15 discontinued the intervention. There were no serious adverse events. There were no differences in secondary efficacy measures (neurological deterioration, infarct volume, and endothelial-dependent flow-mediated dilation) but the trial was not intended to be adequately powered for these outcomes.

The study provides useful information on the tolerability and adherence to RIC, a potentially promising therapy to prevent ischemic brain injury that is the subject of several ongoing trials. Previous studies of RIC in stroke and TIA patients have mostly reported high adherence but have either been limited to short term treatment or studies from a single research group in China. More data on longer term RIC are clearly needed.

The study description and results are presented clearly. I have some suggestions, mostly around the discussion of the findings:

1. The use of a manual blood pressure device might have reduced adherence because it requires more training and effort to use than a simple push-button automated programmable device.

2. The discussion should be more explicit that ideally adherence would be objectively recorded by the device itself, and not rely solely on a patient diary.

3. I would have appreciated even more details on the degree of adherence. This would include: a) the mean or median proportion of expected sessions completed (in addition to the median sessions recorded, which is already reported), and b) finer gradations of percent sessions completed: 50-75% and 76-99%.
4. Clarification: the authors describe completion rates and “fidelity” but it is not clear what fidelity means to them. Is it the same as the percent sessions completed?

5. Some details on the neuroimaging methods should be added.

6. I would say its more than “possible” that most infarct growth would have occurred prior to 24 hours after stroke. In fact, it is likely or even certain that most growth would have occurred before 24 hours. Given the design and results, the trial is much better positioned to evaluate the effect of RIC on recurrent ischemic stroke than infarct growth.

7. The authors should consider briefly discussing prior literature on the dose response between RIC and brain or myocardial protection. How did they decide on using 4 and 6 cycles, or twice daily instead of once daily, and bilateral instead of unilateral.

8. I would be interested to read the authors speculation on the tolerability of bilateral vs. single arm therapy. To me, this seems like it could make a big difference in adherence because the treatment cycles are long and with bilateral therapy neither arm is fully usable when the cuff is inflated. This means that for example it would be difficult to read a book or sip a cup of coffee while undergoing therapy.

**Is the work clearly and accurately presented and does it cite the current literature?**
Yes

**Is the study design appropriate and is the work technically sound?**
Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**
Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**
Yes

**Are all the source data underlying the results available to ensure full reproducibility?**
Yes

**Are the conclusions drawn adequately supported by the results?**
Yes

**Competing Interests:** I am the PI of a trial of remote ischemic conditioning for vascular cognitive impairment (clinicaltrials.gov NCT04109963) funded by the Canadian Institutes of Health Research.

**Reviewer Expertise:** Neurology, stroke, vascular dementia, neuroimaging

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.