Effect of remote ischaemic preconditioning on walking in people with multiple sclerosis: double-blind randomised controlled trial

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ABSTRACT

Background Remote ischaemic preconditioning (RPC) is the exposure of body parts to brief periods of circulatory occlusion and reperfusion. Recent studies have also shown that RPC can improve exercise performance in healthy individuals.

Objective This study aimed to assess the effect of RPC on walking in people with multiple sclerosis (MS).

Methods This was a double-blind randomised controlled clinical trial. We used three cycles of RPC delivered by occluding the upper arm with a blood pressure (BP) cuff inflated to a pressure of 30 mm Hg below the systolic BP. In patients in the sham intervention group, the BP cuff was inflated only to 30 mm Hg below diastolic BP. Outcome measures included the Six-Minute Walk Test (6MWT), gait speed, the Borg rate of perceived exertion (RPE) scale, the tolerability of the RPC using a Numerical Rating Scale for discomfort from 0 to 10, and adverse events. We identified respondents meeting the minimal clinically important difference (MCID) established in the literature in each group.

Results Seventy-five participants completed the study (RPC: 38 and Sham: 37). The distance walked during the 6MWT improved by 1.9% in the sham group and 5.7% in the RPC group (p=0.012). The number of responders meeting MCID criteria in the RPC group was significantly greater compared with the sham intervention group. No serious adverse events occurred.

Conclusion Single cycle of RPC resulted in immediate improvement in walking distances during 6MWT in people with MS.

Trial registration numbers NCT03153553

INTRODUCTION

Regular physical activity improves physical fitness, fatigue, quality of life and gait and also reduces the rate of progression of disability in individuals with multiple sclerosis (MS). 1 However, individuals with MS are less physically active than the general population. Around 78% of people with MS do not participate in any regular physical activity. 2 People with MS often experience problems with gait that limit their participation in physical activity. Problems with gait is a concern for 85% of people with MS. 3 Loss of ambulation in people with MS is due to multiple factors such as muscle weakness, spasticity, ataxia and loss of proprioception. Ongoing disease progression and deconditioning facilitates a self-fulfilling cycle of progressive inactivity. People with MS who are unable to walk are at risk of developing adverse health conditions associated with sedentary lifestyle.

Remote ischaemic preconditioning (RPC) is the exposure of the body to brief periods of circulatory occlusion and reperfusion to protect organs against ischaemic injury. 4 5 6 Although the precise mechanisms of ischaemic conditioning are unknown, RPC is thought to induce changes in gene expression and cellular function, including mitochondrial adaptation to metabolic stress and leucocyte activation. 5 RPC may improve metabolic efficiency by reducing cellular ATP and glycogen depletion and decreasing lactate production. 6 7 8 RPC may also improve skeletal muscle blood flow by inducing vasodilation through increases in nitric oxide production and the number of endothelial progenitor cells. 9 Recent studies have shown that RPC can also improve levels of exercise capacity and performance in athletes and healthy volunteers. 10 11 The aim of this study was to evaluate the efficacy of RPC to enhance gait in people with MS.

MATERIALS AND METHODS

Trial design

This study was a double-blind randomised controlled trial; the patient and the assessor...
were blinded to the intervention. This trial was registered with ClinicalTrials.gov.

**Participants**

Potential patients were identified by consultant neurologists and MS specialist nurses of a regional MS clinic at Royal Hallamshire Hospital, Sheffield, UK, from May 2017 to August 2019. A patient information sheet was given to all potential participants deemed suitable for the trial by the treating team. Participants were given up to 2 weeks to consider their participation in the trial, and those wishing to participate were consented and screened for inclusion and exclusion criteria. Inclusion criteria comprised (1) diagnosis of MS as per 2017 revisions of McDonald’s criteria,13 (2) age 18 or older, (3) sufficient cognitive ability to give informed consent, (4) ability to walk for 6 min and (5) resting systolic BP of less than 170 mm Hg.

Patients with one or more of the following were excluded: (1) cognitive difficulties in giving consent and understanding the questionnaire, (2) inability to walk for 6 min, (3) other neurological conditions that can affect gait like stroke and Parkinson’s disease, (4) systemic illness affecting gait and exercise tolerance and (5) resting systolic BP of 170 mm Hg or more.

**Interventions**

Those eligible to participate were randomised into either the intervention group (RIPC) or the control group using a random number table. The researcher performing the assessments and patients remained blind to group assignment. The study protocol is shown in figure 1. Participants rested in sitting position for 10 min. The resting blood pressure (BP) and heart rate were taken using an automatic BP monitor (Dinamap, GE). Participants were then asked to take part in the Six-Minute Walk Test (6MWT). They were asked to walk on a walkway of 14 m length back and forward for 6 min at a self-determined steady pace. Fluorescent cones were placed on both sides of the walkway to indicate where participants should turn. The total distance walked during this time was measured. Following this, BP and heart rate were measured. The patient was asked to grade the level of exertion using the Borg rate of perceived exertion (RPE) scale.14 BP and heart rate were also measured again after the patient rested for 10 min.

The cuff of a manual BP apparatus was tied around the upper arm of the RIPC group and was inflated to the pressure 30 mm Hg above the resting systolic BP. The inflation was maintained for 5 min followed by cuff deflation lasting 5 min. The cycle was repeated three times.11

The sham intervention was delivered with the manual BP tied to the upper arm. The cuff was inflated 30 mm Hg below the diastolic BP for 5 min followed by deflation for 5 min. The cycle was repeated three times. Participants were then asked to walk for 6 min on the same 14 m walkway. Immediately after the 6 min walk, the participants were asked to rate their level of exertion using the Borg RPE scale, BP, HR, numerical rating scale for discomfort, recoding of adverse events.

The cycle was repeated three times. Participants were then asked to walk for 6 min on the same 14 m walkway. Immediately after the 6 min walk, the participants were asked to rate their level of exertion using the Borg RPE scale, BP, HR, numerical rating scale for discomfort, recoding of adverse events.

Borg RPE scale, and BP and heart rate measurements were taken in the sitting position. Patients were asked if they experienced any discomfort using the Numerical Rating Scale (NRS) from 0 to 10. Any adverse events were also recorded. We particularly looked for redness of skin under the cuff, pain, discomfort or any sensory symptoms of the limb to which RIPC was applied. Following a 10-min rest period, BP and heart rate were measured again.

Outcomes

The primary outcome was percentage improvement in 6MWT. The 6MWT is a test of endurance. The absolute distance change was calculated using the formula postintervention distance–preintervention distance. The percentage improvement was calculated using the formula (postintervention distance–preintervention distance)/preintervention distance)×100. The 6MWT has good reliability and is a strong indicator of exercise tolerance in patients with MS.16 17

Predefined secondary outcomes were gait speed, the Borg RPE scale, the tolerability of the RIPC and the number of people with MS who responded to RIPC. Gait speed was calculated using the formula distance walk from 6MWT (m)/time walk (s). Exertion during 6MWT was assessed before and after intervention using the Borg RPE scale, a valid and reliable tool for measuring the perceived exertion in people with MS.14 The change in exertion was calculated using the formula postintervention Borg scale–preintervention Borg scale. The tolerability of the intervention was examined using an NRS for discomfort due to intervention from 0 to 10 (0 meaning no discomfort and 10 meaning the worst discomfort possible). All adverse events experienced during the trial were recorded. We used the minimal clinically important difference (MCID) established in the literature for defining response. There are three MCIDs reported in the literature for 6MWT for people with MS. They are a relative improvement of 7% in 6MWT distance, absolute distance improvement of 9.1 m from patient perspective and 21.6 m therapist perspective in 6MWT.18 19 The number of participants who had achieved the MCID in each of these three was calculated.

Figure 2  Consort flow diagram. 6MWT1, Six-Minute Walk Test 1; RIPC, remote ischaemic preconditioning.
The literature review showed a mean MCID for the 6MWT of 7% change. Our preliminary data from 22 patients showed that a sample size of 34 in each group would provide 80% power to detect an improvement of 7% after RIPC with a 0.05 two-sided significance level.

**Statistical analysis**

Continuous variables were reported using mean±SD for normally distributed data or median with IQRs 25 and 75 for non-normally distributed data (according to Kolmogorov-Smirnov and Shapiro-Wilk tests). Categorical variables were presented as number (percentage). Paired Student t-tests were used to examine any difference between the distances walked during 6MWT before and after the intervention within each group. Wilcoxon signed-rank tests were used to determine if there was any significant difference between the Borg’s RPE scale before and after intervention within each group. To compare quantitative data between two groups, independent t-test was used for normally distributed data, and Mann-Whitney U-test was employed to analyse for non-normally distributed data. Pearson $\chi^2$ test was used to compare the numbers of responders between groups. All statistical analyses were performed using SSPS Statistics V.18.0. A p value of <0.05 was considered to be statistically significant.

**Results**

We approached 237 patients, of whom 77 consented to take part in the study and 75 completed the study. Of the 160 participants who chose not to participate, 13 did not meet the inclusion criteria; 102 did not give any reason; 33 reported time constraints; and 12 reported that they were not interested in this trial. The consort diagram of the study is shown on figure 2. Two of the recruited participants were excluded from analysis (one in the RIPC group due to systolic BP of >170 mm Hg and one in the sham group due to incomplete data collection).

Baseline characteristics of both sham and RIPC groups are shown in table 1.

Within-group comparisons before and after intervention in the sham and RIPC groups are shown in table 2.

The walking distance improved by 1.9% in the sham group and by 5.7% in the RIPC group. Between-group comparisons are shown in table 3.

There was a statistically significant improvement in the percentage change of distance walked during 6MWT.
Table 3  Comparison between sham and RIPC intervention groups

<table>
<thead>
<tr>
<th></th>
<th>Sham intervention (n=37)</th>
<th>RIPC intervention (n=38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance walked during 6MWT before intervention (m), mean±SD</td>
<td>318.2±124.3</td>
<td>288.3±127.7</td>
<td>0.307*</td>
</tr>
<tr>
<td>Distance walked during 6MWT after intervention (m), mean±SD</td>
<td>324.8±129.4</td>
<td>301.8±123.8</td>
<td>0.434*</td>
</tr>
<tr>
<td>Improvement in distance walked during 6MWT after intervention (m), median (IQR)</td>
<td>7.3 (−3.7 to 17.1)</td>
<td>16.0 (4.8–25.1)</td>
<td>0.026†</td>
</tr>
<tr>
<td>Percentage of improvement after intervention in 6MWT, median (IQR)</td>
<td>1.9 (−0.8 to 0.5)</td>
<td>5.7 (1.3–10.7)</td>
<td>0.012†</td>
</tr>
<tr>
<td>Speed of walking during 6MWT before intervention (m/s), mean±SD</td>
<td>0.88±0.34</td>
<td>0.80±0.35</td>
<td>0.307*</td>
</tr>
<tr>
<td>Speed of walking during 6MWT after intervention (m/s), mean±SD</td>
<td>0.90±0.36</td>
<td>0.84±0.34</td>
<td>0.443*</td>
</tr>
<tr>
<td>Improvement in speed of walking after intervention (m/s), median (IQR)</td>
<td>0.02 (−0.01 to 0.05)</td>
<td>0.05 (0.01–0.07)</td>
<td>0.029†</td>
</tr>
<tr>
<td>Borg RPE scale before intervention, median (IQR)</td>
<td>11 (8.5–13.0)</td>
<td>11.5 (7.8–14.0)</td>
<td>0.381</td>
</tr>
<tr>
<td>Borg RPE scale after intervention, median (IQR)</td>
<td>11 (8.5–13.0)</td>
<td>11 (7.0–13.3)</td>
<td>0.962</td>
</tr>
<tr>
<td>Borg RPE scale change, median (IQR)</td>
<td>0 (0.2)</td>
<td>0 (−2,1)</td>
<td>0.065</td>
</tr>
<tr>
<td>Numerical ratio scale for discomfort due to intervention, median (IQR)</td>
<td>1 (0–2.5)</td>
<td>4 (3–6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p-t-test. †Mann-Whitney U-test.
6MWT, Six-Minute Walk Test; RIPC, remote ischaemic preconditioning; RPE, rate of perceived exertion.

(p=0.012). The NRS for discomfort due to intervention was greater in the RIPC group compared with the sham group (p<0.001). The number of responders as defined by MCID in 6MWT is shown in table 4.

The number of responders in the RIPC group was significantly greater irrespective of the criteria for MCID used.

We did not encounter any serious adverse event and none of the patients withdrew from this study because of side effect. Adverse events of both sham and RIPC intervention groups are shown in table 5.

The common adverse events in RIPC intervention group were tingling (44.7%), redness of skin (42.1%), pins and needles (26.3%), and skin marking (21.1%).

Table 4  Number of patients with MCID in 6MWT after interventions

<table>
<thead>
<tr>
<th>MCID criteria</th>
<th>Sham intervention (n=37)</th>
<th>RIPC intervention (n=38)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of 7% in the distance walked after intervention18</td>
<td>6 (16.2%)</td>
<td>15 (39.5%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Improvement of 9.1 m in distance walked after intervention19</td>
<td>15 (40.5%)</td>
<td>26 (68.4%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Improvement of 21.6 m in the distance walked after intervention19</td>
<td>5 (13.5%)</td>
<td>13 (34.2)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*Pearson χ² test.
MCID, minimal clinically important difference; 6MWT, Six-Minute Walk Test; RIPC, remote ischaemic preconditioning.

Table 5  Adverse events of both sham and RIPC intervention groups, providing number (per cent)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Sham intervention (n=37)</th>
<th>RIPC intervention (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tingling</td>
<td>5 (13.5%)</td>
<td>17 (44.7%)</td>
</tr>
<tr>
<td>Redness of skin</td>
<td>13 (35.1%)</td>
<td>16 (42.1%)</td>
</tr>
<tr>
<td>Pins and needles</td>
<td>2 (5.4%)</td>
<td>10 (26.3%)</td>
</tr>
<tr>
<td>Skin marking</td>
<td>2 (5.4%)</td>
<td>8 (21.1%)</td>
</tr>
<tr>
<td>Pain</td>
<td>0</td>
<td>3 (7.9%)</td>
</tr>
<tr>
<td>Uncomfortable</td>
<td>1 (2.7%)</td>
<td>3 (7.9%)</td>
</tr>
<tr>
<td>Numbness</td>
<td>1 (2.7%)</td>
<td>2 (5.3%)</td>
</tr>
<tr>
<td>Tightness</td>
<td>2 (5.4%)</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Swelling fingers or hand</td>
<td>4 (10.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>1-Unbalanced</td>
<td>1-Slightly dizzy</td>
</tr>
<tr>
<td></td>
<td>2-Cold fingers</td>
<td>1-Hot in forearm and hand</td>
</tr>
<tr>
<td></td>
<td>1-Light headed</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19 (51.4%)</td>
<td>3 (7.9%)</td>
</tr>
</tbody>
</table>

RIPC, remote ischaemic preconditioning.
DISCUSSION
This trial was the first clinical study of RIPC in patients with MS. Previous clinical studies have focused on patients suffering acute coronary events, undergoing cardiac surgery or stroke, while non-clinical studies have mainly involved performance of sports persons.20–22 Such studies have demonstrated the safety and tolerability of RIPC. A recent systematic review demonstrated that RIPC improved time-trial performance in 67% of athletes,24 another demonstrated improved maximal knee extensor strength after a single session of RIPC in chronic stroke.22
Cammaro-Lemero and colleagues recently hypothesised potential mechanistic benefits of RIPC in MS.25 There are two main ways RIPC could induce neuroprotective changes: (1) via ischaemic/hypoxic mechanisms and (2) protection against inflammatory demyelination/neurodegeneration. Unpublished data from a thesis on gait speed in long-distance athletes demonstrated that RIPC produces any sustained benefit in people with MS. This study involved a single quaternary referral centre and recruited only patients who could walk for 6 min, limiting the generalisability of the results. We are in the process of performing a community-based study evaluating the effects of 6 weeks of daily RIPC on activity and gait.

CONCLUSION
This is the first clinical trial of RIPC on gait in patients with MS. A significant number of patients achieved a beneficial MCID in the primary outcome of walking distance. RIPC is a safe and well-tolerated intervention.

Limitations
Our review of literature showed several small single-centre RIPC trials with positive outcomes in different health conditions, only for no beneficial outcome to be identified in subsequent definitive trials. We administered only a single cycle of RIPC in a clinical research setting and studied its immediate effect on 6MWT. As we did not study effects of multiple regular RIPC and longer term effects, we do not know whether RIPC produces any sustained benefit in people with MS. This study involved a single quaternary referral centre and recruited only patients who could walk for 6 min, limiting the generalisability of the results. We are in the process of performing a community-based study evaluating the effects of 6 weeks of daily RIPC on activity and gait.

CONCLUSION
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Contributors KPSN and CM contributed to the design of the study. KPSN was the principal investigator for the study. KPSN, CC, DH, RR, AI, JD, AA, RBL, BS, SP and DP did patient recruitment. KPSN, CC, DH, and RR did consenting and RIPC intervention. LA, EB, KPSN, CC, DH and RR did collection of outcome measures and study management. CC performed the data analysis and prepared the manuscript. KB helped with the data analysis. All authors contributed to the preparation of the final manuscript.

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Disclaimer The views expressed are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

Competing interests None declared.

Patient consent for publication Not required.
REFERENCES


