Effect of Repetitive Transcranial Magnetic Stimulation on Gait Function and Strength Among Patients with Spinal Cord Injury: A Meta-Analysis

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Abstract

Purpose: This meta-analysis investigated the efficacy of repetitive transcranial magnetic stimulation (rTMS) in the context of spinal cord injury (SCI). The study focused on assessing its impact on muscle strength and gait speed, measured through the lower extremities motor score of the American Spinal Injury Association (ASIA) and 10-Meter Walk Test scores (10MWT).

Methods: The PubMed, Cochrane Library, and Embase databases were searched for articles published through Oct 2023. We enrolled only randomized controlled trials. The Cochrane Collaboration risk of bias tool was used for quality assessment. Outcomes were analyzed as standardized mean differences (SMDs) with 95% confidence intervals (CIs). We included four studies with a total of 95 patients.

Results: Our analysis revealed a significant increase in muscle strength of the lower limbs (SMD: 0.451; 95% CI: 0.041 to 0.862; $I^2 = 2.4\%$). The 10-Meter Walk Test scores did not significantly improve after management in the rTMS group (SMD: 0.050; 95% CI: $-0.624$ to $0.523$; $I^2 = 25.7\%$) compared with the sham group, which can be attributed to the high heterogeneity and type 2 error.

Conclusion: Due to limited data in the literature, our results neither support nor discourage the use of rTMS in treating patients with SCI. To explore the potential of rTMS, more research should be conducted to unveil the effectiveness of rTMS among individuals with SCI.

Keywords: Spinal cord injury, Repetitive transcranial magnetic stimulation, Gait, Lower extremities

1. Introduction

The global prevalence of spinal cord injury (SCI) is between 236 and 1009 per million. SCI frequently causes a loss in strength or sensation below the site of injury. Moreover, patients with SCI experience pain, depression, and a lower quality of life due to diminished ambulatory function. Good mobility requires adequate muscle strength for partial weight bearing. Crozier et al. revealed an association between quadriceps strength and subsequent ambulatory function. Kim determined that the flexors, extensors, and abductors of the hip are crucial determinants of mobility.

Apart from resistance training, repetitive transcranial magnetic stimulation (rTMS)
has been used as a novel therapeutic option to improve lower limb strength.\textsuperscript{5} rTMS is a noninvasive brain stimulation technique that either increases or decreases cortical excitability depending on the stimulation parameters.\textsuperscript{6} Moreover, rTMS can alter brain neuronal plasticity through several mechanisms, which contributed to neurotrophic effects of rTMS on dentic and axonal regeneration, including change in brain-derived neurotrophic factor concentration and up-regulating GAP43 expression.\textsuperscript{7,8}

Randomized controlled trials (RCTs) have reported that rTMS can accelerate the recovery of muscle strength and motor function with few adverse events in incomplete spinal cord injury.\textsuperscript{9,10} However, the small sample size and discrepancies between studies may hinder the future application of rTMS. Two articles of meta-analyses have investigated the efficacy of rTMS in treating motor recovery among patients with SCI.\textsuperscript{11,12} Duan et al. concluded that rTMS can improve both lower extremities motor score (LEMS) of the American Spinal Injury Association (ASIA) and the 10-Meter Walk Test (10MWT) score. However, one paper included in the meta-analysis was a non-randomized controlled study, which may have impeded the strength of the findings. Additionally, Krogh et al., and Kesikburun et al. conducted two RCTs in 2021$\&$2023, which showed opposite direction in treatment effect.\textsuperscript{13,14}

We conducted a meta-analysis to evaluate the effect of rTMS on improvement of motor strength and function among patients with SCI. The study focused on assessing its impact on muscle strength and gait speed, measured through the lower extremities motor score of the American Spinal Injury Association (ASIA) and 10-Meter Walk Test scores (10MWT). We chose LEMS score as the primary outcome. The potential moderators of age, stimulation site, and initial ambulatory rate were also assessed in our study.

2. Materials and methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.\textsuperscript{15} We did not register or publish a prior protocol.

2.1. Eligibility criteria

We enrolled RCTs that evaluated rTMS treatment among patients with SCI. All selected articles were required to include 2 or more treatment arms, one of which must be a group treated with rTMS and the other must be a control group. The publication language was no restriction.

2.2. Search strategy

This study was conducted in Oct 2023. We searched articles on PubMed published from 2002 to Oct 2023, Embase from 2002 to Oct 2023, and Cochrane from the first date of publication to Oct 2023. The keywords used were as follows: (“spinal cord injury [MeSH terms]” OR “spinal cord [Title/Abstract]”) AND (“transcranial magnetic stimulation [Title/Abstract]” OR “rTMS [Title/Abstract]” OR “theta burst [Title/Abstract]”)

2.3. Study selection and data extraction

Two reviewers (YTC and YCS) examined titles and abstracts to identify eligible articles. The reference list of retrieved works was subsequently used to search for related papers. The following data were extracted from each study: author, publication year, patient characteristics (patient number, age, illness duration from diagnosis), rTMS details, comparator arm regimens, and clinical outcomes (ASIA LEMS and 10MWT). We employed the quantile estimation approach proposed by McGrath et al. when medians and interquartile ranges were reported instead of means and standard deviations.\textsuperscript{16} Authors or journals were contacted if the data were incomplete or unavailable.

2.4. Quality assessment

We used the Cochrane Collaboration tool for assessing the risk of bias during quality assessment.\textsuperscript{17} The quality of studies was evaluated by 2 reviewers (YTC and YCS) independently. The third author (YCL) adjudication was used for disagreements. The results were summarized using the Review Manager software version 5.3 (Cochrane, London, UK) and are presented in Table 2.
2.5. Statistical analysis

The primary outcome of the meta-analysis was LEMS score, and the secondary outcome was the 10MWT speed. The data were extracted at baseline and after the final rTMS treatment. We used a random effects model for effect size pooling with a 95% confidence interval (CI) and standardized mean differences (SMDs). Between-study heterogeneity was assessed using \( I^2 \), and considerable heterogeneity was determined if \( I^2 > 50 \% \). Subgroup analyses for all outcomes were conducted for age, stimulation site, and initial ambulatory rate to identify any moderating effects. A significant difference between effect sizes was indicated by nonoverlapping 95% CIs. Egger tests was used to detect publication bias, and a two-tailed \( P < .10 \) was considered statistically significant. We applied a sensitivity analysis for the primary outcome by removing one trial at a time and analyzing the remaining trials to estimate each study’s contribution to the overall effect size. All analyses were performed using Comprehensive Meta-Analysis software version 3.

2.6. Certainty of evidence

The certainty of the evidence for the primary outcome was evaluated by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. Due to our study included only RCTs, the results began with high certainty, and the final rating depended on the overall risk of bias, imprecision, inconsistency, indirectness, and publication bias.

3. Results

3.1. Study selection

The initial search in database yield total of 4099 articles. Four RCTs with a total of 95
The number of patients ranged from 19 to 31, and the mean age ranged from 34.7 to 54.5 years old. The number of treatment sessions ranged from 15 to 20. The duration from the first to the last treatment session ranged from 3 to 4 weeks. The total number of pulses ranged from 24000 to 36000, and the pulse per session was 1600 to 1800. The target brain included the vertex and bilateral leg cortex. Other extracted data from the included studies are presented in Table 2.

### 3.2. Risk of bias assessment

Three articles included in our meta-analysis were revealed to have an unclear risk of selection bias because they did not report the details of random sequence generation or allocation concealment (Fig. 2). The articles by Kumru et al. and Soren et al. had a high risk of attrition bias due to incomplete reporting of outcome data.

### 3.3. Outcome and measurement

#### 3.3.1. Lower extremities motor score

The LEMS was used to assess all articles. The LEMS after treatment was significantly better in the rTMS group (SMD: 0.451; 95 % CI: 0.035 to 0.867; $I^2 = 2.41 %$; Fig. 3) than in the sham group. The Egger test indicated no publication bias ($P = .44$). The sensitivity analysis yielded a more positive trend (SMD: 0.641; 95 % CI: 0.158 to 1.123) with low heterogeneity ($I^2 = 0 %$) was observed after we removed the study by Kesikburun et al.

#### 3.3.2. 10-Meter walk test

The 10MWT was used in all three RCTs. The 10MWT performances reported after treatment were not significantly better in the rTMS group (SMD: −0.050; 95 % CI: −0.624 to 0.523; $I^2 = 25.7 %$; Fig. 4) compared with the sham group. The Egger test indicated no publication bias ($P = .26$). The sensitivity analysis did not reveal any differing results. However, a more positive trend (SMD: 0.641; 95 % CI: 0.158 to 1.123) with low heterogeneity ($I^2 = 0 %$) was observed after we removed the study by Kesikburun et al.
0.137; 95 % CI: 0.478 to 0.753) with low heterogenicity (I² = 15 %) was observed after we removed the study by Krogh et al.

### 3.3.3. Subgroup analysis

Results of the subgroup analysis, divided by age, stimulation site, and initial ambulatory rate, are presented in Tables 3–5 respectively. For the group with an initial ambulatory rate of less than 80 %, rTMS improved the LEMS. However, no significant difference was observed among all subgroups.

### 3.4. Certainty of evidence

Overall evidence was assessed using GRADE. The certainty of the evidence of the 10MWT improvements after rTMS treatment showed a low quality of evidence. The level was downgraded due to a high CI and significant between-study heterogeneity. The details are presented in Table 6.

### 4. Discussion

Our systematic review and meta-analysis revealed that rTMS may improve LEMS but not 10MWT. However, due to limited data from insufficient research, our results could not support or discourage the use of rTMS among patients with SCI (see Table 6.1).

The gain in LEMS was consistent with the latest meta-analysis by Duan et al. However, the inclusion of two recently published RCTs conducted by Krogh et al. and Kesikburun et al. showed no significant difference on 10MWT. Although we did not find significant differences between subgroups, the I² decreased to 0 for the 10MWT after the trial by Krogh et al. and Kumru et al. were excluded, who included rTMS group patients (Kumru:0.28 m/s, Krogh: 0.68 m/s) with obviously slower baseline gait speed at baseline compared with sham group (Kumru:0.64 m/s, Krogh: 0.92 m/s).

On the contrary, the differences of baseline speed between rTMS and sham group are less than 0.1 m/s among trials of Benito et al. and Kesiburun et al. We suggest that future studies should have comparable baseline gait speed.

Kumru et al. included patients with more severe SCI and with a lower ambulatory rate, defined as the ability to perform the 10MWT in Kumru’s study, was higher in the real group (71 %) compared with the sham group (40 %) on the follow up period. Such differences may have led to bias when assessing the 10MWT because the real rTMS group consisted of many patients who were originally unable to walk. These patients may have had more severe SCI compared with those who were able to walk before receiving rTMS. We suggest that future studies exercise caution if the patients demonstrate a lower initial ambulation rate.

rTMS affects patients with SCI by increasing the excitatory drive in the corticospinal neuron and reducing corticospinal inhibition. This may result in improvements in muscle power and increased lower limbs muscle power may further enhance ambulatory function; studies have reported a

<table>
<thead>
<tr>
<th>Reference</th>
<th>Detail of interventions</th>
<th>Last follow-up</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benito et al., 2012</td>
<td>vertex, 20Hz, 90 % RMT, 1800 pulses/session over 20 min; 15 sessions/3 weeks</td>
<td>(1) Day after last session of rTMS; (2) 2 weeks after last rTMS</td>
<td>Facial muscle twitching</td>
</tr>
<tr>
<td>Kumru et al., 2016</td>
<td>Vertex, 20Hz, 90 % RMT, 1800 pulses/session over 20 min; 20 sessions/4 weeks</td>
<td>(1) Day after last session of rTMS; (2) 4 weeks after last rTMS</td>
<td>Facial muscle twitching, headache</td>
</tr>
<tr>
<td>Krogh et al., 2021</td>
<td>Bilateral leg motor cortex, 20Hz, 100 % RMT, 1800 pulse/session over 20 min; 20 sessions/4 weeks</td>
<td>MVC, 10MWT, TUG, 6MWT: day after last session</td>
<td>Seizure</td>
</tr>
<tr>
<td>Kesikburun et al., 2023</td>
<td>Vertex, 20Hz, 110 % RMT, 1600 pulse/session over 20 min, 15 sessions/3 weeks</td>
<td>(1) Day after last session of rTMS; (2) 2 weeks after last rTMS</td>
<td>nil</td>
</tr>
</tbody>
</table>

LEMS: lower extremities motor score, 10MWT: 10-Meter Walk Test, 6MWT: 6-Meter Walk Test, TUG: time up and go, MVC: maximum voluntary contraction.
positive correlation between quadricep strength and ambulation rate at 1 year after SCI diagnosis.\textsuperscript{22} This correlation may explain the advancement of LEMS in our meta-analysis. Although the improvement in 10MWT in our meta-analysis did not reach statistical significance, it may have been caused by high heterogeneity and type 2 error. Although no study has discovered moderators of efficacy of rTMS intervention among patients with SCI, rTMS for patients with major depression disorder or fibromyalgia found that disease severity and stimulation parameters may be related to the treatment efficacy.\textsuperscript{23–25} An age of 50 years or more has also been reported as a negative prognostic factor for walking
Fig. 3. Forest plot of standardized mean differences in lower extremities motor score (LEMS) after treatment. Squares indicate effect sizes of individual studies, lines indicate 95% CI, and diamond indicates the summarized effect size.

\[
\text{I}^2 = 2.41\%
\]

Favor control  Favor rTMS

Fig. 4. Forest plot of standardized mean differences in 10-m walk test (10MWT) after treatment. Squares indicate effect sizes of individual studies, lines indicate 95% CI, and diamond indicates the summarized effect size.

\[
\text{I}^2 = 25.7\%
\]

Favor control  Favor rTMS

Table 3. Subgroup analysis by mean age more than fifty-year-old.

<table>
<thead>
<tr>
<th></th>
<th>10MWT</th>
<th>LEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ≤ 50</td>
<td>0.137 (−0.478 to 0.753)</td>
<td>0.387 (−0.156 to 0.93)</td>
</tr>
<tr>
<td>Mean age &gt;50</td>
<td>−0.608 (−1.611 to 0.394)</td>
<td>0.68 (−0.247 to 1.606)</td>
</tr>
<tr>
<td>Total</td>
<td>−0.050 (−0.624 to 0.523)</td>
<td>0.451 (0.041−0.862)</td>
</tr>
</tbody>
</table>

10MWT: 10-Meter Walk Test, LEMS: lower extremities motor score.

Table 4. Subgroup analysis by stimulation site.

<table>
<thead>
<tr>
<th></th>
<th>10MWT</th>
<th>LEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertex</td>
<td>0.147 (−0.409 to 0.702)</td>
<td>0.396 (−0.063 to 0.854)</td>
</tr>
<tr>
<td>Bilateral leg cortex</td>
<td>−0.608 (−1.611 to 0.394)</td>
<td>0.68 (−0.247 to 1.606)</td>
</tr>
<tr>
<td>Total</td>
<td>−0.050 (−0.624 to 0.523)</td>
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</tbody>
</table>

10MWT: 10-Meter Walk Test, LEMS: lower extremities motor score.

Table 5. Subgroup analysis by initial ambulatory rate less than 80 %.

<table>
<thead>
<tr>
<th></th>
<th>10MWT</th>
<th>LEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>initial ambulatory rate ≥ 80 %</td>
<td>0.063 (−0.593 to 0.719)</td>
<td>0.268 (−0.227 to 0.764)</td>
</tr>
<tr>
<td>initial ambulatory rate &lt;80 %</td>
<td>−0.637 (−1.932 to 0.659)</td>
<td>0.855 (0.12−1.591)</td>
</tr>
<tr>
<td>Total</td>
<td>−0.050 (−0.624 to 0.523)</td>
<td>0.451 (0.041−0.862)</td>
</tr>
</tbody>
</table>

10MWT: 10-Meter Walk Test, LEMS: lower extremities motor score.
Table 6. Certainty of evidence for improvement of LEMS after treatment.

<table>
<thead>
<tr>
<th>Number of Participants</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>indirectness</th>
<th>imprecision</th>
<th>Publication bias</th>
<th>Summary of findings, SMD(95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>Serious limitation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious limitation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No serious limitation&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Serious limitation&lt;sup&gt;d&lt;/sup&gt;</td>
<td>undetectable</td>
<td>rTMS: 7.25 (6.62−7.88)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CI: confidence interval; LEMS: lower extremities motor score; rTMS: repetitive transcranial magnetic stimulation; SMD: standardized mean difference. 

<sup>a</sup> All studies included scored unclear risk of bias due to lack of method of random sequence generation or allocation concealment and two of articles had incomplete outcome data. 

<sup>b</sup> The I² was below 50 %. 

<sup>c</sup> No indirectness was detected in this outcome. 

<sup>d</sup> The upper and lower limit of 95 % CI ranged from large to small effect size. 

<sup>e</sup> This was calculated by pooling the rTMS group of the 1 comparison included in the primary outcome, comparing the LEMS score before and after treatment. 

<sup>f</sup> This was calculated by pooling the sham group of the 1 comparison included in the primary outcome, comparing the LEMS before and after treatment.

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<tr>
<th>Number of Participants</th>
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<tr>
<td>95</td>
<td>Serious limitation&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>No serious limitation&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Serious limitation&lt;sup&gt;d&lt;/sup&gt;</td>
<td>undetectable</td>
<td>rTMS: 0.19 (−0.91)</td>
</tr>
</tbody>
</table>

CI: confidence interval; 10MWT: 10 min walking test; rTMS: repetitive transcranial magnetic stimulation; SMD: standardized mean difference. 

<sup>a</sup> All studies included scored unclear risk of bias due to lack of method of random sequence generation or allocation concealment and two of articles had incomplete outcome data. 

<sup>b</sup> The I² was below 50 %. 

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<sup>d</sup> The upper and lower limit of 95 % CI ranged from large to small effect size. 

<sup>e</sup> This was calculated by pooling the rTMS group of the 1 comparison included in the primary outcome, comparing the 10MWT before and after treatment. 

<sup>f</sup> This was calculated by pooling the sham group of the 1 comparison included in the primary outcome, comparing the 10MWT before and after treatment.
recovery after SCI.\textsuperscript{25} We believe that age may also affect the efficacy of rTMS among patients with SCI.

Our study has some strengths. We only included RCTs, which made the evidence in this review robust. Second, our meta-analysis assessed the heterogeneity in the LEMS and 10MWT among patients with SCI receiving rTMS. The results may justify further large-scale RCTs, and the results of the sensitivity analysis may aid future research with avoiding bias when evaluating ambulatory function.

Our meta-analysis has several limitations. First, all the included studies had tested only a few patients. Such low statistical power may result in false negatives. Second, the patient demographics and stimulation parameters were heterogeneous. Although no potential moderators were related to the treatment effects, the possibility of type 2 error caused by low statistical power was high. Third, the concurrent therapy during the study period differed among studies, which may have interfered with the results. Fourth, the 10MWT was not the primary outcome in most of the RCTs enrolled in our review, which may have led to bias. Future studies investigating the role of rTMS in the recovery of gait velocity and muscle strength should employ a larger study population and consider the ambulation rate at baseline for patient characteristics.

5. Conclusion

This meta-analysis revealed that LEMS improved after rTMS treatment among patients with SCI, but 10MWT scores did not become better. However, due to limited availability of data in the existing literature, our results neither definitively support nor discourage the utilization of rTMS in treating SCI patients. To enhance the understanding of this intervention's potential, future studies should not only validate our findings but also explore potential moderating factors that could optimize the effectiveness of rTMS among individuals with SCI.

Conflicts of interest

We declared there is no conflict of interest.

References


