Electromyographic Motor Outcomes in Short- and Long-Term Recovery of Incomplete Spinal Cord Injury Treated with Neuromodulation Techniques

Desfechos Motores Eletroneuromiográficos na Recuperação de Curto e Longo Prazo de Trauma Raquimedular Incompleto Tratados com Técnicas de Neuromodulação

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ABSTRACT

Spinal cord injury (SCI) incidence in the United States vary from 25 to 59 new cases per million inhabitants in a year with average of 40 per million. Neuromodulation consists in devices to neurally regulate the body’s organs for medical benefit. These strategies that strengthen neuronal activity have shown promising results in restoring sensorimotor function after chronic spinal cord injury (SCI). This review was made using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A systematic review of English articles was conducted using MEDLINE/PubMed (NLM) and Biblioteca Virtual em Saúde (BVS). The selected articles were from September 1982 to December 2020. The MeSH and keywords used in both databases were “neuronal plasticity”, “spinal cord injury”, and ”neuromodulation”. Four studies were eligible for inclusion, comprising 79 patients with a mean age 42.67 years and a male:female of 60:19. Three studies evaluated the neuromodulation techniques that combined central nervous system (CNS) and peripheral nervous system (PNS) stimulation. One clinical trial evaluated the PCMS therapeutic potential. Although SCI represents one of the main causes of disability, there are still few quality studies that assess the impact of neuromodulation treatments in this condition. The majority (3/4) of the articles focused in the combination of CNS and PNS stimulation, but the results were controversial, reaffirming the need to perform with better quality articles. More clinical studies should be conducted in order to enhance the knowledge in this type of treatment in SCI patients.

Keywords: Spinal Cord Injury; Neuromodulation; Neuronal Plasticity

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INTRODUCTION

Spinal cord injury (SCI) incidence in the United States in 2020 was estimated at 54 cases per million inhabitants\(^1\). Data from the National Spinal Cord Injury 2020\(^2\) show that between 2010 and 2019 the incidence of automobile injuries was the main cause responsible for 38.29% of SCIs, falls accounted for 31.32%, acts of violence, such as assaults or injuries by fire guns 13.84%, sports 8.46% and finally injuries classified as other causes with 8.09%. Costs associated with spinal cord injury are greatly influenced by the patient’s severity of injury and ther resultant degree of disability\(^3\). In 2011, the average per-person yearly expenses ranged from $334,170 in the first year and $40,589 in each subsequent year for patients with incomplete injury\(^2-4\).

Neuromodulation is a therapeutic method that aims to alter the nerve activity through electric stimulation. Currently, it represents a relevant form of auxiliary treatment for recovery in patients with SCI\(^5-7\). Strategies that strengthen neuronal activity have shown promising results in restoring the sensory function after spinal cord injury\(^6-11\). Current literature showed that neuromodulation through trans spinal stimulation increases the response capacity of the spinal motoneuron. It was noticed that the corticospinal tract proved to be capable of plasticity after injury in animal models, increasing the synaptic and improving the motor control\(^5-11\). However, few studies analyzed the technique therapeutic potential in human subjects. Therefore, our study aims to retrieve from the literature all the studies regarding the use of neuromodulation in incomplete SCI and its motor outcomes in humans.

METHODS

This review was made using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement\(^12\). A systematic review of English articles was conducted using MEDLINE/PubMed (NLM) and Biblioteca Virtual em Saúde (BVS), and the selected articles were from 1982 to 2020. The MeSH and keywords used in both databases were: “neuronal plasticity”, “spinal cord injury” and “neuromodulation”. Four studies were eligible for inclusion, comprising 79 patients with age média de 42,67 anos and a men:woman of 60:19. Três estudos avaliaram técnicas de neuromodulação que combinavam a estimulação do sistema nervoso central (SNC) e do sistema nervoso periférico (SNP). Um ensaio clínico avaliou o potencial terapêutico da PCMS. Embora o TRM represente uma das principais causas de incapacidade, ainda existem poucos estudos de qualidade que avaliem o impacto dos tratamentos de neuromodulação nessa condição. A maioria (3/4) dos estudos enfocou a combinação da estimulação do SNC e SNP, porém os resultados foram controversos, reafirmando a necessidade de realização de artigos de melhor qualidade. Mais estudos clínicos devem ser realizados a fim de ampliar o conhecimento neste tipo de tratamento em pacientes com TRM.

Palavras-Chave: Trauma Raquimedular; Neuromodulação; Neuroplasticidade
Studies were classified according to the Newcastle-Ottawa Scale (NOS). The quality of the randomized clinical trials that met the final criteria was assessed through the JADAD score. This systematic review is registered in the PROSPERO database at the following number: CRD42021237163.

**RESULTS**

A total of four studies were eligible for inclusion (Figure 1), comprising 79 patients with a mean age of 42.67 years and a male:female of 60:19 (10 patients had no SCI, and were used as the control group); 20 patients underwent trans spinal stimulation; 13 underwent PCMS + exercises; 24 underwent PCMS, 10 underwent PAS (Table 1).

The patients were classified according to American Spinal Injury Association (ASIA) motor index score and the ASIA Impairment Scale (AIS) grade: 16 individuals were categorized in AIS A, 16 in AIS B, 15 in AIS C, 22 in AIS D.

Three studies had evaluated neuromodulation techniques that combined central nervous system (CNS) and peripheral nervous system (PNS) stimulation. One clinical trial evaluated the PCMS therapeutic potential.

**Figure 1.** Flowchart of the study.
DISCUSSION

CNS + PNS combined stimulation methods
This review shows the long-term potential of neuromodulation in motor improvement of incomplete SCI. These therapeutic techniques demonstrate statistically significant increase in EMG readings immediately after intervention. Jo et al.\textsuperscript{15} showed in a subset of subjects who completed the 6-month follow-up visit, that MEP amplitude increased after ten sessions and six months in the PCMS + exercise group compared with baseline (P<0.05). However, no differences were observed in MEP amplitude at any time in subjects receiving sham-PCMS + exercise (P = 0.3) after 6 months compared with baseline. Nonetheless, Dongés et al.\textsuperscript{17} reported no improvement in motor outcomes up to 5-22 days (P=0.65). It is possible that exercise training had a cause relation in longer MEP amplitude increase in six months, suggesting that neuromodulation may have better outcomes when combined with exercise training immediately after intervention.

PCMS is likely to elicit spike-timing dependent plasticity (STDP) changes at spinal synapses of somatic motor neurons. In animals, STDP-like plasticity is thought to engage long-term potentiation (LTP)-like mechanisms that depend on N-methyl-D-aspartate (NMDA)\textsuperscript{15}. The short-term reorganization that is rapidly induced by acute injury is probably based on the mechanism of the unmasking of latent synapses of modulation on neurotransmitters, particularly in GABAergic inhibition, while the long term changes after chronic SCI may involve changes of synaptic efficacy induced by LTP, axonal regeneration and sprouting\textsuperscript{16}.

Considering the short-term outcomes. PAS is capable of enhancing corticospinal excitability with increased MEP amplitude in normal subjects for at least 30 minutes\textsuperscript{16-19}.

LTP-like phenomena were observed mainly in SCI patients with good motor recovery\textsuperscript{14-17}. Versace et al.\textsuperscript{16} demonstrated the similar effect of the PAS in patients without SCI and AIS C/D.

Table 1. Characteristics of the studies evaluating neuromodulation in SCI.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Neuromodulation Method</th>
<th>Study design/Quality assessment</th>
<th>Assessment</th>
<th>Number of subjects</th>
<th>Motor outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray et al.\textsuperscript{14}</td>
<td>2019</td>
<td>USA</td>
<td>Trans spinal stimulation</td>
<td>Prospective cohort</td>
<td>Trans spinal Evoked Potential</td>
<td>20</td>
<td>Trans spinal stimulation increases spinal motoneuron responsiveness</td>
</tr>
<tr>
<td>Jo et al.\textsuperscript{15}</td>
<td>2020</td>
<td>USA</td>
<td>1. PCMS + exercise</td>
<td>Randomized Clinical trial</td>
<td>Maximum Voluntary Contraction</td>
<td>38</td>
<td>Our findings suggest that PCMS is an effective strategy to facilitate exercise-mediated recovery in humans with SCI.</td>
</tr>
<tr>
<td>Jo et al.\textsuperscript{15}</td>
<td>2020</td>
<td>USA</td>
<td>2. Sham PCMS + exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jo et al.\textsuperscript{15}</td>
<td>2020</td>
<td>USA</td>
<td>3. PCMS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Versace et al.\textsuperscript{16}</td>
<td>2018</td>
<td>Italy</td>
<td>PAS</td>
<td>Prospective cohort</td>
<td>Muscle Evoked Potentials</td>
<td>10</td>
<td>PAS is capable of enhancing corticospinal excitability with increased MEP amplitude in normal subjects for at least 30 minutes.</td>
</tr>
<tr>
<td>Dongés et al.\textsuperscript{17}</td>
<td>2019</td>
<td>Australia</td>
<td>PCMS</td>
<td>Randomized Clinical trial</td>
<td>Maximum Voluntary Torque</td>
<td>11</td>
<td>There were no differences in baseline measures between days for any variable.</td>
</tr>
</tbody>
</table>

PAS: Paired associative stimulation; PCMS: Paired corticospinal-motor neuronal stimulation.
**CONCLUSION**

Neuromodulation represents a relevant form of auxiliary treatment in the recovery in SCI patients. Individually, these methods showed a great EMG improvement when associated with exercise. Greater improvement was obtained in good motor recovery patients (AIS C/D). However, due to the lack of high quality articles, more clinical studies should be conducted in order to enhance the knowledge in this type of treatment in SCI patients.

**REFERENCES**


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