Use of electrical stimulation for pain relief in a phantom limb – a systematic review


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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Abstract

Introduction and Objective. In people who have undergone amputation, it is common to have phantom pain, which drastically reduces the quality of life. Electrostimulation is a valuable non-invasive clinical technique in which electrical stimuli are applied to the patient to promote symptomatic relief of pain of various origins. The aim of this study was to review the literature on the use of electrostimulation for phantom limb pain relief in amputees.

Review Methods. 1,004 articles were found in databases. After exclusion of duplicate articles, in an automatic and manual way, Phase 1 was carried out – reading of titles and abstracts of 392 articles according to the eligibility criteria by 2 blinded reviewers using the Rayyan QCRI programme; conflicts were resolved in consensus between the 2 reviewers. Thus, 31 articles were selected for Phase 2 – reading in full, leaving 3 articles in this review. The Cochrane Robins 1 instrument was used to assess the quality of bias of the selected studies.

Brief description of the state of knowledge. Three studies were included, with a total number of participants of 56 individuals. All 3 studies showed a reduction in phantom limb pain; however, the overall risk of bias ranged from serious to moderate, which can create doubts with respect to the results observed by the primary researchers.

Summary. Electrostimulation has been shown to be effective in reducing the effects of phantom limb pain, although the number of articles found was small and the risk of bias significant.

Key words: amputation, electrice stimulation, pain perception

INTRODUCTION

The worldwide incidence of limb amputation is estimated to be approximately 1 million people per year. In 2018, more than 59,000 amputations were registered in Brazil [1]. Most patients who have undergone an amputation develop some type of discomfort related to the missing limb, which can evolve into pain. The pain and discomfort may appear both in the stump and in the phantom limb. Phantom limb pain (PLP) is debilitating and greatly reduces the quality of life of these patients [2, 3].

PLP commonly disappears after the prosthesis is implanted, because the brain receives the input that the amputated limb, which is ‘mimicked’ by the prosthesis, has returned to its place. However, in some patients, the pain can be chronic and persist for several years. There are cases where pain also recurs after the initial resolution [4]. Thus, PLP can be severe and difficult to control and must be differentiated from the pain that often appears on the amputation stump due to the inflammatory process inherent in surgical trauma [2, 5, 6].

Among the treatments used, combined pharmacotherapy can be included, that is, the use of analgesic and anti-depressant medicines, invasive methods, psychotherapy and rehabilitation [4, 6, 7]. Physotherapy is important at all stages and electrotherapy is used in amputee rehabilitation [4, 8–10]. The forms of therapy which can be useful to reduce PLP include direct intraneural stimulation, electroacupuncture, biofeedback, transcranial magnetic stimulation, transcutaneous electrical nerve stimulation (TENS) and vibration therapy, among others [11].

Although PLP is a topic discussed in the scientific literature, in recent years, due to its complex nature, there is no exclusive treatment scheme which take into account individual needs [4]. With this in mind, a greater depth in the scientific field with the issue of relief from PLP this study aims to contribute to a better understanding of the use of electrostimulation. Thus, the objective was to carry out a systematic review to verify the efficacy of the use of electrostimulation for the treatment of phantom limb pain.

MATERIALS AND METHOD

Eligibility criteria. The acronym PICOS was used on this study: P (population) – amputees with phantom limb pain; I (intervention) – electrostimulation; C (comparison) – placebo group, control, or other intervention distinct from the experimental group; O (outcome) – pain; and S (study) – clinical trials and quasieperimental studies.
Inclusion criteria included studies with individuals of both genders submitted to unilateral or bilateral amputation for any reason, diagnosed with phantom limb pain, intervention of any electro-stimulation modality, and qualitative and quantitative pain scales.

The exclusion criteria were retrospective and cohort studies, case and transversal studies, expanded abstract, editorials, studies for which texts were not available in full, reviews, letters, personal opinions, books, and book chapters. Also those that used samples from animals and individuals who presented other musculoskeletal dysfunctions (apart from phantom pain).

Information sources. The search was carried out using key words in the PubMed database, with the Medical Subject Headings (MeSH) system, defined descriptors in Health Sciences (DeCS), from the Virtual Health Library (VHL) site, and also free terms. Strategies were developed for the Pubmed, Scopus, Embase, Web of Science, Google Scholar and Cochrane databases, and for the ‘grey’ literature (CAPES Thesis and dissertation bank and Physiotherapy Evidence Database (PEDro)). There was no restriction on language or period. Preliminary searches in all databases were performed on a single day, 25 May 2022, totalling 1,004 references (Appendix 1).

Study selection and data collecting process. The selection process was carried out by 2 reviewers in 2 phases. EndNote Web and Rayyan QCRI (Qatar Computing Research Institute) reference managers were used. Articles were imported from the databases into the Endnote Web reference manager for automatic and manual removal of duplicate articles. They were then imported to Rayyan and the removal of duplicates was performed manually. In this way, the studies included in Phase 1 were defined for reading titles and abstracts by the 2 blinded reviewers. Studies that had a conflict were resolved by consensus, and, if necessary, a tie-breaker by a 3rd reviewer. Phase 2 was based on the evaluation of the full text by the 2 blinded reviewers.

Collected data. Data were collected on study characteristics (authors, year of publication, country), sample size, mean age and gender, amputation levels, evaluation periods, description of intervention, results, and conclusion. The outcome assessed was pain. A table was generated with the characteristics of the summary studies (Tab. 1).

Individual assessment of risk of bias in studies. All included studies were assessed across 7 domains: bias due to confounding, bias due to participant selection, bias in the classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of the reported outcome. Each domain had risk: severe, moderate, low, or unreported. The risk of bias assessment was performed by the 2 blinded reviewers R1 (JAA M) and R2 (IFSC) and conflicts resolved by the 3rd R3 (AA S) with the Cochrane tool, ROBINS I assessment form.

Evaluation of the risk of publication bias. To prevent publication bias, a sensitive search was performed without restriction on language, period, and insertion of a ‘grey’ literature search.

Table 1. Summary of the included studies (n= 3)

<table>
<thead>
<tr>
<th>Author / year / country</th>
<th>Study design</th>
<th>Sample Characteristics</th>
<th>Amputation Level</th>
<th>Intervention protocol</th>
<th>Pain measurement scales</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz &amp; Metzack, 1991. Canada</td>
<td>Crossover-Controlled Trial</td>
<td>N=28; Men:18, Women: 10, Age: a 23 a 73 years (average 52.8)</td>
<td>Amputation above elbow (n=2)</td>
<td>EG: Auricular TENS; PG: Placebo</td>
<td>McGill Pain Questionnaire (MPQ)</td>
<td>EG: F (1.31) 7.09, p &lt;0.01; PG: F (1.34) 7.48, p &lt;0.01.</td>
<td>The results suggest that 10 minutes of auricular TENS significantly decrease phantom pain.</td>
</tr>
<tr>
<td>Bolognini et al, 2015 Italy</td>
<td>Double-blind, crossover, simulated-controlled clinical trial</td>
<td>N= 8; Age: 16 to 90 years</td>
<td>Unilateral lower limb amputation (n=7)</td>
<td>EG: transcranial direct-current active stimulation (tDCS); PG: Simulated transcranial direct current stimulation. Active tDCS (5 consecutive days, Monday to Friday), followed by simulated tDCS (5 consecutive days, Monday to Friday)</td>
<td>Visual Analogue Scale (VAS) (scale 0 to 10)</td>
<td>EG: Active transcranial direct current stimulation: -42%; PG: Simulated transcranial direct current stimulation: -17%.</td>
<td>Stimulation with TDCS can induce stable relief of PLP. Neurmodulation targeting the motor cortex appears to be promising for the neuropathic pain condition, often refractory to classical pharmacological and surgical treatments.</td>
</tr>
<tr>
<td>Vathakul et al, 2022 Thailand</td>
<td>Quasi-experimental study (after/ before) Non-randomized clinical trial</td>
<td>N= 20 Age: average 57.1</td>
<td>Transcranial amputation (n=5); Transfemoral amputation (n=9); Transtibial amputation (n=6)</td>
<td>TENS (30 minutes of application on the limb contralateral to the amputation; or when necessary 45 or 60 minutes)</td>
<td>Numeric Rating Scale (NRS) (scale 0 to 10)</td>
<td>Preintervention: 4.85/10 ± 1.18 Post intervention: 1.15/10 ± 1.38 (3.7±1.59, p &lt;0.001, T-test (95% CI 2.95-4.45).</td>
<td>The application of TENS to the contralateral limb can lead to significant reduction in pain in patients with difficult-to-treat PLP. The suggested duration of treatment is at least 30 minutes and can be extended up to 45 minutes.</td>
</tr>
</tbody>
</table>

Legend: EG: experimental group; PG: placebo group; N: total number of participants; PLP: phantom limb pain; TENS: Transcutaneous electrical nerve stimulation; tDCS: Transcranial direct current active stimulation; PLP: phantom limb pain; MPQ: McGill Pain Questionnaire; VAS: Visual Analogue Scale; NRS: Numeric Rating Scale.
RESULTS

Study selection. 1,004 records were found, 866 in the main databases and 138 in the ‘grey’ literature. The search was carried out in all databases on the same day, 25 May 2022 (Appendix 1). Of the 1,004 studies, 382 were excluded by EndNote. EndNote automatically identified 221 duplicate studies, 216 from the indexed literature and 25 from the ‘grey’ literature; and 161 manually identified, 129 from the indexed literature and 42 from the ‘grey’ literature, leaving 622 studies. Next, of the 622 studies, Rayyan identified another 88 possible duplicates, and after manual analysis 30 duplicate studies were found. This left 592 studies for Phase 1 – reading titles and abstracts. After a primary selection, 31 studies were selected for Phase 2 – reading the full studies. Figure 1 shows the flow chart according to PRISMA [12]. Of the 31 studies, 28 were excluded, 15 due to the study design, 8 due to the inaccessibility of the full text, and 5 due to the wrong study population.

Characteristics of the studies. Of the 3 studies included, 2 were crossover type controlled clinical trials [13,14] and 1 quasi-experimental study (after – before) [15]. No studies were randomised. With a publication date from 1991 – 2022, the sample size of the studies was 56 subjects, with varying levels of amputation.

Individual analysis of the risk of bias. The risk of bias in the pain outcome was assessed by Cochrane’s Robins I tool. The 7 domains individually generated an overall score for each of the 3 studies. The domains of the tool obtained the following results: the first (bias due to confounding) and second domain (bias due to participant selection) there was low risk in 1 of the studies [14], and serious risk in 2 of the studies [13, 15]; the third domain (bias in classification of interventions) in 2 studies moderate risk [14, 15] and 1 serious risk [13]; the fourth domain (bias due to deviations from intended interventions) obtained serious risk in 1 study [13], moderate in 1 [15] and low also in 1 [14]; the fifth domain (bias due to missing data) had a low risk of bias in 2 studies [14, 15] and unreported in 1 study [13]; the sixth domain (bias in measurement of outcomes) had serious risk in 2 studies [13, 15] and low in 1 [14]. The seventh domain (bias in selection of reported outcome) had low risk in all studies; and finally the overall bias score had a serious risk of bias in 2 studies [13, 15] and 2 moderate [14] (Fig. 2).

Intervention protocols. The intervention protocols of the studies by Katz & Melzack [13], Bolognini et al. [14], and Vathakul et al. [15] differed from one another. Katz & Melzack [13] used active and simulated auricular TENS for 2 consecutive days of intervention, with 30 min duration, 10 – 30 V, 2,000 Ω fixed resistance, 4 Hz, 100 µs. On the other hand, Bolognini et al. [14] used active transcranial direct current stimulation (tDCS) for 5 consecutive days, Monday – Friday, followed by simulated tDCS, 5 consecutive days, on the motor cortex for 15 minutes of application, intensity of 1.5 mA. And finally, Vathakul et al. [15] used TENS on the limb contralateral to amputation, for 30 minutes of application, or
when necessary 45 or 60 minutes; increasing intensity until non-algic paraesthesia.

Collection Instruments. For pain measurement, each of the included studies used different instruments: McGill Pain Questionnaire (MPQ) [13], Visual Analogue Scale (VAS) [14] and Numeric Rating Scale (NRS) [15].

Primary endpoint: pain levels. The 3 selected studies showed a decrease in pain levels [13–15]. The study by Bolognini et al. [14] found differences between the groups (F1,7 = 6.64; p = 0.04), thus showing a 9% reduction in the simulated tDCS group and a 28% reduction in active tDCS, for immediate effects, and a 42% reduction (p = 0.04) in the active tDCS week, and a 17% reduction in the Sham tDCS week, with respect to sustained effects of tDCS effects (F2,14 = 5.45; p = 0.02).

The study by Vathakul et al. [15] showed a mean pain reduction score of 3.7/10 in the experimental group and a reduction of 1.5/10 in relation to the control group. Analysing the results obtained from the Katz & Melzack study [13], a difference can be observed between the data collected before TENS (F(1,34) = 7.48; p < 0.01) and the results achieved after TENS (F(1,31) = 7.09; p < 0.01) on the pain scale reported by the study participants.

Amputation levels. The levels of amputation varied among the different studies. The study by Bolognini et al. [14] analysed unilateral upper and lower limb amputation. Katz & Melzack [13] analysed amputation above the elbow (transhumeral), below the elbow, above the knee (transfemoral), and below the knee (transstibial), having a characterisation of the level of amputation similar to the studies by Vathakul et al. [15] who also classified amputation levels in transhumeral, transfemoral and transtibial.

DISCUSSION

The 3 studies included in this review [13–15] all had small samples, which implies a small effect size and consequently large confidence intervals (CI). Similarly, the different scales used to assess the outcome of pain and the reporting of results with different statistics made it impossible to perform a meta-analysis due to heterogeneity among the studies. The increasing need for standardisation of results in future studies should be emphasized, as this will facilitate comparative analysis and pooling of data.

In the risk of bias, 2 studies [13, 15] were classified as high risk and 1 as moderate risk [14], which makes evident the lack of primary studies conducted with greater methodological rigour. The variability among the assessment instruments was great, each using a different instrument to measure the outcome pain. The McGill Pain Questionnaire (MPQ) was used in the study by Katz & Melzack [13], the VAS in the study by Bolognini et al. [14], and the Numeric Rating Scale (NRS) in the study by Vathakul et al.

It should be mentioned that there was a pharmacological intervention in this study, with the presence of analgesics and anti-depressants, demonstrating that the reduction of pain was not entirely due to the application of electro-stimulation.

In the study by Katz & Melzack [13] with the use of TENS, pain was evaluated by MPQ before and after each session, with a modest but statistically significant reduction. There was also an analysis of mood, sleepiness and anxiety scores, which remained unchanged at all test times and sessions, indicating that pain decrease was not mediated by emotional factors. In addition, in this study, patients were asked not to take any anti-pain medication to obtain an accurate description without medication. It should be noted that TENS is used for acute and chronic pain control, both at high and low frequency, with local and contralateral use [16].

In the Bolognini et al. [14] study, pain was evaluated by VAS before and immediately after each daily application of transcutaneous direct current stimulation. An instantaneous reduction in pain intensity was reported after each session, but patients continued with their usual drug intake. In addition to pain intensity, other scales that evaluated sensation and phantom limb movement, different from the other studies, in which electrostimulation also acted positively. This study was the only one to evaluate pain with follow-up after electro-stimulation and was for only one week. In this study, transcranial direct current stimulation was used, which involves the passage of a weak current (1–2 mA), with the aim of modulating cognitive functions [17].

It should be noted that in the 3 studies, no reports were found of adverse effects from the application of electro-stimulation, indicating that it is possibly a safe way to treat PLP.

When evaluating the literature available on platforms focused on the rehabilitation of phantom pain in amputees, pharmacological and drug interventions stand out as the first treatment option, however with no lasting effect [4, 18]. Other therapies include acupuncture, mirror therapy, and biofeedback, among others, but data indicate that as yet no therapy stands out for PLP as the gold standard [11].

Although some of the currently available therapies provide promising results, many patients with HFMD still do not obtain satisfactory pain relief. Therefore, continued advances in the treatment of DMF are of great importance, and a synthesized hypothesis explaining the phenomenon of DMF in the future for the evolution of treatment recommendations based on more specific mechanisms. It is essential that patients with neuropathic pain have regular clinical follow-ups, as response to treatment may be subjective to the mental and/or psychological state.

This review aims to add information regarding the treatment of phantom limb pain, neuropathic pain, electro-stimulation, and amputation. There is great demand for and scarcity in the literature of the theme presented. However, studies with different electro-stimulation intervention protocols were included in the evaluation of outcome pain in HFMD.

Limitations of the study. A limitation of the study was that the 3 included studies had small samples, ranging from 8 – 28 individuals per study. Also, evaluation periods differed, and in some cases were very short and without follow-up, making long-term analyses impossible. In addition, the small number of articles, implied the participation of only 3 of the
vast modalities of electro-stimulation, which impaired the comparison between studies and the estimation of effects between them. Consequently, this resulted in a lower precision in the definitions and analyses of the questions raised, even making meta-analysis impossible due to heterogeneity.

CONCLUSION

It is concluded that electro-stimulation in its multiple modalities has shown to be useful in reducing the effects of phantom limb pain present in amputated individuals. However, the scarcity and the serious risk of bias reveal the need for more primary studies with high methodological quality on the subject addressed.

REFERENCES

### Appendix 1. Database searches

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<thead>
<tr>
<th>Database</th>
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