ESCOLA BAHIANA DE MEDICINA E SAÚDE HUMANA PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA E SAÚDE HUMANA

ENILTON DE SANTANA RIBEIRO DE MATTOS

PROTOCOLOS E DESAFIOS NA INVESTIGAÇÃO DO EFEITO DA ESTIMULAÇÃO ELÉTRICA TRANSCUTÂNEA NA REGENERAÇÃO APÓS LESÕES NERVOSAS PERIFÉRICAS: o processo para o desenvolvimento de um ensaio clínico randomizado

TESE DE DOUTORADO

Salvador-BA
2024

ENILTON DE SANTANA RIBEIRO DE MATTOS

PROTOCOLOS E DESAFIOS NA INVESTIGAÇÃO DO EFEITO DA ESTIMULAÇÃO ELÉTRICA TRANSCUTÂNEA NA REGENERAÇÃO APÓS LESÕES NERVOSAS PERIFÉRICAS: o processo para o desenvolvimento de um ensaio clínico randomizado

Tese de doutorado apresentada ao curso de Pós-graduação em Medicina e Saúde Humana da Escola Bahiana de Medicina e Saúde Pública para obtenção do título de Doutor em Medicina e Saúde Humana.

Orientador: Prof. Dr. Abrahão Fontes Baptista
Coorientador: Prof. Dr. Alex Guedes

Salvador-BA
2024

Dedico este trabalho a minha família.

INSTITUIÇÕES ENVOLVIDAS

EBMSP - Escola Bahiana de Medicina e Saúde Pública

HGE - Hospital Geral do Estado

COM-HUPES/UFBA - Complexo Hospitalar Universitário Professor Edgard Santos, Universidade Federal da Bahia

Universidade Federal do ABC

FONTES DE FINANCIAMENTO

Não houve financiamento de fontes oficiais de pesquisa.

EQUIPE DE PESQUISA

Enilton de Santana Ribeiro de Mattos, médico, cirurgião da mão, doutorando do Programa de Pós-Graduação em Medicina e Saúde Humana da EBMSP;

Abrahão Fontes Baptista, fisioterapeuta, professor associado IV do Centro de Matemática, Computação e Cognição e professor do quadro permanente do programa de pós-graduação em Neurociência e Cognição da UFABC e professor colaborador do Programa de Pós-graduação em Medicina e Saúde da EBMSP;

Alex Guedes, médico, Coordenador e Docente da Disciplina Cirurgia do Aparelho Locomotor e Docente da Disciplina Internato II em Clínica Cirúrgica da Faculdade de Medicina da Bahia - Universidade Federal da Bahia; Supervisor do Programa de Residência Médica em Ortopedia e Traumatologia e Chefe do Grupo de Cirurgia do Joelho do Complexo Hospitalar Universitário Professor Edgard Santos, Universidade Federal da Bahia , Chefe do Grupo de Oncologia Ortopédica do Hospital Santa Izabel, Chefe do Serviço de Cirurgia do Tecido Ósseo e Conectivo do Hospital Aristides Maltez - Liga Bahiana Contra o Câncer;

Paulo Itamar Ferraz Lessa, fisioterapeuta, professor auxiliar da Universidade do Estado da Bahia (UNEB);

Yossi Zana, professor associado IV do Centro de Matemática, Computação e Cognição (CMCC) e professor do quadro permanente do Programa de Pós-graduação em Neurociência e Cognição da UFABC.

AGRADECIMENTOS

Agradeço imensamente a Deus, por ter me dado força e resiliência para encarar todas as adversidades desse período de pandemia mundial e de dificuldades pessoais.

A minha maior motivação de vida: minha pequena Mabi, por me fazer conhecer um amor que não cabe no meu peito, que me motiva a ser melhor, a dar o meu melhor e ilumina meus dias com cada sorriso seu.

A minha esposa, Bárbara, por seu amor em todos esses anos juntos (completamos 20 anos juntos este ano) e por ter dedicado tanto tempo a nossa filha para que eu conseguisse encarar essa grande jornada. Sem o seu apoio nada disso seria possível!

Ao meu coorientador, Professor Alex Guedes, grande incentivador, inspiração profissional e parceiro em diversos trabalhos.

Ao meu orientador, Professor Abrahão, pela oportunidade que me deu de participar de seu grupo de pesquisa mesmo sem me conhecer ou ter referências a meu respeito, aceitou-me de pronto e que acreditou no meu projeto de um dia me tornar doutor.

A todos os meus professores, colegas e pacientes que participaram dessa engrandecedora experiência na pós-graduação.

Sou eternamente grato a todos vocês!

RESUMO

Introdução: As lesões do sistema nervoso periférico são comuns e podem ocorrer devido a uma variedade de razões, incluindo o trauma. A mão humana pode sofrer uma incapacidade significativa devido a lesões nervosas periféricas e estas podem ser extremamente debilitantes para o paciente. O reparo cirúrgico é, normalmente, o método de escolha para o tratamento dessas lesões, porém muitas vezes a regeneração é insuficiente e necessita ser incentivada. A estimulação elétrica de superfície (transcutânea) pós-reparo nervoso vem sendo estudada como forma de acelerar a regeneração nervosa, em sua grande maioria, em modelos experimentais. A translação dos resultados experimentais para seres humanos se faz através de ensaios clínicos randomizados desenho de estudo mais apropriado para avaliar o impacto de uma intervenção. Nesta área de investigação, estes estudos clínicos são raros e muitos apresentam erros como randomização inadequada, erros de alocação, falta de cegamento de pacientes e avaliadores, além de relatos incompletos ou seletivos dos desfechos, o que enfraquece a evidência. **Objetivos:** 1) Estudar a influência da estimulação elétrica de baixa frequência na recuperação da sensibilidade e na participação social de pacientes submetidos à neurorrafia dos nervos digitais da mão; 2) descrever a frequência e a distribuição dos desfechos selecionados em ensaios clínicos randomizados (ECR) que utilizam a estimulação elétrica para tratar lesões nervosas periféricas; 3) analisar como apresentações confusas de desfechos podem levar a interpretações equivocadas; 4) propor estratégias para melhorar a compreensão do leitor nestes estudos. **Métodos:** Esta tese apresenta quatro artigos sendo o primeiro, um protocolo de estudo, descritivo, para realização de um ensaio clínico randomizado sobre a influência da estimulação elétrica periférica de superfície na regeneração nervosa após neurorrafia do nervo digital. Trata-se de um estudo publicado previamente à realização do ECR, no qual descrevemos todo o plano de estudo de forma precisa. Já o segundo artigo é um ECR, duplo-cego e controlado, em pacientes adultos com lesão nervosa traumática aguda de nervos digitais da mão que foram encaminhados ao Serviço de Cirurgia da Mão do Hospital Geral do Estado da Bahia. Todos os pacientes foram submetidos a cirurgia para reparo do nervo digital e o grupo intervenção recebeu a estimulação elétrica pós-operatória enquanto o grupo controle recebeu um procedimento simulado. Todos foram acompanhados ambulatorialmente por pesquisadores que supervisionaram um programa de reabilitação. Foram utilizados como desfechos testes sensoriais quantitativos (Monofilamentos de Semmes-Weinstein e teste de discriminação de dois pontos), aspectos relacionados a qualidade de vida e dor (*Cold Sensitivity Severity Scale e o Pain Disability Index*). O terceiro artigo é um protocolo para realização de uma revisão sistemática sobre estimulação elétrica como intervenção utilizada para promover a regeneração nervosa periférica. Descrevemos neste protocolo a estratégia usada para pesquisa da literatura disponível visando identificar todos os ECR publicados que tratam do uso de estimulação elétrica como forma de incentivar a regeneração em pacientes com lesão nervosa periférica. O quarto artigo é um estudo retrospectivo, descritivo, em metaciência, que por meio de uma busca sistematizada na base de dados PubMed®, incluiu ECR de intervenção que utilizaram a estimulação elétrica como tratamento para lesão de nervo periférico. Os desfechos foram descritos e categorizados segundo classificação específica. **Resultados:** O ECR realizado, revelou uma recuperação gradual da sensibilidade em ambos os grupos, aproximando-se dos níveis normais na avaliação final. A análise estatística mostrou que o tempo de avaliação teve um efeito significativo na sensibilidade dos pacientes (F=7,351, p=0.012 para MSW; F=12,236, p=0,002 para s2PD). A idade se aproximou da significância como covariante (F=3,249, p=0,083). Não foi observado impacto significativo da estimulação elétrica de superfície no pós-operatório entre as variáveis analisadas. Já os resultados encontrados no quarto artigo sobre a descrição de desfechos em ECR nos quais foi utilizada a estimulação elétrica foram: Os desfechos primários dos 14 ECR selecionados foram categorizados como clínicos em 21,5%

dos estudos, substitutos em 57,2%, compostos em 7,1%, subjetivos em 7,1% e como escalas complexas em 7,1%. Eventos adversos foram relatados em 57, 1% dos estudos. **Conclusão:** A estimulação elétrica transcutânea pós-neurorrafia do nervo digital demonstrou que não houve melhora significativa para os desfechos primários de sensibilidade no ECR realizado, indicando a necessidade de mais pesquisas sobre sua eficácia na regeneração nervosa. No artigo que avaliou os desfechos, mais da metade da amostra (53,4%) de ECR de intervenção apresentou desfechos com pouca relevância clínica. Acreditamos na hipótese de que este achado pode prejudicar o leitor, uma vez que confundem a interpretação das evidências científicas. Medidas como as propostas pelo *Core Outcome Measures in Effectiveness Trials* (COMET) para seleção de desfechos em pesquisa poderiam ajudar os profissionais de saúde a melhor entender as intervenções terapêuticas mais apropriadas para os pacientes.

Palavras-chave: Estimulação Elétrica Nervosa Transcutânea; Nervos Periféricos; Regeneração Nervosa; Terapia por Estimulação Elétrica; Lesão do Nervo Periférico.

ABSTRACT

Introduction: Peripheral nervous system injuries are common and can occur due to a variety of reasons, including trauma. The human hand can suffer significant disability due to peripheral nerve injuries and these can be extremely debilitating for the patient. Surgical repair is usually the method of choice for the treatment of these lesions, but regeneration is often insufficient and needs to be encouraged. Electrical stimulation of the surface (transcutaneous) after nerve repair has been studied as a way to accelerate nerve regeneration, mostly in experimental models. The translation of experimental results to humans is done through randomized clinical trials, the most appropriate study design to evaluate the impact of an intervention. In this area of investigation, these clinical studies are rare and many have errors such as inadequate randomization, allocation errors, lack of blinding of patients and evaluators, and incomplete or selective reporting of outcomes, which weakens the evidence. **Objectives:** 1) To study the influence of low-frequency electrical stimulation on the recovery of sensitivity and social participation of patients undergoing neurorrhaphy of the digital nerves of the hand; 2) describe the frequency and distribution of selected outcomes in randomized controlled trials (RCTs) that use electrical stimulation to treat peripheral nerve injuries; 3) analyze how confusing presentations of outcomes can lead to misinterpretations; 4) to propose strategies to improve the reader's understanding in these studies. **Methods:** This thesis presents four articles, the first one being a descriptive study protocol to carry out a planned clinical trial on the influence of surface peripheral electrical stimulation on nerve regeneration after neurorrhaphy of the digital nerve. This is a study published prior to the RCT, in which we describe the entire study plan precisely. The second article is a double-blind, controlled RCT in adult patients with acute traumatic nerve injury to the digital nerves of the hand who were scheduled to attend the Hand Surgery Service of the General Hospital of the State of Bahia. All patients underwent digital nerve repair surgery and the intervention group received postoperative electrical stimulation while the control group received a sham procedure. All were monitored on an outpatient basis by researchers who supervised a rehabilitation program. Quantitative sensory tests (Semmes-Weinstein monofilaments and two-point discrimination test) were used as aspects related to quality of life and pain (Cold Sensitivity Severity Scale and the Pain Disability Index). The third article is a protocol for carrying out a systematic review on electrical stimulation as an intervention used to promote peripheral nerve regeneration. We describe in this protocol the strategy used to research the available literature, aiming to identify all published RCTs that deal with the use of electrical stimulation as a way of encouraging regeneration in patients with peripheral nerve damage. The fourth article is a retrospective, descriptive, metascience study, which, through a systematic search in the PubMed® database, included intervention RCTs that used electrical stimulation as a treatment for peripheral nerve injury. The stages were described and categorized according to the specific classification. **Results:** The RCT carried out revealed a gradual recovery of sensitivity in both groups, approaching normal levels in the final evaluation. Statistical analysis showed that assessment time had a significant effect on patients' sensitivity ($F=7.351$, $p=0.012$ for MSW; $F=12.236$, $p=0.002$ for s2PD). Age approached significance as a covariate ($F=3.249$, $p=0.083$). No significant impact of surface electrical stimulation was observed in the postoperative period among the variables analyzed. The results found in the fourth article on the description of outcomes in RCTs in which electrical stimulation was used were: The primary outcomes of the 14 selected RCTs were categorized as clinical in 21.5% of the studies, substitutes in 57.2%, composites in 7.1%, subjective in 7.1% and as complex scales in 7.1%. Adverse events were reported in 57.1% of studies. **Conclusion**: Post-neurorrhaphy transcutaneous electrical stimulation of the digital nerve demonstrated that there was no significant improvement for the primary sensitivity outcomes in the RCT performed, indicating the need for further research into its efficacy in nerve regeneration. In the

study on outcomes, more than half of the sample (53.4%) of intervention RCTs presented outcomes with little clinical relevance. We believe in the hypothesis that this finding may harm the reader, as it confuses the interpretation of scientific evidence. Measures such as those proposed by the Core Outcome Measures in Effectiveness Trials (COMET) for selecting research outcomes could help health professionals better understand the most appropriate therapeutic interventions for patients.

Keywords: Transcutaneous Electrical Nerve Stimulation. Peripheral Nerves; Nerve Regeneration; Electric Stimulation Therapy; Peripheral Nerve Injury.

LISTA DE ILUSTRAÇÕES

LISTA DE TABELAS

LISTA DE ABREVIATURAS E SIGLAS

2PD	*2 Point Discrimination*
ANOVA	Análise de Variância
ATP	*Adenosine TriPhosphate*
BDNF	*Brain-derived neurotrophic fator*
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CEP	Comitê de Ética em Pesquisa
CONSORT	*Consolidated Standards of Reporting Trials*
CSS	*Cold Severity Sensitvity*
ECR	Ensaio Clínico Randomizado
GAP-43	proteína 43 associada ao crescimento
NMDA	N-Metil-D-aspartato
P	Plasma
PAPPE	Pesquisa para o Desenvolvimento de Tecnologias para Produtos, Serviços e Processos
PES	*Peripheral Electrical Stimulation*
PDI	*Pain Disability Index*
ReBEC	Registro Brasileiro de Ensaios Clínicos
s2PD	*Static 2 Point Discrimination*
SNP	Sistema Nervoso Periférico
SPIRIT	*Standard Protocol Items: Recommendations for Interventional Trials*
SPSS	*Statistical Package for the Social Sciences*
SWM	*Semmes-Weinstein monofilament*
TrKB	*Tropomyosin receptor kinase B*
UFBA	Universidade Federal da Bahia

SUMÁRIO

1 INTRODUÇÃO

1.1 Criação do projeto de pesquisa

Para alguém que se interessa por pesquisa, embarcar na jornada da geração de projetos foi um desafio intrigante, mas repleto de obstáculos a serem superados. Descobri, logo de início, que este caminho estava longe de ser simples. A essência da compreensão reside na habilidade de identificar e abordar problemas significativos dentro do campo de pesquisa. No entanto, essa tarefa é tão complexa quanto a própria geração de novos projetos. Exige um olhar crítico e perspicaz sobre o panorama do nosso campo de estudo, além de uma profunda imersão nas questões que o permeiam. É um processo que demanda paciência, dedicação e, sobretudo, curiosidade. Afinal, é a curiosidade que nos impulsiona a investigar, questionar e explorar novos horizontes de conhecimento.

Entender melhor a respeito dos processos de regeneração dos nervos é algo que sempre me intrigou. Desde minha formação em Cirurgia da Mão, especialidade que me permitiu um contato mais próximo com procedimentos de reconstrução nervosa, busquei investir em conhecimentos que pudessem melhorar meus resultados e, consequentemente, dos meus pacientes. Mas como desenvolver algo? Havia uma semente que precisava ser cuidadosamente examinada, para florescer de forma valiosa. O verdadeiro obstáculo residia em identificar os problemas e transformá-los em questões específicas e capazes de serem estudadas em uma pesquisa.

Nessa jornada, me deparei com uma interessante linha de pesquisa relacionada aos transtornos do plexo braquial, desenvolvida por meu orientador na UFBA. Tratava-se de uma série de estudos sobre o efeito da estimulação elétrica em diversos aspectos relacionados ao sistema nervoso. Após manter contato por e-mail e conhecer seu laboratório de pesquisa, passamos a tentar elaborar um projeto que pudesse dar continuidade a seu trabalho, alinhado também a minha dissertação. Neste contexto, surgiu a ideia de fazermos um ensaio clínico randomizado para avaliar a eficácia da intervenção (estimulação elétrica) em um modelo que fosse prático, factível e que pudéssemos avaliar dentro de 2 anos (tempo previsto para o mestrado). O nervo digital da mão aparece como possibilidade interessante, já que a lesão deste nervo é

extremamente prevalente, a aplicação da intervenção é relativamente fácil e a avaliação dos desfechos é prática.

Nosso projeto de pesquisa foi tomando forma e se organizando, de maneira que conseguimos coletar os dados de boa parte dos pacientes ao término do tempo previsto, a despeito da pandemia de COVID-19, que dificultou e interrompeu muitas pesquisas. Além disso, tivemos a felicidade de termos nosso trabalho promovido ao patamar de uma tese de doutorado, na etapa de qualificação do mestrado, após a avaliação da banca examinadora. Alguns projetos se somaram à dissertação original, sem perder o foco no objetivo inicial de concluirmos nosso ensaio clínico e de elaborarmos a nossa tese ao final da pesquisa.

Encontro eco nas palavras frequentemente atribuídas a Kant, que reverberam em mim: "a inteligência de alguém pode ser medida pela quantidade de incertezas que ele pode suportar". É uma reflexão poderosa, que destaca a importância de lidar com a dúvida e a complexidade inerentes ao processo de geração de ideias. Afinal, é nesse terreno incerto e fértil que encontramos o pensamento inovador.

1.2 Justificativa teórica

As lesões do sistema nervoso periférico são comuns na cirurgia do trauma[1] e podem acometer os nervos da mão em cerca de 10% dos traumatismos deste segmento[2]. São decorrentes, na sua maioria, de acidentes de trabalho ou domésticos e podem ocorrer em todas as idades, sendo que os indivíduos em idade produtiva são mais frequentemente acometidos. Quando atingidos, os nervos digitais podem levar a um quadro de limitação funcional e perda de sensibilidade do dedo lesionado. O tratamento padrão preconizado para este tipo de lesão é a neurorrafia término-terminal utilizando técnica microcirúrgica[3].

A estimulação elétrica como forma de promover a regeneração nervosa já vem sendo utilizada e documentada na literatura há algum tempo, porém, sua grande maioria, apenas em modelos experimentais[4]. Estudos prévios avaliaram a influência da estimulação elétrica na regeneração de tecidos como pele[5], tendão e osso[6], com resultados variados. A regeneração de nervos periféricos através da estimulação elétrica tem sido estudada em modelos animais, essencialmente, por meio de técnicas invasivas. A utilização de eletrodos de superfície é uma

alternativa barata e simples de aplicação da estimulação elétrica, além de oferecer um risco potencial mínimo para o paciente. Apesar dessas vantagens, em geral, os estudos com humanos abordam o uso de correntes elétricas para gerar a contração em um músculo desnervado, e pouco trabalhos utilizam a estimulação elétrica para promover diretamente a regeneração nervosa. Gordon et al.[7] avaliaram a estimulação elétrica em pacientes com Síndrome do Túnel do Carpo e constataram que este tratamento adjuvante acelerou a regeneração axonal. Logo, nosso estudo pode fornecer estratégias novas, úteis e práticas para tratar pacientes com lesão de nervo periférico.

A estimulação elétrica periférica de superfície (PES-SE, do inglês Peripheral Nerve Stimulation with Surface Electrodes) é uma técnica que utiliza correntes elétricas pulsadas para estimular nervos através da pele[8]. Ela tem sido investigada como uma estratégia para promover a regeneração nervosa e melhorar a função sensorial em pacientes com lesões nervosas periféricas[9].

Alguns pontos relevantes para justificar este estudo:

Potencializar a regeneração de nervos:

A estimulação elétrica envolve a aplicação de correntes e pode ser uma ferramenta valiosa visando melhorar o processo de regeneração nervosa. Esta abordagem pode ser extremamente valiosa no processo de regeneração nervosa, especialmente após lesões ou danos aos nervos. Ao aplicar correntes elétricas específicas, é possível promover a atividade celular e o crescimento axonal na tentativa de melhorar a recuperação funcional. A estimulação elétrica com eletrodos de superfície pode oferecer algumas vantagens por ser uma técnica não invasiva o que facilitaria a administração da corrente elétrica, visando potencializar a restauração das funções nervosas.

Bloqueio dos Sinais de Dor:

A PES-SE é capaz de bloquear os sinais de dor transmitidos para o cérebro. Isso ocorre porque ela ativa os nervos periféricos e mecanismos centrais que modulam o processamento periférico e central e a percepção da dor[10].

Durante a estimulação elétrica, a produção de substâncias fisiológicas, como as endorfinas, é aumentada. Essas substâncias têm efeito analgésico e contribuem para o alívio da dor[11].

Pacientes submetidos à neurorrafia dos nervos digitais da mão frequentemente enfrentam dor pós-operatória e desconforto. A PES-SE pode ser utilizada como estratégia analgésica e promover um ganho adicional controlando a dor e melhorando a qualidade de vida desses pacientes.

Melhoria da Circulação Sanguínea e Metabolismo:

A estimulação elétrica pode promover uma melhora do fluxo sanguíneo e aumentar o metabolismo nos tecidos afetados. Isso favorece a regeneração dos nervos danificados[12].

Pacientes com lesões nervosas periféricas podem se beneficiar desse aumento na circulação sanguínea, pois isso fornece nutrientes essenciais para a regeneração.

Recuperação Precoce:

Sobretudo, lesões de nervos periféricos são entidades clínicas que podem levar incapacidade do indivíduo, com repercussões na família e no meio de trabalho. Os tratamentos dessas lesões são geralmente cirúrgicos. Porém, estratégias para promover uma recuperação mais precoce e um retorno da função do membro afetado são extremamente importantes tanto para que o paciente tenha maior chance de retorno ao trabalho quanto para minimizar os custos relacionados às complicações associadas.

Projeto para criação de aparelhos:

Além dos pontos já citados, o orientador da pesquisa está envolvido com um projeto já aprovado pelo Edital PAPPE da Fundação de Amparo à Pesquisa do Estado da Bahia, para a criação de aparelhos de estimulação elétrica funcional para pacientes com lesão de nervo periférico. Para essa colaboração entre a Escola Politécnica e o Instituto de Ciências da Saúde, ambos da UFBA, alguns dados seriam importantes para a fabricação desses dispositivos. É necessário saber se as PES-SE, da forma como estão sendo testadas neste projeto, podem ou não influenciar a

regeneração nervosa periférica, para que se possa concluir o planejamento do dispositivo de estimulação elétrica funcional.

Identificação de desfechos utilizados em pesquisas sobre estimulação elétrica:

A apresentação de desfechos com pouca relevância clínica pode ser um problema em ensaios clínicos de intervenção[13]. Tais desfechos podem prejudicar o leitor, uma vez que confundem a interpretação das evidências científicas. Descrever a distribuição dos desfechos selecionados em ensaios clínicos randomizados que utilizam a estimulação elétrica no tratamento de lesões nervosas periféricas, pode ajudar a evitar interpretações equivocadas e ajudar a promover estratégias para melhorar a compreensão do leitor. Sendo assim, a ideia de acrescentar um estudo metacientífico a esta tese poderá contribuir na melhoria desta área de pesquisa.

A realização de um estudo para avaliar a eficácia da estimulação elétrica nas lesões de nervos periféricos em modelos humanos é bastante pertinente e para tal, nos propusemos a realizar um ensaio clínico randomizado de prova de conceito, com desfechos objetivos e com variáveis de mensuração prática. A implementação da técnica, uma vez comprovada sua eficácia, poderá beneficiar sobremaneira os pacientes com lesão de nervos periféricos, encurtando o tempo de recuperação e auxiliando na readaptação às atividades rotineiras com maior brevidade.

Esta tese apresenta quatro artigos, sendo que destes dois estudos merecem destaque: um ensaio clínico randomizado que avaliou o efeito da estimulação elétrica transcutânea na regeneração de nervos digitais da mão e um outro estudo metacientífico que se concentrou na avaliação e classificação de desfechos relacionados à estimulação elétrica em ensaios clínicos. Mais dois estudos são apresentados na tese e trata-se de protocolos de pesquisa previamente publicados a realização dos trabalhos principais. Estes protocolos estabelecem os parâmetros dos estudos, incluindo os tipos de participantes, os métodos de coleta e análise de dados, as medidas de segurança a tomar e os padrões éticos que devem ser seguidos. Tal prática permite uma avaliação prospectiva da metodologia dos trabalhos, garantindo rigor científico.

2 OBJETIVO

2.1 Objetivos do ensaio clínico sobre a influência da estimulação elétrica transcutânea na regeneração nervosa periférica após neurorrafia de nervos digitais

2.1.1 Objetivo Geral

Estudar a eficácia da PES-SE na regeneração nervosa periférica em humanos.

2.1.2 Objetivo Específico

Estudar a influência da estimulação elétrica periférica de superfície no retorno das funções sensoriais e na participação social do indivíduo submetido à neurorrafia de nervos digitais da mão.

2.2 Objetivos do estudo sobre a avaliação de desfechos em ensaios clínicos da influência da estimulação elétrica na lesão nervosa periférica

Descrever a frequência e a distribuição dos desfechos selecionados em ECR que utilizam a estimulação elétrica para tratar lesões de nervos periféricos, analisar como apresentações confusas de desfechos podem levar a interpretações equivocadas e propor estratégias para melhorar a compreensão do leitor.

3 REVISÃO DE LITERATURA

O presente capítulo destina-se a apresentar a revisão de literatura realizada para fundamentar o estudo.

3.1 Lesão e regeneração do nervo periférico

Danos ao sistema nervoso periférico (dano axonal) podem ocorrer devido a uma variedade de razões, incluindo trauma, isquemia ou inflamação[14]. Em resposta à lesão do nervo periférico, podem ocorrer alterações morfológicas e funcionais[15,16], como formação de neuromas, comprometimento da função motora e sensorial, hiperestesia e intolerância a baixa temperatura[17].

O processo de degeneração extensa que ocorre no axônio distal à lesão é conhecido como degeneração Walleriana. No entanto, o coto proximal, que permanece ligado ao corpo celular, pode se regenerar e crescer em direção ao órgão alvo[18]. A regeneração neural após a lesão pode ser influenciada por uma série de fatores, como idade, nível e extensão da lesão, tempo decorrido antes do reparo(quando necessário) e presença de lesões associadas[19,20].

A regeneração axonal é influenciada por fatores quimiotáxicos e elétricos[21]. Entretanto, se estes fatores não forem adequados (intensos ou prolongados), ou a distância a ser percorrida pelos brotos axonais for muito grande, os neurônios regenerados não funcionarão. É o caso das lesões proximais que ocorrem junto aos corpos celulares no Sistema Nervoso Periférico (SNP), como na lesão traumática do plexo braquial e lesão de raízes nervosas no forame de conjugação[22]. Quando o metabolismo ou o suprimento de nutrientes é afetado, como no diabetes, a regeneração funcional também é prejudicada[23].

Portanto, o incentivo a regeneração funcional é fundamental para o SNP retomar a suas funções normais[24]. As estratégias para melhorar a regeneração do nervo periférico incluem o uso de fatores neurotróficos[25], células-tronco[26,27], ultrassom[28], *laser* de baixa intensidade[29], exercício físico[30] e campos eletromagnéticos[25].

A lesão do tecido neural resulta em um influxo de cálcio que causa correntes elétricas endógenas, aumentando os potenciais elétricos locais[31,32]. Essas correntes são formadas através de gradientes elétricos entre a área afetada e as regiões circundantes e permanecem ativas durante todo o processo regenerativo[33]. A estimulação elétrica exógena pode potencializar este fenômeno natural e, por isso, tem sido usada para promover a regeneração neural e a recuperação precoce do tecido após uma lesão.

3.2 Campos elétricos e regeneração de nervos periféricos

A estimulação elétrica para melhorar a taxa e a velocidade da regeneração do nervo periférico envolve a aplicação de campos elétricos de corrente constante e frequência fixa ou variável, conforme demonstrado em estudos com animais[34,35]. Normalmente são utilizadas correntes elétricas de fluxo unidirecional (correntes elétricas monofásicas, constantes ou pulsadas) ou bidirecionais (correntes elétricas alternadas ou bifásicas).

As correntes elétricas podem ser administradas por meio de eletrodos implantados no próprio nervo, no intraoperatório, ou por meio de estimulação percutânea ou ainda de forma transcutânea. As correntes elétricas monofásicas têm a vantagem da unidirecionalidade; elas podem gerar efeitos eletroforéticos nas proteínas da membrana e, assim, guiar o crescimento do neurito em direção ao cátodo[36]. No entanto, se usadas em alta intensidade ou por longos períodos, as correntes elétricas monofásicas podem causar efeitos prejudiciais devido à própria eletroforese[37]. Embora as correntes bifásicas não ofereçam risco de efeitos eletroforéticos prejudiciais, são menos utilizadas, pois não têm o poder de guiar os neuritos em direção ao órgão-alvo.

Existem diferentes tipos de eletrodos, com alguns sendo mais comumente utlizados que outros. Em geral, quanto mais próximo o eletrodo está do nervo, menor é a amplitude da corrente, pois não há necessidade de superar a impedância exercida pelos tecidos circundantes.

3.2.1 Eletrodos implantados

A estimulação com eletrodos implantados e diferentes tipos de correntes elétricas tem sido o método mais utilizado desde a década de 1980 em modelos experimentais, geralmente para lesões no sóleo[38] e no nervo ciático [39-43]. Todos esses estudos apresentaram resultados

positivos, com melhora dos parâmetros funcionais e/ou morfológicos.

Apenas dois estudos - um sobre lesões do nervo fibular comum[44] e o outro nas lesões do nervo ciático[45] relataram resultados negativos, com menos fibras em regeneração, formação de neuromas e uma menor taxa de mielinização nos grupos estimulados. No entanto, nesses estudos, um dos eletrodos foi colocado dentro de um pequeno tubo de silicone que unia os dois cotos seccionados, levando à interação da corrente elétrica monofásica com o material do tubo. Efeitos deletérios surgiram devido à falta de corrente alternada e, conseqüentemente, destruição de parte do tubo, com impedimento físico à passagem de neuritos.

Para evitar a destruição do tecido, embora as correntes elétricas usadas em todos os estudos mencionados acima fossem monofásicas, as amplitudes das correntes elétricas eram extremamente baixas (abaixo do limite sensível na faixa μA). A estimulação foi geralmente realizada continuamente por algumas semanas antes da análise.

3.2.2 Eletroestimulação percutânea

Eletrodos percutâneos são geralmente agulhas de acupuntura inseridas na pele e conectadas a um gerador de corrente elétrica. Correntes elétricas por meio de eletrodos percutâneos têm sido utilizadas em modelos experimentais e talvez sejam um dos métodos estudados até o momento, sendo os mais simples de aplicar na prática clínica. Este tipo de estimulação tem sido usado em modelos de lesão do nervo ciático[46-49], com os melhores resultados alcançados quando o cátodo foi posicionado distal e o ânodo proximal à lesão. Foram utilizadas correntes elétricas monofásicas, com amplitudes abaixo do limiar sensorial, porém atingindo a intensidade de 1 mA (muito superior à utilizada nas técnicas com eletrodos implantados).

3.2.3 Eletroestimulação intraoperatória

Na eletroestimulação intraoperatória, o nervo é estimulado logo após a lesão, por períodos variáveis. Estudos sobre a eletroestimulação intraoperatória se deram principalmente no nervo ciático[50] e femoral em ratos. Os primeiros estudos usaram correntes elétricas monofásicas; os mais recentes usaram correntes alternadas com frequências de pulso de 20 Hz[51-54]. Estas últimas permitiram uma reinervação mais precisa e rápida; aumentou a expressão do fator neurotrófico derivado do cérebro (BDNF), receptor de tirosina quinase B (TrKB), Tα1-tubulina

e proteína 43 associada ao crescimento (GAP-43) e outros genes/proteínas associados à regeneração; e redução da expressão de neurofilamentos (fenômeno associado à regeneração). Gordon et al.[7] avaliaram o mesmo protocolo de estimulação elétrica em pacientes com denervação dos músculos da região tenar por Síndrome do Túnel do Carpo. Este modelo foi o pioneiro a ser traduzido para os humanos. Eles observaram que o tratamento acelerou a regeneração axonal sem afetar a função. A eletroestimulação intraoperatória difere das demais pela forma de estimulação como também pelo breve tempo de uso (aproximadamente 1–2 horas de estimulação após a lesão).

3.2.4 Estimuladores de nervo implantáveis sem fio de película fina

Utilizando tecnologia estabelecida amplamente, dispositivos sem fio dedicados à estimulação periférica do nervo podem ser utilizados para avaliar a recuperação funcional e fornecer estimulação direta do nervo sem a necessidade de cirurgia para acessá-lo. Demonstrou-se que esses dispositivos melhoram a recuperação funcional após lesão e reparo em um modelo de roedor sem o tempo adicional necessário para fornecer estimulação direta durante o procedimento cirúrgico[55]. Estes dispositivos ainda não tiveram aplicação prática em uma população humana.

3.2.5 Estimulação elétrica de superfície

A utilização de eletrodos de superfície para estimulação elétrica periférica é uma opção não-invasiva, de manejo prático, simples, que evita a solução de continuidade e as reações provocadas por uma cirurgia de implante ou mesmo da estimulação percutânea. Trata-se de uma opção que pode ser utilizada por um período mais longo, principalmente quando associada a correntes elétricas bifásicas[56].

A estimulação elétrica transcutânea surgiu como um método promissor para melhorar o processo de regeneração nervosa. A aplicação de corrente elétrica de baixa frequência através da pele tem como objetivo modular a atividade neural e promover efeitos terapêuticos[57].

Alguns estudos demonstraram que a estimulação elétrica de superfície pode promover a regeneração nervosa de várias maneiras[58]. Primeiro, a estimulação elétrica pode promover a

sobrevivência e o crescimento neuronal, modulando as vias de sinalização intracelular envolvidas no processo de regeneração. Além disso, a estimulação elétrica pode promover a migração de células gliais, como as células de Schwann, que desempenham um papel crucial na regeneração nervosa, facilitando assim a formação de um ambiente propício ao crescimento axonal[59].

Outro mecanismo proposto é que a estimulação elétrica modula a atividade nervosa e reduz a dor associada à lesão nervosa, o que pode melhorar a função nervosa e promover a recuperação funcional. Além disso, o PES está associado à redução da inflamação local, o que pode ajudar a prevenir cicatrizes e promover a regeneração axonal[60].

3.3 Desfechos utilizados em ensaios clínicos sobre estimulação elétrica

Sabe-se que o ECR é o desenho de estudo mais apropriado para avaliar o impacto de uma intervenção. Nesse contexto, os ECR ocupam um dos estágios mais altos da pirâmide de evidências[61]. O mais preocupante, no entanto, é notar que muitos estudos apresentam erros sistematizados como randomização inadequada, erros de alocação, não cegamento de pacientes e avaliadores, além de relatos incompletos ou seletivos dos desfechos, o que pode levar o leitor a equívocos na avaliação dos resultados[62].

O trabalho de Heneghan et al.[62] demonstra que uma das razões pelas quais os ECR podem não traduzir um benefício real para os pacientes é justamente a escolha confusa ou inadequada dos desfechos, optando-se por desfechos pouco claros ou mesmo irrelevantes para a prática clínica. Em seu relato, os autores categorizam os desfechos em: substitutos, compostos e subjetivos, além de mencionar o uso de escalas complexas ou desfechos sem relevância para pacientes e profissionais assistentes na avaliação de intervenções.

Embora os resultados sejam promissores, são necessárias mais pesquisas (com melhores desfechos) para elucidar completamente os mecanismos subjacentes e determinar as melhores práticas para a aplicação de estimulação elétrica de superfície à regeneração nervosa periférica. Com base nas evidências disponíveis, a estimulação elétrica representa uma estratégia terapêutica com potencial para melhorar os resultados clínicos em pacientes com lesões de nervos periféricos[63].

A avaliação destas hipóteses (testar o efeito da estimulação elétrica na regeneração de nervos periféricos e descrever como os desfechos se apresentam em ECR) surge de uma necessidade em compreender melhor uma estratégia nova, que pode ser útil para tratar pacientes com lesão de nervo periférico.

4 MATERIAIS E MÉTODOS

4.1 Effects of transcutaneous electrical stimulation on peripheral nerve regeneration after digital nerve neurorrhaphy

Este é um ensaio clínico randomizado, duplo-cego e controlado que foi realizado em um hospital geral terciário de referência na Bahia.

O Serviço de Cirurgia da Mão do Hospital Geral do Estado da Bahia é o principal hospital público especializado em trauma da mão de todo Nordeste e atua principalmente como centro de referência para outras instituições do estado.

O Departamento de Fisioterapia do Ambulatório da Universidade Federal da Bahia e da UNEB deram o suporte aos pacientes no pós-operatório e as instalações disponíveis nesses centros estão listadas nos dados estendidos[64].

O protocolo do ensaio foi registrado no Registro Brasileiro de Ensaios Clínicos- ReBEC (U1111-1259-1998 em 18 de dezembro de 2020) e segue os Itens do Protocolo Padrão SPIRIT: Lista de Verificação de Recomendações para Ensaios Intervencionistas (SPIRIT)[65].

Pacientes submetidos a neurorrafia por lesões causadas por transecção não segmentar de nervos digitais na mão participaram do estudo, sendo que metade dos participantes recebeu PES (*Neurodyn II*, Ibramed, Brasil) realizado imediatamente após a cirurgia e antes da alta hospitalar e a outra metade recebeu um tratamento simulado (sham) no pós-operatório.

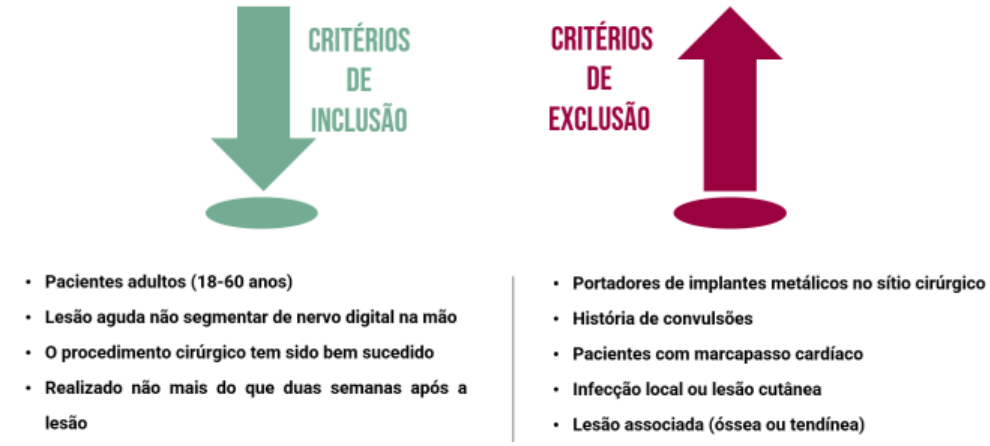
Os participantes e avaliadores de resultados estiveram cegos quanto à alocação de pacientes. Os eletrodos foram colocados na mesma posição e pelo mesmo tempo para o grupo intervenção e no grupo sham. Os avaliadores das medidas de resultado também não sabiam qual intervenção foi atribuída aos participantes.

Trata-se de uma amostra de conveniência na qual foram incluídos pacientes adultos (maiores de 18 anos de ambos os sexos) com lesão aguda traumática não segmentar de nervo digital da mão, encaminhados de outros centros de saúde para o Hospital Geral do Estado da Bahia para correção cirúrgica em no máximo duas semanas após a lesão.

Foram excluídos do estudo pacientes com implantes metálicos no local da cirurgia, que tenham histórico de convulsões, que possuam marca-passo cardíaco ou que apresentem infecção local ou lesão cutânea que impeça a aplicação de eletrodos de superfície.

Os critérios de inclusão e exclusão estão listados na figura 1.

Figura 1 - Critérios de Inclusão e Exclusão



Fonte: Elaborado pelo autor (2024).

4.1.1 Materiais

Material básico constituiu-se de Eletroestimulador *Neurodyn II* - Ibramed, Brasil e eletrodos de silicone-carbono (utilizados para realizar a eletroestimulação em pacientes). Todos os materiais necessários para este estudo estão disponíveis como dados estendidos[66].

4.2.2 Métodos

4.2.2.1 Intervenção

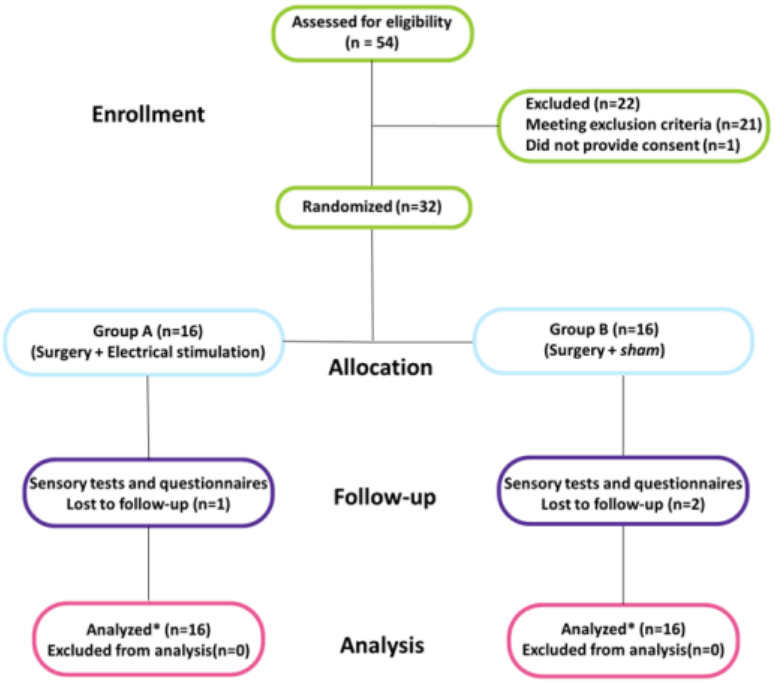
Os pacientes foram divididos e alocados em dois grupos: grupo A (cirurgia + PES); ou grupo B (cirurgia + sham). Uma estratégia de randomização simples foi realizada para atingir grupos equilibrados, usando um recurso online (randomization.com).

A alocação oculta e a estimulação elétrica foram realizadas por profissional não envolvido nas

demais etapas do estudo. Envelopes opacos e lacrados foram usados para tratar da alocação dos participantes. Os participantes só foram randomizados se fornecessem consentimento informado para participar do estudo.

A figura 2 mostra um diagrama de fluxo da jornada dos participantes através do estudo.

Figura 2 - Fluxograma do estudo com base nos critérios CONSORT

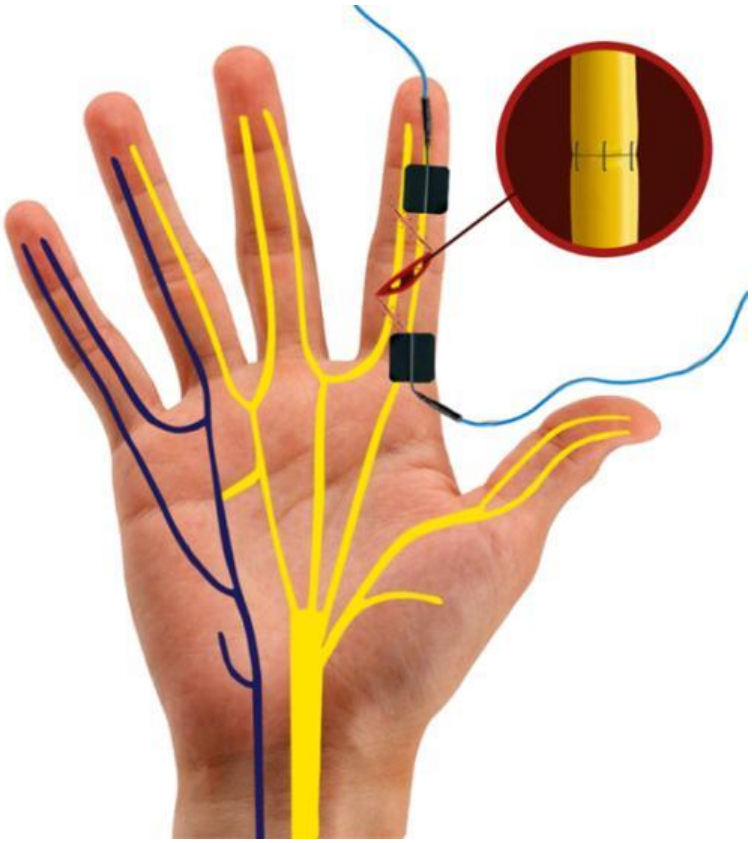


* Intention-to-treat (ITT) analysis

Fonte: Elaborado pelo autor (2024).

Após a cirurgia, ambos os grupos receberam adicionalmente 1 hora de estimulação elétrica (grupo A) ou simulação (grupo B). No total, dois eletrodos de silicone-carbono e gel (medindo 1 x 1 cm) foram usados para todos os participantes, com um colocado exatamente proximal e a outra exatamente distal ao sítio cirúrgico, como demonstrado na figura 3.

Figura 3 - Modelo de lesão nervosa digital reparada do dedo indicador e colocação dos eletrodos.



Fonte: Elaborado pelo autor (2024).

Os dois grupos receberam os seguintes regimes terapêuticos:

- Grupo A: Cirurgia + PES. Os eletrodos produziram uma corrente simétrica, bifásica, pulsátil quadrada com frequência de 20 Hz, largura de pulso de 0,4 ms e amplitude no limiar motor do nervo mediano, por 1 hora imediatamente após a cirurgia (n=16);
- Grupo B: Cirurgia + sham PES. Os eletrodos produziram uma corrente elétrica com pulso quadrado, bifásico, simétrico, frequência de 20 hz, largura de pulso de 0,4 ms, amplitude no limiar motor do nervo mediano até a percepção do paciente e depois a amplitude é retornada para zero e o aparelho mantido ligado por 1 hora imediatamente após a cirurgia (n=16).

Na primeira revisão pós-operatória, o paciente foi avaliado pelo médico no ambulatório. Um fisioterapeuta especializado na área e cego para a intervenção, supervisionou o protocolo de reabilitação que foi monitorado remotamente por meio eletrônico à disposição do paciente (*WhatsApp*, *Skype*, etc.).

Os pacientes foram submetidos a um protocolo de reeducação sensorial das mãos baseado no proposto por Dellon e Jabaley[67], por um período de três meses. Esse protocolo envolveu exercícios de discriminação do toque estático e dinâmico e de objetos de diferentes formas, tamanhos e texturas orientados pelo fisioterapeuta, e o paciente também foi estimulado a realizar exercícios em programa domiciliar.

Isso envolveu um total de 20 sessões monitoradas remotamente com duração aproximada de 30 minutos cada, realizadas, em média, duas vezes por semana. Nenhum vídeo ou foto dos pacientes foi adquirido para garantir a privacidade do paciente e a confidencialidade dos dados. Os pacientes foram também avaliados pessoalmente após um mês e três meses de tratamento pelo autor principal do estudo, que é responsável pelo acompanhamento cirúrgico e pós-operatório dos participantes do estudo, mas cego quanto à alocação do grupo.

Os participantes completaram um total de quatro avaliações presenciais para documentar os resultados, sendo: a) uma avaliação pré-intervenção/estimulação elétrica; b) uma avaliação uma semana pós-estimulação elétrica; c) uma avaliação após um mês pós-operatório; e d) uma avaliação após todas as 20 sessões de reabilitação (três meses pós-operatório).

4.2.2.2 Medidas de Resultado

1. Desfecho primário: Melhora da regeneração nervosa periférica de nervos digitais na mão medida por meio de testes sensoriais quantitativos (monofilamentos de *Semmes-Weinstein* e testes de discriminação de dois pontos medidos e comparados nas quatro avaliações presenciais). A diferença entre os dois braços de tratamento (grupo A - grupo B) medida através dos testes sensoriais (SWM e 2PD) avaliados após a randomização.
2. Desfecho secundário: Melhora das funções sensoriais e da participação social do indivíduo submetido à neurorrafia de nervos digitais da mão medida por meio de dois questionários:

- Escala de Severidade de Sensibilidade ao Frio[68]
- Questionário *Pain Disability Index*[69].

4.2.2.2.1 Teste de Monofilamento de Semmes-Weinstein (SWM)

O teste de monofilamento de Semmes-Weinstein é usado para avaliar a percepção dos limiares de pressão, que refletem a reinervação de alvos periféricos. Usando monofilamentos de diferentes espessuras, a avaliação da percepção de toque / pressão é medida e registrada. Este teste é um marcador primário de recuperação sensitiva e fornece dados quantitativos que podem ser usados para monitorar o paciente durante o curso da regeneração do nervo[70].

Os indivíduos foram solicitados a colocar as mãos sobre uma mesa e manter os olhos fechados durante o teste. Cada filamento, começando com o menor calibre, foi testado no lado da polpa do dedo afetado. O filamento foi aplicado perpendicularmente por 1 a 1,5 segundos, em três tentativas. Uma resposta positiva em pelo menos duas das três tentativas marcou o limiar sensorial[7]. Os resultados do teste foram usados para análise de dados.

4.2.2.2.2 Teste de Discriminação de Dois Pontos (2PD)

O teste de discriminação de dois pontos ou *2 Point Discrimination (2PD)*, descrito pela primeira vez por Weber em 1835[18], é uma ferramenta de avaliação estabelecida para gnose tátil[70]. É definido como a distância entre os pontos de um disco necessária para o paciente sentir dois contatos[71]. Idealmente, é registrado como um valor absoluto em comparação com a porção correspondente do dedo contralateral não lesionado. Os valores normais no dedo variam de 2 a 6 mm (quadro 1).

Quadro 1 - Escala de interpretação do teste de discriminação de dois pontos

Medição	**Interpretação**
2 mm a 5 mm	Normal
6 mm a 10 mm	Justo
11 mm a 15 mm	Ruim
Um ponto de percepção	Protetora
Nenhum ponto percebido	Anestesia

Fonte: Adaptado de Silva et al.[72].

Os esquemas de classificação para o teste de discriminação de dois pontos como o *Medical Research Council*, modificado por Mackinnon & Dellon (*Modified Highet Classification*)[18] , permitem dividir em grupos de intervalos de valores de acordo com o limiar sensível de recuperação (tabela 1).

Tabela 1 - Classificação HIGHET modificada

Sensorial (Recuperação)	**Highet**	**s2PD**	**m2PD**	**Recuperação de sensibilidade**
Fracasso	S0			Sem recuperação da sensibilidade na zona autônoma do nervo.
Pobre	S1 S1 + S2 S2 + S3	> 15 mm	> 7 mm	Recuperação da sensibilidade dolorosa cutânea profunda Recuperação da dor superficial e alguma sensibilidade ao toque Recuperação da sensibilidade dolorosa superficial; Tal como acontece com S2, mas com resposta excessiva; Recuperação da dor e sensibilidade ao toque sem resposta Exagerada.
Boa	S3 +	7-15 mm	4-7 mm	Como em S3, com boa localização do estímulo, mas recuperação imperfeita de 2PD.
Excelente	S4	2-6 mm	2-3 mm	Recuperação sensorial completa.

* s2PD = discriminação estática de dois pontos; m2PD = discriminação móvel de dois pontos.
Fonte: Adaptado de Dunlop et al.[18].

4.2.2.2.3 Escala de gravidade de sensibilidade ao frio (CSS)

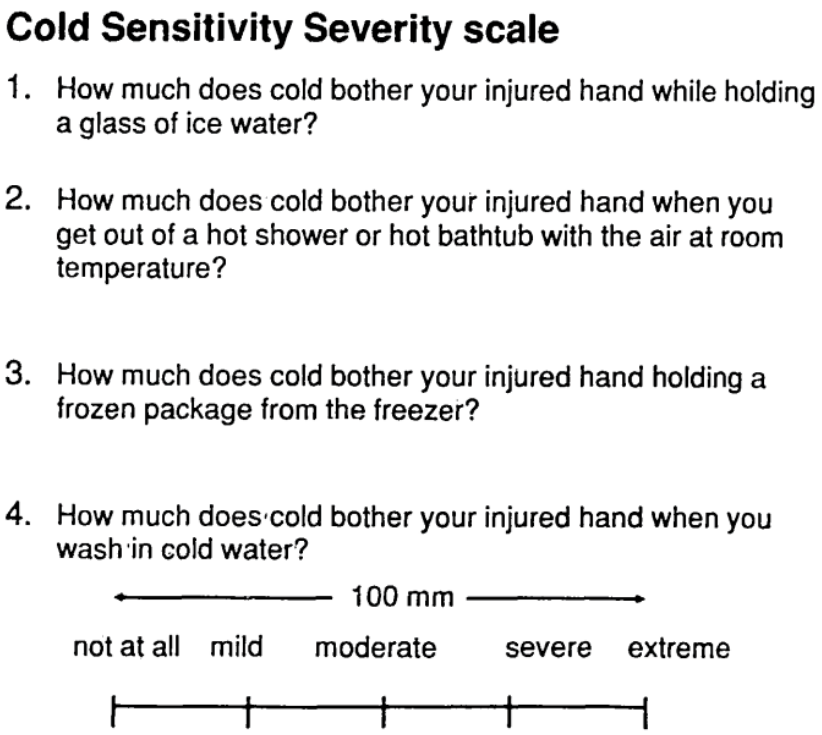
O desenvolvimento de sensibilidade ao frio é relativamente comum após a cirurgia de reparo da lesão de nervos nas mãos. Após certos tipos de lesões, como amputação e danos nos nervos, a hipersensibilidade pode causar incapacidades graves.

A escala de gravidade de sensibilidade ao frio ou *Cold Sensitivity Severity* (*CSS*) desenvolvida por McCabe et al.[73] fornece uma escala confiável para medir a sensibilidade ao frio, incluindo quatro perguntas sobre eventos domésticos que causam sintomas relacionados ao resfriado.

Para responder a cada item, o paciente é solicitado a colocar um “X” em uma linha de 100 mm refletindo a gravidade do sintoma. A linha tem indicadores em intervalos de 25 mm e descritores subjacentes (figura 4).

A pontuação de cada item foi então medida em milímetros a partir do início da linha, com a soma da subescala de quatro itens apropriada dando a pontuação de gravidade da sensibilidade ao frio.

Figura 4 - Escala Cold Sensitivity Severity scale



Fonte: Adaptado de McCabe et al.[73]

4.2.2.2.4 Índice de Incapacidade de Dor

O índice de incapacidade de dor ou *Pain Disability Index (PDI)* é um questionário de sete itens elaborado para avaliar até que ponto a dor interfere nos domínios da vida diária (responsabilidades familiares e domésticas, recreação, atividade social, ocupação, comportamento sexual, autocuidado e atividades de suporte à vida).

Cada item é classificado em uma escala de 0 (sem deficiência) a 10 (deficiência total). A pontuação final (variando de 0 a 70) é calculada somando as pontuações de cada item, com uma pontuação mais alta indicando um nível mais alto de incapacidade devido à dor (figura 3).

A consistência, validade e confiabilidade deste questionário foram testadas e provaram ser úteis em estudos de danos nos nervos[69].

Figura 5 - Pain Disability Index

Family/Home Responsibilities: This category refers to activities of the home or family. It includes chores or duties performed around the house (e.g. yard work) and errands or favors for other family members (e.g. driving the children to school).
No Disability 0 . 1 . 2 . 3 . 4 . 5 . 6 . 7 . 8 . 9 . 10 . Worst Disability

Recreation: This disability includes hobbies, sports, and other similar leisure time activities.
No Disability 0 . 1 . 2 . 3 . 4 . 5 . 6 . 7 . 8 . 9 . 10 . Worst Disability

Social Activity: This category refers to activities, which involve participation with friends and acquaintances other than family members. It includes parties, theater, concerts, dining out, and other social functions.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7.__ 8__. 9__. 10__. Worst Disability

Occupation: This category refers to activities that are part of or directly related to one's job. This includes non-paying jobs as well, such as that of a housewife or volunteer.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Worst Disability

Sex Behaviour: This category refers to the frequency and quality of one's sex life.
No Disability 0 . 1 . 2 . 3 . 4 . 5 . 6 . 7 . 8 . 9 . 10 . Worst Disability

Self Care: This category includes activities, which involve personal maintenance and independent daily living (e.g. taking a shower, driving, get dressed, etc.).
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Worst Disability

Life-Support Activities: This category refers to basic life supporting behaviours such as eating, sleeping and breathing.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Worst Disability

Signature: _____ **Please Print:**_____

Date:_____

Fonte: Wang et al.[70].

4.2.2.3 Tamanho da amostra e alocação do paciente

A alocação dos pacientes e a análise estatística serão feitas por um pesquisador que não terá conhecimento dos procedimentos e grupos.

Uma randomização simples será realizada em envelopes lacrados e opacos, com 16 pacientes por grupo (grupos A e B), totalizando 32 pacientes.

O tamanho da amostra é baseado no estudo de Gordon et al.[7]. Estima-se a amostra considerando um teste de análise de variância (ANOVA) de medidas repetidas com interação entre fatores e inter fatores, com tamanho de efeito de 0,26, erro do tipo alfa de 5%, poder de 80%, dois grupos, três medidas, com correção entre fatores de medidas repetidas de 0,5 e correção de não esfericidade de 1.

Esses parâmetros resultaram em 26 indivíduos na amostra total (13 por grupo), que foram aumentados em 20% para compensar possíveis perdas, resultando em uma amostra final de 32 pacientes (16 por grupo).

A seleção da amostra para compor os dois grupos será realizada por um cirurgião de mão experiente (> 10 anos), por meio de exame clínico e aplicação de instrumentos de avaliação (monofilamentos de *Semmes-Weinstein*, teste de discriminação de dois pontos, *Cold Sensitivity Severity scale* e o questionário *Pain Disability Index*).

4.2.2.4 Armazenamento de dados

Os dados coletados serão documentados em um livro de registro cadastrado à mão, digitados em arquivo no *Microsoft Office Excel* e arquivados no *Google Drive*.

Os questionários *Cold Sensitivity Severity Scale* e *Pain Disability Index* são aplicados a cada participante na última avaliação do cirurgião de mão para serem respondidos individualmente e, ao final da coleta, são importados em formato .xlsx do *Microsoft Office Excel* e arquivados no *Google Drive*.

Todos os dados serão inseridos manual e eletronicamente e armazenados em um *laptop* protegido por senha, disco rígido de computador e dispositivo de armazenamento externo em posse do responsável pela pesquisa e compartilhados virtualmente com o pesquisador supervisor.

Os arquivos dos participantes serão armazenados em ordem numérica e armazenados de forma segura e acessível. Os arquivos dos participantes serão mantidos em armazenamento por um período de cinco anos após a conclusão do estudo.

4.2.2.5 Análise estatística

Todos os testes estatísticos serão realizados usando o *software JASP (V0.18.3).*

Os dados serão avaliados de forma pareada e não-pareada. Para avaliações pareadas (comparações intragrupos) serão utilizadas análises de variância com medidas repetidas (ANOVA *repeated measures* ou Teste de FRIEDMAN), seguidas do pós-teste de STUDENT-NEWMAN-KEULS. Para avaliações não-pareadas (comparações entre grupos), serão utilizadas análises de variância de uma medida (ANOVA *one-way* ou teste de KRUSKAL-WALLIS), seguidas do mesmo pós-teste que as avaliações paramétricas. A escolha dos testes irá depender da normalidade ou da natureza dos dados.

Para análise estatística, será considerado o intervalo de confiança de 95%, com alfa de 5% (P <0,05) e poder de 80%.

A análise descritiva será feita por meio das médias ou medianas associadas às medidas de dispersão aplicáveis (desvio padrão ou quartis 25/75). Tanto as medidas das variáveis em cada estudo quanto a análise estatística serão realizadas às cegas.

A variável independente para ambos os grupos será o uso de correntes elétricas. As variáveis dependentes serão derivadas das avaliações pré e pós-tratamento (monofilamentos de *Semmes-Weinstein*, Teste de Discriminação de Dois Pontos, *Cold Sensitivity Severity Scale* e *Pain Disability Index*).

4.2.2.6 Aspectos éticos

Os pacientes serão informados oralmente no momento da admissão ao hospital sobre a natureza do estudo (incluindo a descrição dos procedimentos que serão usados, possíveis desconfortos e riscos e benefícios esperados, métodos alternativos de tratamento existentes, abordagens de monitoramento e assistência, e pessoal responsável) em linguagem acessível.

Os pacientes receberão esclarecimentos antes e durante o estudo quanto à metodologia, informando que não utilizaremos grupo placebo, sendo possível a inclusão em grupo controle. Serão informados sobre sua liberdade de recusa ou desistência do estudo, em qualquer etapa da pesquisa, sem qualquer penalidade ou prejuízo ao atendimento; a confidencialidade de seus dados; a ausência de reembolso de despesas decorrentes da participação da pesquisa; e as

formas de indenização em caso de eventuais danos decorrentes da pesquisa de acordo com as normas e regulamentações éticas de estudos em humanos da declaração de Helsinki[74].

Os procedimentos que usaremos não geram riscos vitais. Os riscos são mínimos para o paciente, pois utilizar-se-ão correntes elétricas bifásicas de baixa intensidade, que não geram efeitos eletrolíticos na pele, além dos eletrodos de superfície. A estimulação será feita apenas uma vez, minimizando assim a possibilidade de irritações na pele. Nenhum dos procedimentos de avaliação cria riscos para lesões de pele. Caso haja alguma intercorrência em relação aos procedimentos, os pacientes serão encaminhados imediatamente aos médicos do projeto[12]. O Termo de Consentimento Livre e Esclarecido encontra-se no Apêndice A.

4.2 Outcomes evaluation in clinical trials of electrical stimulation influence on peripheral nerve injury

4.2.1 Métodos

Trata-se de um estudo retrospectivo, descritivo, com análise quantitativa, por meio de busca sistematizada na base de dados PubMed®, sem restrições de data, idioma ou fator de impacto dos periódicos. Consideramos apenas ensaios clínicos randomizados em grupos de delineamento paralelo de qualquer sexo, idade e seguimento que tenham recebido qualquer tratamento de estimulação elétrica para lesão de nervo periférico no grupo intervenção e qualquer ou nenhuma intervenção no grupo controle. Foi realizada uma busca por Randomized Controlled Trial no PubMed® utilizando a estratégia descrita na Tabela 2.

[1] O projeto foi submetido ao Comitê de Ética em Pesquisa da Faculdade de Medicina da Bahia da Universidade Federal da Bahia. Os pacientes que concordaram em participar do estudo assinaram o termo de consentimento livre e esclarecido na admissão (dados estendidos), conforme Resolução nº 466, de 12 de dezembro de 2012, do Conselho Nacional de Saúde.

[2] As informações fornecidas pelos pacientes, bem como todos os dados coletados na pesquisa, serão mantidos em sigilo, a fim de preservar sua identidade. Os dados serão mantidos em arquivo com chave do Grupo de Pesquisa, sob responsabilidade do Prof. Abrahão Fontes Baptista.

Tabela 2 - Estratégia de busca.

N	Estratégia de busca
#1	peripheral nerve injury OR Peripheral Nerve Injury OR Nerve Injuries, Peripheral OR Nerve Injury, Peripheral OR Peripheral; Nerve Injuries OR Nerve Injury, Peripheral OR Nerve Injuries, Peripheral OR peripheral nerve regeneration OR peripheral nerve damage OR peripheral nerve crush OR peripheral nerve transection Filters: Randomized Controlled Trial
#2	nerve stimulation OR transcutaneous nerve stimulation OR electrostimulation therapy OR electrode OR Therapeutic Electrical Stimulation OR Electrical Stimulation, Therapeutic OR Stimulation, Therapeutic Electrical OR Therapeutic Electric Stimulation OR Electric Stimulation, Therapeutic OR Stimulation, Therapeutic Electric OR Electrical Stimulation Therapy OR Stimulation Therapy, Electrical OR Stimulation Therapy, Electrical OR Therapy, Electrical Stimulation OR Therapy, Electric Stimulation OR Stimulation Therapy, Electric OR Electrotherapy OR Interferential Current Electrotherapy OR Electrotherapy, Interferential Current OR Magnetic Field Therapy OR electrical stimulation OR peripheral electrical stimulation OR PES OR cuff stimulation OR magnetic stimulation OR peripheral magnetic stimulation Filters: Randomized Controlled Trial
#3	#1 AND #2

Foram excluídos os artigos que não correspondiam a ECR de intervenção ou artigos duplicados. Dois autores independentes selecionaram os artigos por título e resumo utilizando o aplicativo web Rayyan© de acordo com os critérios de inclusão, e eventuais divergências foram resolvidas por consenso. Os artigos selecionados foram lidos na íntegra e os desfechos primários classificados de acordo com os critérios propostos por Heneghan et al.[62] Neste estudo, os autores destacam que uma das razões pelas quais os ensaios clínicos randomizados podem não refletir benefícios reais para os pacientes está relacionada à escolha confusa ou inadequada dos desfechos e categorizam essas escolhas inadequadas em três tipos: desfechos substitutos, compostos e subjetivos. Além disso, mencionam o uso de escalas complexas ou desfechos que não têm relevância para pacientes e profissionais de saúde na avaliação de intervenções.

5 RESULTADOS

Artigo: Effects of transcutaneous electrical stimulation on peripheral nerve regeneration after digital nerve neurorrhaphy.

A elegibilidade foi avaliada em um total de 54 pacientes, destes, 21 não atenderam aos critérios de inclusão e um se recusou a participar do estudo. Nossa análise final abrangeu 16 pacientes no grupo PES e 16 pacientes no grupo sham (Figura 1). No pré-operatório, ambos os grupos apresentaram características basais semelhantes (Tabela 3).

Tabela 3 - Características basais dos pacientes

	Estimulação elétrica (n=16)	Sham (n=16)
Média de idade (variação em anos)	36.6 (18 to 57)	34.2 (21 to 58)
Sexo masculino (%)	9 (56)	12 (75)
Destro (%)	13 (81)	14 (87)
Lesão na mão dominante (%)	6 (38)	8 (50)
Lesão do nervo digital radial (%)	9 (56)	7 (44)
Dedo ferido:		
Polegar (n=8)	4	4
Indicador (n=9)	5	4
Dedo médio (n=2)	1	1
Dedo anular (n=4)	1	3
Dedo mínimo (n=9)	5	4
Diabetes	1	0
Fumante	2	4

Todos os pacientes de ambos os grupos sofreram perda importante da sensibilidade de acordo com a avaliação dos MSW e s2PD tanto no pré quanto uma semana após a operação, portanto, a análise foi realizada apenas nos dados das avaliações posteriores. Foi realizada uma ANOVA com o tempo de avaliação como fator de medida repetida (níveis: 1 e 3 meses de pós-operatório) e o grupo como covariante entre o fator sujeito e a idade (fig. 4). A análise indicou efeito estatisticamente significante dentro do tempo dos sujeitos (F=7,351, p=0,012) sobre MSW (g) e alfa não significativo, porém baixo (F=3,275, p=0,082) entre o efeito da idade dos sujeitos (Tabela 3). Os resultados foram semelhantes quando os valores de MSW foram expressos utilizando a variável tamanho dos filamentos, mas com a idade atingindo um efeito significativo entre os sujeitos (F=6,912, p=0,014). Testes post hoc confirmaram esses resultados, com

diferenças significativas encontradas apenas entre os diferentes tempos de avaliação dentro de um mesmo grupo experimental. A análise foi repetida com o s2PD como variável dependente e os resultados foram essencialmente equivalentes. Apenas a variável tempo alcançou nível de significância (F=12,236, p=0,002) com a covariável idade aproximando a significância (F=3,249, p=0,083).

O CSS e o PDI dos dois grupos, medidos na última avaliação, foram comparados usando um teste t para amostras independentes e não foram encontradas diferenças significativas. Vale ressaltar que essas duas medidas foram altamente correlacionadas (r=0,819, p<0,001).

Avaliando a robustez dos resultados, as análises foram repetidas sem idade como covariante, bem como após a exclusão de um sujeito do grupo A, de 57 anos, que apresentava valores discrepantes de MSW (g) (escore-z≈5). A remoção da covariante de idade não alterou nenhum dos resultados anteriores, mas a remoção do outlier eliminou a significância da idade como covariante.

Em resumo, os resultados mostram que os pacientes de ambos os grupos recuperaram gradualmente sua sensibilidade medida pelos testes de MSW e s2PD, até um nível quase normal na última medição. Entretanto, não houve efeito significativo do tratamento ao final das três medidas no pós-operatório.

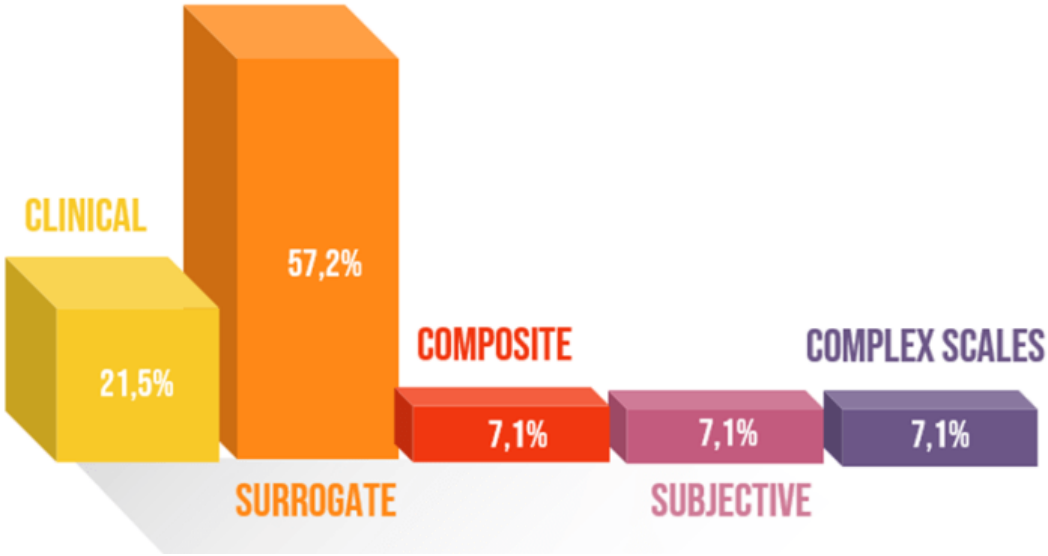
Artigo: Outcomes evaluation in clinical trials of electrical stimulation influence on peripheral nerve injury.

A busca foi realizada no PubMed® em 27/09/2022, sendo encontrados 87 artigos. Após a aplicação dos critérios de inclusão, restaram 14 artigos (Tabela 4). Dentre os 14 ECR selecionados, os desfechos primários foram classificados como clínicos em três estudos (21,5%), como substitutos em oito estudos (57,2%), como compostos em apenas um (7,1%), como subjetivos em apenas um (7,1%) e como utilizando escalas complexas em também em um (7,1%). (Figura 6)

Tabela 4 - Classificação dos desfechos primários

Study	Clinical outcome	Surrogate outcome	Composite outcome	Subjective Outcome	Complex scales and/or lack of relevance
Shoman 2022		X			
Power 2020		X			
Ton 2019	x				
Gall 2016					x
Leung 2015		X			
Wong 2015		X			
Zhou 2012	x				
Gordon 2010			x		
Weintraub 2009	x				
Ghaffariyeh 2009		X			
Gordon 2007		X			
Xiao 2007				x	
Cheng 2001		X			
Cheng 2000		X			

Figura 6 - Distribuição dos desfechos primários



Fonte: Elaborado pelo autor (2024).

6 ARTIGOS

6.1 Artigo publicado: Influence of surface peripheral electrical stimulation on nerve regeneration after digital nerve neurorrhaphy: study protocol for a randomized clinical trial

O primeiro artigo da tese (protocolo do ensaio clínico randomizado) foi publicado em revista internacional com indexação Pubmed, classificada como A3 pela CAPES.

F1000Research F1000Research 2021, 10:219 Last updated: 07 DEC 2021

Check for updates

STUDY PROTOCOL

REVISED **Influence of surface peripheral electrical stimulation on nerve regeneration after digital nerve neurorrhaphy: study protocol for a randomized clinical trial [version 2; peer review: 2 approved]**

Enilton Mattos[1,2], Alex Guedes[2,3], Paulo Itamar Ferraz Lessa[4], Abrahão Fontes Baptista[1,5,6]

[1]Pos Graduate Program in Medicine and Human Health, Escola Bahiana de Medicina e Saúde Pública, Salvador, Bahia, Brazil
[2]Professor Edgard Santos University Hospital Complex, Salvador, Bahia, Brazil
[3]Bahia Medical School, Federal University of Bahia, Salvador, Bahia, Brazil
[4]Bahia State University, Salvador, Bahia, Brazil
[5]Center for Mathematics, Computation and Cognition, Federal University of ABC, São Bernardo do Campo, São Paulo, Brazil
[6]Laboratory of Medical Investigations 54 (LIM-54), São Paulo University, São Paulo, São Paulo, Brazil

v2 **First published:** 17 Mar 2021, **10**:219
https://doi.org/10.12688/f1000research.42120.1
Latest published: 06 Dec 2021, **10**:219
https://doi.org/10.12688/f1000research.42120.2

Abstract
We will study the influence of low intensity and frequency surface peripheral electrical stimulation (PES) on nerve regeneration of digital nerve injuries of the hand after its surgical repair in humans. Participants will be patients with acute traumatic peripheral nerve injury referred to the Hand Surgery Service of the General Hospital of the State of Bahia, a reference service in the state. These patients will undergo surgery followed by PES in the immediate postoperative period. After hospital discharge, they will be followed up on an outpatient basis by researchers, who will remotely supervise a physiotherapy program. Our hypothesis is that PES will positively influence the recovery of sensory function in patients undergoing neurorrhaphy of digital nerves of the hand.
ReBEC registration: U1111-1259-1998 (12/18/2020)

Keywords
Transcutaneous Electric Nerve Stimulation, Peripheral Nerves, Nerve Regeneration, Electric Stimulation Therapy, Peripheral Nerve Injury

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 2 (revision) 06 Dec 2021		
version 1 17 Mar 2021	✓ report	✓ report

1. **Yumin Yang**, Key Laboratory of Neuroregeneration of Jiangsu and Ministry of Education, Co-innovation Center of Neuroregeneration, Nantong University, Nantong, China

2. **Jonas Kolbenschlag**, Eberhard Karls University Tuebingen, Tübingen, Germany
Johannes Heinzel, Eberhard Karls University Tuebingen, Tuebingen, Germany

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Abrahão Fontes Baptista (abrahao.baptista@gmail.com)

Author roles: Mattos E: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Guedes A**: Formal Analysis, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Lessa PIF**: Investigation, Methodology, Project Administration, Resources, Validation, Visualization; **Baptista AF**: Conceptualization, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

How to cite this article: Mattos E, Guedes A, Lessa PIF and Baptista AF. **Influence of surface peripheral electrical stimulation on nerve regeneration after digital nerve neurorrhaphy: study protocol for a randomized clinical trial [version 2; peer review: 2 approved]** F1000Research 2021, **10**:219 https://doi.org/10.12688/f1000research.42120.2

First published: 17 Mar 2021, **10**:219 https://doi.org/10.12688/f1000research.42120.1

REVISED **Amendments from Version 1**

We agree with the reviewer 2 and just add a term to become more clear. The unique difference between the versions is the word "non-segmental" in the Method.

Any further responses from the reviewers can be found at the end of the article

Introduction

Peripheral nerve injury and regeneration

Damage to the peripheral nervous system (axonal damage) can occur due to a variety of reasons including trauma, ischemia, or inflammation (Stoll & Müller, 1999). In response to peripheral nerve injury, morphological and functional changes can occur (Knight, 2000; Robbins, 1974), such as motor and sensory function impairment, hyperesthesia, and low-temperature intolerance (Rosén & Lundborg, 2000). The process of extensive degeneration that occurs when the axon distal to the injury degenerates is known as Wallerian degeneration, however, the proximal stump, which remains attached to the cell body, can regenerate, and grow towards the target organ (Stoll & Müller, 1999).

Neural regeneration following injury is influenced by a number of factors, such as age, level and extent of the injury, time elapsed from injury to repair, and presence of associated injuries (Dunlop *et al.*, 2019; Ruijs *et al.*, 2005). Axonal regeneration is influenced by chemotactic and electrical tracks (Song *et al.*, 2004; Stoll & Müller, 1999): if the tracks are not adequate (high or long), or the distance to be covered by the axonal sprouts is too large, the regenerated neurons will not be functional. This is the case of proximal injuries occurring close to the cell bodies, such as traumatic injury to the brachial plexus and injury of nerve roots in the conjugation foramen (Gordon *et al.*, 2003). When the metabolism or nutrient supply is affected, such as in diabetes, functional regeneration is also impaired (Kennedy & Zochodne, 2005). Therefore, promoting functional regeneration is key for the peripheral nervous system to resume normal functions.

Strategies to improve peripheral nerve regeneration include the use of neurotrophic factors, stem cells (Lopes *et al.*, 2006; Tohill & Terenghi, 2004), ultrasound (Crisci & Ferreira, 2002), low-intensity LASER (Bae *et al.*, 2004), physical exercise (Molteni *et al.*, 2004; Seo *et al.*, 2006), and electromagnetic fields. The latter is based on the fact that tissue injury results in an influx of calcium that causes endogenous electrical currents by increasing local electrical potentials (McCaig *et al.*, 2002; Watson, 1998). These currents are formed through electrical gradients between the affected area and the surrounding regions and remain active throughout the regenerative process (Low & Reed, 2001). Exogenous electrical stimulation has been used to promote neural regeneration and early tissue recovery following injury.

Electric fields and peripheral nerve regeneration

Electrical stimulation to improve the rate and speed of peripheral nerve regeneration involves the application of electrical fields of constant or varying frequency, as demonstrated in animal studies (Baptista *et al.*, 2007, 2008). Electrical currents are usually used, either flowing unidirectional (monophasic, constant or pulsed electrical currents) or bidirectional (alternate or biphasic electrical currents). The electrical currents may be administered through electrodes implanted in the nerve itself, intraoperatively, and using percutaneous or transcutaneous stimulation. Monophasic electrical currents have the advantage of unidirectionality; they can generate electrophoretic effects on membrane proteins and, thus, guide neurite growth towards the cathode (McCaig *et al.*, 2002). However, if used at high intensity or for long periods, the monophasic electrical currents can cause harmful effects due to electrophoresis itself (Low & Reed, 2001). Although biphasic currents do not offer the risk of harmful electrophoretic effects, they are less commonly used, as they do not have the power to guide the neurites towards the target organ.

There are different types of electrodes, with some predominating over others. In general, the closer the electrode is to the nerve, the smaller the current amplitude, as there is no need to overcome the impedance exerted by the surrounding tissues.

Implanted electrodes. Stimulation with implanted electrodes and different types of electrical currents have been the most used method since the 1980s in experimental models, generally for lesions in the soleus (Nix & Hopf, 1983) and sciatic (Beveridge & Politis, 1988; Kerns *et al.*, 1991; Mendonça *et al.*, 2003; Politis *et al.*, 1988; Pomeranz & Campbell, 1993) nerves. All of these studies showed positive results, with improvements in functional and/or morphological parameters.

Only two studies—one on lesions of the common fibular nerve (McGinnis & Murphy, 1992) and the other on lesions of the sciatic nerve (Hanson & McGinnis, 1994)—reported negative results, with fewer regenerating fibers, formation of neuromas, and a lower rate of myelination in the stimulated groups. However, in these studies, one of the electrodes was

placed inside a small silicone tube that joined the two sectioned stumps, leading to the interaction of the single-phase electric current with the material of the tube. Deleterious effects arose due to the lack of alternating current and, consequently, destruction of part of the tube, with physical impediment to the passage of neurites.

To avoid tissue destruction, although the electrical currents used in all of the above-mentioned studies were monophasic, electrical current amplitudes were extremely low (below the sensitive threshold in the μA range). Stimulation was usually performed continuously for a few weeks prior to analysis.

Percutaneous electrostimulation. Percutaneous electrodes are usually acupuncture needles inserted into the skin and connected to an electric current generator. Electric currents through percutaneous electrodes have been used in experimental models and perhaps they are, of the methods studied so far, the simplest to apply in clinical practice. This type of stimulation has been used in models of sciatic nerve injury (Chen *et al.*, 2001; Inoue *et al.*, 2003; McDevitt *et al.*, 1987; Pomeranz *et al.*, 1984), with the best results achieved when the cathode was placed distal and the anode proximal to the lesion. Monophasic electrical currents were used, with amplitudes below the sensory threshold, yet reaching the intensity of 1 mA (much higher than that used in techniques with implanted electrodes).

Intraoperative electrostimulation. In intraoperative electrostimulation, the nerve is stimulated shortly following injury, for varying periods of time. Studies on intraoperative electrostimulation have mostly used the sciatic (Scott, 1991) and femoral (Al-Majed *et al.*, 2000a, 2000b, 2004; Brushart *et al.*, 2002) nerves. The first studies used monophasic electrical currents; the most recent ones used alternating currents with pulse frequencies of 20 Hz (Al-Majed *et al.*, 2000a, 2000b, 2004; Brushart *et al.*, 2002). The latter allowed more precise and faster reinnervation; increased the expression of brain-derived neurotrophic factor (BDNF), tyrosine receptor kinase B (TrKB), Tα1-tubulin, and growth associated protein 43 (GAP-43), and other genes/proteins associated with regeneration; and reduced expression of neurofilaments (a phenomenon associated with regeneration). This model has been the only one to be translated to humans, so far. Gordon *et al.* (2010) evaluated the same electrical stimulation protocol in patients with denervation of the muscles of the thenar region due to carpal tunnel syndrome. They observed that the treatment accelerated axonal regeneration without affecting function. Intraoperative electrostimulation differs from others, in addition to the form of stimulation, for the brief time it is used (approximately 1–2 hours of stimulation following injury).

Thin-film wireless implantable nerve stimulators. Using widely established technology, wireless devices dedicated to peripheral nerve stimulation have been used to improve functional recovery in a rodent model, without the additional time needed to provide direct stimulation during the surgical procedure (Ray *et al.*, 2017). This strategy has not yet had practical application in humans.

Surface electrodes. The use of transcutaneous surface electrodes is a non-invasive option that can be used for a longer period, especially when associated with biphasic electrical currents. Its handling is practical and simple, avoiding the reactions provoked by implant surgery or percutaneous stimulation.

Previous studies have evaluated the influence of peripheral electrical stimulation (PES) through surface electrodes on the regeneration of tissues such as tendons (Burssens *et al.*, 2003, 2005), skin (Kaada & Emru, 1988; Kjartansson *et al.*, 1988; Khalil & Merhi, 2000; Liebano *et al.*, 2003), and bone (Kahn, 1982), with varying results. This modality is associated with effects such as increased blood flow (from Sandberg *et al.*, 2007; de Vries *et al.*, 2007) and collagen synthesis (Burssens *et al.*, 2005). However, electrical currents with amplitudes above 1 mA are needed, which may be related to decreased concentrations of adenosine triphosphate (ATP) (Cheng *et al.*, 1982) and, consequently, inhibition of peripheral nerve regeneration.

Electrical fields may influence blood circulation/perfusion, promoting an increase in axonal sprouting and nerve regeneration (McCaig *et al.*, 2005). Low frequency electrical currents can selectively activate sensory C fibers and increase the expression of neuropeptides such as substance P, which generate vasodilation (Burssens *et al.*, 2005; Kashiba & Ueda, 1991; Kjartansson *et al.*, 1988). Also, low-frequency PES (2–10 Hz) is usually associated with rhythmic muscle contraction, which can have circulatory effects (Dobsák *et al.*, 2006). However, recent evidence has suggested that high-frequency PES, which is used without producing muscle contraction, also increases circulation. de Vries *et al.* (2007) demonstrated an increase in coronary circulation as a result of high-frequency PES.

The most studied effects of PES are related to pain control. Analgesia caused by high-frequency PES activates δ-opioid receptors, while low-frequency PES activates μ-opioid receptors (Kalra *et al.*, 2001; Sluka & Walsh, 2003). Sinatra & Ford (1979) demonstrated that the chronic use of morphine for 14 days leads to a delay in peripheral nerve regeneration, as reflected by a lower number of axonal profiles, decreased removal of myelin debris, and hypertrophy and proliferation of

Schwann cells. Zeng *et al.* (2007) also demonstrated that exposure to morphine, acting via μ-opioid receptors, increases the regeneration of unmyelinated fibers, while inhibiting the regeneration of myelinated fibers after ischiatic nerve crush injury.

The fundamental difference between the studies that showed stimulating or inhibitory effects on the regeneration of the peripheral nervous system via the activation of opioid receptors was the prolonged time of use, which may have led to the development of pharmacological tolerance. Chandran & Sluka (2003) demonstrated that repeated high- and low-frequency PES for 20 minutes a day, led to opioid tolerance on day 4. Mao *et al.* (2002) demonstrated that this effect is mediated by the *N*-methyl-D-aspartate (NMDA)–caspase pathway, which leads to apoptosis of neuronal cells in the spinal cord. Therefore, the prolonged use of PES can lead to the development of opioid tolerance and neurotoxicity of the cells involved in regeneration. A brief use of PES, which does not lead to opioid tolerance, could however, be an important strategy to promote regeneration (de Assis *et al.*, 2014), but this has not so far been investigated in humans.

Objectives

Our overall aim is to study the influence of PES on peripheral nerve regeneration in humans. Specifically, we will study the influence of PES on recovery of sensory function, and on the social participation of patients undergoing neurorrhaphy of digital nerves of the hand.

Protocol

This is a randomized, double-blinded, controlled clinical trial that will be carried out in a reference tertiary general hospital in Bahia, Brazil. This protocol has been registered at ReBEC (U1111-1259-1998 on 18th December 2020) and follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (de Santana Ribeiro de Mattos *et al.*, 2021d). Patients undergoing neurorrhaphy for injuries caused by transection of digital nerves in the hand will be involved in the study. Half the participants will have PES (Endophasys, KLD, Brazil) performed immediately after surgery and before hospital discharge and the other half will receive a SHAM treatment. The participants and outcome assessors will be blinded to patient allocation. The electrodes will be placed in the same position and for the same amount of time for the intervention group as the sham group. The outcome measures evaluators will not know which intervention was assigned to the participants.

Participants

A convenience sample of adult patients (over 18 years old of both sexes) with acute traumatic non-segmental digital nerve injury referred from others health centers to the General Hospital of the State of Bahia to undergo surgical repair within a maximum of 2 weeks after the injury will be included. Patients with metal implants at the surgery site, who have a history of seizures, who have a cardiac pacemaker, or who have a local infection or skin lesion that prevents the application of surface electrodes will be excluded from the study.

Materials

Basic material: Endophasys Electrostimulator – KLD, Brazil and silicone-carbon electrodes (used to perform electro-stimulation in the patients).

All materials required for this study are available as extended data (de Santana Ribeiro de Mattos *et al.*, 2021a).

Setting

The Hand Surgery Service of the General Hospital of the State of Bahia is the foremost public tertiary trauma hospital and act mainly as referral center for other institutions in Bahia, Brazil. Outpatient Federal University of Bahia Physiotherapy Department will support the patients after surgery. The available facilities at these centers are listed in the extended data (de Santana Ribeiro de Mattos *et al.*, 2021b).

Intervention

Figure 1 shows a flow diagram of the participants' journey through the study. Patients will be divided and allocated to two groups: group A (surgery + PES); or group B (surgery + sham). A simple randomization strategy will be performed to achieve balanced groups, using an online resource (randomization.com). The hidden allocation and electrical stimulation will be performed by a professional not involved in other stages of the study. Opaque and sealed envelopes will be used to address participant allocation. Participants will only be randomized if they provide informed consent to participate in the trial.

Following surgery, both groups will additionally receive 1 hour of either electrical stimulation (group A) or sham (group B). In total, two silicone-carbon and gel electrodes (measuring 1 × 1 cm) will be used for all participants, with one placed

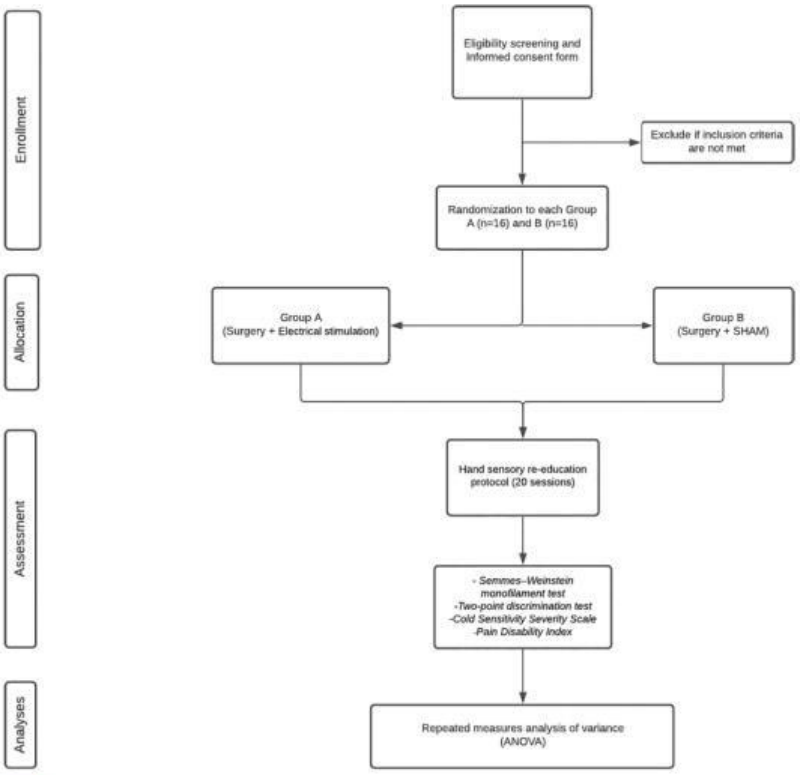


Figure 1. Flow chart of the study based on CONSORT criteria.

exactly proximal and the other exactly distal to the surgical site. The two groups will receive the following therapeutic regimens:

- *Group A: Surgery + PES.* The electrodes will produce a square-pulsed, biphasic, symmetrical current at a frequency of 20 Hz, pulse width of 0.4 ms, and amplitude at the motor threshold of the median nerve, for 1 hour directly after surgery (n = 16);

- *Group B: Surgery + sham PES.* The electrodes will produce a square-pulsed, biphasic, symmetric electric current at a frequency of 20 Hz, pulse width of 0.4 ms, and amplitude at the motor threshold of the median nerve, for 1 hour directly after surgery (the same as Group A) but the electrostimulator will be turned on only until the patient is aware of it, after which the amplitude will be set to zero (n = 16).

In the first post-operative review, the patient will be evaluated by the doctor at the outpatient clinic. A physiotherapist specialized in the area and blinded to the intervention will guide on the rehabilitation protocol that will be monitored remotely by electronic means available to the patient (WhatsApp, Skype, etc.). Patients will undergo a hand sensory re-education protocol based on the one proposed by Dellon & Jabaley (1982) for a period of 3 months. This protocol involves exercises for discrimination of static and dynamic touch and objects of different shapes, sizes, and textures guided by the physiotherapist, and the patient is also stimulated to perform a home program exercises. This will involve a

total of 20 remote monitored sessions lasting about 30 minutes each, carried out, on average, twice per week. No videos or photos of the patients will be acquired to guarantee the patient's privacy and data confidentiality.

Patients will be evaluated in person after every 10 treatment sessions by the main author of the study, who is responsible for the surgical and postoperative follow-up of the study participants but blinded to group allocation.

Participants must complete a total of 4 face-to-face assessments to document the results:

- 1 pre-intervention/electrical stimulation
- 1-week post-electrical stimulation
- 1 after 10 rehabilitation sessions
- 1 after all 20 rehabilitations sessions

The research will be completed within 1 year.

Outcome measures

- **Primary outcome:** Improvement of peripheral nerve regeneration of digital nerves in the hand measured using quantitative sensory tests (Semmes-Weinstein monofilaments and two-point discrimination tests measured and compared in the four presential assessments). The difference between the two treatment arms (group A × group B) measured through the sensory tests (SWM and 2PD) will be evaluated after randomization.

- **Secondary outcome:** Improvement of sensory functions and social participation of the individual submitted to neurorrhaphy of digital nerves of the hand measured through questionnaires (Cold Sensitivity Severity Scale described by McCabe *et al.* (1991), and the Pain Disability Index questionnaire recommended by Novak *et al.*, 2010).

Semmes–Weinstein monofilament test (SWM). The Semmes–Weinstein monofilament test is used to assess the perception of pressure thresholds, which reflect the reinnervation of peripheral targets. Using scored probes, the assessment of perception of touch/pressure is measured and recorded. This test is a prime marker of functional recovery and provides quantitative data that can be used to monitor the patient during the course of nerve regeneration (Wang *et al.*, 2013).

Subjects were asked to place their hands over a table, and keep their eyes closed during this test. Each filament, starting with the smallest caliber, was tested over the pulp side of the affected finger. The filament was applied perpendicularly for 1 to 1.5 s in three trials. A positive response in at least 2 of the 3 trials marked the sensory threshold (Gordon *et al.*, 2010). We used the test results for data analysis.

Two-point discrimination test (2PD). The two-point discrimination test, first described by WEBER in 1835 (Dunlop *et al.*, 2019), is an established assessment tool for tactile gnosis (Wang *et al.*, 2013). It is defined as the distance between compass points necessary for the patient to feel two contacts (Rosén & Lundborg, 2000). Ideally, it is recorded as an absolute value compared to the corresponding portion of the contralateral, uninjured finger. Normal values in an undamaged strip of the finger vary from 2 to 6 mm (Table 1).

Classification schemes for the two-point discrimination test such as the Medical Research Council (1954), modified by MACKINNON & DELLON (Modified Highet Classification), allow to divide into groups of value ranges according to the sensitive threshold of recovery (Table 2).

Cold Sensitivity Severity Scale (CSS). The development of cold sensitivity is quite common after surgery and hand injury. After certain types of injuries, such as amputation and nerve damage, hypersensitivity can cause severe disability. The Cold Sensitivity Severity Scale developed by McCabe *et al.* (1991) provides a reliable scale to measure cold sensitivity. The CSS scale includes four questions about events in the home that cause cold-related symptoms. To respond to each item, the patient is asked to place an X on a 100 mm line reflecting the severity of the symptom. The line had indicators at 25 mm intervals and underlying descriptors. The score for each item was then measured in millimeters from the beginning of the line, with the sum of the appropriate four-item subscale giving the cold-sensitivity severity score.

Table 1. Interpretation scale of the two-point discrimination test (reproduced from Silva *et al.*, 2014).

Measurement	Interpretation
2 mm to 5mm	Normal
6 mm to 10 mm	Fair
11 mm to 15 mm	Poor
One point of perception	Protective
No point perceived	Anesthesia

Table 2. Modified HIGHET's classification (reproduced from Dunlop *et al.*, 2019).

Sensory recovery	Highet	s2PD	m2PD	Recovery of sensibility
Failure	S0			No recovery of sensibility in the autonomous zone of the nerve
Poor	S1 S1+ S2 S2+ S3	 >15 mm	 >7 mm	Recovery of deep cutaneous pain sensibility Recovery of superficial pain and some touch sensibility Recovery of superficial pain sensibility As with S2, but with over response Recovery of pain and touch sensibility with no over response
Good	S3+	7–15 mm	4–7 mm	As in S3, but with good localisation of the stimulus but imperfect recovery of 2PD
Excellent	S4	2–6 mm	2–3 mm	Complete sensory recovery

s2PD = static two-point discrimination; m2PD = moving two-point discrimination.

Pain Disability Index. The Pain Disability Index is a seven-item questionnaire designed to assess the extent to which pain interferes in the domains of daily life (family and household responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life support activity). Each item is rated on a scale from 0 (no disability) to 10 (total disability). The final score (ranging from 0 to 70) is calculated by adding the scores of each item, with a higher score indicating a higher level of disability due to pain (Figure 2). The consistency, validity, and reliability of this questionnaire has been tested and proved to be useful in studies of nerve damage (Novak *et al.*, 2010).

Sample size and patient allocation

Patient allocation and statistical analysis will be done by a researcher (AFB) who will be blinded to the procedures and groups. A simple randomization will be performed using sealed and opaque envelopes. There will be 16 patients per group (groups A and B), totaling 32 patients. The sample size is based on the study by Gordon *et al.* (2010), as this is the only randomized clinical trial in the literature. We estimated the sample considering a repeated measures analysis of variance (ANOVA) test with interaction between and inter factors, with an effect size of 0.26 (according to Gordon *et al.*, 2010), alpha-type error of 5%, power of 80%, two groups, three measures, with correction between factors of repeated measures of 0.5, and correction of non-sphericity of 1. These parameters resulted in 26 individuals in the total sample (13 per group), which were increased by 20% to compensate for possible losses, resulting in a final sample of 32 patients (16 per group). The selection of the sample to compose the two groups will be carried out by an experienced (>10 years) hand surgeon, through the clinical examination and application of evaluation tools (Semmes-Weinstein monofilaments, two-point discrimination tests, Cold Sensitivity Severity Scale and the Pain Disability Index).

Data management

The collected data will be recorded in a hand-registered logbook and typed in EXCEL, archived in Google Drive. The Cold Sensitivity Severity Scale and Pain Disability Index questionnaires are applied to each participant in the last evaluation by the hand surgeon to be answered individually and, at the end of the collection, are imported in excel format and archived in Google Drive. All data will be entered manually and electronically and stored on a password-protected laptop, computer hard drive, and external storage device in possession of the responsible for search and virtually shared with the supervisor researcher. Participant files will be stored in numerical order and stored in a secure and accessible place and manner. Participant files will be maintained in storage for a period of 5 years after completion of the study.

Table 6. Pain Disability Index questionnaire.

Family/Home Responsibilities: This category refers to activities of the home or family. It includes chores or duties performed around the house (e.g. yard work) and errands or favors for other family members (e.g. driving the children to school).
No Disability 0 . 1 . 2 . 3 . 4 . 5 . 6 . 7 . 8 . 9 . 10 . Worst Disability

Recreation: This disability includes hobbies, sports, and other similar leisure time activities.
No Disability 0 . 1 . 2 . 3 . 4 . 5 . 6 . 7 . 8 . 9 . 10 . Worst Disability

Social Activity: This category refers to activities, which involve participation with friends and acquaintances other than family members. It includes parties, theater, concerts, dining out, and other social functions.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7.__ 8__. 9__. 10__. Worst Disability

Occupation: This category refers to activities that are part of or directly related to one's job. This includes non-paying jobs as well, such as that of a housewife or volunteer.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Worst Disability

Sex Behaviour: This category refers to the frequency and quality of one's sex life.
No Disability 0 . 1 . 2 . 3 . 4 . 5 . 6 . 7 . 8 . 9 . 10 . Worst Disability

Self Care: This category includes activities, which involve personal maintenance and independent daily living (e.g. taking a shower, driving, get dressed, etc.).
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Worst Disability

Life-Support Activities: This category refers to basic life supporting behaviours such as eating, sleeping and breathing.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Worst Disability

Signature: _____ **Please Print:**_____

Date:_____

Figure 2. Pain Disability Index questionnaire. (Reproduced from Wang *et al.*, 2013).

Statistical analysis

All statistical tests will be performed using SPSS (V25.0, IBM Corporation, New York, USA). The data will be evaluated in a paired and non-paired way. For paired evaluations (intra-group comparisons), repeated measures ANOVA or the Friedman test will be used, followed by the Student–Newman–Keuls post-test. For non-paired assessments (comparisons between groups), analysis of variance of a measure (one-way ANOVA or the Kruskal–Wallis test) will be used, followed by the Student–Newman–Keuls post-test. The choice of tests will depend on the normality or the nature of the data.

For statistical analysis, the 95% confidence interval will be considered, with an alpha of 5% ($P < 0.05$) and power of 80%. Descriptive analysis will be done through the averages or medians associated with the applicable dispersion measures (standard deviation or quartiles 25/75). Both the measurements of the variables in each study and the statistical analysis will be performed blindly.

The independent variable for both groups will be the use of electric currents. The dependent variables will be derived from the pre- and post-treatment assessments (Semmes-Weinstein monofilaments, two-point discrimination, Cold Sensitivity Severity Scale and Pain Disability Index).

Ethical aspects

Patients will be informed orally at the time of admission to the hospital about the nature of the study (including the description of the procedures that will be used, possible discomforts and risks and expected benefits, existing alternative treatment methods, monitoring and assistance approaches, and responsible staff) using accessible language.

Patients will receive clarifications before and during the study regarding the methodology, stating that we will not use a placebo group, and inclusion in a control group is possible. They will be informed about their freedom to refuse to participate or withdraw from the study, at any stage of the research, without any penalty nor prejudice to care; the

confidentiality of their data; the absence of reimbursement of expenses resulting from the participation of the research; and the forms of indemnity in the event of any damages resulting from the research in accordance with the ethical standards and regulations of human studies of the Helsinki declaration (2014).

The procedures that we will use do not generate vital risks. The risks are minimal for patients, since we will use low-intensity biphasic electrical currents, which do not generate electrolytic effects on the skin, in addition to surface electrodes. The stimulation will be done only once, thus minimizing the possibility of skin irritation. None of the assessment procedures creates risks for skin injuries. If there are any complications regarding the procedures, patients will be immediately referred to the doctors who accompany them and are part of the project.

The project was submitted to the Research Ethics Committee of the Faculty of Medicine of Bahia, Federal University of Bahia. Patients who agree to participate in the study will sign an informed consent form on admission (extended data), according to Resolution No. 466 of December 12, 2012, of the National Health Council.

The information provided by the patients, as well as all data collected from the research will be kept confidential, to preserve their identity. Data will be kept in a file with a key from the Research Group on Musculoskeletal Dynamics at the Federal University of Bahia (UFBA), under the responsibility of Prof. Abrahão Fontes Baptista.

Plans for dissemination

The study findings will be published in a thesis and research article. This work is linked to the master's degree of Enilton de Santana Ribeiro de Mattos (Graduate Program of the Bahiana School of Medicine and Public Health, under the guidance of Prof. Abrahão Fontes Baptista and co-supervision of Prof. Alex Guedes).

Study status

The study will start after the project has been approved by the Research Ethics Committee (CEP) of the Faculty of Medicine of the Federal University of Bahia, Federal University of Bahia and upon receiving all the materials needed. The study is scheduled to run for 10–12 months from October 2020 to October 2021 as described in Table 3 (we are at the Treatment Stage according to the Milestone schedule as of February 2020).

Discussion

The main contributions of this study are discussed below.

Scientific impact

The use of electric currents to promote peripheral nerve regeneration has been studied in experimental animal models, and, essentially, through invasive techniques. Surface electrodes are cheaper and offer minimal potential risk for the patient. Despite these advantages, in general, studies with humans address the use of electrical currents to generate contraction of the denervated muscle, but not to directly promote regeneration. This study could provide novel, useful, and practical strategies to treat patients with peripheral nerve damage.

Table 3. Milestone schedule.

Milestone	Bimonthly periods				
	1	2	3	4	5
Literature review	x	x	x	x	x
Project submission to the ethics committee		x			
Treatment stage (surgical stage, electrostimulation, rehabilitation)			x	x	x
Analysis and writing of clinical results			x	x	x
Analysis and writing of statistical results				x	x
Project qualification			x		
Thesis writing			x	x	x
Submission of articles		x	x	x	x
Thesis defense and submission of the final article				x	x

Technological impact
We are involved with a project that has already been approved by the PAPPE Public Notice of the State of Bahia Foundation for Research Support, for the creation of functional electrical stimulation devices for patients with peripheral nerve damage. For this collaboration between the Polytechnic School and the Institute of Health Sciences, both from UFBA, some data would be important for the manufacture of these devices. It is necessary to know whether electrical currents, as they are being tested in this project, may or may not influence peripheral nerve regeneration, so that we can complete the planning of the functional electrical stimulation device.

Economic and social impact
Peripheral nerve injuries are clinical entities that are usually underdiagnosed and undertreated. This has consequences, such as worker incapacity, with repercussions on their families and means of work. Transection injury treatments are usually exclusively surgical. However, strategies to speed recovery and return to function are extremely important both for the patients to have a greater chance of returning to work and to minimize costs related to associated complications.

In the city of Salvador, patients with peripheral nerve damage who have low purchasing power are usually operated on at the general hospital of the state and tend to have difficulties in carrying out their rehabilitation, as they do not have a service available for this situation. This research project is part of a larger perspective, with the creation of a reference service for the rehabilitation of patients with peripheral nerve damage, which should work within the Physiotherapy Service of Professor Edgard Santos University Hospital Complex, Federal University of Bahia. In addition to patients with digital nerve injuries, this service can serve all other patients who are operated on in acute situations or who have chronic neuropathies and need specialized care.

Data availability
Underlying data
No data are associated with this article.

Extended data
Figshare:

List of study materials: https://doi.org/10.6084/m9.figshare.13636685 (de Santana Ribeiro de Mattos *et al.*, 2021a)

Available facilities: https://doi.org/10.6084/m9.figshare.13636694 (de Santana Ribeiro de Mattos *et al.*, 2021b)

Participant information sheet and consent form: https://doi.org/10.6084/m9.figshare.13681825 (de Santana Ribeiro de Mattos *et al.*, 2021c)

Reporting guidelines
Figshare: SPIRIT checklist for 'Influence of surface peripheral electrical stimulation on nerve regeneration after digital nerve neurorrhaphy: study protocol for a randomized clinical trial.

https://doi.org/10.6084/m9.figshare.13584764.v1 (de Santana Ribeiro de Mattos *et al.*, 2021d)

References

Al-Majed AA, Brushart TM, Gordon T: **Electrical stimulation accelerates and increases expression of BDNF and TrkB mRNA in regenerating rat femoral motoneurons.** *Eur. J. Neurosci.* 2000a; **12**(12): 4381–4390.
PubMed Abstract | Publisher Full Text

Al-Majed AA, Neumann CM, Brushart TM, *et al.*: **Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration.** *J. Neurosci.* 2000b; **20**(7): 2602–2608.
PubMed Abstract | Publisher Full Text | Free Full Text

Al-Majed AA, Tam SL, Gordon T: **Electrical stimulation accelerates and enhances expression of regeneration-associated genes in regenerating rat femoral motoneurons.** *Cell. Mol. Neurobiol.* 2004; **24**(3): 379–402.
PubMed Abstract | Publisher Full Text

Bae CS, Lim SC, Kim KY, *et al.*: **Effect of Ga-As laser on the regeneration of injured sciatic nerves in the rat.** *In Vivo.* 2004; **18**(4): 489–495.
PubMed Abstract

Baptista AF, de Souza Gomes JR, Oliveira JT, *et al.*: **A new approach to assess function after sciatic nerve lesion in the mouse - adaptation of the sciatic static index.** *J. Neurosci. Methods.* 2007; **161**(2): 259–264.
PubMed Abstract | Publisher Full Text

Baptista AF, Gomes JRS, Oliveira JT, *et al.*: **High- and low-frequency transcutaneous electrical nerve stimulation delay sciatic nerve regeneration after crush lesion in the mouse.** *J. Peripher. Nerv. Syst.* 2008; **13**(1): 71–80.
PubMed Abstract | Publisher Full Text

Beveridge JA, Politis MJ: **Use of exogenous electric current in the treatment of delayed lesions in peripheral nerves.** *Plast. Reconstr. Surg.* 1988; **82**(4): 573–579.
PubMed Abstract | Publisher Full Text

Brushart TM, Hoffman PN, Royall RM, *et al.*: **Electrical stimulation promotes motoneuron regeneration without increasing its speed or conditioning the neuron.** *J. Neurosci.* 2002; **22**(15): 6631–6638.
PubMed Abstract | Publisher Full Text | Free Full Text

Burssens P, Forsyth R, Steyaert A, *et al.*: **Influence of burst TENS stimulation on the healing of Achilles tendon suture in man.** *Acta Orthop. Belg.* 2003; **69**(6): 528–532.
PubMed Abstract

Burssens P, Forsyth R, Steyaert A, *et al.*: **Influence of burst TENS stimulation on collagen formation after Achilles tendon suture in man. A histological evaluation with Movat's pentachrome stain.** *Acta Orthop. Belg.* 2005; **71**(3): 342–346.
PubMed Abstract

Chandran P, Sluka KA: **Development of opioid tolerance with repeated transcutaneous electrical nerve stimulation administration.** *Pain.* 2003; **102**(1–2): 195–201.
PubMed Abstract | Publisher Full Text

Cheng N, Van Hoof H, Bockx E, *et al.*: **The effects of electric currents on ATP generation, protein synthesis, and membrane transport of rat skin.** *Clin. Orthop. Relat. Res.* 1982; (171): 264–272.
PubMed Abstract

Chen YS, Hu CL, Hsieh CL, *et al.*: **Effects of percutaneous electrical stimulation on peripheral nerve regeneration using silicone rubber chambers.** *J. Biomed. Mater. Res.* 2001; **57**(4): 541–549.
PubMed Abstract | Publisher Full Text

Crisci AR, Ferreira AL: **Low-intensity pulsed ultrasound accelerates the regeneration of the sciatic nerve after neurotomy in rats.** *Ultrasound Med. Biol.* 2002; **28**(10): 1335–1341.
PubMed Abstract | Publisher Full Text

de Assis DCM, Lima ÊM, Goes BT, *et al.*: **The parameters of transcutaneous electrical nerve stimulation are critical to its regenerative effects when applied just after a sciatic crush lesion in mice.** *Biomed. Res. Int.* 2014; **2014**: 572949.
PubMed Abstract | Publisher Full Text

Dellon AL, Jabaley ME: **Reeducation of sensation in the hand following nerve suture.** *Clin. Orthop. Relat. Res.* 1982; (163): 75–79.
PubMed Abstract

de Santana Ribeiro de Mattos E, Guedes A, Lessa PIF, *et al.*: **List of materials study number U1111-1259-1998. *figshare.*** *Dataset.* 2021a.
Publisher Full Text

de Santana Ribeiro de Mattos E, Guedes A, Lessa PIF, *et al.*: **Available facilities study number U1111-1259-1998. *figshare.*** *Dataset.* 2021b.
Publisher Full Text

de Santana Ribeiro de Mattos E, Guedes A, Lessa PIF, *et al.*: **Consent term study number U1111-1259-1998. *figshare.*** 2021c.
Publisher Full Text

de Santana Ribeiro de Mattos E, Guedes A, Lessa PIF, *et al.*: **SPIRIT-Checklist-for randomised studies protocols.doc. *figshare.*** *Dataset.* 2021d.
Publisher Full Text

de Vries J, Anthonio RL, Dejongste MJL, *et al.*: **The effect of electrical neurostimulation on collateral perfusion during acute coronary occlusion.** *BMC Cardiovasc. Disord.* 2007; **7**: 18.
PubMed Abstract | Publisher Full Text

Dobsák P, Nováková PM, Siegelová J, *et al.*: **Low-frequency electrical stimulation increases muscle strength and improves blood supply in patients with chronic heart failure.** *Circ. J.* 2006; **70**(1): 75–82.
PubMed Abstract | Publisher Full Text

Dunlop RLE, Wormald JCR, Jain A: **Outcome of surgical repair of adult digital nerve injury: a systematic review.** *BMJ Open.* 2019; **9**(3): e025443.
PubMed Abstract | Publisher Full Text | Free Full Text

Gordon T, Amirjani N, Edwards DC, *et al.*: **Brief post-surgical electrical stimulation accelerates axon regeneration and muscle reinnervation without affecting the functional measures in carpal tunnel syndrome patients.** *Exp. Neurol.* 2010; **223**(1): 192–202.
PubMed Abstract | Publisher Full Text

Gordon T, Sulaiman O, Boyd JG: **Experimental strategies to promote functional recovery after peripheral nerve injuries.** *J. Peripher. Nerv. Syst.* 2003; **8**(4): 236–250.
PubMed Abstract | Publisher Full Text

Hanson SM, McGinnis ME: **Regeneration of rat sciatic nerves in silicone tubes: characterization of the response to low intensity dc stimulation.** *Neuroscience.* 1994; **58**(2): 411–421.
PubMed Abstract | Publisher Full Text

Inoue M, Hojo T, Yano T, *et al.*: **The effects of electroacupuncture on peripheral nerve regeneration in rats.** *Acupunct. Med.* 2003; **21**(1–2): 9–17.
PubMed Abstract | Publisher Full Text

Kaada B, Emru M: **Promoted healing of leprous ulcers by transcutaneous nerve stimulation.** *Acupunct Electrother. Res.* 1988; **13**(4): 165–176.
PubMed Abstract | Publisher Full Text

Kahn J: **Transcutaneous electrical nerve stimulation for nonunited fractures; a clinical report.** *Phys. Ther.* 1982; **62**(6): 840–844.
PubMed Abstract | Publisher Full Text

Kalra A, Urban MO, Sluka KA: **Blockade of opioid receptors in rostral ventral medulla prevents antihyperalgesia produced by transcutaneous electrical nerve stimulation (TENS).** *J. Pharmacol. Exp. Ther.* 2001; **298**(1): 257–263.
PubMed Abstract

Kashiba H, Ueda Y: **Acupuncture to the skin induces release of substance P and calcitonin gene-related peptide from peripheral nerve terminals of primary sensory neurons in the rat.** *Am. J. Chin. Med.* 1991; **19**(3–4): 189–197.
PubMed Abstract | Publisher Full Text

Kennedy JM, Zochodne DW: **Impaired peripheral nerve regeneration in diabetes mellitus.** *J. Peripher. Nerv. Syst.* 2005; **10**(2): 144–157.
PubMed Abstract | Publisher Full Text

Kerns JM, Fakhouri AJ, Weinrib HP, *et al.*: **Electrical stimulation of nerve regeneration in the rat: the early effects evaluated by a vibrating probe and electron microscopy.** *Neuroscience.* 1991; **40**(1): 93–107.
PubMed Abstract | Publisher Full Text

Khalil Z, Merhi M: **Effects of aging on neurogenic vasodilator responses evoked by transcutaneous electrical nerve stimulation: relevance to wound healing.** *J. Gerontol. A Biol. Sci. Med. Sci.* 2000; **55**(6): B257–B263.
PubMed Abstract | Publisher Full Text

Kjartansson J, Lundeberg T, Samuelson UE, *et al.*: **Transcutaneous electrical nerve stimulation (TENS) increases survival of ischaemic musculocutaneous flaps.** *Acta Physiol. Scand.* 1988; **134**(1): 95–99.
PubMed Abstract | Publisher Full Text

Knight KL: *Cryotherapy in the Treatment of Sports Injuries.* São Paulo: Manole; 2000; 304.

Liebano RE, Ferreira LM, Neto MS: **Experimental model for transcutaneous electrical nerve stimulation on ischemic random skin flap in rats.** *Acta Cir. Bras.* 2003; **18**: 54–59.
Publisher Full Text

Lopes FRP, de Moura Campos LC, Corrêa JD Jr, *et al.*: **Bone marrow stromal cells and resorbable collagen guidance tubes enhance sciatic nerve regeneration in mice.** *Exp. Neurol.* 2006; **198**(2): 457–468.
PubMed Abstract | Publisher Full Text

Low J, Reed A: *Electrotherapy Explained.* São Paulo: Manole; 2001; 472.

Mao J, Sung B, JiRR, *et al.*: **Neuronal apoptosis associated with morphine tolerance: evidence for an opioid-induced neurotoxic mechanism.** *J. Neurosci.* 2002; **22**(17): 7650–7661.
PubMed Abstract | Publisher Full Text | Free Full Text

McCabe SJ, Mizgala C, Glickman L: **The measurement of cold sensitivity of the hand.** *J. Hand Surg. Am.* 1991; **16**(6): 1037–1040.
PubMed Abstract | Publisher Full Text

McCaig CD, Rajnicek AM, Song B, *et al.*: **Has electrical growth cone guidance found its potential?.** *Trends Neurosci.* 2002; **25**(7): 354–359.
PubMed Abstract | Publisher Full Text

McCaig CD, Rajnicek AM, Song B, *et al.*: **Controlling cell behavior electrically: current views and future potential.** *Physiol. Rev.* 2005; **85**(3): 943–978.
PubMed Abstract | Publisher Full Text

McDevitt L, Fortner P, Pomeranz B: **Application of weak electric field to the hindpaw enhances sciatic motor nerve regeneration in the adult rat.** *Brain Res.* 1987; **416**(2): 308–314.
PubMed Abstract | Publisher Full Text

McGinnis ME, Murphy DJ: **The lack of an effect of applied d.c. electric fields on peripheral nerve regeneration in the guinea pig.** *Neuroscience.* 1992; **51**(1): 231–244.
PubMed Abstract | Publisher Full Text

Mendonça AC, Barbieri CH, Mazzer N: **Directly applied low intensity direct current enhances peripheral nerve regeneration in rats.** *J. Neurosci. Methods.* 2003; **129**(2): 183–190.
PubMed Abstract | Publisher Full Text

Molteni R, Zheng JQ, Ying Z, *et al.*: **Voluntary exercise increases axonal regeneration from sensory neurons.** *Proc. Natl. Acad. Sci. U. S. A.* 2004;

101(22): 8473–8478.
PubMed Abstract | Publisher Full Text | Free Full Text

Nix WA, Hopf HC: **Electrical stimulation of regenerating nerve and its effect on motor recovery.** *Brain Res.* 1983; **272**(1): 21–25.
PubMed Abstract | Publisher Full Text

Novak CB, Anastakis DJ, Beaton DE, *et al.*: **Relationships among pain disability, pain intensity, illness intrusiveness, and upper extremity disability in patients with traumatic peripheral nerve injury.** *J. Hand Surg. Am.* 2010; **35**(10): 1633–1639.
PubMed Abstract | Publisher Full Text

Politis MJ, Zanakis MF, Albala BJ: **Facilitated regeneration in the rat peripheral nervous system using applied electric fields.** *J. Trauma.* 1988; **28**(9): 1375–1381.
PubMed Abstract | Publisher Full Text

Pomeranz B, Campbell JJ: **Weak electric current accelerates motoneuron regeneration in the sciatic nerve of ten-month-old rats.** *Brain Res.* 1993; **603**(2): 271–278.
PubMed Abstract | Publisher Full Text

Pomeranz B, Mullen M, Markus H: **Effect of applied electrical fields on sprouting of intact saphenous nerve in adult rat.** *Brain Res.* 1984; **303**(2): 331–336.
PubMed Abstract | Publisher Full Text

Ray WZ, Mahan MA, Guo D, *et al.*: **An update on addressing important peripheral nerve problems: challenges and potential solutions.** *Acta Neurochir.* 2017; **159**(9): 1765–1773.
PubMed Abstract | Publisher Full Text

Robbins SL: *Structural and Functional Pathology.* Rio de Janeiro: Interamericana; 1974; 1421.

Rosén B, Lundborg G: **A model instrument for the documentation of outcome after nerve repair.** *J. Hand Surg. Am.* 2000; **25**(3): 535–543.
PubMed Abstract | Publisher Full Text

Ruijs ACJ, Jaquet JB, Kalmijn S, *et al.*: **Median and ulnar nerve injuries: a meta-analysis of predictors of motor and sensory recovery after modern microsurgical nerve repair.** *Plast. Reconstr. Surg.* 2005; **116**(2): 484–494.
PubMed Abstract | Publisher Full Text

Sandberg ML, Sandberg MK, Dahl J: **Blood flow changes in the trapezius muscle and overlying skin following transcutaneous electrical nerve stimulation.** *Phys. Ther.* 2007; **87**(8): 1047–1055.
PubMed Abstract | Publisher Full Text

Scott JJ: **Recovery of denervated muscle receptors following treatments to accelerate nerve regeneration.** *Brain Res.* 1991; **563**(1–2): 195–202.
PubMed Abstract | Publisher Full Text

Seo TB, Han IS, Yoon JH, *et al.*: **Involvement of Cdc2 in axonal regeneration enhanced by exercise training in rats.** *Med. Sci. Sports Exerc.* 2006; **38**(7): 1267–1276.
PubMed Abstract | Publisher Full Text

Silva PG, Jones A, Araujo PMP, *et al.*: **Assessment of light touch sensation in the hands of systemic sclerosis patients.** *Clinics (Sao Paulo).* 2014; **69**(9): 585–588.
PubMed Abstract | Publisher Full Text | Free Full Text

Sinatra RS, Ford DH: **The effects of acute and chronic morphine treatment on the process of facial nerve regeneration.** *Brain Res.* 1979; **175**(2): 315–325.
PubMed Abstract | Publisher Full Text

Sluka KA, Walsh D: **Transcutaneous electrical nerve stimulation: basic science mechanisms and clinical effectiveness.** *J. Pain.* 2003; **4**(3): 109–121.
PubMed Abstract | Publisher Full Text

Song B, Zhao M, Forrester J, *et al.*: **Nerve regeneration and wound healing are stimulated and directed by an endogenous electrical field in vivo.** *J. Cell Sci.* 2004; **117**(Pt 20): 4681–1690.
PubMed Abstract | Publisher Full Text

Stoll G, Müller HW: **Nerve injury, axonal degeneration and neural regeneration: basic insights.** *Brain Pathol.* 1999; **9**(2): 313–325.
PubMed Abstract | Publisher Full Text

Tohill M, Terenghi G: **Stem-cell plasticity and therapy for injuries of the peripheral nervous system.** *Biotechnol. Appl. Biochem.* 2004; **40**(Pt 1): 17–24.
PubMed Abstract | Publisher Full Text

Wang Y, Sunitha M, Chung KC: **How to measure outcomes of peripheral nerve surgery.** *Hand Clin.* 2013; **29**(3): 349–361.
PubMed Abstract | Publisher Full Text | Free Full Text

Watson T: **Electrical stimulation for wound healing**. Kitchen S, Bazin S: *Clayton Electrotherapy.* São Paulo: Manole; 1998; 311–337. Chapter 21.

Zeng YS, Nie JH, Zhang W, *et al.*: **Morphine acts via mu-opioid receptors to enhance spinal regeneration and synaptic reconstruction of primary afferent fibers injured by sciatic nerve crush.** *Brain Res.* 2007; **1130**(1): 108–113.
PubMed Abstract | Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 1

Reviewer Report 16 November 2021

https://doi.org/10.5256/f1000research.45186.r98628

✔ **Jonas Kolbenschlag**
BG Trauma Center Tuebingen, Department of Hand, Plastic, Reconstructive and Burn Surgery, Eberhard Karls University Tuebingen, Tübingen, Germany
Johannes Heinzel
BG Trauma Center Tuebingen, Department of Hand, Plastic, Reconstructive and Burn Surgery, Eberhard Karls University Tuebingen, Tuebingen, Germany

I think this is a highly interesting study protocol and the planned study has been thoughtfully conceptualized. I have no major concerns to raise, but I wonder whether the authors plan to include patients undergoing direct repair of non-segmental nerve defects only? I think this is implicated by using the term neurorrhaphy in the title of the manuscript but is not clearly stated in the protocol itself. Although I would deem an investigation of the effects of PES very interesting, I would recommend only to include patients with direct repair of non-segmental lesions. An experimental and control(SHAM) group, respectively, with segmental nerve damages could be included in further experiments however, to study the effects of PES following reconstruction of segmental nerve lesions.

All in all, I consider the work at hand highly interesting and a valuable addition to the field.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

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

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Peripheral Nerve, Microcirculation

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

Author Response 26 Nov 2021

ENILTON MATTOS, Escola Bahiana de Medicina e Saúde Pública, Salvador, Brazil

Thank you for the good comment. We agree with your comment that the repair of non-segmental nerve defects is not clearly stated in the protocol and we have corrected it.
Best regards,
Enilton Mattos

Competing Interests: No competing interests were disclosed.

Reviewer Report 22 June 2021

https://doi.org/10.5256/f1000research.45186.r86882

Yumin Yang
Key Laboratory of Neuroregeneration of Jiangsu and Ministry of Education, Co-innovation Center of Neuroregeneration, Nantong University, Nantong, China

I think this is an excellent manuscript, and it deserves to be accepted. This article studied the influence of low intensity and frequency surface peripheral electrical stimulation (PES) on nerve regeneration of digital nerve injuries of the hand after its surgical repair in humans. This study could provide novel, useful, and practical strategies to treat patients with peripheral nerve damage. If the effects of different stimulus intensity, time and stimulus parts can be studied more systematically, it will be a more perfect study.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

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

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Influence of surface peripheral electrical stimulation on nerve regeneration

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.

Author Response 23 Jun 2021

ENILTON MATTOS, Escola Bahiana de Medicina e Saúde Pública, Salvador, Brazil

Dear professsor Yumin Yang,
Thank you very much for the considerations.
Best regards,
Enilton Mattos

Competing Interests: No competing interests

6.2 Artigo em vias de submissão: Effects of transcutaneous electrical stimulation on peripheral nerve regeneration after digital nerve neurorrhaphy: A randomized clinical trial

Original Article

EFFECTS OF TRANSCUTANEOUS ELECTRICAL STIMULATION ON PERIPHERAL NERVE REGENERATION AFTER DIGITAL NERVE NEURORRHAPHY: A RANDOMIZED CLINICAL TRIAL

Enilton de Santana Ribeiro de Mattos[1-3] (https://orcid.org/0000-0003-2039-9744)

Yossi Zana[4] (https://orcid.org/0000-0003-0539-7492)

Paulo Itamar Ferraz Lessa[5] (https://orcid.org/0000-0003-4127-131X)

Alex Guedes[2,3,6] (https://orcid.org/0000-0001-7013-7107)

Abrahão Fontes Baptista[1,4,7] (0000-0001-7870-3820)

1. Programa de Pós-Graduação da Escola Bahiana de Medicina e Saúde Pública, Salvador, BA, Brazil.
2. Unidade do Sistema Neuro-Músculo-Esquelético, Empresa Brasileira de Serviços Hospitalares, Universidade Federal da Bahia, Salvador, BA, Brazil.
3. Programa de Residência Médica em Ortopedia e Traumatologia, Complexo Hospitalar Universitário Professor Edgard Santos, Empresa Brasileira de Serviços Hospitalares, Universidade Federal da Bahia, Salvador, BA, Brazil.
4. Centro de Matemática, Computação e Cognição, Universidade Federal do ABC, São Bernardo do Campo, São Paulo, Brazil
5. Universidade do Estado da Bahia, Salvador, BA, Brazil.
6. Departamento de Cirurgia Experimental e Especialidades Cirúrgicas, Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Salvador, BA, Brazil.

7. Laboratório de Investigações Médicas 54 (LIM-54), Universidade de São Paulo, São Paulo, São Paulo, Brazil

The study was conducted at Programa de Pós-Graduação da Escola Bahiana de Medicina e Saúde Pública and at Unidade do Sistema Neuro-Músculo-Esquelético, Empresa Brasileira de Serviços Hospitalares, Universidade Federal da Bahia, Salvador, BA, Brazil.

Correspondence: Enilton de Santana Ribeiro de Mattos, Avenida Araújo Pinho 421/804, Canela Salvador, BA, Brazil CEP 40110150. eniltonmattos@hotmail.com.

All authors declare no potential conflict of interest related to this article.

Abstract

Background: The human hand can suffer significant disability from upper extremity nerve injuries. Strategies like neurotrophic factors, stem cells, and electrical stimulation aim to enhance peripheral nerve regeneration. The surface electrical stimulation has been studied on recovery post nerve repair. This study aims to investigate the impact of low-frequency electrical stimulation on sensitivity outcomes in patients with digital nerve injuries. *Methods:* A randomized controlled trial was conducted with 32 patients divided into two groups: one received surgery followed by real electrical stimulation, while the other received surgery and then sham stimulation. The stimulation parameters included a square-pulsed, biphasic current at 20 Hz for 1 hour postoperatively. Assessment tools such as Semmes-Weinstein monofilaments and two-point discrimination tests were utilized preoperatively at 1 week, 1- and 3-months post-operation. *Results*: The outcomes revealed a gradual recovery of sensitivity

in both groups, nearing normal levels by the final assessment. However, no significant impact of surface electrical stimulation was observed post-surgery. *Conclusion*: The study on transcutaneous electrical stimulation post digital nerve neurorrhaphy did not significantly improve sensitivity outcomes in our sample, indicating the need for further research on its efficacy in nerve regeneration.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

The human hand is a rich sensory and motor multifunctional tool that have dexterous control to perform essential manipulation tasks[1]. Peripheral nerve injuries to the upper extremities can cause significant disability[2] and may have multiple causes, including trauma, ischemia, or inflammation[3]. Sensory dysfunction, hyperesthesia, and cold intolerance[4] can result from an injury to the digital nerves of the hand. Efforts have been made to refine microsurgical repair and although improvements in outcomes have been achieved, some limitations still remain. Promoting functional regeneration is fundamental for the peripheral nervous system to recovery normal functions[5].

Strategies to improve peripheral nerve regeneration include the use of neurotrophic factors, stem cells[6,7], ultrasound[8], low intensity lasers[9], physical therapy exercise[10,11] and electromagnetic fields. Brief postoperative low-frequency electrical stimulation to increase the rate and speed of peripheral nerve regeneration is a promising option[12] and it involves the application of electric fields of constant or varying frequency[13,14].

There are different ways to deliver the peripheral electrical stimulation (PES) such as implanted electrodes[15,16], percutaneous electrostimulation[17,18] (acupuncture needles inserted

into the skin and connected to an electric current generator), intraoperative electrostimulation[19,20,21,22,23], thin-film wireless implantable nerve stimulators[24] and the surface electrodes[25]. The use of transcutaneous surface electrodes is a non-invasive, practical, and simple option, avoiding the reactions provoked by implant surgery or percutaneous stimulation.

On the basis of these features, we hypothesized that PES may influence peripheral nerve regeneration in humans. We conducted a randomized clinical trial to study the influence of surface PES on recovery of sensory function, cold sensitivity and the pain disability on the social participation of patients undergoing neurorrhaphy of digital nerves of the hand.

Materials and Methods

This clinical trial was conducted at a general hospital in Bahia, Brazil from December 19, 2020, to June 10, 2022. Prior to participants recruitment, the study was registered in the Brazilian Clinical Trial Registry (ReBEC registration number: U1111-1259-1998) on December 18, 2020. The study underwent ethical review by the Research Ethics Committee at the Faculty of Medicine of Bahia and the protocol was previously published[26] to enable prospective evaluation of trial methodology, scientific rigor, ethical prerequisites according to the Declaration of Helsinki[27].

Trial Design and Participants. This study was a prospective, randomized, double-blinded, controlled clinical trial. The participants included patients undergoing neurorrhaphy for injuries resulting from digital nerve transection in the hand. Half of the participants received peripheral electrical stimulation using the Neurodyn II device (Ibramed, Brazil) within the first 24 hours after surgery. The other half received a sham treatment. The baseline characteristics of the patients are shown in Table I.

The participants and outcome assessors were blinded to patient allocation. The electrodes were positioned identically and applied for the same duration in both the intervention group (PES) and the sham group.

Table I. Baseline patient characteristics.

	Electrical stimulation (n=16)	Sham (n=16)
Mean age (range in *years*)	36.6 (18 to 57)	34.2 (21 to 58)
Male sex (*no. [%]*)	9 (56)	12 (75)
Right-handed (*no. [%]*)	13 (81)	14 (87)
Injury to the dominant hand (no. [%])	6 (38)	8 (50)
Injury to the radial digital nerve (*no. [%]*)	9 (56)	7 (44)
Injured Finger		
Thumb (n=8)	4	4
Index (n=9)	5	4
Midlle (n=2)	1	1
Ringer (n=4)	1	3
Litlle (n=9)	5	4
Diabetes	1	0
Smoker	2	4

Randomization, Allocation Concealment, and Blinding. Patients were divided into two groups: Group A (surgery + PES) and Group B (surgery + sham). Simple randomization was employed to achieve balanced groups, utilizing an online resource (randomization.com). The allocation process and electrical stimulation were carried out by a professional not involved in other stages of the study. Opaque and sealed envelopes were used to conceal participant allocation. Randomization occurred only for participants who provided informed consent to participate in the trial.

Interventions. Patients were assigned to two groups:

1. Group A (Surgery + PES): Patients underwent surgery followed by 1 hour of electrical stimulation. The electrodes delivered a square-pulsed, biphasic, symmetrical

current at a frequency of 20 Hz, with a pulse width of 0.4 ms. The amplitude was set to the motor threshold of the median nerve. Sixteen patients were included in this group.

2. Group B (Surgery + sham PES): Similar to Group A, patients in this group also received surgery followed by 1 hour of faked electrical stimulation. The electrostimulator was turned on only until the patient became aware of it, after which the amplitude was set to zero. Again, sixteen patients were part of this group.

See Figure 1 for a detailed CONSORT[28](Consolidated Standards of Reporting Trials) flowchart that illustrates the participants' excursion through the study.

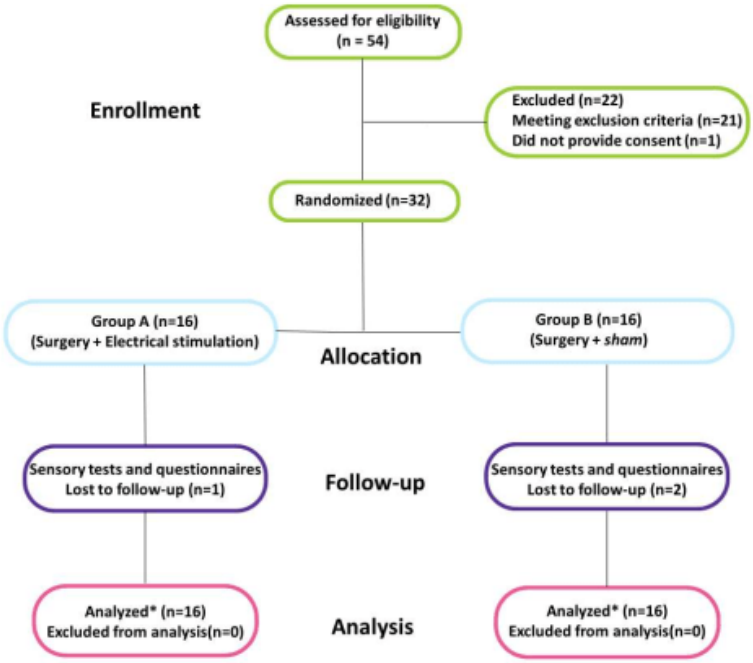


Figure 1. CONSORT 2010 flowchart diagram of patient screening, intervention, and follow-up.

* Intention-to-treat (ITT) analysis

Patients of both groups were equipped with two silicone-carbon and gel electrodes (each measuring 1 × 1 cm). One electrode was placed exactly proximal to the surgical site, while the other was positioned distally (Figure 2).

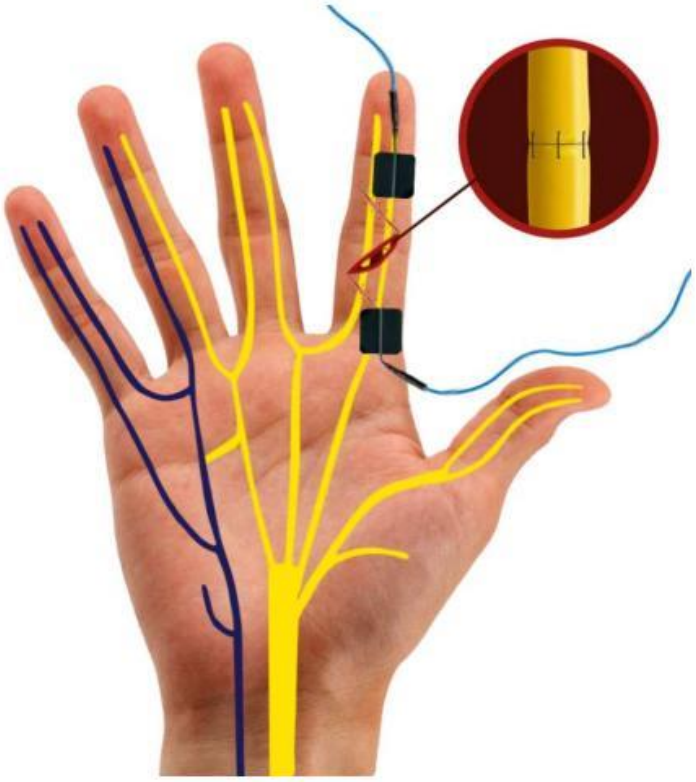


Figure 2. Model of a repaired digital nerve injury of the index finger and the electrodes placement.

A specialized physiotherapist, blinded to the intervention, guided the rehabilitation protocol. This protocol was remotely monitored using electronic means such as WhatsApp or Skype. Patients underwent a hand sensory re-education program based on the approach proposed by Dellon & Jabaley[29] focused on hand sensory re-education over a 3-month period. The patient was also encouraged to perform a home-based program.

Additionally, patients underwent in-person evaluations by the surgeon responsible for surgical and postoperative follow-up. Overall, participants completed a total of four face-to-face assessments to document their progress:

- Pre-intervention
- One week after intervention
- One month after intervention and part of the rehabilitation sessions
- Three months after intervention and all 20 rehabilitation sessions.

The 3-month timeframe was selected on the premise that nerve regeneration would likely be accomplished within this period, considering the relatively short distance for regeneration (2-6 cm) and an anticipated growth rate ranging from 1 to 3 mm per day[30]. Inclusion and exclusion criteria are provided in Figure 3.

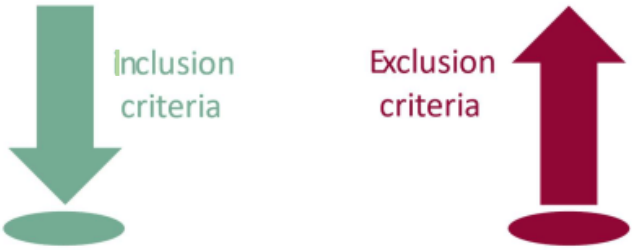


Figure 3. Inclusion and Exclusion Criteria

Outcomes measures. We evaluated the outcomes of peripheral nerve regeneration in digital nerves of the hand. The primary outcome focused on improvement, which we measured using quantitative sensory tests. Specifically, we employed the Semmes–Weinstein monofilament test (SWM) and static two-point discrimination (s2PD) tests during four in-person assessments. The difference in outcomes between two treatment groups (Group A vs. Group B) was assessed after randomization.

Additionally, the secondary outcome aimed to measure improvements in terms of cold sensitivity and the pain disability on the social functions for individuals who underwent neurorrhaphy of digital nerves in the hand. We used two patient-reported outcome questionnaires: the Cold Sensitivity Severity Scale (CSS)[31] and the Pain Disability Index (PDI)[32].

The SWM test, a crucial marker of functional recovery, assesses perception of pressure thresholds related to peripheral reinnervation[33]. During the test, participants placed their hands over a table with closed eyes. We applied scored probes perpendicularly to the pulp side of the affected finger for 1 to 1.5 seconds in three trials. A positive response in at least 2 out of 3 trials indicated the sensory threshold[23].

The s2PD test serves as an established assessment tool for evaluating tactile gnosis[2,34]. It measures the ability to distinguish between two nearby points touching the skin, ensuring they are truly distinct rather than perceived as a single point. The test estimates the minimum distance necessary for the patient to perceive the two pressure points as separate contacts[35]. It reflects the degree of innervation in a specific skin area. The Medical Research Council classification, modified by Mackinnon & Dellon, allows grouping based on different value ranges related to the sensitive recovery threshold[33,36] (Table II).

Table II. Modified HIGHET's classification (reproduced from Dunlop et al., 2019).

Sensory recovery	Highet	s2PD	m2PD	Recovery of sensibility
Failure	S0			No recovery of sensibility in the autonomous zone of the nerve
Poor	S1			Recovery of deep cutaneous pain sensibility
	S1+			Recovery of superficial pain and some touch sensibility
	S2			Recovery of superficial pain sensibility
	S2+			As with S2, but with over response
	S3	>15 mm	>7 mm	Recovery of pain and touch sensibility with no over response
Good	S3+	7-15 mm	4-7 mm	As in S3, but good localization of the stimulus but imperfect recovery of 2PD
Excellent	S4	2-6 mm	2-3 mm	Complete sensory recovery

s2PD = static two-point discrimination; m2PD = moving two-point discrimination

Cold Sensitivity Severity Scale offers a reliable way to assess cold sensitivity. In cases like amputation or nerve damage, hypersensitivity can occur and lead to significant disability. The CSS consists of four questions related to cold-induced symptoms. The total score provides the cold-sensitivity severity score.

Pain Disability Index: This seven-item questionnaire evaluates how pain affects various aspects of daily life. Each item is rated from 0 (no disability) to 10 (total disability) and the final score (ranging from 0 to 70) reflects the level of disability due to pain. This index has demonstrated consistency, validity, and reliability in studies related to nerve damage[32].

Sample Size Calculation. The sample size was determined based on the study conducted by Gordon et al. (2010). We calculated the sample size considering a repeated measures analysis of variance (ANOVA) test, accounting for interactions between and within factors. The effect size, as reported by Gordon et al. (2010), was 0.26. Additionally, we set an alpha-type error of 5%, a statistical power of 80%, and worked with two groups and three measures. Corrections were applied for both repeated measures (0.5) and non-sphericity (1). These parameters led to

an initial sample of 26 individuals. To account for potential losses, we increased the sample size by 20%, resulting in a final sample of 32 patients (16 per group). The participants of the two groups were examined by an experienced hand surgeon through the application of evaluation tools, including SWM, s2PD tests, CSS, and PDI.

Statistical Analysis. All statistical tests were performed using JASP (V0.18.3). The data were evaluated in a paired and non-paired way. For paired evaluations (intra-group comparisons), repeated measures ANOVA or the Friedman test were used, followed by the Student–Newman–Keuls post-test. For non-paired assessments (comparisons between groups), analysis of variance (one-way ANOVA or the Kruskal–Wallis test) has been used, followed by the Student–Newman–Keuls post-test. The choice of tests depended on the normality or the nature of the data. For statistical analysis, the 95% confidence interval was considered, with an alpha of 5% ($P < 0.05$) and power of 80%. Descriptive analysis was performed through means or medians associated with the applicable dispersion measures (standard error of the mean or quartiles 25/75). Both measurements of the variables in each study and statistical analysis were performed blindly. The independent variable for both groups was the use of electric current. The dependent variables were derived from the pre- and post-treatment assessments (SWM, s2PD, CSS and PDI).

Results

Eligibility was evaluated in a total of 54 patients; of these, 21 did not meet the inclusion criteria and one declined to participate. Our final analysis encompassed 16 patients in the PES group and 16 patients in the sham group (Fig. 1). Preoperatively, both groups exhibited similar baseline characteristics. All patients of both groups suffered from severe loss of sensitivity according to MSW and s2PD evaluation both before and a week after the operation, thus the

analysis was performed only on data from posterior evaluations. An ANOVA was performed with time of assessment as a repeated measure factor (levels: 1 and 3- months post-operation), and group as a between subject factor and age as covariant (Fig. 4). The analysis indicated statistically significant within subjects' effect (F=7.351, p=0.012) of time on MSW (g) and a non-significant, but low alpha (F=3.275, p=0.082) between subjects' effect of age. Results were similar when MSW values were expressed in needle size, but with age reaching significant between subjects' effect (F=6.912, p=0.014). Post hoc testes confirmed these results, with significant differences found only between the different times of evaluation within the same experimental group. The analysis was repeated with the s2PD as the dependent variable and results were essentially equivalent. Only time variable achieved significance level (F=12.236, p=0.002) with covariant age approximating significance (F=3.249, p=0.083). CSS and PDI of the two groups, as measured in the last assessment, were compared using an independent samples t-test and no significant differences were found. It is noteworthy that these two measurements were highly correlated (r=0.819, p<0.001).

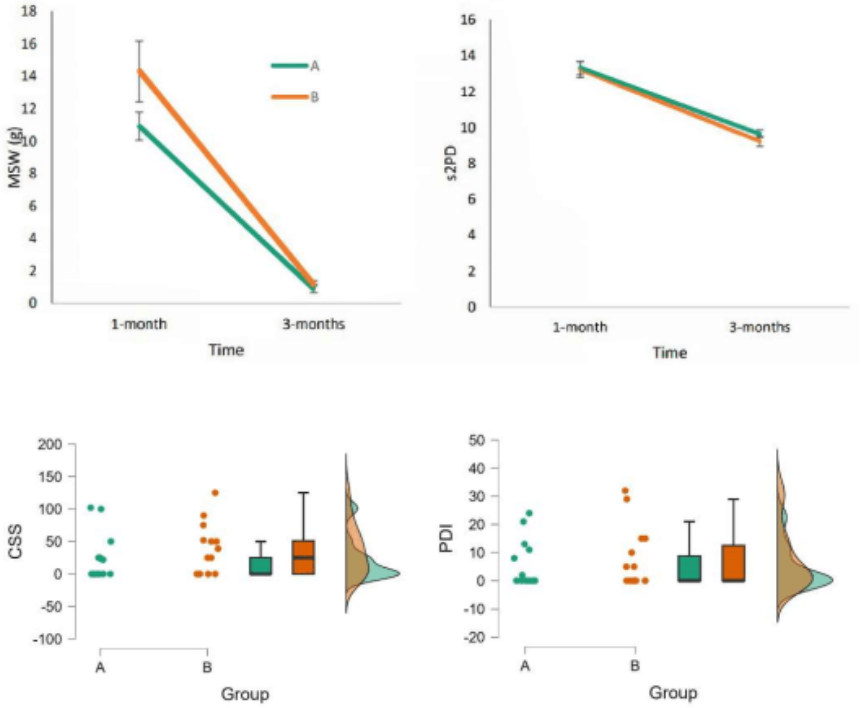


Figure 4. Top panels: Average MSW (g, left panel) and s2PD (mm, right panel) of Group A (PES, green line) and B (sham, orange line) 1- and 3-months post-operation. Bottom-panels: Boxplot of CSS (left panel) and PDI (right panel) for Groups A and B. Error bars represent standard error of the mean.

Evaluating the robustness of the results, the analyses were repeated without age as a covariant as well as after excluding one subject from group A, aged 57, that had discrepant MSW (g) values (z-score≈5). Removal of the age covariant altered none of the previous results, but removal of the outlier eliminated the significance of the age as a covariant. In summary, the results show that patients from both groups recovered gradually their sensitivity as measured by MSW and s2PD tests, up to almost normal level at the last measurement.

However, no significant effect was found to the treatment at the end of the three measurements moments after the operation.

Discussion

This study explored the efficacy of surface PES on recovery of sensory function. The results show that patients from both groups recovered gradually their sensitivity as measured by MSW and s2PD tests, up to almost normal at the last measurement. However, no significant effect was found to the PES at the end of the three measurements moments after the operation. It is unlikely that the hypothesized effect of the treatment was masked by the good recovery of the patients, as after 1-months sensibility was still highly affected. The age of the patients might play a role, but its influence was minor at best. Sensitivity to cold and pain disability were measured only in the last stage and presented high variability, thus it is hard to conclude strongly that the treatment did not affect this aspect.

Transcutaneous electrical stimulation holds promise in nerve regeneration, offering a non-invasive approach with potential practical benefits[37]. It can be utilized circumventing the complications of surgical implantation or percutaneous stimulation[38,39]. Some research indicates that it may take up to 8 weeks for the regenerating axons to cover a distance of 25mm and the use of PES may reduce this period[20,40]. Previous results demonstrated that subjects who received stimulation exhibited earlier and better outcomes around 3 months post-surgery[40]. Gordon at al. conducted an innovative randomized controlled trial (RCT) of 21 patients undergoing carpal tunnel decompression surgery. After surgery, the experimental group received electrical stimulation with implanted wires for one hour, set at 20 Hz, 4-6 volts, and pulse duration between 0.1 and 0.8 milliseconds. Impressively, improvements in electrophysical measurements occurred within six to eight weeks, whereas slower recovery was observed in the control group[23]. In a double-blind RCT, Wong and colleagues investigated

PES effects following repair of 31 transected digital nerves. The PES protocol (20 Hz, <30 V, 0.1–0.4 ms) led to significantly improved sensory outcomes, however, functional recovery remained unchanged[40]. In 2020, Power et al. conducted a trial to examine the impact of electrical stimulation after cubital tunnel decompression surgery. Thirty-one patients underwent one hour of PES (20 Hz, <30 V, 0.1 ms) after the surgery. Over the follow-up period, the PES group exhibited notable enhancements in Motor Unit Number Estimation (MUNE) compared to the control group[41].

Some studies reported adverse findings that contradict prior research that has highlighted the advantageous impact of direct current electric fields on the regeneration of peripheral nerves[42,43]. In our study, the s2PD and SWM testing did not demonstrate that PES significantly enhances the reinnervation of receptors responsible for tactile sensation in the skin of the digital pulp. In face of this scenario, the efficacy of applied fields in enhancing peripheral nerve regeneration *in vivo* appears to be uncertain.

Cold intolerance[44] and pain[45] often manifest with substantial debilitation after nerve damage in the hand. Previous studies linked symptom severity to the extent of sensory restoration post-nerve injury, with individuals exhibiting poorer nerve recovery experiencing more severe symptoms[45,46]. In our sample, isolated digital nerve injury does not appear to be associated with worse outcomes in terms of pain and cold intolerance as evaluated by CSS and PDI among the analyzed groups. These bad outcomes seem to be a problem more related to cases of finger replantation, more severe vascular compromise, and proximal nerve injuries of the median and ulnar nerves.

Postoperative therapy following hand neurorrhaphy is considered standard care[47] and was prescribed for both groups in our study. Not providing hand therapy would be unethical, as rehabilitation is commonly prescribed post-surgery in real-life scenarios and omitting it could

compromise the external validity of the study. However, it is acknowledged that there may be an interaction effect between the instituted therapies[48], making it challenging to precisely measure any potential benefits.

One limitation of PES is that the surgery should preferably be carried out under general anesthesia. A recent study[49] shows that the use of perioperative lidocaine significantly reduced the positive effects of electrical stimulation on nerve regeneration. Current practice in hand surgery is moving toward local or regional anesthesia, which offers the advantages of slightly lower perioperative risk, faster transition, and better postoperative analgesia. Therefore, suggesting this treatment without studying the method of administration under standard anesthesia may not be clinically acceptable.

A second limitation of this study is that the functional results took into account some subjective information from the patients. Neurophysiological assessments can serve as a sensitive indicator for evaluating disease severity and progression in adults. Nevertheless, the limitation in using conduction studies arises due to the laceration of a single digital branch observed in all studied subjects. Contamination occurs from signal volume conduction via the sensory nerve action potential generated by the intact branch on the opposite side of the digit[40]. Recent outcomes research following nerve injuries has increasingly focused on functional outcomes and patient-reported results[50].

Conclusion

In this study, the use of surface electrical stimulation after neurorrhaphy of digital nerves of the hand did not improve postoperative sensitivity measured by MSW and s2PD tests and was not associated with better results in terms of sensitivity to cold and pain involving the outcomes

studied. However, additional studies are needed to continue exploring the efficacy and safety of electrical stimulation use in nerve regeneration.

References

1. Liu, M. J., Xiong, C. H., Xiong, L., & Huang, X. L. (2016). Biomechanical Characteristics of Hand Coordination in Grasping Activities of Daily Living. PLoS ONE, 11(1), e0146193. doi: 10.1371/journal.pone.0146193
2. Dunlop, R. L. E., Wormald, J. C. R., & Jain, A. (2019). Outcome of surgical repair of adult digital nerve injury: a systematic review. BMJ Open, 9, e025443. doi: 10.1136/bmjopen-2018-025443
3. Stoll, G., & Müller, H. W. (1999). Nerve injury, axonal degeneration and neural regeneration: basic insights. Brain Pathology, 9(2), 313–325. doi: 10.1111/j.1750-3639.1999.tb00229.x
4. Rosén, B., & Lundborg, G. (2000). A model instrument for the documentation of outcome after nerve repair. Journal of Hand Surgery, 25(3), 535–543. doi: 10.1053/jhsu.2000.6458
5. Güvenç, K., Ateş, E., & Asfuroğlu, Z. M. (2023). Factors affecting functional outcomes after surgery to repair extensive volar forearm lacerations with nerve injuries identified via quantitative and qualitative methods. Journal of Joint Diseases and Related Surgery, 34(2), 405–412. doi: 10.52312/jdrs.2023.1067. PMID: 37462645; PMCID: PMC10367148.
6. Lopes, F. R. P., Moura Campos, L. C., Corrêa, J. D. Jr., et al. (2006). Bone marrow stromal cells and resorbable collagen guidance tubes enhance sciatic nerve regeneration in mice. Experimental Neurology, 198(2), 457–468. doi: 10.1016/j.expneurol.2005.12.019.
7. Tohill, M., & Terenghi, G. (2004). Stem-cell plasticity and therapy for injuries of the peripheral nervous system. Biotechnology and Applied Biochemistry, 40(Pt 1), 17–24. doi: 10.1042/BA20030173

8. Crisci, A. R., & Ferreira, A. L. (2002). Low-intensity pulsed ultrasound accelerates the regeneration of the sciatic nerve after neurotomy in rats. Ultrasound in Medicine & Biology, 28(10), 1335–1341. doi: 10.1016/s0301-5629(02)00576-8
9. Bae, C. S., Lim, S. C., Kim, K. Y., et al. (2004). Effect of Ga-As laser on the regeneration of injured sciatic nerves in the rat. In Vivo, 18(4), 489–495.
10. Molteni, R., Zheng, J. Q., Ying, Z., et al. (2004). Voluntary exercise increases axonal regeneration from sensory neurons. Proceedings of the National Academy of Sciences of the United States of America, 101(22), 8473–8478. doi: 10.1073/pnas.0401443101
11. Seo, T. B., Han, I. S., Yoon, J. H., et al. (2006). Involvement of Cdc2 in axonal regeneration enhanced by exercise training in rats. Medicine and Science in Sports and Exercise, 38(7), 1267–1276. doi: 10.1249/01.mss.0000227311.00976.68
12. Geremia, N. M., Gordon, T., Brushart, T. M., Al Majed, A. A., & Verge, V. M. K. (2007). Electrical stimulation promotes sensory neuron regeneration and growth-associated gene expression. Experimental Neurology, 205, 347–359.
13. Baptista, A. F., Souza Gomes, J. R., Oliveira, J. T., et al. (2007). A new approach to assess function after sciatic nerve lesion in the mouse - adaptation of the sciatic static index. Journal of Neuroscience Methods, 161(2), 259–264. doi: 10.1016/j.jneumeth.2006.11.016
14. Baptista, A. F., Gomes, J. R. S., Oliveira, J. T., et al. (2008). High- and low-frequency transcutaneous electrical nerve stimulation delay sciatic nerve regeneration after crush lesion in the mouse. Journal of Peripheral Nervous System, 13(1), 71–80. doi: 10.1111/j.1529-8027.2008. 00160.x
15. Mendonça, A. C., Barbieri, C. H., & Mazzer, N. (2003). Directly applied low intensity direct current enhances peripheral nerve regeneration in rats. Journal of Neuroscience Methods, 129(2), 183–190. doi: 10.1016/s0165-0270(03)00207-3

16. Politis, M. J., Zanakis, M. F., & Albala, B. J. (1988). Facilitated regeneration in the rat peripheral nervous system using applied electric fields. Journal of Trauma, 28(9), 1375–1381. doi: 10.1097/00005373-198809000-00012

17. Chen, Y. S., Hu, C. L., Hsieh, C. L., et al. (2001). Effects of percutaneous electrical stimulation on peripheral nerve regeneration using silicone rubber chambers. Journal of Biomedical Materials Research, 57(4), 541–549. doi: 10.1002/1097-4636(20011215)57:4<541:aid-jbm1200>3.0.co;2-y

18. Inoue, M., Hojo, T., Yano, T., et al. (2003). The effects of electroacupuncture on peripheral nerve regeneration in rats. Acupuncture in Medicine, 21(1–2), 9–17. doi: 10.1136/aim.21.1-2.9

19. Al-Majed, A. A., Brushart, T. M., & Gordon, T. (2000a). Electrical stimulation accelerates and increases expression of BDNF and TrKB mRNA in regenerating rat femoral motoneurons. European Journal of Neuroscience, 12(12), 4381–4390. doi: 10.1046/j.1460-9568.2000. 01341.x

20. Al-Majed, A. A., Neumann, C. M., Brushart, T. M., et al. (2000b). Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration. Journal of Neuroscience, 20(7), 2602–2608. doi: 10.1523/JNEUROSCI.20-07-02602.2000

21. Al-Majed, A. A., Tam, S. L., & Gordon, T. (2004). Electrical stimulation accelerates and enhances expression of regeneration-associated genes in regenerating rat femoral motoneurons. Cellular and Molecular Neurobiology, 24(3), 379–402. doi: 10.1023/b:cemn.0000022770. 66463.f7

22. Brushart, T. M., Hoffman, P. N., Royall, R. M., et al. (2002). Electrical stimulation promotes motoneuron regeneration without increasing its speed or conditioning the neuron. Journal of Neuroscience, 22(15), 6631–6638. doi: 10.1523/JNEUROSCI.22-15-06631.2002

23. Gordon, T., Amirjani, N., Edwards, D. C., et al. (2010). Brief post-surgical electrical stimulation accelerates axon regeneration and muscle reinnervation without affecting the functional measures in carpal tunnel syndrome patients. Experimental Neurology, 223(1), 192–202. doi: 10.1016/j.expneurol.2009.09.020

24. Ray, W. Z., Mahan, M. A., Guo, D., et al. (2017). An update on addressing important peripheral nerve problems: challenges and potential solutions. Acta Neurochirurgica, 159(9), 1765–1773. doi: 10.1007/s00701-017-3203-3

25. Chandran, P., & Sluka, K. A. (2003). Development of opioid tolerance with repeated transcutaneous electrical nerve stimulation administration. Pain, 102(1–2), 195–201. doi: 10.1016/s0304-3959(02)00381-0.

26. Mattos, E., Guedes, A., Lessa, P. I. F., & Baptista, A. F. (2021). Influence of surface peripheral electrical stimulation on nerve regeneration after digital nerve neurorrhaphy: study protocol for a randomized clinical trial. F1000Research, 10, 219. doi: 10.12688/f1000research.42120.2. PMID: 34909180; PMCID: PMC8596177.

27. World Medical Association. (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA, 310(20), 2191-4.

28. Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gøtzsche, P. C., Devereaux, P. J., Elbourne, D., Egger, M., & Altman, D. G. (2010). CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ, 340, c869. doi: 10.1136/bmj.c869. PMID: 20332511; PMCID: PMC2844943.

29. Dellon, A. L., & Jabaley, M. E. (1982). Reeducation of sensation in the hand following nerve suture. Clinical Orthopaedics and Related Research, (163), 75–79.

30. Sunderland, S. (1947). Rate of regeneration in human peripheral nerves. Archives of Neurology and Psychiatry, 58, 1-6.

31. McCabe, S. J., Mizgala, C., & Glickman, L. (1991). The measurement of cold sensitivity of the hand. Journal of Hand Surgery, 16(6), 1037–1040.
32. Novak, C. B., Anastakis, D. J., Beaton, D. E., et al. (2010). Relationships among pain disability, pain intensity, illness intrusiveness, and upper extremity disability in patients with traumatic peripheral nerve injury. Journal of Hand Surgery, 35(10), 1633–1639.
33. Wang, Y., Sunitha, M., & Chung, K. C. (2013). How to measure outcomes of peripheral nerve surgery. Hand Clinics, 29(3), 349–361.
34. Dunlop, R. L. E., Wormald, J. C. R., & Jain, A. (2019). Outcome of surgical repair of adult digital nerve injury: a systematic review. BMJ Open, 9(3), e025443.
35. Rosén, B., & Lundborg, G. (2000). A model instrument for the documentation of outcome after nerve repair. Journal of Hand Surgery, 25(3), 535–543.
36. Slutsky, D. J. (2014). The management of digital nerve injuries. The Journal of Hand Surgery, 39(6), 1208–1215.
37. Juckett, L., Saffari, T. M., Ormseth, B., Senger, J. L., & Moore, A. M. (2022). The Effect of Electrical Stimulation on Nerve Regeneration Following Peripheral Nerve Injury. Biomolecules, 12(12), 1856.
38. Burssens, P., Forsyth, R., Steyaert, A., et al. (2003). Influence of burst TENS stimulation on the healing of Achilles tendon suture in man. Acta Orthopaedica Belgica, 69(6), 528–532.
39. Burssens, P., Forsyth, R., Steyaert, A., et al. (2005). Influence of burst TENS stimulation on collagen formation after Achilles tendon suture in man. A histological evaluation with Movat's pentachrome stain. Acta Orthopaedica Belgica, 71(3), 342–346.
40. Wong, J. N., Olson, J. L., Morhart, M. J., & Chan, K. M. (2015). Electrical stimulation enhances sensory recovery: a randomized controlled trial. Annals of Neurology, 77(6), 996-1006.

41. Power, H. A., Morhart, M. J., Olson, J. L., & Chan, K. M. (2020). Postsurgical Electrical Stimulation Enhances Recovery Following Surgery for Severe Cubital Tunnel Syndrome: A Double-Blind Randomized Controlled Trial. Neurosurgery, 86(4), 769–777.

42. McGinnis, M. E., & Murphy, D. J. (1992). The lack of an effect of applied d.c. electric fields on peripheral nerve regeneration in the guinea pig. Neuroscience, 51(1), 231–244.

43. Hanson, S. M., & McGinnis, M. E. (1994). Regeneration of rat sciatic nerves in silicone tubes: characterization of the response to low intensity dc stimulation. Neuroscience, 58(2), 411–421.

44. Irwin, M. S., Gilbert, S. E., Terenghi, G., Smith, R. W., & Green, C. J. (1997). Cold intolerance following peripheral nerve injury. Natural history and factors predicting severity of symptoms. Journal of Hand Surgery, 22(3), 308-316.

45. Novak, C. B., Anastakis, D. J., Beaton, D. E., Mackinnon, S. E., & Katz, J. (2010). Relationships among pain disability, pain intensity, illness intrusiveness, and upper extremity disability in patients with traumatic peripheral nerve injury. Journal of Hand Surgery, 35(10), 1633-1639.

46. Aman, M., Zimmermann, K. S., Glaser, J. J., Daeschler, S. C., Boecker, A. H., & Harhaus, L. (2024). Revealing digital nerve lesions-A comprehensive analysis of 2084 cases of a specialized center. Injury. Advance online publication. doi: 10.1016/j.injury.2024.111514.

47. Gupta, S. (2023). Hand Nerve Injury Repair Treatment & Management. Medscape. Retrieved from https://emedicine.medscape.com/article/1287077-overview?form=fpf.

48. Royston, P., & Sauerbrei, W. (2009). Two Techniques for Investigating Interactions between Treatment and Continuous Covariates in Clinical Trials. The Stata Journal, 9(2), 230-251.

49. Keane, G. C., Marsh, E. B., Hunter, D. A., Schellhardt, L., Walker, E. R., & Wood, M. D. (2023). Lidocaine Nerve Block Diminishes the Effects of Therapeutic Electrical Stimulation to Enhance Nerve Regeneration in Rats. Hand, 18(1_suppl), 119S-125S.

50. Heneghan, C., Goldacre, B., & Mahtani, K. R. (2017). Why clinical trial outcomes fail to translate into benefits for patients. Trials, 18(1), 122.

6.3 Artigo publicado: Influence of electrical stimulation on peripheral nerve regeneration: Protocol for a systematic review

O terceiro artigo foi publicado na revista *Research, Society and Development*, é de um protocolo para realização de uma revisão sistemática que havíamos planejado fazer para compor nossa tese. Entretanto, logo em seguida a publicação deste protocolo, duas outras revisões (sendo uma sistemática e outra narrativa) foram publicadas, o que nos fez optar por aproveitar a estratégia de busca e realizar um estudo metacientífico avaliando desfechos em estudos de estimulação elétrica.

Research, Society and Development, v. 10, n. 17, e230101724942, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i17.24942

Influence of electrical stimulation on peripheral nerve regeneration: Protocol for a systematic review

Influência da estimulação elétrica na regeneração nervosa periférica: Protocolo para uma revisão sistemática

Influencia de la estimulación eléctrica en la regeneración de los nervios periféricos: Protocolo para una revisión sistemática

Received: 12/19/2021 | Reviewed: 12/24/2021 | Accept: 12/25/2021 | Published: 12/27/2021

Enilton de Santana Ribeiro de Mattos
ORCID: https://orcid.org/0000-0003-2039-9744
Federal University of Bahia, Brazil
E-mail: eniltonmattos@hotmail.com
Alex Guedes
ORCID: https://orcid.org/0000-0001-7013-7107
Federal University of Bahia, Brazil
Santa Izabel Hospital, Holy House of Mercy of Bahia, Brazil
E-mail: alexguedes2003@yahoo.com.br
Mateus dos Santos Viana
ORCID: https://orcid.org/0000-0001-9021-7657
Federal University of Bahia, Brazil
E-mail: vianamateus@hotmail.com
Abrahão Fontes Baptista
ORCID: https://orcid.org/0000-0001-7870-3820
Federal University of ABC, Brazil
São Paulo University, Brazil
E-mail: abrahao.baptista@gmail.com

Abstract
This is a protocol for a systematic review (intervention). Electrical stimulation (ES) is a therapeutic strategy used to improve peripheral nerve regeneration that involves the application of electrical fields of constant or varying frequency. We are going to lead a literature search to identify all published and unpublished randomized controlled trials that describe the use of ES in patients with peripheral nerve injury. We will compare: Electrical stimulation (application of electrical fields of constant or varying frequency) versus sham in patients with peripheral nerve injury; Electrical stimulation versus standard treatment (physiotherapy) in patients with peripheral nerve injury; Electrical stimulation versus no treatment in patients with peripheral nerve injury. Considering the scenario of very numerous strategies and different techniques of ES to stimulate nerve regeneration, decisions to recommend them should consider these uncertainties and should be summarized intended its application in clinical practice. The objective of this review is to assess the influence of electrical stimulation (ES) on nerve regeneration in individuals with peripheral nerve injury.
Keywords: Peripheral Nerves; Nerve Regeneration; Electric Stimulation Therapy; Peripheral Nerve Injury.

Resumo
Trata-se de um protocolo para uma revisão sistemática (intervenção). A estimulação elétrica (EE) é uma estratégia terapêutica utilizada para melhorar a regeneração nervosa periférica que envolve a aplicação de campos elétricos de frequência constante ou variada. Vamos conduzir uma pesquisa da literatura disponível para identificar todos os ensaios controlados randomizados publicados e não publicados que descrevem o uso de ES em pacientes com lesão nervosa periférica. Vamos comparar: Estimulação elétrica (aplicação de campos elétricos de frequência constante ou variada) versus simulação em pacientes com lesão nervosa periférica; Estimulação elétrica versus tratamento padrão (fisioterapia) em pacientes com lesão nervosa periférica; Estimulação elétrica versus nenhum tratamento em pacientes com lesão nervosa periférica. Considerando o cenário de numerosas e diferentes estratégias de EE para promover a regeneração nervosa, as decisões para recomendá-las devem considerar essas incertezas e devem ser sumarizadas visando sua aplicação na prática clínica. O objetivo desta revisão é avaliar a influência da estimulação elétrica na regeneração nervosa em indivíduos com lesão nervosa periférica.
Palavras-chave: Nervos Periféricos; Regeneração Nervosa; Terapia por Estimulação Elétrica; Traumatismos dos Nervos Periféricos.

Research, Society and Development, v. 10, n. 17, e230101724942, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i17.24942

Resumen

Es un protocolo para una revisión sistemática (intervención). La estimulación eléctrica (EE) es una estrategia terapéutica utilizada para mejorar la regeneración nerviosa periférica que implica la aplicación de campos eléctricos de frecuencia constante o variada. Realizaremos una investigación de la literatura disponible para identificar todos los ensayos controlados aleatorios publicados y no publicados que describan el uso de EE en pacientes con daño a los nervios periféricos. Comparemos: Estimulación eléctrica (aplicación de campos eléctricos de frecuencia constante o variada) versus simulación en pacientes con lesión nerviosa periférica; Estimulación eléctrica versus tratamiento estándar (fisioterapia) en pacientes con daño a los nervios periféricos; Estimulación eléctrica versus ningún tratamiento en pacientes con daño a los nervios periféricos. Teniendo en cuenta el escenario de numerosas y diferentes estrategias de EE para promover la regeneración nerviosa, las decisiones para recomendarlas deben considerar estas incertidumbres y deben resumirse para aplicarlas en la práctica clínica. El objetivo de esta revisión es evaluar la influencia de la estimulación eléctrica en la regeneración nerviosa en individuos con daño a los nervios periféricos.

Palabras clave: Nervios Periféricos; Regeneración Nerviosa; Terapia por Estimulación Eléctrica; Traumatismos de los Nervios Periféricos.

1. Introduction

1.1 Description of the Condition

Harm to the peripheral nerves can occur due to a variety of reasons, including trauma, metabolic insults and inflammation (Stoll & Müller, 1999). Morphological functional changes can occur in response to peripheral nerve injury, such as motor and/or sensory function impairment, hyperesthesia, and low-temperature intolerance (Stoll & Müller, 1999; Mattos et al., 2021). Peripheral nerve regeneration occurs, but sometimes it is hampered by the type of the lesion, the presence of comorbidities such as diabetes, lesions of the musculoskeletal system and the distance from the lesion to the target organs (Dunlop et al., 2019). In the presence of these obstacles, nerve regeneration may be improved by a series of pharmacological and non-pharmacological strategies, including the use of external electric fields (Baptista et al., 2008).

1.2 Description of the Intervention

Electrical stimulation to improve the rate and speed of peripheral nerve regeneration involves the application of electrical fields of constant or varying frequency, as demonstrated in animal studies (Stoll & Müller, 1999; Mattos et al., 2021; Baptista et al., 2008). Electrical currents are usually used, either flowing unidirectional (monophasic, constant, or pulsed electrical currents) or bidirectional (alternate or biphasic electrical currents) (Baptista et al., 2008). The use of bidirectional electrical currents is preferable, as it does not provoke electrophoretic phenomena and consequent skin lesion (Low & Reed, 2001). However, this approach needs to be further investigated in human beings in clinical settings.

1.3 How the Intervention Might Work

The electrical currents may be administered through electrodes implanted in the nerve itself, intraoperatively, and using percutaneous or transcutaneous stimulation. The electric field improves the expression of neurotransmitters, growth factors and adhesion molecules, that may increase and guide regeneration (McCaig et al., 2005) Furthermore, it may guide endogenous stem-cells to the lesion site.

1.4 Objective

To assess the influence of electrical stimulation (ES) on nerve regeneration in individuals with peripheral nerve injury.

2. Methodology

This systematic review will be conducted in accordance with the recommendations of Cochrane Handbook for Systematic Reviews of Intervention (Cumpston et al., 2019) The protocol was prospectively registered at the PROSPERO

Research, Society and Development, v. 10, n. 17, e230101724942, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i17.24942

database (registration number CRD42021256292) and the reporting will be prepared following the PRISMA statement (Moher et al., 2010).

2.1 Criteria for Considering Studies for this Review

Types of Studies

We will include randomized controlled trials (RCT).

Types of Participants

Adult patients (over 18 years old of both sexes) with peripheral nerve injury submitted to ES.

Stimulation for internal organs such as bladder, esophagus (dysphagia) or vesicle and stimulation for central neurological conditions such as stroke and spine or root or spinal cord injuries will not be included.

Types of Interventions

Experimental Intervention

We will analyze the following comparisons:

1. Electrical stimulation (application of electrical fields of constant or varying frequency) versus sham in patients with peripheral nerve injury.
2. Electrical stimulation (application of electrical fields of constant or varying frequency) versus standard treatment (physiotherapy) in patients with peripheral nerve injury.
3. Electrical stimulation (application of electrical fields of constant or varying frequency) versus no treatment in patients with peripheral nerve injury.

Comparator Intervention

We will include the following comparators:

1. Sham (i.e., a procedure that simulate ES).
2. Non-pharmacological standard treatment, including physiotherapy.
3. No intervention.

Types of Outcome Measures

Primary Outcomes

Patients will be evaluated according to:

1. Quantitative sensory tests including mechanical detection thresholds through Semmes–Weinstein monofilament, two-point discrimination, vibratory testing; and thermal detection (cold and warm) thresholds.
2. Functional status assessed through scales and/or questionnaires and functional testing.
3. Aspects related to pain, and quality of life.

Secondary Outcomes

Improvement in nerve conduction studies.

Timing of Outcome Assessment

We will extract outcomes post-intervention (i.e., at the end of the treatment) at the time points reported in the studies and group.

Research, Society and Development, v. 10, n. 17, e230101724942, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i17.24942

Hierarchy of Outcome Measures

If studies report multiple measures of an eligible outcome, we will include the data based on several considerations. If several measures of an outcome are available on the same hierarchy level used in a study, we will prioritize the outcome measures according to the order specified for each of the outcomes. If several outcome measures on the same scale are available, we will give priority to the outcome measure that is most frequently used across all the included studies.

2.2 Search Methods for Identification of Studies

See also the search strategy extended data in Figshare (de Santana Ribeiro de Mattos et al., 2021).

Electronic Searches

We will conduct a literature search to identify all published and unpublished randomized controlled trials. The literature search will identify potential studies in all languages. We will translate the non-English language papers and fully assess them for potential inclusion in the review as necessary. We will place no restrictions on publication date.

We will use the following electronic search databases for identifying potential studies:

- The Cochrane Central Register of Controlled Trials (CENTRAL).
- PubMed/MEDLINE.
- EMBASE.
- PEDro.
- BVS (LILACS).

2.3 Data Collection and Analysis

Selection of Studies

Two reviewers authors (EM and MSV) will independently screen titles and trial abstracts that have been identified by the search strategy for potential inclusion in the review using predefined inclusion and exclusion criteria. They will assess each trial for potential duplicate publication. Differences will be resolved by discussion and consensus with a third review author (AFB or AG). The same reviewer authors will retrieve and review the complete report of all selected articles.

2.4 Data Extraction and Management

Two independent reviewer authors will record the following study and patient characteristics:

- Setting (single or multi-center).
- Country of origin.
- Enrolment period.
- Year of publication, format (abstract or journal article).
- Study design.
- Inclusion and exclusion criteria.
- Indications for ES.
- Types of performed ES.
- Duration and number of ES application.
- Patient demographics and characteristics including gender, mean age and co-morbidities
- Outcomes.
- Dropouts or loss to follow-up.

Research, Society and Development, v. 10, n. 17, e230101724942, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i17.24942

- Study quality (generation of allocation sequence, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias).

2.5 Assessment of Risk of Bias in Included Studies

Two reviewer authors (EM e MSV) will independently assess the risk of bias for each study using version 2 of the Cochrane 'Risk of Bias' tool (RoB 2) (Sterne et al., 2019) outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Cumpston et al., 2019) Any disagreements will be resolved by discussion or by involving the third review author (AFB or AG). We will assess the risk of bias of a specific result of randomized trials according to the following domains:

- Bias arising from the randomization process.
- Bias due to deviations from intended interventions.
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias in selection of the reported result.

We will assess the risk of bias for the outcomes of the included trials presented in the 'Summary' table. For the purposes of this review, we are interested in quantifying the effect of ES at baseline, regardless of whether the interventions are received as intended (the intention-to-treat effect).

We will use the signaling questions in the RoB 2 tools and rate each domain as 'low risk of bias', 'some concerns', or 'high risk of bias'.

We will summarize the 'risk of bias' judgements across different studies for each of the domains listed for each outcome. The overall risk of bias within the trial for the result is the least favorable assessment across the domains; however, where a trial is judged to have some concerns for multiple domains, we will judge the overall risk of bias as high, based on the approach outlined in Table 8.2.b of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011).

2.6 Measures of Treatment Effect

We will express dichotomous outcomes as risk ratios (RR) of nerve regeneration with a 95% confidence interval (CI) and express continuous outcomes as mean differences (MD) with 95% CIs. We will not exclude trials with zero events in both arms from meta-analysis (Friedrich et al., 2007) We will calculate the numbers of patients needed to treat (or harm) by 1/(risk difference), expressed with 95% CIs. For outcomes for which data are not reported or are reported in a different format, we will contact authors for clarification. We will use the intention-to-treat (ITT) sample (all randomized patients) in the analysis.

2.7 Unit of Analysis Issues

We will use the patient as the unit of analysis.

2.8 Dealing with Missing Data

We will contact authors for any missing data from included studies.

2.9 Assessment of Heterogeneity

We will assess heterogeneity with the Chi2 test ($P < 0.15$ = significant heterogeneity) and I2 statistic (> 25% = heterogeneity) using a random-effects model.

Research, Society and Development, v. 10, n. 17, e230101724942, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i17.24942

2.10 Assessment of Reporting Biases

We will estimate publication bias by examining the relationship between the treatment effects and the standard error of the estimate using a funnel plot.

2.11 Data Synthesis

If the treatments, participants, and the underlying clinical question are similar enough for a meta-analysis to be considered meaningful, we will undertake meta-analyses. For quantitative data, where possible, odds ratio (for categorical outcome data) or standardized mean differences (for continuous data) and their 95% confidence intervals will be calculated from the data generated by each included randomized controlled trial. If appropriate with available data, results from comparable groups of studies will be pooled into statistical meta-analysis using. We will use the Cochrane Review Manager 5 Software (The Nordic Cochrane Centre, 2011). Heterogeneity between combined studies will be tested using standard chi-square test. Where statistical pooling is not possible the findings will be presented in narrative form.

2.12 Subgroup Analysis and Investigation of Heterogeneity

We are planning to perform the following subgroup analyses a priori:

1. Risk of bias (high versus low versus unclear).
2. Publication type (abstracts versus full text).
3. Method of ES delivery.
4. Electrode placement and pulse width.
5. Age of participants.
6. Type of the lesion.

Any additional analysis will be reported as post hoc. We will compare subgroups using a formal statistical test for subgroup differences.

2.13 Sensitivity Analysis

We will perform a priori sensitivity analysis to assess the robustness of our conclusions. This will involve:

1. ITT versus per-protocol (PP) analysis.
2. Meta-analysis modeling (fixed versus random effects).

3. Results and Discussion

Numerous strategies (including different techniques of ES) have been studied over the past decades to stimulate nerve regeneration (Al-Majed et al., 2000; Al-Majed et al., 2000; Elzinga et al., 2015). Although most studies in the field were done in laboratory animals (Gordon & Borschel, 2017), the use of electrical fields to improve peripheral nerve regeneration has been translated to the clinical practice, and some results are now found in the peer review literature, such as case studies, and randomized controlled trials (Gordon et al., 2008). However, these results have not been summarized as a metanalysis. The use of electric currents to promote peripheral nerve regeneration has been studied in experimental animal models, and, essentially, through invasive techniques. Electrical stimulation is cheaper and offer minimal potential risk for the patient (Gordon, 2016).

This review could provide useful, and practical strategies to treat patients with peripheral nerve damage.

Peripheral nerve injuries are usually underdiagnosed and undertreated. This has consequences, such as worker incapacity, with repercussions on their families and time away from work. Transection nerve injury treatments are usually

Research, Society and Development, v. 10, n. 17, e230101724942, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i17.24942

surgical. However, strategies to speed recovery and return to function are extremely important both for the patients to have a greater chance of returning to work and to minimize costs related to associated complications.

It is fundamental for the advancement of science, and improvement of society that publications respect scientific integrity (Mesquita, 2017). Another contribution of this paper is to make clear the information on the conduct of this systematic review ensuring integrity, avoiding scientific fraud and discuss for the promotion of good practices in research.

We plan to present the results further in a final systematic review as described above in the Methodology section.

4. Final Considerations

This review aims to study if electrical stimulation has any influence on nerve regeneration in humans with damage on peripheral nerves, based on the RCT available in the literature. We plan to identify, critically appraise, summarize and provide the certainty about the best, currently available evidence on the effects (benefits and harms) of ES in humans.

The study findings will be published in a thesis and systematic review. This work is linked to the master's degree of Enilton de Santana Ribeiro de Mattos (Graduate Program of the Bahiana School of Medicine and Public Health, under the guidance of Prof. Abrahão Fontes Baptista and co-supervision of Prof. Alex Guedes) with a scientific, economic, and social impact.

References

Al-Majed, A. A., Brushart, T. M., & Gordon, T. (2000). Electrical stimulation accelerates and increases expression of BDNF and trkB mRNA in regenerating rat femoral motoneurons. The European journal of neuroscience, 12(12), 4381–4390.

Al-Majed, A. A., Neumann, C. M., Brushart, T. M., & Gordon, T. (2000). Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration. The Journal of neuroscience: the official journal of the Society for Neuroscience, 20(7), 2602–2608. https://doi.org/10.1523/JNEUROSCI.20-07-02602.2000

Baptista, A. F., Gomes, J. R., Oliveira, J. T., Santos, S. M., Vannier-Santos, M. A., & Martinez, A. M. (2008). High- and low-frequency transcutaneous electrical nerve stimulation delay sciatic nerve regeneration after crush lesion in the mouse. Journal of the peripheral nervous system: JPNS, 13(1), 71–80. https://doi.org/10.1111/j.1529-8027.2008.00160.x

Cumpston, M., Li, T., Page, M. J., Chandler, J., Welch, V. A., Higgins, J. P., & Thomas, J. (2019). Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane database of systematic reviews, 10, ED000142. https://doi.org/10.1002/14651858.ED000142

de Santana Ribeiro de Mattos, E., Guedes, A., Baptista, A. F., & Viana, M. dos S. (2021). Search Strategy Extended Data [Data set]. figshare. https://doi.org/10.6084/M9.FIGSHARE.15134877.V1

Dunlop, R., Wormald, J., & Jain, A. (2019). Outcome of surgical repair of adult digital nerve injury: a systematic review. BMJ open, 9(3), e025443. https://doi.org/10.1136/bmjopen-2018-025443

Elzinga, K., Tyreman, N., Ladak, A., Savaryn, B., Olson, J., & Gordon, T. (2015). Brief electrical stimulation improves nerve regeneration after delayed repair in Sprague Dawley rats. Experimental neurology, 269, 142–153. https://doi.org/10.1016/j.expneurol.2015.03.022

Friedrich, J. O., Adhikari, N. K., & Beyene, J. (2007). Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. BMC medical research methodology, 7, 5. https://doi.org/10.1186/1471-2288-7-5

Gordon, T., & Borschel, G. H. (2017). The use of the rat as a model for studying peripheral nerve regeneration and sprouting after complete and partial nerve injuries. Experimental neurology, 287(Pt 3), 331–347. https://doi.org/10.1016/j.expneurol.2016.01.014

Gordon, T., Brushart, T. M., & Chan, K. M. (2008). Augmenting nerve regeneration with electrical stimulation. Neurological research, 30(10), 1012–1022. https://doi.org/10.1179/174313208X362488

Gordon T. (2016). Electrical Stimulation to Enhance Axon Regeneration After Peripheral Nerve Injuries in Animal Models and Humans. Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics, 13(2), 295–310. https://doi.org/10.1007/s13311-015-0415-1

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., Savovic, J., Schulz, K. F., Weeks, L., Sterne, J. A., Cochrane Bias Methods Group, & Cochrane Statistical Methods Group (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed.), 343, d5928. https://doi.org/10.1136/bmj.d5928

Low, J., & Reed, A. (2001). Electrotherapy explained: principles and practice. Butterworth-Heinemann.

Research, Society and Development, v. 10, n. 17, e230101724942, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i17.24942

Mattos, E., Guedes, A., Lessa, P., & Baptista, A. F. (2021). Influence of surface peripheral electrical stimulation on nerve regeneration after digital nerve neurorrhaphy: study protocol for a randomized clinical trial. F1000Research, 10, 219. https://doi.org/10.12688/f1000research.42120.2

McCaig, C. D., Rajnicek, A. M., Song, B., & Zhao, M. (2005). Controlling cell behavior electrically: current views and future potential. Physiological reviews, 85(3), 943–978. https://doi.org/10.1152/physrev.00020.2004

Mesquita, C.T. (2017). Integrity in scientific research. International Journal of Cardiovascular Sciences. 30(1),1-3. https://www.scielo.br/j/ijcs/a/TJWJ4SNLVK7g6ydkYBzS3Ln/?format=pdf&lang=en

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group (2010). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International journal of surgery (London, England), 8(5), 336–341. https://doi.org/10.1016/j.ijsu.2010.02.007

Sterne, J., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H. Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., McAleenan, A., & Higgins, J. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed.), 366, l4898. https://doi.org/10.1136/bmj.l4898

Stoll, G., & Müller, H. W. (1999). Nerve injury, axonal degeneration and neural regeneration: basic insights. Brain pathology (Zurich, Switzerland), 9(2), 313–325. https://doi.org/10.1111/j.1750-3639.1999.tb00229.x

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan) Version 5.1.1 (2011). Copenhagen: The Nordic Cochrane Centre. https://revman.cochrane.org/#/myReviews

6.4 Artigo submetido: Outcomes evaluation in clinical trials of electrical stimulation influence on peripheral nerve injury

Original Article

OUTCOMES EVALUATION IN CLINICAL TRIALS OF ELECTRICAL STIMULATION INFLUENCE ON PERIPHERAL NERVE INJURY

Enilton de Santana Ribeiro de Mattos[1-3] (https://orcid.org/0000-0003-2039-9744)

Alex Guedes[2,3,4] (https://orcid.org/0000-0001-7013-7107)

Abrahão Fontes Baptista[1,5,6] (0000-0001-7870-3820)

1. Programa de Pós-Graduação da Escola Bahiana de Medicina e Saúde Pública, Salvador, BA, Brazil.
2. Unidade do Sistema Neuro-Músculo-Esquelético, Empresa Brasileira de Serviços Hospitalares, Universidade Federal da Bahia, Salvador, BA, Brazil.
3. Programa de Residência Médica em Ortopedia e Traumatologia, Complexo Hospitalar Universitário Professor Edgard Santos, Empresa Brasileira de Serviços Hospitalares, Universidade Federal da Bahia, Salvador, BA, Brazil.
4. Departamento de Cirurgia Experimental e Especialidades Cirúrgicas, Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Salvador, BA, Brazil.
5. Centro de Matemática, Computação e Cognição, Universidade Federal do ABC, São Bernardo do Campo, São Paulo, Brazil
6. Laboratório de Investigações Médicas 54 (LIM-54), Universidade de São Paulo, São Paulo, São Paulo, Brazil

The study was conducted at Programa de Pós-Graduação da Escola Bahiana de Medicina e Saúde Pública and at Unidade do Sistema Neuro-Músculo-Esquelético, Empresa Brasileira de Serviços Hospitalares, Universidade Federal da Bahia, Salvador, BA, Brazil.

Correspondence: Enilton de Santana Ribeiro de Mattos, Avenida Araújo Pinho 421/804, Canela
Salvador, BA, Brazil CEP 40110150. eniltonmattos@hotmail.com.
Mobile Number +55 71 98761-2612.

All authors declare no potential conflict of interest related to this article.

Original Article

OUTCOMES EVALUATION IN CLINICAL TRIALS OF ELECTRICAL STIMULATION INFLUENCE ON PERIPHERAL NERVE INJURY

SUMMARY

Objectives: To describe the frequency and distribution of outcomes selected in randomized clinical trials (RCTs) that use electrical stimulation (ES) to treat peripheral nerve lesions, analyze how confusing presentations of outcomes can lead to misinterpretation and propose strategies to improve the reader's understanding. Methods: A retrospective, descriptive study was carried out through a systematized search on the PubMed® database without restrictions in which only intervention RCTs that use ES

treatment for peripheral nerve injury were included, whose outcomes were analyzed. Results: The primary outcomes of the 14 selected RCTs were categorized as clinical in 21.5% studies, surrogate in 57.2%, composite in 7.1%, subjective in 7.1%, and as complex scales in 7.1%. Adverse events were reported in 57. 1% of studies. Conclusion: The presentation of outcomes with little clinical relevance represented more than half of the sample (53.4%) of intervention RCTs. Such studies can harm the reader since they confuse the interpretation of scientific evidence. Measures such as those proposed by the Core Outcome Measures in Effectiveness Trials (COMET) for selection of research outcomes could help health professionals in understanding and choosing the most appropriate therapeutic interventions for patients. Level of Evidence IIc, "Outcomes" Research; Ecological studies.

Keywords: Outcome Assessment, Health Care; Randomized Controlled Trials as Topic; Electric Stimulation Therapy, Peripheral Nerve Injury.

INTRODUCTION

Peripheral nerve injuries can cause a considerable incapacity for patients in social and occupational quality of life.[1] Plenty of effort has gone into sophisticating microsurgical techniques aiming to remove barriers to nerve healing and achieve improvements in axon regrowth effects, but important limitations persist. As an example, upper limb nerves repairs show good outcomes in, at best, only 42% of patients.[2]

Axonal damage to peripheral nerves can occur due to a variety of reasons including trauma, ischemia, or inflammation. Morphological and functional changes can occur, such as motor and sensory function loss, hyperesthesia, and low-temperature intolerance.[3,4] The peripheral nerves' regeneration is influenced by various factors such

as individual age, level and extent of the lesion, time elapsed before repair and presence of associated lesions.[3-5]

Researchers are looking for adjuvants to enhance axon regeneration. One promising technique is transient post-surgical low-frequency electrical stimulation. The results of this augmentation therapy and its mechanisms of action have been studied extensively in animals´models.[6] ES is an encouraging intervention to promote nerve regeneration on the injured nerve, having been shown to improve early regenerative stages, including neuronal survival and axonal sprout formation.[6]

It is known that the Randomized Controlled Trial (RCT) is the most appropriate study design to evaluate the impact of an intervention. In this context, RCTs occupy one of the highest stages in the evidence pyramid.[7] The most worrying, however, is to note that many studies present systematized errors such as inadequate randomization, allocation errors, non-blinding of patients and evaluators, in addition to incomplete or selective reports of outcomes, which may lead the reader to misconceptions in the evaluation of the results.[8]

The paper performed by Heneghan et al.[8] demonstrates that one of the reasons why the RCTs may not translate a real benefit for patients is precisely the confusing choice or even failure of outcomes, opting for outcomes that are unclear or even irrelevant to clinical practice. In their report, the authors categorize the badly chosen outcomes in substitute, composite and subjective, besides mentioning the use of complex scales or lack of relevance for patients and assistant professionals in the evaluation of interventions **(Figure 1)**.

The objectives of this study are to describe the frequency and distribution of outcomes selected in randomized clinical trials that use electrical stimulation to treat

peripheral nerve lesions, to analyze how confusing presentations of outcomes can lead to papers' misinterpretation and to propose strategies to improve the reader's understanding.

METHODS

A retrospective, descriptive study, with quantitative analysis was carried out through a systematized search on the PubMed® database without restrictions on date, language, or impact factor of journals. We only consider RCT in parallel design groups of any sex, age and follow-up that has received any ES treatment for peripheral nerve injury in the intervention group and any intervention or no intervention in the control group. A search for Randomized Controlled Trial was carried out in the PubMed® using the strategy described in the **Table 1**.

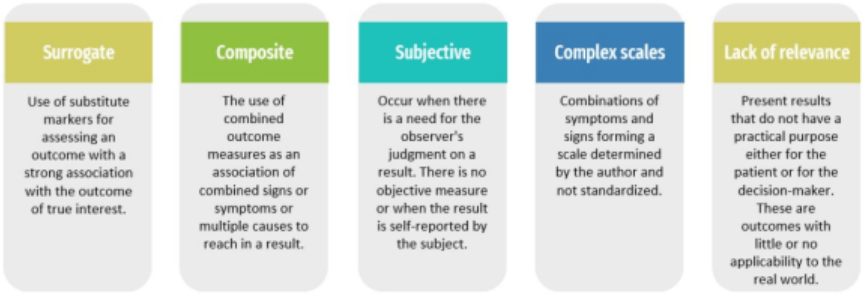
Table 1. Search strategy.

N	Search strategy
#1	peripheral nerve injury OR Peripheral Nerve Injury OR Nerve Injuries, Peripheral OR Nerve Injury, Peripheral OR Peripheral; Nerve Injuries OR Nerve Injury, Peripheral OR Nerve Injuries, Peripheral OR peripheral nerve regeneration OR peripheral nerve damage OR peripheral nerve crush OR peripheral nerve transection Filters: Randomized Controlled Trial

#2	nerve stimulation OR transcutaneous nerve stimulation OR electrostimulation therapy OR electrode OR Therapeutic Electrical Stimulation OR Electrical Stimulation, Therapeutic OR Stimulation, Therapeutic Electrical OR Therapeutic Electric Stimulation OR Electric Stimulation, Therapeutic OR Stimulation, Therapeutic Electric OR Electrical Stimulation Therapy OR Stimulation Therapy, Electrical OR Stimulation Therapy, Electrical OR Therapy, Electrical Stimulation OR Therapy, Electric Stimulation OR Stimulation Therapy, Electric OR Electrotherapy OR Interferential Current Electrotherapy OR Electrotherapy, Interferential Current OR Magnetic Field Therapy OR electrical stimulation OR peripheral electrical stimulation OR PES OR cuff stimulation OR magnetic stimulation OR peripheral magnetic stimulation Filters: Randomized Controlled Trial
#3	#1 AND #2

Papers that did not correspond to intervention RCTs or duplicate articles were excluded. Two independent authors selected the articles by title and abstract using the Rayyan© web applicative according to the inclusion criteria, and eventual divergences were resolved through consensus. The selected articles were read in full, and the primary outcomes classified according to the criteria proposed by Heneghan et al.[8] **(Figure 1)**.

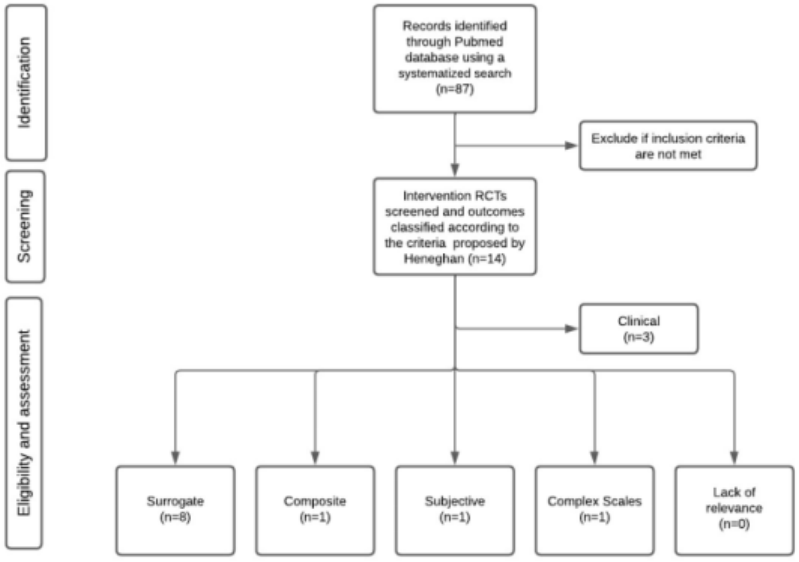
Figure 1. Badly chosen outcomes according to Heneghan et al.[8]



RESULTS

The search was carried out in PubMed® on 09/27/2022, and a total of 87 articles were found. After applying the inclusion criteria, 14 articles remained **(Figure 2)**.

Figure 2. Study flow chart



Among the 14 RCTs selected, the primary outcomes were classified as clinical in 3 studies (21.5%), as surrogate in eight studies (57.2%), as composite in one (7.1%), as subjective in one (7.1%) and as using complex scales in one (7.1%) **(Table 2) (Figure 3).**

Table 2. Primary outcomes classification

Study	**Clinical outcome**	**Surrogate outcome**	**Composite outcome**	**Subjective Outcome**	**Complex scales and/or lack of relevance**
Shoman 2022		x			
Power 2020		x			
Ton 2019	x				
Gall 2016					x
Leung 2015		x			
Wong 2015		x			

Zhou 2012	x				
Gordon 2010			x		
Weintraub 2009	x				
Ghaffariyeh 2009		x			
Gordon 2007		x			
Xiao 2007				x	
Cheng 2001		x			
Cheng 2000		x			

Figure 3. Primary outcomes distribution

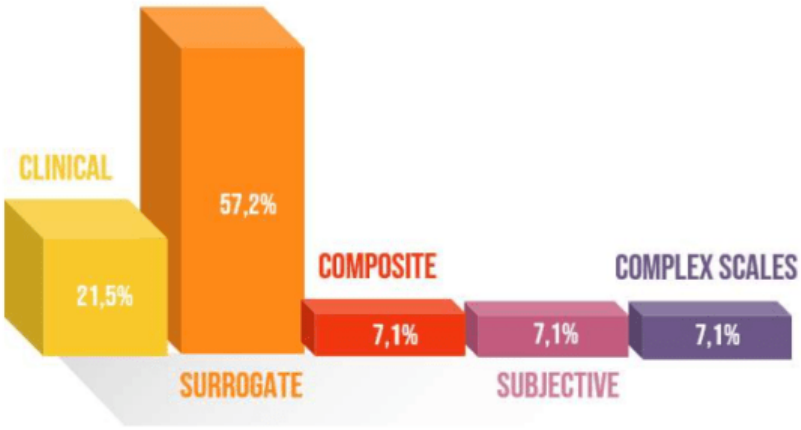
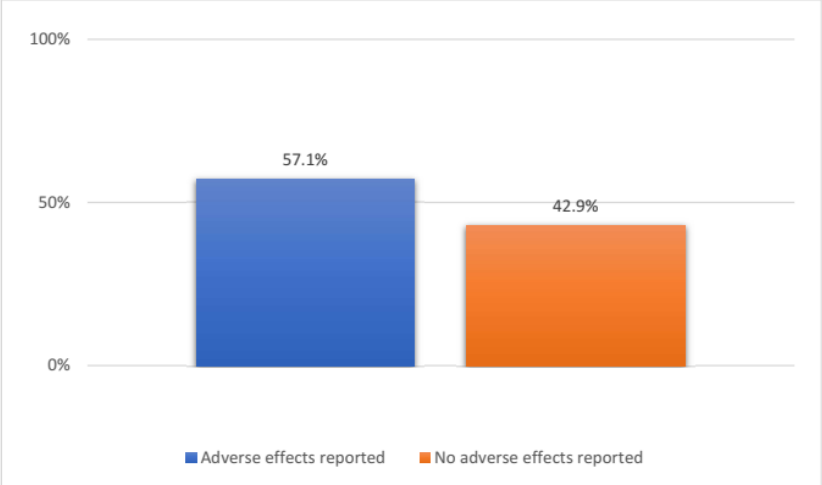


Figure 4. Adverse effects sample distribution

No results in the read articles were considered as lack of relevance. Eight papers (57.1%) reported adverse events **(Figure 4)**.

DISCUSSION

In our sample, we found that in most of the papers (78.5%), measures incapable of demonstrate a relevant clinical improvement for patients were used in their primary outcomes, thus present a limited impact on health practice. Of the total, 57.2% (8) used surrogate outcomes, 7.1% (1) used composite outcomes, 7.1% (1) used subjective



outcomes and 7.1% (1) used complex scales to assess outcomes. These types of outcomes usually do not assess the patients' clinical status, suggesting that the majority of interventional RCTs using ES does not translate improvements in their health. However, it cannot be affirmed that these studies have no scientific importance, since the use of substitute or even compound outcomes may be useful in early stages of RCTs, estimating the so-called pre-test probability of the tested hypothesis (Bayesian decision theory).[9,10] Many clinical outcomes require a longer follow-up than surrogate or compound outcomes

and the choice for these makes feasible conducting studies, as a shorter follow-up time may provide the researcher with the ability to decide whether to proceed with research.[8,11]

The purpose of most health scientific publication is to validate practices that advance patient care, thus ensuring improvement in their quality of life. From this perspective, randomized clinical trials have the function of testing hypotheses and evaluate them based on the outcomes chosen for research purposes.[11] RCTs are at the top of the pyramid of evidence.[7]

Outcomes can be defined as indicators to measure the effect of an intervention. In the context of RCTs, the selection of outcomes requires a lot of attention and is an important part of a research plan, because depending on the objectives of the study, either to evaluate the pre-test probability of a hypothesis or its clinical validity, some parameters will be more important than others.[12] This wide range of articles using outcomes that do not adequately assess the patients' clinical condition indicates that most intervention RCTs that approaches electrical stimulation to treat peripheral nerve injury are not able to correctly translate an improvement in the patients' health status.[13]

Clinical outcomes are those that reflect the real-world environment and the needs that truly impact the patient's life and, therefore, are related to quality of life after an intervention. Thus, these types of outcomes should be linked to medical practice.[8,12,13]

Viergever et al.[14] showed an increase in the amount of RCTs, without necessarily having an increase in the quality of the studies, underestimating the potential benefits that this type of study can promote. It is known that although RCTs are at the top of the evidence pyramid and are important for decision making, they can have a high cost and demand great effort from the scientific team. Thus, to mitigate these costs and simplify the work, many researchers use outcome measures that may be confusing or that do not translate into clinical improvement for patients.[12,13,15]

Heneghan et al.[8] explain that one of the reasons why RCTs cannot convert into benefits for patients is exactly the mistaken in outcomes choice, opting for unclear ones, without relevance in clinical practice. The authors divide the outcomes into clinical and others considered badly chosen which are: surrogate, composite and subjective, besides mentioning the use of complex scales in the evaluation of interventions and lack of relevance to patients and decision makers as potential design flaws in clinical trials.

The surrogate outcomes are indirect measures used to estimate a clinical result and present as the main value the fact that they are defined by means of continuous variables, easy to measure and of short-term response. This fact decreases the follow-up time of the studies.[12,13,15] In theory, a surrogate outcome becomes an effective substitute for the clinical outcome, when the effects of the intervention on the substitute safely predict the overall effect on the clinical outcome. This relationship should be the main way of action of the intervention on the clinical outcome.[13] In practice, this requirement often fails. Despite this, we can say that most of surrogate outcomes were well chosen in our sample because ES is an innovative and promising treatment for nerve injuries and studies in this area are still considered as proof of principle. In these cases, smaller studies that use well-chosen surrogate outcomes are justified because they are an important step that precedes further studies with bigger samples to prove the efficacy of this type of intervention in humans and its actual effect size.

The incorporation of new interventions in clinical practice, however, could generate problems especially if studies related to these interventions use surrogates' outcomes as evidenced by Rupp et al.[16] In their study the authors showed that although surrogate outcomes were sufficient for FDA approval of new anti-cancer drugs, these medications were not able to increase patients' survival or improve quality of life; therefore, caution should be used in interpreting such outcomes.

Composite outcomes are characterized by the evaluation of factors combined in the measure of the outcome, which promotes a reduction in the sample sizes, besides presenting potential for confusing interpretation of the results due to the combination of factors.[17] Subjective outcomes are marked by the need for judgment by the researcher or occur when they are reported by patients. The use of complex scales is related to the combination of signs and symptoms in scales created by the authors of the study, which becomes problematic because these are not validated and reliable measurements as the RCTs require.[8]

Regarding the adverse events report in the studied sample, it was observed that, of the 14 RCTs analyzed, six did not. This is a considerable number because it is essential that the complications resulting from an intervention be reported in the RCTs, since this information is of enormous importance in clinical practice, allowing the reader to analyze its benefit-harm ratio.

One of the limitations of our study were to not evaluate the quality of the journals in which the studies were published - the impact factor is a type of metric that the reader should observe very carefully because its multifactorial aspect can sometimes influence less attentive readers. Another limitation concerns the type of intervention evaluated; the sample was composed of only 14 RCTs because ES is a new type of intervention in humans, with few published articles.

The Center for Outcome Measures in Efficacy Trials (COMET)[18] is an initiative that proposes a solution to the cited problems. It recommends the development and application of outcomes that should be measured and reported in clinical trials for specific diseases or experimental populations. Its main role is to develop guidelines on how to choose outcome measurement tools for the results included in a study. As recommendations made by COMET are important to propose outcomes measures that

represent the clinic and to help researchers make more appropriate choices. The positive aspects of this initiative are to standardize such outcomes[19] to facilitate the readers' understanding, and the combined analysis of data in meta-analyses.

CONCLUSIONS

Scientific papers which produce unclear outcomes to readers or have minimal clinical impact for patients can represent a critical difficulty described in the medical literature.

In the studied sample, which included the primary outcomes in 14 intervention RCTs using electrical stimulation to treat peripheral nerve lesions, 21.5% were considered as clinical outcomes, 57.2% as surrogate, 7.1% as composite, 7.1% as complex scales and 7.1% as subjective outcomes. 57.1% of the articles did not report adverse events. The presentation of outcomes that have little clinical relevance represented more than half of the sample (78.5%).

These lacking outcomes can generate confusion in healthcare decision-making process, leading to choose interventions that do not bring real benefits to patients.

Proposals such as COMET initiative for the selection of research outcomes could help health professionals to comprehend and select the most appropriate therapeutic interventions for patients.

REFERENCES

1. Willand MP, Nguyen MA, Borschel GH, Gordon T. Electrical Stimulation to Promote Peripheral Nerve Regeneration. Neurorehabil Neural Repair. 2016;30(5):490-496.

2. Goldie BS, Coates CJ, Birch R. The long term result of digital nerve repair in no-man's land. J Hand Surg Br. 1992;17(1):75-77.
3. Mattos ESR, Guedes A, Lessa PIF, Baptista AF. Influence of surface peripheral electrical stimulation on nerve regeneration after digital nerve neurorrhaphy: study protocol for a randomized clinical trial. F1000Res. 2021;10:219.
4. Mattos ESR, Guedes A, Viana MS, Baptista AF. Influence of electrical stimulation on peripheral nerve regeneration: Protocol for a systematic review. Res., Soc. Dev. 2021; 10:e230101724942.
5. Dunlop RLE, Wormald JCR, Jain A. Outcome of surgical repair of adult digital nerve injury: a systematic review. BMJ Open. 2019;9(3):e025443.
6. Lal D, Hetzler LT, Sharma N, Wurster RD, Marzo SJ, Jones KJ, et al. Electrical stimulation facilitates rat facial nerve recovery from a crush injury. Otolaryngol Head Neck Surg. 2008;139(1):68-73.
7. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. Evid Based Med. 2016;21(4):125-127.
8. Heneghan C, Goldacre B, Mahtani KR. Why clinical trial outcomes fail to translate into benefits for patients. Trials. 2017;18(1):122.
9. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med. 1996;125(7):605-613.
10. Rescorla M. Bayesian modeling of the mind: From norms to neurons. Wiley Interdiscip Rev Cogn Sci. 2021;12(1):e1540.
11. Coutinho MSSA. Surrogate and relevant clinical endpoints. What are they and how to interpret them? Rev Bras Hipertens. 2002;9(1):24-28.
12. Lonn E. The use of surrogate endpoints in clinical trials: focus on clinical trials in cardiovascular diseases. Pharmacoepidemiol Drug Saf. 2001;10(6):497-508.

13. Twaddell S. Surrogate outcome markers in research and clinical practice. Aust Prescr. 2009;32:47–50

14. Viergever RF, Li K. Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013. BMJ Open. 2015;5(9):e008932.

15. Evans SR. Fundamentals of clinical trial design. J Exp Stroke Transl Med. 2010;3(1):19-27.

16. Rupp T, Zuckerman D. Quality of Life, Overall Survival, and Costs of Cancer Drugs Approved Based on Surrogate Endpoints. JAMA Intern Med. 2017;177(2):276-277.

17. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials. JAMA. 2003;289(19):2554.

18. Prinsen CAC, Vohra S, Rose MR et al. Core Outcome Measures in Effectiveness Trials (COMET) initiative: protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a 'core outcome set'. Trials. 2014;15:247.

19. Pacheco RL, Latorraca COC, Oliveira RA, Carmo VS, Riera R. Iniciativa COMET. Escolhendo desfechos em ensaios clínicos randomizados. Diagn Tratamento. 2019;24(1):12-15.

7 DISCUSSÃO

7.1 Discussão sobre os resultados do ensaio clínico randomizado

O ensaio clínico randomizado intitulado "*Effects of transcutaneous electrical stimulation on peripheral nerve regeneration after digital nerve neurorrhaphy: a randomized clinical trial*" explorou a eficácia do PES de superfície na recuperação da função sensorial. Os resultados mostraram que os pacientes de ambos os grupos recuperaram gradualmente sua sensibilidade medida pelos testes de MSW e s2PD, próximos ao normal na última medição. No entanto, nenhum efeito significativo foi encontrado para o PES ao final das três medidas momentos após a cirurgia. A idade dos pacientes pode desempenhar algum papel no processo de regeneração, mas sua influência foi, na melhor das hipóteses, pequena na amostra estudada. A sensibilidade ao frio e a incapacidade para dor foram mensuradas apenas no último estágio e apresentaram alta variabilidade, sendo difícil concluir que o tratamento não afetou esse aspecto.

Estudos anteriores avaliaram a influência da estimulação elétrica periférica (PES) por meio de eletrodos de superfície na regeneração de tecidos como os tendões[75,76], pele[77-80] e osso[81], com resultados variados. Esta modalidade está associada a efeitos como aumento do fluxo sanguíneo[82,83] e síntese de colágeno[76]. No entanto, correntes elétricas com amplitudes acima de 1 mA são necessárias, o que pode estar relacionado à diminuição das concentrações de trifosfato de adenosina (ATP)[77] e, conseqüentemente, a inibição da regeneração nervosa periférica.

Os campos elétricos podem influenciar a circulação/perfusão sanguínea, promovendo um aumento no surgimento axonal e regeneração do nervo[78]. Correntes elétricas de baixa frequência podem ativar seletivamente as fibras C sensoriais e aumentar a expressão de neuropeptídeos, como a substância P, que geram vasodilatação[79-81]. Além disso, PES de baixa frequência (2-10 Hz) geralmente está associado à contração muscular rítmica, que pode ter efeitos circulatórios[82]. No entanto, algumas evidências sugerem que PES de alta frequência, usado sem produzir contração muscular, também aumenta a circulação, como de Vries et al.[83] demonstraram no seu estudo em artérias coronárias.

A estimulação elétrica transcutânea é promissora na regeneração nervosa, oferecendo uma abordagem não invasiva com potenciais benefícios práticos[84]. Pode ser utilizado para contornar as complicações do implante cirúrgico ou estimulação percutânea[75,76]. Algumas pesquisas indicam que os axônios regenerados podem levar até oito semanas para percorrer uma distância de 25mm e o uso de PES pode reduzir esse período[52,85]. Resultados anteriores demonstraram que indivíduos que receberam estimulação apresentaram resultados mais precoces e melhores em torno de três meses após a cirurgia [86]. Gordon e col. conduziram um ensaio clínico randomizado e controlado inovador com 21 pacientes submetidos à cirurgia de descompressão do túnel do carpo. Após a cirurgia, o grupo experimental recebeu estimulação elétrica com fios implantados por uma hora, regulados em 20 Hz, 4-6 volts e duração de pulso entre 0,1 e 0,8 milissegundos. Impressionantemente, melhoras nas medidas eletrofísicas ocorreram dentro de seis a oito semanas, enquanto uma recuperação mais lenta foi observada no grupo controle[7]. Em um ECR duplo-cego, Wong et al. investigaram os efeitos do PES após o reparo de 31 nervos digitais transeccionados. O protocolo PES (20 Hz, <30 V, 0,1–0,4 ms) levou a uma melhora significativa nos resultados sensoriais, no entanto, a recuperação funcional permaneceu inalterada[86]. Em 2020, Power e colaboradores[87] realizaram um estudo para examinar o impacto da estimulação elétrica após a cirurgia de descompressão do túnel cubital. Trinta e um pacientes foram submetidos a uma hora de PES (20 Hz, <30 V, 0,1 ms) após a cirurgia. Durante o período de acompanhamento, o grupo PES exibiu melhoras notáveis na Estimativa do Número de Unidades Motoras (MUNE) em comparação com o grupo controle[87].

Protocolos de estimulação elétrica de curta duração (especificamente, 10 minutos) poderiam melhorar a tradução clínica e simplificar os procedimentos perioperatórios[4]. Estudos utilizando modelos de camundongos não revelaram diferença significativa nos desfechos entre uma hora ou 10 minutos (a 16 Hz, com duração de 100 microssegundos) de estimulação elétrica. A PES de curta duração pode produzir efeitos terapêuticos semelhantes a uma sessão de uma hora em modelos murinos submetidos à transecção e reparo do nervo[88]. No entanto, o protocolo mais estudado para administrar a terapia por estimulação elétrica em humanos envolve a sua aplicação dentro de uma hora imediatamente após o reparo do nervo.

McGinnis (1992) e Hansom (1994) relataram efeitos negativos da estimulação elétrica na regeneração nervosa[44,45]. Essa divergência de resultados levanta questões sobre a eficácia dos campos aplicados no aumento da regeneração de nervos periféricos *in vivo*. Em nosso estudo,

os testes s2PD e SWM não demonstraram que o PES aumenta significativamente a reinervação de receptores responsáveis pela sensação tátil na pele da polpa digital.

A incerteza em relação aos benefícios do PES pode ser atribuída a vários fatores. Primeiramente, a heterogeneidade das lesões nervosas e a variabilidade individual podem influenciar as respostas à estimulação elétrica. Além disso, a intensidade, duração e frequência dos campos elétricos podem desempenhar um papel significativo. Estudos futuros devem considerar esses fatores e explorar mecanismos subjacentes para esclarecer a eficácia do PES na regeneração nervosa.

Os efeitos mais estudados do PES estão relacionados ao controle da dor. A analgesia causada por PES de alta frequência ativa os receptores δ-opioides, enquanto o PES de baixa frequência ativa os receptores μ-opioides[89,90]. Sinatra e Ford[91] demonstraram que o uso crônico de morfina por 14 dias leva a um retardo na regeneração nervosa periférica, refletido por um menor número de perfis axonais, diminuição da remoção de resíduos de mielina e hipertrofia e proliferação de Células de Schwann. Zeng et al.[92] também demonstraram que a exposição à morfina, agindo via receptores μ-opioides, aumenta a regeneração das fibras amielínicas, ao mesmo tempo que inibe a regeneração das fibras mielinizadas após lesão por esmagamento do nervo ciático.

A diferença fundamental entre os estudos que mostraram efeitos estimulantes ou inibidores da regeneração do sistema nervoso periférico por meio da ativação de receptores opioides foi o tempo de uso prolongado, o que pode ter levado ao desenvolvimento de tolerância farmacológica. Chandran e Sluka[93] demonstraram que PES repetidos de alta e baixa frequência por 20 minutos por dia, levaram à tolerância aos opioides no dia 4. Mao et al.[94] demonstrou que este efeito é mediado pelo N-Metil-D-aspartato (NMDA) - via da caspase, que leva à apoptose de células neuronais na medula espinhal. Portanto, o uso prolongado de PES pode levar ao desenvolvimento de tolerância aos opioides e neurotoxicidade das células envolvidas na regeneração. Um breve uso de PES, que não leva à tolerância aos opióides, pode, no entanto, ser uma estratégia importante para promover a regeneração[95], mas isso foi pouco investigado até agora em humanos.

A intolerância ao frio[96] e a dor[69] frequentemente se manifestam como complicações após lesão nervosa na mão. Estudos anteriores relacionaram a gravidade dos sintomas à extensão da restauração sensorial pós-lesão nervosa, com indivíduos exibindo pior recuperação nervosa experimentando sintomas mais graves[69,97]. Em nossa amostra, a lesão isolada do nervo digital não esteve associada a piores desfechos em termos de dor e intolerância ao frio avaliados pelos questionários aplicados (CSS e PDI) entre os grupos analisados. Essas complicações pós-operatórias parecem ser um problema mais relacionado a casos de traumas mais complexos como reimplante digital, comprometimento vascular mais grave e lesões mais proximais dos nervos mediano e ulnar.

Um protocolo para reabilitação pós-operatório de neurorrafias ao nível da mão é considerado um tratamento adjuvante padrão[98] e foi prescrito para ambos os grupos em nosso estudo. Não oferecer tal procedimento com a terapia especializada da mão seria antiético, pois a reabilitação é comumente prescrita no pós-operatório em cenários da vida real e omiti-la poderia comprometer a validade externa do estudo. No entanto, reconhece-se que pode haver um efeito de interação entre as terapias instituídas, tornando difícil mensurar com precisão eventuais benefícios do PES.

Uma limitação do PES é que a cirurgia deve ser realizada preferencialmente sob anestesia geral. Um estudo recente[99] mostra que o uso de lidocaína no perioperatório reduziu significativamente os efeitos positivos da estimulação elétrica na regeneração nervosa. Entretanto, a prática atual em cirurgia da mão está caminhando para utilização cada vez mais rotineira da anestesia local ou regional, que oferece as vantagens de menor risco perioperatório, recuperação mais rápida do paciente no pós-operatório imediato e melhor analgesia. Portanto, sugerir esse tratamento sem estudar o método de administração sob anestesia padrão pode não ser clinicamente aceitável. Uma vez comprovada sua eficácia, acreditamos que a estimulação elétrica poderia estar indicada em casos de maior gravidade em que se utilize a anestesia geral.

Uma segunda limitação deste estudo é que os resultados funcionais levaram em consideração algumas informações subjetivas dos pacientes. A avaliação neurofisiológica pode servir como um indicador sensível para avaliar a gravidade e a progressão da doença em adultos. No entanto, a limitação na utilização de estudos de condução decorre da laceração de um único ramo digital observada em todos os sujeitos estudados. A contaminação ocorre pela condução do volume de

sinal via potencial de ação do nervo sensitivo gerado pelo ramo intacto no lado oposto do dedo[86]. Pesquisas recentes de resultados após lesões nervosas têm se concentrado cada vez mais em resultados funcionais e resultados relatados pelos pacientes[62].

Intervenções em saúde podem ter seus efeitos mascarados quando aplicadas a populações com menor gravidade da condição-alvo. Ao avaliarmos o impacto de uma intervenção, a eficácia pode não ser totalmente aparente se a população estudada não estiver em alto risco para os desfechos que a intervenção pretende prevenir ou mitigar[100]. Isto pode levar a uma subestimação da verdadeira eficácia da intervenção numa população de maior risco. Isto realça a importância de selecionar uma população de estudo apropriada que reflita o grupo-alvo com maior probabilidade de se beneficiar da intervenção. Em nossa amostra, o fato de termos escolhido um modelo de estimulação em nervo digital que tem, habitualmente, uma rápida recuperação e bom prognóstico, pode ter contribuído para que potenciais benefícios promovidos pelo PES não fossem evidentes.

Um problema inerente a qualquer método de pesquisa de artigos é o viés de publicação. O viés de publicação é o fenômeno no qual os estudos publicados em periódicos revisados por pares têm maior probabilidade de relatar resultados estatisticamente significativos do que os estudos que relatam conclusões não significativas, especialmente para estudos menores. Portanto, os estudos publicados podem não ser representativos de todos os estudos realizados sobre uma questão clínica específica, podem superestimar os estudos que mostram resultados "positivos" e podem explicar algumas das diferenças entre algumas meta-análises e grandes ensaios clínicos randomizados[101].

7.2 Discussão sobre os desfechos em ensaios clínicos sobre a influência da estimulação elétrica na lesão nervosa periférica

No artigo intitulado "*Outcomes evaluation in clinical trials of electrical stimulation influence on peripheral nerve injury*" sobre os desfechos em ensaios clínicos que utilizaram a estimulação elétrica no tratamento das lesões nervosas, observamos que, na maioria dos artigos publicados (78,5%), medidas incapazes de demonstrar melhora clínica relevante para os pacientes foram utilizadas como desfechos primários, apresentando, portanto, impacto limitado na prática de saúde. Do total, 57,2% utilizaram desfechos substitutos, 7,1% utilizaram desfechos compostos, 7,1% utilizaram desfechos subjetivos e 7,1% utilizaram escalas complexas para avaliar

desfechos. Esses tipos de desfechos geralmente não avaliam o estado clínico dos pacientes, sugerindo que a maioria dos ECRs intervencionistas usando a estimulação elétrica não traduz melhorias em sua saúde. No entanto, não se pode afirmar que esses estudos não tenham importância científica, uma vez que o uso de desfechos substitutos ou mesmo compostos pode ser útil em estágios iniciais de ECRs, estimando a chamada probabilidade pré-teste da hipótese testada (teoria bayesiana da decisão)[102,103]. Muitos desfechos clínicos requerem um seguimento mais longo do que os desfechos substitutos ou compostos e a escolha por estes torna viável a realização de estudos, uma vez que um menor tempo de seguimento pode proporcionar ao pesquisador a capacidade de decidir se deseja prosseguir com a pesquisa[104].

O objetivo da maioria das publicações científicas em saúde é validar práticas que promovam o cuidado ao paciente, garantindo assim a melhoria de sua qualidade de vida. Nessa perspectiva, os ensaios clínicos randomizados têm a função de testar hipóteses e avaliá-las com base nos desfechos escolhidos para fins de pesquisa[104]. Os ECR estão no topo da pirâmide de evidências[61].

Os desfechos podem ser definidos como indicadores para medir o efeito de uma intervenção. No contexto dos ECR, a seleção de desfechos requer muita atenção e é parte importante de um plano de pesquisa, pois dependendo dos objetivos do estudo, seja para avaliar a probabilidade pré-teste de uma hipótese ou sua validade clínica, alguns parâmetros serão mais importantes do que outros[105]. Essa ampla gama de artigos que utilizam desfechos que não avaliam adequadamente a condição clínica dos pacientes indica que a maioria dos ECR de intervenção que aborda a estimulação elétrica para o tratamento da lesão nervosa periférica não é capaz de traduzir corretamente uma melhora no estado de saúde dos pacientes[106].

Os desfechos clínicos são aqueles que refletem o ambiente do mundo real e as necessidades que realmente impactam a vida do paciente e, portanto, estão relacionados à qualidade de vida após uma intervenção. Assim, esses tipos de desfechos devem estar ligados à prática médica[62,105,106]. Viergever et al.[107] mostraram um aumento na quantidade de ECR, sem necessariamente haver um aumento na qualidade dos estudos, subestimando os potenciais benefícios que esse tipo de estudo pode promover. Sabe-se que, embora os ECR estejam no topo da pirâmide de evidências e sejam importantes para a tomada de decisão, eles podem ter um custo elevado e exigir grande esforço da equipe científica. Assim, para mitigar esses custos e simplificar o trabalho, muitos

pesquisadores utilizam medidas de desfecho que podem ser confusas ou que não se traduzem em melhora clínica para os pacientes[105,106,108].

Heneghan et al.[62] explicam que uma das razões pelas quais os ECR podem não se converter em benefícios para os pacientes é o equívoco na escolha dos desfechos, quando se opta por desfechos pouco claros, sem relevância na prática clínica. Os autores dividem os desfechos em clínicos e outros considerados mal escolhidos que são: substitutos, compostos e subjetivos, além de citarem o uso de escalas complexas na avaliação das intervenções e a falta de relevância para pacientes e tomadores de decisão, como potenciais falhas de desenho em ensaios clínicos. Os desfechos substitutos são medidas indiretas utilizadas para estimar um resultado clínico e apresentam como valor principal o fato de serem definidos por meio de variáveis contínuas, de fácil mensuração e de resposta de curto prazo. Esse fato diminui o tempo de seguimento dos estudos[105,106,108]. Teoricamente, um desfecho substituto torna-se um substituto efetivo para o desfecho clínico, quando os efeitos da intervenção sobre o substituto predizem com segurança o efeito global sobre o desfecho clínico. Essa relação deve ser principal forma de ação da intervenção sobre o desfecho clínico[106]. Na prática, essa exigência muitas vezes falha. Apesar disso, podemos dizer que a maioria dos desfechos substitutos foi bem escolhida em nossa amostra, pois a estimulação elétrica é um tratamento inovador e promissor para lesões nervosas e estudos nessa área ainda são considerados como prova de conceito. Nesses casos, estudos menores e que utilizem desfechos substitutos bem escolhidos justificam-se por serem um passo importante que antecede novos estudos com amostras maiores para comprovar a eficácia desse tipo de intervenção em humanos e seu real tamanho de efeito.

A incorporação de novas intervenções na prática clínica, no entanto, poderia gerar problemas, especialmente se os estudos relacionados a essas intervenções utilizarem desfechos substitutos, como evidenciado por Rupp et al.[109] Em seu estudo, os autores mostraram que, embora os desfechos substitutos fossem suficientes para a aprovação de novas drogas antineoplásicas pelo FDA, esses medicamentos não foram capazes de aumentar a sobrevida dos pacientes ou melhorar a qualidade de vida; portanto, deve-se ter cautela na interpretação de tais desfechos.
Os desfechos compostos caracterizam-se pela avaliação de fatores combinados na medida do desfecho, o que promove redução no tamanho da amostra, além de apresentar potencial de interpretação confusa dos resultados devido à combinação de fatores[110]. Os desfechos subjetivos são marcados pela necessidade de julgamento por parte do pesquisador ou ocorrem

quando são relatados pelos pacientes. O uso de escalas complexas está relacionado à combinação de sinais e sintomas em escalas criadas pelos autores do estudo, o que se torna problemático por não serem medidas validadas e confiáveis como os ECR exigem[62].

Em relação ao relato de eventos adversos na amostra estudada, observou-se que, dos 14 ECR analisados, seis não o fizeram. Esse número é considerável, pois é fundamental que as complicações decorrentes de uma intervenção sejam relatadas nos ECR, uma vez que essas informações são de enorme importância na prática clínica, permitindo ao leitor analisar sua relação custo-benefício.

Uma das limitações do nosso estudo foi não avaliar a qualidade dos periódicos em que os estudos foram publicados - o fator de impacto é um tipo de métrica que o leitor deve observar com muita atenção, pois seu aspecto multifatorial pode, por vezes, influenciar leitores menos atentos. Outra limitação diz respeito ao tipo de intervenção avaliada; a amostra foi composta por apenas 14 ECR, pois a estimulação elétrica é um novo tipo de intervenção em humanos, com poucos artigos publicados.

O Center for Outcome Measures in Efficacy Trials (COMET)[111] é uma iniciativa que propõe uma solução para os problemas citados. Recomenda o desenvolvimento e a aplicação de desfechos que devem ser medidos e relatados em ensaios clínicos para doenças específicas ou populações experimentais. Seu principal papel é desenvolver diretrizes sobre como escolher instrumentos de mensuração de resultados para os resultados incluídos em um estudo. As recomendações feitas pelo COMET são importantes para propor medidas de desfecho que representem a clínica e para ajudar os pesquisadores a fazerem escolhas mais adequadas. Os aspectos positivos dessa iniciativa são a padronização desses resultados[112], para facilitar a compreensão dos leitores, e a análise combinada dos dados em meta-análises.

8 CONCLUSÕES

A seguir, encontram-se as conclusões para os artigos contidos na tese apresentada.

Conclusão do artigo 6.2: "Effects of transcutaneous electrical stimulation on peripheral nerve regeneration after digital nerve neurorrhaphy: A randomized clinical trial".

Em nosso ensaio clínico randomizado, o uso da estimulação elétrica de superfície após neurorrafia dos nervos digitais da mão não melhorou a sensibilidade pós-operatória medida pelos testes MSW e s2PD e não se associou a melhores resultados em termos de sensibilidade ao frio e à dor envolvendo os desfechos estudados. No entanto, estudos adicionais são necessários para continuar explorando a eficácia e a segurança do uso da estimulação elétrica na regeneração nervosa.

Conclusão do artigo 6.4: "Outcomes evaluation in clinical trials of electrical stimulation influence on peripheral nerve injury".

Na amostra estudada em nosso estudo metacientífico, que incluiu os desfechos primários em 14 ECR de intervenção utilizando estimulação elétrica para tratar lesões nervosas periféricas, 21,5% foram considerados desfechos clínicos, 57,2% substitutos, 7,1% compostos, 7,1% escalas complexas e 7,1% desfechos subjetivos. 57,1% dos artigos não relataram eventos adversos. A apresentação de desfechos com pouca relevância clínica representou mais da metade da amostra (78,5%).

Artigos científicos que produzam resultados pouco claros para os leitores ou tenham impacto clínico mínimo para os pacientes podem representar uma dificuldade crítica descrita na literatura médica.

Desfechos inadequados podem gerar confusão no processo de tomada de decisão em saúde, levando à escolha de intervenções que não trazem benefícios reais aos pacientes.
Propostas como a iniciativa COMET para a seleção de desfechos de pesquisa poderiam ajudar os profissionais de saúde a compreenderem e selecionar as intervenções terapêuticas mais apropriadas para os pacientes.

REFERÊNCIAS

1. Noble J, Munro CA, Prasad VSSV, et al. Analysis of upper and lower extremity peripheral nerve injuries in a population of patients with multiple injuries. J Trauma. 1998;45(1):116-122.

2. Renner A, Cserkuti F, Hankiss I. Late results after nerve transplantation on the upper extremities. Handchir Mikrochir Plast Chir. 2004;36(1):13-18.

3. Jain A, Dunlop R, Hems T, Tang J. Outcomes of surgical repair of a single digital nerve in adults. J Hand Surg Eur Vol. 2019;44:560-565.

4. Liu Y, Fox PM. The role of electrical stimulation in peripheral nerve regeneration: current evidence and future directions. J Hand Surg Glob Online. 2024;1-4.

5. Machado A, Santana E, Tacani P, Liebano R. The effects of transcutaneous electrical nerve stimulation on tissue repair: A literature review. Can J Plast Surg. 2012;20(4):237-40.

6. Ferrigno B, Bordett R, Duraisamy N, Moskow J, Arul M, Rudraiah S, Nukavarapu S, Vella A, Kumbar S. Bioactive polymeric materials and electrical stimulation strategies for musculoskeletal tissue repair and regeneration. Bioact Mater. 2020;5:468-85.

7. Gordon T, Amirjani N, Edwards DC, et al. Brief post-surgical electrical stimulation accelerates axon regeneration and muscle reinnervation without affecting the functional measures in carpal tunnel syndrome patients. Exp Neurol. 2010;223(1):192-202.

8. Jones I, Johnson M. Transcutaneous Electrical Nerve Stimulation. Anesthesiology In-Training Exam Review. 2009.

9. Al-Majed A, Neumann C, Brushart T, Gordon T. Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration. J Neurosci. 2000;20:2602-2608.

10. Koçyiğit F, Akalın E, Gezer N, Orbay O, Koçyiğit A, Ada E. Functional Magnetic Resonance Imaging of the Effects of Low-frequency Transcutaneous Electrical Nerve Stimulation on Central Pain Modulation: A Double-blind, Placebo-controlled Trial. Clin J Pain. 2012;28:581–588.

11. Nakagawa-Yagi Y, Hara H, Yoshida Y, Midorikawa A, Hara A. Discovery of a novel effect of electric field exposure on human plasma beta-endorphin and interleukin-12 levels: Insight into mechanisms of pain alleviation and defense against infection by electric field therapy.

12. Lu M, Ho C, Hsu S, Lee H, Lin J, Yao C, Chen Y. Effects of Electrical Stimulation at Different Frequencies on Regeneration of Transected Peripheral Nerve. Neurorehabil Neural Repair. 2008;22:367-373.

13. Meira DA, Moriyama LE, Santos CCS, Moreira FD, Guedes A, de Mattos ESR. Evaluation of outcomes in intervention randomized clinical trials - distal radius fractures. Acta Ortop Bras. 2023 Sep 8;31(spe3):e267872.

14. Stoll G, Müller HW. Nerve injury, axonal degeneration and neural regeneration: basic insights. Brain Pathol. 1999;9(2):313–325.

15. Robbins SL. Structural and Functional Pathology. Rio de Janeiro: Interamericana; 1974;1421.

16. Knight KL. Cryotherapy in the Treatment of Sports Injuries. São Paulo: Manole; 2000;304.

17. Rosén B, Lundborg G. A model instrument for the documentation of outcome after nerve repair. J Hand Surg Sou. 2000;25(3):535-543.

18. Dunlop RLE, Wormald JCR, Jain A. Outcome of surgical repair of adult digital nerve injury: a systematic review. BMJ Open. 2019;9(3):e025443.

19. Ruijs ACJ, Jaquet JB, Kalmijn S, et al. Median and ulnar nerve injuries: a meta-analysis of predictors of motor and sensory recovery after modern microsurgical nerve repair. Plast Reconstr Surg. 2005;116(2):484–494.

20. Song B, Zhao M, Forrester J, et al. Nerve regeneration and wound healing are stimulated and directed by an endogenous electrical field in vivo. J Cell Sci. 2004;117(Pt 20):4681–1690.

21. Tessier-Lavigne M, Placzek M. Target attraction: Are developing axons guided by chemotropism? Trends Neurosci. 1991;14:303-310.

22. Höke A, Brushart T. Introduction to special issue: Challenges and opportunities for regeneration in the peripheral nervous system. Exp Neurol. 2010;223:1-4.

23. Ristow M. Neurodegenerative disorders associated with diabetes mellitus. J Mol Med. 2004;82:510-529.

24. Kennedy JM, Zochodne DW. Experimental strategies to promote functional recovery after peripheral nerve injuries. J Peripher Nerv Syst. 2005;10(2):144-157.

25. Frostick S, Yin Q, Kemp G. Schwann cells, neurotrophic factors, and peripheral nerve regeneration. Microsurgery. 1998;18.

26. Lopes FRP, Campos LCM, Corrêa JD Jr, et al. Bone marrow stromal cells and resorbable collagen guidance tubes enhance sciatic nerve regeneration in mice. Exp Neurol. 2006;198(2):457–468.

27. Tohill M, Terenghi G. Stem-cell plasticity and therapy for injuries of the peripheral nervous system. Biotechnol Appl Biochem. 2004;40(Pt 1):17–24.

28. Crisci AR, Ferreira AL. Low-intensity pulsed ultrasound accelerates the regeneration of the sciatic nerve after neurotomy in rats. Ultrasound Med Biol. 2002;28(10):1335–1341.

29. Bae CS, Lim SC, Kim KY, et al. Effect of Ga-As laser on the regeneration of injured sciatic nerves in the rat. In Vivo. 2004;18(4):489–495.

30. Seo TB, Han IS, Yoon JH, et al. Voluntary exercise increases axonal regeneration from sensory neurons. Med Sci Sports Exerc. 2006;38(7):1267-1276.

31. McCaig CD, Rajnicek AM, Song B, et al. Has electrical growth cone guidance found its potential? Trends Neurosci. 2002;25(7):354–359.

32. Watson T. Electrical stimulation for wound healing. In: Kitchen S, Bazin S, Clayton Electrotherapy. São Paulo: Manole; 1998. p. 311–337. Capítulo 21.

33. Low J, Reed A. Electrotherapy Explained. São Paulo: Manole; 2001;472.

34. Baptista AF, de Souza Gomes JR, Oliveira JT, et al. A new approach to assess function after sciatic nerve lesion in the mouse - adaptation of the sciatic static index. J Neurosci Methods. 2007;161(2):259–264.

35. Baptista AF, Gomes JRS, Oliveira JT, et al. High- and low-frequency transcutaneous electrical nerve stimulation delay sciatic nerve regeneration after crush lesion in the mouse. J Peripher Nerv Syst. 2008;13(1):71-80.

36. Bedlack R, Wei M, Loew L. Localized membrane depolarizations and localized calcium influx during electric field-guided neurite growth. Neuron. 1992;9:393-403.

37. Kotwal A, Schmidt C. Electrical stimulation alters protein adsorption and nerve cell interactions with electrically conducting biomaterials. Biomaterials. 2001;22(10):1055-64.

38. Nix WA, Hopf HC. Electrical stimulation of regenerating nerve and its effect on motor recovery. Brain Res. 1983;272(1):21-25.

39. Beveridge JA, Politis MJ. Use of exogenous electric current in the treatment of delayed lesions in peripheral nerves. Plast Reconstr Surg. 1988;82(4):573-579.

40. Kerns JM, Fakhouri AJ, Weinrib HP, et al. Electrical stimulation of nerve regeneration in the rat: the early effects evaluated by a vibrating probe and electron microscopy. Neuroscience. 1991;40(1):93-107.

41. Mendonça AC, Barbieri CH, Mazzer N. Directly applied low intensity direct current enhances peripheral nerve regeneration in rats. J Neurosci Methods. 2003;129(2):183-190.

42. Politis MJ, Zanakis MF, Albala BJ. Facilitated regeneration in the rat peripheral nervous system using applied electric fields. J Trauma. 1988;28(9):1375-1381.

43. Pomeranz B, Campbell JJ. Weak electric current accelerates motoneuron regeneration in the sciatic nerve of ten-month-old rats. Brain Res. 1993;603(2):271-278.

44. McGinnis ME, Murphy DJ. The lack of an effect of applied d.c. electric fields on peripheral nerve regeneration in the guinea pig. Neuroscience. 1992;51(1):231-244.

45. Hanson SM, McGinnis ME. Regeneration of rat sciatic nerves in silicone tubes: characterization of the response to low intensity dc stimulation. Neuroscience. 1994;58(2):411-421.

46. Chen YS, Hu CL, Hsieh CL, et al. Effects of percutaneous electrical stimulation on peripheral nerve regeneration using silicone rubber chambers. J Biomed Mater Res. 2001;57(4):541-549.

47. Inoue M, Hojo T, Yano T, et al. The effects of electroacupuncture on peripheral nerve regeneration in rats. Acupunct Med. 2003;21(1-2):9-17.

48. McDevitt L, Fortner P, Pomeranz B. Application of weak electric field to the hindpaw enhances sciatic motor nerve regeneration in the adult rat. Brain Res. 1987;416(2):308-314.

49. Pomeranz B, Mullen M, Markus H. Effect of applied electrical fields on sprouting of intact saphenous nerve in adult rat. Brain Res. 1984;303(2):331-336.

50. Scott JJ. Recovery of denervated muscle receptors following treatments to accelerate nerve regeneration. Brain Res. 1991;563(1-2):195-202.

51. Al-Majed AA, Brushart TM, Gordon T. Electrical stimulation accelerates and increases expression of BDNF and TrKB mRNA in regenerating rat femoral motoneurons. Eur J Neurosci. 2000;12(12):4381-4390.

52. Al-Majed AA, Neumann CM, Brushart TM, et al. Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration. J Neurosci. 2000;20(7):2602-2608.

53. Al-Majed AA, Tam SL, Gordon T. Electrical stimulation accelerates and enhances expression of regeneration-associated genes in regenerating rat femoral motoneurons. Cell Mol Neurobiol. 2004;24(3):379-402.

54. Brushart TM, Hoffman PN, Royall RM, et al. Electrical stimulation promotes motoneuron regeneration without increasing its speed or conditioning the neuron. J Neurosci. 2002;22(15):6631-6638.

55. Ray WZ, Mahan MA, Guo D, et al. An update on addressing important peripheral nerve problems: challenges and potential solutions. Acta Neurochir. 2017;159(9):1765–1773.

56. Albert E, Alves N, Barbosa F. Efeitos da estimulação elétrica transcutânea na regeneração nervosa periférica: uma revisão sistemática. Rev Bras Neurol. 2019;27(3):45-52.

57. Silva A, Santos R, Pereira M. Papel da estimulação elétrica transcutânea na modulação da dor e na regeneração nervosa de nervos periféricos. J Neurosci Res. 2020;15(2):78-87.

58. Souza P, Lima M. Estimulação elétrica transcutânea como terapia adjuvante na recuperação funcional de lesões nervosas periféricas: uma revisão integrativa. Acta Neurol Bras. 2021;39(1):112-125.

59. Oliveira C, Costa L. Mecanismos de ação da estimulação elétrica transcutânea na regeneração nervosa: uma perspectiva molecular. J Neurophysiol. 2018;42(4):231-245.

60. Shapira Y, Sammons V, Forden J, et al. Brief Electrical Stimulation Promotes Nerve Regeneration Following Experimental In-Continuity Nerve Injury. Neurosurgery. 2018;85(1):156-163.

61. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. Evid Based Med. 2016;21(4):125-127.

62. Heneghan C, Goldacre B, Mahtani KR. Why clinical trial outcomes fail to translate into benefits for patients. Trials. 2017;18(1):122.

63. Ni L, Yao Z, Zhao Y, et al. Electrical stimulation therapy for peripheral nerve injury. Front Neurol. 2023;14.

64. de Santana Ribeiro de Mattos E, Guedes A, Lessa PIF, et al. Available facilities study number U1111-1259-1998. figshare. Dataset. 2021.

65. de Santana Ribeiro de Mattos E, Guedes A, Lessa PIF, et al. SPIRIT Checklist-for randomised studies protocols.doc. figshare. Dataset. 2021.

66. de Santana Ribeiro de Mattos E, Guedes A, Lessa PIF, et al. List of materials study number U1111-1259-1998. figshare. Dataset. 2021.

67. Dellon AL, Jabaley ME. Reeducation of sensation in the hand following nerve suture. Clin Orthop Relat Res. 1982;(163):75-79.

68. Carlsson I, Nilsson J, Dahlin L. Cut-off value for self-reported abnormal cold sensitivity and predictors for abnormality and severity in hand injuries. J Hand Surg Eur Vol. 2010;35(5):409-16.

69. Novak CB, Anastakis DJ, Beaton DE, et al. Relationships among pain disability, pain intensity, illness intrusiveness, and upper extremity disability in patients with traumatic peripheral nerve injury. J Hand Surg Am. 2010;35(10):1633-1639.

70. Wang Y, Sunitha M, Chung KC. How to measure outcomes of peripheral nerve surgery. Hand Clin. 2013;29(3):349-361.

71. Rosén B, Lundborg G. A model instrument for the documentation of outcome after nerve repair. J Hand Surg Am. 2000;25(3):535-543.

72. Silva PG, Jones A, Araujo PMP, et al. Assessment of light touch sensation in the hands of systemic sclerosis patients. Clinics (Sao Paulo). 2014;69(9):585-588.

73. McCabe SJ, Mizgala C, Glickman L. The measurement of cold sensitivity of the hand. J Hand Surg Am. 1991;16(6):1037-1040.

74. World Medical Association. The World Medical Association-Declaration of Helsinki [Internet]. Helsinki, Finland, 2014 [Accessed Dec 10, 2021]. Available from: <https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/>.

75. Burssens P, Forsyth R, Steyaert A, et al. Influence of burst TENS stimulation on the healing of Achilles tendon suture in man. Acta Orthop Belg. 2003;69(6):528-532.

76. Burssens P, Forsyth R, Steyaert A, et al. Influence of burst TENS stimulation on collagen formation after Achilles tendon suture in man. A histological evaluation with Movat's pentachrome stain. Acta Orthop Belg. 2005;71(3):342-346.

77. Kaada B, Emru M. Promoted healing of leprous ulcers by transcutaneous nerve stimulation. Acupunct Electrother Res. 1988;13(4):165-176.

78. Kjartansson J, Lundeberg T, Samuelson UE, et al. Transcutaneous electrical nerve stimulation (TENS) increases survival of ischaemic musculocutaneous flaps. Acta Physiol Scand. 1988;134(1):95-99.

79. Khalil Z, Merhi M. Effects of aging on neurogenic vasodilator responses evoked by transcutaneous electrical nerve stimulation: relevance to wound healing. J Gerontol A Biol Sci Med Sci. 2000;55(6):B257-B263.

80. Liebano RE, Ferreira LM, Neto MS. Experimental model for transcutaneous electrical nerve stimulation on ischemic random skin flap in rats. Acta Cir Bras. 2003;18:54-59.

81. Imtiyaz T, Makhdoomi D, Nabi N, Athar H, Handoo N, Gayas M, Bashir M. Effect of static magnetic field, transcutaneous electrical nerve stimulation on fracture healing in rabbits. J Entomol Zool Stud. 2018;6:1509-16.

82. Sandberg ML, Sandberg MK, Dahl J. Blood flow changes in the trapezius muscle and overlying skin following transcutaneous electrical nerve stimulation. Phys Ther. 2007;87(8):1047-1055.

83. de Vries J, Anthonio RL, Dejongste MJL, et al. The effect of electrical neurostimulation on collateral perfusion during acute coronary occlusion. BMC Cardiovasc Disord. 2007;7:18.

84. Cheng N, Van Hoof H, Bockx E, et al. The effects of electric currents on ATP generation, protein synthesis, and membrane transport of rat skin. Clin Orthop Relat Res. 1982;(171):264-272.

85. Juckett L, Saffari TM, Ormseth B, Senger JL, Moore AM. The Effect of Electrical Stimulation on Nerve Regeneration Following Peripheral Nerve Injury. Biomolecules. 2022;12(12):1856.

86. Wong JN, Olson JL, Morhart MJ, Chan KM. Electrical stimulation enhances sensory recovery: a randomized controlled trial. Ann Neurol. 2015;77(6):996-1006.

87. Power HA, Morhart MJ, Olson JL, Chan KM. Postsurgical Electrical Stimulation Enhances Recovery Following Surgery for Severe Cubital Tunnel Syndrome: A Double-Blind Randomized Controlled Trial. Neurosurgery. 2020;86(4):769-777.

88. Roh J, Schellhardt L, Keane GC, Hunter DA, Moore AM, Snyder-Warwick AK, Mackinnon SE, Wood MD. Short-Duration, Pulsatile, Electrical Stimulation Therapy Accelerates Axon Regeneration and Recovery following Tibial Nerve Injury and Repair in Rats. Plast Reconstr Surg. 2022;149:681e–690e.

89. Kalra A, Urban MO, Sluka KA. Blockade of opioid receptors in rostral ventral medulla prevents antihyperalgesia produced by transcutaneous electrical nerve stimulation (TENS). J Pharmacol Exp Ther. 2001;298(1):257-263.

90. Sluka KA, Walsh D. Transcutaneous electrical nerve stimulation: basic science mechanisms and clinical effectiveness. J Pain. 2003;4(3):109-121.

91. Sinatra RS, Ford DH. The effects of acute and chronic morphine treatment on the process of facial nerve regeneration. Brain Res. 1979;175(2):315-325.

92. Zeng YS, Nie JH, Zhang W, et al. Morphine acts via mu-opioid receptors to enhance spinal regeneration and synaptic reconstruction of primary afferent fibers injured by sciatic nerve crush. Brain Res. 2007;1130(1):108-113.

93. Chandran P, Sluka KA. Development of opioid tolerance with repeated transcutaneous electrical nerve stimulation administration. Pain. 2003;102(1–2):195-201.

94. Mao J, Sung B, Ji RR, et al. Neuronal apoptosis associated with morphine tolerance: evidence for an opioid-induced neurotoxic mechanism. J Neurosci. 2002;22(17):7650-7661.

95. de Assis DCM, Lima ÊM, Goes BT, et al. The parameters of transcutaneous electrical nerve stimulation are critical to its regenerative effects when applied just after a sciatic crush lesion in mice. Biomed Res Int. 2014;2014:572949.

96. Irwin MS, Gilbert SE, Terenghi G, Smith RW, Green CJ. Cold intolerance following peripheral nerve injury. Natural history and factors predicting severity of symptoms. J Hand Surg. 1997;22(3):308-316.

97. Aman M, Zimmermann KS, Glaser JJ, Daeschler SC, Boecker AH, Harhaus L. Revealing digital nerve lesions-A comprehensive analysis of 2084 cases of a specialized center. Injury. 2024.

98. Gupta S. Hand Nerve Injury Repair Treatment & Management. Medscape. 2023. Retrieved from https://emedicine.medscape.com/article/1287077-overview?form=fpf.

99. Keane GC, Marsh EB, Hunter DA, Schellhardt L, Walker ER, Wood MD. Lidocaine Nerve Block Diminishes the Effects of Therapeutic Electrical Stimulation to Enhance Nerve Regeneration in Rats. Hand. 2023;18(1_suppl):119S-125S.

100. Clarke GM, Conti S, Wolters AT, Steventon A. Evaluating the impact of healthcare interventions using routine data. BMJ. 2019;365.

101. Easterbrook P, Gopalan R, Berlin J, Matthews D. Publication bias in clinical research. Lancet. 1991;337:867-872.

102. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med. 1996;125(7):605-613.

103. Rescorla M. Bayesian modeling of the mind: From norms to neurons. Wiley Interdiscip Rev Cogn Sci. 2021;12(1):e1540.

104. Coutinho MSSA. Surrogate and relevant clinical endpoints. What are they and how to interpret them? Rev Bras Hipertens. 2002;9(1):24-28.

105. Lonn E. The use of surrogate endpoints in clinical trials: focus on clinical trials in cardiovascular diseases. Pharmacoepidemiol Drug Saf. 2001;10(6):497-508.

106. Twaddell S. Surrogate outcome markers in research and clinical practice. Aust Prescr. 2009;32:47–50.

107. Viergever RF, Li K. Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013. BMJ Open. 2015;5(9):e008932.

108. Evans SR. Fundamentals of clinical trial design. J Exp Stroke Transl Med. 2010;3(1):19-27.

109. Rupp T, Zuckerman D. Quality of Life, Overall Survival, and Costs of Cancer Drugs Approved Based on Surrogate Endpoints. JAMA Intern Med. 2017;177(2):276-277.

110. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials. JAMA. 2003;289(19):2554.

111. Prinsen CAC, Vohra S, Rose MR et al. Core Outcome Measures in Effectiveness Trials (COMET) initiative: protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a 'core outcome set'. Trials. 2014;15:247.

112. Pacheco RL, Latorraca COC, Oliveira RA, Carmo VS, Riera R. Iniciativa COMET. Escolhendo desfechos em ensaios clínicos randomizados. Diagn Tratamento. 2019;24(1):12-15

APÊNDICES

APÊNDICE A – Termo de Consentimento Livre e Esclarecido

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

HOSPITAL GERAL DO ESTADO

DADOS SOBRE A PESQUISA CIENTÍFICA

I. TÍTULO DO PROJETO DE PESQUISA: "Influência da estimulação elétrica transcutânea na regeneração nervosa periférica após neurorrafia de nervos digitais: ensaio clínico randomizado".

II. PESQUISADOR RESPONSÁVEL: Abrahão Fontes Baptista[1]

III. INSTITUIÇÃO/DEPARTAMENTO: Hospital Geral do Estado e Serviço de Fisioterapia da UFBA. Programa de Pós-Graduação em Medicina e Saúde Humana da Escola Bahiana de Medicina e Saúde Pública.

IV. PESQUISADORES PARTICIPANTES: Enilton de Santana Ribeiro de Mattos[2], Alex Guedes[3], Paulo Itamar Ferraz Lessa[4], Cleber Luz Santos[2]

1 Programa de Pós-graduação em Neurociência e Cognição, Universidade Federal do ABC – UFABC, São Paulo, Brasil.
2 Complexo Hospitalar Universitário Professor Edgar Santos, Bahia, Brasil.
3 Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Bahia, Brasil.
4 Clínica Escola de Fisioterapia, Universidade do Estado da Bahia, Bahia, Brasil

V. ENDEREÇO:

Largo do Terreiro de Jesus, s/n. Centro Histórico, CEP 40.026-010 Salvador, Bahia, Brasil (cepfmb@ufba.br)

HGE- Av. Vasco da Gama, s/n - Brotas, Salvador - BA, 40286-901

VI. TELEFONES PARA CONTATO: (71) 3283-5564 / (71) 98761-2612

Prezado,

Você está sendo convidado a participar como voluntário desta pesquisa. Leia atentamente o que segue e, caso tenha alguma dúvida, pergunte ao pesquisador responsável pelo estudo até que todas as informações sejam totalmente esclarecidas.

Assinando este Termo de Consentimento, estou ciente de que:

OBJETIVO DO ESTUDO: Verificar a influência da estimulação elétrica através de eletrodos de superfície na regeneração nervosa periférica de nervos digitais na mão.

1. PROCEDIMENTO DA PESQUISA: Os pacientes que foram submetidos a cirurgia para reparo do nervo lesado no HGE, receberão uma estimulação elétrica transcutânea com eletrodos de superfície ainda enquanto internados para verificar a influência da mesma na regeneração nervosa. Serão posteriormente acompanhados ambulatorialmente após a alta hospitalar.

2. PROCEDIMENTO DAS SESSÕES DE REABILITAÇÃO: Associado a este tratamento os pacientes se submeterão a um protocolo de reeducação sensorial da mão por três meses, num total de 20 sessões, com cerca de 30 minutos de duração, realizadas em média duas vezes por semana. Os pacientes também receberão instruções para realização de exercícios domiciliares.

3. RISCOS E DESCONFORTO: Os procedimentos que iremos usar não geram riscos vitais. Os riscos são mínimos (irritação da pele), já que usaremos correntes elétricas bifásicas de baixa intensidade, que não geram efeitos eletrolíticos na pele, além de eletrodos de superfície. A estimulação será feita uma única vez, minimizando a possibilidade de irritação. Se ocorrerem quaisquer complicações quanto aos procedimentos os pacientes serão imediatamente encaminhados para os médicos que os acompanham e fazem parte do projeto.

4. CONFIDENCIALIDADE: A sua identidade será mantida em total sigilo e preservada em todas as situações que envolvam discussão, apresentação ou publicação dos resultados da pesquisa.

5. CUSTO E PAGAMENTOS: Você não terá nenhuma despesa para participar desta pesquisa, a não ser eventuais gastos com locomoção até o local da pesquisa. Também como não será efetuado nenhum tipo de pagamento ou compensação por sua participação.

6. DESISTÊNCIA: A sua recusa em participar do procedimento não lhe trará nenhum prejuízo, estando livre para abandonar o experimento a qualquer momento e sem justificativa.

BENEFÍCIOS POTENCIAIS: O uso de corrente elétricas com o objetivo de promover a regeneração nervosa periférica tem sido estudado em animais de experimentação. Estratégias para acelerar a recuperação e devolver, na medida do possível, funcionalidade às pessoas lesadas são extremamente importantes tanto para que elas tenham maior chance de voltar ao trabalho quanto para minimizar gastos inadequados com as complicações do quadro. Os resultados deste trabalho podem ser pioneiros no sentido de se descobrir estratégias úteis e práticas para se tratar pacientes com lesão nervosa periférica. Os pacientes serão beneficiados por terem à sua disposição um serviço de reabilitação muito pouco disponível na cidade.

7. COMITÊ DE ÉTICA EM PESQUISA EM SERES HUMANOS - CEP da Faculdade de Medicina da Universidade Federal da Bahia é um colegiado interdisciplinar e independente, que tem por finalidade analisar as pesquisas desenvolvidas em seres humanos realizadas por docentes, alunos e pesquisadores de outras instituições (que tenham sido devidamente encaminhadas pela Comissão Nacional de Ética em Pesquisa) sob os aspectos ético e legal (enquadrando-se na legislação vigente para a espécie, especialmente a RESOLUÇÃO Nº 466, DE 12 DE DEZEMBRO DE 2012, do Conselho Nacional de Saúde.

Como voluntário, você tem todo o direito de entrar em contato com este Comitê a qualquer momento e sem prévia comunicação com os pesquisadores envolvidos na pesquisa da qual você participa como voluntário.

CONVITE PARA PARTICIPAR DA PESQUISA

Eu, _____,
RG/CPF nº_____, concordo em participar voluntariamente do estudo intitulado “Influência da estimulação elétrica transcutânea na regeneração nervosa periférica após neurorrafia de nervos digitais: ensaio clínico randomizado”. Reconheço que li ou que me foi explicado em linguagem de meu entendimento o documento de consentimento anexado. Tive a oportunidade de perguntar sobre o estudo e todas as minhas dúvidas foram respondidas de maneira satisfatória.

Estou ciente de que minha privacidade será respeitada, mantendo a minha identidade sobre sigilo, e que autorizo a divulgação dos resultados obtidos. Entendo que tenho a liberdade de retirar esta autorização e descontinuar minha participação deste estudo a qualquer momento e sem qualquer prejuízo para mim.

Este Termo de Consentimento é feito em duas (2) vias, sendo que uma permanecerá em meu poder e outra com o pesquisador responsável.

_____, de _____, de 20____

_____ _____

Voluntário Pesquisador Responsável

APÊNDICE B – List of materials study number U1111-1259-1998

Influence of transcutaneous electrical stimulation on peripheral nerve regeneration after digital nerve neurorraphy: study protocol for a randomized clinical trial

de Santana Ribeiro de Mattos E, Guedes A, Itamar Ferraz Lessa P and Fontes Baptista A

Study registration number and date:

UTN: U1111-1259-1998

Record date: 12/18/2020

URL: https://ensaiosclinicos.gov.br/trial/10591

All materials required for this study are listed below:

List of materials.

Item	Qty.	Material	Price per unit (R$)	Total (R$)
Consumable supplies (MN Comércio-Sao Paulo-Brazil)				
1	01	NCM Preferred Lisa 1/8" 46 cm × 61 cm × 3.2 mm	310.00	310.00
2	01	NCM Preferred Perf. 1/8" 46 cm × 61 cm × 3.2 mm	310.00	310.00
3	01	Lining LuxaFoam Lisa 50 cm × 10 cm × 3.2 mm	64.00	64.00
4	01	LuxaFoam Lining Perf. 50 cm × 10 cm × 3.2 mm	75.00	75.00
5	01	Self-adhesive velcro hook 1" - M	10.50	10.50
6	01	Self-adhesive velcro hook 1" - 22.5M	143.00	143.00
7	01	Self-adhesive velcro hook 2" - M	15.50	15.50
8	01	Self-adhesive velcro hook 2" - 22.5M	245.00	245.00
9	01	Velcro ring 1" - M	7.30	7.30
10	01	Velcro ring 1" - 25M	80.00	80.00
11	01	Velcro ring 2" - M	9.20	9.20
12	01	Velcro ring 2" - 25M	125.00	125.00
13	01	Velfoam Fixing Strip 1" - 2M	55.00	55.00
14	01	Velfoam Fixing Strip 1" - 5M	88.00	88.00
15	01	Velfoam Fixing Strip 1" - 9.10M	140.00	140.00
16	01	Velfoam Fixing Strip 2" - 2M	70.00	70.00
17	01	Velfoam Fixing Strip 2" - 5M	124.00	124.00
18	01	Velfoam Fixing Strip 2" - 9.10M	200.00	200.00

19	01	Cushionstrap Fixing Strip 1" - 2M	68.00	68.00
20	01	Cushionstrap Fixing Strip 1" - 5M	102.00	102.00
21	01	Cushionstrap Fixation Strip 1" - 18.20M	260.00	260.00
22	01	Cushionstrap Fixing Strip 2" - 2M	80.00	80.00
23	01	Cushionstrap Fixing Strip 2" - 5M	138.00	138.00
24	01	Cushionstrap Fixing Strip 2" - 18.20M	390.00	390.00
25	01	Length for dynamic orthosis - Aluminum bar 17.5 cm	100.00	100.00
26	01	Length for dynamic orthosis - Aluminum bar 12.5 cm	100.00	100.00
27	01	Length for dynamic orthosis - Aluminum Bar Multi Digi 10 cm	145.00	145.00
28	01	Comp. for dynamic orthosis - Aluminum bar 5 cm	90.00	90.00
29	01	Comp. for dynamic orthosis - Curved bar w/ foot 12.5 cm	110.00	110.00
30	01	Comp. for dynamic orthosis - Curved bar with foot 15 cm	110.00	110.00
31	01	Comp. for dynamic orthosis - Curved bar 17.5 cm	110.00	110.00
32	01	Comp. for dynamic orthosis - Butterfly Screw	15.00	15.00
33	01	Comp. for dynamic orthosis - Guide Screw	15.00	15.00
34	01	Comp. for dynamic orthosis - Support for rubber bands	15.00	15.00
35	01	Comp. for dynamic orthosis - Transparent Nylon Screw	7.00	7.00
36	01	Comp. for dynamic orthosis - Aluminum screw	7.20	7.20
37	01	Suede cover	20.00	20.00
38	01	Rubber bands (package)	75.00	75.00
39	01	Thermoplastic marker	20.00	20.00
40	01	Screen for thermoplastic 26 cm × 51cm	40.00	40.00
		SUBTOTAL	4,088.70	4,088.70
Equipment				
41	01	110-V Electric Orthosis Heater	1,200.00	1,200.00
42	01	Thermoplastic heater - Blower (110 V or 220 V)	410.00	410.00
43	01	Multipurpose Scissors	50.00	50.00

44	01	Soft Touch Scissors	50.00	50.00
45	01	Hand orthosis mold kit	265.00	265.00
46	01	Thermometer	350.00	350.00
47	02	Endophasys Electrostimulator - KLD	2,500.00	5,000.00
48	01	Digital analgesimeter (Von Frey) - Insight	7,388.00	7,388.00
SUBTOTAL			12,213.00	14,713.00

APÊNDICE C – Available facilities study number U1111-1259-1998

Influence of transcutaneous electrical stimulation on peripheral nerve regeneration after digital nerve neurorraphy: study protocol for a randomized clinical trial

de Santana Ribeiro de Mattos E, Guedes A, Itamar Ferraz Lessa P and Fontes Baptista A

Study registration number and date:

UTN: U1111-1259-1998

Record date: 12/18/2020

URL: https://ensaiosclinicos.gov.br/trial/10591

Available facilities:

Federal University of Bahia

- Outpatient Physiotherapy Department;
- Professionals: 4 physiotherapists;
- Extension course students: 12 students;
- Resident physicians at the Orthopedics Department at HUPES: 12 residents.
- Physical structure: approximately 80 m^2, divided into 2 offices, 2 Pilates and RPG rooms, 8 boxes, and 1 mechanotherapy gym;
- Equipment: 12 stretchers, 2 ultrasound devices, 1 short-wave device, proprioception devices (trampoline, round and square boards), 2 TENS/FES, kinesiotherapy devices (Bobath ball, stick, power web, Digiflex), parallel bars;
- Computers - 2 computers.

Ambulatory SESAO - Occupational Health Service

- Workers assistance service;
- Physical structure: 4 offices;
- Audiometry room;
- Ultrasound room;
- Electromyography room (MIOTEC 4-channel Miotool electromyograph, with a computer and printer).

Orthopedics Ward of the General Hospital of the State

- 2 beds, average volume of 200 hand surgeries/month.

CEMEAFI - Sports Medicine and Physical Activity Center (UFBA–FIEB–SESI partnership)

- Norm/Cybex isokinetic equipment.

APÊNDICE D – Consent term study number U1111-1259-1998

FREE AND INFORMED CONSENT TERM

DATA ON SCIENTIFIC RESEARCH

I. RESEARCH PROJECT

TITLE: "Influence of transcutaneous electrical stimulation on peripheral nerve regeneration after digital nerve neurorrhaphy: randomized clinical trial".

II. RESPONSIBLE RESEARCHER: Abrahão Fontes Baptista[1]

III. INSTITUTION/DEPARTMENT: State General Hospital and Physiotherapy Service of UFBA. Graduate Program in Medicine and Human Health, Bahia N. School of Medicine and Public Health.

IV. RESEARCHERS PARTICIPANTS: Enilton de Santana Ribeiro de Mattos[2],Alex Guedes[3],Paulo Itamar Ferraz Lessa[4], Cleber Luz Santos[2]

1 Graduate Program in Neuroscience and Cognition, Federal University of ABC - UFABC, São Paulo, Brazil.

2 University Hospital Complex Professor Edgar Santos, Bahia, Brazil.

3 Faculty of Medicine of Bahia, Federal University of Bahia, Bahia, Brazil.

4 Clinic a School of Physiotherapy, State University of Bahia, Bahia, Brazil

V. ADDRESS:

Largo do Terreiro de Jesus, s/n. Centro Histórico, CEP 40.026-010 Salvador, Bahia, Brazil (cepfmb@ufba.br)

HGE- Av. Vasco da Gama, s/n - Brotas, Salvador - BA, 40286-901

VI. CONTACT PHONES: (71) 3283-5564 / (71) 98761-2612

Dear

You are being invited to participate as a volunteer in this survey. Read carefully what followsand, if you have any questions, ask the researcher responsible for the study until all the information is fully clarified.

By signing this Consent Form, I am aware that:

STUDY OBJECTIVE: To verify the influence of electrical stimulation through surface electrodes on peripheral nerve regeneration of digital nerves in the hand.

1. RESEARCH PROCEDURE: Patients who underwent surgery for repair of the injured nerve in HGE, will receive a transcutaneous electrical stimulation with surface electrodes still while hospitalized to verify the influence of the same on nerve regeneration . They will later be followed up on an outpatient basis after hospital discharge.

2. REHABILITATION SESSION PROCEDURE: In addition to this treatment, patients will undergo a three-month sensory reeducation protocol for a total of 20 sessions, about 30 minutes long, performed on average twice a week. Patients will also receive instructions for home exercises.

3. RISKS AND DISCOMFORT: The procedures we will use do not create vital risks. The risks are minimal (skin irritation), since we will use low intensity biphasic electric currents, which do not generate electrolyte effects on the skin, in addition to surface electrodes. Stimulation will be done only once, minimizing the possibility of irritation. If any complications occur regarding the procedures, patients will be immediately referred to the accompanying physicians and are part of the project.

4. CONFIDENTIALITY: Your identity will be kept in complete secrecy and preserved in all situations involving discussion, presentation or publication of research results.

5. COST AND PAYMENTS: You will not have any expense to participate in this survey, other than any expenses with locomotion to the research site. Also,as no payment or compensation will be made for your participation.

6. Withdrawal: Your refusal to participate in the procedure will not cause any harm, being free to abandon the experiment at any time and without justification.

POTENTIAL BENEFITS: The use of electric current in order to promote peripheral nerve regeneration has been studied in experimental animals. Andstrategies to accelerate recovery and return, as far as possible, functionality to injured people are extremely important both so that they have a greater chance of returning to work and to minimize inadequate expenses with the complications of the condition. The results of this work may be pioneers in the sense of discovering useful and practical strategies to treat patients with peripheral nerve damage. Patients will benefit from having at their disposal a rehabilitation service very little available in the city.

7. ETHICS COMMITTEE ON RESEARCH IN HUMAN BEINGS - CEP of the Faculty of Medicine of the Federal University of Bahia is an interdisciplinary and independent collegiate, whose purpose is to analyze the research developed in human beings carried out by teachers, students and researchers from other institutions (which have been duly forwarded by the National Commission of Ethics in Research) under the ethical and legal aspects (falling within the current legislation for the species, especially RESOLUTION No. 466, OF DECEMBER 12, 2012,of the National Health Council. As a volunteer, you have every right to contact this Committee at any time and without prior communication with the researchers involved in the research in which you participate as a volunteer.

INVITATION TO PARTICIPATE IN THE SURVEY

I, _____

RG/CPF nº_____I acknowledge that I have read or been explained to me in the language of my understanding the attached consent document. I had the opportunity to ask about the study and all my questions were answered satisfactorily.

I am aware that my privacy will berespected, maintaining my identity on confidentiality,and that I authorize the disclosure of the resultsobtained. I understand that I am free to withdraw this authorization and discontinue my participation in this study at any time and without any prejudice to myself.

This Consent Form is made in two (2) ways, one of which will remain in my power and the other with the responsible researcher.

(Date:)

_____ _____

Patient Responsible Researcher

ANEXOS

ANEXO A – Questionário do Índice de Incapacidade para Dor *(PDI)*

HGE
Hospital Geral do Estado

Questionário do Índice de Incapacidade para Dor *(PDI)*. (Fonte:Adaptado WANG et al., 2013.)

1. Responsabilidades Familiares/Domiciliares: Esta categoria refere-se às atividades do lar ou da família. Inclui tarefas ou tarefas realizadas ao redor da casa (por exemplo, trabalho no quintal) e recados ou favores para outros membros da família (por exemplo, levar as crianças para a escola).

   Sem Deficiência 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Pior Incapacidade

2. Recreação: Essa deficiência inclui hobbies, esportes e outras atividades similares de lazer.

   Sem Deficiência 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Pior Incapacidade

3. Atividade Social: Esta categoria refere-se a atividades, que envolvem a participação com amigos e conhecidos além dos familiares. Inclui festas, teatro, shows, jantar fora e outras funções sociais.

   Sem Deficiência 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7.__ 8__. 9__. 10__. Pior Incapacidade

4. Ocupação: Esta categoria refere-se a atividades que fazem parte ou diretamente relacionadas ao seu trabalho. Isso inclui também empregos não remunerados, como o de uma dona de casa ou voluntária.

   Sem Deficiência 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Pior Incapacidade

5. Comportamento Sexual: Esta categoria refere-se à frequência e qualidade da vida sexual.

   Sem Deficiência 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Pior Incapacidade

6. Autocuidado: Esta categoria inclui atividades, que envolvem manutenção pessoal e vida diária independente (por exemplo, tomar banho, dirigir, se vestir, etc.).

   Sem Deficiência 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Pior Incapacidade

7. Atividades de suporte à vida: Esta categoria refere-se a comportamentos básicos de suporte à vida, como comer, dormir e respirar.

   Sem Deficiência 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7__. 8__. 9__. 10__. Pior Incapacidade

Nome:

Assinatura: _____ Data:_____

ANEXO B – Escala de Gravidade de Sensibilidade ao Frio *(CSS)*

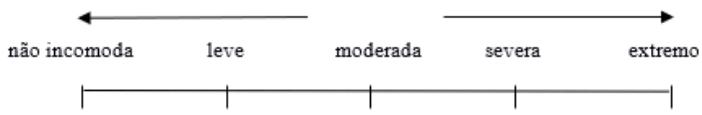
HGE
Hospital Geral do Estado

(Ctrl)

Escala *Cold Sensitivity Severity scale*

PARTE 2 (Para cada pergunta, marcar dentre as opções "não incomoda até incômodo extremo)

- Quanto frio incomoda sua mão que foi machucada enquanto segura um copo de água gelada?
- Quanto o frio incomoda sua mão machucada quando você sai de um chuveiro quente ou banheira quente com o ar em temperatura ambiente?
- Quanto frio incomoda sua mão machucada segurando um pacote congelado do congelador?
- Quanto frio incomoda sua mão que foi machucada quando você se lava em água fria?



Nome:

Assinatura: _____ Data:_____

Fonte: Adaptado de McCabe et al.

ANEXO C – Parecer Consubstanciado do CEP

UFBA - FACULDADE DE MEDICINA DA BAHIA (FMB) DA UNIVERSIDADE FEDERAL DA BAHIA

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: INFLUÊNCIA DA ESTIMULAÇÃO ELÉTRICA TRANSCUTÂNEA NA REGENERAÇÃO NERVOSA PERIFÉRICA APÓS NEURORRAFIA DE NERVOS DIGITAIS: ENSAIO CLÍNICO RANDOMIZADO

Pesquisador: Abrahão Fontes Baptista

Área Temática:

Versão: 4

CAAE: 30497620.5.0000.5577

Instituição Proponente: FACULDADE DE MEDICINA DA BAHIA

Patrocinador Principal: MINISTERIO DA CIENCIA, TECNOLOGIA E INOVACAO

DADOS DO PARECER

Número do Parecer: 4.171.388

Apresentação do Projeto:

O investigador solicita emenda ao protocolo justificando "Em virtude da pandemia, parte do acompanhamento dos pacientes se dará de maneira virtual baseado no mesmo protocolo para todos os participantes."

SOLICITAÇÃO: O investigador deve esclarecer sucintamente, o que será mudado no protocolo esclarecendo o que será feito e como será feito de maneira virtual. Anexar carta com as mudanças pretendidas, que devem constar no projeto e na plataforma Brasil.

MUDANÇAS; Os pacientes se submeterão a um protocolo de reeducação sensorial da mão baseado naquele proposto por DELLON & JABALEY (1982) por um período de três meses, num total de 20 sessões com cerca de 30 minutos de duração, realizadas, em média, duas vezes por semana. Na primeira revisão pós operatória, os pacientes serão avaliados e orientados quanto ao protocolo de reabilitação que será monitorado de maneira remota por um fisioterapeuta especialista na área através do meio eletrônico disponível para o paciente (Whatsapp,Skype e etc).Nenhum vídeo ou foto será adquirido, no sentido de garantir a privacidade do paciente e sigilo de seus dados. Os pacientes serão avaliados presencialmente a cada dez sessões de tratamento pelo autor principal do estudo que é responsável pelo acompanhamento cirúrgico e pós operatório dos participantes do estudo, porém que é cego as intervenções que estão sendo testadas. Os participantes deverão

Endereço: Largo do Terreiro de Jesus, s/n
Bairro: PELOURINHO **CEP:** 40.026-010
UF: BA **Município:** SALVADOR
Telefone: (71)3283-5564 **Fax:** (71)3283-5567 **E-mail:** cepfmb@ufba.br

777

perfazer um total de QUATRO avaliações presenciais (uma pré-intervenção e outras TRÊS até finalizarem o tratamento) para documentação dos resultados. Cada sessão terá duração média de 30 minutos até que completem um total de 20 sessões. A pesquisa será encerrada no prazo de um ano, tendo os pacientes completado o tratamento.

Medidas de evolução:Os pacientes serão avaliados segundo: a) Testes Sensoriais Quantitativos(estesiometria, monofilamentos de SEMMES-WEINSTEIN, teste de discriminação entre dois pontos);b)Aspectos sociodemográficos de qualidade de vida e dor. A avaliação sensitiva será feita por meio dos testes clínicos de sensibilidade e pela aplicação de questionários: a estesiometria, o teste dosmonofilamentos de SEMMES-WEINSTEIN, o teste de discriminação entre dois pontos, a escala de sensibilidade ao frio (Cold Sensitivity Severity Scale) e o questionário Pain Disability Index.
ADEQUADO

Objetivo da Pesquisa:
NÃO MUDAM.

Avaliação dos Riscos e Benefícios:
NÃO MUDAM.

Comentários e Considerações sobre a Pesquisa:
VER ACIMA

Considerações sobre os Termos de apresentação obrigatória:
NÃO MUDAM

Recomendações:
NÃO HÁ.

Conclusões ou Pendências e Lista de Inadequações:
NÃO HÁ PENDÊNCIAS.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações	PB_INFORMAÇÕES_BÁSICAS_159794	21/07/2020		Aceito

Básicas do Projeto	_E1.pdf	17:06:43		Aceito
Parecer Anterior	CARTACOMjustificativasPRETENDIDAS.docx	21/07/2020 17:06:21	Enilton de Santana Ribeiro de Mattos	Aceito
Projeto Detalhado / Brochura Investigador	ProjetoAFBEniltonFinal.pdf	21/07/2020 17:00:09	Enilton de Santana Ribeiro de Mattos	Aceito
Folha de Rosto	folhaderosto.pdf	01/04/2020 15:59:17	Enilton de Santana Ribeiro de Mattos	Aceito
Declaração do Patrocinador	termoEnilton.pdf	01/04/2020 10:13:41	Enilton de Santana Ribeiro de Mattos	Aceito
Declaração de Pesquisadores	termoequipeTiago.pdf	01/04/2020 10:08:43	Enilton de Santana Ribeiro de Mattos	Aceito
Declaração de Pesquisadores	termoequipePaulo.pdf	01/04/2020 10:08:32	Enilton de Santana Ribeiro de Mattos	Aceito
Declaração de Pesquisadores	termoequipeGislane.pdf	01/04/2020 10:08:19	Enilton de Santana Ribeiro de Mattos	Aceito
Declaração de Pesquisadores	termoequipeAbraao.pdf	01/04/2020 10:07:59	Enilton de Santana Ribeiro de Mattos	Aceito
Declaração de Pesquisadores	termo_equipe_pesquisa_cleber.pdf	01/04/2020 10:07:19	Enilton de Santana Ribeiro de Mattos	Aceito
Declaração de Pesquisadores	termoequeipeAlex.pdf	01/04/2020 10:07:02	Enilton de Santana Ribeiro de Mattos	Aceito
Orçamento	ORCAMENTO_DETALHADO.docx	08/03/2020 11:33:19	Enilton de Santana Ribeiro de Mattos	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_Enilton.docx	08/03/2020 11:24:35	Enilton de Santana Ribeiro de Mattos	Aceito
Declaração do Patrocinador	CNPq_Detalhamento_Proposta.pdf	08/03/2020 11:23:46	Enilton de Santana Ribeiro de Mattos	Aceito
Outros	ANUENCIA_FST_UFBA.pdf	27/01/2020 16:49:54	Enilton de Santana Ribeiro de Mattos	Aceito
Outros	carta_anuencia_HGE.pdf	27/01/2020 15:24:05	Enilton de Santana Ribeiro de Mattos	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

UFBA - FACULDADE DE MEDICINA DA BAHIA (FMB) DA UNIVERSIDADE FEDERAL DA BAHIA

Continuação do Parecer: 4.171.388

SALVADOR, 23 de Julho de 2020

Assinado por:
Eduardo Martins Netto
(Coordenador(a))

Endereço: Largo do Terreiro de Jesus, s/n
Bairro: PELOURINHO **CEP:** 40.026-010
UF: BA **Município:** SALVADOR
Telefone: (71)3283-5564 **Fax:** (71)3283-5567 **E-mail:** cepfmb@ufba.br

ANEXO D – Registro PROSPERO da Revisão Sistemática

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

Influence of electrical stimulation on peripheral nerve regeneration : a systematic review

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

01/06/2021

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/12/2021

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Enilton de Santana Ribeiro de Mattos

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Enilton Mattos

7. * Named contact email.

Give the electronic email address of the named contact.

eniltonmattos@hotmail.com

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

Av. Araujo Pinho 421, ap 804, Salvador -Bahia - Brazil / CEP 40110150

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+5571987612612

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Complexo Hospitalar Universitário Professor Edgar Santos

Organisation web address:

http://www2.ebserh.gov.br/web/hupes-ufba

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr Enilton de Santana Ribeiro de Mattos. Complexo Hospitalar Universitário Professor Edgar Santos-HUPES
Dr Mateus dos Santos Viana. Complexo Hospitalar Universitário Professor Edgar Santos
Professor Alex Guedes. Complexo Hospitalar Universitário Professor Edgar Santos
Professor Abrahão Fontes Baptista. Center for Mathematics, Computation and Cognition, Federal University of ABC, São Bernardo do Campo, São Paulo, Brazil

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

no funding sources/sponsors

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Does electrical stimulation (ES) have any influence on nerve regeneration compared with SHAM or standard treatment in patients with peripheral nerve injury?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

PubMed (MEDLINE)/EMBASE/Cochrane Central Register of Controlled Trials (CENTRAL)/Cochrane Library/PEDro/ BVS (LILACS) : Electric Stimulation Therapy AND Peripheral Nerve Injury AND randomized controlled trial; no language or publication date restriction

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

(((((eletrical stimulation) OR (peripheral electrical stimulation)) OR (PES)) OR (cuff stimulation)) OR (magnetic stimulation)) OR (peripheral magnetic stimulation) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter])) AND (((((peripheral nerve injury) OR (peripheral nerve regeneration)) OR (peripheral nerve damage)) OR (peripheral nerve crush)) OR (peripheral nerve transection) AND randomizedcontrolledtrial[Filter]))

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Damage to the peripheral nervous system (axonal damage) can occur due to a variety of reasons including trauma, ischemia, or inflammation.Electrical stimulation to improve the rate and speed of peripheral nerve regeneration involves the application of electrical fields of constant or varying frequency.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Adult patients (over 18 years old of both sexes) with peripheral nerve injury.
Stimulation for internal organs such as the bladder, esophagus (dysphagia) or vesicle and stimulation for central neurological conditions such as stroke and spine/root/spinal cord injuries will not be evaluated.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Electrical stimulation to improve the rate and speed of peripheral nerve regeneration involves the application of electrical fields of constant or varying frequency. Electrical currents are usually used, either flowing unidirectional (monophasic, constant or pulsed electrical currents) or bidirectional (alternate or biphasic electrical currents).

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

SHAM or standard treatment (physiotherapy) or no treatment in patients with peripheral nerve injury.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Randomized Controlled Trials

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

Damage to the peripheral nervous system can occur due to a variety of reasons, including trauma, metabolic insults, and inflammation. In response to peripheral nerve injury, morphological and functional changes can occur, such as motor and sensory function impairment, hyperesthesia, and low-temperature

intolerance.Electrical stimulation to improve the rate and speed of peripheral nerve regeneration includes the application of electrical fields of constant or varying frequency.This review aim to study if electrical stimulation have any influence on nerve regeneration in humans with damage on peripheral nerves, based on the RCT avaible in the literature.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Patients will be evaluated according to:

- Quantitative sensory tests (Semmes–Weinstein monofilament test and two-point discrimination test, quantitative sensory testing (QST) to yield warm (WDT) and cold detection thresholds (CDT), motor testing, etc);

- Aspects related to quality of life and pain.(DASH or other questionnaire or scale);

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Effect size of 0.26 , according to GORDON in: GORDON, T; AMIRJANI, N; EDWARDS, DC; CHAN, KM. Brief post-surgical electrical stimulation accelerates axon regeneration and muscle reinnervation without affecting the functional measures in carpal tunnel syndrome patients. Exp Neurol, v. 223, n. 1, p. 192–202, 2010.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

- Improvement in nerve conduction studies

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Based on a pivotal paper by Geremia et al; the number of regenerated sensory axons following electrical stimulation was 397+/?321 (SD) compared to the controls.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

We will include randomised trials.Two review authors will independently screen titles and trial abstracts that have been identified by the search strategy for potential inclusion in the review using predefined inclusion criteria and exclusion criteria. We will assess each trial for potential duplicate publication.The software that

will be used for selection and recording is the Rayyan and Mendeley . We will resolve disagreements by discussion and consensus with a third review author. The same two review authors will retrieve and review the complete report of all selected articles.We will place no restrictions on date, language, or publication

[illegible] follow-up, details of any 'run in' period, number of study

centres and location, study setting, and date of study start and completion.

-Participants: N randomised, N lost to follow-up/withdrawn with reasons, N analysed for each outcome, mean age, age

range, sex,inclusion criteria, and exclusion criteria.

-Interventions: intervention, comparison, concomitant, ES devices, electrode placement, stimulus current dose, frequency of ES administration (N times), N total ES delivered

-Outcomes: outcomes specified and collected, and time points reported;

We will contact investigators to verify key study characteristics and to obtain missing numerical outcome data when relevant and will document details regarding the correspondence. Where possible, we will calculate missing SDs using other data from the trial, such as CIs, based on methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Two review authors will independently assess the methodological quality of the included studies based on the following validity criteria. We will resolve disagreement by discussion and consensus with a third review author. The original authors may be contacted for further clarification as necessary.We will report any other important concerns about bias identified in the studies.We will use the version 2 of the Cochrane 'Risk ofbias' tool (RoB 2) (Sterne 2019), outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2019b). We plan to use the RoB 2 MicrosoM Excel tool to manage the 'Risk of bias assessment (MicrosoM Excel 2019; RoB 2 MicrosoM Excel tool 2019).Any disagreements will be resolved by discussion or by involving the third review author.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

We will include randomised trials and use an electronic data collection form for study characteristics and outcome data that has been piloted on at least one included study.We will express dichotomous outcomes as risk ratios (RR) of electrical stimulation with a 95% confidence interval (CI) and express continuous outcomes as mean differences (MD) with 95% CIs.We will calculate the numbers of patients needed to treat (or harm) by 1/(risk difference), expressed with 95% CIs.For outcomes for which data are not reported or are reported in a different format, we will contact authors for clarification.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

We plan to carry out the following subgroup analyses for any outcomes with substantial heterogeneity.

-Method of ES delivery

-Electrode placement and pulse width

-Treatment schedule.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Living systematic review
No

Meta-analysis
No

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention

No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
Yes

Neurological
Yes

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders

No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Brazil

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

No

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Electric Stimulation Therapy ; Peripheral Nerve Injury ;randomized controlled trial and controlled clinical trial

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

This review is being undertaken as part of the planning for a randomised trial to compare the effect of electrical stimulation (ES) on nerve regeneration compared with SHAM on peripheral nerve injury.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

ANEXO E – Análise estatística detalhada

Testes estatísticos realizados utilizando o *software JASP (V0.18.3)* do artigo 6.2: “Effects of transcutaneous electrical stimulation on peripheral nerve regeneration after digital nerve neurorrhaphy: A randomized clinical trial”

Results

Repeated Measures ANOVA: MSW

Within Subjects Effects

Cases	Sphericity Correction	Sum of Squares	df	Mean Square	F	p
MSW (RM)	None	99.210	1.000	99.210	7.351	0.012
MSW (RM) ✻ Group	None	37.180	1.000	37.180	2.755	0.109
MSW (RM) ✻ Idade	None	10.221	1.000	10.221	0.757	0.392
Residuals	None	350.900	26.000	13.496		

Note. Sphericity corrections not available for factors with 2 levels.
Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p
Group	37.311	1	37.311	2.201	0.150
Idade	55.511	1	55.511	3.275	0.082
Residuals	440.657	26	16.948		

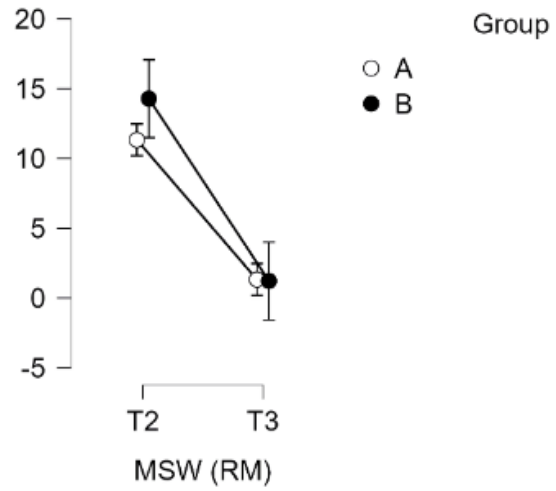
Note. Type III Sum of Squares

Descriptives

Descriptives

MSW (RM)	Group	N	Mean	SD	SE	Coefficient of variation
T2	A	15	11.333	3.498	0.903	0.309
	B	14	14.286	6.988	1.868	0.489
T3	A	15	1.331	1.816	0.469	1.364
	B	14	1.226	0.617	0.165	0.504

Descriptives plots



Assumption Checks

Test for Equality of Variances (Levene's)

	F	df1	df2	p
MSW (T2) (g)	3.333	1	27	0.079
MSW (T3) (g)	2.384	1	27	0.134

Post Hoc Tests

Post Hoc Comparisons - Group ✻ MSW (RM)

		Mean Difference	SE	t	Cohen's d	p_{tukey}	$p_{scheffe}$	p_{bonf}	p_{holm}
A, T2	B, T2	-3.222	1.457	-2.212	-0.826	0.134	0.194	0.189	0.063
	A, T3	9.924	1.344	7.382	2.544	< .001	< .001	< .001	< .001
	B, T3	9.922	1.454	6.825	2.543	< .001	< .001	< .001	< .001
B, T2	A, T3	13.147	1.454	9.044	3.370	< .001	< .001	< .001	< .001
	B, T3	13.144	1.392	9.443	3.369	< .001	< .001	< .001	< .001
A, T3	B, T3	-0.003	1.457	-0.002	-7.272×10^{-4}	1.000	1.000	1.000	0.998

Note. Computation of Cohen's d based on pooled error.
Note. P-value adjusted for comparing a family of 6

Repeated Measures ANOVA: MSW (E.size)

Within Subjects Effects

Cases	Sphericity Correction	Sum of Squares	df	Mean Square	F	p
MSW (RM)	None	2.789	1.000	2.789	42.145	< .001
MSW (RM) ✻ Group	None	0.003	1.000	0.003	0.053	0.820
MSW (RM) ✻ Idade	None	0.209	1.000	0.209	3.152	0.088
Residuals	None	1.721	26.000	0.066		

Note. Sphericity corrections not available for factors with 2 levels.
Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p
Group	0.047	1	0.047	0.217	0.645
Idade	1.482	1	1.482	6.912	0.014
Residuals	5.575	26	0.214		

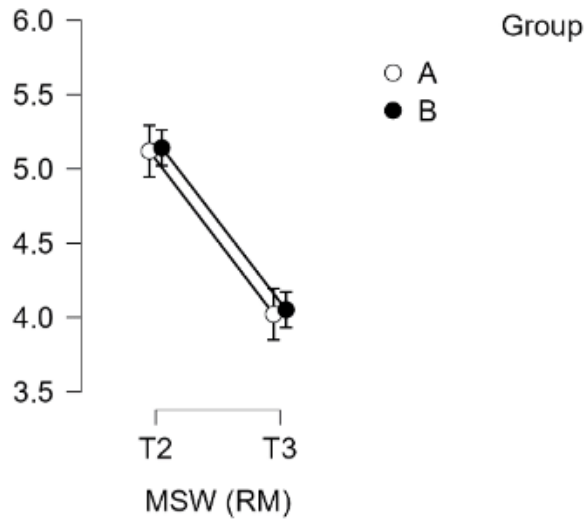
Note. Type III Sum of Squares

Descriptives

Descriptives

MSW (RM)	Group	N	Mean	SD	SE	Coefficient of variation
T2	A	15	5.119	0.293	0.076	0.057
	B	14	5.141	0.211	0.057	0.041
T3	A	15	4.022	0.658	0.170	0.164
	B	14	4.052	0.296	0.079	0.073

Descriptives plots



Assumption Checks

Test for Equality of Variances (Levene's)

	F	df1	df2	p
MSW E.size (T2)	0.218	1	27	0.644
MSW E.size (T3)	0.944	1	27	0.340

Post Hoc Tests

Post Hoc Comparisons - Group ✻ MSW (RM)

		Mean Difference	SE	t	Cohen's d	p_{tukey}	$p_{scheffe}$	p_{bonf}	p_{holm}
A, T2	B, T2	-0.041	0.140	-0.296	-0.110	0.991	0.993	1.000	1.000
	A, T3	1.109	0.094	11.775	2.960	< .001	< .001	< .001	< .001
	B, T3	1.036	0.140	7.416	2.766	< .001	< .001	< .001	< .001
B, T2	A, T3	1.150	0.140	8.232	3.070	< .001	< .001	< .001	< .001
	B, T3	1.077	0.097	11.054	2.876	< .001	< .001	< .001	< .001
A, T3	B, T3	-0.073	0.140	-0.519	-0.194	0.954	0.965	1.000	1.000

Note. Computation of Cohen's d based on pooled error.
Note. P-value adjusted for comparing a family of 6

Repeated Measures ANOVA: s2PD

Within Subjects Effects

Cases	Sphericity Correction	Sum of Squares	df	Mean Square	F	p
s2PD (RM)	None	18.254	1.000	18.254	12.236	0.002
s2PD (RM) ✻ Group	None	1.269	1.000	1.269	0.851	0.365
s2PD (RM) ✻ Idade	None	0.010	1.000	0.010	0.007	0.934
Residuals	None	38.790	26.000	1.492		

Note. Sphericity corrections not available for factors with 2 levels.
Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p
Group	2.428	1	2.428	0.916	0.347
Idade	8.610	1	8.610	3.249	0.083
Residuals	68.904	26	2.650		

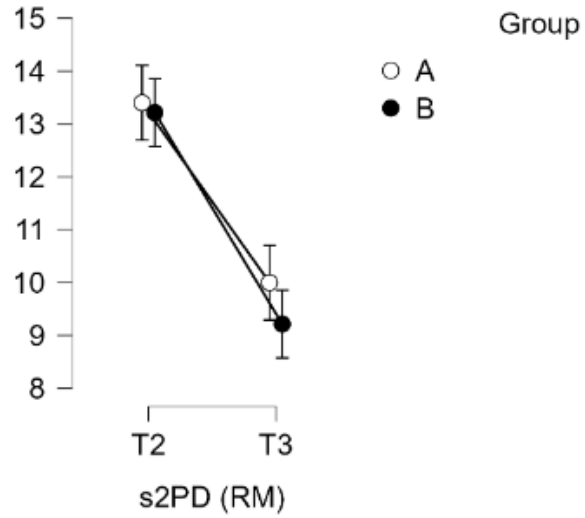
Note. Type III Sum of Squares

Descriptives

Descriptives

s2PD (RM)	Group	N	Mean	SD	SE	Coefficient of variation
T2	A	15	13.400	1.404	0.363	0.105
	B	14	13.214	1.718	0.459	0.130
T3	A	15	10.000	1.604	0.414	0.160
	B	14	9.214	1.051	0.281	0.114

Descriptives plots



Assumption Checks

Test for Equality of Variances (Levene's)

	F	df1	df2	p
s2PD (T2)	1.580	1	27	0.219
s2PD (T3)	0.345	1	27	0.562

Post Hoc Tests

Post Hoc Comparisons - Group ✻ s2PD (RM)

		Mean Difference	SE	t	Cohen's d	p_{tukey}	$p_{scheffe}$	p_{bonf}	p_{holm}
A, T2	B, T2	0.114	0.537	0.212	0.079	0.997	0.997	1.000	0.833
	A, T3	3.402	0.447	7.612	2.364	< .001	< .001	< .001	< .001
	B, T3	4.111	0.536	7.665	2.857	< .001	< .001	< .001	< .001
B, T2	A, T3	3.289	0.536	6.131	2.285	< .001	< .001	< .001	< .001
	B, T3	3.997	0.463	8.638	2.778	< .001	< .001	< .001	< .001
A, T3	B, T3	0.709	0.537	1.319	0.493	0.555	0.631	1.000	0.387

Note. Computation of Cohen's d based on pooled error.
Note. P-value adjusted for comparing a family of 6

Independent Samples T-Test: CSS, PDI

Independent Samples T-Test

	t	df	p
CSS	-1.045	29	0.305
PDI	-0.720	29	0.477

Note. Student's t-test.

Independent Samples T-Test: CSS, PDI

Independent Samples T-Test

	t	df	p
CSS	-1.045	29	0.305
PDI	-0.720	29	0.477

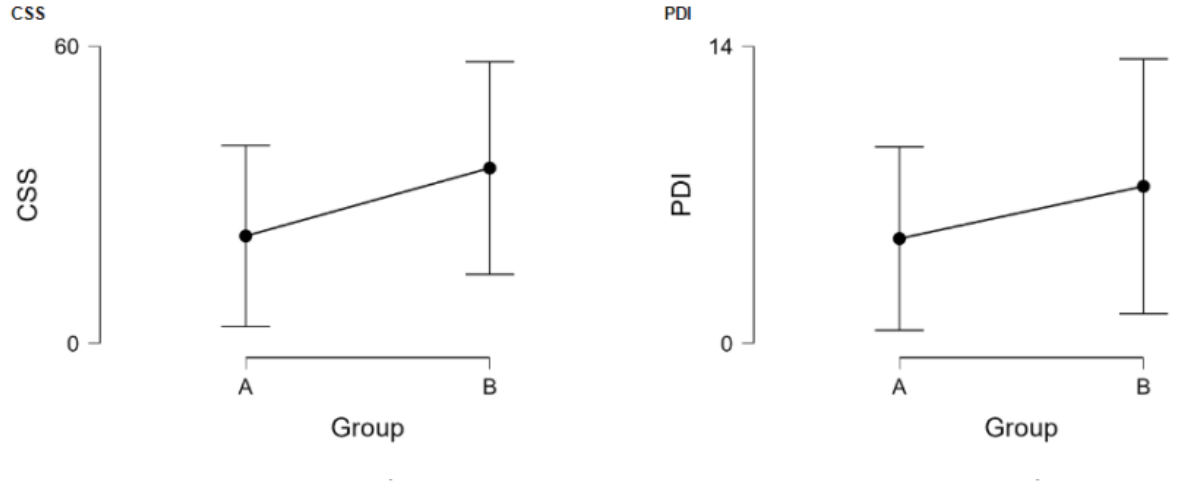
Note. Student's t-test.

Descriptives

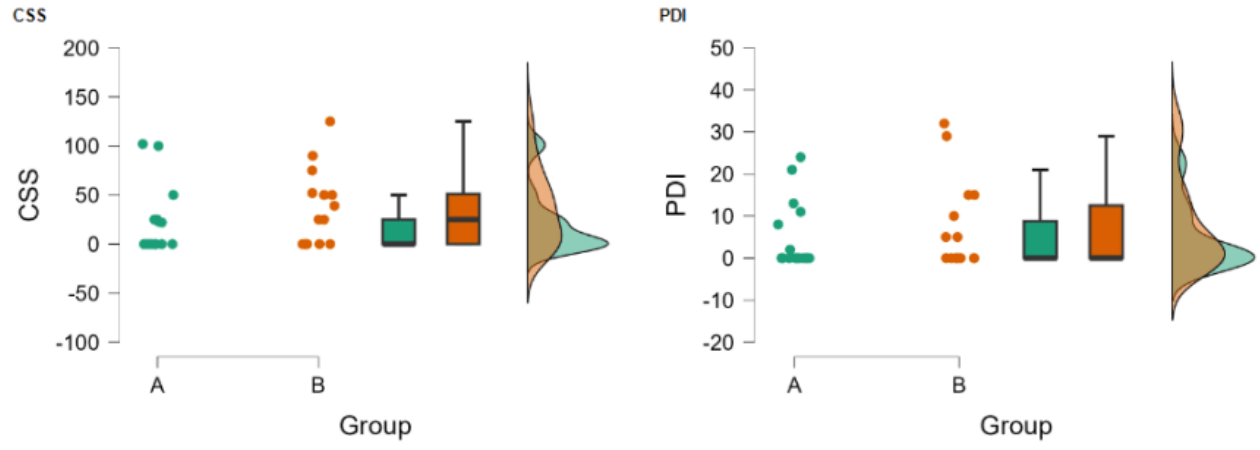
Group Descriptives

	Group	N	Mean	SD	SE	Coefficient of variation
CSS	A	16	21.688	34.294	8.574	1.581
	B	15	35.400	38.755	10.007	1.095
PDI	A	16	4.938	8.103	2.026	1.641
	B	15	7.400	10.835	2.798	1.464

Descriptives Plots



Raincloud Plots



Correlation

Pearson's Correlations

Variable		Idade	MSW (T2) (g)	MSW (T3) (g)	Grade MSW(T2)	Grade MSW(T3)	s2PD (T2)	s2PD (T3)	CSS	PDI
1. Idade	Pearson's r	—								
	p-value	—								
2. MSW (T2) (g)	Pearson's r	0.242	—							
	p-value	0.099	—							
3. MSW (T3) (g)	Pearson's r	0.400*	0.309	—						
	p-value	0.013	0.051	—						
4. Grade MSW(T2)	Pearson's r	NaN	NaN	NaN	—					
	p-value	NaN	NaN	NaN	—					
5. Grade MSW(T3)	Pearson's r	-0.353	-0.324	-0.732	NaN	—				
	p-value	0.974	0.957	1.000	NaN	—				
6. s2PD (T2)	Pearson's r	0.295	0.537**	0.299	NaN	-0.101	—			
	p-value	0.057	0.001	0.058	NaN	0.699	—			
7. s2PD (T3)	Pearson's r	0.295	0.304	0.718***	NaN	-0.364	0.339*	—		
	p-value	0.053	0.055	< .001	NaN	0.978	0.036	—		
8. CSS	Pearson's r	0.161	0.671***	0.384*	NaN	-0.460	0.476**	0.325*	—	
	p-value	0.193	< .001	0.017	NaN	0.995	0.005	0.037	—	
9. PDI	Pearson's r	0.065	0.632***	0.442**	NaN	-0.457	0.569***	0.353*	0.819***	—
	p-value	0.364	< .001	0.006	NaN	0.995	< .001	0.026	< .001	—

Note. All tests one-tailed, for positive correlation.
▪ The variance in Grade MSW(T2) is equal to 0
* p < .05, ** p < .01, *** p < .001, one-tailed