UNIVERSIDADE DE BRASÍLIA/FACULDADE DE CEILÂNDIA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA REABILITAÇÃO
CURSO DE MESTRADO ACADÊMICO

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CONTRACTION FATIGUE, STRENGTH ADAPTATIONS, AND DISCOMFORT DURING CONVENTIONAL VERSUS WIDE-PULSE, HIGH-FREQUENCY, NEUROMUSCULAR ELECTRICAL STIMULATION: A SYSTEMATIC REVIEW

DISSERTAÇÃO

BRASÍLIA

2021

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CONTRACTION FATIGUE, STRENGTH ADAPTATIONS, AND DISCOMFORT DURING CONVENTIONAL VERSUS WIDE-PULSE, HIGH-FREQUENCY, NEUROMUSCULAR ELECTRICAL STIMULATION: A SYSTEMATIC REVIEW

Dissertação apresentada ao Programa de Pós Graduação em Ciências da Reabilitação, como parte dos requisitos necessários à obtenção do título de Mestre.

Orientador: João Luiz Quagliotti Durigan

Brasília

2021

Ficha catalográfica elaborada automaticamente,
com os dados fornecidos pelo(a) autor(a)

Bastos, Júlia Aguillar Ivo
BB327c CONTRACTION FATIGUE, STRENGTH ADAPTATIONS, AND DISCOMFORT DURING CONVENTIONAL VERSUS WIDE-PULSE, HIGH FREQUENCY, NEUROMUSCULAR ELECTRICAL STIMULATION: A SYSTEMATIC REVIEW / Júlia Aguillar Ivo Bastos; orientador João Luiz Quagliotti Durigan. -- Brasília, 2021.
77 p.

Dissertação (Mestrado - Mestrado em Ciências da Reabilitação) -- Universidade de Brasília, 2021.

1. Electric Stimulation. 2. Fatigue. 3. Muscle Strength. 4. Torque. 5. Perception Discomfort. . I. Durigan, João Luiz Quagliotti, orient. II. Título.

DEDICATÓRIA

Dedico esta dissertação primeiramente a Deus, meu guia em todos os momentos. À minha querida mãe, Elizabeth, e ao meu companheiro, Pedro.

AGRADECIMENTOS

Agradeço a Deus por vigiar meu caminho até aqui. Agradeço a toda minha linda família que sempre me apoiou e compreendeu minhas escolhas. Em especial a duas pessoas que jamais me deixam esmorecer, minha mãe, Elizabeth, que é minha força e minha inspiração, e ao Pedro, meu amado companheiro e grande incentivador.

Agradeço a Universidade de Brasília que me abriu portas e me apresentou a grandes professores e colegas. Ao meu orientador, professor Dr. João Luiz Quagliotti Durigan, por compartilhar tanto ensinamento e por sua incansável e admirável orientação ao longo de todo o processo. Também agradeço ao grupo de pesquisa Gplast, especialmente aos amigos Karenina, Jonathan, Álvaro e Leandro, por toda parceria e colaboração.

Obrigada aos professores Dr. Wagner Rodrigues Martins e Dr. Gerson Cipriano Júnior, que colaboraram em meu primeiro manuscrito e foram extremamente importantes para o processo de aprendizagem e escrita desta dissertação.

I also would like to thank Professor David Frederic Collins for all the time dedicated to my manuscript and for the always editing with great considerations. It was a pleasure to have your collaboration in this manuscript.

A todos, o meu muito obrigada!

APRESENTAÇÃO

Em março de 2019 iniciei o mestrado no Programa de Pós-graduação em Ciências da Reabilitação da Universidade de Brasília – Faculdade de Ceilândia, sob orientação do Prof. Dr. João Luiz Quaglioti Durigan. Em outubro de 2019 o projeto intitulado "Influência do posicionamento de eletrodos e tipo de corrente utilizada nas adaptações neuromusculares induzidas pela estimulação elétrica neuromuscular: Implicações na reabilitação" foi aprovado pelo Comitê de Ética e Pesquisa da Faculdade de Ceilândia (CEP/FCE) (CAAE: 14734619.3.0000.8093), e a partir deste momento iniciamos as coletas dos participantes que se voluntariaram à pesquisa, em novembro de 2019.

Avaliamos 4 participantes, em um total de 13 sessões realizadas, com nenhum participante completando as 9 sessões necessárias para este estudo. O projeto e os dados coletados até aquele momento foram, então, apresentados no exame de qualificação em março de 2020. Os membros da banca concordaram que devido a diferença do número de sujeitos para cada corrente, não havia valores semelhantes entre os grupos, e, por isso, não foi possível naquele momento avaliar e interpretar os resultados parciais apresentados. Durante a qualificação os examinadores sugeriram algumas modificações no projeto, principalmente relacionadas ao protocolo de pesquisa, dentre elas: o posicionamento do participante no dinamômetro isocinético, a especificação do estimulador elétrico utilizado, uma melhor utilização da Escala Visual Analógica (EVA) para análise de desconforto sensorial, controle de possível efeito da fadiga; e sugeriram uma revisão na forma de análise estatística das variáveis do estudo. As modificações sugeridas foram aceitas e em seguida foi feita uma emenda ao CEP/FCE com as alterações necessárias no projeto, aprovada posteriormente por este Comitê.

Dias após o exame de qualificação, devido a pandemia de COVID-19 no Brasil, o Distrito Federal decretou estado de quarentena e isolamento, desenvolvendo ao longo das semanas diferentes medidas de contenção da pandemia, dentre elas o fechamento de Universidades, paralisando por tempo indeterminado as atividades presenciais, incluindo a utilização dos laboratórios. Neste cenário, o laboratório de treinamento de força da Faculdade de Educação Física – Universidade de Brasília, onde as coletas estavam sendo realizadas, seguiu as recomendações e paralisou suas atividades. Com essa medida, a

continuidade do ensaio clínico inicialmente proposto ficou comprometida, e está interrompida até a data da apresentação deste trabalho.

Tendo em vista a incerteza acerca do retorno das atividades como eram antes do início da pandemia, e com o objetivo de não comprometer o prazo para defesa de mestrado e de não gerar maiores intempéries ao programa de pós-graduação, em acordo com meu orientador, decidimos propor a minha dissertação de mestrado com uma revisão sistemática que já havíamos iniciado no final de 2019, com a colaboração dos professores Dr. Wagner Rodrigues Martins e Dr. Gerson Cipriano Júnior, da Universidade de Brasília (UnB) e do professor Dr. David Frederic Collins, da Universidade de Alberta – Canadá. A parceria com o professor David Collins se formou deste o início do projeto de mestrado, com a construção da metodologia de pesquisa do ensaio clínico "Influência do posicionamento de eletrodos e tipo de corrente utilizada nas adaptações neuromusculares induzidas pela estimulação elétrica neuromuscular: Implicações na reabilitação" e a escrita desta revisão sistemática proporcionou uma maior aproximação, resultando na construção deste estudo, que tem o professor Dr. David Frederic Collins como um dos autores.

As análises feitas nesta revisão sistemática têm total relação com o ensaio clínico que tivemos que interromper devido aos acontecimentos, e os resultados encontrados aqui servirão de suporte teórico para quando retornarmos às atividades no laboratório. Caso a vacinação em massa ocorra ainda neste semestre e os casos de COVID-19 reduzam, o recrutamento de pesquisa será retomado no segundo semestre de 2021. Além disso, estamos seguindo as recomendações dos especialistas do Plano de contingência da UnB para enfrentamento da pandemia de COVID-19.

Assim, o ensaio clínico "Influência do posicionamento de eletrodos e tipo de corrente utilizada nas adaptações neuromusculares induzidas pela estimulação elétrica neuromuscular: Implicações na reabilitação" será concluído posteriormente na forma de doutoramento por mim, pois acreditamos no potencial desse estudo, pensado com elevado rigor metodológico e homogeneidade dos parâmetros das correntes escolhidas, com objetivo de colaborar com a literatura acerca do tema, frequentemente afetada pela baixa qualidade metodológica e heterogeneidade dos parâmetros escolhidos.

RESUMO EXPANDIDO

Título: FADIGA INDUZIDA PELA CONTRAÇÃO EVOCADA, ADAPTAÇÕES DE FORÇA MUSCULAR E DESCONFORTO DURANTE ESTIMULAÇÃO ELÉTRICA NEUROMUSCULAR CONVENVIONAL VERSUS PULSO LARGO DE ALTA FREQUÊNCIA: UMA REVISÃO SISTEMÁTICA

Introdução: A estimulação elétrica neuromuscular (EENM) é usada para gerar contrações com o objetivo de restaurar a função e melhorar a força e resistência muscular. A EENM convencional ($CONV_{EENM}$) envolve pulsos relativamente curtos (~ 0,1-0,5 ms) entregues em baixas frequências (~ 20-50 Hz), normalmente por meio de eletrodos sobre um músculo, estimulando axônios motores por meio de "vias periféricas". A contração por meio de vias periféricas recruta unidades motoras em uma ordem não fisiológica e aleatória. Assim, a $CONV_{EENM}$ resulta em maior fadiga induzida pela contração, definida como um declínio no torque ao longo do tempo. A EENM também pode utilizar pulsos mais largos, com frequências mais altas (PL_{EENM}: 1 ms de largura de pulso, frequência ~ 100 Hz). A PL_{EENM} foi desenvolvida para reduzir a fadiga induzida pela contração e melhorar os resultados de programas de EENM, gerando contrações por meio de "vias centrais", portanto, de uma maneira mais fisiologicamente relevante do que a $CONV_{EENM}$. No entanto, se a fadiga induzida pela contração é de fato reduzida ou os resultados da EENM são melhores com o uso de PL_{EENM} ainda não é claro.

Até o momento, não há uma revisão sistemática que compare $CONV_{EENM}$ e PL_{EENM} para orientar a prática clínica em relação à EENM. Esta revisão, portanto, foi desenvolvida para sumarizar a pesquisa comparando $CONV_{EENM}$ e PL_{EENM}, para avaliar os efeitos destas intervenções em desfechos importantes para programas baseados em EENM. As descobertas ajudarão os profissionais de saúde a entender melhor os efeitos da EENM no sistema neuromuscular e contribuirão para uma base de evidências para desenvolver estratégias em programas de EENM.

Objetivos: O principal objetivo desta revisão sistemática foi comparar os efeitos de dois tipos de EENM, $CONV_{EENM}$ e PL_{EENM}, na fadiga induzida pela contração, adaptações de força e desconforto percebido em populações clínicas e não-clínicas.

Hipóteses: Nossa hipótese inicial foi de que a fadiga induzida pela contração seria menor e haveria maior ganho de força na PL_{EENM}. Também levantamos a hipótese de que a $CONV_{EENM}$ adicionaria menos desconforto durante a sessão de EENM.

Métodos: As bases de dados pesquisadas incluíram Pubmed, Embase, MEDLINE, Web of Science, SciELO, EBSCO, LILACS, PEDro, Cochrane e EMBASE. Dois revisores independentes selecionaram estudos e extraíram informações. Os estudos foram selecionados se comparassem $CONV_{EENM}$ com PL_{EENM} com fadiga induzida pela contração, adaptações de força ou desconforto percebido como resultados. Um desfecho primário foi a fadiga induzida pela contração, quantificada como um declínio no torque em contrações evocadas por EENM durante uma única sessão. As adaptações de força, definidas como uma mudança no torque produzido durante as contrações voluntárias máximas (CVMs) realizadas antes e depois de um programa de treinamento com EENM, também foi um resultado primário. O resultado secundário foi o desconforto percebido conforme avaliado usando a escala visual analógica (EVA).

A qualidade dos estudos foi avaliada usando a escala PEDro, e a qualidade geral foi avaliada usando os critérios da *Grading of Recommendations, Assessment, Development, and Evaluation.*

Resultados: Oito estudos foram incluídos, com um total de 171 participantes. Em estudos de curto e longo prazo, quando calculada a média de todos os participantes não-clínicos, não houve diferença entre $CONV_{EENM}$ e PL_{EENM} para todos os resultados ou a PL_{EENM} produziu mais fadiga. Em um subconjunto de participantes não-clínicos ("respondedores"), no entanto, a PL_{EENM} reduziu a fadiga induzida pela contração durante uma única sessão. Estudos de longo prazo não encontraram diferenças entre os protocolos para fadiga ou adaptações de força. A qualidade metodológica dos estudos selecionados foi considerada muito baixa.

Discussão: Esta é a primeira revisão sistemática a sumarizar pesquisas comparando $CONV_{EENM}$ e PL_{EENM} em desfechos relevantes para programas de EENM, especificamente a respeito de fadiga induzida pela contração, adaptações de força e desconforto percebido. Em geral, não encontramos diferenças entre $CONV_{EENM}$ e PL_{EENM} para fadiga e desconforto em estudos de curto e longo prazo em populações não-clínicas e para adaptações de força e fadiga em pacientes com esclerose múltipla (EM) em um estudo de longo prazo, portanto, propomos que fisioterapeutas alcançariam resultados

semelhantes usando $CONV_{EENM}$ ou PL_{EENM}. A PL_{EENM} reduziu a fadiga induzida pela contração, no entanto, em um subconjunto de participantes não-clínicos, os “respondedores”.

O desconforto percebido foi avaliado em um estudo de curto prazo no qual os escores da EVA não foram diferentes entre $CONV_{EENM}$ e PL_{EENM}. A $CONV_{EENM}$, no entanto, exigia mais corrente do que a PL_{EENM} para obter a mesma amplitude de contração inicial, portanto, esperava-se que a $CONV_{EENM}$ induzisse mais desconforto. Mais estudos são necessários para comparar os efeitos de PL_{EENM} e $CONV_{EENM}$ no desconforto percebido.

Conclusão: Os resultados dos estudos de curto e longo prazo sugerem que, em geral, em um grupo de participantes não-clínicos, não há diferença entre $CONV_{EENM}$ e PL_{EENM} para fadiga induzida pela contração, adaptações de força ou desconforto percebido. Há evidências, no entanto, de que uma única sessão de PL_{EENM} pode reduzir a fadiga induzida pela contração, em comparação com $CONV_{EENM}$, para um segmento da população não-clínica (os "respondedores"), mas exacerba a fadiga induzida pela contração para outros (os “não-respondedores”). A longo prazo, não foram identificadas diferenças entre $CONV_{EENM}$ e PL_{EENM} para adaptações de força muscular e fadiga em populações clínicas e não-clínicas. A qualidade metodológica, no entanto, foi muito baixa e futuros ensaios clínicos randomizados bem planejados devem ser realizados para estabelecer os parâmetros de EENM ideais para reduzir a fadiga induzida pela contração, aumentar a força muscular e reduzir o desconforto percebido em participantes clínicos e não-clínicos.

Palavras-chave: Estimulação Elétrica, Fadiga, Força Muscular, Torque, Desconforto Percebido.

ABSTRACT

Background: Neuromuscular electrical stimulation (NMES) can be delivered in a conventional form ($CONV_{NMES}$) and using relatively wide-pulses and high-frequencies ($WPHF_{NMES}$). $WPHF_{NMES}$ was developed to reduce contraction fatigue and improve outcomes of NMES-based programs, however, there are no systematic reviews to assess its' efficacy and help guide the selection of stimulus parameters during NMES.

Objectives: Compare the effects of $CONV_{NMES}$ versus $WPHF_{NMES}$ on contraction fatigue, strength adaptations, and perceived discomfort in clinical and non-clinical populations.

Methods: Data sources included Pubmed, Embase, MEDLINE, Web of Science, SciELO, EBSCO, LILACS, PEDro, Cochrane Library, and EMBASE. Two independent reviewers selected studies and extracted information. Studies were selected if they compared $CONV_{NMES}$ with $WPHF_{NMES}$ with contraction fatigue, strength adaptations or perceived discomfort as outcomes. Study quality was assessed using the PEDro scale, and overall quality was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation criteria.

Results: Eight studies (n=171 participants) were included. In short- and long-term studies, when averaged across all non-clinical participants, there was either no difference between $CONV_{NMES}$ and $WPHF_{NMES}$ for all outcomes or $WPHF_{NMES}$ produced more fatigue. In a subset of non-clinical participants ("responders"), however, $WPHF_{NMES}$ reduced contraction fatigue during a single session. Long-term studies found no differences between protocols for fatigue or strength adaptations. Methodological quality of the selected studies was very low.

Conclusion: $WPHF_{NMES}$ reduces contraction fatigue only in the short-term and in non-clinical responder participants and may exacerbate fatigue in non-responders. New clinical studies with good methodological quality may affect the results presented in this review.

Key-words: Electric Stimulation, Fatigue, Muscle Strength, Torque, Perception Discomfort.

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LIST OF ABBREVIATIONS

CNS: Central nervous system

CONV: Conventional

CP: Cerebral palsy

FTI: Force time integral

MFIS: Modified fatigue impact scale

MS: Multiple sclerosis

MVC: Maximal voluntary contraction

NMES: Neuromuscular electrical stimulation

RCT: Randomized controlled trial

VAS: Visual analog scale

VOL: Voluntary exercise

WPHF: Wide-pulse high-frequency

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INTRODUCTION

Neuromuscular electrical stimulation (NMES) is used to generate contractions to restore function and improve muscle strength and endurance (1–4). During NMES, pulses of electrical current are delivered through electrodes on the skin over a muscle belly or a nerve trunk. NMES activates motor and/or sensory axons, generating contractions through peripheral and/or central pathways, respectively (5). Conventional NMES ($CONV_{NMES}$) involves relatively brief pulses of current (~0.1-0.5ms) delivered at low frequencies (~20-50Hz) (6–10), typically through electrodes over a muscle belly, and this produces contractions by stimulating motor axons, thus through "peripheral pathways" (11–20). Generating contractions through peripheral pathways recruits motor units in an unphysiological, random, order with respect to type and at unphysiologically-high rates (21). Accordingly, $CONV_{NMES}$ results in significantly more contraction fatigue, defined as a decline in torque over time, than voluntary exercise (10,22,23). NMES can also be delivered using longer duration current pulses (i.e. wide pulse widths) and higher frequencies ($WPHF_{NMES}$: 1ms of pulse widths, frequency ~100Hz). $WPHF_{NMES}$ was developed to reduce contraction fatigue and improve outcomes of NMES-based programs by generating contractions through "central pathways", thus in a more physiologically-relevant manner than $CONV_{NMES}$. Whether contraction fatigue is reduced or NMES outcomes are improved when using $WPHF_{NMES}$, however, is presently unclear.

$WPHF_{NMES}$ generates contractions through central pathways because a larger sensory input is sent to the central nervous system (CNS) during $WPHF_{NMES}$ than $CONV_{NMES}$. Wider pulse widths during $WPHF_{NMES}$ activate more sensory axons relative to motor axons because sensory axons have a longer strength-duration time constant than motor axons, thus longer pulses are required to bring sensory axons to threshold than motor axons (9,24–26). Also, higher pulse frequencies during $WPHF_{NMES}$ send more impulses to the CNS per unit time than during $CONV_{NMES}$, further increasing sensory input to the CNS. In some participants, described as "responders", the combination of wider pulses and higher frequencies produce contractions that gradually increase over time. The increase in force has been called "extra force" (27) and has been attributed to the recruitment of spinal motor neurons via central pathways (26–28). Extra force does not develop when the nerve is blocked with anesthetic between the stimulation site and the muscle (27) and thus is related to central mechanisms such as post-tetanic potentiation of neurotransmitter release at the Ia synapse, summation of subthreshold excitatory

postsynaptic potentials and/or activation of persistent inward currents in motor neurons (27,29,30). Regardless, generating contractions via central pathways recruits motor units in their physiological order, with fatigue-resistant units first, and some that discharge asynchronously from one and other at physiologically low rates (21,31). While these ideas about motor unit recruitment during NMES provided the rationale for developing $WPHF_{NMES}$ (9,25,26), the short-term effects on contraction fatigue, and long-term effects on strength adaptations, of $WPHF_{NMES}$ remain to be confirmed. Further, perceived discomfort limits NMES sessions by restricting high muscle force levels or increasing contraction fatigue (32,33).

To date, there is no systematic review that compares $CONV_{NMES}$ and $WPHF_{NMES}$ to guide clinical practice regarding NMES. This review, therefore, was developed to summarize the research comparing $CONV_{NMES}$ and $WPHF_{NMES}$, following the Cochrane collaboration (34) recommendations, to assess the effects of these interventions on outcomes important for NMES-based programs. Specifically, we compared the effects of $CONV_{NMES}$ and $WPHF_{NMES}$ on contraction fatigue, strength adaptations and perceived discomfort in individuals with neurological or musculoskeletal injury and in non-clinical participants. The findings will help health care practitioners better understand the effects of NMES on the neuromuscular system and will contribute to an evidence-base upon which to develop NMES strategies.

OBJECTIVES

The objective of this systematic review is to compare the effects of two types of NMES, $CONV_{NMES}$ and $WPHF_{NMES}$, on contraction fatigue, strength adaptations and perceived discomfort in clinical and non-clinical populations.

HYPOTHESIS

Our primary hypothesis was that contraction fatigue would be lower and there would be greater strength in $WPHF_{NMES}$. We also hypothesized that $CONV_{NMES}$ would add lower discomfort during the NMES session.

METHODS

The protocol of this systematic review has been registered on the International Prospective Register of Systematic Reviews - PROSPERO (registration number: CRD42020153907, accessed at https://www.crd.york.ac.uk/PROSPERO/) (Appendix III).

Criteria for considering studies for this review

Types of studies

We included only published randomized controlled trials (RCTs) and cross-over trials.

Types of participants

Trials involving participants with neurological and/or musculoskeletal disorders or non-clinical participants (≥ 18 years of age) were included.

Types of interventions

Studies were included that compared one or more of our 3 outcome measures between $CONV_{NMES}$ and $WPHF_{NMES}$. Stimulus waveforms were either biphasic or monophasic and applied over a muscle belly or nerve trunk. As the objective was to compare between two types of NMES, we did not assess passive comparators such as placebo or sham therapy or an active comparator, such as another intervention.

Types of outcome measures

Primary outcomes

A primary outcome was contraction fatigue, quantified either as a decline in torque over repeated NMES-evoked contractions during a single session, a decrease in the ability to generate torque during maximal voluntary contractions (MVCs) performed before and after a single NMES session or through self-reports. Strength adaptations, defined as a change in torque produced during MVCs performed before and after an NMES training program, was also a primary outcome.

Secondary outcomes

The secondary outcome was perceived discomfort as assessed using the visual analogue scale (VAS).

Search methods for identification of studies

The titles, abstracts, and full texts of potentially relevant papers were screened without restrictions on language and date of publication.

Electronic searches

We searched nine electronic databases: PUBMED, MEDLINE, Web of Science (all databases), SciELO, EBSCO (Academic Search Premier, CINAHL, SPORTDicus), LILACS, PEDro, Cochrane and EMBASE, from April 2020 to August 2020.

The search strategy was established following the PICO strategy for patients with history of neurological or musculoskeletal injury and non-clinical population submitted to $CONV_{NMES}$ and $WPHF_{NMES}$ on contraction fatigue, strength adaptations and perceived discomfort outcomes. Descriptors used in our search strategy, without restrictions on language and date of publication, were "neurological injuries", "musculoskeletal injuries", "healthy individuals", "neuromuscular electrical stimulation", "wide pulse high frequency", "muscle force", "contraction fatigue" and "perceived discomfort". The searches were adapted for each database to identify all relevant articles.

Searching other resources

We searched reference lists of the relevant studies, but no extra searches were done in gray literature or for studies non-published.

Data collection and analysis

Selection of studies

Two authors independently screened titles and abstracts retrieved by the search strategy for eligibility and assessed whether each fulfilled the inclusion criteria. If necessary, a more in-depth search through the full-text was conducted. Both authors approved the inclusion of the studies in the review without discrepancy regarding eligibility, however, a third author would have arbitrated in the case of discrepancy.

Data extraction and management

Two authors independently extracted the following information from the selected articles: participant characteristics (total number, age, gender, inclusion and exclusion criteria); description of the interventions (NMES characteristics); tools used to assess outcomes and results. We planned to contact authors of studies in cases of missing data.

Quality assessment

Study quality was assessed using the PEDro scale, which includes 11 items: 1) eligibility criteria (not used to calculate score); 2) random allocation; 3) concealed allocation; 4) baseline comparability; 5) blinded subjects; 6) blinded therapists; 7) blinded assessors; 8) adequate follow-up; 9) intention-to-treat analysis; 10) between-group statistical comparisons; 11) point estimate and variability. Each item was marked as "yes (1/0)" or "no (0/0)" and provided a 0 to 10 scale (35). Scores were either extracted from the PEDro database or, for studies not in PEDro, were rated by two reviewers independently.

Data analysis and synthesis

We planned to assess the statistical heterogeneity of data with an I^2 test as we expected low (I^2 value up to 25%) or moderate (I^2 value up to 50%) heterogeneity. However, we were unable to combine outcome measures, due to differences in how outcomes were collected and the inclusion of studies with different stimulation parameters and different outcome measures, so data are described qualitatively.

Data synthesis for this review combined data from RCTs and cross-over trials. Cross-over trials were included, without knowing whether the first intervention's effects, defined by each study's randomization, interfere with those of the second. Two studies subdivided the participants into two subgroups, responders and non-responders to $WPHF_{NMES}$ (7,9); however, the references were not duplicated due to the subdivision, due to the small sample sizes. Thus, these studies were analyzed considering the subgroups, but still as a single reference.

Quality of evidence

The overall quality of evidence was assessed according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). GRADE has

five domains: 1) Study design and risk of bias; 2) Inconsistency; 3) Indirectness; 4) Imprecision and 5) Other factors (e.g., reporting bias, publication bias). The quality of the evidence was classified as follows. High quality of evidence: consistent results in at least 75% of the clinical trials of good methodological quality, presenting consistent, direct, and precise data with no suspicious or known publication bias, and further research is unlikely to alter the estimate or the confidence in the results. Moderate quality of evidence: at least one domain is not met, and new research is likely to have a significant impact on the confidence in the effect estimate. Low-quality evidence: two of the domains are not met, and further research is likely to have a significant impact on the confidence in the effect estimate and is likely to alter the estimate. Very low-quality evidence: three domains are not met, the results will be highly uncertain (36).

RESULTS

Description of studies

Results of the search

The search retrieved 5407 records. After removing duplicate articles and following screening and eligibility procedures described by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses (34); and outlined in Appendix IV (*Figure 1*), eight articles were included. (6–10,37–39).

Included studies

All of the characteristics of the studies are presented in Appendix IV (*Table 1*).

Setting

All studies were multicenter trials, carried out in three different countries: Switzerland (6,8), France (7,9,10,39), and the United States (37,38) between 2014-2018.

Design of the studies

The included studies were short-term (i.e. single session) (6–10,39) or long-term (i.e. multi-session “training” studies) (37,38) designs.

Participants

Included studies evaluated a total of 171 participants, including 27 participants with multiple sclerosis (MS) (38) and 144 non-clinical participants (6–10,37,39), with a mean age ranging from 26 (39) to 73.5 (37).

Interventions

The summary of all parameters used in interventions is presented in Appendix IV (*Table 2*).

The included trials used $WPFH_{NMES}$ with the following parameters.

- Frequency: Seven trials used a 100Hz frequency (6–9,37–39), and one trial used 80Hz (10).
- Pulse Width: All studies used 1ms pulse width (6–10,37–39).

The included trials used $CONV_{NMES}$ with the following parameters.

- Frequency: Two trials used 50Hz of frequency (37,38), five trials used a 25Hz frequency (6–9,39), and one trial used 20Hz (10).
- Pulse Width: Six studies used 50µs pulse width (6–10,39) and two used 26µs (37,38).

For both $WPHF_{NMES}$ and $CONV_{NMES}$, the trials used the following parameters.

- Electrode size: Two studies used a ($50cm^2$) electrodes (6,8), three of them used a ($65cm^2$) and ($45cm^2$) (7,9,39), only one study used ($130cm^2$) electrodes, other trial used ($7cm^2$) or ($10cm^2$) (38), one used ($6cm^2$) (37) and another one with 1cm diameter (10).
- TON (stimulus duration) and TOFF (rest duration): one study performed 6 seconds of TON and TOFF (10), four trials performed 20 seconds of TON, and different durations of TOFF, 20 seconds (7,39), 40 seconds (8), and 90 seconds (9). Two trials realized 4-second TON and 12-second TOFF (37,38) and one study used 10 seconds of TON and 300 or 600 seconds of TOFF (6).
- The number of contractions: One trial performed one contraction (6), while two others performed 5 (9) and 40 (10), three of the studies did the same amount, 20 (7,8,39); one trial performed 38 (38) and the last one, 75 (37).

- Electrode placement: Only one study positioned the electrodes on the tibial nerve (10), while the other six placed them on the triceps surae muscle belly (6–9,37,39) and only one at dorsi and plantar flexor muscles (38).
- Stimulation intensity: One trial performed stimulation about 5% of MVC (9), four performed about 10% (6–8,39), and one about 20% (10). The other performed 10% of MVC for dorsiflexors and 20% of MVC for plantar flexors (38). And one study performed de maximum tolerated intensity (37).

Three studies had a third comparator group: voluntary exercise (VOL) (6,7,39). The results for studies with this comparator, in addition to the $WPHF_{NMES}$ and $CONV_{NMES}$, were: mean force and FTI were also similar in the three conditions (6,39); one study just showed the comparable relationship of metabolic demand for contractions evoked by WPHF with VOL contractions (7). Although these were not considered according to the inclusion criteria.

Outcomes

The studies reported the following outcomes:

- Contraction Fatigue: Six short-term studies (6–10,39) and one long-term study (38).
- Strength adaptations: Two long-term studies (37,38).
- Perceived Discomfort: One short-term study (8).

None of the included studies reported any adverse events.

Excluded studies

Trials were excluded at the full-text stage if they did not match the inclusion criteria or matched specific exclusion criteria (Figure 1). Reasons for exclusion were as follows: four studies did not compare the use of $CONV_{NMES}$ versus $WPHF_{NMES}$ (40–43) and one study did not assess de included outcomes. Clair-Auger and colleagues (2012) compared low (20 Hz) and high (100 Hz) frequencies, but with the same pulse width (1 ms) or non-constant frequencies (20-100-20 Hz) with different pulse widths (0.1 ms and 1 ms) (40). Gregory and colleagues (2007) combined eight different frequencies (from 10 to 100 Hz) with seven different pulse widths (from 0.1 to 0.7 ms) (41). Jadidi and colleagues (2009) used three stimulus durations (1 ms single square-wave pulse, 10 and

450 ms square wave pulse train) and two stimulus intensities adjusted to perceived intensity (42). Laborde and colleagues (2004) compared two different frequencies (20 Hz and 80 Hz) in individuals after anterior cruciate ligament surgery (43). Neyroud and colleagues (2016) analyzed the variation in force during a single contraction, which characterizes an analysis of extra force, not contraction fatigue (44).

Quality assessment

The methodological quality of the included studies is described in Appendix IV (*Table 3*). Two studies (37,38) were indexed in PEDro, and their scores were extracted from the database. The other studies (6–10,39) were rated by the reviewers. PEDro total scores ranged from 4 to 7 and had an average score of 5, on a scale from 0 to 10.

Effects of interventions

We could not pool the included studies data in meta-analysis due to heterogeneity between comparisons and outcomes reported. Therefore, we described the results of the studies in a descriptive form. According to GRADE, for contraction fatigue and strength adaptations outcomes, the overall quality of the evidence was the same, rated as very low quality evidence, downgraded by (a) risk of bias: for contraction fatigue, two studies did not performed random allocation and only one of the included studies reported a double-blind blinded procedure, for strength adaptations, the studies did not described the type of randomization and one study reported a blinded procedure of participants and the two studies reported a blinded procedure of investigators responsible for analyzing the data; (b) inconsistency, because the included studies presented substantial methodological differences and also showed different directions of results, with positive effects for one group or another, depending on the trial, so, the effects between studies were inconsistent; (c) indirectness, because the outcomes could be considered as surrogate outcomes for the most trials, and for contraction fatigue outcome, only one study did not present acute results; (d) imprecision, just because the comparisons are under optimal information size.

Primary outcomes

Short-term studies

Contraction fatigue during NMES

All six short-term studies (6–10,39) compared $CONV_{NMES}$ versus $WPHF_{NMES}$ for contraction fatigue which was assessed using three outcome measures.

Five short-term studies (6–10) assessed contraction fatigue by calculating the total force time integral (FTI; area under the force trace) over repeated contractions of a fatigue protocol in non-clinical participants. In two studies (6,10) FTI was not different between $CONV_{NMES}$ and $WPHF_{NMES}$. Another study (8) reported a lower FTI during $WPHF_{NMES}$ than $CONV_{NMES}$ of the triceps surae muscles, consistent with greater contraction fatigue using $WPHF_{NMES}$. In two additional studies participants were divided into "responders" and "non-responders" to $WPHF_{NMES}$. Responders were those in whom torque increased during a contraction, consistent with a contribution via reflex pathways. In non-responders torque remain flat, consistent with contractions produced by stimulation of motor axons alone. $WPHF_{NMES}$ produced a greater FTI than $CONV_{NMES}$ in responders, although FTI was not different between the two types of NMES in non-responders (9), or non-responders showed lower FTI for $WPHF_{NMES}$ (7).

Four short-term studies assessed contraction fatigue by calculating mean force over all contractions of a fatigue protocol in non-clinical populations (7,8,10,39). In two studies (10,39), mean force was not significantly different between NMES types. In one study that classified participants into responders and non-responders (7), mean force was greater during $WPHF_{NMES}$ than $CONV_{NMES}$ in responders with no difference between protocols for non-responders, similar to the result in the same study for FTI and consistent with the idea that $WPHF_{NMES}$ reduces contraction fatigue but only in responders.

Overall, when assessed across all participants most studies (6,10,39) showed no differences in contraction fatigue between $CONV_{NMES}$ and $WPHF_{NMES}$, although one showed greater fatigue during $WPHF_{NMES}$ (8). Of note, $WPHF_{NMES}$ produced less fatigue than $CONV_{NMES}$ in responders, while in non-responders there were no differences in fatigue between protocols (9) or $WPHF_{NMES}$ produced greater fatigue (7).

MVC

In two short-term studies (8,10) with non-clinical participants torque produced during plantarflexion MVCs was assessed before and after a single NMES session and the amount that MVCs decreased was not different after $CONV_{NMES}$ or $WPHF_{NMES}$.

Long-term studies

Contraction fatigue during NMES

One long-term (six week) study (38) compared contraction fatigue between $CONV_{NMES}$ and $WPHF_{NMES}$ in people with MS. Fatigue was self-reported using the Modified Fatigue Impact Scale (MFIS) questionnaire and, although scores declined over time with both protocols, scores were not different between $CONV_{NMES}$ and $WPHF_{NMES}$.

Strength adaptations

Two long-term studies (37,38) compared strength adaptations between $CONV_{NMES}$ and $WPHF_{NMES}$, by assessing how much force produced during MVCs increased after repeated NMES sessions. The quality of evidence for these studies was very low and was downgraded by the risk of bias, inconsistency, indirectness, and imprecision. Mani and colleagues (37) assessed MVCs around multiple joints in non-injured older adults after six weeks of $CONV_{NMES}$ or $WPHF_{NMES}$ over the ankle plantar flexors. Although there was a significant increase in plantar flexor MVC, the increase was not different between $CONV_{NMES}$ and $WPHF_{NMES}$. Almuklass and colleagues (38) evaluated MVCs before and after 6-weeks of $WPHF_{NMES}$ or $CONV_{NMES}$ over the ankle dorsiflexors and plantar flexors in participants with MS (38) and they also found a significant increase in strength of the stimulated muscles post-NMES that was not different between NMES protocols.

Secondary outcome

Perceived discomfort

One short-term study (8) with a non-clinical population assessed perceived discomfort using a visual analog scale score (VAS) and found no difference between $CONV_{NMES}$ and $WPHF_{NMES}$.

DISCUSSION

This is the first systematic review to summarize research comparing $CONV_{NMES}$ and $WPHF_{NMES}$ on outcomes relevant for NMES-based programs, specifically, contraction fatigue, strength adaptations and perceived discomfort. The findings

contribute to an evidence-base for physical therapy practice related to NMES and have broader implications for designing and developing rehabilitative technologies. In general, we found no differences between $CONV_{NMES}$ and $WPHF_{NMES}$ for fatigue and discomfort in both short- and long-term studies in non-clinical populations and for strength adaptations and fatigue in patients with MS in a long-term design, thus we propose that physical therapists would achieve similar outcomes using $CONV_{NMES}$ or $WPHF_{NMES}$. $WPHF_{NMES}$ did reduce contraction fatigability, however, in a subset of non-clinical participants, the "responders", in whom $WPHF_{NMES}$ generates contractions in part through central or reflex pathways. Nonetheless, according to the GRADE recommendations (36), the quality of evidence was very low for contraction fatigue and strength adaptations, thus new findings may alter the conclusions presented in this review and the present findings should be interpreted cautiously.

Contraction fatigue was assessed using a range of outcomes measures in six short-term and one long-term study. Contraction fatigue, assessed as the total mean force during a single NMES session, was not different between $CONV_{NMES}$ and $WPHF_{NMES}$ in four short-term studies with non-clinical participants (7,8,10,39). Similarly, Martin and colleagues (10) found no difference between $CONV_{NMES}$ and $WPHF_{NMES}$ when fatigue was assessed as the total FTI in non-clinical participants and Almuklass and colleagues (38) reported no difference in fatigue between protocols when assessed over a long-term study using a MFIS questionnaire. Although fatigue was not different between protocols in the study of Martin et al. (10), the mechanisms responsible for fatigue were different, as during $WPHF_{NMES}$ a decline in the number of active motor units was the main mechanism and intramuscular processes predominated during $CONV_{NMES}$ (10). This progressive decline in number of active motor units during $WPHF_{NMES}$ is consistent the progressive decrease in the excitability of motor axons under the stimulating electrodes that develops when using high NMES frequencies (45). Indeed, Neyroud and colleagues found a lower FTI during $WPHF_{NMES}$ than $CONV_{NMES}$, suggesting more contraction fatigue during $WPHF_{NMES}$, which the authors attributed to the higher frequencies during $WPHF_{NMES}$ and resulting higher metabolic cost (8). Thus, when using $WPHF_{NMES}$ to reduce contraction fatigue with there is a trade-off between the high NMES frequencies (>80 Hz) required to maximize central recruitment (46) and minimize contraction fatigue, and the low NMES frequencies (~20 Hz) that minimize fatigue that arises from decreased motor axon excitability (45) and increased metabolic demand (10). It may be that the optimal parameters for delivering NMES to reduce contraction fatigue are yet to be

identified. Interestingly, in the study of Neyroud (8) although the decline in FTI during the stimulation depended on NMES protocol, the decline in MVC torque after the NMES sessions did not, which may be due to the small amplitude of the NMES-evoked contractions (10% MVC) which would have fatigued only a small portion of motor units recruited during the "test" MVCs (8). Accordingly, contraction fatigue may be underestimated when quantified by MVC force loss and the FTI or mean force recorded during NMES sessions is a more sensitive index of contraction fatigue during NMES.

In two short-term studies (7,9) fatigue was evaluated after dividing participants into those who "responded" during $WPHF_{NMES}$ and those who did not. Responders were participants in whom contractions developed in part via central pathways, producing "extra force" thought to be beneficial for reducing contraction fatigue by preferentially recruiting fatigue-resistant motor units (7,9,47). Both studies (7,9) that made this distinction found that $WPHF_{NMES}$ reduced contraction fatigue compared to $CONV_{NMES}$ only in responders, regardless of how fatigue was quantified. In non-responders, fatigue during $WPHF_{NMES}$ was either not different than during $CONV_{NMES}$ when assessed as the mean force (7) or the FTI (9) and in one study fatigue was greater during $WPHF_{NMES}$ when assessed as the FTI (7). Therefore, it appears responders represent a subset of the non-clinical population in whom $WPHF_{NMES}$ reduces contraction fatigue by recruiting fatigue-resistant motor units via central pathways. The different fatigue assessment methods, different NMES session durations and rest times between protocols (Table 1 for further details) may account for much of the variability in the results for this outcome measure.

Strength adaptations were assessed after six weeks of either $CONV_{NMES}$ or $WPHF_{NMES}$ in two long-term studies (37,38). In these studies, NMES was applied three times a week over the ankle dorsiflexor and plantar flexor muscles in participants with MS (38) or over the plantar flexors in non-injured older adults (37). In both studies there were no differences between $CONV_{NMES}$ or $WPHF_{NMES}$ for gait speed, walking endurance or strength adaptations post-NMES. Strength adaptations were assessed by comparing MVCs performed before and after the six weeks of both NMES-types (37,38). Further long-term studies are needed to establish, and optimize, strength adaptations induced using different NMES protocols that incorporate assessment tools with greater sensitivity than MVC.

Perceived discomfort was assessed in one short-term study (8) in which VAS scores were not different between $CONV_{NMES}$ and $WPHF_{NMES}$. $CONV_{NMES}$, however,

required more current than $WPHF_{NMES}$ to obtain the same initial contraction amplitude, thus one might have expected $CONV_{NMES}$ to induce more discomfort. The lack of a difference in discomfort between protocols may be associated with the low contraction amplitude (10% MVC) (48) and lack of discriminative capability of the VAS measure (32). This low initial contraction amplitude was chosen to minimize antidromic block to allow maximal central recruitment (26,46). Further studies are needed to compare the effects of $WPHF_{NMES}$ versus $CONV_{NMES}$ on perceived discomfort.

Study limitations

We conducted a comprehensive literature search across multiple databases, however, this search yielded studies predominantly in English-language journals and may not have captured studies in non-English journals and regional databases. Also, the variability between evaluations and clinical heterogeneity between studies precluded us from performing meta-analyses, limiting this review to descriptive rather than quantitative comparisons. Multiple outcome measures were also a limitation as they made even descriptive comparisons between studies difficult.

The quality of the included studies was very low and ranged from 4 to 7 points on the PEDro scale. As none of the selected studies utilized a triple-blinding methodology (subject, therapist, and assessor) and non-blinded studies often have larger effect sizes, smaller p-values, and higher frequency of significant results (49), rigorous studies with blinded evaluations should be conducted in this field to increase methodological quality. The lack of quality studies in this area markedly limited the ability to differentiate between $CONV_{NMES}$ and $WPHF_{NMES}$ regarding contraction fatigue, strength adaptations and discomfort.

Conclusions

The results of both short- and long-term studies suggest that in general, across a group of non-clinical participants, there is no difference between $CONV_{NMES}$ and $WPHF_{NMES}$ for contraction fatigue, strength adaptations or perceived discomfort. There is evidence, however, that a single session $WPHF_{NMES}$ may reduce contraction fatigue, compared to $CONV_{NMES,}$ for a segment of the non-clinical population (the “responders”) but exacerbate contraction fatigue for others (the “non-responders”). In the long-term, no differences were identified between $CONV_{NMES}$ and $WPHF_{NMES}$ for muscle strength adaptations and fatigue in clinical and non-clinical populations. The methodological

quality, however, was very low and future well-designed RCTs should be conducted to establish the optimal NMES parameters to reduce contraction fatigue, increase muscle strength, and reduce perceived discomfort in clinical and non-clinical participants.

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2020 Sep;

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APPENDICES

Appendix I – Submission proof

Brazilian Journal of Physical Therapy

CONTRACTION FATIGUE, STRENGTH ADAPTATIONS, AND DISCOMFORT DURING CONVENTIONAL VERSUS WIDE-PULSE, HIGH-FREQUENCY, NEUROMUSCULAR ELECTRICAL STIMULATION: A SYSTEMATIC REVIEW

--Manuscript Draft--

Manuscript Number:	BJPT-D-21-00078
Article Type:	Review Article
Keywords:	Electric Stimulation, Fatigue, Muscle Strength, Torque, Perception Discomfort.
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Abstract:	Background: Neuromuscular electrical stimulation (NMES) can be delivered in a conventional form (CONVNMES) and using relatively wide-pulses and high-frequencies (WPHFNMES). WPHFNMES was developed to reduce contraction fatigue and improve outcomes of NMES-based programs, however, there are no systematic reviews to assess its' efficacy and help guide the selection of stimulus parameters during NMES. Objectives: Compare the effects of CONVNMES versus WPHFNMES on contraction fatigue, strength adaptations, and perceived discomfort in clinical and non-clinical populations. Methods: Data sources included Pubmed, Embase, MEDLINE, Web of Science, SciELO, EBSCO, LILACS, PEDro, Cochrane Library, and EMBASE. Two independent reviewers selected studies and extracted information. Studies were selected if they compared CONVNMES with WPHFNMES with contraction fatigue, strength adaptations or perceived discomfort as outcomes. Study quality was assessed using the PEDro scale, and overall quality was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation criteria. Results: Eight studies (n=171 participants) were included. In short- and long-term studies, when averaged across all non-clinical participants, there was either no difference between CONVNMES and WPHFNMES for all outcomes or WPHFNMES produced more fatigue. In a subset of non-clinical participants ("responders"), however, WPHFNMES reduced contraction fatigue during a single session. Long-term studies found no differences between protocols for fatigue or strength adaptations. Methodological quality of the selected studies was very low. Conclusion: WPHFNMES reduces contraction fatigue only in the short-term and in non-clinical responder participants and may exacerbate fatigue in non-responders. New clinical studies with good methodological quality may affect the results presented in this review.

Appendix II - Author Guidelines for submission

INTRODUCTION

Types of article

The **Brazilian Journal of Physical Therapy (BJPT)** publishes original research articles, reviews, and brief communications on topics related to physical therapy and rehabilitation, including clinical, basic or applied studies on the assessment, prevention and treatment of movement disorders. Our Editorial Board is committed to disseminate high-quality research in the field of physical therapy. The BJPT follows the principle of publication ethics included in the code of conduct of the Committee on Publication Ethics (COPE).The BJPT accepts the submission of manuscripts with up to 3,500 words (excluding title page, abstract, references, tables, figures and legends). Information contained in appendices will be included in the total number of words allowed. A total of five (5) combined tables and figures is allowed.

The following types of study can be considered for publication, if directly related to the journals scope:

a) Intervention studies (clinical trials): studies that investigate the effect(s) of one or more interventions on outcomes directly related to the BJPTs scope. The World Health Organization defines a clinical trial as any research study that prospectively allocates human participants or groups of humans to one or more health-related interventions to evaluate the effect(s) on health outcome(s). Clinical trials include single-case experimental studies, case series, nonrandomized controlled trials, and randomized controlled trials. Randomized controlled trials (RCTs) must follow the CONSORT (Consolidated Standards of Reporting Trials) recommendations, which are available at: http://www.consort-statement.org/consort-statement/overview0/. The CONSORT checklist and Statement Flow Diagram, available at http://www.consort-statement.org/consort-statement/flow-diagram, must be completed and submitted with the manuscript. Clinical trials must provide registration that satisfies the requirements of the International Committee of Medical Journal Editors (ICMJE), e.g. http://clinicaltrials.gov/ and/or http://www.anzctr.org.au. The complete list of all clinical trial registries can be found at: http://www.who.int/ictrp/network/primary/en/index.html. We suggest that all authors register clinical trials prospectively via the website http://www.clinicaltrials.gov.

Note: We do not accept single case studies and series of cases (i.e. clinical trials without a comparison group).

b) Observational studies: studies that investigate the relationship(s) between variables of interest related to the BJPTs scope. Observational studies include cross-sectional studies, cohort studies, and case-control studies. All observational studies must be reported following the recommendation from the STROBE statement (http://strobe-statement.org/index.php?id=strobe-home).

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topic, including opinions, attitudes, motivations, and behavioral patterns without quantification. Qualitative studies include documentary and ethnographic analysis.

d) Systematic reviews: studies that analyze and/or synthesize the literature on a topic related to the scope of the BJPT. Systematic reviews that include meta-analysis will have priority over other systematic reviews. Those that have an insufficient number of articles or articles with low quality in the Methods section and do not include an assertive and valid conclusion about the topic will not be considered for peer-review analysis. The authors must follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist to format their systematic reviews. The checklist is available at http://www.prisma-statement.org/PRISMAStatement/Default.aspx and must be filled in and submitted with the manuscript. Potential authors are encouraged to read the following tutorial, which contains the minimum requirements for publication of systematic reviews in the BJPT: Mancini MC, Cardoso JR, Sampaio RF, Costa LCM, Cabral CMN, Costa LOP. Tutorial for writing systematic reviews for the Brazilian Journal of Physical Therapy (BJPT). Braz J Phys Ther. 2014 Nov-Dec; 18(6):471-480.

e) Studies on the translation and cross-cultural adaptation of questionnaires or assessment tools: studies that aim to translate and/or cross-culturally adapt foreign questionnaires to a language other than that of the original version of existing assessment instruments. The authors must use the checklist (Appendix) to format this type of paper and adhere to the other recommendations of the BJPT. The answers to the checklist must be submitted with the manuscript. At the time of submission, the authors must also include written permission from the authors of the original instrument that was translated and/or cross-culturally adapted.

f) Methodological studies: studies centered on the development and/or evaluation of clinimetric properties and characteristics of assessment instruments. The authors are encouraged to use the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) to format methodological papers, in addition to following BJPT instructions. Important: Studies that report electromyographic results must follow the Standards for Reporting EMG Data recommended by ISEK (International Society of Electrophysiology and Kinesiology), available at http://www.isek.org/wp-content/uploads/2015/05/Standards-for-Reporting-EMG-Data.pdf.

g) Clinical trial protocols: The BJPT welcomes the publication of clinical trial protocols. We only accept trial protocols that are substantially funded, have ethics approval, have been prospectively registered and of very high quality. We expect that clinical trial protocols must be novel and with a large sample size. Finally, authors have to provide that the clinical trial is on its first stages of recruitment. Authors should use the SPIRIT statement while formatting the manuscript (http://www.spirit-statement.org).

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i) Masterclass articles: This type of article presents the state of art of any topic that is important to the field of physical therapy. All masterclass articles are invited manuscripts and the authors must be recognized experts in the field. However, authors can send e-

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BEFORE YOU BEGIN

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If the work involves the use of human subjects, the author should ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript should be in line with the Recommendations for the Conduct, Reporting,

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Authorship

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted

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2. 1. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. *Heliyon*. 2018;19:e00205. https://doi.org/10.1016/j.heliyon.2018.e00205.

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3. Strunk W Jr, White EB. *The Elements of Style.* 4th ed. New York, NY: Longman; 2000.

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4. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, eds. *Introduction to the Electronic Age.* New York, NY: E-Publishing Inc; 2009:281–304.

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5. Cancer Research UK. Cancer statistics reports for the UK. http://www.cancerresearchuk.org/ aboutcancer/statistics/cancerstatsreport/; 2003 Accessed 13 March 2003.

Reference to a dataset:
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Appendix III - Registration of the systematic review protocol

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Appendix IV - Manuscript submitted

CONTRACTION FATIGUE, STRENGTH ADAPTATIONS, AND DISCOMFORT DURING CONVENTIONAL VERSUS WIDE-PULSE, HIGH-FREQUENCY, NEUROMUSCULAR ELECTRICAL STIMULATION: A SYSTEMATIC REVIEW

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Acknowledgments: This work was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brasil (CAPES Finance Code 001; the PVEX - Programa de professor visitante no exterior - 88881.172234/2018-01); Universidade de Brasília (DPI Process number: 03/2020); and Conselho Nacional de Desenvolvimento Científico e Tecnológico (Research Scholarship in Physical Therapy - Process numbers: 312136/2018-8).

Declarations of interest: None.

Record: This review was registered in the prospective international registry of systematic reviews/PROSPERO (Registration Number: CRD42020153907, accessed at https://www.crd.york.ac.uk/PROSPERO/).

ABBREVIATIONS:

CNS: Central nervous system

CONV: Conventional

CP: Cerebral palsy

FTI: Force time integral

MFIS: Modified fatigue impact scale

MS: Multiple sclerosis

MVC: Maximal voluntary contraction

NMES: Neuromuscular electrical stimulation

RCT: Randomized controlled trial

VAS: Visual analog scale

VOL: Voluntary exercise

WPHF: Wide-pulse high-frequency

ABSTRACT

Background: Neuromuscular electrical stimulation (NMES) can be delivered in a conventional form ($CONV_{NMES}$) and using relatively wide-pulses and high-frequencies ($WPHF_{NMES}$). $WPHF_{NMES}$ was developed to reduce contraction fatigue and improve outcomes of NMES-based programs, however, there are no systematic reviews to assess its' efficacy and help guide the selection of stimulus parameters during NMES.
Objectives: Compare the effects of $CONV_{NMES}$ versus $WPHF_{NMES}$ on contraction fatigue, strength adaptations, and perceived discomfort in clinical and non-clinical populations.
Methods: Data sources included Pubmed, Embase, MEDLINE, Web of Science, SciELO, EBSCO, LILACS, PEDro, Cochrane Library, and EMBASE. Two independent reviewers selected studies and extracted information. Studies were selected if they compared $CONV_{NMES}$ with $WPHF_{NMES}$ with contraction fatigue, strength adaptations or perceived discomfort as outcomes. Study quality was assessed using the PEDro scale, and overall quality was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation criteria.
Results: Eight studies (n=171 participants) were included. In short- and long-term studies, when averaged across all non-clinical participants, there was either no difference between $CONV_{NMES}$ and $WPHF_{NMES}$ for all outcomes or $WPHF_{NMES}$ produced more fatigue. In a subset of non-clinical participants ("responders"), however, $WPHF_{NMES}$ reduced contraction fatigue during a single session. Long-term studies found no differences between protocols for fatigue or strength adaptations. Methodological quality of the selected studies was very low.
Conclusion: $WPHF_{NMES}$ reduces contraction fatigue only in the short-term and in non-clinical responder participants and may exacerbate fatigue in non-responders. New clinical studies with good methodological quality may affect the results presented in this review.

Key-words: Electric Stimulation, Fatigue, Muscle Strength, Torque, Perception Discomfort.

PROSPERO registration: ----------.

INTRODUCTION

Neuromuscular electrical stimulation (NMES) is used to generate contractions to restore function and improve muscle strength and endurance (1–4). During NMES, pulses of electrical current are delivered through electrodes on the skin over a muscle belly or a nerve trunk. NMES activates motor and/or sensory axons, generating contractions through peripheral and/or central pathways, respectively (5). Conventional NMES ($CONV_{NMES}$) involves relatively brief pulses of current (~0.1-0.5ms) delivered at low frequencies (~20-50Hz) (6–10), typically through electrodes over a muscle belly, and this produces contractions by stimulating motor axons, thus through "peripheral pathways" (11–20). Generating contractions through peripheral pathways recruits motor units in an unphysiological, random, order with respect to type and at unphysiologically-high rates (21). Accordingly, $CONV_{NMES}$ results in significantly more contraction fatigue, defined as a decline in torque over time, than voluntary exercise (10,22,23). NMES can also be delivered using longer duration current pulses (i.e. wide pulse widths) and higher frequencies ($WPHF_{NMES}$: 1ms of pulse widths, frequency ~100Hz). $WPHF_{NMES}$ was developed to reduce contraction fatigue and improve outcomes of NMES-based programs by generating contractions through "central pathways", thus in a more physiologically-relevant manner than $CONV_{NMES}$. Whether contraction fatigue is reduced or NMES outcomes are improved when using $WPHF_{NMES}$, however, is presently unclear.

$WPHF_{NMES}$ generates contractions through central pathways because a larger sensory input is sent to the central nervous system (CNS) during $WPHF_{NMES}$ than $CONV_{NMES}$. Wider pulse widths during $WPHF_{NMES}$ activate more sensory axons relative to motor axons because sensory axons have a longer strength-duration time constant than motor axons, thus longer pulses are required to bring sensory axons to threshold than motor axons (9,24–26). Also, higher pulse frequencies during $WPHF_{NMES}$ send more impulses to the CNS per unit time than during $CONV_{NMES}$, further increasing sensory input to the CNS. In some participants, described as "responders", the combination of wider pulses and higher frequencies produce contractions that gradually increase over time. The increase in force has been called "extra force" (27) and has been attributed to the recruitment of spinal motor neurons via central pathways (26–28). Extra force does not develop when the nerve is blocked with anesthetic between the stimulation site and the muscle (27) and thus is related to central mechanisms such as post-tetanic potentiation of neurotransmitter release at the Ia synapse, summation of subthreshold excitatory postsynaptic potentials and/or activation of persistent inward currents in motor neurons

(27,29,30). Regardless, generating contractions via central pathways recruits motor units in their physiological order, with fatigue-resistant units first, and some that discharge asynchronously from one and other at physiologically low rates (21,31). While these ideas about motor unit recruitment during NMES provided the rationale for developing $WPHF_{NMES}$ (9,25,26), the short-term effects on contraction fatigue, and long-term effects on strength adaptations, of $WPHF_{NMES}$ remain to be confirmed. Further, perceived discomfort limits NMES sessions by restricting high muscle force levels or increasing contraction fatigue (32,33).

To date, there is no systematic review that compares $CONV_{NMES}$ and $WPHF_{NMES}$ to guide clinical practice regarding NMES. This review, therefore, was developed to summarize the research comparing $CONV_{NMES}$ and $WPHF_{NMES}$, following the Cochrane collaboration (34) recommendations, to assess the effects of these interventions on outcomes important for NMES-based programs. Specifically, we compared the effects of $CONV_{NMES}$ and $WPHF_{NMES}$ on contraction fatigue, strength adaptations and perceived discomfort in individuals with neurological or musculoskeletal injury and in non-clinical participants. The findings will help health care practitioners better understand the effects of NMES on the neuromuscular system and will contribute to an evidence-base upon which to develop NMES strategies.

MATERIAL AND METHODS

The protocol of this systematic review has been registered on the International Prospective Register of Systematic Reviews - PROSPERO (registration number ----------).

Criteria for considering studies for this review

Studies design and Participants

Only published randomized controlled trials (RCTs) and cross-over trials involving participants with neurological and/or musculoskeletal disorders or non-clinical participants (≥ 18 years of age) were included.

Types of interventions

Studies were included that compared one or more of our 3 outcome measures between $CONV_{NMES}$ and $WPHF_{NMES}$. Stimulus waveforms were either biphasic or monophasic and applied over a muscle belly or nerve trunk. As the objective was to

compare between two types of NMES, we did not assess passive comparators such as placebo or sham therapy or an active comparator, such as another intervention.

Outcomes

A primary outcome was contraction fatigue, quantified either as a decline in torque over repeated NMES-evoked contractions during a single session, a decrease in the ability to generate torque during maximal voluntary contractions (MVCs) performed before and after a single NMES session or through self-reports. Strength adaptations, defined as a change in torque produced during MVCs performed before and after an NMES training program, was also a primary outcome. The secondary outcome was perceived discomfort as assessed using the visual analogue scale (VAS).

Search strategy

We searched nine electronic databases: PUBMED, MEDLINE, Web of Science (all databases), SciELO, EBSCO (Academic Search Premier, CINAHL, SPORTDicus), LILACS, PEDro, Cochrane, and EMBASE, from April 2020 to August 2020. Descriptors used in our search strategy, without restrictions on language and date of publication, were "neurological injuries", "musculoskeletal injuries", "healthy individuals", "neuromuscular electrical stimulation", "wide pulse high frequency", "muscle force", "contraction fatigue" and "perceived discomfort". The searches were adapted for each database to identify all relevant articles.

Selection of studies

Two authors independently screened titles and abstracts retrieved by the search strategy for eligibility and assessed whether each fulfilled the inclusion criteria. If necessary, a more in-depth search through the full-text was conducted. Both authors approved the inclusion of the studies in the review without discrepancy regarding eligibility, however, a third author would have arbitrated in the case of discrepancy.

Data extraction

Two authors independently extracted the following information from the selected articles: participant characteristics (total number, age, gender, inclusion and exclusion criteria); description of the interventions (NMES characteristics); tools used to assess outcomes and results. We planned to contact authors of studies in cases of missing data.

Quality assessment

Study quality was assessed using the PEDro scale, which includes 11 items: 1) eligibility criteria (not used to calculate score); 2) random allocation; 3) concealed allocation; 4) baseline comparability; 5) blinded subjects; 6) blinded therapists; 7) blinded assessors; 8) adequate follow-up; 9) intention-to-treat analysis; 10) between-group statistical comparisons; 11) point estimate and variability. Each item was marked as "yes (1/0)" or "no (0/0)" and provided a 0 to 10 scale (35). Scores were either extracted from the PEDro database or, for studies not in PEDro, were rated by two reviewers independently.

Data analysis and synthesis

We planned to assess the statistical heterogeneity of data with an I^2 test as we expected low (I^2 value up to 25%) or moderate (I^2 value up to 50%) heterogeneity. However, we were unable to combine outcome measures, due to differences in how outcomes were collected and the inclusion of studies with different stimulation parameters and different outcome measures, so data are described qualitatively.

Data synthesis for this review combined data from RCTs and cross-over trials. Cross-over trials were included, without knowing whether the first intervention's effects, defined by each study's randomization, interfere with those of the second. Two studies subdivided the participants into two subgroups, responders and non-responders to $WPHF_{NMES}$ (7,9); however, the references were not duplicated due to the subdivision, due to the small sample sizes. Thus, these studies were analyzed considering the subgroups, but still as a single reference.

Quality of evidence

The overall quality of evidence was assessed according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). GRADE has five domains: 1) Study design and risk of bias; 2) Inconsistency; 3) Indirectness; 4) Imprecision and 5) Other factors (e.g., reporting bias, publication bias). The quality of the evidence was classified as follows. High quality of evidence: consistent results in at least 75% of the clinical trials of good methodological quality, presenting consistent, direct, and precise data with no suspicious or known publication bias, and further research is unlikely to alter the estimate or the confidence in the results. Moderate quality of

evidence: at least one domain is not met, and new research is likely to have a significant impact on the confidence in the effect estimate. Low-quality evidence: two of the domains are not met, and further research is likely to have a significant impact on the confidence in the effect estimate and is likely to alter the estimate. Very low-quality evidence: three domains are not met, the results will be highly uncertain (36).

RESULTS

The search retrieved 5407 records. After removing duplicate articles and following screening and eligibility procedures described by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses (34); and outlined in Figure 1, eight articles were included. (6–10,37–39).

FIGURE 1

Characteristics of included studies

Included studies evaluated a total of 171 participants in short-term (i.e. single session) (6–10,39) or long-term (i.e. multi-session "training" studies) (37,38) designs, including 27 participants with multiple sclerosis (MS) (38) and 144 non-clinical participants (6–10,37,39). Studies were carried out in Switzerland (6,8), France (7,9,10,39), and the United States (37,38) between 2014-2018. Key study characteristics are presented in Table 1. All short-term studies (6–10,39) and one long-term study (38) assessed contraction fatigue. Both long-term studies (37,38) assessed strength adaptations. Perceived discomfort was evaluated in one study (8). A summary of key NMES parameters studies is presented in Table 2. Three studies (6,7,39) included another comparator intervention, in addition to $CONV_{NMES}$ and $WPHF_{NMES}$: voluntary exercise (VOL) (6,7,39), although these were not considered according to the inclusion criteria.

TABLE 1

TABLE 2

Quality assessment

The methodological quality of the included studies is described in Table 3. Two studies (37,38) were indexed in PEDro, and their scores were extracted from the database.

The other studies (6–10,39) were rated by the reviewers. PEDro total scores ranged from 4 to 7 and had an average score of 5, on a scale from 0 to 10.

TABLE 3

Effects of interventions

We could not pool data from the included studies in meta-analysis due to heterogeneity between comparisons and outcomes reported. Therefore, results are described descriptively.

Contraction fatigue

There was very low-quality of evidence for contraction fatigue which was downgraded by the risk of bias, inconsistency, indirectness, and imprecision.

Short-term studies

Contraction fatigue during NMES

All six short-term studies (6–10,39) compared $CONV_{NMES}$ versus $WPHF_{NMES}$ for contraction fatigue which was assessed using three outcome measures.

Five short-term studies (6–10) assessed contraction fatigue by calculating the total force time integral (FTI; area under the force trace) over repeated contractions of a fatigue protocol in non-clinical participants. In two studies (6,10) FTI was not different between $CONV_{NMES}$ and $WPHF_{NMES}$. Another study (8) reported a lower FTI during $WPHF_{NMES}$ than $CONV_{NMES}$ of the triceps surae muscles, consistent with greater contraction fatigue using $WPHF_{NMES}$. In two additional studies participants were divided into "responders" and "non-responders" to $WPHF_{NMES}$. Responders were those in whom torque increased during a contraction, consistent with a contribution via reflex pathways. In non-responders torque remain flat, consistent with contractions produced by stimulation of motor axons alone. $WPHF_{NMES}$ produced a greater FTI than $CONV_{NMES}$ in responders, although FTI was not different between the two types of NMES in non-responders (9), or non-responders showed lower FTI for $WPHF_{NMES}$ (7).

Four short-term studies assessed contraction fatigue by calculating mean force over all contractions of a fatigue protocol in non-clinical populations (7,8,10,39). In two studies (10,39), mean force was not significantly different between NMES types. In one

study that classified participants into responders and non-responders (7), mean force was greater during $WPHF_{NMES}$ than $CONV_{NMES}$ in responders with no difference between protocols for non-responders, similar to the result in the same study for FTI and consistent with the idea that $WPHF_{NMES}$ reduces contraction fatigue but only in responders.

Overall, when assessed across all participants most studies (6,10,39) showed no differences in contraction fatigue between $CONV_{NMES}$ and $WPHF_{NMES}$, although one showed greater fatigue during $WPHF_{NMES}$ (8). Of note, $WPHF_{NMES}$ produced less fatigue than $CONV_{NMES}$ in responders, while in non-responders there were no differences in fatigue between protocols (9) or $WPHF_{NMES}$ produced greater fatigue (7).

MVC

In two short-term studies (8,10) with non-clinical participants torque produced during plantarflexion MVCs was assessed before and after a single NMES session and the amount that MVCs decreased was not different after $CONV_{NMES}$ or $WPHF_{NMES}$.

Long-term studies

Contraction fatigue during NMES

One long-term (six week) study (38) compared contraction fatigue between $CONV_{NMES}$ and $WPHF_{NMES}$ in people with MS. Fatigue was self-reported using the Modified Fatigue Impact Scale (MFIS) questionnaire and, although scores declined over time with both protocols, scores were not different between $CONV_{NMES}$ and $WPHF_{NMES}$.

Strength adaptations

Two long-term studies (37,38) compared strength adaptations between $CONV_{NMES}$ and $WPHF_{NMES}$, by assessing how much force produced during MVCs increased after repeated NMES sessions. The quality of evidence for these studies was very low and was downgraded by the risk of bias, inconsistency, indirectness, and imprecision. Mani and colleagues (37) assessed MVCs around multiple joints in non-injured older adults after six weeks of $CONV_{NMES}$ or $WPHF_{NMES}$ over the ankle plantar flexors. Although there was a significant increase in plantar flexor MVC, the increase was not different between $CONV_{NMES}$ and $WPHF_{NMES}$. Almuklass and colleagues (38) evaluated MVCs before and after 6-weeks of $WPHF_{NMES}$ or $CONV_{NMES}$ over the ankle dorsiflexors and plantar flexors in participants with MS (38) and they also found a

significant increase in strength of the stimulated muscles post-NMES that was not different between NMES protocols.

Perceived discomfort

One short-term study (8) with a non-clinical population assessed perceived discomfort using a visual analog scale score (VAS) and found no difference between $CONV_{NMES}$ and $WPHF_{NMES}$.

DISCUSSION

This is the first systematic review to summarize research comparing $CONV_{NMES}$ and $WPHF_{NMES}$ on outcomes relevant for NMES-based programs, specifically, contraction fatigue, strength adaptations and perceived discomfort. The findings contribute to an evidence-base for physical therapy practice related to NMES and have broader implications for designing and developing rehabilitative technologies. In general, we found no differences between $CONV_{NMES}$ and $WPHF_{NMES}$ for fatigue and discomfort in both short- and long-term studies in non-clinical populations and for strength adaptations and fatigue in patients with MS in a long-term design, thus we propose that physical therapists would achieve similar outcomes using $CONV_{NMES}$ or $WPHF_{NMES}$. $WPHF_{NMES}$ did reduce contraction fatigability, however, in a subset of non-clinical participants, the "responders", in whom $WPHF_{NMES}$ generates contractions in part through central or reflex pathways. Nonetheless, according to the GRADE recommendations (36), the quality of evidence was very low for contraction fatigue and strength adaptations, thus new findings may alter the conclusions presented in this review and the present findings should be interpreted cautiously.

Contraction fatigue was assessed using a range of outcomes measures in six short-term and one long-term study. Contraction fatigue, assessed as the total mean force during a single NMES session, was not different between $CONV_{NMES}$ and $WPHF_{NMES}$ in four short-term studies with non-clinical participants (7,8,10,39). Similarly, Martin and colleagues (10) found no difference between $CONV_{NMES}$ and $WPHF_{NMES}$ when fatigue was assessed as the total FTI in non-clinical participants and Almuklass and colleagues (38) reported no difference in fatigue between protocols when assessed over a long-term study using a MFIS questionnaire. Although fatigue was not different between protocols in the study of Martin et al. (10), the mechanisms responsible for fatigue were different, as during $WPHF_{NMES}$ a decline in the number of active motor units was the main

mechanism and intramuscular processes predominated during $CONV_{NMES}$ (10). This progressive decline in number of active motor units during $WPHF_{NMES}$ is consistent the progressive decrease in the excitability of motor axons under the stimulating electrodes that develops when using high NMES frequencies (40). Indeed, Neyroud and colleagues found a lower FTI during $WPHF_{NMES}$ than $CONV_{NMES}$, suggesting more contraction fatigue during $WPHF_{NMES}$, which the authors attributed to the higher frequencies during $WPHF_{NMES}$ and resulting higher metabolic cost (8). Thus, when using $WPHF_{NMES}$ to reduce contraction fatigue with there is a trade-off between the high NMES frequencies (>80 Hz) required to maximize central recruitment (41) and minimize contraction fatigue, and the low NMES frequencies (~20 Hz) that minimize fatigue that arises from decreased motor axon excitability (40) and increased metabolic demand (10). It may be that the optimal parameters for delivering NMES to reduce contraction fatigue are yet to be identified. Interestingly, in the study of Neyroud (8) although the decline in FTI during the stimulation depended on NMES protocol, the decline in MVC torque after the NMES sessions did not, which may be due to the small amplitude of the NMES-evoked contractions (10% MVC) which would have fatigued only a small portion of motor units recruited during the "test" MVCs (8). Accordingly, contraction fatigue may be underestimated when quantified by MVC force loss and the FTI or mean force recorded during NMES sessions is a more sensitive index of contraction fatigue during NMES.

In two short-term studies (7,9) fatigue was evaluated after dividing participants into those who "responded" during $WPHF_{NMES}$ and those who did not. Responders were participants in whom contractions developed in part via central pathways, producing "extra force" thought to be beneficial for reducing contraction fatigue by preferentially recruiting fatigue-resistant motor units (7,9,42). Both studies (7,9) that made this distinction found that $WPHF_{NMES}$ reduced contraction fatigue compared to $CONV_{NMES}$ only in responders, regardless of how fatigue was quantified. In non-responders, fatigue during $WPHF_{NMES}$ was either not different than during $CONV_{NMES}$ when assessed as the mean force (7) or the FTI (9) and in one study fatigue was greater during $WPHF_{NMES}$ when assessed as the FTI (7). Therefore, it appears responders represent a subset of the non-clinical population in whom $WPHF_{NMES}$ reduces contraction fatigue by recruiting fatigue-resistant motor units via central pathways. The different fatigue assessment methods, different NMES session durations and rest times between protocols (Table 1 for further details) may account for much of the variability in the results for this outcome measure.

Strength adaptations were assessed after six weeks of either $CONV_{NMES}$ or $WPHF_{NMES}$ in two long-term studies (37,38). In these studies, NMES was applied three times a week over the ankle dorsiflexor and plantar flexor muscles in participants with MS (38) or over the plantar flexors in non-injured older adults (37). In both studies there were no differences between $CONV_{NMES}$ or $WPHF_{NMES}$ for gait speed, walking endurance or strength adaptations post-NMES. Strength adaptations were assessed by comparing MVCs performed before and after the six weeks of both NMES-types (37,38). Further long-term studies are needed to establish, and optimize, strength adaptations induced using different NMES protocols that incorporate assessment tools with greater sensitivity than MVC.

Perceived discomfort was assessed in one short-term study (8) in which VAS scores were not different between $CONV_{NMES}$ and $WPHF_{NMES}$. $CONV_{NMES}$, however, required more current than $WPHF_{NMES}$ to obtain the same initial contraction amplitude, thus one might have expected $CONV_{NMES}$ to induce more discomfort. The lack of a difference in discomfort between protocols may be associated with the low contraction amplitude (10% MVC) (43) and lack of discriminative capability of the VAS measure (32). This low initial contraction amplitude was chosen to minimize antidromic block to allow maximal central recruitment (26,41). Further studies are needed to compare the effects of $WPHF_{NMES}$ versus $CONV_{NMES}$ on perceived discomfort.

Study limitations

We conducted a comprehensive literature search across multiple databases, however, this search yielded studies predominantly in English-language journals and may not have captured studies in non-English journals and regional databases. Also, the variability between evaluations and clinical heterogeneity between studies precluded us from performing meta-analyses, limiting this review to descriptive rather than quantitative comparisons. Multiple outcome measures were also a limitation as they made even descriptive comparisons between studies difficult.

The quality of the included studies was very low and ranged from 4 to 7 points on the PEDro scale. As none of the selected studies utilized a triple-blinding methodology (subject, therapist, and assessor) and non-blinded studies often have larger effect sizes, smaller p-values, and higher frequency of significant results (44), rigorous studies with blinded evaluations should be conducted in this field to increase methodological quality. The lack of quality studies in this area markedly limited the ability to differentiate

between $CONV_{NMES}$ and $WPHF_{NMES}$ regarding contraction fatigue, strength adaptations and discomfort.

Conclusions

The results of both short- and long-term studies suggest that in general, across a group of non-clinical participants, there is no difference between $CONV_{NMES}$ and $WPHF_{NMES}$ for contraction fatigue, strength adaptations or perceived discomfort. There is evidence, however, that a single session $WPHF_{NMES}$ may reduce contraction fatigue, compared to $CONV_{NMES,}$ for a segment of the non-clinical population (the "responders") but exacerbate contraction fatigue for others (the non-responders). In the long-term, no differences were identified between $CONV_{NMES}$ and $WPHF_{NMES}$ for muscle strength adaptations and fatigue in clinical and non-clinical populations. The methodological quality, however, was very low and future well-designed RCTs should be conducted to establish the optimal NMES parameters to reduce contraction fatigue, increase muscle strength, and reduce perceived discomfort in clinical and non-clinical participants.

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Figure 1: PRISMA flow diagram showing the results of the searches.

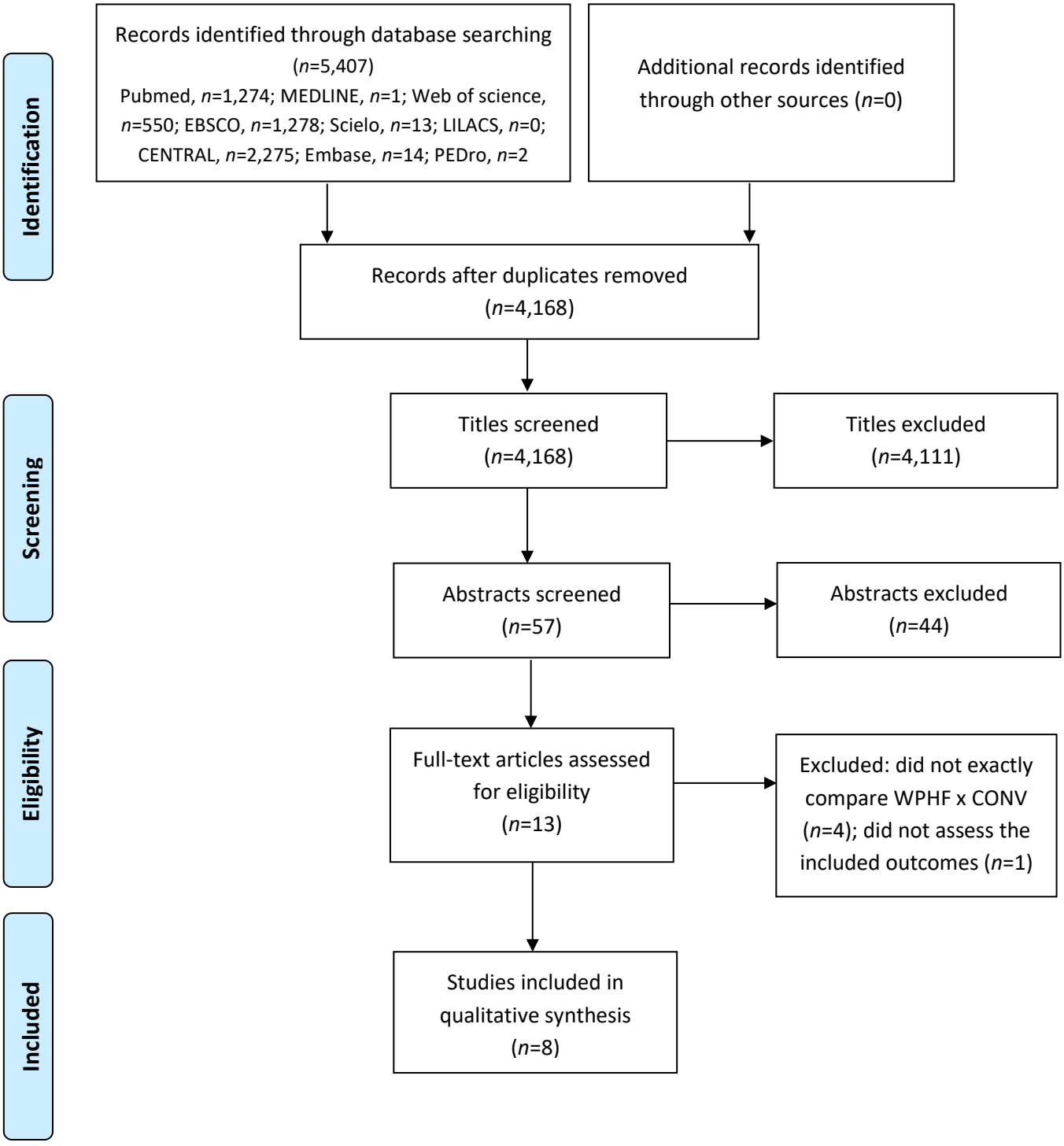

Table 1. Key characteristics.

Year	Author	Study design	Participants	Sample size	Age (years)	Gender (% male)	Another intervention comparison	Outcomes	Results
2016	Martin et al.[10]	Crossover	Non-clinical	11	28 ± 8	72,70%	x	Contraction fatigue	MVC and FTI were similar for both protocols.
2014	Neyroud et al.[8]	Crossover	Non-clinical	14	27 ± 4	78,50%	x	Contraction fatigue; Discomfort	FTI (main index of muscle fatigue) in WPHF was smaller (more fatigue in WPHF). MVC decrease similar for both. Discomfort scores were similar for both.
2014	Silva et al.[6]	Crossover	Non-clinical	13	30 ± 7	69,20%	VOL	Contraction fatigue	FTI were similar in the two conditions.
2015	Wegrzyg et al.[7]	Crossover	Non-clinical	18	29 ± 7	72,20%	VOL	Contraction fatigue	For the responder group, the total FTI (fatigue index) was similar for both, the non-responders showed lower FTI for WPHF (more fatigue). In the responder group the Mean Force for WPHF was greater, and no difference between protocols in non-responders.
2014	Wegrzyk et al.[9]	Crossover	Non-clinical	42	28 ± 6	47,60%	x	Contraction fatigue	For responder group the FTI was greater for WPHF, the non-responder group showed no differences.
2017	Wegrzyg et al.[39]	Crossover	Non-clinical	16	26 ± 5	66,6%*	VOL	Contraction fatigue	Mean Force was not different between the protocols.

2018	Almuklass et al.[38]	RCT	Multiple sclerosis patients	27 (13 NP, 14 WP)	NP 54.9 ± 4.5; WP 50.4 ± 9.0	NA	x	Contraction fatigue; Strength adaptations	Decrease in fatigue level (MFIS questionnaire) for both protocols. MVC force of the dorsiflexors in the affected leg increased at week 11 and of the plantar flexors in the less affected leg at week 7 for both protocols.
2018	Mani et al.[37]	RCT	Older adults	30 (15 NP, 15 WP)	73.5 ± 4.8	43,33%	x	Strength adaptations	MVC force increased in plantar flexor at week 7 for both protocols.

*values available only for data before sample loss. *Note:* MVC: maximum voluntary contraction; FTI: force time integral; VOL: voluntary contraction; CP: cerebral pasy patients; RCT: randomized clinical trial; NP: narrow-pulse group; WP: wide-pulse group; NA: not available; MFIS: Modified Fatigue Impact Scale

Table 2. Summary of NMES parameters.

Year	Author	Study design	Experimental session duration	Sessions / week	Total weeks	Rest between sessions	Frequency WPHF (Hz)	Frequency CONV (Hz)	Width WPHF (ms)	Width CONV (µs)	Electrode size (cm)	Ton-Toff (seconds)	Number of contractions	Electrode placement	Intensity (mA)
2016	Martin et al.[10]	Short-term	2-2.5 hours	NAP	NAP	7 days	80	20	1	50	1 (diameter); 10x13	6-6	40	Tibial Nerve	20% MVC
2014	Neyroud et al.[8]	Short-term	NA	NAP	NAP	6 to 9 days	100	25	1	50	10x5	20-40	20	Triceps Surae Muscle Belly	10% MVC
2014	Silva et al.[6]	Short-term	NA	NAP	NAP	5-10 minutes	100	25	1	50	10x5	10-300/600	1	Triceps Surae Muscle Belly	10% MVC
2015	Wegrzyg et al.[7]	Short-term	2 hours	NAP	NAP	NA	100	25	1	50	5x13; 5x9	20-20	20	Triceps Surae Muscle Belly	10% MVC
2014	Wegrzyk et al.[9]	Short-term	1 hour	NAP	NAP	5-10 minutes	100	25	1	50	5x13; 5x9	20-90	5	Triceps Surae Muscle Belly	5% MVC
2017	Wegrzyg et al.[39]	Short-term	2 hours	NAP	NAP	NA (both currents on the same day)	100	25	1	50	5x13; 5x9	20-20	20	Triceps Surae Muscle Belly	10% MVC (8.5 a 11.5%)

2018	Almuklass et al.[38]	Long-term	50 minutes	3	6	NA	100	50	1	26	2×3.5 or 2×5	4-12	38	Dorsiflexor and Plantar Flexor Muscles	10% MVC for Dorsiflexors; 20% MVC for Plantar Flexors
2018	Mani et al.[37]	Long-term	NA	3	6	NA	100	50	1	26	2x3	4-12	75	Triceps Surae Muscle Belly	Maximum tolerated

Note: NA: not avaiable; NAP: not aplicable; Hz: Hertz; ms: milisecond; µs: microsecond; cm: centimeter; mA: milliampere; MVC: maximal voluntary contraction.

Table 3. Methodological quality of included articles (PEDro scale).

Author (Year)	Random allocation	Concealed allocation	Groups similar at baseline	Subjects blinding	Therapist blinding	Assessor blinding	Adequate follow-up	Intention-to-treat analysis	Between-group comparisons	Point estimate and variability	Total
Martin et al. (2016)[10]	Y	N	Y	N	N	N	N	N	Y	Y	4
Neyroud et al. (2014)[8]	N	N	Y	N	N	N	Y	Y	Y	Y	5
Silva et al. (2014)[6]	N	N	Y	N	N	N	Y	Y	Y	Y	5
Wegrzyk et al. (2015)[7]	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Wegrzyk et al. (2014)[9]	Y	N	Y	Y	N	N	Y	Y	Y	Y	7
Wegrzyk et al. (2017)[39]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Almuklass et al. (2018)[38]	Y	N	Y	Y	N	Y	N	N	Y	Y	6
Mani et al. (2018)[37]	Y	N	Y	N	N	Y	N	N	Y	Y	5

N, No; Y, Yes.