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Efeitos da Reabilitação Robótica Usando o Dispositivo Erigo® em Pacientes com Lesão Neurológica

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LISTA DE ABREVIATURAS E SIGLAS

AVE- Acidente Vascular Encefálico
CRSr- Coma Recovery Scale Revised
ECG- Escala de Coma de Glasgow
EENM- Estimulação Elétrica Neuromuscular
ECR- Ensaio Clínico Randomizado
EQ-5D- EuroQol-5D questionnaire
FIM- Functional Independence Measure
GC- Grupo Controle
GCS- Glasgow Coma Scale
GI- Grupo Intervenção
MMSE- Mini-Mental State Examination
MRC- Medical Research Council
NIHSS- National Institutes of Health Stroke Scale
RS- Revisão Sistemática
TCE- Traumatismo Cranioencefálico
TUG- Timed Up and Go
VAS- Visual Analog Scale
1RM- Test of Maximum Repetition

SUMÁRIO

RESUMO

As lesões neurológicas abrangem um grupo de patologias decorrentes de doenças cerebrais vasculares, neurodegenerativas ou traumáticas. Entre seus principais comprometimentos a funcionalidade pode ser afetada temporária ou permanentemente. A abordagem precoce na reabilitação neurológica determina a recuperação motora e cognitiva, entre elas a reabilitação robótica pode otimizar a recuperação desses pacientes. O primeiro estudo desta dissertação revisou sistematicamente os efeitos do dispositivo Erigo® em pacientes com lesão neurológica sobre a segurança, espasticidade, força muscular, funcionalidade e alteração do nível de consciência. Cinco bases de dados foram pesquisadas e nove ensaios clínicos (totalizando 347 pacientes) foram incluídos. Foi avaliado o efeito crônico da reabilitação robótica de forma isolada ou associada à outra terapia física, comparado à terapia placebo ou fisioterapia convencional. Os resultados indicaram que o dispositivo Erigo® como estratégia de reabilitação robótica é seguro para pacientes com lesão neurológica e parece reduzir a espasticidade em pacientes após acidente vascular encefálico (AVE). Os efeitos sobre a funcionalidade, o nível de consciência e a força muscular parecem incertos. O segundo estudo apresenta um protocolo de ensaio clínico randomizado que objetiva avaliar os efeitos da reabilitação robótica utilizando o dispositivo Erigo® sobre a funcionalidade de pacientes com AVE na fase subaguda. Quarenta pacientes com AVE serão randomizados para um grupo controle (fisioterapia da rotina) ou grupo intervenção (fisioterapia de rotina mais reabilitação robótica). As intervenções ocorrerão todos os dias na fase hospitalar e 3 vezes/semana após a alta, totalizando aproximadamente 18 sessões. Os grupos serão avaliados previamente às intervenções, após a décima sessão e ao final de seis semanas de tratamento ou 18 sessões. A funcionalidade será considerada o desfecho primário do estudo. Força muscular, espasticidade, arquitetura muscular de quadríceps e ecogenicidade, mobilidade, grau de incapacidade e dependência, qualidade de vida, segurança da terapia, tempo de permanência hospitalar e mortalidade serão considerados desfechos secundários.

Palavras-chaves: doenças arteriais intracranianas; robótica; reabilitação neurológica.

ABSTRACT

Neurological injuries include a group of pathologies resulting from vascular, neurodegenerative or traumatic brain diseases. Among its main commitments, functionality can be affected temporarily or permanently. The early approach in neurological rehabilitation determines motor and cognitive recovery and the robotic rehabilitation can optimize the recovery of these patients. The first study in this dissertation systematically reviewed the effects of robotic rehabilitation with the Erigo® device on patients with neurological injury on safety, spasticity, muscle strength, functionality and changes in the level of consciousness. Five database were searched and nine clinical trials (totalizing 347 patients) were included. The chronic effect of robotic rehabilitation was evaluated alone or in association with other therapy, compared to placebo or conventional physical therapy. The results indicated that the Erigo® device as robotic rehabilitation strategic is safe for patients with neurological injury and appears reduce spasticity in patients after stroke. The effects on functionality, level of consciousness and muscle strength seem uncertain. The second study presents a randomized clinical trial protocol that aims to evaluate the effects of robotic rehabilitation using the Erigo® device on the functionality of patients with stroke in the subacute phase. Forty patients with stroke will be randomized to a control group (routine physical therapy) or intervention group (routine physical therapy plus robotic rehabilitation). Interventions will take place every day in the hospital phase and 3 times/week after discharge, totalizing approximately 18 sessions. The groups will be evaluated before the interventions, after the tenth session, and at the end of six weeks of treatment or 18 sessions. Functionality will be considered the primary outcome of the study. Muscle strength, spasticity, quadriceps muscle architecture and echogenicity, mobility, degree of disability and dependence, quality of life, cardiorespiratory repercussions, length of hospital stay and mortality will be considered as secondary outcomes.

Keywords: Brain Diseases; Robotics; Neurological Rehabilitation;

1. INTRODUÇÃO

As lesões neurológicas abrangem um grupo de patologias decorrentes de doenças cerebrais vasculares, neurodegenerativas ou traumáticas. As consequências dessas lesões podem levar a transtornos temporários ou permanentes, conforme a região afetada. As lesões neurológicas são uma das principais causas de incapacidades e mortes mundiais, afetando a qualidade de vida e gerando grandes encargos socioeconômicos (1).

O acidente vascular encefálico (AVE) trata-se de uma doença cardiovascular, tendo duas grandes categorias de classificação, isquêmica e hemorrágica (2). O AVE está classificado como segunda causa de mortalidade mundial e está no grupo das doenças cardiovasculares que permanecem como as principais causas de óbitos nos últimos 15 anos (3). A urgência no tratamento ao paciente com AVE determina seu comprometimento cerebral e motor, do mesmo modo que a precocidade na reabilitação é recomendada a partir da estabilidade hemodinâmica (4).

Entre os comprometimentos, podemos citar déficits motores, sensoriais, de comunicação e/ou cognitivos. A apatia se manifesta em 50% dos sobreviventes em um ano após o evento, sendo o isolamento social e a depressão um grande contribuinte para a redução das atividades de vida diária (5).

Da mesma forma, as doenças neurodegenerativas fazem parte de um processo natural de envelhecimento celular, as quais por uma ação crônico-degenerativa trazem alterações cognitivas, sensório-motoras, prejuízo da independência funcional e da qualidade de vida (6). O diagnóstico e as intervenções terapêuticas precoces, através das tecnologias assistivas e o acompanhamento multidisciplinar, conseguem minimizar os desfechos naturais das doenças e aumentara sobrevida (7,8).

Ainda no grupo de lesões cerebrais, o traumatismo cranioencefálico (TCE) decorre de uma força externa no crânio, a qual não seja apenas lesões superficiais no rosto. A incidência global de TCE para todas as causas e gravidades são de 939 casos por 100.000 pessoas. Estimativas mostram que 64 a 74 milhões de novos casos de TCE ocorrerão no mundo a cada ano (9).

Na sua fisiopatologia pode-se identificar lesões primárias, resultante imediato ao trauma, e secundárias, as quais decorrem de alterações estruturais devido a lesão primária. A gravidade do TCE é comumente classificada pela Escala de Coma de Glasgow (ECG) e a maioria dos desfechos fatais estão no grupo de lesões moderadas a graves (10). Considerando a morbidade física e psicológica em um paciente após TCE, surge a necessidade da reabilitação precoce com o objetivo de melhorar o nível de consciência, as sequelas motoras e os déficits sensoriais, assim como para auxiliar o retorno às atividades de vida diárias (11,12).

O uso de tecnologias assistivas, como a reabilitação robótica, trata-se de um recurso adicional à fisioterapia convencional e que acelera a recuperação (13).

O uso de pranchas ortostáticas na reabilitação de pacientes críticos em unidades de terapia intensiva já se mostrou um recurso seguro e eficaz para a readaptação do paciente na posição vertical (14). Na mesma linha de tratamento, a prancha robótica Erigo® permite além dos benefícios do ortostatismo passivo, a movimentação passiva de joelhos e quadril associado à estimulação elétrica neuromuscular (EENM) (15).

A evidência disponível até o presente momento, no que tange a reabilitação robótica através do dispositivo Erigo® para pacientes com lesões neurológicas é escassa e apresenta protocolos heterogêneos, além disso, no melhor do nosso conhecimento não existem estudos com delineamento adequado que avaliaram a segurança deste dispositivo para a reabilitação desta população, por isto a necessidade deste estudo.

Esta dissertação está estruturada no formato de: referencial teórico contextualizando as lesões neurológicas e a reabilitação robótica com o dispositivo Erigo®; artigo 1 abordando a segurança do dispositivo em pacientes com lesões neurológicas através de uma revisão sistemática e artigo 2, apresentando um protocolo de ensaio clínico randomizado para avaliar o efeito da reabilitação robótica com Erigo® em pacientes pós AVE.

2. OBJETIVOS

2.1 Objetivo Geral

Verificar o efeito crônico da reabilitação robótica utilizando o dispositivo Erigo® em pacientes com lesões neurológicas sobre a segurança.

2.2 Objetivos Específicos

- Revisar sistematicamente os efeitos da reabilitação robótica utilizando o dispositivo Erigo® em pacientes com lesões neurológicas sobre os desfechos de segurança, força muscular, funcionalidade, espasticidade e estado de coma.

- Propor um protocolo de ensaio clínico randomizado para reabilitação de pacientes com AVE utilizando a mesma tecnologia.

3. FUNDAMENTAÇÃO TEÓRICA

As lesões neurológicas apresentam uma grande incidência mundial e afetam diretamente a qualidade de vida dos pacientes. Dentre as quais, as doenças cerebrovasculares apresentam maior número de internações, seguidas das lesões neurodegenerativas; e devido à alta complexidade anatômica e funcional do sistema nervoso central, o paciente pode apresentar uma variedade de alterações motoras e cognitivas (1). Na sequência são apresentados os principais grupos de lesões e seus comprometimentos.

3.1 Acidente vascular encefálico

O acidente vascular encefálico é caracterizado pela interrupção súbita do fluxo sanguíneo central, o qual gera prejuízos a função cerebral e repercussões periféricas. O seu diagnóstico precoce visa em minimizar lesões cerebrais, tratar complicações médicas, identificar a etiologia precisa do evento e o tratamento a longo prazo com fisioterapia (16).

Entre seus efeitos socioeconômicos está a associação entre nível educacional e o pior estado funcional até 1 ano após evento. Em consequência, o risco de um novo evento vascular cerebral e maior risco de mortalidade, estão relacionados a um baixo *status* socioeconômico. O investimento em atenção primária e ênfase nos fatores de risco consiste na tentativa de alguns centros para a redução da disparidade no tratamento aos pacientes (17).

No AVE isquêmico ocorre uma oclusão arterial, que leva a morte celular progressiva dos tecidos irrigados. A reversão precoce dessa oclusão vai determinar a área afetada e seus respectivos comprometimentos cognitivos e motores. Essa reversão pode ocorrer com intervenções endovasculares medicamentosas e mecânicas (18).

Os tratamentos com trombolíticos intravenosos consistem na terapia padrão em um paciente com AVE isquêmico agudo, porém com uma janela de tempo pequena desde o início dos sintomas. A trombectomia também passou a ser uma opção terapêutica para grandes oclusões arteriais, dentro das 24 horas do evento. Tal abordagem pode ser realizada usando dispositivos que interrompem, aspiram ou recuperam os coágulos. A trombectomia mecânica

consiste em um tratamento isolado ou como um complemento a trombólise química (19).

No estudo de Rodrigues *et al* (20) foi avaliado a eficácia e segurança do tratamento endovascular em pacientes com AVE isquêmico. O grupo que recebeu tratamento endovascular (trombectomia com *stent)* em adição a trombólise intravenosa tiveram bons resultados, sem aumento prejudicial dos efeitos, e os pacientes tornaram-se independentes funcionalmente em comparação ao grupo que recebeu os cuidados usuais da medicina (ativador do plasminogênio tecidual recombinante).

No AVE hemorrágico, ocorre um sangramento intracerebral agudo associado, na maioria dos casos, com hipertensão arterial, angiopatia amilóide, aneurisma sacular rompido e mal formação vascular (21). É menos prevalente que o AVE isquêmico e em relação ao seu manejo pode haver necessidade de ventilação mecânica, reversão de medicamentos de anticoagulantes e antiagregantes plaquetários, controle da pressão arterial e pressão intracraniana, como também intervenções cirúrgicas para evacuação do hematoma (22). Entre suas medidas de tratamento, o controle da hipertensão não apresenta consenso entre os estudos sobre qual alvo pressórico a ser seguido. Na metanálise de Qureshi *et al* (23) em que usou dados de dois ensaios, INTERACT2 e ATACH-2, em pacientes com controle pressórico no AVE hemorrágico, sugeriram que a redução intensiva no nível da pressão arterial sistólica não fornece um benefício clínico incremental. Quando analisados os desfechos morte e incapacidade em até 3 meses após intervenções, não mostraram diferença nos escores finais da Escala Modificada de Rankin, conforme o grupo de tratamento para o manejo da pressão arterial.

Todo paciente pós AVE isquêmico ou hemorrágico, com algum comprometimento físico ou cognitivo, deve passar por uma avaliação multidisciplinar e iniciar a reabilitação. Os benefícios do cuidado especializado conseguem reduzir os índices de mortalidade, aumentando a independência funcional e qualidade de vida. Entre os comprometimentos com alta prevalência, está a hemiplegia e hemiparesia, que afeta principalmente o equilíbrio e a marcha. A abordagem precoce é fundamental, porém a reabilitação pode não trazer a funcionalidade total do membro afetado. Os recursos utilizados para melhorar as habilidades, contam com equipamentos que promovem o

ortostatismo, treinamentos eletromecânicos para a marcha, uso de EENM e realidade virtual (24).

3.2 Doenças neurodegenerativas

As doenças neurodegenerativas são o grupo de patologias que afetam o sistema nervoso central e que ocasionam uma degeneração progressiva e morte de neurônios. Os pacientes com diagnóstico de alguma doença neurodegenerativa vão apresentar acometimentos cognitivos e motores conforme o curso das desordens. Tais enfermidades ainda não apresentam terapias curativas e conforme a progressão das doenças ocorrem um agravamento dos sintomas, interferindo diretamente na qualidade de vida de seus portadores (25).

Nesse cenário a reabilitação tenta restaurar a capacidade física, psicológica e social para reduzir a incapacidade a longo prazo. O uso de novas abordagens, como a realidade virtual, vem auxiliando na reabilitação motora convencional para facilitar o processo de reaprendizagem (26).

Entre uma das doenças neurológicas, crônica e progressiva, a esclerose múltipla apresenta como principal sintoma o comprometimento motor. O estudo de Russo *et al* (27) trouxe novas estratégias de reabilitação a esses pacientes, o qual hipotetizou que o uso intensivo da reabilitação robótica associada a realidade virtual bidimensional teria seu benefício motor potencializado, em comparação a fisioterapia convencional. Em seus resultados ocorram uma melhora significativa para todos os desfechos avaliados no grupo intervenção, enquanto, o grupo controle só apresentou melhora no teste *Timed Up and Go*.

3.3 Traumatismo crânio encefálico

O traumatismo crânio encefálico é provocado por uma força física externa ao crânio resultando em alterações cerebrais momentâneas ou permanentes (28). O TCE causa grande comprometimento físico e cognitivo, e em sua forma moderada e grave levará a algum grau de incapacidade ao paciente, que por sua vez impedirá o retorno às suas atividades de vida diária (29). Seu tratamento irá depender da avaliação inicial do nível de consciência ou sinais e sintomas que indicam lesão intracraniana (30).

A avalição da gravidade e deterioração neurológica do TCE é auxiliada pela Escala de Coma de Glasgow (ECG), e assim como a tomografia computadorizada detectará fraturas do crânio, hematomas intracranianos e edema cerebral (31).

Os comprometimentos cognitivos incluem alterações na atenção, memória e funções executivas, podendo também apresentar incapacidades comportamentais e emocionais. As lesões motoras em decorrência do TCE se apresentam conforme a área cerebral afetada. A ocorrência de ataxias, está relacionada a lesões a nível do cerebelo, como também, tremores intencionais, resultante de lesões extrapiramidais. Na avaliação da resposta motora também pode-se identificar lesões mais complexas, como hemiparesias, as quais sugerem lesões intracraniana contralateral ao *déficit*, e comprometimentos bilaterais, paralisias ou tetraparesias, sugerindo lesões medulares (11).

No contexto da reabilitação de pacientes com TCE, esta pode exigir maior complexidade e limitação, pela frequência de paraplegias ou paraparesias comparando com os acometimentos por um AVC, que na sua maioria exibem hemiparesias ou hemiplegias unilaterais. No entanto, muitos indivíduos com TCE são mais jovens e têm menos comorbidades em comparação aos acometidos por AVC, pontos que auxiliam na maior neuroplasticidade durante a reabilitação (25).

Na revisão sistemática de Morris *et al* (32) avaliou-se o efeito do exercício físico no comprometimento cognitivo de pacientes após TCE. As intervenções utilizadas nos programas de reabilitação estavam segmentadas em intervenções únicas ou combinadas a outras tecnologias, como a realidade virtual. No entanto, os resultados são inconsistentes em relação aos benefícios do exercício físico para os comprometimentos cognitivos, além de alto risco de vieses nos estudos selecionados.

O estudo de Esquenazi *et al* (33) abordou intervenções terapêuticas no comprometimento da locomoção de pacientes com TCE crônico. Os indivíduos foram randomizados para reabilitação em 3 modos diferentes de intervenção: robô efetor final (G-EO), exoesqueleto robótico (Lokomat) ou esteira manual com assistência parcial. Todos os participantes eram hemiparéticos e tiveram ganhos positivos em relação a velocidade da marcha, independente da intervenção. A

velocidade da marcha auto selecionada teve um aumento em todas as intervenções, com acréscimo maior no grupo que utilizou o dispositivo Lokomat.

Na revisão de Synnot *et al* (34) foi avaliado os efeitos de intervenções para a espasticidade muscular esquelética em pacientes com TCE. Entre as intervenções farmacológicas mais estudadas estavam o baclofeno e toxina botulínica, já entre os tratamentos não farmacológicos mais frequentes encontravam-se fisioterapia, talas, pranchas ortostáticas e EENM. A qualidade dos estudos foi limitada, devido aos vieses metodológicos. Desse modo, não há evidências suficientes para orientar a melhor conduta na prática clínica para manejo da espasticidade.

As lesões cerebrais adquiridas, resultantes de eventos traumáticos ou não traumáticos podem levar ao estado vegetativo ou mínimo estado da consciência. No estado vegetativo os pacientes podem apresentar reflexos complexos, manter a pressão arterial, funções respiratórias e cardíacas, mas não demostrar funções cognitivas. Já no mínimo estado de consciência os pacientes apresentam interação limitada com o ambiente e pode ocorrer alguma melhoria com tempo (35). Apesar do prognóstico incerto, a reabilitação deve iniciar o mais precoce possível (36), tendo como um componente importante a mudança de posição e verticalização no caso destes pacientes. O estímulo de várias vias sensoriais e reações posturais permite a otimização do nível de consciência e o despertar (37).

3.4 Reabilitação robótica

A reabilitação robótica trata-se de uma tecnologia assistida que complementa as técnicas da fisioterapia convencional. Diversos dispositivos foram criados para melhorar a recuperação dos pacientes de forma não invasiva, visando a estimulação compensatória das regiões não danificadas e posteriormente o mecanismo de neuroplasticidade para restaurar funções motoras perdidas (38).

Há uma ampla gama de dispositivos robóticos disponíveis no mercado que auxiliam no ganho de funcionalidade, mobilidade e força muscular (37,39). Serão abordados aqui brevemente os mais utilizados: cicloergômetro, prancha ortostática e prancha robótica.

O cicloergômetro permite a rotação cíclica dos membros inferiores ou membros superiores e está entre as intervenções mais adotadas na reabilitação (40). Sua programação disponibiliza a realização do movimento passivo e/ou a transição do movimento passivo para o movimento ativo pelo paciente (41). Estudos já demostram resultados positivos em relação ao uso desta tecnologia sobre desfechos como atividade motora, capacidade funcional submáxima e funcionalidade (42).

A prancha ortostática consiste em outro recurso para a reabilitação de pacientes críticos. Esta permite a verticalização do paciente em até 90º, mesmo em ventilação mecânica. Entre seus benefícios, pode-se citar a readaptação à posição vertical, uma vez que, o sistema nervoso central tem seus ajustes autonômicos prejudicados, como também, o alongamento das cadeias musculares posteriores, evitando contraturas. Ainda, a função dos sistemas pulmonar e gástrico são favorecidas. (43).

Nesse mesmo contexto do ortostatismo, a simulação da marcha também pode ser realizada com uso de robôs exoesqueletos ou dispositivos robóticos associados à EENM. Em uma revisão sistemática de Bruni *et al* (44), foi avaliado a função motora em pacientes pós AVE, usando diversas terapias assistidas por robô *versus* fisioterapia convencional. Pode-se concluir que os pacientes com AVC subagudo treinados com dispositivos robóticos em combinação com o tratamento da fisioterapia convencional, alcançaram melhores resultados para uma marcha independente, do que aqueles submetidos à fisioterapia convencional isoladamente. Além disso, o treinamento robótico quando associado a EENM produziram mais benefícios na recuperação da marcha, quando comparados a terapia robótica isolada.

Nesse cenário, a prancha robótica Erigo® (Hocoma, Volketswil, Switzerland) apresenta todas as vantagens do movimento dos membros inferiores e do ortostatismo. Permite uma inclinação em até 90º, a movimentação passiva de joelhos e quadril associado à EENM (45).

No estudo de Geiger *et al* (46) foi avaliado o perfil eletromiográfico de quatro músculos dos membros inferiores, em indivíduos saudáveis. A atividade muscular foi avaliada durante a terapia com Erigo®, durante a tarefa de subir escadas e durante a subida real de escadas. O principal resultado encontrado

foi o padrão similar de estimulação eletromiográfico durante a pisada no Erigo® em comparação ao desempenho real de subir escadas.

Já o estudo de Kuznetsov *et al* (47) avaliou a segurança e a viabilidade, especialmente nas reações de ortostatismo, de pacientes após AVE na reabilitação robótica. Os pesquisadores selecionaram uma amostra de conveniência, e alocaram em três grupos: 1) Reabilitação robótica com o robô Erigo® e estimulação elétrica funcional (robô-FES); 2) Somente Erigo® (robô) e, 3) Somente verticalização na prancha do Erigo® (controle). Em seus achados, nenhum dos pacientes no grupo robô-FES e robô tiveram hipotensão postural ou reações ortostáticas quando em verticalização, considerando a diminuição da pressão arterial sistólica de ≥20mmHg e na pressão diastólica de ≥10mmHg. No entanto, 52% dos pacientes do grupo controle apresentaram hipotensão, mas sem necessidade de interromper a terapia.

Em relação ao nível de consciência, o estudo de Krewer *et al* (48), randomizou 50 pacientes em estado vegetativo ou mínimo estado de consciência, com tratamento convencional em prancha ortostática *versus* robô Erigo®. A escala de coma (Coma Recovery Scale-revised - CRSr) foi utilizada para a avaliação neurocomportamental dos pacientes após três semanas de intervenções. Os resultados da CRSr tiveram melhora em ambos os grupos, porém a prancha ortostática apresentou resultados superiores a terapia com o robô Erigo®.

Em contrapartida, no estudo de Frazzitta *et al* (15), com 40 pacientes que apresentavam o mesmo acometimento, o grupo reabilitado com o robô Erigo® apresentou melhora nos escores da CRSr comparado ao grupo controle após seis semanas de tratamento.

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ARTIGO 1

Efeitos da Reabilitação Robótica Usando o Dispositivo Erigo® em Pacientes com Lesão Neurológica: uma Revisão Sistemática de Ensaios Clínicos Randomizados e Meta-análise.

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Abstract

Introduction: The early approach in neurological rehabilitation determines the motor and cognitive recovery of patients. Robotic rehabilitation can be a strategy to optimize the recovery of patients with neurological injuries.

Objective: To systematically review the effects of robotic rehabilitation with the Erigo® device on patients with neurological injury on safety, spasticity, muscle strength, functionality, and changes in the level of consciousness.

Methods: MEDLINE, SciELO, EMBASE, The Cochrane Library - CENTRAL, and PEDro databases were consulted without the restriction of date and language. Randomized controlled trials that evaluated the chronic effect of robotic rehabilitation and compared it to conventional or placebo therapy, isolatedly or in association with other therapy, were selected. The risk of bias was assessed with the use of the RoB 2.0 tool**.**

Results: Nine studies were included, totaling 347 patients. The robotic rehabilitation performed by the Erigo® device proved to be safe for neurological patients. The meta-analysis showed an improvement for spasticity (MD = 0.29; 95% CI = −0.49 to −0.08; I^2 = 0%), but there was no significant increase in muscle strength in patients with stroke (MD = 0.25; CI 95% = -0.22 to -0,71; I^2 = 0%). Erigo® seems to have positive effects on functionality and level of consciousness in patients with severe acquired brain injury and vegetative or minimally conscious state. All studies present some concerns for the risk of bias.

Conclusion: Erigo® as a robotic rehabilitation strategy is safe for patients with neurological injury appears to reduce spasticity in patients with stroke. The effects on muscle strength, functionality, and level of consciousness remain uncertain.

Keywords: Neurological Rehabilitation; Robotics; Systematic Review.

Introduction

Neurological injuries cover a group of vascular, neurodegenerative, or traumatic brain diseases and can lead to temporary or permanent disorders, depending on the affected brain region. They are one of the main causes of disabilities and deaths worldwide, impacting the quality of life and generating great socioeconomic burdens.[1] Among the diseases that cause neurological damage, it is important to highlight, mainly, traumatic brain injury (TBI), stroke, and neurodegenerative diseases. Together, the people affected with these kinds of disease represent the largest number of patients who need assistance in their leisure activities and specialized care.[2]

Stroke is classified as the second cause of mortality worldwide and it is in the group of cardiovascular diseases that remain as the main causes of death in the last 15 years.[3] The overall incidence of TBI for all causes is 939 cases per 100.000 people. Estimates show that 64 to 74 million new cases of TBI are expected each year in the world.[4] Besides, concerning neurodegenerative diseases, a worldwide incidence of approximately 135 million cases is forecast for the coming decades, and they progress as the patient ages.[5] As a the great complexity of the brain structure, damage to a part of the brain results in characteristic clinical manifestations, among them the pattern and distribution of weakness, type of weakness (upper motor neuron versus lower motor neuron type), and presence or absence of sensory deficit.[6] These diseases cause a series of complications and physical and cognitive deficiencies, with reduced functionality being one of the main changes, with an impact on the activities of daily living and on the quality of life of these patients.[7]

Rehabilitation is essential to improve the quality of life and gain functionality. The early approach to the rehabilitation of physical impairments in a neurological patient determines motor and sensory recovery, as well as the return to activities of daily living.[8] Among the resources to optimize the rehabilitation process, there is the Erigo® robotic board (Hocoma, Volketswil, Switzerland). This resource presents all the advantages for the movement of the lower limbs and orthostatism. It allows an inclination of up to 90º and the passive

movement of the knees and hips associated with functional electrical stimulation (FES).[9]

Calabrò *et al*[10] demonstrated in a preliminary randomized controlled clinical trial that robotic rehabilitation with the Erigo® device can be a safe and viable therapy, especially for orthostatic reactions in patients with stroke. On the other hand, Krewer *et al,*[11] in a randomized clinical trial with Vegetative State or Minimally Conscious State patients, observed that the most cause for an interruption in treatment with Erigo® was the occurrence of hypotension, with a reduction in symptoms over the course of time.

Considering the lack of robust evidence, this study aimed to answer, through a systematic review of randomized clinical trials, the following questions:1) Is robotic rehabilitation using the Erigo® device safe for patients with neurological injuries? 2) Does the Erigo® device improve the functionality and muscle strength of patients with neurological injuries? 3) Does the Erigo® device change the spasticity and levels of consciousness of this population?

Methods

This study is a systematic review of randomized clinical trials (RCTs) with meta-analysis, carried out according to the recommendations proposed by the Cochrane Handbook for Systematic Reviews of Interventions[12] and reported as specified by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[13] The protocol is registered on the PROSPERO platform (CRD42020173603).

Data sources and search strategy

The databases MEDLINE (via PubMed), Scientific Electronic Library Online (SciELO), EMBASE, The Cochrane Library – Cochrane Central Register of Controlled Trials (CENTRAL), Physiotherapy Evidence Database (PEDro) were searched. Besides, a manual search was performed in the bibliographic references of already published studies. The search terms included “Spinal Cord Injuries”, “Stroke”, “Persistent Vegetative State”, “Brain Injury”, “Chronic”,

“Robotics”, “ERIGO”. Keywords related to the outcomes of interest and the type of publication were not included to increase the sensitivity of the search. There were no language or publication date restrictions. The complete search strategy is available in Table 1 (Supplementary material).

Selection of studies

The RCTs that evaluated the chronic effect of robotic rehabilitation using the Erigo® device and compared it to placebo or conventional physical therapy, isolated or in association with other therapy, in patients diagnosed with neurological disease or injury, with impairment of functionality, were included. Studies in which the treatment time was less than 10 sessions and studies with incomplete data (abstracts) were excluded.

The safety of the therapy assessed by monitoring the cardiac parameters (blood pressure, heart rate, oxygen saturation) was defined as the primary endpoint explored by this systematic review. Among the secondary studied outcomes, the following outcomes were investigated: functionality assessed by the Fugl Meyer, Functional Independence Measure or Tinetti scale; muscle strength evaluated by the Medical Research Council (MRC) scale or dynamometry; spasticity appraised by the Ashworth scale; coma state and level of consciousness assessed by the Coma Recovery Scale-Revised (CRSr).

All identified publications were inserted into software for managing references and duplicates were excluded. Initially, studies were selected by titles and abstracts by two independent reviewers (ABG and NCR). Abstracts that did not provide sufficient information for eligibility at this stage were selected for full-text evaluation, which was also performed independently by peers (ABG and NCR). Disagreements in the two stages of study selection were discussed between ABG and NCR, and if there was no consensus, a third reviewer was consulted (JS).

Data extraction and risk of bias assessment

After selecting the studies, the reviewers (ABG and NCR) extracted the data on a standardized form. Variables such as author and year of publication, type of study, population, sample size, gender and age, comparator group, type and protocol of intervention, outcomes of interest, and instruments for measuring outcomes were collected.

The evaluation of the methodological quality of the studies was carried out using the “Risk of Bias Toll for Randomized Trials” (RoB 2.0) scale of the Cochrane collaboration for RCTs, in which the following items are considered: “Randomization process”; “Deviations from intended interventions”; “Missing outcome data”; “Measurement of the outcome”; “Selection of the reported result”. The quality of each item was categorized into “low risk of bias”, “high risk of bias” or “some concerns” and, then, a global score (overall) was given for each outcome assessed.[14]

Data synthesis and analysis

Most of the results of the studies contemplated in this systematic review were presented descriptively due to the variety of populations as well as the measurement instruments and/or intervention protocols.

When possible, data were grouped with the aid of a meta-analytical approach. After data extraction, pooled effect estimates were obtained by the comparison of the change from baseline at the end of the study for each group. A random-effects model was, then, used, with the DerSimonian and Laird variance estimator, and the results were presented as mean difference (MD) with a 95% confidence interval (95%CI). A value of $p<0.05$ was considered significant. Statistical heterogeneity between studies was assessed via I^2. Finally, meta-analyses were performed by means of the R statistical software, version 3.5.2.

Results

Description of the studies

The search strategy identified a total of 2,482 studies, of which nine met the eligibility criteria, totaling 347 patients. Only two studies with stroke patients were included in the meta-analysis and, since the others did not present comparative values (pre and post-intervention), the data were incomplete or represented different populations. Figure 1 shows the flowchart of the selection of studies.

The most frequent neurological injury in the studies was brain injury, represented by ischemic and hemorrhagic stroke, which is predominant in males (57.34%). Also, all studies (347 patients) reported the monitoring of cardiorespiratory signs during the interventions. However, two studies[11,15] did not describe the absolute values in the manuscript.

The comparison groups to the therapy with the Erigo® device performed conventional physiotherapy, associated or not with verticalization. One study[16] used it as a comparator for robotic rehabilitation with Erigo® with conventional physiotherapy sessions associated with a device for mobilizing the legs in the supine position.

Regarding the protocol with the Erigo® device, there was a variation in the maximum angle of the board from 60º to 90º. Only three studies[15,17,18] reported the steps/minutes ratio used in their protocols, which varied between 18 to 40 steps/minute. The parameters used for the FES were reported in only one study,[10] but it only mentions the muscle groups in which the electric current was applied and its intensity (30mA) (table 1).

In general, the protocols included 10 to 24 sessions, lasting 15 to 60 minutes, and a weekly frequency of three to six times/week. Table 1 shows in detail the main characteristics of the studies.

Risk of bias assessment

According to the RoB 2.0 tool, all studies included in this systematic review presented a low risk of bias for the “Missing outcome data” category. For the randomization process, five studies[10,16,18–20] presented “some concerns”. Similarly, for the domain “Measurement of the outcome”, five studies[16–20] presented “some concerns”. For the domain “Selection of the reported result”, only two studies[11,15] were considered as “low risk of bias”. All studies presented

“some concerns” for the category “Deviations from intended intervention”. The overall for all included RCTs showed "some concerns". The assessment of the risk of bias is fully presented in table 2.

Effects of the intervention

Stroke and Severe Brain Trauma

There was no evidence of postural hypotension or other adverse events during the intervention with the Erigo® device in five study[10,16,18–20] included in this systematic review. One study[21] did not describe whether or not there was an adverse event during the protocol.

Regarding the spasticity outcome, the meta-analysis (figure 2) included two articles with patients com stroke,[19,21] totaling 140 patients, and showed improvement of spasticity in the group that performed the robotic intervention with Erigo® (MD = 0.29; CI 95% = −0.49 to −0.08; I^2 = 0%).

The assessment of muscle strength is reported in three of the included studies (160 patients),[10,20,21] and all used the Medical Research Council scale as a measuring instrument. The meta-analysis (figure 3) performed with two articles[20,21] did not show a significant increase in muscle strength in patients with stroke when compared to the control group (MD = 0.25; CI 95% = -0.22 to -0.71; I^2 = 0%) in stroke patients.

The study by Calabrò *et al* [10] did not enter the quantitative analysis due to the presentation of the MRC scale scores in a different format. Their sample was composed of patients in the sub-acute phase of stroke, who underwent the intervention with Erigo® and showed an increase in the muscle strength of the lower limbs compared to the control group that received Bobath sessions and training for the vertebral position sitting and standing (Erigo®: 2 ± *1 vs* control: 1 ± 1; p = 0.03).

Functionality after robotic rehabilitation with Erigo® was verified in two[10,18] of the included studies (64 patients) in this systematic review. The evaluation was carried out with three scales: in the study by Ancona *et al*,[18] the Tinetti and Functional Independence Measure (FIM) scales were used, while the Fugl-Meyer scale for lower limbs was used in the study by Calabrò *et al*.[10]

Ancona *et al*[18] presented the results for functionality to patients with severe acquired brain injury in relation to the baseline (T0) after the 10th session with Erigo® (T1) and at the end of the treatment cycle (after the 20th session with Erigo® - T2). An improvement was observed in the intervention group with the Erigo® device in the Tinetti scale scores (T0: 2.73 ± 3.73; T1: 6.14 ± 4.06; T2: 8.50 ± 4.82; $p < 0.001$) and in the FIM scale (T0: 52.82 ± 16.60; T1: 58.55 ± 18.71; T2: 62.59 ± 21.54; $p < 0.001$). In the control group, an analogous response was observed in the improvement from T0 to T2 and from T1 to T2, respectively, in the Tinetti (T0-T2: 4.00 ± 4.04 to 7.77 ± 5.04; T1-T2: 5.68 ± 4.39 to 7.77 ± 5.04; $p < 0.05$) and in the FIM scales (T0-T2: 52.55 ± 23.92 to 61.23 ± 26.93; T1-T2: 55.64 ± 24.80 to 61.23 ± 26.93; $p < 0.001$). The authors did not present a comparison between groups for this outcome.

Regarding the study by Calabrò *et al,*[10] the group the patients with stroke that received the Erigo® intervention performed better in its score for the Fugl-Meyer scale, compared to the control group (Erigo®:+92 ± 10; control:+58 ± 7; $p = 0.008$).

Vegetative State or Minimally Conscious State

One study[15] did not evidence of postural hypotension or other adverse events during the intervention with the Erigo®. In the studies by Krewer *et al*[11] and Taveggia *et al*,[17] the highest number of therapy interruptions occurred due to postural hypotension, with greater frequency in patients who performed only the verticalization of the table in comparison to those who performed the mobilization of the lower limbs in addition to the verticalization (Erigo®).

In relation to the assessment of the spasticity outcome, in the study by Krewer *et al*,[11] 44 patients were randomized for treatment with the Erigo® device versus tilt table. At the initial evaluation, 29 patients had mild spasticity (n = 14 Erigo®; n = 15 tilt table) and seven presented moderate spasticity (n = 4 Erigo®; n = 3 tilt table). After three weeks of interventions, there was no difference between the groups for this outcome ($p = 0.277$).

The level of consciousness was assessed in six of the studies[10,11,15,17–19] that were included in this systematic review, with the aim of identifying changes in cognitive function after robotic treatment with the Erigo® device or control.

However, the Coma Recovery Scale-Revised (CRSr) proposed as an evaluation method for this outcome in this systematic review was only used by three studies,[11,15,17] which represents 83 patients.

In the rehabilitation protocol used by Frazzitta *et al*,[15] it is possible to identify that 11 patients in the intervention group with the Erigo® device (73.3%) versus seven in the control group (43.7%) reached the maximum CRSr score (23 points). Comparing the groups, there was a significant improvement for the group that performed the verticalization with Erigo® (p = 0.03).

Krewer *et al*[11] compared the rehabilitation with the Erigo® device versus verticalization only. After three weeks of treatment, both groups increased their scores, indicating an improved level of consciousness [Erigo®:12 (10-14, 5-18) to 14 (10-18, 4-23); verticalization: 12 (9-14, 3-15) to 17 (12-20, 8-23)]. Considering the comparison of intra-individual changes, the verticalization group showed significantly higher CRSr score values, when compared to individuals rehabilitated with the Erigo® device (p = 0.02).

The study by Taveggia *et al*,[17] involving only eight patients, showed no change in the level of consciousness regarding the interventions made with the Erigo® versus verticalization, after 24 sessions.

Discussion

This is the first systematic review with meta-analysis to demonstrate that the robotic rehabilitation performed by the Erigo® device is safe and appears to reduce the spasticity of patients with stroke. The effects on muscle strength, functionality, and level of consciousness in patients with stroke, severe acquired brain injury and vegetative or minimally conscious state remain uncertain.

The safety of robotic rehabilitation with the Erigo® device was assessed by the analysis of the variation in vital signs such as heart rate and blood pressure. The main adverse effect of immobilization and bed rest is the alteration of the cardiovascular system, leading to a sharp reduction in blood pressure when patients face orthostasis. Physiologically, in the supine position, there is an accumulation of 500 to 1000ml of blood in the lower extremities and in the chest, which temporarily leads to a reduction in venous return to the heart, the

subsequent reduction in cardiac output, and in blood pressure. When the individual transfers from the supine position to the standing position, in response to the baroreflex, there is an increase in the sympathetic activity, subsequent increase in peripheral vascular resistance, venous return, and cardiac output. This compensatory mechanism, due to the change in posture, leads to a drop in systolic blood pressure (5 to 10mmHg), an increase in diastolic blood pressure (5 to 10mmHg), and an increase in heart rate (10 to 25 beats).[22,23]

Six studies included in this systematic review,[10,15,16,18–20] did not show adverse effects or significant reactions to orthostatism. In two studies,[11,17] patients in a vegetative or minimal state of consciousness, had postural hypotension during training with Erigo®. Taveggia *et al*[17] reported that there was a reduction in reactions to orthostatism with the course of treatment. Krewer *et al*[11] report that training interruptions occurred less frequently in the Erigo® intervention group.

Postural hypotension has a multifactorial etiology, including neurodegenerative conditions and neuropathies. Also, the use of antihypertensive drugs and even the reduced sensitivity of baroreceptors, which is related to age, may justify the inability that some patients have to adapt.[23]

Spasticity consists of a motor disorder characterized as a component of the upper motor neuron syndrome and of multifactorial origin, including stroke, cerebral palsy, trauma, and spinal cord injury.[24,25] According to the meta-analysis presented in this review, training with the Erigo® device showed improvement in spasticity in stroke patients. However, the quantitative analysis included small sample size, wide confidence interval, and clinical trials that presented some concerns for methodological biases, indicating the need for further studies to strengthen this finding.

Our results corroborate the systematic review carried out by Fang *et al,*[26] who investigated the effect of robot-assisted gait training on spasticity and pain in patients with spinal cord injury. The authors highlight that such results can be justified by the sensory information that the rhythmic movement provided by robotic devices generates, reducing, hence, reflexes and joint stiffness.

In addition to the verticalization and rhythmic movement of the lower limbs, the Erigo® device enables simultaneous neuromuscular electrical stimulation for

the leg muscles. Thus, the improvement in spasticity evidenced by this review may also be related to this therapeutic resource.

Sharif *et al*,[27] compared the efficacy of FES versus conventional electrical stimulation in the gait rehabilitation of patients after stroke and showed a superior benefit of FES therapy regarding the reduction of spasticity. A justification for the positive results with the use of FES is that its application increases motor coordination, reducing spasticity, whereas conventional electrical stimulation presents greater gains for strength and muscle mass.

Some of the clinical trials included in this systematic review that evaluated muscle strength in stroke patients did not present complete data (pre and post-intervention), so the meta-analysis was performed with only two studies and the results were not significant when comparing robotic rehabilitation to the control group. Similarly, to the spasticity outcome, the sample size of the analyzed studies was small, the confidence intervals wide, and there were concerns related to the risk of bias, indicating the need for studies with greater methodological rigor.

Corroborating our findings, the systematic review by Ambrosini *et al,*[28] subjected patients with sub-acute stroke to cycling training versus cycling associated with FES. The findings showed no significant difference between the groups for the increase in muscle strength, tone, and static balance. Also, the quality of the evidence was limited (low to moderate), since the results were based on publications with small sample sizes and high heterogeneity.

On the other hand, the lack of positive effects on muscle strength can be attributed to the training volume. Kuznetsov *et al*[29] through a controlled, but non-randomized study (convenience sample), obtained an increase in lower limb muscle strength in stroke patients who had performed 30 sessions of robotic rehabilitation and FES, compared to the group that used only the tilt table training.

Regarding functionality, robotic rehabilitation using the Erigo® device seems to have positive effects on this outcome in patients with neurological lesions, as demonstrated by Calabrò *et al*.[10] In contrast, Ancona *et al*[18] showed positive results on functionality after robotic rehabilitation, but they did not present a comparison between the intervention and control groups. For this reason, we cannot affirm that Erigo® is superior to conventional neurorehabilitation therapy.

Other systematic reviews[30,31] reiterate that robotic rehabilitation by means of different devices significantly improves functionality in patients with neurological injuries when compared to conventional treatment. This is supposedly due to the mechanism of neural plasticity since new neural connections are favored when high-intensity, repetitive training occurs.

The level of consciousness seems to improve for patients who perform robotic rehabilitation using Erigo®, in comparison to conventional physical therapy, as demonstrated by Frazzita *et al.*[15] However, considering the studies by Krewer *et al*[11] and Taveggia *et al*,[17] Erigo® was not shown to be superior to tilt table verticalization therapy for this outcome.

Multisensory stimulation helps to increase the consciousness of comatose patients, who can be stimulated by recruiting the ascending reticular activator system or collateral pathways if the former is injured. The ascending reticular activator system is responsible for the state of cortical alertness and rehabilitation with the use of verticalization. It can also assist in this system, favoring the contralateral sensorimotor cortical organization and reducing adverse actions to orthostatism.[32,33]

In general, this systematic review highlights the low reproducibility of RCTs published so far on the effects of Erigo® in patients with neurological injury. The lack of information on the applied protocols, such as angulation of the orthostatic board, number of steps per minute, electrical stimulation parameters, and data on monitoring vital signs (before, during, and after interventions) precludes greater inferences about this technology.

Although the reproducibility of the studies is impaired and the risk of bias presented by all RCTs is moderate, this systematic review synthesized the panorama of robotic rehabilitation with the Erigo® device in the literature, making it possible to guide the application of this technology in clinical practice for the treatment of patients with neurological injuries.

Robotic rehabilitation using the Erigo® device can be an initial rehabilitation strategy during hospitalization and after hospital discharge for patients with motor and cognitive impairments after brain and spinal cord injuries. However, better-designed RCTs with larger sample sizes are needed to strengthen these findings and elucidate the real benefits of this therapy.

Conclusion

Robotic rehabilitation using the Erigo® device is safe for patients with neurological injury and appears to reduce spasticity in patients with stroke. The effects on muscle strength, functionality, and level of consciousness remain uncertain. It is important to reiterate that the methodological quality of the clinical trials included in this review is limited. Therefore, the results should be interpreted with caution.

Authors' contributions

All authors contributed to the construction/design of the study so that the final approved version could be published.

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Conflicts of interest

None.

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Table 1. Characteristics of included studies

Author, Year	Participants	Intervention / Comparison	Sample (%F/M)	Age ± SD (years-old)	Protocol	Outcome measures of interest and instruments
Ancona et al., 2019	Severe acquired brain injury (Ischemic stroke, hemorrhagic stroke, traumatic brain injury).	ERIGO + Convencional Neurorehabilitation / Convencional Neurorehabilitation	44 IG:22 (36,3/63,6) CG: 22 (31,8/68,1)	IG: 59,52 ± 22,16 CG: 68,12 ± 1,60	**IG: Protocol** 1ª session: 60º; 2ª session: 65º; 3ª session: 70º; 4ª session: 75º; 5ª session: 80º. Progression. Step not reported; FES not reported; 45 min of Convencional Neurorehabilitation + 30 min of verticalization with ERIGO; 20 sessions; 5 days/week. **CG: Protocol** Passive and active joint mobilization, maintenance of sitting position on the bed and wheelchair, facilitation of transfers from bed to wheelchair and verticalization with a traditional tilting table. 75 min; 20 sessions; 5 days/week.	- Cardiorespiratory signs: blood pressure, heart rate, peripheral oxygen saturation. - Functionality: Tinetti scale. Functional Independence Measure. - Level of consciousness: Scores of the National Institutes of Health Stroke Scale
Calabrò et al., 2015	Stroke sub-acute	ERIGO + Conventional Physiotherapy / Verticalization + Conventional Physiotherapy	20 IG: 10 (60/40) CG: 10 (50/50)	IG: 71 ± 3 CG: 70 ± 5	**IG: Protocol** 1ª a 3ª session: 10 a 30º over 15 min. 30 steps/min. 5ª session: 60º over 15 min. 35 steps/min. 10ª session: 90º. 40 steps/min. FES: intensity 30 mA, shift of ±10 mA; Six-channel stimulator (bíceps femoris, quadríceps femoris, tibialis anterios and gastrocnemius); **CG: verticalization** Protocol: 15 min based on Bobath method. 15 min simples tilt-table. 45 min of standard physical treatment program, followed by verticalization. 30 sessions; 5 days/week for 6 weeks.	- Cardiorespiratory signs: mean blood pressure, mean heart rate, mean oxygen saturation. Fatigue and discomfort: Visual analogic scale. - Functionality: Fugl-Meyer scale for lower limbs. - Muscle Strength**:** Muscle Research Council. - Level of consciousness Ravens Coloured Progressive Matrices test.

Frazzitta et al., 2016	Vegetative State or Minimally Conscious State	ERIGO + Conventional Physiotherapy / Conventional Physiotherapy	31 IG: 15 (40/60) CG: 16 (31,25/68, 75)	IG: 53 ± 15 CG: 69 ± 16	**IG: Protocol** Gradually increased from 0°to 20°,40° and then 60° in a time span of nine min. 20 steps/min. Not reported FES; 30 min of conventional in-bed physiotherapy + 30 min of ERIGO; 15 sessions; 5x/week (Monday-Friday). **CG:** Conventional in-bed physiotherapy (mobilization exercises in the supine and sitting position on bed, without out-of-bed mobilization nor verticalization). 60 min/day, from Monday to Friday, throughout the ICU stay. 15 sessions; 5x/week (Monday-Friday).	- Cardiorespiratory signs: mean arterial pressure, heart rate, oxygen saturation. **(no data)** - Level of consciousness: Levels of Cognitive Functioning, Disability Rating Scale, Glasgow Coma Scale, Coma Recovery Scale-Revised.
Krewer et al., 2015	Vegetative State or Minimally Conscious State	ERIGO + Conventional Physiotherapy / Tilt table + Conventional Physiotherapy	44 IG: 22 (45,4/54,4) CG: 22 (36,3/63,6)	IG: 53 ± 15 CG: 52 ± 14	**IG:** 70º Not reported steps; Not reported FES; 60min; 10 sessions over 3 weeks; 3 to 4 sessions/week. **CG:** Tilt table + conventional physiotherapy 60min; 10 sessions over 3 weeks; 3 to 4 sessions/week.	- Cardiorespiratory signs: Blood pressure, heart rate, oxygen saturation. **(not data).** - Spasticity: Modified Ashworth Scale. - Level of consciousness: Coma Recovery Scale-Revised,
Kumar et al., 2020	Stroke (Ischemic or hemorrhagic)	ERIGO / Conventional Physiotherapy	110 IG: 55 (45,5/54,5) CG: 55 (45,5/54,5)	IG: 50,80 ± 6,86 CG: 51,36 ± 8,10	**IG: Protocol** 1 week: 30º for 40 min; 2-3 week: 50º for 40 min; 4 week: 75º for 40 min. Not reported steps; Not reported FES; 40 min + 15 min exercise program for upper extremities; 6x/week; 4 weeks. **CG:** Mobilization exercises in supine and sitting position on bed, without out-of-bed mobilization nor verticalization. 50 to 60 min/day; 30 days. **IG+CG:** During 30 and 90 days, subjects were asked to perform a home exercise program.	- Cardiorespiratory signs: Blood pressure. (**only pre-intervention data)** - Muscle Strength: Medical Research Council. - Spasticity: Modified Ashworth Scale

Rocca et al., 2016	Severe brain trauma	ERIGO + Conventional Physiotherapy / CG 1- Conventional Physiotherapy CG 2- MOTOmed Letto® + Conventional Physiotherapy	30 IG: 10 (40/60) CG1: 10 (40/60) CG2: 10 (50/50)	CG1: 50,5 CG2: 53,5 IG: 58,8	**IG: Protocol** First step: 0º, started leg movements. 5 min. Secund step: progressively put in a vertical position (at 30°–50°–70° for 10 min each). Started leg movements. 30 min. Third step: the patient was returned to a supine position. 10 min. Not reported steps; Not reported FES; **CG1: Protocol** mobilized out of bed only by physiotherapists. **CG2: Protocol** MOTOmed Letto® 30 min, 5 days/week. **IG+CG1+CG2** Patients in groups 1 and 3 were mobilized in bed by physiotherapists, according to usual clinical physiotherapy standard recommendations in our hospital. Patients in group 2 were mobilized in bed by either physiotherapist and with a MOTOmed® session of almost 30 min 5 days/week.	- Cardiorespiratory signs: Blood pressure, heart rate. respiratory rate
Taveggia et al., 2015	Vegetative State or Minimally Conscious State	ERIGO / Verticalization	8 IG:4 (50/50) CG:4 (50/50)	IG: 65 ± 8 CG: 63 ± 16	**IG: Protocol** Verticalization with a tilt table at 30º, after 10 min, 65º. 18 steps/min; Not reported FES; 30 min; 24 sessions; 3x/week. **CG:** Robotic verticalization system, but an inactive lower-limb movement system. Verticalization with a tilt table at 30º, after 10 min, 65º. 30 min; 24 sessions; 3x/week.	- Cardiorespiratory signs: mean arterial pressure, heart rate. - Level of consciousness: Levels of Cognitive Functioning, Coma Recovery Scale-Revised.
Yadav et al., 2018	Stroke	ERIGO / Conventional Physiotherapy	30 IG: 15 (33,3/66,6)	IG: 49,87 ± 8,41 CG: 49,53 ± 6,22	**IG: Protocol** Phase 1: 30º for 40 min, after 12 min at 0º. Legs moved passively. Phase 2: 50º for 40 min, after 12 min at 0º. Legs moved passively.	- Cardiorespiratory signs: Blood pressure. - Muscle Strength: Medical Research Council.

			CG: 15 (53,3/46,6)		Phase 3: 75º for 40 min, after 12 min at 0º. Legs moved passively. Not reported steps; Not reported FES; 40 min + 15 min exercise program for the upper extremities; 6x/week; 4 weeks. **CG:** Range of motion; prevent spasticity; common mat activities; Bridging exercises; Stretching; Gentle and controlled weight-bearing exercises; Balance and coordination exercises. 50 to 60 min/day; 6x/week; 4 weeks.	
Yadav et al., 2018 (pilot)	Stroke (Ischemic and hemorrhagic)	ERIGO / Conventional Physiotherapy	30 IG: 15 (33,3/66,6) CG: 15 (53,3/46,6)	IG 49,87 ± 8,41 CG 49,53 ± 6,22	**IG: Protocol** Phase 1: 30º for 40 min, after 12 min at 0º. Legs moved passively. Phase 2: 50º for 40 min, after 12 min at 0º. Legs moved passively. Phase 3: 75º for 40 min, after 12 min at 0º. Legs moved passively. Not reported steps; Not reported FES; 40 min + 15 min exercise program for the upper extremities; 6x/week; 4 weeks. **CG:** Range of motion; prevent spasticity; common mat activities; Bridging exercises; Hamstring; Gentle and controlled weight-bearing exercises; Balance and coordination exercises. 50 to 60 min/day; 6x/week; 4 weeks.	- Cardiorespiratory signs: Blood pressure, heart rate. - Spasticity: Modified Ashworth Scale - Level of consciousness: Glasgow Coma Scale, Mini-Mental State Examination, National Institutes of Health Stroke Scale.

Legend: F: female; **M:** male; **CG:** control group; **IG:** intervention group; **FES:** functional electrical stimulation;

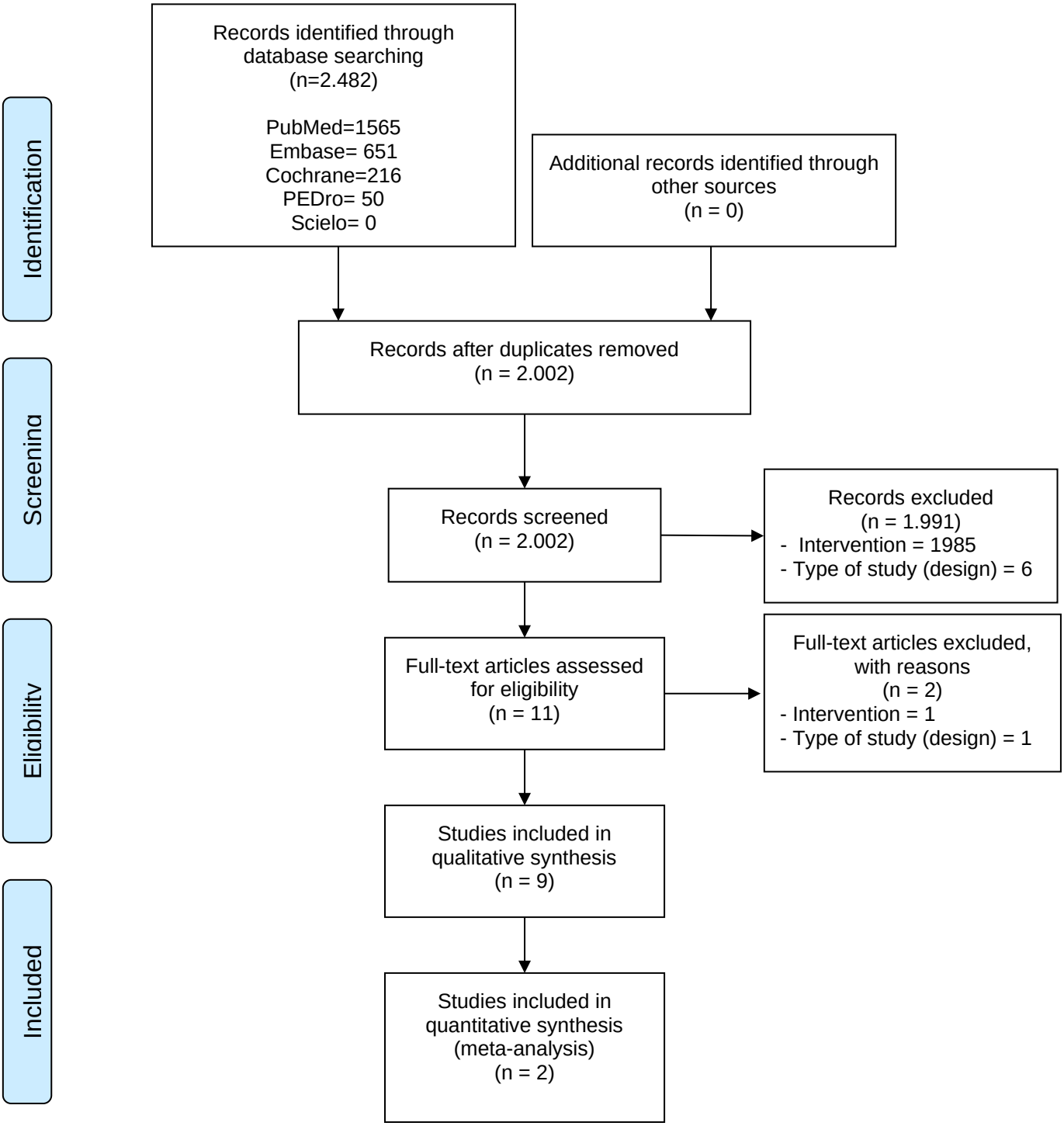

Figure 1. Flowchart of study selection

Table 2. Evaluation of the risk of bias using the Rob 2 tool from Cochrane

Author, Year	Randomization process	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Ancona et al., 2019 Cardiorespiratory signs, Functionality	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Calabró et al., 2015 Cardiorespiratory signs, Functionality, Muscle Strength	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Frazzitta et al., 2016 Level of consciousness	Low	Some concerns	Low	Low	Low	Some concerns
Krewer et al., 2015 Spasticity, Level of consciousness	Low	Some concerns	Low	Low	Low	Some concerns
Kumar et al., 2020 Muscle Strength, Spasticity	Low	Some concerns	Low	Low	Some concerns	Some concerns
Rocca et al., 2016 Cardiorespiratory signs	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Taveggia et al., 2014 Cardiorespiratory signs Level of consciousness	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Yadav et al., 2018 (pilot) Cardiorespiratory signs, Spasticity	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Yadav et al., 2018 Cardiorespiratory signs, Muscle Strength	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns

Spasticity

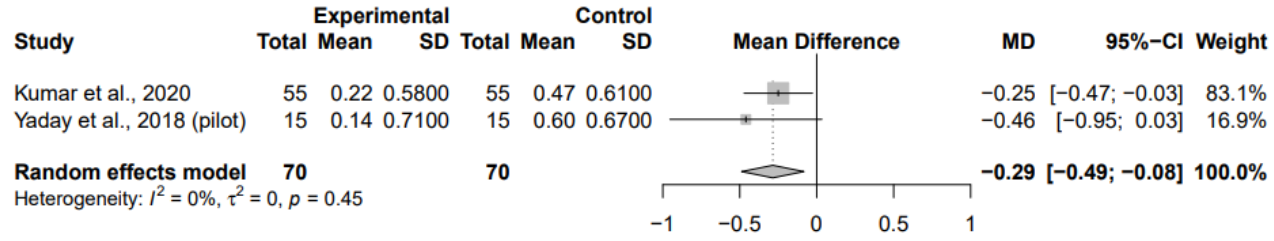

Figure 2. MD and 95% CI on spasticity evaluated by Scale Modified Ashworth for Erigo® *vs* control group. Abbreviations: CI, confidence interval; MD, mean difference.

Muscle Strength

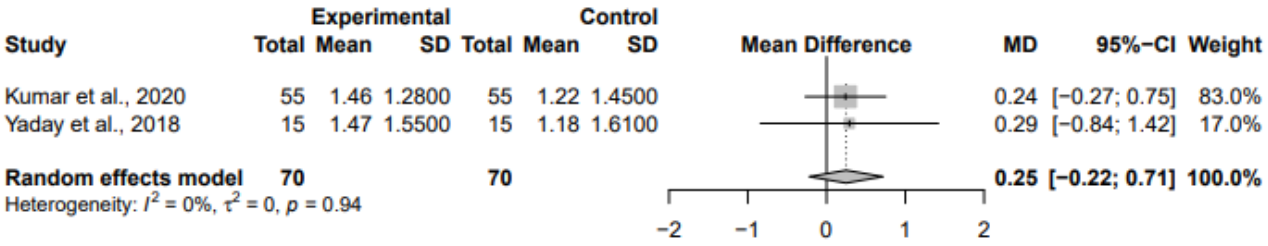

Figure 3. MD and 95% CI on muscle strength evaluated by Medical Research Council for Erigo® *vs* control group. Abbreviations: CI, confidence interval; MD, mean difference.

ARTIGO 2

ROBOTIC REHABILITATION IN STROKE PATIENTS: A PROTOCOL OF A RANDOMIZED CLINICAL TRIAL

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Abstract

Background: Individuals who have suffered a stroke may present motor impairment, sensory and cognitive changes, which negatively affect functionality. The objective of this study protocol is evaluating the effect of robot-assisted orthostatic board training and neuromuscular electrical stimulation (robotic rehabilitation) on the functionality of subacute stroke patients. **Methods/Design:** Forty patients with stroke will be randomized to a control group (conventional physical therapy) or intervention group (conventional physical therapy plus robotic rehabilitation). Interventions will take place every day in the hospital phase and 3 times/week after discharge, totaling approximately 18 sessions. The groups will be evaluated before the interventions, after the tenth session, and at the end of six weeks of treatment or 18 sessions. Functionality will be considered the primary outcome of the study and will be assessed using the Fugl-Meyer Scale. We considered as secondary outcomes muscle strength (Medical Research Council and maximum repetition test), spasticity (Modified Ashworth Scale), quadriceps muscle architecture and echogenicity (ultrasound), mobility (Time Up Go test), degree of disability and dependence (Rankin scale), quality of life (EQ-5D questionnaire), cardiorespiratory repercussions (monitoring vital signs), length of hospital stay (in days) and mortality (number of deaths). For data analysis, repeated-measures ANOVA with Bonferroni post hoc will be used to compare the effect of the groups' interaction with time. The level of significance adopted will be 5%. **Trial registration:** Clinical Trial Registry number NCT04494685.

Keywords: Brain Diseases; Robotics; Clinical trial; Rehabilitation; Electrical stimulation.

Background

Stroke is among the most prevalent cardiovascular diseases in the world, and in Brazil it represents 20.73% of cases of hospitalization in patients over 40 years, strongly impacting the costs to the health system [1]. Affected patients have different functional impairments, depending on the location on the brain and the type of injury. Motor paralysis or paresis are the main outcomes that result in detriment to performance in carrying out activities of daily living [2] and impaired quality of life [3].

The rehabilitation process, including physical therapy should be started as early as possible, once the patient is hemodynamically stable. Prolonged bed rest, besides causing muscle atrophy and deconditioning, affects adequate cerebral blood flow. Such long-term changes may affect the sympathetic nervous system and contribute to intolerance to orthostasis [4, 5]. Early rehabilitation, besides reducing complications resulting from prolonged bed rest, stimulates the afferent sensory nervous system and reduces spasticity in patients [6]. In this context, in order to improve patient care in the subacute stroke innovations are necessary in the rehabilitation process and early interventions.

The robotic board emerges as a new ergometric technology, which facilitates lower limb exercises through a robot associated with neuromuscular electrical stimulation (NMES) [6]. It is a resource that allows passive orthostasis up to 90º, as well as the passive movement of knees and hips [7]. Among the benefits of orthostasis are biomechanical alignment, with stretching and unloading of weight in the joints, optimization of volumes and lung expansion, in addition to spatial information on adjustments to the central nervous system allowing better stimuli and autonomic adaptations [8].

The Erigo® robotic board (Hocoma, Volketswil, Switzerland) proved to be a safe and effective device for stroke patients [9, 10], however, the literature lacks robust

evidence, with well-defined protocols, reproducible and with adequate sample size. Thus, further research is needed to assess the effects of this therapy on stroke patients, for subsequent implementation of this resource in rehabilitation centers.

The objective of this protocol is to evaluate through a randomized, single-blind clinical trial, the effect of robot-assisted orthostatic board training and neuromuscular electrical stimulation (robotic rehabilitation) on the functionality, muscle strength, spasticity, quadriceps muscle architecture and echogenicity, mobility, degree of disability and dependence, quality of life, cardiorespiratory repercussions, length of hospital stay and mortality of subacute stroke patients.

Methods/Design

Design and ethical aspects

The study was designed as a randomized, single-blind clinical trial. The research project was approved by the Ethics Committee of the Irmandade da Santa Casa de Misericórdia de Porto Alegre (ICSMPA) and of the Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, RS, Brazil (CAEE: 21991819.5.3001.5345; report number 4.096.671) and the protocol was registered at ClinicalTrials.gov (NCT04494685). All patients will sign the free and informed consent form prior to carrying out any procedure and in the case of incapacity, the consent will be given by the relative.

Any changes that occur in the study protocol during the recruitment of volunteers or data collection will be communicated to the institution's Ethics Committee and ClinicalTrials.gov.

Participants

The study population consists of stroke patients. The sample will consist of patients with ischemic stroke, in the subacute phase (48 hours after the event), admitted to Hospital São José in the ISCMPA hospital complex. They are patients of both sexes, aged between 18 and 85 years and who have hemiparesis or muscle weakness defined by the Medical Research Council (MRC) with a score of less than 48 points[11]. In addition, the selected patients must be able to understand simple commands and report signs of discomfort. Neither a history of stroke without motor sequelae prior to current hospitalization, nor the need for ventilatory support or tracheostomy will be considered exclusion criteria.

Patients with an evolution from ischemic to hemorrhagic events, those who do not develop compensatory hemodynamic adjustments after the postural change in the orthostatic board or who present important hemodynamic changes during training will be excluded.

Randomization

Randomization will be carried out through the www.randomization.com website. The sequence of numbers will be generated by a researcher "blind" to the study, at a 1:1 ratio. The sequence of numbers will be revealed to the physiotherapists who will carry out the proposed protocols only at the beginning of the intervention program in order to guarantee the concealment of the allocation. Patients will be randomized to the control group (CG) which will receive conventional physical therapy or to the intervention group (IG), which will perform robotic rehabilitation using Erigo® equipment (Hocoma, Volketswil, Switzerland) in addition to conventional physical therapy.

Outcomes and evaluations

Functional independence will be considered the primary outcome of the study. Muscle strength, spasticity, quadriceps muscle architecture and echogenicity, mobility, degree of disability and dependence after stroke, quality of life, cardiorespiratory repercussions, length of hospital stay, and mortality will be measured as secondary outcomes.

Prior to the evaluations, medical records will be consulted to collect personal, demographic, anthropometric data, medical diagnosis, previous comorbidities, and information on medications used by patients.

Functionality evaluation

Functionality will be assessed using the Fugl-Meyer Scale. This scale allows assessing the mobility and the ability to perform different activities that require from sensorimotor functions to walking after stroke. It consists of six domains: a range of motion, pain, sensitivity, motor function of the upper and lower extremities, balance, coordination, and speed. The score for each item ranges from 0 to 2, where 0 = cannot be performed; 1 = partially accomplished; 2 = completely accomplished. The total score ranges from 0 to 266 points. The higher the score the better is the functionality. Less than 50 points in the score indicate severe motor impairment, 50-84 marked, 85-95 moderate, and 96-99 light, patients must have at least moderate impairment to be enrolled in the study [12].

Muscle Strength evaluation

For the evaluation of muscular strength, the MRC scale and the test of maximum repetition (1RM) will be used.

The MRC scale comprises a score of 1 to 5 for each muscle group, as follows: 0 = no contraction, 1 = flicker or trace contraction; 2 = active movement, with gravity eliminated; 3 = active movement against gravity; 4 = active movement against gravity and resistance; and 5 = normal muscle strength. The total score ranges from 0 (for quadriplegia) to 60 points (for preserved muscle strength), including shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and dorsiflexion of the ankle movements, all scored bilaterally. A score below 48 is conclusive for muscle weakness acquired in the intensive care unit [11].

The 1RM test will be performed to evaluate the dynamic strength of the quadriceps muscle. For this, an extension chair will be used (7Cinco - Pro Sport Fitness, Porto Alegre / RS, Brazil). In the sitting position, with the hips and knees at 90◦ flexion, the patient will be instructed to extend both knees against the resistance placed in the anterior region of the ankles until the maximum range of motion. If two repetitions are completed, the load will be increased until the patient can perform a single maximum repetition across the range of motion without postural compensations [13].

Spasticity evaluation

The modified Ashworth Scale will be used to evaluate spasticity. This scale consists of an ordinal classification of 5 points for grading the resistance found during passive stretching, where 0 indicates normal muscle tone and 4 indicates a severe increase in tone, causing flexion or extension stiffness.

The patient will be placed in the supine position and the tests will be applied to the lower and upper limbs. When a muscle with flexion function is tested, the joint will be positioned in maximum flexion and the extension will be performed in one second and the same process will be carried out for a muscle that performs the extension [14].

Muscle architecture and echogenicity evaluation

The assessment of muscle architecture and echogenicity will occur by acquiring ultrasound images of the medial and lateralis vastus and rectus femoris by a high-resolution ultrasound device (Vivid-i, GE, USA). Specifically, the quadriceps muscle thickness (vastus lateralis, vastus medialis, and rectus femoris), the cross-sectional area of the rectus femoris, and its echogenicity will be evaluated. To assess the thickness of the vastus lateralis and rectus femoris the midpoint between the greater trochanter and the lateral condyle of the femur will be used as a reference point, while measurements of the vastus medialis will be performed at 25-30% of this distance, according to patient characteristics. Three images will be obtained with the ultrasound transducer longitudinally positioned on the muscle fibers of each of the knee extensor muscles to assess muscle thickness [15]. To assess the cross-sectional area and echogenicity of the rectus femoris, three images will be obtained, however, the ultrasound transducer will be positioned transversely on the rectus femoris, with the midpoint between the greater trochanter and the lateral condyle of the femur being used as a reference [16]. Finally, all images will be analyzed using the ImageJ software.

Mobility evaluation

Mobility will be assessed by the Timed Up and Go (TUG) test. This test consists of transferring from a sitting to a standing position, walking for three meters, changing direction during gait, and transferring from a standing to a sitting position. The shorter the time to perform the test the better is the performance [17].

During the TUG test, an inertial sensor (BTS G-Walk, Kinetec, Porto Alegre, RS, Brazil) will be attached to the patient's waist, at the height of the L4-L5 spaces, using a

semi-elastic band. This sensor will allow monitoring gait phases and linear accelerations in three orthogonal axes (anteroposterior, medio-lateral and vertical) through a wireless network, transmitting the signals via Bluetooth to a computer. The time required to get up, acceleration, time, and speed of rotation will be monitored as well as the time required to sit [18, 19].

Degree of disability and dependence evaluation

The modified Rankin scale will be used to determine the degree of disability and dependence after a stroke. This instrument has 6 scores, where: 0 = asymptomatic; 1 = symptoms without disabilities; 2 = mild disability; 3 = moderate disability; 4 = moderate to severe disability; 5 = severe disability and 6 = death [20].

Quality of life evaluation

Quality of life will be assessed using the EuroQol-5D (EQ-5D) questionnaire. This is a generic instrument that assesses mobility, personal care, usual activities, pain/malaise, and anxiety/depression and allows to create a general index of the value of an individual's health status. The number 1 indicates the best state of health (perfect health) and 0 the worst state of health (death) [21].

Cardiorespiratory parameters evaluation

Vital signs will be checked prior to the first intervention and during the 18 sessions to assess the cardiorespiratory response and intervention safety. The following will be measured: systolic and diastolic blood pressure; heart rate; peripheral arterial oxygen saturation; and also the dyspnea index using the modified Borg effort scale and pain using the visual analog scale (VAS).

Length of hospital stay

The days between the patient's admission and hospital discharge will be counted to assess the total length of hospital stay.

In general, the evaluations will be carried out by a researcher who is blind to the interventions at three moments, at baseline, after the 10th session, and at the end of the protocols (18th session). Some particularities: the application of the Fugl-Meyer scales, MRC, Modified Ashworth Scale, Rankin Scale, and the assessment of quadriceps muscle architecture and quality of life will be performed prior to interventions. In the 10th session, the Fugl-Meyer Scale, MRC, the Modified Ashworth Scale will be reapplied and the mobility and muscle strength tests will be performed (TUG and 1RM test respectively). At the end of the protocols or after the 18th session, all evaluations will be repeated.

Study Protocol

Intervention

Interventions will take place during the hospital phase and after discharge. During hospitalization, protocols will be performed daily, once a day. After discharge, patients from both groups will be seen at the Rehabilitation Center of Pavilhão Pereira Filho of ISCMPA, by physiotherapists specialized in robotics, three times a week, on alternate days, totaling 18 sessions at the end of the protocols. It is observed that resistance training with shorter protocols has been able to contribute to neural adaptation and increased muscle fiber cross-sectional area in healthy patients [22, 23].

The CG will perform conventional physical therapy during the hospital phase, conducted by physiotherapists at the hospital. The exercises proposed during hospitalization aim at early mobilization, tone modulation, maintenance of joint amplitudes, maintenance/gain of muscle strength, improvement of balance, and gain of functional independence. After hospital discharge, in the outpatient phase, the same group will perform an exercise protocol according to the objectives established by the Guidelines for Adult Stroke Rehabilitation and Recovery [24]. Knee and hip flexion and extension movements will be worked on; hip adduction and abduction, respecting the articular physiology of each joint; weight transfer in the sitting position and in orthostasis; mini-squat and gait training. In the end global stretching of the upper and lower limbs will be carried out. Outpatient care will last 30 minutes and three series with 10 repetitions for each exercise will be performed. A progression to four series will be established from the 10^{th} session, as well as a maximum therapy time of 40 minutes.

The IG will perform robotic rehabilitation in the hospital phase, replacing the conventional physiotherapy session conducted by physiotherapists in hospital as well as after discharge. Robotic rehabilitation performed using the Erigo® device (Hocoma, Volketswil, Switzerland) provides orthostasis assisted by an orthostatic board, passive and assisted movement of the legs, in addition to NMES of the quadriceps and hamstring muscles simultaneously with the mobilization of the legs. The NMES will be applied through self-adhesive electrodes size 7.5x13 (model CF7515, Arktus, São Paulo, SP, Brazil), with the following parameters: 50 Hz frequency, 500 μs pulse width, three seconds of ramp and current intensity according to the patient's tolerance, as long as the muscle contraction is visible [25, 26].

The rehabilitation protocol performed using the Erigo® device will be based on the overload principle [27] as proposed below:

1st session: Initially the orthostatic board will be tilted until reaching 30º. If there is no hemodynamic decompensation, the inclination will be increased to 80º and the patient will remain in this position for 15 to 20 minutes, not exceeding the 500-step mark until the end of the therapy. The robot will perform the hip and knee flexion/extension movements at a cadence of 16-20 steps/minute. The driving force will be between 100-80%. For the remaining sessions, the patient will be vertical and the mobilization of the lower limbs associated with NMES will begin immediately. The return to the starting position will have a progression similar to the initial one.

2nd to 4th session: If the patient is adapted to the inclination of the board when it reaches 90º the robot will perform the flexion/extension movements of the hip and knee respectively for 30 minutes. Cadence: 20-24 steps/minutes; driving force 80-60%.

5th to 7th session: At 90º angle; 30-minute session; cadence 24-28 steps/minutes; driving force 60-40% by the end of the protocol.

8th to 10th session: At 90º angle; 40-minute session; cadence 28-32 steps/minutes.

11th to 13th session: At 90º angle; 40-minute session; cadence 32-36 steps/minutes.

14th to 18th session: At 90º angle; 40-minute session; cadence 36-40 steps/minutes. The 18th session will be performed with a driving force of 40%.

Vital signs will be continuously monitored during robotic rehabilitation. Hemodynamic decompensation (systolic pressure with reduction > 20 mmHg and diastolic pressure > 10 mmHg or heart rate with elevation > 30 bpm from baseline), a significant fall in peripheral arterial oxygen saturation, tachypnea, ventilatory effort, sweating, malaise reported by the patient will be considered criteria for the interruption of training. If, in the second subsequent session of the protocol, the patient does not tolerate the intervention again or presents hemodynamic instability, he will be excluded

from the study. The group composition flowchart, assessment, and intervention procedures are shown in Figure 1.

To ensure adherence to treatment, all patients need to perform at least 15 out of the 18 robotic rehabilitation or conventional physical therapy sessions provided by the protocol. In addition, if any major adverse effect occurs as a result of the interventions proposed in this protocol, the researchers will provide medical assistance to the patient and the protocol will be reviewed.

Data analysis

The sample was calculated using the Gpower® software version 3.1 and was based on a study by Calabrò et al. [9] that evaluated the effect of robotic rehabilitation using the Erigo® device in stroke patients. The muscle strength assessed by the MRC scale was adopted as the outcome to estimate the sample size, using a mean difference between the control and intervention groups of +1 and +2 respectively, the standard deviation of ± 1, alpha error of 5% and 80% power. Thus, the sample size was estimated to be 17 patients per group. Predicting losses, 20 patients will be recruited per group.

After data collection, for data analysis, generalized estimating equation (GEE) will be used to analyze the effect of the intervention between the groups. The level of significance adopted will be 5% ($p<0.05$).

All data collected during the study will be stored on a computer by one of the team's researchers and copies will be made daily to a second device for security reasons. Patient identification data will be kept confidential by identifier numbers and the results of the study will be disclosed only at events and in scientific journals.

Discussion

This protocol of a randomized clinical trial may bring a new perspective on the rehabilitation of patients with subacute stroke, demonstrating whether robotic rehabilitation using the Erigo® device has positive effects on functionality and whether robotic rehabilitation is better than conventional physical therapy for this population.

In addition, this study intends to establish a reproducible protocol for the rehabilitation of stroke patients in the Erigo® device, establishing a progression of steps and muscle activation by the patient, following the principle of work overload.

List of abbreviations

CG: Control group; EQ-5D: EuroQol-5D; IG: Intervention group; ICSMPA: Irmandade da Santa Casa de Misericórdia de Porto Alegre; MRC: Medical Research Council; NMES: Neuromuscular electrical stimulation; 1RM: Test of maximum repetition; TUG: Timed Up and Go; VAS: Visual analog scale.

Declarations

Ethics approval and consent to participate

The research project was approved by the Ethics Committee of the ICSMPA and of the Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil (CAEE: 21991819.5.0000.5335; report number 3.722.469) and the protocol was registered at ClinicalTrials.gov (NCT04494685). All patients will sign the free and informed consent form prior to carrying out any procedure.

Consent for publication

All volunteers are aware of this publication and have clarified the importance of the study and publication of the manuscript.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that there is no conflict of interest.

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Authors' contributions

ABG conceived of the study, designed, planned and wrote the manuscript. RDMP, AHEG, TTR, and NCR conceived, designed, planned and revised of the study. JS conceived of the study, designed, planned, wrote and revised the manuscript. All authors read and approved of the manuscript.

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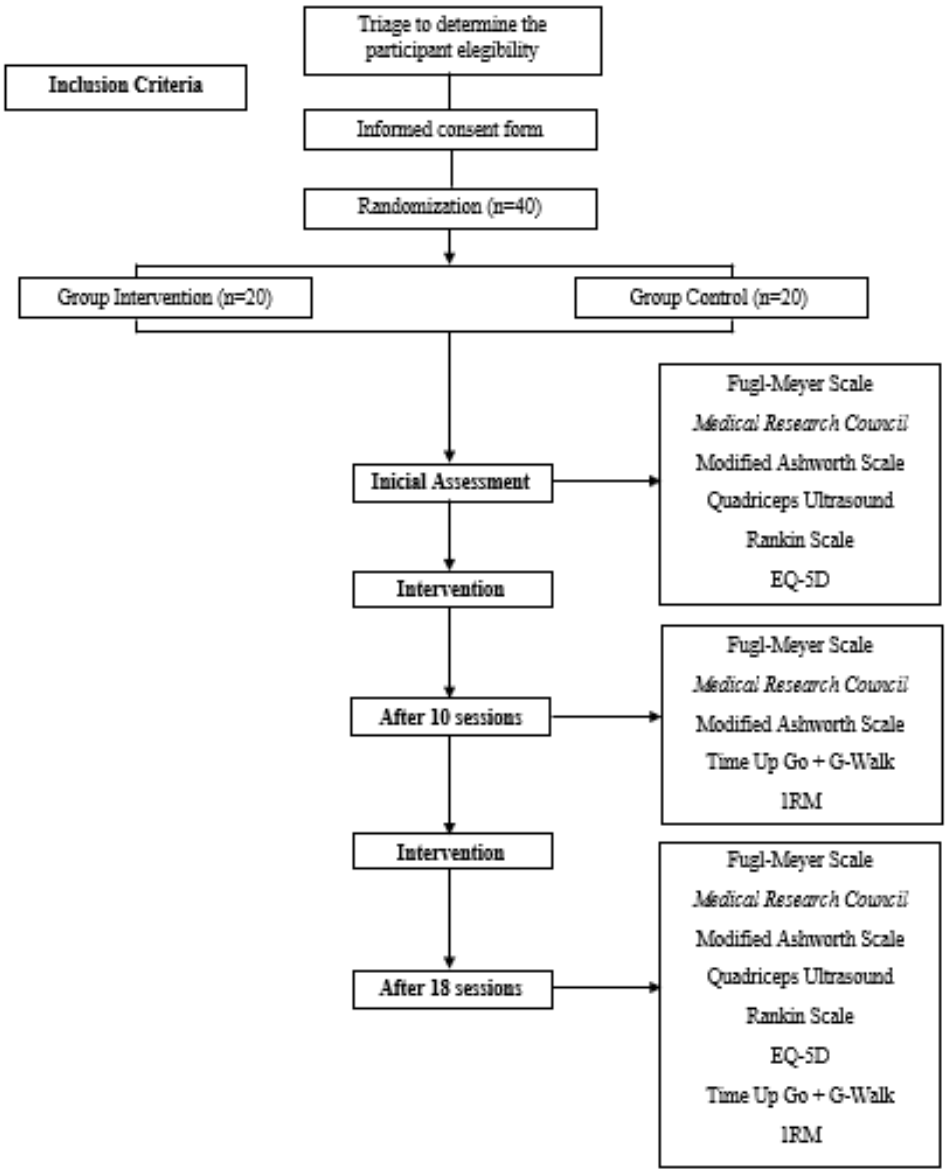

Figure legends

Figure 1: Flowchart of groups composition, evaluations and intervention

CONCLUSÕES FINAIS

A partir dos achados contemplados na revisão sistemática apresentada nesta dissertação podemos concluir que o dispositivo robótico Erigo® é seguro para a mobilização de pacientes com lesões neurológicas, como também apresenta alguns benefícios em relação a espasticidade de pacientes com AVE e severa desordem da consciência.

O segundo artigo apresentado nesta dissertação buscou reproduzir um protocolo de ensaio clínico randomizado com o uso da reabilitação robótica em pacientes pós AVE isquêmico. Nosso protocolo será utilizado como base para a realização de um ensaio clínico randomizado devido à heterogeneidade dos estudos publicados até o momento, visando fortalecer a evidência existente.

Novos ensaios clínicos se fazem necessários nesta temática com maior número de pacientes e protocolos de reabilitação passíveis de reprodutibilidade, a fim de reforçar nossos achados e elucidar outros benefícios do dispositivo Erigo® para pacientes com lesões neurológicas.

ANEXO A- Comprovante de aprovação do projeto pelo Comitê de Ética em Pesquisa da Irmandade Santa Casa de Misericórdia de Porto Alegre

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

PARECER CONSUBSTANCIADO DO CEP

Elaborado pela Instituição Coparticipante

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: EFEITOS DA REABILITAÇÃO ROBÓTICA EM PACIENTES PÓS ACIDENTE VASCULAR CEREBRAL: UM ENSAIO CLÍNICO RANDOMIZADO

Pesquisador: Rodrigo Della Méa Plentz

Área Temática:

Versão: 1

CAAE: 21991819.5.3001.5345

Instituição Proponente: Universidade Federal de Ciências da Saúde de Porto Alegre

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.096.671

Apresentação do Projeto:

Os pacientes acometidos por um acidente vascular cerebral (AVC)apresentam diferentes comprometimentosfuncionais dependendo da localização no território encefálico. Nesse contexto, a equipe multiprofissional visa buscar alternativas na recuperação da funcionalidade pós-AVC e favorecer a alta hospitalar precoce. Este estudo tem como objetivo avaliar o efeito da reabilitação robótica através do treinamento em prancha ortostática assistida por robô e eletroestimulação neuromuscular (EENM), sobre a funcionalidade em pacientes pós-AVC. Trata-se de um ensaio clínico randomizado, com pacientes da unidade de internação do Hospital São José da Irmandade Santa Casa de Misericórdia de Porto Alegre(ISCMPA),os quais serão alocados em grupo fisioterapia convencional ou grupo reabilitação robótica (que receberá a fisioterapia de rotina e a reabilitação robótica). Os grupos serão avaliados previamente a qualquer intervenção fisioterapêutica, no momento da alta hospitalar e ao final de cinco semanas de tratamento. Serão mensurados os seguintes desfechos: independência funcional, força muscular periférica, arquitetura muscular,espasticidade, resposta cardiorrespiratória, mobilidade, amplitude de movimento, tempo de internação hospitalar e taxa de mortalidade. Hipotetiza-se que a reabilitação robótica apresenta resultados superiores em relação à fisioterapia convencional em pacientes pós-AVC sobre os desfechos avaliados neste trabalho.

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Objetivo da Pesquisa:

Objetivo Primário:

Avaliar os efeitos do treinamento em prancha ortostática assistido por robô e EENM (reabilitação robótica) sobre a funcionalidade de pacientes pós

AVC na fase subaguda e crônica.

Objetivo Secundário:

Avaliar os efeitos do treinamento em prancha ortostática assistida por robô e EENM sobre a força muscular periférica;

Avaliar os efeitos do treinamento em prancha ortostática assistida por robô e EENM sobre a arquitetura muscular e ecogenicidade;

Avaliar os efeitos do treinamento em prancha ortostática assistida por robô e EENM sobre a espasticidade;

Avaliar os efeitos do treinamento em prancha ortostática assistida por robô e EENM sobre a resposta cardiorrespiratória;

Avaliar os efeitos do treinamento em prancha ortostática assistida por robô e EENM sobre a mobilidade;

Avaliar os efeitos do treinamento em prancha ortostática assistida por robô e EENM sobre a amplitude de movimento;

Avaliar os efeitos do treinamento em prancha ortostática assistida por robô e EENM sobre o tempo de permanência hospitalar;

Avaliar os efeitos do treinamento em prancha ortostática assistida por robô e EENM sobre a taxa de mortalidade.

Avaliação dos Riscos e Benefícios:

Riscos:

O tratamento com o aparelho automático tem alguns riscos: tontura, mal-estar, desconforto no peito e nas pernas (devido a faixa de segurança que ficará presa no seu peito e nas suas pernas para que o senhor não caia do aparelho) ou ainda dor muscular após o exercício. O fisioterapeuta

responsável pelo treinamento estará monitorando os sintomas e se for necessário ele interromperá o exercício e comunicará o médico.

Benefícios:

Os possíveis benefícios desta intervenção consistem na melhora da funcionalidade e mobilidade. Melhora das funções motoras como, incremento da

força muscular das pernas, ganho de amplitude de movimentos e redução da espasticidade.

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UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3303-8804 **E-mail:** cep@ufcspa.edu.br

Possíveis benefícios cardiovasculares, como também,
redução da permanência hospitalar e taxas de mortalidade

Comentários e Considerações sobre a Pesquisa:

O projeto de pesquisa está de acordo com as exigências do Sistema CEP-CONEP.

Considerações sobre os Termos de apresentação obrigatória:

Adequados.

Recomendações:

Recomenda-se o encaminhamento ao pesquisador para que dê início à pesquisa.

Conclusões ou Pendências e Lista de Inadequações:

Não foram apresentados óbices éticos.

Considerações Finais a critério do CEP:

De acordo com o parecer do relator.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1478414.pdf	27/05/2020 11:17:00		Aceito
Outros	Termo_Compromisso_Entrega_Relatorios_UFCSPA.pdf	27/05/2020 11:16:26	Rodrigo Della Méa Plentz	Aceito
Outros	CartaResposta.docx	23/09/2019 19:42:53	Andrieli Barbieri Garlet	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEFundacao.docx	19/09/2019 20:04:42	Andrieli Barbieri Garlet	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLESantaCasa.docx	19/09/2019 20:03:53	Andrieli Barbieri Garlet	Aceito
Projeto Detalhado / Brochura Investigador	ProjetoDeMestrado.pdf	03/09/2019 23:19:21	Andrieli Barbieri Garlet	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:

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Bairro: Sarmento **CEP:** 90.050-170
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3303-8804 **E-mail:** cep@ufcspa.edu.br

Não

PORTO ALEGRE, 18 de Junho de 2020

Assinado por:
EDI CÁRMEN PULROLNIK
(Coordenador(a))

Endereço: Rua Sarmento Leite ,245
Bairro: Sarmento **CEP:** 90.050-170
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Anexo B- Normas de formatação do periódico Brazilian Journal of Physical Therapy.

GUIDE FOR AUTHORS

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, non-randomized 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).

c) Qualitative studies: studies that focus on understanding needs, motivations, and human behavior. The object of a qualitative study is guided by in-depth analysis of a 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). Funding solely based upon scholarships or fellowships are not considered as substantially funded.

h) Short communications: the BJPT will publish one short communication per issue (up to six a year) in a format similar to that of the original articles, containing 1200 words and up to two figures, one table, and ten references.

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-mails to the editor in chief with an expression of interest to submit a masterclass article to the BJPT.

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:
- E-mail address
- Full postal address

All necessary files have been uploaded:
Manuscript:
- Include keywords
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- All tables (including titles, description, footnotes)
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- Manuscript has been 'spell checked' and 'grammar checked'
- All references mentioned in the Reference List are cited in the text, and vice versa

- Permission has been obtained for use of copyrighted material from other sources (including the Internet)
- A competing interests statement is provided, even if the authors have no competing interests to declare
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- Referee suggestions and contact details provided, based on journal requirements

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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, Editing and Publication of Scholarly Work in Medical Journals and aim for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. The terms sex and gender should be used correctly.

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Declaration of interest

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to avoid using "he, she," or "he/she." We recommend avoiding the use of descriptors that refer to personal attributes such as age, gender, race, ethnicity, culture, sexual orientation, disability or health condition unless they are relevant and valid. These guidelines are meant as a point of reference to help identify appropriate language but are by no means exhaustive or definitive.

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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Divide your article into clearly defined sections. Each subsection is given a brief heading. Each heading should appear on its own separate line. Subsections should be used as much as possible when cross-referencing text: refer to the subsection by heading as opposed to simply 'the text'.

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This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

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If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

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Keywords

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

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- Supply files that are too low in resolution;
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Anexo C- Normas de formatação do periódico BMC Musculoskeletal Disorders.

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The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

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The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. The abstract must include the following separate sections:

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The methods section should include:

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University site

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FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

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