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Patrícia Graef Vaz

Estimulação Cerebral Não-Invasiva na Reabilitação de Indivíduos com Hemiparesia Crônica após Acidente Vascular Cerebral

Porto Alegre
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Tese submetida ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Ciências da Saúde de Porto Alegre como requisito para a obtenção do grau de Doutor.

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Epígrafe

“Não é sobre chegar no topo do mundo e saber que venceu. É sobre escalar e sentir que o caminho te fortaleceu.”

(Ana Vilela)

RESUMO

O acidente vascular cerebral (AVC) é uma doença cerebrovascular de alta incidência e morbidade na população brasileira, sendo considerada uma das principais causas de incapacidade no adulto. A lesão cerebral ocasionada pelo AVC gera um padrão mal adaptado na atividade neural e modulação entre os hemisférios cerebrais, provocando um desajuste na inibição inter-hemisférica e prejudicando a recuperação funcional do paciente. A estimulação magnética transcraniana repetitiva (EMTr) e a estimulação transcraniana por corrente contínua (ETCC) vêm sendo estudadas como recursos durante o processo de reabilitação, pois atuam no bloqueio ou na redução da plasticidade mal adaptativa podendo reduzir a competição inter-hemisférica.

Há evidências de que a EMTr a ETCC produzem resultados promissores para a melhora da destreza, motricidade, força e função motora de sujeitos após AVC. Além disso, estudos recentes têm investigado os efeitos da estimulação cerebral não invasiva em ambos os hemisférios, como um método que possa maximizar os efeitos na excitabilidade cortical e a recuperação da função motora em indivíduos após AVC. O número de estudos ainda é pequeno e os resultados ainda são controversos. Por isso, há necessidade de maiores investigações sobre os protocolos e os efeitos da EMTr e ETCC em pacientes após AVC. O objetivo desta tese foi verificar os efeitos da EMTr e da ETCC na recuperação funcional de indivíduos com hemiparesia crônica após AVC. Para isso, duas revisões sistemáticas com meta-análise e um ensaio clínico randomizado foram realizados e compõem o trabalho final.

Os resultados encontrados nos artigos realizados mostram que ainda há evidências insuficientes para afirmar que a EMTr associada ao treinamento de membros superiores apresenta efeitos superiores quando comparada à utilização apenas de treinamento de membro superior em indivíduos após AVC crônico. Quanto à utilização da estimulação cerebral não invasiva na reabilitação da marcha, os resultados mostraram que há evidências de qualidade moderada para os efeitos positivos da utilização tanto da EMTr quanto da ETCC no desempenho da marcha de indivíduos em fase aguda e crônica após AVC. Porém, pesquisas futuras são necessárias para investigar os efeitos da estimulação cerebral não-invasiva na habilidade da caminhada e na força muscular de membros inferiores, assim como a

diferença entre os protocolos de inibição e excitação cortical. Por fim, verificamos que a estimulação bi-cefálica, utilizando EMTr de alta frequência no hemisfério contralesional combinado com ETCC anodal no hemisfério ipsilesional induziu melhora na função motora do membro superior, na força muscular do membro superior e na destreza manual de forma similar quando comparado a utilização de apenas uma modalidade de estimulação (EMTr de alta frequência ou ETCC anodal).

De modo geral, podemos concluir que a estimulação cerebral não-invasiva tem se mostrado um método satisfatório e seguro para modular a função do cérebro humano e tem sido considerado uma intervenção promissora para o tratamento dos comprometimentos motores após AVC, porém é necessário o seguimento das pesquisas na área incluindo novos estudos com protocolos padronizados de tratamento com o intuito de otimizar os efeitos terapêuticos da EMTr e da ETCC em pacientes após AVC.

ABSTRACT

Stroke is one of the leading causes of adult disability worldwide. The interhemispheric competition model proposes that motor deficits in stroke patients are a result of reduced output from the affected hemisphere and excess transcallosal inhibition of the affected hemisphere from the unaffected hemisphere. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have been used as a promising intervention for treating posts-stroke motor deficits.

There is evidence that rTMS and tDCS produces promising results for improved dexterity, motricity, muscular strength and motor function in post-stroke subjects. In addition, recent studies have investigated the effects of noninvasive cerebral stimulation in both hemispheres as a method that can maximize the effects on cortical excitability and motor function recovery in post-stroke subjects. The number of studies is still small and the results are controversial. Therefore, further investigations are still need to establish protocols and to verify the effects after stroke. The objective of this thesis was to verify the effects of rTMS and tDCS on motor functional recovery of individuals with chronic hemiparesis after stroke. For this, two systematic reviews with meta-analysis and randomized clinical trial were performed and are part of the final work.

The results found in the articles show that there is still insufficient evidence to afirm that rTMS associated with upper limb training presents superior effects when compared to the use of only upper limb training in individuals following chronic stroke. Regarding the use of non-invasive brain stimulation in gait rehabilitation, the results showed that there is evidence of moderate quality for the positive effects of both rTMS and rTMS on the gait performance of individuals in acute and chronic phase after stroke. However, future research is needed to investigate the effects of non-invasive brain stimulation on walking ability and lower limb muscle strength, as well as the difference between cortical inhibition and excitation protocols. Finally, we found that bi-cephalic stimulation using high-frequency rTMS in the contralesional hemisphere combined with anodal tDCS in the ipsilesional hemisphere induced improvement in upper limb motor function, upper limb muscle strength and manual dexterity similarly when compared to the use of only one stimulation modality (high frequency rTMS or anodal tDCS).

In general, we can conclude that noninvasive cerebral stimulation has been shown to be a safe and satisfactory method to modulate human brain function and has been considered a promising intervention for the treatment of motor impairment after stroke, but it is necessary to follow the researches in the field including new studies with standardized treatment protocols with the aim of optimizing the therapeutic effects of rTMS and tDCS in patients following stroke.

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LISTA DE ABREVIATURAS E SIGLAS

AVC	Acidente vascular cerebral
AVD's	Atividades de vida diária
EMTr	Estimulação magnética transcraniana repetitiva
ETCC	Estimulação transcraniana por corrente contínua
M1	Córtex motor primário
OMS	Organização mundial da saúde
SNC	Sistema nervoso central

ARAT	*Action research arm test*
AtDCS	*Anodal transcranial direct current stimulation*
BBT	*Box and block test*
CG	*Control group*
CI	*Confidence interval*
FDI	*First dorsal interosseous*
FMA	*Fugl-Meyer assessment*
HF-Rtms	*High frequency of repetitive transcranial magnetic stimulation*
HRQoL	*Health related quality of life*
IG	*Intervention group*
JTHF	*Jebsen-Taylor hand function test*
LH-Rtms	*Low frequency of repetitive transcranial magnetic stimulation*
MAL	*Motor activity log*
MAS	*Modified ashworth scale*
MD	*Mean deviation*
MEP	*Motor evoked potential*
MI-LE	*Motricity index lower-limb*
NHPT	*Nine-hole peg test*
NIBS	*Non-invasive brain stimulation*
PRISMA	*Preferred reporting items for systematic review and meta-analyses*
RCT	*Randomized clinical trial*
Rmt	*Resting motor threshold*
Rtms	*Repetitive transcranial magnetic stimulation*
SAT	*Speed–accuracy tradeoff*

SMD	*Standardized mean deviation*
SS-QoL	*Stroke scale quality of life*
tDCS	*Transcranial direct current stimulation*
TUG	*Timed up & go test*
WMFT	*Wolf motor function test*
WMFT FAS	*Score of ability function of Wolf motor function test*
WMFT time	*Performed time of Wolf motor function test*

SUMÁRIO

1. INTRODUÇÃO

Modificações no estilo de vida como alterações nutricionais e demográficas ocorridas ao longo do século XX na população brasileira vêm transformando o perfil da incidência de doenças no Brasil. A alta prevalência de fatores de risco como obesidade, sedentarismo, maus hábitos alimentares, tabagismo e hipertensão arterial sistêmica,[1] bem como a diminuição nos índices de natalidade e fecundidade associada ao aumento da expectativa média de vida têm construído um novo perfil de morbimortalidade. Neste contexto, as doenças crônicas não transmissíveis lideram as causas de morte no país.[2]

Dados epidemiológicos revelam que essas doenças são as que demandam mais ações, procedimentos e serviços, sendo responsáveis por altos custos diretos em saúde, os quais totalizam, anualmente, 7,5 bilhões de reais em gastos ambulatoriais e internações.[3] Dentre o grupo das doenças cerebrovasculares, o acidente vascular cerebral (AVC) tornou-se umas das principais causas de morte, já sendo considerado a segunda maior causa de morte no mundo. Observa-se uma incidência anual de 156 casos a cada 100.000 habitantes e mortalidade de 52,61 óbitos por 100 mil habitantes.[4] Além da alta incidência de mortalidade, o AVC é considerado umas das principais causas de incapacidade no adulto.[5]

A má perfusão encefálica após quadros isquêmicos ou hemorrágicos de AVC, sob o ponto de vista clínico, gera distúrbios sensório-motores que decorrem em hemiparesia, incoordenação motora, hipertonia espástica do membro superior e inferior contralaterais à lesão, além de fraqueza muscular generalizada.[6-7] O comprometimento sensório-motor tanto de membro superior quanto inferior estão entre as deficiências físicas mais persistentes e significativas após AVC.[8-9] Os membros superiores e inferiores são de suma importância para a realização das atividades de vida diária (AVD's) e dificuldades na execução de tarefas simples causam um aumento na dependência funcional com consequente diminuição da participação do indivíduo na sociedade.[10]

Em condições de normalidade, a atividade neural ocorre de modo conjunto e balanceado em termos de ação inibitória mútua. Após o AVC esse equilíbrio é perdido, gerando um padrão anormal de atividade entre os hemisférios cerebrais e provocando um desajuste na inibição inter-hemisférica. O córtex motor primário (M1) do hemisfério intacto pode influenciar negativamente a recuperação funcional, devido ao aumento

inibitório exercido sobre o M1 do hemisfério lesado. A existência de competição inter-hemisférica cerebral prejudica a recuperação dos movimentos do braço parético e piora o grau de paresia dos pacientes com comprometimento motor. [11-12] Essa condição de desequilíbrio cortical pode prejudicar a reabilitação e recuperação motora dos pacientes com hemiparesia crônica após AVC.[13]

O uso de ferramentas de neuromodulação, como a estimulação cerebral não invasiva, vem sendo estudada como recurso durante o processo de reabilitação, pois atua no bloqueio ou na redução da plasticidade mal adaptativa podendo reduzir a competição inter-hemisférica.[12, 14-15] A estimulação cerebral não invasiva, como a estimulação magnética transcraniana (EMT) e a estimulação transcraniana por corrente contínua (ETCC), baseia-se no conceito de competição inter-hemisférica para promover um reajuste na atividade cortical, facilitando a atividade elétrica no hemisfério adjacente à lesão ou induzindo a inibição da atividade cortical no hemisfério contralateral (sadio).[13]

Levando em consideração a alta prevalência do AVC na população, a importância dos membros superiores e inferiores para a independência funcional e desempenho das atividades de vida diária, bem como o aumento da utilização da estimulação cerebral não-invasiva na prática clínica, pretende-se com essa tese contribuir para o conhecimento acerca das possibilidades de intervenção terapêutica a fim de intensificar a recuperação funcional do membro superior e inferior parético em indivíduos com hemiparesia crônica após AVC. Contudo, o objetivo deste trabalho foi verificar os efeitos da EMTr e da ETCC na recuperação funcional de indivíduos com hemiparesia crônica após AVC. Para isso, duas revisões sistemáticas com meta-análise e um ensaio clínico randomizado foram realizados e compõem esta tese.

2. REVISÃO DE LITERATURA

2.1 ACIDENTE VASCULAR CEREBRAL

O AVC é definido, segundo a Organização Mundial de Saúde (OMS), como um quadro clínico resultante da perturbação focal ou global da função cerebral, de rápido desenvolvimento, supostamente de origem vascular, com sintomas que perduram 24 horas ou mais, ou que levam à morte sem outra causa aparente, a não ser de origem vascular.[16]

As classificações existentes para o AVC são definidas com base na etiologia do distúrbio que acomete a vascularização cerebral. A maioria dos casos de AVC é de etiologia isquêmica (cerca de 80%), e a artéria mais comumente obstruída é a artéria cerebral média ou suas ramificações profundas. Os eventos hemorrágicos ocorrem em menor escala (cerca de 20% dos casos).[17] Independente da etiologia, o AVC resulta, frequentemente, em prejuízo das vias sensório-motoras[18] caracterizando-se como uma das principais causas de incapacidade no adulto.[5]

De acordo com dados da OMS, cerca de 15 milhões de pessoas sofrem AVC por ano, no mundo. Desses, aproximadamente cinco milhões morrem e cinco milhões ficam com algum tipo de sequela. No Brasil os estudos epidemiológicos ainda são poucos e, provavelmente, não revelam o real impacto das doenças vasculares na população brasileira. O Ministério da Saúde (2006) relata, no entanto, que as doenças circulatórias são responsáveis pelo impacto expressivo na mortalidade da população brasileira, correspondendo a 32% dos óbitos em 2002. Considerando todas as causas de morte no Brasil no período, o AVC foi responsável por 10,18% dessas mortes.[19] A morbidade nos indivíduos que sobrevivem após o AVC é um dado bastante preocupante. Cerca de 50-60% dos sobreviventes permanecem com algum grau de prejuízo motor, afetando principalmente a função motora e tornando os indivíduos parcialmente dependentes na realização das AVD's.[20-21] Isto mostra que grande parte dos gastos públicos, tanto em países desenvolvidos quanto em desenvolvimento, são destinados aos cuidados com esses indivíduos. Uma projeção mostra que os gastos decorrentes do AVC chegarão em torno de 61 milhões de dólares por dia em 2020.[22]

2.2 COMPROMETIMENTO MOTOR

Dentre os principais comprometimentos motores após AVC pode-se destacar a hemiparesia;[6-7, 21] a fadiga; o prejuízo na coordenação motora e na destreza; a hipertonia espástica decorrente da interrupção dos circuitos neurais reguladores e do prejuízo da integridade funcional do arco reflexo segmentar;[23] a presença de clônus, a hipereflexia e as anormalidades do controle motor voluntário.[24-25] As alterações são observadas tanto no membro superior quanto no membro inferior após a lesão, porém, a função do membro superior permanece entre as deficiências físicas mais persistentes e significativas no paciente após AVC, mesmo quando programas regulares de reabilitação são seguidos.[8, 26] Essa persistência no déficit motor também pode ser explicada devido a alterações de excitabilidade cortical que ocorrem após uma lesão cerebral, que acabam favorecendo um desequilíbrio na ação inibitória mútua entre os dois hemisférios. Essa competição inter-hemisférica pode comprometer a reabilitação e reforçar os desajustes no controle motor.[13]

A fraqueza muscular também é um comprometimento neuromotor comum em uma variedade de desordens neurológicas centrais e está relacionada diretamente à imobilidade, redução acentuada da atividade física e das condições clínicas sistêmicas.[7] A capacidade de produzir força muscular envolve fatores estruturais, como área de secção transversa e proporção relativa dos tipos de fibras musculares, além de fatores neuro-mecânicos, como relação de comprimento-tensão, força-velocidade e recrutamento de unidades motoras.[27] O comprometimento de qualquer um desses fatores afeta a capacidade de exercer força e reitera a definição de fraqueza muscular.[28] Durante muito tempo afirmou-se que a fraqueza muscular encontrada em pacientes após AVC não era um mecanismo "real", mas apenas resultado do distúrbio de inervação recíproca e da atividade muscular antagonista espástica exacerbada. Acreditava-se que somente o estado contínuo de contração da musculatura antagonista seria responsável por prejudicar a intensidade na geração de força, o índice de produção de força e a coordenação intersegmentar.[29] No entanto, as investigações contemporâneas não conseguiram encontrar provas da contração muscular antagonista continuada durante os movimentos e, em vez disso, demonstraram ativação reduzida da musculatura agonista no membro parético.[29-31]

Atualmente a fraqueza muscular é reconhecida como um fator limitante na recuperação de pacientes após AVC e está diretamente relacionada às dificuldades

no desempenho e independência nas AVD's.[10, 28, 32] Dentre os grupamentos musculares sinergistas na produção de movimentos funcionais do membro superior, os graus de força produzidos por contração isométrica voluntária máxima na preensão palmar e na flexão do ombro são considerados, de forma interdependente, como os principais preditores da função do membro superior em pacientes após AVC.[33-34] A fraqueza muscular no membro inferior, que também é evidente nesses indivíduos, e está associada ao comprometimento no controle motor, gerando padrões anormais e comprometimento na performance da marcha.[35] Após o AVC, os indivíduos normalmente demonstram redução da velocidade de caminhada, diminuição do comprimento da passada e cadência. Essas alterações refletem em um mal desempenho na caminhada e, consequentemente, as atividades na comunidade podem se tornar limitadas e ocasionar um isolamento do indivíduo da sociedade.[36]

2.3 REABILITAÇÃO NEUROFUNCIONAL E ESTIMULAÇÃO CEREBRAL NÃO INVASIVA

Em seres humanos, ocorrem graus variáveis de recuperação espontânea após o AVC. A recuperação mais rápida e pronunciada ocorre durante o primeiro mês, continua de forma mais discreta durante os três primeiros meses e gradativamente reduz ao longo dos meses seguintes.[20] Com relação aos processos relacionados à recuperação motora espontânea, três deles podem ser citados: (a) mudanças na organização funcional do tecido cerebral cortical que circunda a área lesada[37] ativação de áreas motoras e fibras corticoespinais no hemisfério não afetado e (c) aumento na ativação de áreas além da motora primária, como área motora suplementar, córtex parietal inferior, cingulado e ínsula.[38] Embora a recuperação motora seja caracterizada por uma grande variabilidade interindividual e possa ser influenciada por uma série de fatores biológicos e ambientais, existem fortes evidências de que os melhores resultados terapêuticos dependem da escolha e execução adequada da atividade, intensidade e frequência do tratamento.[39-40]

O retorno da função em indivíduos com hemiparesia está relacionado à plasticidade adaptativa nas regiões motoras encefálicas, corticais e subcorticais, em especial daquelas que permaneceram ilesas.[41] Sabe-se que a experiência motora é capaz de produzir mudanças plásticas em encéfalos de animais adultos saudáveis e após lesão.[42-44] Isso porque o tratamento de reabilitação após lesões encefálicas

provoca reorganização no tecido cortical adjacente à lesão, alteração das representações somatotópicas corticais,[5, 45] aumento da expressão de proteínas e modificações na morfologia dendrítica.[46] Essa tendência das sinapses e dos circuitos neuronais de se modificarem em função da atividade está diretamente relacionada à recuperação motora das funções perdidas e é denominada "neuroplasticidade".[38] Estudos realizados em modelos animais revelam que a execução de uma tarefa motora promove plasticidade proporcional ao tempo, continuidade, intensidade e complexidade da tarefa, sendo específica para as áreas de representação encefálica dos segmentos corporais treinados.[47-48] No entanto, deve haver cuidado na escolha do tipo de treinamento, já que diferentes estratégias de reabilitação têm influências variadas na plasticidade neural e na recuperação da função após lesão do sistema nervoso central (SNC).[49]

Os principais objetivos da reabilitação do paciente neurológico são de maximizar a independência funcional nas AVDs e minimizar a imobilização de longo prazo e as incapacidades motoras.[50] A ciência da reabilitação tem hoje diversas formas de tratamento baseada em evidências, no entanto, não há um consenso sobre qual terapia seria a melhor para o paciente com comprometimento neuromotor após AVC.

O uso de ferramentas de neuromodulação, como a estimulação cerebral não invasiva, também tem sido estudada como recurso durante programas de reabilitação, pois atuam no bloqueio ou na redução da plasticidade mal adaptativa, podendo reduzir a competição inter-hemisférica.[12, 14-15] A estimulação cerebral não invasiva, como a EMTr e a ETCC, baseia-se no conceito de competição inter-hemisférica para promover um reajuste na atividade cortical, facilitando a atividade elétrica no hemisfério adjacente à lesão ou induzindo a inibição da atividade cortical no hemisfério contralateral (sadio).[13]

Tanto a EMTr quanto a ETCC visam alterar a excitabilidade cortical.[12] A EMTr (Fig. 1) é uma técnica que utiliza um campo eletromagnético, por meio da indução de cargas elétricas no parênquima cerebral (indução eletromagnética), transformando-se em campo elétrico no córtex atingindo.[51] É uma técnica que emite vários pulsos repetitivos e fornece impulsos elétricos contínuos no cérebro, de modo a produzir alterações a longo prazo na excitabilidade cortical.[12] Em relação ao número de pulsos repetitivos por unidade de tempo, existem dois tipos de EMTr: baixa frequência (≤ 1Hz) e alta frequência (> 3Hz).[52] O uso da EMTr de alta frequência aumenta o fluxo

sanguíneo cerebral na área com consequente aumento da atividade cerebral. A EMTr de baixa frequência, por outro lado, diminui a atividade cerebral.[53]

Figura 1. Estimulação Magnética Transcraniana Repetitiva (adaptado de Kakuda et al, 2012)

A ETCC (Fig. 2) reversivelmente polariza as regiões do cérebro através de aplicação tópica de fracas correntes contínuas.[12] Baseia-se na alteração do potencial de repouso da membrana neuronal para induzir alterações da excitabilidade cortical.[54] São necessários dois eletrodos, ânodo e cátodo, que, dispostos em diferentes montagens, criam um fluxo de corrente elétrica contínua de baixa intensidade que atinge uma região específica do córtex cerebral, modulando-a de acordo com a polaridade: a estimulação anódica despolariza a membrana neuronal facilitando o disparo neuronal, enquanto a estimulação catódica tem efeito oposto de inibir o disparo neuronal em função da hiperpolarização da membrana neuronal.[55-56]

Figura 2 Estimulação Transcraniana por Corrente Contínua (adaptado de Siebner et al, 2004)

Devido à capacidade relativa de alvo focal, do perfil de segurança, do custo relativamente baixo e dos resultados preliminares positivos, essas técnicas têm sido extensivamente testadas para a reabilitação de pacientes pós AVC.[14] A utilização isolada da EMT tem demonstrado, em pacientes hemiparéticos após AVC, melhora da função motora do membro superior parético,[57] melhora na contração muscular de músculos do membro inferior parético[58-59] e diminuição da espasticidade.[60] Estudos

utilizando, isoladamente, a ETCC também demonstraram benefícios para pacientes após AVC, como aumento da força muscular do membro inferior,[61] melhora dos movimentos voluntários de plantiflexão e dorsiflexão,[62] aumento na velocidade do movimento ativo de pinça[12] e na melhora funcional do membro superior.[63] Os efeitos benéficos da estimulação unilateral podem ser explicados porque uma alteração na excitabilidade em um hemisfério pode produzir efeitos de excitabilidade indireta no outro hemisfério por meio de projeções inter-hemisféricas.[64] Assim, tanto a EMTr como a tDCS são capazes de alterar, potencialmente, a excitabilidade diretamente na região estimulada e indiretamente na região homóloga do hemisfério oposto.

Há evidências de que a inserção de atividades motoras antes ou após a EMTr[65-66] ou durante a ETCC[67] produzem resultados promissores para a melhora da destreza, motricidade, força e função da mão parética de pacientes crônicos após AVC. Além disso, estudos recentes têm investigado os efeitos da estimulação cerebral não invasiva em ambos os hemisférios, aplicadas simultaneamente ou uma na sequência da outra, como um método que possa maximizar os efeitos na excitabilidade cortical e na recuperação da função motora em indivíduos após AVC. O número de estudos ainda é pequeno e os resultados ainda são controversos tanto utilizando protocolos de estimulação bi-hemisférica com uma modalidade como tDCS[68-70] ou ETMr[71-72], quanto utilizando a associação das duas modalidades tDCS+ETMr.[73-74]

Torna-se importante a investigação dos estudos realizados até o momento sobre a utilização da EMTr e da ETCC na melhora das funções motoras do membro superior e da reabilitação da marcha em indivíduos após AVC para averiguar os reais benefícios da utilização dessas técnicas na reabilitação após AVC. Além disso, o pequeno número de estudos realizados sobre a utilização da estimulação bi-cefálica com duas modalidades de estimulação cerebral não invasiva mostra a necessidade de mais estudos com o intuito de otimizar a recuperação motora de indivíduos após AVC.

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4. OBJETIVOS

4.1 OBJETIVO GERAL

O objetivo deste trabalho foi verificar os efeitos da EMTr e da ETCC na recuperação funcional de indivíduos com hemiparesia crônica após AVC. Para isso, duas revisões sistemáticas com meta-análise e um ensaio clínico randomizado foram realizados e compõem esta tese.

4.2 OBJETIVOS ESPECÍFICOS

1 – Investigar os efeitos da ETMr combinada com o treinamento do membro superior na recuperação funcional do membro superior após AVC (Artigo 1).

2 – Verificar a eficácia da estimulação cerebral não invasiva na reabilitação da marcha em pacientes com AVC agudo ou crônico (Artigo 2).

3 – Verificar o efeito da estimulação cerebral não invasiva bi-cefálica na recuperação da função motora do membro superior após AVC (Artigo 3).

5. ARTIGOS

5.1 ARTIGO 1

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Review article

Transcranial magnetic stimulation combined with upper-limb training for improving function after stroke: A systematic review and meta-analysis

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ABSTRACT

Background: Several neuromodulation treatments have been developed, and their effects have been studied in recent years in order to improve neurological rehabilitation after a stroke. The association between upper-limb training and repetitive transcranial magnetic stimulation (rTMS) has provoked controversies and produced inconclusive results.
Objective: The purpose of this study was to investigate the effects of rTMS combined with upper-limb training versus sham rTMS combined with upper-limb training on the upper-limb recovery after a stroke.
Methods: A systematic review with meta-analysis was performed. The eligible studies were randomized controlled trials with stroke subjects, and the outcomes were related to upper-limb motor/functional status and spasticity.
Results: A total of 3234 citations were identified, and 11 studies were included. The meta-analysis included eight studies with 199 participants and did not show any difference between groups, neither for upper-limb function nor for spasticity (upper-limb function [0.03 (95% CI: −0.25 to 0.32; I^2 0%)] and Modified Ashworth Scale [−0.31 (95% CI: −0.78 to 0.17; I^2 43%)]).
Conclusion: The current state of the literature is not enough to support the hypothesis that a combination of rTMS and upper-limb training has a stronger effect on upper-limb function than upper-limb training alone.

Contents

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1. Introduction

Stroke is one of the main causes of long-term neurological disability worldwide [1]. Among those patients who have survived a stroke, it is estimated that around 55–75% will present some degree of long-term sensory-motor impairment [2]. Upper-limb motor ability is commonly affected after a stroke, and in 70% of patients it is responsible for restrictions on functional tasks and daily activities [3,4].

Repetitive transcranial magnetic stimulation (rTMS) is a promising non-invasive neuromodulatory intervention that aims to maximize recovery of function after stroke [5,6]. Two distinct protocols have been employed: excitatory (high-frequency) stimulation of the damaged hemisphere and inhibitory (low-frequency) stimulation of the undamaged hemisphere. rTMS aims to restore the disrupted equilibrium and the inter-hemispheric communication in order to rebalance the inter-hemispheric competition and promote functional recovery [7–9].

In a similar way, motor training is capable of inducing neuroplasticity even in mature brains [10–12]. Rehabilitation approaches induce lasting cortical reorganization in both hemispheres and promote adaptations to the cortical maps [13–16]. Recent studies have shown that upper-limb training procedures such as muscle strengthening, facilitation techniques, task-oriented training, constraint-induced movement therapy and motor imagery may contribute to improving upper-limb motor function in stroke survivors [17,18]. These mechanisms support the reorganization of cortical functions that promote sensory-motor recovery after upper-limb training [7,8,19–23]. Despite the very well-known effect of sensory-motor therapy for stimulating neuroplasticity after stroke, the functional outcome after regular treatments has notable limitations. This is evident since about 50–60% of patients remain with some degree of motor impairment [24].

The association between upper-limb training and rTMS has also been studied [25–36], but the results are still inconclusive. Considering the effects of neuroplasticity, the association between rTMS and upper-limb training may induce more noticeable rehabilitation and upper-limb recovery in post-stroke patients. Therefore, the aim of this systematic review with meta-analysis was to determine the effectiveness of rTMS combined with upper-limb training for promoting upper-limb recovery after a stroke.

Table 1
Literature search strategy used for the PubMed database.

#1 Patient	"Stroke"[Mesh] OR "Stroke" OR "Strokes" OR "Apoplexy" OR "CVA (Cerebrovascular Accident)" OR "CVAs (Cerebrovascular Accident)" OR "Cerebrovascular Accident" OR "Cerebrovascular Accidents" OR "Cerebrovascular Apoplexy" OR "Apoplexy, Cerebrovascular" OR "Cerebrovascular Stroke" OR "Cerebrovascular Strokes" OR "Stroke, Cerebrovascular" OR "Strokes, Cerebrovascular" OR "Vascular Accident, Brain" OR "Brain Vascular Accident" OR "Brain Vascular Accidents" OR "Vascular Accidents, Brain" OR "Cerebral Stroke" OR "Cerebral Strokes" OR "Stroke, Cerebral" OR "Strokes, Cerebral" OR "Stroke, Acute" OR "Acute Stroke" OR "Acute Strokes" OR "Strokes, Acute" OR "Cerebrovascular Accident, Acute" OR "Acute Cerebrovascular Accident" OR "Acute Cerebrovascular Accidents" OR "Cerebrovascular Accidents, Acute"
#2 Intervention 1	"Transcranial magnetic stimulation"[Mesh] OR "Magnetic Stimulation, Transcranial" OR "Magnetic Stimulations, Transcranial" OR "Stimulation, Transcranial Magnetic" OR "Stimulations, Transcranial Magnetic" OR "Transcranial Magnetic Stimulations" OR "Transcranial Magnetic Stimulation, Paired Pulse" OR "Transcranial Magnetic Stimulation, Repetitive" OR "Transcranial Magnetic Stimulation, Single Pulse" OR "rTMS" OR "repetitive transcranial magnetic stimulation" OR "Deep Brain Stimulation" [Mesh] OR "Deep Brain Stimulations" OR "Stimulation, Deep Brain" OR "Stimulations, Deep Brain" OR "Brain Stimulation, Deep" OR "Electrical Stimulation of the Brain" OR "Magnetic Field Therapy" [Mesh] OR "Field Therapies, Magnetic" OR "Field Therapy, Magnetic" OR "Magnetic Field Therapies" OR "Therapies, Magnetic Field" OR "Therapy, Magnetic Field" OR "Magnetic Stimulation Therapy" OR "Magnetic Stimulation Therapies" OR "Stimulation Therapies, Magnetic" OR "Stimulation Therapy, Magnetic" OR "Therapies, Magnetic Stimulation" OR "Therapy, Magnetic Stimulation"
#3 Intervention 2	"Exercise" [Mesh] OR "Exercises" OR "Exercise, Physical" OR "Exercises, Physical" OR "Physical Exercise" OR "Physical Exercises" OR "Exercise, Isometric" OR "Exercises, Isometric" OR "Isometric Exercises" OR "Isometric Exercise" OR "Exercise, Aerobic" OR "Exercise, Aerobic" OR "Aerobic Exercises" OR "Aerobic Exercises" OR "Aerobic Exercise" OR "Physical Therapy Modalities" [Mesh] OR "Modalities, Physical Therapy" OR "Modality, Physical Therapy" OR "Physical Therapy Modality" OR "Physiotherapy (Techniques)" OR "Physiotherapies (Techniques)" OR "Physical Therapy Techniques" OR "Physical Therapy Technique" OR "Techniques, Physical Therapy" OR "Exercise Movement Techniques" [Mesh] OR "Movement Techniques, Exercise" OR "Exercise Movement Technics" OR "Pilates-Based Exercises" OR "Exercises, Pilates-Based" OR "Pilates Based Exercises" OR "Pilates Training" OR "Training, Pilates" OR "Exercise Therapy" [Mesh] OR "Therapy, Exercise" OR "Exercise Therapies" OR "Therapies, Exercise" OR "Occupational Therapy" [Mesh] OR "Therapy, Occupational" OR "Occupational Therapies" OR "Therapies, Occupational" OR "Constraint-induced Movement Therapy" OR "Repetitive Facilitation Exercise" OR "Robot-Assisted training" OR "Mirror Therapy" OR "Task Oriented Training" OR "Strength training" OR "Resistance Training" OR "Physical Rehabilitation" OR "Kinesiotherapy" OR "Range of motion exercise" OR "Bobath" OR "Proprioceptive Neuromuscular Facilitation"
#4 Type of study	#4) Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw] (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos [mh] OR placebo*[tw] OR random*[tw] OR research design [mh: noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR crossover studies [mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal [mh] NOT human [mh])
Search	#1 and #2 and #3 and #4

2. Methods

This systematic review was performed in accordance with the Cochrane Collaboration [37] and is presented according to the suggestions made in the Preferred Reporting Items for Systematic Review and Meta-analyses: The PRISMA Statement [38].

2.1. Search criteria

We conducted an extensive search of the literature up to November 2015 using electronic databases including MEDLINE, PubMed, EMBASE, Cochrane Central Register of Controlled Trials (Cochrane CENTRAL) and

Physiotherapy Evidence Database (PEDro). The search terms were used individually or in combination and included "stroke," "transcranial magnetic stimulation," "physical therapy modalities" and a string of predetermined words, which yielded a high sensitivity in the search for randomized controlled trials [39]. The complete search strategy used for the PubMed database is shown in Table 1.

To enhance the sensitivity of the search, words related to the outcomes of interest were not included. The references included in the published articles were used as an additional source to identify other clinical trials. The terms were adjusted to fit the requirements of each electronic database.

2.2. Study selection

Studies eligible for this review were randomized controlled trials and randomized controlled crossover trials, from which we analyzed only the first period as a parallel-group design for stroke individuals with outcomes related to upper-limb motor function. The inclusion criteria were randomized controlled trials (RCTs), randomized controlled crossover trials, experimental group(s) receiving repetitive transcranial magnetic stimulation (rTMS) combined with upper-limb training for motor function rehabilitation, and a control group that received sham rTMS combined with upper-limb training. The exclusion criteria were a sample including acute stroke or children stroke survivors and theses and articles published in abstract form only, including conference proceedings. The primary outcome was upper-limb motor function recovery and the second outcome was spasticity.

In the initial searches, two reviewers (the first and the second authors) separately and independently screened the titles and abstracts of the identified studies. A standard screening checklist based on the eligibility criteria was employed for each study. Studies that did not meet the criteria according to the titles or abstracts were excluded. A second review to determine the eligibility of the retrieved studies was performed independently. The two reviewers screened the full-text versions of the remaining studies, including those potentially eligible and uncertain. All discrepancies related to trial eligibility were solved by a third reviewer (the third author).

Those studies with insufficient information were excluded. Procedures for estimating missing data [40] were performed when possible. Abstracts published in academic conferences were evaluated by case, and the authors were contacted for details when necessary.

2.3. Data extraction and quality assessment

The two reviewers developed a data extraction sheet, and disagreements regarding the data extraction were solved through discussion. When consensus was not reached, the third author arbitrated. The following data were extracted from the included studies: methodological design, number of subjects, comparison groups, intervention protocols and results of the outcomes.

The intervention protocol consisted of the parameters of rTMS (frequencies, pulses and the cerebral hemisphere), the time of intervention, the number of sessions and the type of exercise for upper-limb training. The outcome extracted was upper-limb motor functional status (arm function, global hand function and hand dexterity), which was assessed by means of the Fugl-Meyer Assessment (FMA), the Wolf Motor Function Test (WMFT), the Action Research Arm Test (ARAT), the Box and Block Test (BBT), the Jebsen-Taylor Hand Function Test (JTHF), the Nine-Hole Peg Test (NHPT) and the Motor Activity Log (MAL). The outcome extracted for spasticity was assessed by means of the Modified Ashworth Scale (MAS). In the case of missing or unpublished data, we have attempted to contact the authors. The study was excluded if data were still insufficient after this procedure.

All papers were carefully evaluated and classified according to their methodological quality or risk of bias by means of the Cochrane Collaboration's tool [37]. The Cochrane risk-of-bias tool consists of five domains, including sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Each domain comprises three outcomes: low, high, and unclear risk of bias. Studies with a low risk of bias in three or more domains were considered trials of a moderate to high methodological quality and were included in the final meta-analysis.

2.4. Synthesis and analysis of quantitative data

The outcome measures consisted of upper-limb motor function status and spasticity. We used five different scales for the upper-limb motor function assessment and one scale for spasticity in the meta-analysis (as previously cited).

For quantitative synthesis, pooled-effect estimates were obtained by calculating the change from the baseline to the end of study. Regarding the continuous outcomes, if the unit of measurement was consistent across trials, the results were presented as the weighted mean difference (MD) with 95% confidence intervals (95% CIs). For those cases where studies did not use the same unit of measurement, we calculated standardized mean differences (SMDs) instead of MDs.

Given the heterogeneity of outcome measurements, calculations were performed using the random effects method ($I^2 > 0$). The statistical heterogeneity of the treatment effects among studies was assessed using Cochran's Q test and the inconsistency I^2 test, in which values above 25% and 50% were considered indicative of moderate and substantial heterogeneity, respectively. The importance of the observed value of I^2 depends on (i) the magnitude and direction of the effects and (ii) the strength of the evidence for heterogeneity (e.g. a p value from the chi-squared test or a confidence interval for I^2) [37]. A p value ≤0.05 was considered statistically significant. All analyses were conducted using Review Manager, version 5.3.

3. Results

The electronic search strategy identified a total of 3234 studies, and 11 clinical trials [26–36] with a total of 199 subjects were included in the systematic review. Fig. 1 shows a flow diagram of the included studies.

3.1. Characteristics of studies

The characteristics of the included studies are summarized in Table 2. The 11 included studies reported data on upper-limb motor function status, but only eight were included in the meta-analysis. Three studies [27,28,35] were not included in the meta-analysis due to lack of enough data, even after contact with the authors. For the primary outcome, we performed an analysis grouping eight studies in five sensitivities analyses. Studies were divided according to the different scales used for upper-limb function assessment: four studies [26,30,31,36] used the FMA to evaluate the motor recovery of the upper limb, three studies [26,32,36] analyzed the WMFT functional ability scores (WMFT-FAS), four studies [26,32,33,36] examined the WMFT performance time scores (WMFT-TIME), three studies [29,30,34] analyzed the ARAT scores to evaluate global hand function and two studies [32,33] used the BBT to evaluate functional hand movements. Only two studies were included in the meta-analysis of spasticity [30,31].

In eight studies [26,27,30–32,34–36], the rTMS stimulation frequency was 1 Hz, ranging from 1200 to 1800 pulses in the unaffected hemisphere. In three studies, the rTMS was applied with 10 Hz (50 pulses), 20 Hz (50 trains of 40 stimuli) and 50 Hz (theta burst stimulation) frequencies in the damaged hemisphere [28,29,33]. The type of exercise associated with rTMS also varied between studies: in four studies [29–31,36], patients underwent conventional physical therapy or occupational therapy; three studies [27,32,35] delivered task-related exercises; two studies [26,33] performed constraint-induced movement therapy; one study [34] carried out voluntary muscle contraction of the upper-

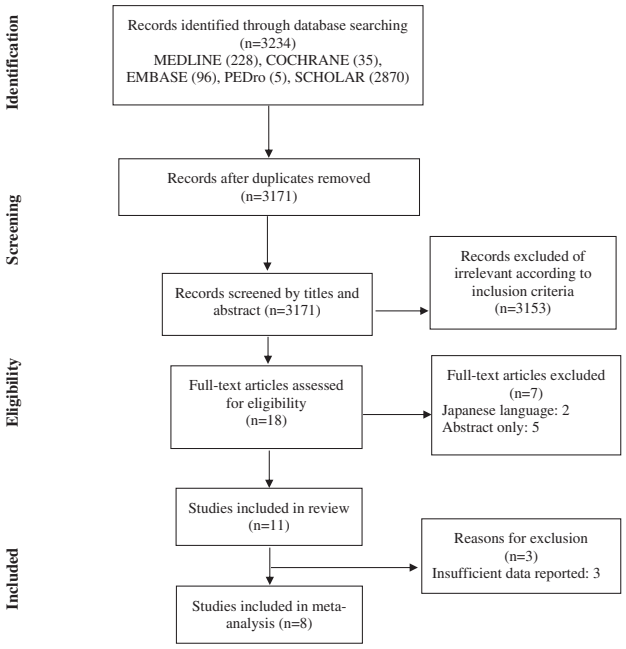


Fig. 1. The flow diagram of studies included in the review.

Table 2
Characteristics of studies included in systematic review.

Author, year	Intervention group (IG)	Participants (onset of stroke in months ± SD)	Control group (CG)	N (IG/CG)	Age ± SD (IG/CG)	Masculine gender (IG/CG)	Protocol
1. Abo et al., 2014	rTMS + occupational therapy (NEURO group)	Chronic stroke patients (65.1 ± 4.2)	Constraint-Induced Movement Therapy (CIMT group)	66 44/22	57.7 ± 12.7/60.3 ± 10.6	26/12	IG: 22 sessions (daily - two sessions per day): rTMS (1200 pulses of 1 Hz applied to the nonlesional hemisphere - 20 min) + occupational therapy (120 min) CG: 11 sessions (daily): constraint-induced movement therapy (shaping techniques and repetitive task practices – 6 h per day) Outcomes: Wolf Motor Function Test (WMFT); Fugl-Meyer Motor Assessment (FMA - upper extremity part)
2. Avenanti et al., 2012	rTMS + physiotherapy and physiotherapy + rTMS	Chronic stroke patients (31.5 ± 22.7)	Sham rTMS + physiotherapy, and physiotherapy + sham rTMS	30 8/8/7/7	Not reported	Not reported	IG: 20 sessions (2 time-locked daily interventions): rTMS (1.500 pulses, 1 Hz, 90% of resting motor threshold – 25 min) + physiotherapy (standard task-oriented upper-limb exercises – 45 min) *The other group change the order of intervention CG: 20 sessions (2 time-locked daily interventions): sham rTMS (1.500 pulses, 90% of resting motor threshold – 25 min) + physiotherapy (standard task-oriented upper-limb exercises – 45 min) *The other group change the order of intervention Outcome: the Jebsen-Taylor Hand Function Test (JHFT), the Nine-Hole Peg Test (NHPT), and the Box and Block Test (BBT)
3. Chang et al., 2012	rTMS + finger motor training	Chronic stroke patients (10 ± 2.6)	Sham rTMS + finger motor training	21 11/10	58.1 ± 14/59.5 ± 11	6/4	IG: 10 sessions (daily for two weeks): rTMS (50 pulses of 10 Hz, 80% resting motor threshold in lesional hemisphere - 20 min) + finger motor learning tasks (50 s) CG: 10 sessions (daily for two weeks): sham rTMS (20 min) + finger motor learning tasks (50 s) Outcomes: Jebsen Hand Function Test (JHFT)

Table 2 (*continued*)

Author, year	Intervention group (IG)	Participants (onset of stroke in months ± SD)	Control group (CG)	N (IG/CG)	Age ± SD (IG/CG)	Masculine gender (IG/CG)	Protocol
4. Di Lazzaro et al., 2013	rTMS + physical therapy	Chronic stroke patients (32.4 ± 3.4)	Sham rTMS + physical therapy	12 6/6	59.5 ± 12.4/57.5 ± 12.3	3/4	IG: 10 sessions (daily): rTMS (theta burst stimulation, 3 pulses are given at 50 Hz, repeated every 200 ms for a total of 600 pulses, 80% active motor threshold in contralesional hemisphere) + physiotherapy (1 h) CG: 10 sessions (daily): sham rTMS + physiotherapy (1 h) Outcomes: Action Research Arm Test (ARAT), Jebsen-Taylor Test (JTT) and Nine Hole Pegboard Test (NHPT)
5. Etoh et al., 2013 (crossover)	Motor-before-sham rTMS + repetitive-facilitation exercises	Chronic stroke patients (29.9 ± 18.8)	Motor-following-sham rTMS + repetitive-facilitation exercises	18 9/9	Not reported	7/7	IG: 20 sessions (daily, 5 days a week for 4 weeks): motor rTMS sessions (240 pulses, 1-Hz to the contralesional motor cortex, 90% of the resting motor threshold – 10 sessions - 4 min) + sham rTMS (10 session - 4 min) + repetitive facilitation exercises (40 min) CG: 20 sessions (daily, 5 days a week for 4 weeks): sham rTMS sessions (10 sessions - 4 min) + motor rTMS (240 pulses, 1-Hz to the contralesional motor cortex, 90% of the resting motor threshold – 10 sessions - 4 min) + repetitive facilitation exercises (40 min) Outcomes: Fugl-Meyer Assessment (FMA), Action Research Arm Test (ARAT), Simple Test for Evaluating Hand Function (STEF) and Modified Ashworth Scale (MAS)
6. Galvão et al., 2014	rTMS + physical therapy	Chronic stroke patients (53.4 ± 7.8)	Sham rTMS + physical therapy	20 10/10	57.4 ± 12/64.63 ± 6.8	6/7	IG: 10 sessions (3 d/week): rTMS (1500 pulses; 1 Hz; 90% of resting motor threshold in contralesional hemisphere) + physiotherapy (30 min) CG: 10 sessions (3 d/wk): sham rTMS + physiotherapy (30 min) Outcomes: Modified Ashworth Scale (MAS), Fugl-Meyer Assessment (FMA)
7. Higgins et al., 2013	rTMS + task oriented training	Chronic stroke patients (114.5 ± 27.6)	Sham-rTMS + task oriented training	9 4/5	74 ± 8/60 ± 11	3/3	IG: 8 sessions (twice/week): rTMS (1200 pulses, 1 Hz, 110% of the motor threshold in contralesional hemisphere) + task oriented training (90 min) CG: 8 sessions (twice/wk): sham-rTMS + task oriented training (90 min) Outcomes: Box and Block Test (BBT), Wolf Motor Function Teste (WMFT), Motor Activity Log (MAL)
8. Malcolm et al., 2007	rTMS + CIT	Chronic stroke patients (46.2 ± 0.85)	Sham rTMS + CIT	19 9/10	68.4 ± 8.4/65.7 ± 5.1	5/6	IG: 10 sessions (daily): rTMS (2000 stimuli were administered as 50 trains of 40 stimuli, 20 Hz, 90% of the motor threshold in lesional hemisphere) + constraint-induced therapy (5 h daily) CG: 10 sessions (daily): sham rTMS + constraint-induced therapy (5 h daily) Outcome: Wolf Motor Function Test (WMFT), Motor Activity Log (MAL) and Box and Block Test (BBT)
9. Pomeroy et al., 2007	a- rTMS + real VMC	Acute stroke patients (1 ± 0.3)	b- rTMS + placebo VMC c- Placebo-rTMS + real VMC d- Placebo-rTMS + placebo VMC	27 6/5/9/7	88	3/2/2/2	IG: a- 8 sessions (daily) rTMS (1200 pulses, 1-Hz, 120% motor threshold in 5 blocks of 40 separated by 3 min delivered to the lesioned hemisphere) + real VMC (the paretic elbow was repeatedly flexed/extended for 5 min); CG: b- 8 sessions (daily) rTMS (1200 pulses, 1-Hz, 120% motor threshold in 5 blocks of 40 separated by 3 min delivered to the lesioned hemisphere) + placebo-VMC (subjects viewed pairs of drawings of upper limbs and reported their likeness); c- 8 sessions, daily, placebo-rTMS (used a dummy coil) + real VMC (the paretic elbow was repeatedly flexed/extended for 5 min); d- 8 sessions, daily, placebo-rTMS (used a dummy coil) + placebo-VMC (subjects viewed pairs of drawings of upper limbs and reported their likeness) Outcome: Action Research Arm Test (ARAT)
10. Rose et at., 2014	rTMS + functional task practice (FTP)	Chronic stroke patients (61.6 ± 1.7)	Sham-rTMS + functional task practice (FTP)	21 11/10	64.7 ± 7/64.6 ± 9	8/5	IG: 16 sessions (4 times/week for 4 weeks): rTMS (1200, 1 Hz, 100% of motor threshold) + FTP (all tasks were functional in nature and included reaching, grasping and/or manipulation of objects performed with the paretic upper-limb only by 1-h). CG: 16 sessions (4 times/week for 4 weeks): sham-rTMS + FTP (all tasks were functional in nature and included reaching, grasping and/or manipulation of objects performed with the paretic upper-limb only by 1-h). Outcome: Wolf Motor Function Test (WMFT); Fugl-Meyer Assessment (FMA); Action Research Arm Test (ARAT); Motor Activity Log (MAL) and Modified Ashworth Scale (MAS)

(*continued on next page*)

Table 2 (*continued*)

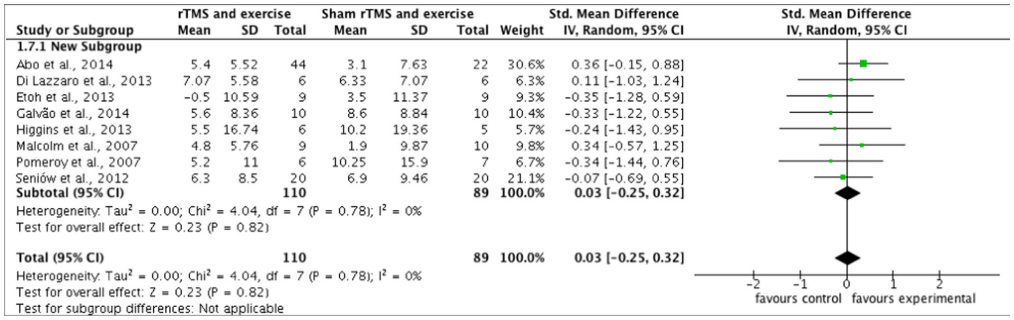
Author, year	Intervention group (IG)	Participants (onset of stroke in months ± SD)	Control group (CG)	N (IG/CG)	Age ± SD (IG/CG)	Masculine gender (IG/CG)	Protocol
11. Seniow et al., 2012	rTMS + physiotherapy (Bobath concept)	Acute stroke patients (1 ± 0.1)	Sham-rTMS + physiotherapy (Bobath concept)	40 20/20	63.5 ± 8.7/63.9 ± 9.2	12/14	IG: 15 sessions (5 days per week for 3 weeks): rTMS (1800 pulses, 1 Hz, 90% of the resting motor - 30 min) + physiotherapy (motor training included active and active-assistive exercises of the affected hand - 45 min) CG: 15 sessions (5 days per week for 3 weeks): sham-rTMS (30 min) + physiotherapy (motor training included active and active-assistive exercises of the affected hand - 45 min) Outcome: Wolf Motor Function Test (WMFT); Fugl-Meyer Motor Assessment (FMA) and National Institutes of Health Stroke Scale (NIHSS)

Abbreviations: N, sample number; rTMS, repetitive transcranial magnetic stimulation; CIT, constraint-induced therapy; VMC, voluntary muscle contraction.

limbs; and one study [28] conducted motor training for the fingers. The average intervention times were 20 min for rTMS and 45 min for upper-limb training. The majority of the studies [28,29,31,33] performed 10 intervention sessions, but the number of sessions ranged from 8 [32,34] to 22 [26] sessions. The majority of studies performed sessions on consecutive days [26,28–30,33,34,36]. Control groups received the same intervention time and the same training for the upper limb, but they also received sham rTMS. Among the eleven included studies, nine [26–33,35] evaluated chronic stroke patients and two [34,36] analyzed acute stroke patients. The time after stroke ranged from 1 [34,36] to 114.5 months [32]. The motor deficit of the upper limb was mild to moderate in all studies, as evaluated by the Brunnstrom stage for hand and fingers (score of 4 or 5). The majority of the selected studies included hemorrhagic and ischemic stroke subjects, and only three studies [29,34,35] included only ischemic stroke patients.

Table 3
Risk of bias of the included studies.

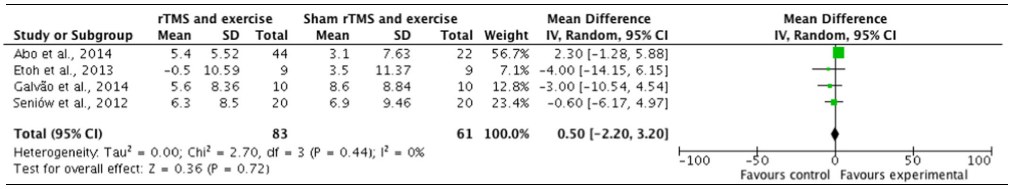
Author	Adequate sequence generation	Allocation concealment	Blinding of patients and investigators	Blinding of outcome assessors	Description of losses and exclusions	Intention-to-treat analysis
Abo et al., 2014	Yes	No	No	No	Yes	Not reported
Avenanti et al., 2012	Yes	Yes	Yes	Yes	Yes	Not reported
Chang et al., 2012	No	No	No	No	Yes	No
Di Lazzaro et al., 2013	Yes	Yes	Yes	Yes	No	Not reported
Etoh et al., 2013	No	No	Yes	Yes	No	Not reported
Galvão et al., 2014	Yes	Yes	Yes	Yes	Yes	No
Higgins et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes
Malcolm et al., 2007	No	No	Yes	Yes	No	Not reported
Pomeroy et al., 2007	Yes	Yes	Yes	Yes	Yes	Not reported
Rose et al., 2014	Yes	No	Yes	Yes	Yes	No
Seniów et al., 2012	Yes	Yes	No	Yes	Yes	No



The standardized mean difference (SMD) and 95% confidence interval (CI)

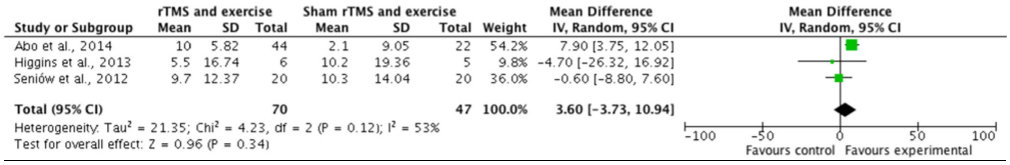
Fig. 2. Forest plots from the meta-analysis of difference of rTMS + upper-limb training and Sham-rTMS + upper-limb training of effects in upper-limb demonstrating estimates of effect size with 95% confidence intervals (CIs).

A. Fugl-Meyer Assessment (FMA)



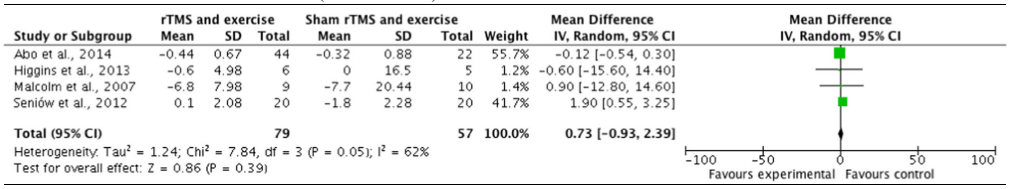
The mean difference and 95% confidence interval (CI)

B. Wolf Motor Function Test – function score (WMFT-FAS)



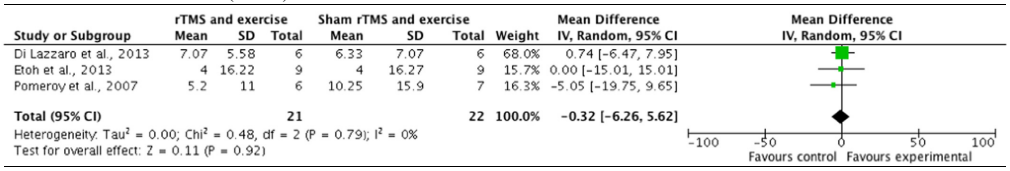
The mean difference and 95% confidence interval (CI)

C. Wolf Motor Function Test – time score (WMFT-TIME)



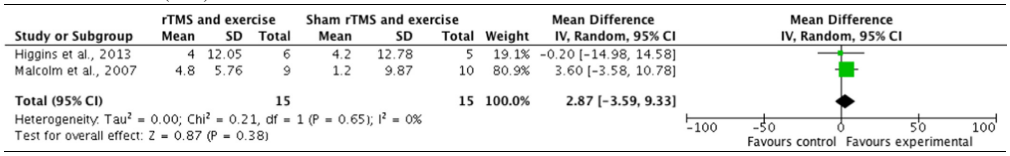
The mean difference and 95% confidence interval (CI)

D. Action Research Arm Test (ARAT)



The mean difference and 95% confidence interval (CI)

E. Boxand Block Test (BBT)



The mean difference and9 5% confidence interval (CI)

Fig. 3. Forest plots from the meta-analyses of difference of rTMS + upper-limb training and Sham-rTMS + upper-limb training of effects in upper-limb function separated for scales, demonstrating estimates of effect size with 95% confidence intervals (CIs).

Outcomes related to adverse events or side effects were not reported in 10 of the 11 studies analyzed. Only one study [27] reported tolerable headache complaints after rTMS. Cases of scalp discomfort during rTMS were reported, but severe side effects were not observed. The included studies did not report any case of participant withdrawal due to adverse effects.

3.2. Methodological quality

Among the included studies in this systematic review, 73% presented adequate sequence generation, 73% reported blinding, 82% reported blinding of the investigators and 73% described losses to follow-up and

exclusions, showing a low risk for bias regarding these characteristics. Among the studies, 55% reported adequate allocation concealment, showing a moderate risk of bias. However, only 9% performed intention-to-treat analysis, showing a high risk of bias. Only one study [32] fulfilled all the quality criteria (Table 3).

3.3. Effects of interventions

3.3.1. Upper-limb function

All the included studies analyzed the effects of rTMS associated with exercise. The comparison was performed with either the combination of sham rTMS and exercise or exercise alone. Scores for upper-limb motor function increased for both groups in 64% of studies [26,27,29,31–33,36]. Four studies [28–30,33] demonstrated improvement of the upper-limb motor functional status only for the intervention group. One study [35] reported no significant improvement after intervention for any group. Another study [32] showed improvement of the upper-limb function only for the control group.

Meta-analysis data from eight studies [26,27,30–34,36] showed no difference regarding motor function recovery when rTMS and upper-limb training were compared to sham rTMS and upper-limb training [upper-limb function (SMD = 0.03, 95% CI: −0.25 to 0.32; I^2 0%)] (Fig. 2). In the sensitivity analysis, there was also no significant difference between groups (Fig. 3): four studies used the FMA [26,30,31,36] (MD = 0.50, 95% CI: −2.2 to 3.2; I^2 0%) (Fig. 3A); three studies used the WMFT-FAS [26,32,36] (MD = 3.6, 95% CI: −3.73 to 10.94; I^2 53%) (Fig. 3B); four studies used the WMFT-TIME scores [26,32,33,36] (MD = 0.73, 95% CI: −0.93 to 2.39; I^2 62%) (Fig. 3C); three studies used the ARAT [29,30,34] (MD = −0.32, 95% CI: −6.26 to 5.62; I^2 0%) (Fig. 3D); and two studies used the BBT [32,33] (MD = 2.87, 95% CI: −3.59 to 9.33; I^2 0%) (Fig. 3E). A total of 199 stroke patients were included in this analysis.

3.3.2. Spasticity

Two studies [30,31] that included a total of 38 stroke patients evaluated muscle spasticity and did not find any difference between groups (MD = −0.31, 95% CI: −0.78 to 0.17; I^2 43%) (Fig. 4).

4. Discussion

This is the first systematic review reporting the effects of rTMS and exercise programs (physical therapy) on the upper-limb recovery of chronic stroke patients. This systematic review with meta-analysis showed that rTMS combined with upper-limb training has no additional effect on the upper-limb rehabilitation of chronic stroke patients when compared to exercise programs alone.

In this review, both intervention groups showed an improvement in upper-limb motor function immediately after the treatment and in the follow-up evaluation. It is not surprising that upper-limb training induced motor and functional improvements in stroke patients [17,18]. Although some studies [26–28,30,33] have shown better results from the combination of rTMS and upper-limb training compared to upper-limb training alone, the lack of a significant difference may result from the small sample sizes of the included studies.

Sensory-motor impairments after a stroke include hemiparesis, loss of motor coordination, sensory deficit and muscle spasticity [41,42]. In terms of physiological conditions, the electrical activity between both hemispheres is a coordinated and balanced process with mutually inhibitory actions. After a brain injury such as a stroke, an abnormal pattern of neuronal activity occurs, disrupting the regular interhemispheric communication [43,44].

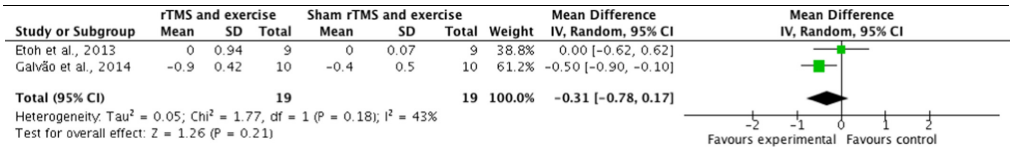
This excitability imbalance is due to a maladjustment in the interhemispheric inhibition, in which the intact primary motor cortex (M1) negatively influences functional recovery. This occurs as a consequence of transcallosal inhibition after cortical and subcortical cerebrovascular lesions and inhibits the activity of the injured cortex. This results in inhibitory activity into the injured cortex [45–47]. Neuroimaging studies have demonstrated increased M1 activity in the intact hemisphere when the paretic hand is trying to perform movements. This condition is more noticeable in those severe cases of sensory-motor compromise [3].

The use of rTMS as a rehabilitation tool for stroke patients has increased in recent years [5,6]. rTMS is a painless, non-invasive method that modulates cortical excitability at the stimulation site. It is able to deliver an electrical current through an insulated coil, which can up-regulate or down-regulate the neuronal excitability [9] in a long-term pattern. The modulation of excitability depends on the rTMS parameters and can result in facilitation or suppression. For instance, high-frequency rTMS (>5 Hz, excitatory rTMS) facilitates cortical excitability, whereas low-frequency rTMS (1 Hz, inhibitory rTMS) decreases cortical excitability [9].

The majority of studies included in this review used low frequencies to inhibit the non-affected side. Only one study used 1 Hz to stimulate the affected side, and two studies used high frequencies to stimulate the affected side. There is still no consensus regarding the optimal number of rTMS sessions and the most appropriate time for intervention. In the included studies, the average time for the sessions was 20 min of rTMS performed during 10 daily sessions. This is in accordance with the rTMS guidelines for clinical and research applications [48].

Sensory-motor recovery after a brain injury includes several mechanisms such as the expression of growth factors, axonal sprouting, synaptogenesis and synaptic strengthening [49,50]. Several studies have reported that activity-dependent brain plasticity is proportional to the complexity of motor learning and correlates with functional recovery after a stroke [51–53]. Recent studies have shown that upper-limb training procedures such as muscle strengthening, facilitation techniques, task-oriented training, constraint-induced movement therapy and motor imagery contribute to improving upper-limb motor function after stroke [17,18]. Even though all the exercise protocols used in the included studies emphasized functional upper-limb activities, the protocols were diverse and included constraint-induced movement therapy, sequential finger training tasks, voluntary motor contraction, functional training and task-oriented training.

Considering the potential of both forms of rehabilitation (rTMS and upper-limb training) for upper-limb recovery, studies have evaluated



The standard mean difference and 95% confidence interval (CI)

Fig. 4. The mean difference and 95% confidence interval (CI) in spasticity for the Modified Ashworth Scale.

the benefits of combining these two techniques [26–36]. Although some non-randomized studies have demonstrated significant improvements in the upper-limb motor function and spasticity after combined treatment [54–56], the randomized studies showed discrepancies among results. In this review, both groups (intervention and control) showed improvements in scores of upper-limb function immediately after the end of the treatment and in the follow-up. Five studies [26–28,30,33] showed better results in the combination of rTMS with upper-limb training compared to upper-limb training alone, but in the meta-analysis this difference was not observed. This inconsistency may have resulted from the small sample sizes of the analyzed studies as well as from the small number of included studies. Moreover, differences among the included studies may have influenced our results. These include the wide variation regarding time after the stroke, outcomes, upper-limb treatment and EMT protocols.

The methodological quality of the analyzed studies showed a low risk of bias for the majority of the characteristics (presented adequate sequence generation, reported blinding, reported blinding of the investigators and described losses to follow-up and exclusions). However, the analysis has indicated a moderate and high risk of bias for adequate allocation concealment and intention-to-treat analyses, respectively.

According to the number and methodological quality of the available studies, a level B recommendation was proposed for low frequency rTMS when applied to the contralesional hemisphere of chronic stroke patients [57]. It is very relevant to point out that rTMS is a high-cost treatment modality, and for this reason it is not available for all patients. Our results demonstrate that upper-limb training alone is able to induce similar results for upper-limb recovery when compared to rTMS plus upper-limb training.

5. Conclusion

This systematic review with meta-analysis synthesizes evidence of the effects of combining rTMS and upper-limb training for the upper-limb rehabilitation of chronic stroke patients. There is insufficient evidence to support the claim of the greater effectiveness of combined rTMS and upper-limb training as compared to upper-limb training alone. New studies with larger sample sizes, standardized rTMS and upper-limb protocols are needed to clarify the effectiveness of combining these treatment methods.

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5.2 ARTIGO 2

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Noninvasive brain stimulation improves gait performance after stroke: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND AND PURPOSE: Noninvasive brain stimulation (NIBS) has been receiving considerable interest as a potential adjuvant for rehabilitation after stroke. The aim of this meta-analysis was to examine the effectiveness of NIBS for gait rehabilitation in acute and chronic post-stroke subjects. METHODS: Sources included the following electronic databases: MEDLINE, Cochrane, EMBASE, SCOPUS, and PEDro. Two independent reviewers assessed the eligibility of studies based on the predefined inclusion criteria. The primary outcome was gait performance (assessed by the Timed Up & Go test and walking cadence) and the secondary outcomes were lower limb muscle strength and walking ability (assessed by the lower extremity Motricity Index and Functional Ambulation Classification). RESULTS: Ten randomized controlled trials were included in the meta-analysis, with 209 participants. Significant enhancement on gait performance was found after treatment with NIBS (SMD 0.51 [95% CI, 0.23 to 0.79; I^2 0%, p=0.0003]). Gait performance improved after excitatory stimulation of the lesional cortical region (SMD 0.52 [95% CI, 0.15 to 0.88; I^2 11%, p=0.006]), but not after inhibitory stimulation of the contralesional cortex (SMD 0.37 [95% CI, 0.17 to 0.91; I^2 0%, p=0.18]). NIBS was not able to induce improvements either on lower limb muscle strength (MD 1.66 [95% CI, -1.72 to 5.03; I^2 35%, p=0.34) or on walking ability (MD 0.25 [95% CI: -0.26 to 0.75; I^2 90%, p=0.34]). CONCLUSIONS: This systematic review with meta-analysis synthesizes moderate-quality evidences that NIBS is effective for improving gait performance after stroke but not for lower limb muscle strength and walking ability.

Key words: transcranial direct current stimulation, transcranial magnetic current stimulation, lower limb, muscle strength, walking, neurological rehabilitation, physical therapy modalities.

INTRODUCTION

Stroke is the leading cause of adult disability around the world [1]. One of the most common causes of disability after a stroke is the lower-limb motor impairment. Many stroke survivors have impaired lower limb muscle strength, walking ability, cadence and gait performance [2, 3].

An important question that remains unanswered is the most effective approach to improve motor recovery after stroke. Several stroke rehabilitation programs are focused on improving gait performance, balance and locomotor skills [2, 4, 5]. For this purpose, noninvasive brain stimulation (NIBS) has been used as a potential adjuvant treatment [6].

Transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are considered types of NIBS, and both can modulate cortical excitability and facilitate neuroplasticity [7]. According to the protocol, NIBS can be used to reduce or increase the motor cortical excitability. The inhibitory protocol consists of applying the stimuli on the non-lesioned cortex to decrease the inhibitory action from the non-affected hemisphere to the affected one [7]. For this purpose, the low-frequency rTMS (< 1 Hz) [8, 9] or the cathodal tDCS [10] must be used. On the other hand, to increase the motor cortical excitability, the high-frequency rTMS (> 5 Hz) [9] and anodal tDCS [10] must be delivered to the affected hemisphere [7].

Several randomized clinical trials (RCT) have investigated the effects of rTMS [11-14] and tDCS [10, 15-19] on gait performance, walking ability and lower limb muscle strength after stroke. Even though results are still inconclusive, some of these studies have reported improvements on spatiotemporal gait parameters [19] and lower limb muscle strength [10, 15, 17].

Specific gait performance tests have been used to evaluate subjects after stroke. The Timed “Up & Go” test (TUG) [16, 18, 19] and walking cadence are among the most utilized [10, 15, 17, 19]. On the other hand, walking ability may be assessed by means of the Functional Ambulation Classification (FAC). This scale categorizes subjects into six levels (from non-functional to independent) depending on how much assistance they require from someone else when walking, regardless of assistive device [15, 20]. Additionally, among the available tools for measuring muscle strength, the lower extremity Motricity Index (MI-LE) has been used as a simple, brief and feasible measure that can predict mobility outcomes in post-stroke subjects [21].

Therefore, this systematic review with meta-analysis aims to determine the effectiveness of NIBS combined or not combined with exercise to improve gait performance, lower limb strength and walking ability after stroke.

METHODS

Protocol

This meta-analysis was conducted in accordance with the Cochrane Collaboration [22] and is presented as suggested by the Preferred Reporting Items for Systematic Review and Meta-Analyses: The PRISMA Statement [23].

Eligibility Criteria

We included randomized controlled clinical trials and randomized controlled crossover trials (from which we analyzed only the first period as a parallel-group design) that reported the effect of tDCS or rTMS for improving gait performance in subjects with acute or chronic stroke. We only included studies with at least one group treated with tDCS or rTMS and one control group receiving sham tDCS or sham rTMS combined or not combined with other type of therapy. We excluded studies that enrolled infant stroke survivors, and thesis or articles published only as abstracts, including conference proceedings.

The primary outcome was gait performance as assessed by: (a) the required time in seconds to perform the Timed up and Go (TUG) test; (b) walking cadence (number of steps per minute). The secondary outcomes were: (a) lower-limb muscle strength (assessed by the lower extremity Motricity Index (MI-LE)); (b) walking ability (assessed by the Functional Ambulation Classification (FAC)).

Search Strategy

Literature searches were conducted up to September 2016, using electronic databases including MEDLINE (accessed by Pubmed), Embase, Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), SCOPUS, Scielo and Physiotherapy Evidence Database (PEDro). The following broad search terms were used: “stroke”, “brain ischemia”, “transcranial direct current stimulation”, “transcranial magnetic stimulation” and a string of predetermined words, which yielded a high

sensibility in the search for randomized controlled trial [24]. The terms were adjusted to fit the requirements of each electronic database. To enhance the sensitivity of the search, words related to the outcomes of interest were not included.

Study selection and data extraction

Two independent review authors (PG and APS) screened titles and abstracts of the identified studies. A standard screening checklist based on the eligibility criteria was used for each study. A third reviewer (CS) solved all disagreements related to the trial eligibility and assisted the decision of including or excluding studies. PG and APS independently extracted the following information from included studies: methodological design, number of subjects, comparison groups, intervention protocols and outcomes. Disagreements were solved by consensus. In some cases, authors were contacted for data clarification.

Risk of bias assessment

We assessed the risk of bias in the included studies using the Cochrane risk of bias assessment tool [22]. Study quality assessment included random sequence generation, allocation concealment, blinding of investigators, participants, assessors and outcomes assessors, intention-to-treat analysis and description of losses and exclusions. Each domain was scored as ‘‘high’’, ‘‘low’’ or ‘‘unclear’’ risk of bias [22]. Studies with a low risk of bias in three or more domains were suggested as trials of a moderate to high methodological quality.

Data Analysis

For quantitative synthesis, pooled-effect estimates were obtained by comparing the change from the baseline to the end of study. Regarding the continuous outcomes, if the unit of measurement was consistent across trials, the results were presented as the weighted mean difference (MD) with 95% confidence intervals (95% CIs). For those cases where studies have not used the same outcomes, we calculated standardized mean differences (SMDs) instead of MDs. Statistical heterogeneity was assessed using I^2 statistic, which values above 25% and 50% were considered as indicative of moderate and high heterogeneity, respectively. Fixed effects model should be used to combine studies when I^2 value was lower than 50%. Otherwise, random effects model would be used [22]. A p value ≤ 0.05 was considered statistically significant. All analyses

were conducted using Review Manager, version 5.3.

We calculated six separate meta-analyses. First, we analyzed the effects of NIBS (rTMS and tDCS) on gait performance. Then, we separately performed three sensitivity analyses: (a) investigating the effects of rTMS and tDCS on gait performance, (b) the effects of NIBS on different stages of stroke: acute (<3 month since the ictus) and chronic (>6 month since the ictus) and (c) the effects of different types of NIBS: excitatory or inhibitory. Finally, we conducted another two analyses to verify the effect of NIBS on lower limb strength and walking ability.

RESULTS

The electronic search strategy has identified a total of 2114 studies, of which 10 were included in this review [10-19]. A total of 209 subjects was enrolled in the studies included in the meta-analysis. The Figure 1 shows the flow diagram of the study.

Description of Studies

Characteristics of the included studies are summarized in Table 1. Four studies investigated the use of rTMS (n=112) [11-14] and six studies analyzed the use of tDCS (n=97) [10, 15-19]. Considering the primary outcome, all studies evaluated the gait performance in stroke subjects and used different tests and scales to analyze this outcome. Four studies used results from TUG [13, 16, 18] and six studies used the cadence [10-12, 14, 15, 17, 19]. Regarding secondary outcomes, three studies used the MI-LE to evaluate lower limb strength [10, 15, 17] and five studies used FAC scale to analyze walking ability [10, 15-17, 19].

The included studies enrolled acute [11, 12, 15, 16, 18] and chronic post-stroke subjects [10, 13, 14, 17]. The included type of stroke was ischemic [10, 15-18] or ischemic/hemorrhagic [11-14, 19]. Much of studies has combined the NIBS with some type of exercise (Lokomat, Conventional Physical Therapy, Physical Therapy with motor imagery, Motor Rehabilitation, Robot-assisted gait training or Task Oriented Training for lower limb) compared to a control group (Sham tDCS or Sham rTMS with or without exercise). Only two studies have not combined NIBS with exercise. One study investigated only the effect of rTMS [13] and another one has assessed the effect of a single bi-cephalic tDCS session (excitatory anodal delivered over the lesional

hemisphere and inhibitory cathodal over the contralesional hemisphere) [18].

Regarding rTMS protocols, two studies used low frequency (1 Hz) to inhibit the contralesional cortex [13, 14] and two studies used high frequency (10Hz) to excite the lesional cortex [11, 12]. Sessions lasted from 10 min [14] to 20 min [12, 13], and the number of sessions were five [13], ten [14], twenty [12] and thirty [11].

About tDCS protocols, the current intensities for anodal tDCS stimulation were 1.5 mA [17], 2 mA [15, 19] and 2.5 mA [10] to excite the lesional cortex. One study has used cathodal tDCS to inhibit the contralesional cortex with a 2.5 mA current [16]. Another study used 2 mA bi-cephalic tDCS to simultaneously inhibit the contralesional and excite the lesional cortex [18]. Sessions lasted from 10 min [15, 16] to 20 min [10, 19] in 10 consecutive daily sessions [10, 15-17]. Time of stimulation ranged between seven and 20 min [10, 17, 19] and the number of sessions ranged between one and 12 (three times per week) [18, 19]. (Table 2)

Risk of Bias

Among the included studies, 60% presented blinding of participants and personnel and 60% presented blinding of outcome assessment, showing a low risk of bias for these analyses. On the other hand, the following assessment presented unclear or high risk of bias: 30% reported adequate random sequence generation, 20% presented allocation concealment, 20% performed intention-to-treat analysis and 40% described losses and exclusions (Figure 2). Therefore, only 40% of the included studies showed moderate to high methodological quality.

Effects of interventions

NIBS x Sham NIBS on gait performance

Ten studies [10-19] (n=209) evaluated the effects of NIBS on gait performance and were included in the meta-analyses. NIBS, combined or not combined with another type of exercise, induced a significant improvement on gait performance when compared to sham NIBS (SMD 0.51 [95% CI, 0.23 to 0.79; I^2 0%, p=0.0003]) (Figure 3A). A primary sensitivity analysis, showed that both rTMS and tDCS had positive effects on gait performance (rTMS: SMD 0.59 [95% CI, 0.21 to 0.97; I^2 0%, p=0.002]; tDCS: SMD 0.44 [95% CI, 0.00 to 0.88; I^2 10%, p=0.05]) (Figure 3B). The second sensitivity analysis, showed that NIBS in acute stroke and chronic stroke had positive

effect on gait performance (acute stroke: SMD 0.58 [95% CI, 0.19 to 0.96; I^2 4%, p=0.003]; chronic stroke: SMD 0.43 [95% CI, 0.01 to 0.85; I^2 0%, p=0.04]) (Figure 3C). In addition, the third sensitivity analysis showed that excitatory NIBS (high frequency rTMS and anodal tDCS) was effective to improve gait performance (SMD 0.52 [95% CI, 0.15 to 0.88; I^2 11%, p=0.006]). On the other hand, inhibitory NIBS (low frequency rTMS and cathodal tDCS) showed no difference between groups on gait performance (SMD 0.37 [95% CI, 0.17 to 0.91; I^2 0%, p=0.18]) (Figure 3D).

Lower limb muscle strength

Three studies assessed the lower limb muscle strength [10, 15, 17] (n=64) and were included in the meta-analysis. NIBS combined with exercise was not able to induce significant improvement on lower limb muscle strength when compared to sham NIBS (MD 1.66 [95% CI, -1.72 to 5.03; I^2 35%, p=0.34) (Figure 4A).

Walking ability

Five studies [10, 15-17, 19] (n=83) assessed the walking ability and were included in the meta-analysis. NIBS combined with exercise was not able to induce significant improvement on walking ability when compared to sham NIBS (MD 0.25 [95% CI: -0.26 to 0.75; I^2 90%, p=0.34]) (Figure 4B).

DISCUSSION

This systematic review with meta-analysis aimed to determine the effectiveness of NIBS combined or not with other types of therapy for gait rehabilitation after stroke. To the best of our knowledge, this is the first systematic review with meta-analysis evaluating the effect of NIBS for gait rehabilitation after stroke. The meta-analysis showed that NIBS can improve gait performance and may be used as an adjunct treatment for post-stroke subjects. Nevertheless, NIBS seems to have no effect on lower limb muscle strength and walking ability.

After stroke, subjects present sensory-motor impairments including hemiparesis, loss of motor coordination, sensory deficit and muscle spasticity [25-27]. Furthermore, an abnormal pattern of neuronal activity occurs, disrupting the regular

inter-hemispheric communication [28-30]. These characteristics contribute for decrease on TUG performance, walking cadence and make rehabilitation even harder [3].

New strategies as NIBS have been investigated as an attempt to improve the stroke rehabilitation. rTMS and tDCS are the most common types of NIBS [7]. These approaches are based on the interhemispheric competition model, and are able to improve both cognitive [31] and motor function [32, 33]. Our results agree with these findings showing that rTMS and tDCS enhance TUG performance and walking cadence. Considering that walking is an important component of activities and participation according to the International Classification of Functioning, Disability and Health (ICF), the improvement on gait performance is pivotal for the subject's daily-life activity.

Early rehabilitation is most effective after stroke, although the window of time for recovery never closes. The plasticity processes decrease over time, especially six months after the injury [34, 35]. Our analysis showed that the NIBS would be able to optimize recovery of gait performance more significantly in the acute phase after brain injury. However, in the chronic phase some benefits were also observed. This improvement shows that, even in the chronic phase, NIBS can optimize the surviving neuronal networks, allowing new plasticity strategies and functional recovery.

According to the set protocol (stimulation parameters and type of stimulation), NIBS can increase or decrease cortical excitability. rTMS may be used to modulate abnormal brain excitability in two different ways: (a) high-frequency rTMS delivered to the affected hemisphere, (b) low-frequency rTMS delivered to the unaffected hemisphere [36]. The anodal tDCS delivered to the primary motor cortex (M1) increases corticospinal excitability, and cathodal stimulation of M1 decreases corticospinal excitability [7]. In our third sensitive analysis, six studies using excitatory stimulation showed increase on gait performance in those subjects who received 10Hz rTMS or anodal tDCS [10-12, 15, 17, 19]. However, among the three studies using 1Hz rTMS or cathodal tDCS [13, 14, 16], only one has showed significant improvement on gait performance. Then, this meta-analysis found no significant effect of inhibitory stimulation on gait performance. This result can be explained because a high current intensity is needed to stimulate the cortical lower limb representation area. This higher current amplitude is necessary because the cortical lower limbs representation has a deepest and more vertical orientation compared to the upper limbs [37, 38].

Concerning the lower limb muscle strength and walking ability (secondary outcomes), no significant results were found in the meta-analysis. Among the five

included studies for walking ability analysis [10, 15-17, 19], only one showed significant improvement in the FAC [19]. Regarding the paretic lower limb strength, three studies were included in the meta-analysis [10, 15, 17], and only one showed significant improvement in the intervention group [15]. This difference may be due to the longer period of time subjects underwent rehabilitation therapies [15]. Also, the small number of included studies in the meta-analysis and the reduced sample sizes may explain this result.

Studies included in this review used different parameters of NIBS considering dosing parameters (frequencies and intensity), sessions per day, and days per week. Nevertheless, all studies follow safety, ethical considerations, and application guidelines for the use of rTMS and tDCS in clinical practice and research [9, 39]. In this sense, it is important that more studies are carried out to standardize protocols with clinical effectiveness.

The average treatment effect sizes have been calculated to evaluate the efficacy of interventions. It is based on thresholds defined by Cohen, which categorize effect sizes as small [standardized mean difference (SMD) of 0.2], medium (SMD of 0.5), and large (SMD of 0.8) [40] (SMD is the difference in means between active and control groups divided by their pooled standard deviation). Our study has found a medium effect size (SMD – 0.51) when evaluating the effectiveness of treatment with NIBS on gait performance of post-stroke subjects when compared to sham intervention.

Limitations of the Review

Results are favorable to the NIBS therapy, combined or not combined with other type of intervention, for gait performance of subjects after stroke. One important limitation of this study is that several studies have shown some biases. Seven studies did not properly describe the generation of a random sequence and only two has clearly described allocation concealment. Six studies reported the patient and assessors blinding. Six studies did not report drop-outs as well as the patient's exclusions. Additionally, only four studies have used the intention to treat analysis. Another limitation is that NIBS protocols are still quite varied. Even though some guidelines have already been established, there is no consensus about the ideal parameters to be applied to post-stroke subjects.

CONCLUSION

This systematic review with meta-analysis synthesizes evidences of the effects of NIBS on gait rehabilitation after acute and chronic stroke. In brief, when comparing rTMS or tDCS with sham stimulation, with or without other type of therapy, there is moderate-quality evidence for positive effects of NIBS on gait performance.

At present, studies support NIBS for improving gait performance after stroke in clinical practice. Future researches should aim to examine the effects of NIBS on walking ability and lower limb muscle strength, as well as to explore differences between excitatory and the inhibitory stimulations.

DISCLOSURE

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Table 1 - Characteristics of studies included in systematic review

Author, Year	Intervention	Participants	Control	N (IG/CG)	Age Mean ± SD (IG/CG)	Male gender (IG/CG)	Protocol
tDCS							
Chang et al., 2015	Anodal tDCS + Conventional Physical Therapy	Acute Stroke Subjects	Sham tDCS + Conventional Physical Therapy	24 (12/12)	59.9±10.2/ 65.8±10.6	Not reported	IG: anodal tDCS: 10 sessions, daily for 2 weeks, 10 min at 2 mA + Conventional Physical Therapy: 12 sessions, daily for 2 weeks (Monday-Friday: 2.5 h/day; Saturday: 1 h/day). CG: sham tDCS: 10 sessions, daily for 2 weeks, 10 min (current only delivered during the first 15 s) + Conventional Physical Therapy: 12 sessions, daily for 2 weeks (Monday-Friday: 2.5 h/day; Saturday: 1 h/day). Outcomes: MEP; walking cadence; FM-LE; MI-LE; FAC; BBS.
Danzl et al., 2013	Anodal tDCS+Lokomat	Chronic Stroke Subjects	Sham tDCS+Lokomat	8 (4/4)	Not reported	4/4	IG: anodal tDCS: 12 sessions, 3 times per week for 4 weeks, 20 min, 2 mA + Lokomat for 20-40min. CG: sham tDCS: 12 sessions, 3 times per week, 20 min (current set to ramp up and then down over the first 75 seconds of the session) + Lokomat for 20-40min. Outcomes: 10MWT, TUG, BBS, FAC, SIS-16.
Fusco et al., 2014	Cathodal tDCS + Motor Rehabilitation	Acute Stroke Subjects	Sham tDCS + Motor Rehabilitation	11 (5/6)	58.36 ± 14.35	3/2	IG: cathodal tDCS: 10 sessions, daily for 2 weeks, 10 min at 1.5mA + Motor Rehabilitation: twice a day, 45 min for each session. CG: sham-tDCS + Motor Rehabilitation: twice a day, 45 min for each session. Outcomes: TUG; 6MWT; 10MWT; RMI; FAC.

Geroin et al., 2011	Anodal tDCS + Robot-assisted gait training	Chronic Stroke Subjects	Sham tDCS + Robot assisted gait training	30 (10/10/10)	63.6±6.7/ 63.3±6.4/ 61.1±6.3	8/6/9	IG: 10 sessions, daily for two weeks, 50-minute (Robot-assisted gait training) + anodal tDCS (1.5mA) during 7 min. CG: 10 sessions, daily for two weeks, 50-minute (Robot-assisted gait training) + sham tDCS (current stimulator was switched off) during the first 7 min. Other group: Walking exercises according to the Bobath Concept. Outcomes: 6MWT; 10MWT; walking cadence; FAC; RMI; MI-LE; MAS.
Picelli et al., 2015	Anodal tDCS + tsDCS + Robot-assisted gait training	Chronic Stroke Subjects	Sham tDCS + tsDCS + Robot-assisted gait training	30 (10/10/10)	64.8±6.0/ 61.0±7.2/ 62.8±11.8	7/7/8	IG: anodal tDCS + tsDCS: 10 sessions, daily for two weeks, 20 min. Robot-assisted gait training + tDCS (2 mA for 20 min during the Robot-assisted gait training) + cathodal tsDCS (2.5 mA for 20 min) CG: sham tDCS + tsDCS: 10 sessions, daily for two weeks, 20 min. Robot-assisted gait training + sham tDCS (2 mA for only 2 min) + cathodal tsDCS. Other group: tDCS + sham tsDCS: 10 sessions, daily for two weeks, 20 min. Robot-assisted gait training + anodal tDCS (2 mA for 20 min) + sham tsDCS. Outcome: 6MWT; FAC; MI-LE; MAS; walking cadence.
Tathis et al., 2014	Bi-cephalic tDCS	Acute Stroke Subjects	Bi-cephalic Sham tDCS	14 (7/7)	67.3±11.8/ 56.4±12.3	5/6	IG: bi-cephalic tDCS: single session, 2mA for 15min. CG: bi-cephalic sham tDCS: single session (2 mA providing the initial sensory experience and subsequently turned off, less than 30 seconds). Outcomes: POMA and TUG.

rTMS							
Wang et al., 2012	rTMS + Task-Oriented Training	Chronic Stroke Subjects	Sham rTMS + Task-Oriented Training	24 (12/12)	64.90±12.3/ 62.98±10.88	7/8	IG: rTMS: 10 sessions, daily for two weeks, 90% resting motor threshold and a train of 600 pulses (1 Hz) for 10 min + task-oriented training for 30 min. CG: Sham rTMS: 10 sessions, daily for two weeks + task-oriented training for 30 min. Outcomes: FM-LE, walking cadence.
Ji & Kim., 2015	rTMS + Conventional Physical Therapy	Acute Stroke Subjects	Sham rTMS + Conventional Physical Therapy	39 (20/19)	55.65±8.95/ 56.36/10.44	Not reported	IG: rTMS: 20 sessions, daily for four weeks, 10Hz was applied daily to the hotspot of the lesional hemisphere in 10-second trains, with 50-second intervals between trains, for 20 min (total 2.000 pulses) + 30 min of Conventional Physical Therapy CG: Sham rTMS: 20 sessions, daily for four weeks, sham rTMS for 20 min + Conventional Physical Therapy for 30 min. Outcomes: walking cadence.
Ji et al., 2014	rTMS + Physical Therapy with motor imagery	Acute Stroke Subjects	Sham rTMS + Physical Therapy with motor imagery	29 (15/14)	49±11/44.28 ±8.52	9/8	IG: rTMS: 30 sessions, daily for six weeks, 10 Hz rTMS was applied to the hotspot (10 sec trains with 50 sec interval) for 15 min + Physical Therapy with motor imagery, 30 min. CG: sham rTMS: 30 sessions, daily for six weeks, sham rTMS did not apply + physical therapy with motor imagery, 30 min. Outcomes: walking cadence.

Ratsgoo et al., 2016	rTMS	Chronic Stroke Subjects	Sham rTMS	20 (10/10)	54.6±11.75 / 49.7±11	8/8	IC: rTMS: 5 sessions, daily for one week, rTMS a train of 1000 pulses of 1-Hz, intensity of 90% of the tibialis anterior motor threshold over 20 min CG: sham rTMS: 5 sessions, daily for one week, sham rTMS (application of an audio coil, no magnetic stimulation was delivered to the brain). Outcomes: MAS, TUG, FM-LE.

IG, Intervention group; CG, Control Group; tDCS, transcranial direct current stimulation; tsDCS, transcutaneous spinal direct current stimulation; rTMS, repetitive transcranial magnetic stimulation; N, sample number; MEP, Motor-evoked potential; FM-LE, Fugl Meyer Lower Extremity; MI-LE, Lower extremity Motricity Index; FAC, Functional Ambulatory Category scale; BBS, Berg Balance Scale; 10MWT, 10 Meter Walk Test; TUG, Timed Up and Go Test; SIS-16, Stroke Impact Scale 16; 6MWT, 6-Minute Walking Test; RMI, Rivermead Mobility Index; RAGT, MAS, Modified Ashworth Scale; POMA, Performance Oriented Mobility Assessment. 1

Table 2. Noninvasive brain stimulations protocols

Author, Year	Time of stimulation	Intensity or Frequency of current	Number of sessions
rTMS			
Inhibitory			
Wang et al., 2012	10min	1Hz	10 (daily)
Ratsgoo et al., 2016	20min	1Hz	5 (daily)
Excitatory			
Ji & Kim., 2015	20min	10Hz	20 (daily)
Ji et al., 2014	15min	10Hz	30 (daily)
tDCS			
Inhibitory			
Fusco et al., 2014	10min	1.5mA	10 (daily)
Excitatory			
Chang et al., 2015	10min	2mA	10 (daily)
Danzl et al., 2013	20min	2mA	12 (3x/wk)
Geroin et al., 2011	7min	1.5mA	10 (daily)
Picelli et al., 2015	20min	2.5mA	10 (daily)
Bi-cefhalic			
Tathis et al., 2014	15min	2mA	1

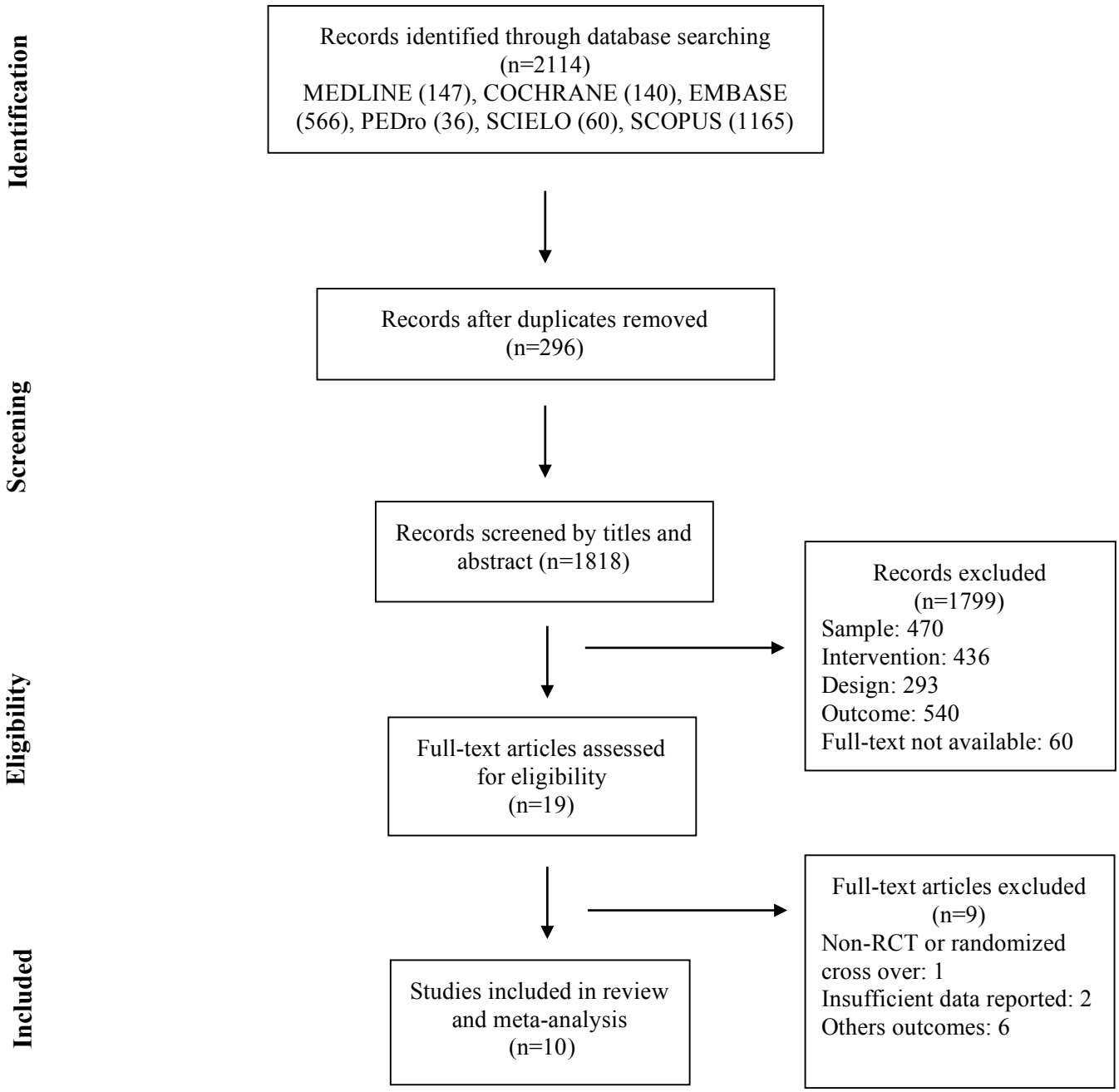


Figure 1. The flow diagram of studies included in the review.

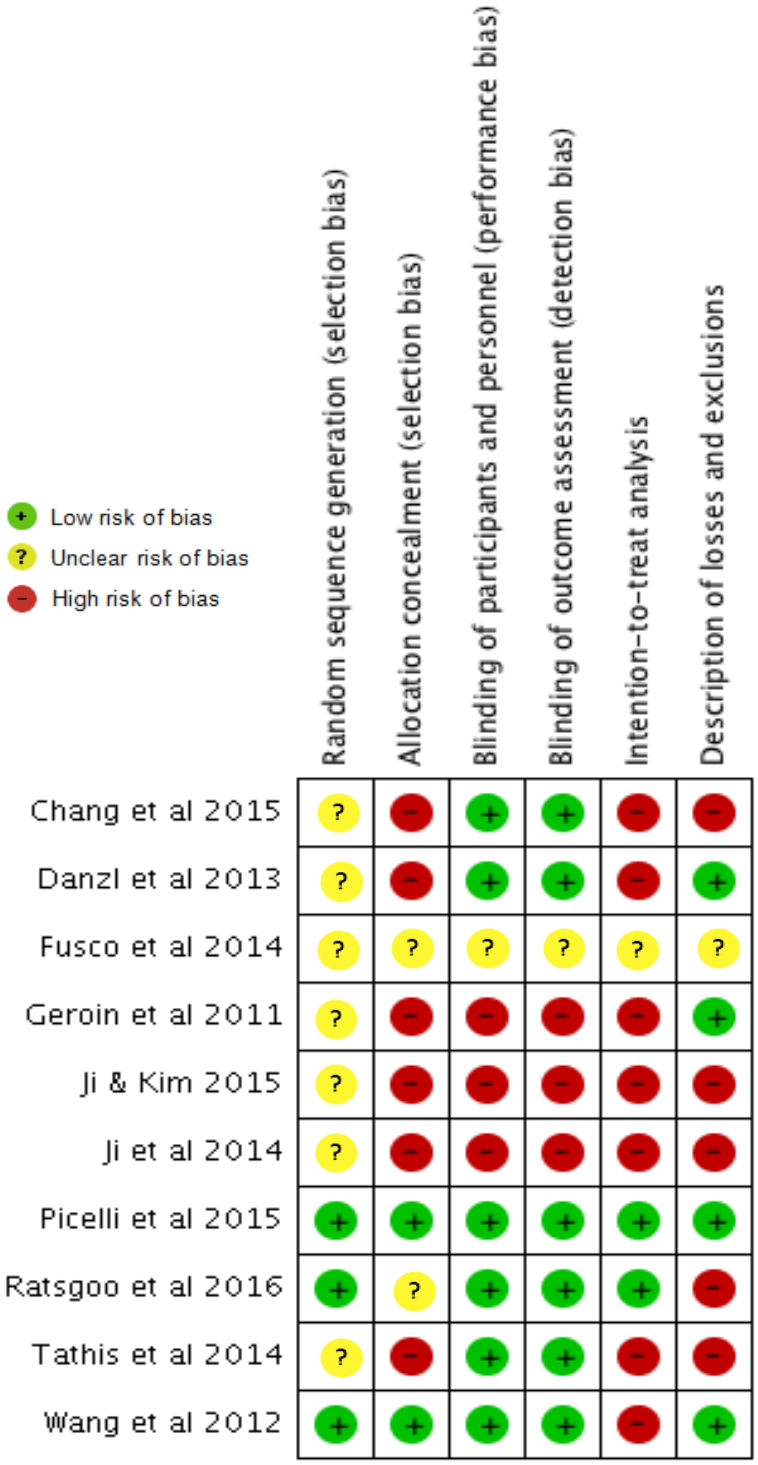
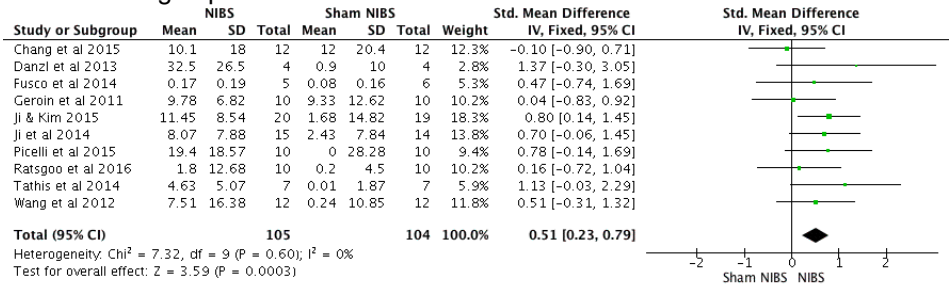


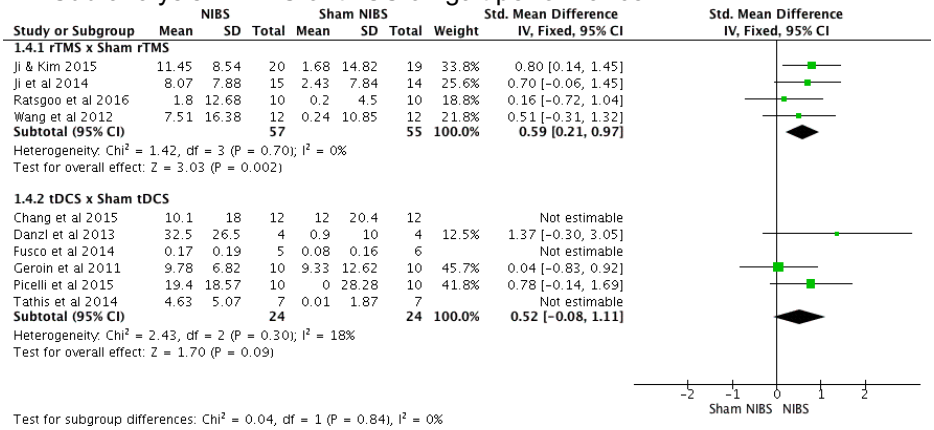
Figure 2. Risk of Bias assessment for ten groups

Primary Outcome:

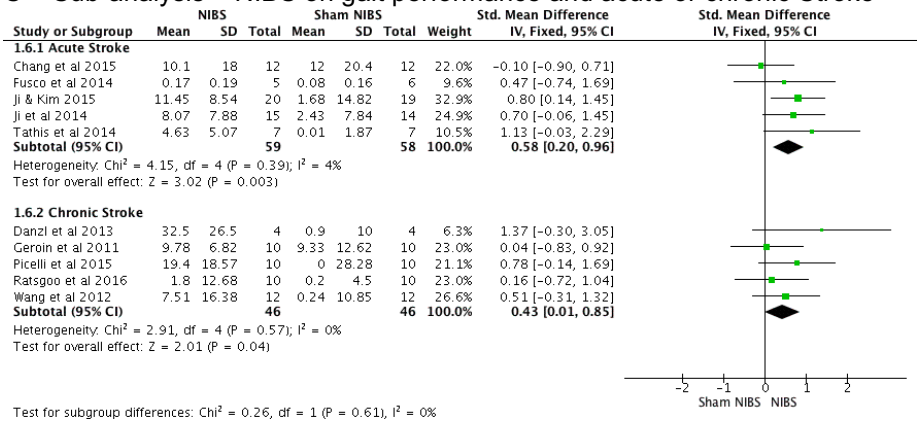
A – NIBS on gait performance



B – Sub-analysis – rTMS or tDCS on gait performance



C – Sub-analysis – NIBS on gait performance and acute or chronic Stroke



D – Sub-analysis – Excitatory or inhibitory stimulation on gait performance

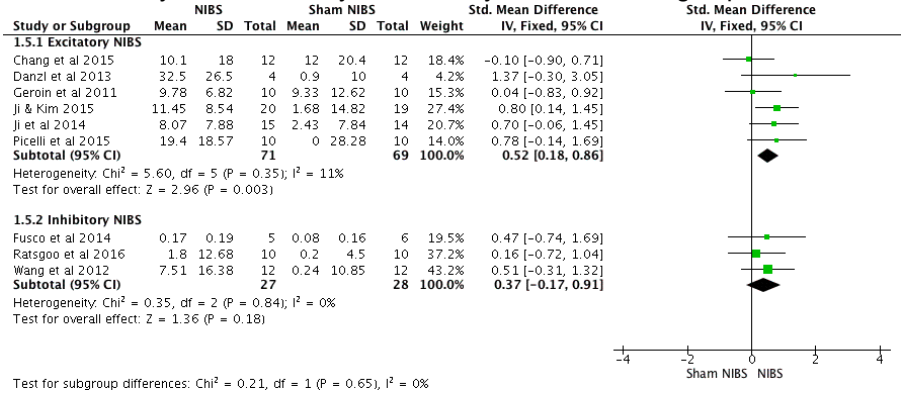
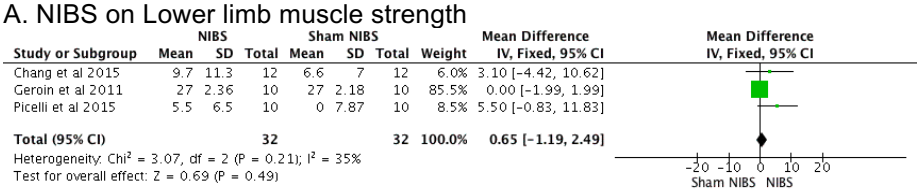


Figure 3. The standard mean difference and 95% confidence interval (CI) of NIBS on gait performance (A), rTMS or tDCS on gait performance (B),

NIBS on gait performance and acute or chronic stroke (C) and Excitatory or inhibitory stimulation on gait performance (D)

Secondary outcomes:

A. NIBS on Lower limb muscle strength



B. NIBS on Walking ability

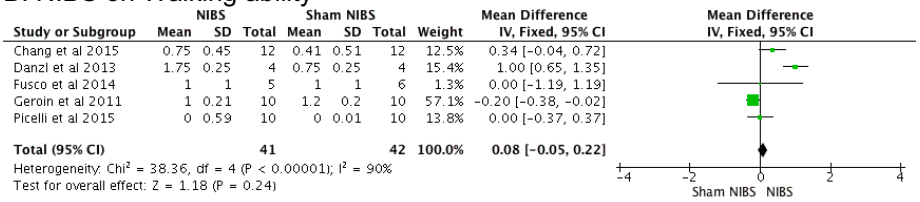


Figure 4. The standard mean difference and 95% confidence interval (CI) of NIBS on lower limb muscle strength (A) and NIBS on walking ability (B).

5.3 ARTIGO 3

Revista que será submetido: JOURNAL OF PHYSIOTHERAPY

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Repetitive transcranial magnetic stimulation combined with transcranial direct current stimulation for upper-limb motor function recovery after stroke: a randomised trial

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ABSTRACT

Question: Does dual-mode stimulation combining low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) with anodal transcranial direct current stimulation (atDCS) improve upper-limb motor function more than unimodal LF-rTMS or unimodal atDCS after stroke? **Design:** An assessor-blinded, randomised trial. **Participants:** Twenty-four subjects from Mãe de Deus Hospital and local community. **Intervention:** Participants were randomly assigned to received 1Hz LF-rTMS over the contralesional hemisphere, 1mA atDCS over the ipsilesional hemisphere or bilateral dual-mode stimulation comprising LF-rTMS+atDCS. All participants received 10 sessions (3x/wk) for 20 minutes. **Outcome measures:** Outcome measures were taken at baseline and after 4 weeks of treatment. The primary outcome was manual dexterity measured by Box and Block Test. Secondary outcomes were upper limb function measured by the Wolf Motor Function Test (WMFT), grip strength assessed by manual dynamometer and quality of life assessed by Stroke Specific Quality of Life. **Results:** All participants completed the study. No severe adverse effects were reported during the sessions. There was no difference between groups for any outcomes. Manual dexterity, WMFT performance time and grip strength were improved after both LF-rTMS+atDCS and atDCS protocols. WMFT functional ability was enhanced on LF-rTMS group. Improvements in quality of life were observed for both LF-rTMS and atDCS groups. **Conclusion:** Unimodal LF-rTMS, unimodal atDCS and dual-mode LF-rTMS+atDCS similarly induce improvement on manual dexterity, upper limb motor function, grip strength and quality of life of chronic post-stroke participants. **Trial Registration:** NCT02817867

INTRODUCTION

Stroke is one of the leading causes of adult disability worldwide[1]. Sensorimotor and cognitive impairments are common post-stroke consequences. Motor function impairments impact negatively the quality of life, independence, and in performing everyday household chores and work-related activities[2]. Post-stroke consequences impose a significant burden on the victim, their family, and society. Researchers have identified the importance on developing new effective rehabilitation therapies to improve motor function of post-stroke survivors. The interhemispheric competition model proposes that motor deficits in stroke subjects are a result of reduced output from the affected hemisphere and excessive transcallosal inhibition from the unaffected hemisphere to the affected one[3]. The interhemispheric competition model-based therapies are new promising strategies in stroke rehabilitation[4,5].

Non-invasive brain stimulation (NIBS) is a method based on the interhemispheric competition model used to modulate human brain function. This technique has shown encouraging results for treating post-stroke motor deficits[4]. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are two of the most promising NIBS modalities. rTMS acts like a neurostimulator and involves a continuous train or periodic trains of pulses that change the corticospinal excitability. The effect depends on the pacing rate. High frequency[6] (HF) stimulation (i.e., >3 Hz) increases cortical excitability while low frequency[7] (LF) stimulation (i.e., ≤1 Hz) decreases cortical excitability[8]. Thus, HF-rTMS is applied over the ipsilesional cortical area and LF-rTMS is applied over contralesional cortical area[9]. On the other hand, tDCS acts rather as a neuromodulator and is an easier electrophysiological tool to handle, much smaller and portable at the patient's bedside. tDCS delivers weak polarizing direct currents to the cortex via two large electrodes placed on the scalp[9]. The active electrode is applied over the targeted cortex area and a direct current generator (0.5–2.5 mA) is delivered to modify the threshold of cortical neurons and the underlying cortex excitability. tDCS is polarity dependent: anodal tDCS (atDCS) increases the network excitability and cathodal tDCS (ctDCS) decreases the network excitability[9]. Thus, atDCS is applied over the ipsilesional cortex and ctDCS is applied over the contralesional area.

Several studies have evaluated the therapeutic benefits of rTMS and tDCS alone or combined with other therapies in cognitive neuroscience, psychiatry,

neurology, and neurorehabilitation[10,11] to improve motor recovery, upper-limb and lower limb function[3,12-14]. Currently, new modalities of brain modulation have been studying to maximize the effects of motor function through the stimulation of more than two sites or with multi-modal stimulation by combining different modalities [14-23]. However, there have been few studies investigating the effectiveness of bi-hemispheric stimulation using both rTMS and tDCS for improving motor function after stroke[15,18,23] and it remains unclear how protocols can be optimized to maximize their therapeutic effects.

The research question for this randomised clinical trial was:

Does dual-mode stimulation combining LF-rTMS with anodal tDCS improve upper-limb motor function more than unimodal LF-rTMS and unimodal anodal tDCS after stroke?

METHOD

Design

An appraiser-blinded, randomised trial was undertaken (Figure 1) according to CONSORT guidelines for randomized clinical trials[24]. Participants' allocations were placed in opaque, sequentially numbered and sealed envelopes that were held off-site for randomised into three groups (LF-rTMS group; atDCS group and rTMS+tDCS group). Once a participant passed the screening process and completed the initial assessment, the next envelope was opened and the group allocation was revealed. The participant was considered to have entered the trial at this point. The trial was registered with the Clinical Trials Registry (NCT02817867). The authors certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed.

Participants

All participants admitted to the Mãe de Deus Hospital in the previous 5 years and from the local community through advertisements in local newspapers and social media were screened for inclusion. The inclusion criteria were: (1) subcortical stroke diagnosis, which has resulted in hemiparesis for at least 6 months and not more than 5 years (chronic condition)[25]; (2) Brunnstrom stage 3-5 for hand-fingers (ie, the ability,

at least subjectively, to flex the fingers with/without extension)[26]; (3) age at intervention between 18-85 years; (4) history of a single stroke only or more than one cerebrovascular lesions in the same hemisphere; (5) no cognitive impairment (a cut-off point of 20 and 24 on the Mini-Mental State Examination was set for illiterate and literate subjects, respectively)[27]; (6) no documented epileptic discharges on pretreatment electroencephalogram; and (7) no current use of antiepileptic medications for the prevention of seizures. Participants were excluded for the following reasons: (1) painful shoulder, adhesive capsulitis or gleno-humeral subluxation; (2) other neurological or orthopedic conditions involving the upper limbs (musculoskeletal diseases, peripheral neuropathy, joint replacement); (3) contraindications for rTMS according to the guidelines suggested by Wassermann (eg, cardiac pacemakers, intracranial implants, implanted medication pumps, and pregnancy)[28].

Intervention

NIBS protocols were performed by a single investigator (MPM). Participants allocated to LF-rTMS group received 10 sessions (3x/wk), during 20 minutes. Neuro-MS (NEUROSTFD - Ivanovo, 153032, Russia) equipped with an air-cooled figure-of-eight coil (each loop 70 mm in diameter) was used. The coil was placed tangentially to the scalp over the hand area of the primary motor cortex (M1). The exact site of stimulation was defined as the location where stimulation of a slightly suprathreshold intensity elicited the largest motor evoked potential (MEP) in the first dorsal interosseous (FDI) muscle. The placement of the coil was maintained by marking the actual point on the skin of the head. Magnetic stimulation was applied at 80% of the *resting motor threshold (*rMT) at 1 Hz frequency in contralesional M1. A total of 1200 pulses was generated during each session. The rMT was determined in each subject once before treatment and was defined as the minimum stimulus intensity able to elicit MEP of at least 50 mV in at least 5 of 10 consecutive stimulations.

Participants allocated in the atDCS group received 10 sessions (3x/wk), during 20 minutes of 1mA intensity. The battery-driven constant current stimulator DC-STIMULATOR PLUS (NeuroConn Technology – Germany) was used with a saline-soaked pair of surface sponge electrodes (35 cm^2). The anodal electrode was positioned on the M1 of the affected hemisphere (C3 or C4 (10/20 international EEG system) depending on the lesion side). Another electrode was placed over the contralateral supraorbital area.

Participants allocated in the LF-rTMS + atDCS group received 10 sessions (3x/wk) of LF-rTMS over the contralesional M1 during 10 minutes (using the same parameters of the LF-rTMS group), followed by 10 minutes of atDCS over the ipsilesional M1 (using the same parameters of the atDCS group).

Outcome measures

Blinded assessors evaluated all participants before randomisation and at the end of the 4-week intervention period. Two assessors received training prior to assessment and were given assessment protocols to improve inter-subjects' reliability. Additional demographic data to describe the sample were collected prior to randomisation. These data included age, gender, time since injury, type of acquired brain injury, affected side, the number of events and Brunnstrom stage.

Primary outcome:

Manual dexterity

Manual dexterity was assessed by Box and Block Test (BBT)[29]. Required materials are one wooden box, 150 cubes (2.5 cm), a stopwatch, and an evaluation form. Subjects were seated and first used the less affected side to move cubes during 1 minute. When the test began, the participant should grasp one block at a time with the dominant hand, transport the block over the partition, and release it into the opposite compartment. The greater the number of blocks per minute, the better was the performance of manual dexterity.

Secondary outcome:

Upper-limb function

Upper-limb function was assessed by Wolf Motor Function Test (WMFT)[30]. WMFT contains 15 function-based tasks. The performance time (WMFT time) and functional ability scale (WMFT FAS) on the 15 function-based items were administered in this study. The speed at which functional tasks can be completed is measured by performance time and the movement quality when completing the tasks is measured by functional ability. The maximum time allowed to complete an item is 120 seconds. For functional ability scoring, we used a 6-point ordinal scale, where 0 = does not attempt with the involved arm and 5 = arm does participate/ movement appears to be normal. Test-retest reliability, interrater reliability, criterion validity, and construct

validity of the WMFT have been ascertained in post-stroke subjects[26].

Grip strength

Maximal force was measured by hand-held dynamometer (kgf) (Jamar® Hydraulic Hand Dynamometer). Three grip strength measures were recorded in a standardized instruction and position (each participant was seated in a chair that maintained 90 degrees of knee and hip flexion with the upper limb resting on a table located at the front. With the affected upper limb supported, the participant held the dynamometer and performed the test). The highest score was recorded.

Quality of life

The quality of life was measured by Stroke Specific Quality of Life (SS-QoL)[31]. This scale contains 49 items distributed into 12 domains (energy, family role, language, mobility, humor, personality, self-care, social role, reasoning, upper-limb functions, vision, and work/productivity) made up from interviews with hemiplegics, who identified the areas most severely affected by stroke. There are three response possibilities on a 1-to-5 scale: the amount of help needed to perform specific tasks; the amount of difficulty experienced when it is necessary to carry out a task; the degree of agreement with statements about functionality. The summary score ranges 49 to 245 with a higher score indicating a better health-related quality of life (HRQoL). Their reference point for the answers is the previous week. Due to the probability that some of the individuals were illiterate or semiliterate, and to avoid misinterpretations, the questionnaire was verbally administered by means of an interview by a single trained examiner.

Data analysis

The sample size was determined a priori[32]. Enrolment of 24 participants ensured that this trial was powered to detect a difference of 5.5 points in manual dexterity (with SD of 3.9) with 80% power, a two-tailed alpha of 5% and an expected dropout rate of 20%.

Data were analyzed with descriptive (frequencies, mean, standard deviation, 95% CI of mean/median differences). For all statistical calculations, SPSS ver. 20.0 (IBM, Ar-monk, NY, USA) was used. Data were evaluated regarding normality criteria. Repeated measures ANOVA to analyze significant effects of time and interaction between time and group, with Tukey post hoc for all data was used. For within-group

comparisons t-test was used for normally distributed variables (grip strength, manual dexterity, and quality of life). For non-normally distributed variables, WMFT FAS and WMFT time, we used Wilcoxon test. Data were analyzed according to the principle of 'intention to treat'. All analyses considered a significance level of 0.05.

RESULTS

Flow of participants through the study

A total of 275 participants with acquired brain injury were screened over the trial period. Twenty-four were eligible to be included in the study and were randomised. The flow of the participants through the study is illustrated in Figure 1. Baseline demographic and clinical characteristics of enrolled participants are displayed in Table 1. The three groups were similar at baseline. After completion of the intervention, all participants performed the outcome measures. Overall, most of the participants presented an ischemic event with more than one year of injury, the right side of the affected body and were in the stage of recovery where the spasticity begins to lose its intensity, appear the movements deviated from the combined synergies and movements, reflecting mild to moderate disability.

Adherence to the study protocol

All participants received the intervention to which they were initially allocated. Participants in three groups received a mean of 10 sessions, for 20 minutes of stimulations during the 4-week intervention period. The LF-rTMS + atDCS group received 10 minutes of each stimulation mode, ending in 20 minutes of stimulation. No severe adverse effect was reported during the sessions. One participant (2.4%) reported an adverse effect (a headache episode) following the first atDCS – it subsided within 24 hours. One participant (2.4%) in the LF-rTMS group reported that during treatment he noticed decreased strength in the uncommitted upper limb, but this symptom was not verified in the final strength assessment.

Effects of the intervention

Manual dexterity

The between-group comparisons for manual dexterity showed no time*group interaction. Data analyses evidenced a time effect (p=0.001). Manual dexterity improved in atDCS and LF-rTMS+atDCS groups from baseline to post intervention (p=0.037 and p=0.011, respectively; see Table 2 for details).

Upper-limb function

The between-group comparisons for upper limb function (WMFT FAS and WMFT time) showed no time*group interaction. However, data analyses evidenced a time effect (p=0.001 and p=0.003, respectively]. In the LF-rTMS group, there was a significant positive change in WMFT FAS from baseline to post-intervention (p=0.011). Both atDCS and LF-rTMS+atDCS groups improved on WMFT time (p=0.018 for both). Thus, results evidenced improvements for functional ability in LF-rTMS group and for upper limb performance time in atDCS and LF-rTMS+atDCS groups (Table 2).

Grip strength

The between-group comparisons for grip strength indicated no time*group interaction. Data analyses evidenced a time effect ($p<0.001$). A significant improvement in grip strength from baseline was found for atDCS and LF-rTMS+atDCS groups (p=0.006 and p=0.022, respectively; Table 2).

Quality of life

The between-group comparisons showed no significant time*group interaction. Data analyses evidenced a time effect ($p<0.001$). LF-rTMS and atDCS groups significantly improved from baseline to post-intervention (p=0.023 and p=0.020, respectively; Table 2).

DISCUSSION

We investigated the effects of LF-rTMS over the contralesional M1 combined with atDCS over the ipsilesional M1 for upper-limb motor function of chronic post-stroke

subjects. The present results demonstrated no difference among unimodal LF-rTMS, unimodal atDCS and combined dual-mode (LF-rTMS+atDCS) in any of the clinical scores evaluated. However, we verified that LF-rTMS was able to induce improvements on WMFT functional ability and quality of life; atDCS induced improvements on manual dexterity, WMFT time, grip strength and quality of life; and LF-rTMS+atDCS induced improvements on manual dexterity, WMFT time and grip strength.

NIBS is based on interhemispheric competition theory occurring after stroke. Brain unilateral lesions cause an imbalance between dominant and non-dominant hemispheres that may interfere with the natural recovery process, especially after a stroke[4,23]. It is believed that increasing the excitability of the ipsilesional cortical region and decreasing the excitability of the contralesional cortical region may restore the balance between hemispheres and promote the recovery process[23,33]. Several studies have been based on this theory. They showed improvements in motor function after applying ipsilesional HF-rTMS or contralesional LF-rTMS, and after using ipsilesional atDCS or contralesional ctDCS, in post-stroke subjects[16,17,34-36].

Regarding bi-hemispheric NIBS the results are still inconclusive. Some studies have reported superior improvements on upper limb motor function after bi-hemispheric NIBS [5,37,38,39] while others have found no difference at all[40,41]. Studies using bilateral stimulation and different types of NIBS after stroke are even more scarce[23]. Takeuchi (2012)[23] showed that a single session combining inhibitory rTMS over the unaffected hemisphere and excitatory tDCS over the affected hemisphere may prevent the deterioration of bimanual movement induced by inhibitory rTMS. It was also demonstrated that sequential motor tasks can be performed faster after stimulation with HF-rTMS over the ipsilesional M1 combined with simultaneous ctDCS over the contralesional M1[18]. Cho et al (2017)[15] showed that dual-mode NIBS with the simultaneous application of 10Hz rTMS and ctDCS over the bilateral M1 was safe and superior to 10 Hz rTMS alone for improving motor function in subacute stroke[15]. Our results have shown no difference among unimodal LF-rTMS, unimodal atDCS or combined dual-mode (LF-rTMS+atDCS) on manual dexterity, upper limb function, grip strength and quality of life in chronic post-stroke subjects. These results could be explained by methodological discrepancies and the variety of protocols among studies.

In the present study, we used a 10 minutes LF-rTMS protocol followed by 10 minutes atDCS as dual-mode protocol. Kwon et al (2016)[18] showed that ctDCS (2mA)

followed by HF-rTMS do not induce improvements on motor accuracy, but enhancements on movement time performance. In that study, authors also reported improvements in accuracy and movement time of sequential motor tasks when stimulations were simultaneously done during 10 min. Like our protocol, Takeuchi (2012)[23] used a dual-mode protocol with atDCS (1mA) and LH-rTMS, but they simultaneously applied the current during 20 minutes. Maybe a higher intensity direct current (2mA) applied simultaneously with rTMS for longer than 10 minutes is needed to induce a significant upper limb function improvement in chronic post-stroke subjects.

Muscular weakness is a frequent condition after stroke and may compromise activities of daily living and limit function in subjects with hemiparesis. Therefore, muscle strength increase can promote functional improvement, and potentially change the quality of life[42]. Our results demonstrated grip strength enhancement in atDCS and LF-rTMS+atDCS groups. These two groups also showed a more pronounced improvement in manual dexterity as well as in WMFT time. Moreover, all intervention groups similarly increased the quality of life, even in the lack of significance for the rTMS+atDCS group. Results of SS-QoL indicate that a score above 60% of the maximum total score may be considered as an acceptable health-related quality of life[43].

This study has some limitations that must be highlighted. We did not include a control group for comparison. This study also did not provide any data regarding the long-term efficacy of the interventions. We did not use methods to collect data on neural excitability directly, such as measuring motor-evoked potentials (MEP) with transcranial magnetic stimulation (TMS) or by studying interhemispheric interactions using paired-pulse techniques. Future research with large sample size, control group and with follow-up evaluation are necessary to explore the neurophysiology underlying the behavioral effects found in the present study.

In summary, according to our results, 10 sessions of unimodal LF-rTMS, unimodal atDCS and dual-mode LF-rTMS+atDCS induce similar improvements on manual dexterity, upper limb function, grip strength and quality of life in chronic post-stroke subjects.

What is already known on this topic:

Non-invasive brain stimulation (NIBS) is a safe and powerful method used to modulate human brain function and has been recognized as a promising intervention for treating post-stroke motor deficits. rTMS and tDCS alone or combined with other therapies have demonstrated therapeutic benefits in motor function after stroke. Few studies have reported the effects of bilateral stimulation and still remains unclear how to optimize the protocols to reach better therapeutic effects.

What this study adds:

Dual mode LF-rTMA+atDCS does not demonstrated superior results in motor function, grip strength, manual dexterity and quality of life of chronic post-stroke subjects when compared to unimodal brain stimulation.

Ethics approval: Ethics Committee of Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil. Written consent was obtained from all participants or their next of kin before data collection began.
Competing interest: The authors declare no conflict of interest.

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Provenance: Not invited. Peer reviewed.

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Table 1- Baseline characteristics of participants.

Characteristics	rTMS (n=8)	tDCS (n=8)	rTMS+tDCS (n=8)
Age (yr), mean (SD)	67 (5)	65 (18)	65 (8)
Gender, n male (%)	3 (37,5)	6 (75)	3 (37,5)
Time since ABI (mth), mean (SD)	29 (12)	23 (9)	35 (21)
Type of ABI, n			
haemorrhagic	2	1	0
ischemic	6	7	8
Number of events, n			
1	6	7	8
2	2	1	0
Affected side, n right (%)	6 (75)	5 (62,5)	4 (50)
Brunnstrom (0 to 7), mean (SD)	4,1 (1)	3,9 (0,6)	4,3 (0,9)

tDCS = transcranial magnetic stimulation, rTMS = repetitive transcranial magnetic stimulation, ABI = acquired brain injury.

Table 2 - Mean (SD) or median (min-max), mean (SD) differences within, and mean (95% CI) differences between groups for all outcomes.

Outcome	Groups						Difference within groups			Difference between groups		
	Week 0			Week 4			Week 4 – Week 0			Week 4 – Week 0		
	LF-rTMS	atDCS	Dual-mode	LF-rTMS	atDCS	Dual-mode	LF-rTMS	atDCS	Dual-mode	LF-rTMS x atDCS	LF-rTMS x Dual-mode	atDCS x Dual-mode
BBT (blocks)	27 (22)	27 (14)	34 (25)	33 (28)	39 (22)	38 (25)	6 (2.6)	12* (13)	4* (2.8)	2.44 (-26.6 to 31)	6.0 (-35 to 23)	3.56 (-32.6 to 25)
WMFT FAS (0-75)	63 (21-74)	56 (32-73)	60 (30-75)	66 (22-75)	67.5 (32-75)	61 (37-75)	2.75* (1.83)	4.9 (6.6)	2.75 (3.15)	3.31 (-19 to 26)	3.0 (-26 to 19.8)	0.31 (-22 to 23)
WMFT time (s)	41.5 (2.1-94)	48.2 (2.9-52)	35.7 (1.9-69.7)	30.5 (1.2-87)	35.4 (2.2-52)	28.4 (1.2-29)	-2.36 (3.35)	-2.45* (4.82)	-9.66* (22.5)	18.47 (-52 to 15)	18.95 (-14.5 to 52)	0.48 (-33 to 34)
Grip strength (kgf)	15 (8.4)	16.5 (9.3)	16.6 (8.9)	15.9 (7.2)	20 (11.1)	20.8 (9.8)	0.9 (3.04)	3.5* (2.5)	4.2* (3.9)	2.81 (-8.4 to 14)	3.25 (-14.7 to 8.2)	0.44 (-11.9 to 11)
SS-QoL (49-245)	184.9 (25)	177.1 (26.4)	184 (24.9)	199.9 (20.2)	197.5 (17)	203.5 (37.5)	15* (15)	20.38* (19.16)	19.5 (25.4)	5.06 (-35 to 25)	1.38 (-31 to 28.8)	6.44 (-36.6 to 24)

LF-rTMS, low frequency repetitive magnetic stimulation; atDCS, anodal transcranial direct current stimulation; Dual-mode, low frequency repetitive magnetic stimulation plus anodal transcranial direct current stimulation; WMFT FAS, functional ability score of Wolf Motor Function Test; WMFT time, performance time of Wolf Motor Function Test; BBT, box and block test; SS-QoL, stroke scale quality of life. *Statistical difference (p<0,05).

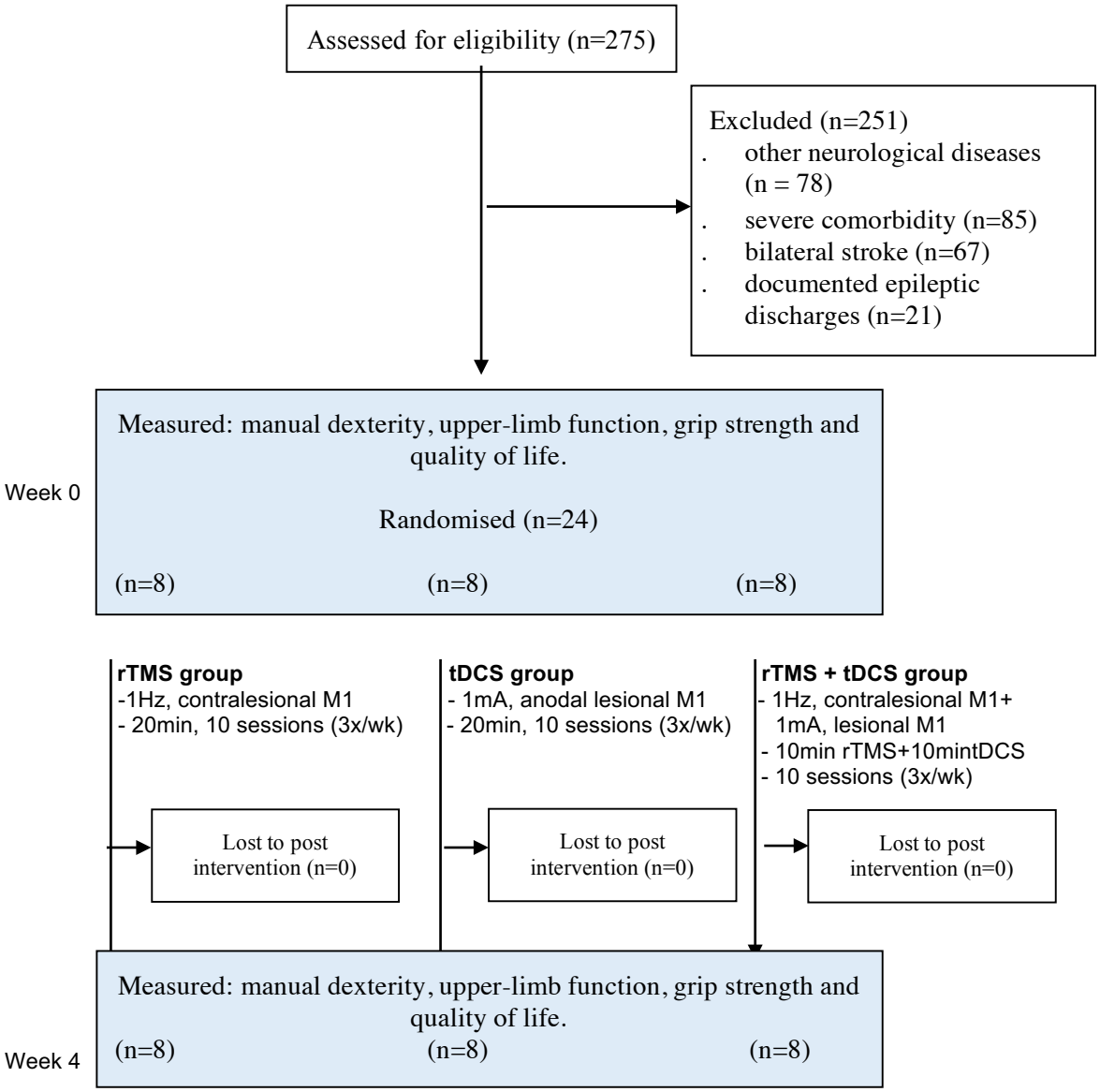

Figure 1. Design and flow of participants through the trial.

6. CONCLUSÃO GERAL E PERSPECTIVAS

O AVC é uma das principais causas de incapacidade no adulto e ainda com alta prevalência na população mundial. Apesar do grande número de estudos já publicados demonstrando os benefícios de diferentes métodos de reabilitação para esta população, muitos indivíduos ainda permanecem, em uma fase crônica da doença, com algum grau de comprometimento motor. Essa condição compromete as atividades de vida diária e dificulta a inserção e a participação desse indivíduo na sociedade.

Diante dessa realidade, considera-se importante mais estudos na área com o intuito de favorecer e intensificar a reabilitação e a recuperação funcional de indivíduos com sequelas motoras após o AVC. Estudos recentes têm demonstrado os benefícios da estimulação cerebral não-invasiva para essa população e dentre as modalidades mais utilizadas estão a estimulação magnética transcraniana repetitiva (EMTr) e a estimulação transcraniana por corrente contínua (ETCC). Ainda há muitas divergências quanto aos reais benefícios desses tratamentos e quais os melhores protocolos a serem utilizados. O presente estudo teve como objetivo verificar os efeitos da EMTr e da ETCC na recuperação funcional de indivíduos com hemiparesia crônica após AVC. Para isso, duas revisões sistemáticas com meta-análise e um ensaio clínico randomizado foram realizados para compor o trabalho.

De modo geral, podemos concluir que há evidências insuficientes para afirmar que a EMTr associada ao treinamento de membros superiores apresenta efeitos superiores quando comparada à utilização apenas de treinamento de membro superior em indivíduos após AVC crônico. Novos estudos com tamanho amostral maior e protocolos padronizados de tratamento são necessários para afirmar a efetividade da associação dessas terapias. Quanto à utilização da estimulação cerebral não invasiva na reabilitação da marcha, podemos afirmar que há evidências de qualidade moderada para os efeitos positivos da utilização tanto da EMTr quanto da ETCC no desempenho da marcha de indivíduos em fase aguda e crônica após AVC. Porém, pesquisas futuras são necessárias para investigar os efeitos da estimulação cerebral não-invasiva na habilidade da caminhada e na força muscular de membros inferiores, assim como a diferença entre os protocolos de inibição e excitação cortical. Por fim, verificamos que a estimulação bi-cefálica, utilizando EMTr

de alta frequência no hemisfério contralesional combinado com ETCC anodal no hemisfério ipsilesional induziu melhora na função motora do membro superior, na força muscular do membro superior e na destreza manual de forma similar quando comparado a utilização de apenas uma modalidade de estimulação (EMTr de alta frequência ou ETCC anodal).

Sabemos que a estimulação cerebral não-invasiva tem se mostrado um método satisfatório e seguro para modular a função do cérebro humano e tem sido considerado uma intervenção promissora para o tratamento dos comprometimentos motores após AVC. Porém, como perspectivas, nosso grupo seguirá estudando o benefício da estimulação cerebral não-invasiva em pacientes após o AVC, bem como em outras patologias neurológicas. Além disso, consideramos importante o seguimento de novos estudos com protocolos padronizados da utilização dessa terapia com o intuito de otimizar os efeitos terapêuticos nesses pacientes.

ANEXOS

ANEXO A – Parecer consubstanciado do CEP

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Efeito da associação entre correntes de estimualções cerebrais e fortalecimento muscular na reabilitação de pacientes com hemiparesia crônica após acidente vascular cerebral: estudo clínico randomizado.

Pesquisador: ALINE DE SOUZA PAGNUSSAT

Área Temática:

Versão: 2

CAAE: 14909013.7.0000.5345

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

Patrocinador Principal: FUND COORD DE APERFEICOAMENTO DE PESSOAL DE NIVEL SUP

Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 362.532

Data da Relatoria: 15/08/2013

Apresentação do Projeto:

A hipótese desse trabalho é que a associação entre a Estimulação Magnética Transcraniana, a Estimulação Transcraniana por Corrente Contínua e o Fortalecimento Funcional induzirá melhora significativa na recuperação da função sensório-motora do que comparado à utilização das técnicas de reabilitação citadas se utilizadas isoladamente em pacientes com hemiparesia crônica após AVC.

Objetivo da Pesquisa:

Objetivo Primário: Verificar a eficácia da associação da Estimulação Magnética Transcraniana repetitiva (EMTr) inibitória no córtex motor contralesional, da Estimulação Transcraniana por Corrente Contínua (ETCC) no córtex motor ipsilesional e de um Protocolo de Fortalecimento Funcional na recuperação da função sensório-motora do membro superior em pacientes com hemiparesia crônica após AVC.

Objetivo Secundário: (1) Avaliar o efeito da associação da Estimulação Magnética Transcraniana repetitiva (EMTr) com a Estimulação Transcraniana por Corrente Contínua (ETCC): a. Na melhora da força de preensão manual; b. Na melhora da destreza da mão; c. Na recuperação da função sensorial da mão; d. Na recuperação da função motora do membro superior; e. Na melhora das AVDs; f. Na melhora da qualidade de vida.

(2) Avaliar o efeito do uso combinado da EMTr e ETCC associado ao protocolo de fortalecimento funcional: a. Na melhora da força de preensão manual; b. Na melhora da destreza da mão; c. Na recuperação da função sensorial da mão; d. Na recuperação da função motora do membro superior; e. Na melhora das AVDs; f. Na melhora da qualidade de vida.

Avaliação dos Riscos e Benefícios:

Riscos: Os riscos estão relacionados as estimulações cerebrais, alguns pacientes poderão sentir certos desconfortos dependendo do protocolo de tratamento que irão receber, como dor muscular devido aos exercícios de fortalecimento, irritação cutânea devido aos eletrodos da estimulação transcraniana ou dor de cabeça durante as estimulações magnéticas transcranianas. Benefícios: O paciente será beneficiado por poder receber um tratamento de reabilitação do membro superior afetado após o AVC com provável melhora e recuperação da função sensorial e motora do membro superior. Isso possibilitará uma melhora na realização das suas atividades de vida diária.

Comentários e Considerações sobre a Pesquisa:

Metodologia Proposta: Será conduzido um estudo clínico randomizado, com avaliadores alheios aos grupos experimentais (unicego), onde pacientes com diagnóstico de AVC e hemiparesia crônica serão submetidos à combinação de técnicas de neuromodulação específicas associadas a um protocolo de fortalecimento funcional para averiguar os efeitos sobre a recuperação da função motora, sensorial e qualidade de vida.

Critério de Inclusão: Para serem incluídos no estudo os pacientes deverão: (1) Ter diagnóstico de AVC subcortical, o qual tenha resultado em hemiparesia há pelo menos 6 meses e no máximo há 5 anos (condição crônica) (HARRIS et al, 2010); (2) Estágio de Brunnstrom para mão e dedos de 3-5 (capacidade de fletir os dedos do membro superior afetado na sua totalidade de amplitude de movimento). (3) Idade de entre 18-90 anos. 4) História de um único AVC (sem lesão cerebral bilateral). (5) Apresentar pontuação mínima de 20 na avaliação da capacidade cognitiva analisada por meio da versão traduzida e adaptada do Mini Mental State Examination (MMSE) (FOLSTEIN et al., 1975) (ANEXO I). (6) Sem uso atual de medicamentos antiepilépticos para a prevenção de convulsões.

Critério de Exclusão: Serão excluídos do estudo indivíduos que: (1) Que apresente desordem musculoesquelética secundária que envolva as extremidades superiores, como ombro doloroso, capsulite adesiva ou subluxação da glenoumeral; (2) Que possuam sequela em hemiplegia ou ainda, que possuam limitaçãode ADM ativa de

ombro a qual impeça 60o de flexão anterior de ombro; (3) Que possuam déficit visual importante, sem uso de lentes corretivas. (4) Que apresente contraindicação (presença de implantes metálicos) ou riscos à Estimulação Magnética Transcraniana avaliados por questionário padrão (Rossi et al, 2009) (ANEXO II). Amostra 102 pacientes divididos:

Experimento A Grupo Ia Os pacientes serão submetidos a 10 sessões, de 20 minutos cada com frequência de três vezes por semana do Protocolo de Estimulação Magnética Transcraniana repetitiva (EMTr). Grupo IIa Os sujeitos desse grupo serão submetidos a 10 sessões, de 20 minutos cada com frequência de três vezes por semana do Protocolo de Estimulação Transcraniana por Corrente Contínua (ETCC). Grupo IIIa Nesse grupo os sujeitos serão submetidos à combinação da EMTr e da ETCC. Serão utilizados os mesmos padrões citados para cada protocolo, porém será realizado uma sessão de 10min de EMTr e, imediatamente após, uma sessão de 10min de ETCC, totalizando 20min.

Experimento B Grupo Ib Os sujeitos desse grupo serão submetidos à combinação da EMTr e da ETCC. Serão utilizados os mesmos padrões citados para cada protocolo, com uma sessão de 10min de EMTr e, imediatamente após, uma sessão de 10min de ETCC. A duração total de cada sessão será de 20 minutos.. Grupo IIb A intervenção para esse grupo será realizada com a associação da estimulação da EMTr + ETCC, uma após a outra com os mesmos parâmetros utilizados para o grupo Ib. E durante os 10min de ETCC será realizado, concomitantemente, o Protocolo de Fortalecimento Funcional. Dessa forma, a sessão terá duração total de 20 minutos.

Grupo IIIb Este grupo será submetidos apenas ao protocolo de Fortalecimento Funcional durante 20 min.

Considerações sobre os Termos de apresentação obrigatória:

Financiamento: Apresentado orçamento de R$ 1949,80. O material permanente necessário para a execução do projeto está disponível no Departamento de Fisioterapia da Universidade Federal de Ciências da Saúde de Porto Alegre e os aparelhos de Estimulação Magnética Transcraniana e de Estimulação Transcraniana por Corrente Contínua também já estão disponíveis no local onde serão realizadas as intervenções. As fontes de financiamento serão do Programa de Apoio à Pós-Graduação (PROAP) e de recursos próprios.

TCLE: Adequado.

Termo de compromisso para utilização dos dados: Adequado.

Recomendações:

Conclusões ou Pendências e Lista de Inadequações:

O orçamento foi assinado pelos pesquisadores, devido ao financiamento próprio e CAPES. Os custos serão de responsabilidade dos pesquisadores. O projeto está adequado e aprovado.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

De acordo com o Parecer do relator.

PORTO ALEGRE, 16 de Agosto de 2013

Assinador por:

José Geraldo Vernet Taborda (Coordenador)

ANEXO B – Normas da Revista Journal of the Neurological Science (Artigo 1)

JOURNAL OF THE NEUROLOGICAL SCIENCES
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AUTHOR INFORMATION PACK

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    - Conclusions (succinct statement of data interpretation)
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        - Example 1: Clinical Trial Registration-URL: http://www.clinicaltrials.gov. Unique identifier: NCT00123456.
        - Example 2: Clinical Trial Registration-URL: http://www.controlled-trials.com. Unique identifier: ISRCTN70000879.
        - Example 3: Clinical Trial Registration-URL: http://www.chictr.org. Unique identifier: ChiCTR-RCH-14004884.
        - Example 4: Clinical Trial Registration-This trial was not registered because enrollment began prior to July 1, 2005.

Text

- The following are typical main headings: Materials and Methods, Results, Discussion, and Summary.
- Abbreviations must be defined at first mention in the text, tables, and figures.
- Introduction: This section should briefly introduce the context of the results to be presented and should duplicate what is contained elsewhere in the manuscript

Methods:

- For any apparatuses used in Methods, the complete names of manufacturers must be supplied.
- For human subjects or patients, describe their characteristics.
- For animals used in experiments, state the species, strain, number used, and other pertinent descriptive characteristics.
- When describing surgical procedures on animals, identify the preanesthetic and anesthetic agents used, and state the amount or concentration and the route and frequency of administration for each. The use of paralytic agents, such as curare or succinylcholine, is not an acceptable substitute for anesthetics.
- For other invasive procedures on animals, report the analgesic or tranquilizing drugs used. If none were used, provide justification for such exclusion.
- Manuscripts that describe studies on humans must indicate that the study was approved by an institutional review committee and that the subjects gave informed consent.
- Manuscripts involving animals must indicate that the study was approved by an institutional animal care and use committee.
- Reports of studies on both animals and humans must indicate that the procedures followed were in accordance with institutional guidelines.
- All drugs should be referred to by their generic names rather than trade names. The generic chemical identification of all investigational drugs must be provided.

- A statistical subsection must be provided at the end of the Methods section describing the statistical methodology employed for the data presented in the manuscript.
- The Methods section should provide essential information related to the conduct of the study presented in the manuscript. For methodology previously published by the authors, the prior publication should be referenced and a copy of the paper provided to the reviewers, if necessary.
- The Methods section should only contain material that is absolutely necessary for comprehension of the results section. Additional (more detailed) methods can be provided as a data supplement.
- Prevention of bias is important for experimental stroke research (see **Macleod et al, *Stroke*.2009;40:e50-e52**). For studies where the primary objective is the preclinical testing of therapies, the following checklist items must be adhered to and clearly documented in the manuscript:
    - Animals: Species, strains and sources must be defined. For genetically modified animals, wildtype controls including background and back-crossing must be defined.
    - Statistics and sample size: Specific statistical methods must be defined, including parametric versus nonparametric and multigroup analyses, and sample size powering based on expected variances and differences between groups.
    - Inclusions and exclusions: Specific criteria for inclusions and exclusions must be specified. For example, only animals where blood flow reductions fall below a certain threshold are included. Or only animals with a certain degree of neurological deficits are included. Once animals are randomized (see below), all excluded animals must be reported, including explicit presentation of mortality rates.
    - Randomization, allocation concealment and blinding: All animals must be randomized. Investigators responsible for surgical procedures or drug treatments must be blinded. End point assessments must be performed by investigators blinded to the groups for which each animal is assigned.
- Any submitted meta-analyses should follow the PRISMA or MOOSE guidelines. The authors must clearly state in the Methods section which guideline was followed. Details on PRISMA can be found here **http://www.prisma-statement.org.** Details on MOOSE can be found via the **EQUATOR Network**.

Results:
This section should succinctly report the results of experimental studies and clinical research or clinical series/observations.

New December 2016: Confidence intervals should be reported instead of P values for estimated parameters, such as odds ratios and relative risks; P values should be reported only for relevant analytic tests. Authors are encouraged to avoid the pitfalls associated with the misuse of P values as measures of significance. Please refer to "The ASA's Statement on p-Values: Context, Process, and Purpose." *The American Statistician.* 2016.70;2: 129-133. **http://dx.doi.org/10.1080/00031305.2016.1154108**.

Discussion:

This section should not reiterate the results but put the results in appropriate context regarding relevant literature and the importance of new observations contained in the manuscript.

Summary/Conclusions:
A brief paragraph summarizing the results and their importance may be included but is not required.

Acknowledgments

The acknowledgments section lists all substantive contributions of individuals. Authors should obtain written, signed permission from all individuals who are listed in the "Acknowledgments" section of the manuscript, because readers may infer their endorsement of data and conclusions. These permissions must be provided to the Editorial Office. Please see the Acknowledgment Permission Form. The corresponding author must mark the following statement on the ONLINE ONLY Copyright Transfer Agreement form or Licensing Agreement, certifying that (1) all persons who have made substantial contributions in the manuscript (e.g., data collection, analysis, or writing or editing assistance), but who do not fulfill authorship criteria, are named with their specific contributions in the Acknowledgments section of the manuscript; (2) all persons named in the Acknowledgments section have provided the corresponding author with written permission to be named in the manuscript; and (3) if an Acknowledgments section is not included, no other persons have made substantial contributions to this manuscript.

Sources of Funding

Authors must list all sources of research support relevant to the manuscript in this location. All grant funding agency abbreviations should be completely spelled out, with the exception of the NIH. Note that funding should be listed separately from disclosures.

Disclosures

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References

- Accuracy of reference data is the author's responsibility. Verify all entries against original sources, especially journal titles, inclusive page numbers,

publication dates, accents, diacritical marks, and spelling in languages other than English.

- Do not list the month/issue/day (the number in parentheses) in the reference.
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Example References:

Print journal reference: Parker SA, Bowry R, Wu T-C, Noser EA, Jackson K, Richardson L, et al. Establishing the First Mobile Stroke Unit in the United States Stroke. 2015;46:1384-1391.

Online journal references: Chamberlain AM, Brown RD, Alonso A, Gersh BJ, Killian JM, Weston SA, et al. No Decline in the Risk of Stroke Following Incident Atrial Fibrillation Since 2000 in the Community: A Concerning Trend. J Am Heart Assoc. 2016;5:e003408.

Li J, Liu J, Liu M, Zhang S, Hao Z, Zhang J, et al. Closure versus medical therapy for preventing recurrent stroke in patients with patent foramen ovale and a history of cryptogenic stroke or transient ischemic attack. Cochrane Database of Systematic Reviews. 2015; 9: CD009938.

Publish-Ahead-of-Print reference: Knutson JS, Gunzler DD, Wilson RD, Chae J. Contralaterally Controlled Functional Electrical Stimulation Improves Hand Dexterity in Chronic Hemiparesis: A Randomized Trial. [published online ahead of print September 8, 2016]. Stroke. 2016. http://stroke.ahajournals.org/content/early/2016/09/08/STROKEAHA.116.013791.abstract. Accessed September 9, 2016.

Book Reference: Caplan L. Caplan's Stroke: A Clinical Approach. 4rd Ed. Philadelphia, PA: Saunders; 2009.

Website reference: Stroke Death Rates, Total Population Age 65+. National Heart Disease and Stroke Maps. National Center for Chronic Disease Prevention and Health Promotion, Division for Heart Disease and Stroke Prevention. http://www.cdc.gov/dhdsp/maps/national_maps/stroke65_all.htm. Accessed September 6, 2016.

Web sites generally follow this format: Author names (if any). Title of information or page. Name of website. URL. Publication date (if any). Access date.

Software Manual Reference: StataCorp. Stata statistical software: Release 12. College Station, TX: StataCorp LP; 2011.

Government Bulletin: Author. Title of bulletin. Place of publication: Name of issuing department or agency; publication date. Page numbers (if any). Publication number (if any). Series number (if any).

Database reference: CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

Figure Legends

Provide figure legends on a separate page of the manuscript.
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- Each table must be typed on a separate sheet and double-spaced, if possible. The table number should be Arabic, followed by a period and a brief informative title.
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- Tables should be cell-based (i.e., constructed using Microsoft Word tables or Excel). Do not use tabs or hard returns. Do not supply tables as graphics.
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- Use indenting within the stub column to indicate subgroups. Do not use bold, shading, rules, etc.
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- The combined total number of figures and tables is limited to 6 (3 for Brief Reports). Each figure may contain up to 4 panels (i.e., parts A to D) and must conform to the requirements for figures described below.
- Authors should be pleased with the figure submission quality before submission. We recommend that you print the figure at its final publication size to check the quality.

- Figures should be submitted as high-resolution TIFF or EPS files. PowerPoint files are discouraged because elements within the figure (such as axis labels) may shift location or drop out during conversion. If there are no other options, then a PPT file may be accepted. JPEG, Word, and Excel files should not be used. See Artwork and Table Guidelines (PDF) for instructions for creating high-quality digital art.
- Figures should be supplied at the highest resolution possible for optimal clarity. Color figures should be at least 300 dpi; halftones, 600 dpi; and line art, 1200 dpi.
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    - 1 column: 3.25 inches wide (8 cm or 19.5 picas)
    - 2 columns: 6.80 inches wide (17.272 cm or 40.8 picas)
- Color figures should be in RGB (red/green/blue) mode. If a figure is supplied in CMYK (cyan/magenta/yellow/black) mode, there may be a shift in the appearance of colors, especially fluorescents. Figures that will appear in black and white should be submitted in black and white.
- For line and bar graphs and pie charts, ensure that the colors/lines/symbols used for the different sets of data are easily distinguishable. Hair lines are hard to reproduce as are lines that are too thick, as they may make it hard to distinguish between the coordinates.
- Graphs and charts should have a white background.
- Labels for panels should be uppercase letters (A, B, C, D) in boldface Arial or Helvetica.
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- Multipart figures may be set at 2 columns across the page and should be laid out horizontally if appropriate.
- Use the same font (typeface) throughout the figure. Sans serif fonts, such as Arial and Helvetica, work best.
- Use the largest font size possible without distorting the figures. Text for super- or subscripts should be no smaller than 6 points.
- Whenever possible, all text within a figure should be the same size. If this is not possible, the font size should vary by no more than 2 points.
- Label units of measure consistently with the text and legend. Follow the AMA for unit abbreviations.
- Incorporate figure keys into the legend rather than including them as part of the figure whenever possible.
- Avoid heading/Title on the figure. Title information should be included in the figure legends.
- Any abbreviations or symbols used in the figures must be defined in the figure or figure legend.
- Follow AMA 9th edition for footnote style in legends.
- If the figure is reprinted/adapted from another source, please provide a permission letter and include the source in the legend as noted above.
- Supply a scale bar with photomicrographs.
- Authors are responsible for the cost of printing color illustrations. Authors are also responsible for obtaining from the copyright holder permission to reproduce previously published artwork.

- See AMA, 10th edition, Section 4.2 for more information on figures.

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- This optional section provides an opportunity for authors to present supporting materials to the manuscript. The manuscript appears both in the print version and online, whereas Online Supplements are independent from the manuscript and appear only online in the format submitted by the authors. Online Supplements undergo peer review and therefore must be submitted simultaneously with original submissions.
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    - Number supplementary figures and tables as Figure I, Figure II, Table I, Table II, etc.
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    - When referring to online-only material in the print version of the manuscript, use the phrase “please see http://stroke.ahajournals.org”
- Data Supplements appear only online and will not appear in reprints of the article. The Editorial Office is not responsible for converting files to a suitable format.

ANEXO D – Normas da Revista Journal of Physiotherapy (Artigo 3)

JOURNAL OF PHYSIOTHERAPY

Author Information

Journal of Physiotherapy (JoP) is the first Open Access core physiotherapy journal; it welcomes contributions that are relevant to the science or practice of physiotherapy.

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CONTENT

Original Research

The Editorial Board is committed to publishing excellent research and will consider the following types of papers:

• Systematic reviews

Systematic reviews are strongly preferred over narrative (non-systematic) reviews. High quality systematic reviews with firm conclusions are a publication priority. However, systematic reviews are unlikely to be published if they find there is not enough good quality evidence to review or if the literature is inconclusive. Note that this journal gives priority to systematic reviews that are prospectively registered in a publicly available register (e.g., PROSPERO at http://www.crd.york.ac.uk/PROSPERO). Authors should submit evidence of registration when submitting a manuscript for consideration. There are specific guidelines available for this type of study at the end of the Presentation section of these Author Guidelines.

• Clinical trials

All clinical trials submitted to JoP must have been registered in a publicly-accessible trials register. We will accept any register that satisfies the International Committee of Medical Journal Editors requirements (such as The Australian New Zealand Clinical Trial Registry at http://www.anzctr.org.au). Authors must provide the name and website address of the register and the trial registration number on submission. The journal will only accept trials that have been registered prospectively unless data collection began before 2006, in which case retrospective registration is acceptable. There are specific guidelines available for this type of study at the end of the Presentation section.

• Economic analyses

• Experimental studies

• Qualitative studies

Qualitative research refers to research where the analysis of data involves qualitative judgements. Commonly qualitative research explores aspects of the human, social world. Qualitative research methodologies include narrative inquiry, case studies, naturalistic inquiry, ethnography, hermeneutics, phenomenology, and survey research using open-ended questions. There are specific guidelines available for this type of study at the end of the Presentation section.

• Epidemiological studies

• Observational studies

• Narrative reviews
Narrative reviews critically appraise and summarise literature on a common topic area but do not set specific criteria for selecting literature to be included or a specific review protocol. A narrative review draws together major arguments in a field of discourse or provides a significant historical review of an important aspect of physiotherapy. Narrative reviews should be on topics that do not lend themselves to systematic reviews, e.g., examination of the mechanisms underlying a clinical phenomenon. Narrative reviews will almost always be invited and will be considered only if they are written by authors with extensive research experience in the field, usually reflected in multiple significant publications. Authors considering submission of a narrative review should first consult the Journal Editor regarding potential suitability of the review for publication. Narrative reviews of intervention, diagnosis, and prognosis will generally not be accepted.

The following types of studies are a low priority:
• Studies of the reliability or validity of clinical measurement procedures
• Surveys of physiotherapy students
• Surveys of physiotherapy practice
• Any survey with a low response rate (less than 70%)

Submission of these types of studies should be accompanied by a short (less than 100 words) explanation of why the study would be of particular interest to readers of JoP. The Editorial Board will decide, on the basis of this explanation and the abstract, whether the manuscript should be considered for publication. If accepted, such studies will be published as papers of less than 2000 words with no more than one table or figure.

The following types of studies are not accepted:

• Clinical practice guidelines
Although the journal is particularly interested in presenting the recommendations of clinical practice guidelines to its readers, clinical practice guidelines are often developed by consensus and may be endorsed by a professional body. This can make it difficult to apply the Journal's normal process of peer review. Therefore, particularly relevant guidelines that have been developed using a rigorous process and endorsed by a high quality professional body, such as NHMRC, will be summarised in the Appraisal section of the journal, but will not be republished. Details of the location where hard or electronic copies of the full guidelines are available will be given in the summary.
• Pilot studies
Pilot clinical trials are those that are not designed to have adequate statistical power. Their purpose is to test the feasibility of an intervention in terms of recruitment and delivery of the intervention, as well as to examine the rate of dropouts. They usually provide information to power a future trial and do not therefore reach firm conclusions.

Manuscript length (not including title page, abstract, references, tables or figure legends) depends on the type of study:
• Systematic reviews: up to 5000 words
• Clinical trials, experimental and qualitative studies: up to 3500 words
• Observational studies: up to 2500 words

Authors may be invited, or in some cases required, to place important supplementary material as electronic addenda (eAddenda) on the JoP web site.

MANUSCRIPT PRESENTATION

Research manuscripts should consist of a title page, abstract, text, references, tables, and figures. Manuscripts should be prepared with 2.5 cm margins and a footer containing an abbreviated title, the first author's family name, page number and date. The abstract, introduction, method, results, and discussion should be 1.5 line-spaced, but all other text should be single-spaced. Put a double return between paragraphs. Download the journal's manuscript template.

Title Page

The title of the manuscript should not be more than 25 words and should be in two parts. Give the main results of the study followed by a colon and the method used, e.g., 'A resource-efficient exercise program after discharge from rehabilitation improves standing ability in people after stroke: a randomised trial'. Download example titles for different research designs.

Then, list all authors and their degrees, positions, institutions, country, and email address. Nominate a corresponding author for the review who is authorised to negotiate and approve editorial revisions, provide his/her title (Professor, Dr, etc.), and give contact details (email address). You may nominate a different corresponding author for publication; provide his/her title (Professor, Dr, etc.) and short contact details (department/institution, postal address and email address).

Provide a running head of up to six words. Next, for indexing purposes, select up to five key words from the Index Medicus Medical Subject Headings (MeSH). MeSH Headings can be found on the PubMed MeSH browser at http://www.nlm.nih.gov/mesh/meshhome.html.

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Abstract

An abstract of no more than 250 words is required for all submissions using the headings: Question, Design, Participants, Intervention, Outcome measures, Results, Conclusion, and Trial registration (if appropriate). The results should include estimates of effect sizes and their confidence intervals rather than *p* values. Abstracts should not

contain references. Download examples of abstracts for different research designs

Introduction

The introduction should justify the aims of the research. Only references essential to understanding these aims should be included. Introductions rarely need to be longer than five paragraphs. At the end of the introduction, list the research questions as given in the Abstract again. Download Research question examples for different research designs

Method

Use the subheadings: Design; Participants, therapists, centres; Intervention; Outcome measures; and Data analysis, as appropriate to the design of the study. Restrict headings to no more than two levels of importance (i.e., avoid sub-subheadings). Where aspects of the method have been described in other widely-available publications a reference to those publications may suffice, whereas newly-developed procedures should be described in more detail.

In the **Design** section, describe the overall design, especially the timing of intervention and measurement, and any randomisation or blinding procedures.

In the **Participants, therapists, centres** section, outline the recruitment procedures and the inclusion and exclusion criteria for eligibility of participants, therapists, and centres.

In the **Intervention** section, give as much detail as necessary so that the intervention could be faithfully replicated by a reader. If this requires extensive material, consider placing some in an Appendix, which can be an electronic-only addendum to the paper.

In the **Outcome measures** section, state the impairment/activity limitation/participation restriction being collected (e.g., walking) and its measurement with units (e.g., velocity during 10 m Walk Test in m/s). Other examples are: strength measured as peak isometric elbow extensor torque using hand-held dynamometry in Nm, or pain measured as intensity at rest on a 10 cm VAS in cm. It can be useful to divide outcome measures into those examining impairments vs activity limitations vs participation restrictions. It is only necessary to refer to manufacturers' information for equipment when the precise specifications could be important to interpretation of the study. Information should be placed in a footnote at the end of the text, coded using consecutive, superscripted lower case letters.

In the **Data analysis** section, outline any *a priori* power analysis carried out to determine the number of participants needed for the study. Outline any conversions or calculations made with the data. Explain how the research questions are answered by the interpretive tests but do not name the statistical package used if it is widely available.

Results

The first subheading should be **Flow of participants, therapists, and centres**

through the study where the numbers at each point in the study are presented as well as baseline characteristics. The remainder of the results should report only the data that answer the research questions and should be organised under subheadings that reflect those questions. Pertinent results should be reported using text and/or tables and/or figures; tables are more useful than figures because exact values are given. Avoid repeating in the text data presented in tables or figures. Do not duplicate data in tables and figures.

When reporting data, be conscious of the precision of the data and only report a meaningful number of decimal places. Usually, report numbers between 0 and 1 to 2 decimal places, between 1 and 10 to 1 decimal place, and above 10 with no decimal place.

All data reported as numbers should also be given as a percentage of the sample (in brackets) rounded off, e.g., 17 (34%) participants were men. All data reported as means should also be accompanied by the standard deviation (in brackets), e.g., the mean height of participants was 1.53 m (SD 0.23).

When reporting the results of interpretive tests, report the size of the effect rather than its statistical significance, e.g., 'People with arthritis were twice as likely to sprain their ankle (OR 0.50, 95% CI 0.25 to 0.75)' or 'People after stroke walked 0.65 m/s (95% CI 0.60 to 0.70) slower than their age-matched healthy counterparts', but not 'People with asthma were significantly more breathless after exercise (p = 0.02)'.

Discussion

New and important findings should be emphasised but, as a rule, data already presented in the Method and Results sections should not be repeated. Implications and limitations of the findings and their clinical application should be discussed. The length of the Discussion should be commensurate with the number of important findings; usually it will be less than 750 words. Do not include a separate conclusion at the end of the Discussion.

References

Only essential references should be cited. Most research will require fewer than 30 references. If the research requires considerably more (e.g., systematic reviews of areas with many clinical trials), references may be provided as supplementary material or eAddenda.

The referencing style used by the journal is the JAMA style, which can be found as a standard referencing style in EndNote, RefWorks, Mendeley, and Zotero. If you use reference management software such as these, please convert your paper to the JAMA style before submission. Journal titles should be abbreviated according to the journals list in PubMed. Please ensure that all references are complete and presented using numbered style.

Data references

This journal encourages you to cite underlying or relevant datasets in your manuscript

by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. This identifier will not appear in your published article. [dataset] 5. Oguro, M, Imahiro, S, Saito, S, Nakashizuka, T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. http://dx.doi.org/10.17632/xwj98nb39r.1.

Tables

Tables should appear after the references and each table should start on a separate page. They should be numbered consecutively in the order to which they are referred in the text. A short caption should be given above each table (e.g., 'Table 1. Characteristics of participants.'). Within the table, give the units of outcome measures in brackets and italics, e.g., *(m/s)*. When reporting counts (frequencies), give percentages in brackets. Use abbreviations for time (i.e., *s, min, hr*, etc.) and amount (i.e., *kg, deg, Nm*, etc.) without a legend explaining them. Where abbreviations for physiotherapy-specific terms are used (e.g., ROM, MCP, etc.), provide a legend below the table. Tables should be presented with a minimum of horizontal lines and no vertical lines. Download examples of tables.

Figures

Figures should start on a separate page after the tables. They should be displayed at the proposed publication size and numbered consecutively in the order to which they are referred in the text. A short caption should be given below each figure, e.g., 'Figure 1. Mean (SD) effect of posture on forced expiratory volume for the experimental group (closed circles) and the control group (open circles)'. Do not place boxes around figures. Do not put axes on the top and right sides of graphs. Use symbols and/or line types rather than colour to differentiate data. Where several graphs refer to closely-related material, present them as separate panels of a single figure labelled A, B, C, etc., and provide one caption explaining what is in each panel. Photographs should be in sharp focus, have simple backgrounds, and be in black and white unless colour is essential to illustrate the point (e.g., MRI).

For publication, photographs should be supplied as digital images saved at a minimum of 300 dpi in .jpg format. Graphs and line drawings generated by commonly-used graphing programs (such as Microsoft Excel) are acceptable. Written permission should be obtained for use of previously published Figures and Tables, and for publication of photographs of recognisable subjects. These documents should be uploaded with the final manuscript once it has been accepted.

Boxes

When information needs to be listed but is not a table (contains numbers) or a figure (photograph, graph, or flow diagram), then it should be called a Box. Boxes should be numbered consecutively in the order to which they are referred in the text. A short caption should be given above each box (e.g., 'Box 1. Elements of a viable patient education program.') Download examples of boxes formatted to these specifications.

Style

Manuscripts should be written in simple, direct, and grammatically-correct English. Use Australian/English spelling. Use gender neutral and non-labelling language (e.g., 'People with back pain' rather than 'back pain patients'). When people are enrolled in a trial, use 'participant' rather than 'subjects'. Use capitals (upper case letters) sparingly but capitalise proper nouns. Divisions of the data set are also capitalised (e.g., 'Group 1' or 'Stage 2'). See previous issues for other specific aspects of JoP style.

Click below for the guidelines and examples available for the following types of studies:
• Systematic Review guidelines
• Systematic Review examples
• Clinical Trial guidelines
• Clinical Trials examples
• Qualitative Study guidelines
• Papers reporting the results of questionnaires guidelines

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