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Maira Jaqueline da Cunha

Associação entre estimulação transcraniana por corrente contínua e órtese elétrica funcional na reabilitação do paciente com sequela de acidente vascular cerebral

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

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Dedico esta tese às três pessoas
mais importantes da minha vida: Mãe, Pai e Mana!
As três pessoas que não mediram esforços para
me apoiar em todas as minhas decisões,
sempre com muita dedicação e amor.
Se não fosse por eles, hoje eu não seria ninguém.

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“Viva como se fosse morrer amanhã. Aprenda como se fosse viver para sempre”

“Vivi come se dovessi morire domani. Impara come se dovessi vivere per sempre.”

“Live as if you were to die tomorrow. Learn as if you were to live forever.”

Mahatma Gandhi.

RESUMO

O acidente vascular cerebral (AVC) é a principal causa de incapacidade de longo prazo em adultos em todo o mundo. Após um AVC, ocorre um desequilíbrio inter-hemisférico que afeta negativamente a recuperação funcional. A queda do pé é uma deficiência comum após o AVC, a qual está relacionada a altos graus de deficiência motora, fraqueza ou falta de controle voluntário dos músculos dorsiflexores do tornozelo e/ou aumento da espasticidade dos músculos flexores plantares. Essas deficiências motoras geram adaptações biomecânicas da marcha que podem resultar em diminuição da velocidade da caminhada, da mobilidade funcional e da qualidade de vida. Dessa forma, a estimulação transcraniana por corrente contínua (tDCS) tem sido utilizada como uma alternativa terapêutica que pode ajudar a reestabelecer o equilíbrio inter-hemisférico, induzir plasticidade e auxiliar na recuperação do desempenho motor. Há evidências de sua utilização na melhora da mobilidade funcional e da força muscular do membro inferior parético. A estimulação elétrica funcional (FES) no nervo fibular através do dispositivo estimulador de queda do pé (*Foot Drop Stimulator* - FDS) tem sido utilizada como alternativa para corrigir o movimento do pé e tornozelo após o AVC. Os indivíduos crônicos pós-AVC normalmente obtêm resultados modestos com os métodos tradicionais de reabilitação. Acredita-se que a combinação da estimulação central e periférica poderia maximizar os ganhos na reabilitação dessa condição. Desse modo, o objetivo geral desta tese foi avaliar o efeito da tDCS e FES aplicada sobre o nervo fibular comum (FES convencional ou FDS) na reabilitação do membro inferior de indivíduos com hemiparesia crônica após AVC. Para isso, uma revisão sistemática com meta-análise (artigo 1), estudo quase experimental (artigo 2) e um ensaio clínico randomizado (artigos 3, 4 e 5) foram realizados.

Os resultados encontrados no artigo 1 mostram uma baixa qualidade de evidência para efeitos positivos da FES no fibular comum na velocidade da marcha quando combinada com fisioterapia. A FES pode melhorar a dorsiflexão ativa de tornozelo, o equilíbrio e a mobilidade funcional. O artigo 2 mostra que o treinamento com FDS melhora o movimento ativo de dorsiflexão do tornozelo durante o ciclo da marcha, bem como a distância percorrida ao longo das sessões de treino. O artigo 3, 4 e 5 revelam que a tDCS parece não adicionar

efeitos ao treinamento com FDS na melhora da mobilidade funcional, espasticidade, qualidade de vida e performance da marcha. Além disso, a tDCS não induz efeito adicional na melhora da plasticidade e do comprometimento motor do membro inferior de indivíduos com hemiparesia crônica após AVC.

Consideramos esses achados relevantes, pois podem subsidiar a decisão clínica de usar ou não a tDCS nesta população. Considerando que não encontramos efeitos no modo de estimulação bi-hemisférico, mais ensaios clínicos, com diferentes montagens e protocolos de aplicação, são necessários para verificar se o tDCS é eficaz na reabilitação de membros inferiores após AVC em fase crônica. De modo geral, a FES no nervo fibular comum pode ser usada como uma terapia complementar para reabilitação de indivíduos com hemiparesia crônica após AVC.

Palavras-chave: Acidente Vascular Cerebral; Reabilitação no AVC; Extremidade inferior; Estimulação transcraniana por corrente contínua; Estimulação elétrica; Neuromodulação; Estimulação elétrica funcional

ABSTRACT

Stroke is the major cause of long-term disability in adults worldwide. After a stroke, occurs an interhemispheric unbalance that negatively affects functional recovery. Foot drop is a common impairment after stroke, which is related to higher degrees of motor impairment, weakness or lack of voluntary control of ankle dorsiflexor muscles, and increased spasticity of plantar flexor muscles. These motor impairments generate gait biomechanical adaptations that may result in decreased walking speed, functional mobility and quality of life. In such way, the transcranial direct current stimulation (tDCS) has been used as a therapeutic alternative that stimulates the inter-hemispheric rebalancing, induces the plasticity, and contributes to motor improvement. The functional electrical stimulation (FES) on the peroneal nerve by foot drop stimulator device (FDS) has been used as an alternative to correct the ankle movement after stroke. Chronic post-stroke individuals normally achieve modest results under traditional methods of rehabilitation. It is believed that the combination of central and peripheral stimulation could maximize rehabilitation gains in this condition. Overall, the aim of this thesis was to study and evaluate the effect of tDCS and FES applied on the common fibular nerve on lower limb rehabilitation of individuals with chronic hemiparesis after stroke. For this purpose, a systematic review with meta-analysis (article 1), a quasi-experimental study (article 2) and a randomized clinical trial (articles 3, 4 and 5) were performed. The results of the article 1 reveal a low quality of evidence for positive effects of FES on gait speed when combined with physiotherapy. FES can improve ankle dorsiflexion, balance, and functional mobility. Article 2 shows a positive effect on the ankle active movement during the gait cycle. In addition, FDS, combined with gait training, is able to increase the total distance walked after treatment. Articles 3, 4 and 5 show that tDCS does not seem to add effects to training with FDS in improving functional mobility, spasticity, quality of life and gait performance. Furthermore, tDCS does not induce an additional effect in improving plasticity and motor impairment of the lower limb of individuals with chronic hemiparesis after stroke. We consider these findings relevant because they can support the clinical decision of using or not the bi-cephalic tDCS for this population. Considering that we found no effects on the bicephalic stimulation mode,

additional clinical trials with different montage of stimulation are warranted to verify the effectiveness of tDCS on lower limb rehabilitation in chronic post-stroke. In general, FES in the common fibular nerve may be used as an alternative complementary therapy to rehabilitation of individuals with chronic hemiparesis after stroke.

Keywords: Stroke; Stroke rehabilitation; lower extremity; Transcranial direct current stimulation; Electric stimulation; Neuromodulation; Functional electrical stimulation.

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LISTA DE ABREVIATURAS E SIGLAS

ADM	Amplitude de movimento
AVC	Acidente Vascular Cerebral
CI	*Confidence interval*
CONSORT	*Consolidated Standards of Reporting Trials*
FDS	*Foot Drop Stimulator*
FES	*Functional electrical stimulation*
	Eletroestimulação functional
FMA	*Fugl-Meyer assessment*
IGF-I	*Insulin-like growth factor 1*
IGFBPs	*Insulin growth factor–binding proteins*
IL-6	Interleucina-6
IL-10	Interleucina-10
M1	*Primary motor cortex*
	Córtex motor primário
MAS	*Modified Ashworth scale*
PRISMA	*Preferred Reporting Items for Systematic Reviews and Meta- Analyses*
RCT	*Randomized controlled trial*
ROM	*Range of motion*
SMD	*Standardized mean deviation*
SS-QOL	*Stroke Specific Quality of life Scale.*
STROBE	*Strengthening the Reporting of Observational Studies in Epidemiology*
tDCS	T*ranscranial Direct Current Stimulation*
	Estimulação Transcraniana por Corrente Contínua
TUG	*Timed up and go test*
TNF-α	Fator de necrose tumoral alfa
LL	*Lower limb*
	Extremidade inferior

SUMÁRIO

1 INTRODUÇÃO

O aumento na expectativa de vida da população mundial, a diminuição das taxas de mortalidade nas últimas décadas, modificações no estilo de vida, bem como alterações nutricionais e demográficas revelaram uma mudança na incidência de doenças (Katan and Luft, 2018). Atualmente, o acidente vascular cerebral (AVC) representa a segunda maior causa de morte no mundo (Katan and Luft, 2018) e a principal causa de incapacidade de longo prazo em adultos (Feigin et al., 2017; Writing Group et al., 2016), sendo que, no Brasil, é uma das principais causas de morte e incapacidade (Bensenor et al., 2015; Lotufo and Bensenor, 2013). O aumento da predisposição ao desenvolvimento de doenças crônicas não contagiosas, como o AVC, pode ser explicado pela alta prevalência nos fatores de risco modificáveis, como hipertensão arterial sistêmica, tabagismo, obesidade, sedentarismo, ingestão de álcool, estresse psicossomático, depressão, fatores cardíacos e nutricionais (O'Donnell et al., 2010). Além desses, a idade avançada (Andre-Petersson et al., 2007), o gênero (mais prevalente em homens) (Askim et al., 2012) e a história familiar também podem influenciar o aumento na incidência de AVC (Polotsky and Polotsky, 2010).

Após o AVC, os indivíduos apresentam alterações sensório-motoras que afetam a capacidade desses indivíduos em realizar atividades corriqueiras, tais como segurar objetos, caminhar em diferentes terrenos, além de subir e descer escadas (Bonnyaud et al., 2013; Dorsch et al., 2012; Faria-Fortini et al., 2011). Dados revelam que mais de 50% dos indivíduos pós-AVC não são capazes de andar independentemente (Hankey et al., 2007). Um problema comum após o AVC é o pé caído, uma condição que pode resultar da fraqueza ou falta de controle voluntário dos músculos dorsiflexores do tornozelo e/ou do aumento da espasticidade dos músculos flexores plantares. O pé caído compromete o movimento de dorsiflexão do tornozelo e prejudica o contato inicial do pé com o solo durante o ciclo da marcha (Chisholm et al., 2013; Sheffler and Chae, 2015). Consequentemente, os indivíduos pós-AVC podem apresentar uma caminhada mais lenta, com menor eficiência e maior risco de quedas (Roerdink et al., 2007). A limitação da caminhada gera um impacto direto na mobilidade funcional (Ng

et al., 2017), levando a um quadro de insatisfação e diminuição de qualidade de vida (Robinson et al., 2011).

Embora a recuperação funcional após AVC não seja completamente compreendida, acredita-se que após a lesão ocorra alteração no padrão de atividade entre os hemisférios cerebrais, provocando desajuste na inibição inter-hemisférica (Murase et al., 2004). Em condições fisiológicas, ambos os hemisférios funcionam de forma equilibrada, exercendo controle inibitório mútuo (Nowak et al., 2009). Após um AVC, esse equilíbrio é interrompido e ocorre um aumento da excitabilidade no hemisfério não afetado e uma diminuição da excitabilidade no hemisfério afetado (Murase et al., 2004). Assim, o hemisfério não afetado inibe excessivamente o afetado, levando a perdas do controle neuromotor e dificultando a recuperação motora (Nowak et al., 2009; Takeuchi and Izumi, 2012). Nesse sentido, é importante investigar se o restabelecimento do equilíbrio entre os dois hemisférios apresenta um papel importante na reabilitação após um AVC.

A recuperação após AVC é um processo complexo que ocorre provavelmente pela combinação de processos espontâneos e/ou dependentes da prática motora (Kwakkel et al., 1996). A neuroplasticidade pode estar relacionada à capacidade do sistema nervoso em responder a estímulos e principalmente recuperar a função motora (Dimyan and Cohen, 2011). O fator neurotrófico derivado do encéfalo (do inglês – *brain derived neurotrophic factor* – BDNF) desempenha uma função importante na plasticidade neuronal pós-AVC (Jickling and Sharp, 2015) e pode ser secretado em resposta à atividade física (He et al., 2013).

A recuperação da função motora em indivíduos em uma fase crônica pós-AVC pode ser modesta com métodos tradicionais de reabilitação e, muitas vezes, esses indivíduos não são o alvo da pesquisa clínica (Winstein et al., 2016). A combinação de abordagens de reabilitação tem sido proposta para melhorar a recuperação funcional após o AVC (Menezes et al., 2018). Métodos de neuro-reabilitação têm sido desenvolvidos para tratar essas duas condições: inibição inter-hemisférica desequilibrada e pé caído. A estimulação transcraniana por corrente contínua (tDCS) modula a excitabilidade cortical (Chang et al., 2015), e induz à plasticidade (Adeyemo et al., 2012; Elsner et al., 2016; Schlaug and Renga, 2008).Outra estratégia bastante utilizada na prática

clínica é a eletroestimulação funcional (FES). A FES pode ser aplicada no nervo fibular, por meio de aparelhos denominados *Foot Drop stimulator* (FDS), induzindo efeitos clínicos positivos na reabilitação da marcha pós-AVC (Hong et al., 2018; Lin et al., 2018; Pereira et al., 2012).

Dentro desse contexto há uma preocupação em estudar formas de intervenções que possam aumentar a eficácia das terapias de reabilitação em pacientes pós-AVC em diferentes estágios de recuperação. Com isso, o objetivo geral desta tese foi avaliar o efeito da utilização do FES, aplicado por meio da FDS, sobre a modificação no padrão da marcha de indivíduos com hemiparesia crônica após AVC e verificar o efeito da associação entre tDCS e FDS na reabilitação do membro inferior e na marcha de pacientes com hemiparesia crônica após AVC.

2 REVISÃO DE LITERATURA – CONTEXTUALIZAÇÃO

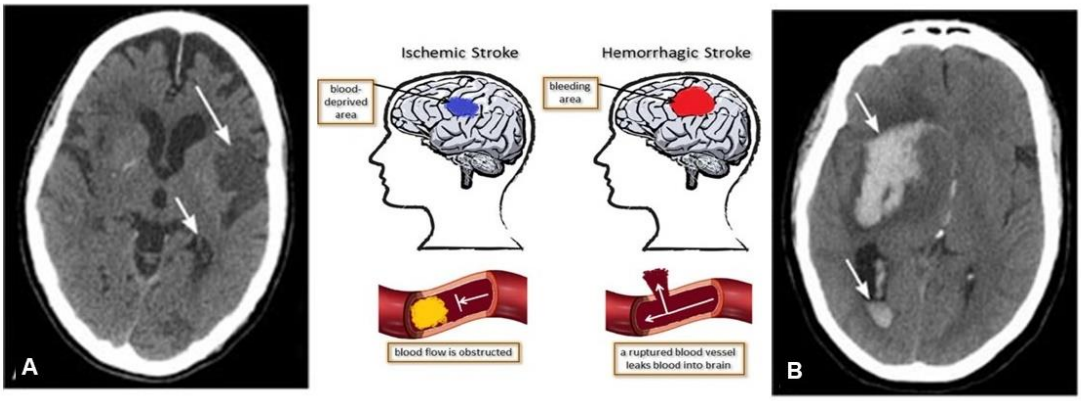
2.1 ACIDENTE VASCULAR CEREBRAL (AVC)

O Acidente Vascular cerebral (AVC) é definido como um quadro clínico decorrente de lesões focais ou globais do sistema nervoso central causado por alterações vasculares da função cerebral, resultando em sintomas como hemiparesia, incoordenação motora e hipertonia espástica do membro superior e inferior contralateral à lesão(Eng and Tang, 2007; Manji et al., 2007).

O AVC pode ser classificado de acordo com a etiologia do distúrbio que acomete a vascularização cerebral (Figura 1), sendo o de etiologia isquêmica mais prevalente (cerca de 87% dos casos) (Benjamin et al., 2018). O AVC isquêmico caracteriza-se pela obstrução de um vaso sanguíneo, seja por acúmulo de gordura ou coágulo de sangue, interrompendo a irrigação sanguínea ao encéfalo. O AVC de etiologia hemorrágica apresenta menor prevalência (cerca de 13% dos casos) (Benjamin et al., 2018), e caracteriza-se pelo enfraquecimento da parede do vaso, sendo por um aneurisma (dilatação formada na área enfraquecida do vaso), ou por uma má formação arteriovenosa, resultando em rompimento e, consequentemente, extravasamento de sangue para a região irrigada por este vaso (Qureshi et al., 2001). Independente da etiologia, o AVC gera distúrbios sensório-motores tanto de membros superiores

quanto inferiores, distúrbios cognitivos (memória e aprendizado) e comportamentais (Ferreira and Pinto, 2008; Wolf and Rognstad, 2013). As alterações sensório-motoras presentes no AVC afetam a capacidade desses indivíduos em realizar atividades corriqueiras, tais como segurar objetos, caminhar em diferentes terrenos, além de subir e descer escadas (Bonnyaud et al., 2013; Dorsch et al., 2012; Faria-Fortini et al., 2011). A limitação da caminhada na própria habitação e em ambiente externo gera um impacto direto na mobilidade funcional (Eng and Tang, 2007), levando a um quadro de insatisfação e diminuição de qualidade de vida, por limitar a sua participação social e pessoal (Robinson et al., 2011).

Figura 1. AVC Isquêmico versus hemorrágico.



(A) AVC isquêmico AVC isquêmico com exemplo da tomografia computadorizada mostrando duas regiões (seta) indicando infarto devido à falta de oxigênio no tecido cerebral causada a obstrução vascular; (B) AVC hemorrágico com exemplo da tomografia computadorizada mostrando a área hiperdensa causada pelo sangramento no interior do tecido cerebral.

Modificadas de: (Crouch, 2013) and (Yew and Cheng, 2009)

2.1.1 Comprometimento Sensório-Motor

A lesão do neurônio motor superior causada pelo AVC resulta em comprometimentos sensório-motores, incluindo hemiparesia, déficits proprioceptivos e espasticidade (Bohannon and Andrews, 1987; Kim and Choi,

2016). Essas alterações, combinadas com o desequilíbrio no padrão de ativação muscular, interferem na execução precisa e eficaz dos movimentos voluntários, tanto no membro superior quanto no membro inferior (Kitatani et al., 2016; Kornatz et al., 2005).

O comprometimento motor após AVC apresenta-se em diferentes níveis, podendo ser classificado em leve, moderado ou grave, de acordo com a pontuação da escala clínica *Fugl-Meyer Assessment* (FMA) (Fugl-Meyer, 1980). A pontuação máxima para o membro inferior é de 34 pontos, sendo que 0 à 19 os indivíduos são classificados com comprometimento grave; 20 à 28 moderado e ≥29 pontos leve (Daly et al., 2011).

2.1.2 Alteração da Marcha no AVC

Pacientes que sofreram AVC apresentam padrões da marcha diferentes dos observados em pessoas saudáveis e estão associados a um risco aumentado de queda (Balaban and Tok, 2014; Robinson et al., 2011). Dentre os pacientes que sofreram AVC, cerca de 20% a 30% dos pacientes perderam a capacidade de andar, devido às perdas do controle neuromotor (Bugane et al., 2012). Mesmo após vários graus de recuperação espontânea, cerca de 50% dos indivíduos hemiparéticos não conseguem andar independentemente e apresentam alguma limitação na marcha (Hankey et al., 2007).

A marcha normal tende a ser simétrica, com pequenas diferenças entre os membros na força vertical e na medição dos parâmetros temporais (Kim and Eng, 2003; Patterson et al., 2008). Em contraste, a marcha hemiparética é caracterizada por assimetria, com controle motor seletivo deficiente, atraso nas reações de equilíbrio, redução da descarga de peso no membro parético durante a fase de apoio e inadequada progressão do corpo para frente durante fase de balanço. Além disso, essa deficiência no lado parético requer ajustes compensatórios do lado não parético (Balasubramanian et al., 2007).

Uma característica marcante na marcha hemiplégica inclui queda do pé, associado ou não a uma inversão do pé (equinovaro) (Sheffler and Chae, 2015). Uma condição que resulta de uma fraqueza ou falta de ativação voluntária dos músculos dorsiflexores e/ou de um aumento da espasticidade dos músculos flexores plantares (Chisholm et al., 2013; Pittock et al., 2003; Stewart, 2008). Os indivíduos também apresentam um déficit para impulsionar o membro inferior

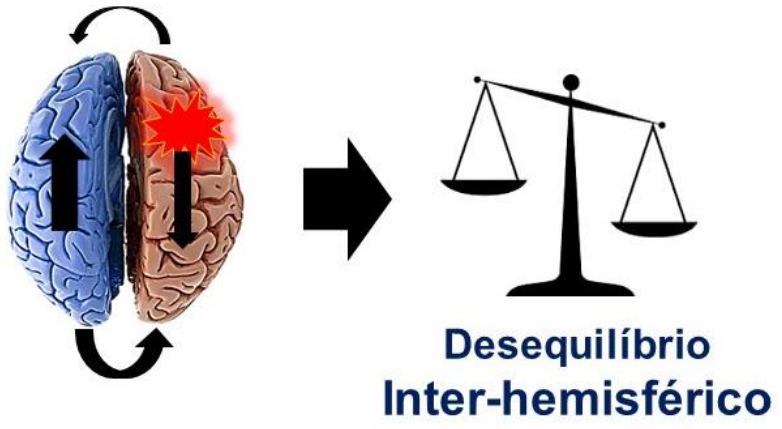
afetado à frente. Sendo assim, o membro afetado apresenta uma redução no pico de flexão de joelho durante a fase de balanço da marcha. Como estratégia compensatória, muitos realizam a circundução do quadril, em resposta à diminuição da dorsiflexão do tornozelo, para liberação do pé durante a fase de balanço. Na fase de apoio, a flexão plantar excessiva prejudica o contato inicial do pé, obrigando o indivíduo a apoiar a superfície com antepé ou com toda a superfície plantar, em vez de realizar o contato normal com o calcanhar (Chisholm et al., 2013; Sheffler and Chae, 2015). Os movimentos compensatórios geram adaptações biomecânicas que podem resultar em uma marcha lenta, ineficiente e com instabilidade, com alto custo energético, aumento do risco de quedas e dependência nas atividades da vida diária (Patterson et al., 2010a; Patterson et al., 2010b; Stein et al., 2010; Tyson et al., 2013; Waters and Mulroy, 1999).

Os padrões de marcha podem apresentar variações de um indivíduo para o outro (Roth et al., 1997). São características da marcha hemiplégica: redução da velocidade de caminhada (Goldie et al., 1996), redução da cadência (Woolley, 2001) e alterações na fase de apoio e na fase de balanço (Bohannon and Smith, 1987; Kim and Choi, 2016). Normalmente, após o AVC, os indivíduos apresentam tempo de apoio no lado parético reduzido e/ou um aumento no tempo de apoio e uma diminuição no período de balanço no lado não parético em comparação com o membro contralateral (Kim and Eng, 2003; Titianova et al., 2003). Um aumento no tempo de duplo apoio também pode ser observado, juntamente com uma tendência de aumento do suporte no membro inferior não afetado (Woolley, 2001). Em contraste, o padrão de comprimento de passo é menos consistente, pois os indivíduos pós-AVC constituem um grupo heterogêneo. Sendo assim, alguns podem exibir maior comprimento do passo no lado parético, enquanto outros exibem o comprimento do passo não parético mais longo (Balasubramanian et al., 2007). A gravidade da lesão, bem como a localização e tipo, e as complicações associadas, como amplitude limitada de movimento articular e controle de tronco, podem ser determinantes para o nível de disfunção (Alexander et al., 2009; Balaban and Tok, 2014).

2.1.3 Competição inter-hemisférica

Em condições normais, a atividade neural dos hemisférios cerebrais funciona de modo equilibrado através de controle inibitório mútuo, conhecido como inibição inter-hemisférica. Quando ocorre uma lesão cerebral, esse equilíbrio é perdido, gerando um padrão anormal de atividade entre os hemisférios cerebrais e provocando um desajuste na inibição inter-hemisférica (Murase et al., 2004) (Figura 2). Sendo assim, o córtex motor primário do hemisfério intacto pode influenciar negativamente a recuperação funcional sobre o córtex motor primário do hemisfério lesado devido ao aumento inibitório exagerado e, assim, gerar um comprometimento motor e prejudicar a recuperação funcional pós-AVC (Nowak et al., 2009; Takeuchi and Izumi, 2012). Acredita-se que a manutenção do déficit motor acaba favorecendo um desequilíbrio na ação inibitória mútua entre os dois hemisférios. Essa plasticidade “mal adaptativa” pode comprometer a reabilitação e reforçar os desajustes no controle motor (Nowak et al., 2009).

Figura 2. Figura representativa da alteração na competição inter-hemisférica.



Lesão no hemisfério esquerdo representada em vermelho. O hemisfério afetado (rosa) apresenta diminuição da excitabilidade cortical (seta preta menor). O hemisfério contralateral (azul) à lesão encontra-se excessivamente estimulado (seta preta maior) em virtude da pouca inibição recebida pelo hemisfério lesado. Consequentemente, o hemisfério contralateral inibe ainda mais o hemisfério afetado.

(Fonte: o autor)

2.1.4 Neuroplasticidade no AVC

As pesquisas atuais na área das neurociências têm avançado no conhecimento a respeito da fisiopatologia da lesão gerada no AVC, com intuito de desenvolver abordagens terapêuticas mais eficientes. A plasticidade neural pode modificar a estrutura e/ou a função do sistema nervoso central após um AVC (Chen et al., 2010). A recuperação após AVC é um processo complexo que ocorre, provavelmente, pela combinação de processos espontâneos e/ou dependentes da prática motora (Kwakkel et al., 1996). Com base nesses dados, acredita-se que, promovendo plasticidade no cérebro lesado, estar-se-ia indiretamente promovendo a recuperação do paciente. A experiência motora é capaz de induzir plasticidade em encéfalos maduros em condições de normalidade ou pós-lesão (Adkins et al., 2006; Kleim et al., 2003). As terapias restauradoras pós-AVC atuam sobre a relação entre recuperação motora e plasticidade cortical com o intuito de aumentar o potencial de recuperação funcional. A partir da experiência motora ocorre uma reorganização no tecido cortical (Carmichael, 2003; Nudo et al., 1996), através da regeneração dos axônios ou dendritos nos hemisférios cerebrais homolateral ou contralaterais à lesão associada ao aumento da expressão de proteínas (Gonzalez and Kolb, 2003), sendo essa capacidade cerebral o alicerce da reabilitação neurológica (Young and Tolentino, 2011).

Acredita-se que neurotrofinas podem ser medidas como biomarcadores de recuperação motora funcional, desempenhando uma relação entre reabilitação/atividade física e plasticidade neural. Dentre essas neurotofinas, podemos destacar o BDNF (He et al., 2013), o fator de crescimento insulínico-I (IGF-I) e proteínas ligantes de fator de crescimento insulínico (IGFBPs) (Goliwas et al., 2015).

O BDNF desempenha um papel-chave importante na neuroplasticidade pós-AVC e está envolvido no processo de aprendizagem (Jickling and Sharp, 2015). Os níveis sanguíneos de BDNF podem ser considerados uma medida indireta de neuroplasticidade e podem estar associados aos níveis cerebrais de BDNF (Luo et al., 2019), uma vez que a molécula passa por transporte bidirecional através da barreira hematoencefálica (Lee et al., 2008; Pan et al.,

1998). Estudo prévio encontrou níveis séricos mais baixos de BDNF associados à pior função motora na fase crônica pós-AVC (Stanne et al., 2016).

Em algumas doenças neurológicas crônicas, os níveis de BDNF diminuem enquanto há um aumento de substâncias pró-inflamatórias (Pascotini et al., 2018). O BDNF pode melhorar o efeito anti-inflamatório por meio do aumento da expressão de interleucina-10 (IL-10) e diminuição do fator de necrose tumoral alfa (TNF-α) (Jiang et al., 2010). Nesse sentido, a neuroinflamação pode ter papel central na patogênese e recuperação funcional pós-AVC. Acredita-se que há uma ligação entre o recrutamento de células imunes, os níveis de mediadores pró-inflamatórios e a ruptura da barreira hematoencefálica que causa perda neuronal (Denes et al., 2011). Neste sentido, o TNF-α e a interleucina-6 (IL-6) são citocinas pró-inflamatórias envolvidas na fase aguda da inflamação sistêmica e sua concentração permanece elevada em condições inflamatórias crônicas, como acidente vascular cerebral, contribuindo para a amplificação do tamanho e gravidade da lesão (Denes et al., 2011).

O fator de crescimento semelhante à insulina 1 (IGF-1) também é um hormônio com fortes efeitos anabólicos, como aumento da massa muscular, que possui algumas propriedades neurotróficas associadas à sinaptogênese no sistema nervoso central (Kooijman et al., 2009). O IGF-1 pode até cruzar a barreira hematoencefálica no sistema nervoso central em resposta ao exercício e hipertrofia muscular (Glass, 2005). Uma isoforma deste fator de crescimento (IGF-1 muscular) pode ser sintetizada pelo músculo esquelético, em resposta à sobrecarga mecânica (contração e alongamento), possuindo papel fundamental no processo de hipertrofia muscular (Lima et al., 2008). Os efeitos do IGF-1 são modulados por sua associação com proteínas de ligação ao fator de crescimento da insulina (IGFBPs). Um total de seis IGFBPs foram identificadas: IGFBP-1 à IGFBP-6. Aproximadamente 99% do IGF-1 circulante está ligado a IGFBPs, sendo a IGFBP-3 considerada a principal espécie em circulação. As IGFBPs controlam a atividade do IGF-1 (Glass, 2005). Acredita-se que as concentrações séricas de IGF-1 e IGFBP-3 após o AVC apresentam correlação positiva com o desempenho físico (Jogie-Brahim et al., 2009), e associação negativa com atrofia muscular no pós-AVC crônico (Silva-Couto et al., 2014).

2.2 TRATAMENTO PARA OS DÉFICITS DE MARCHA APÓS AVC

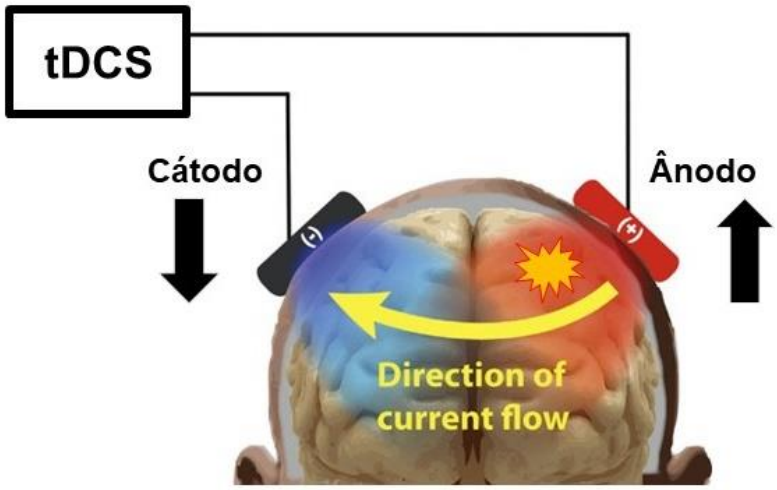
A recuperação da marcha é um dos principais objetivos na reabilitação de pacientes que apresentam AVC, visando à aquisição de padrões funcionais e/ou o aumento da velocidade da caminhada. Recentemente, métodos de neuro reabilitação têm sido aplicados para auxiliar a recuperação de indivíduos após o AVC. Dentro desse contexto, destaca-se a utilização da estimulação transcraniana por corrente contínua (tDCS) associada à atividade sensório-motora periférica com o objetivo de otimizar a melhora funcional através da plasticidade neuronal (Bolognini et al., 2009; Lindenberg et al., 2012; Reis et al., 2009).

2.2.1 Estimulação transcraniana por corrente contínua (tDCS)

As ferramentas de neuromodulação, como a tDCS, possuem efeitos em funções cognitivas e motoras em indivíduos com comprometimento neurológicos (Feng et al., 2013; Stagg and Johansen-Berg, 2013). Acredita-se que tDCS normalize as redes corticospinais excitatórias e inibitórias reduzindo a competição inter-hemisférica e plasticidade mal adaptativa (Adeyemo et al., 2012; Elsner et al., 2016; Schlaug and Renga, 2008). tDCS possui diferentes efeitos fisiológicos, dependendo do tamanho e do posicionamento dos eletrodos, da intensidade, da densidade da corrente e da duração da estimulação (Woods et al., 2016). O posicionamento dos eletrodos no modo bi-cefálico surge como uma boa alternativa para normalizar as redes corticospinais excitatórias e inibitórias. Este modo de estimulação utiliza a estimulação anódina (a-tDCS) e a catódica (c-tDCS) ao mesmo tempo, sendo que a primeira atua de forma a estimular a atividade neuronal, enquanto a segunda atua inibindo esta atividade (Cambiaghi et al., 2010). Tanto a a-tDCS no hemisfério afetado, quanto a c-tDCS no hemisfério não afetado são utilizadas com o objetivo principal de promover a plasticidade neuronal e restabelecer o equilíbrio funcional entre os hemisférios cerebrais (Schlaug and Renga, 2008). Estudos recentes relataram efeitos positivos da tDCS bi-cefalica na recuperação funcional do membro superior em indivíduos pós-AVC crônico (Ludemann-Podubecka et al., 2014; Salazar et al., 2020).

Nesse sentido, estudos investigaram o efeito da tDCS na reabilitação do membro inferior em sujeitos agudos/subagudos (Chang et al., 2015; Manji et al., 2018) e crônicos (Seo et al., 2017) pós-AVC. Sua utilização mostra-se benéfica nestes indivíduos, tendo em vista que há evidências de sua utilização na melhora da mobilidade funcional (Chang et al., 2015; Li et al., 2018) e da força muscular do membro inferior parético (Tanaka et al., 2009). Além disso, acredita-se que a tDCS associada a atividades sensório-motoras periféricas possa otimizar a recuperação motora (Bolognini et al., 2009; Lindenberg et al., 2012; Reis et al., 2009). Esses resultados incentivam o uso do tDCS associado à terapia motora, com o intuito de melhorar o controle locomotor e déficits no equilíbrio na marcha dos pacientes com lesões neurológicas.

Figura 3. Figura representativa da aplicação bi-cefálica da estimulação transcraniana por corrente contínua (tDCS).



Eletrodo ânodo posicionado sobre o hemisfério lesado para aumentar a excitabilidade cortical (sinal positivo, eletrodo vermelho). Eletrodo cátodo sobre o hemisfério contralateral à lesão para diminuir a excitabilidade cortical (sinal negativo, eletrodo preto).
(Adaptado de: https://caputron.com/pages/what-is-tdcs)

2.2.2 *Foot Drop Stimulator* (FDS)

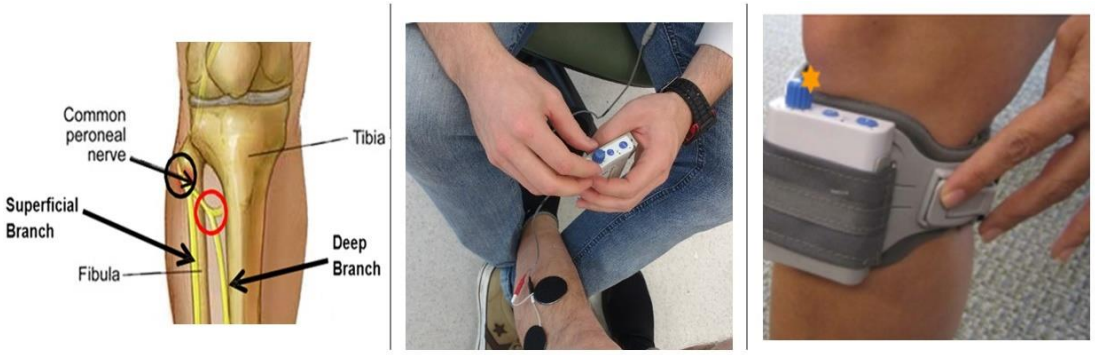
Os principais objetivos dos tratamentos disponíveis aos pacientes após AVC são a melhora da marcha e da funcionalidade nas atividades de vida diária. No que diz respeito à reabilitação da marcha desses pacientes, busca-se corrigir os déficits dos músculos dorsiflexores e flexores plantares, que, junto com a alteração do tônus muscular, são responsáveis pela presença do pé caído (Chen et al., 1999; Daviet et al., 2002; Hesse et al., 1994).

A utilização da estimulação elétrica através da FES é um método terapêutico capaz de reduzir disfunções da marcha após AVC (Hong et al., 2018; Lin et al., 2018; Pereira et al., 2012). O estímulo pode ser aplicado por meio de equipamentos convencionais de estimulação elétrica ou por meio do FDS com sensores de inclinação. Vários estimuladores de queda do pé estão disponíveis comercialmente. O dispositivo FDS consiste em um dispositivo que aplica o FES no nervo fibular comum, promovendo o movimento de dorsiflexão e eversão de tornozelo e pé (Bethoux et al., 2015; Everaert et al., 2013; Stein et al., 2010). O estímulo da FDS permite que o pé saia do chão durante a fase de balanço, melhorando, assim, o contato inicial e resposta de carga durante a fase de apoio da marcha. Além de promover movimentos de tornozelo mais precisos (Kottink et al., 2004), a utilização desse dispositivo facilita a flexão do quadril e joelho durante a fase de balanço (Everaert et al., 2010; Stein et al., 2010). Esses benefícios levariam a um padrão de caminhada mais próximo da normalidade, melhorando a qualidade, a simetria da marcha e diminuindo o gasto energético durante a caminhada (Burridge et al., 1997; Hausdorff and Ring, 2008; Laufer et al., 2009; Ring et al., 2009; Stein et al., 2006; Stein et al., 2010).

Estudos que compararam a utilização do padrão ouro para pé caído AFOs (do inglês – Ankle Foot orthosis) e a FDS demonstraram que há ganhos equivalentes em ambos os dispositivos no que se refere à melhora na velocidade da marcha e no equilíbrio estático. Contudo, como em alguns casos a órtese limita o movimento de tornozelo, os pacientes têm perda de mobilidade do tornozelo e diminuição da atividade muscular (Hesse et al., 1999; Vistamehr et al., 2014), o que pode impactar no equilíbrio neuromuscular e na dinâmica da marcha (Cattaneo et al., 2002; Vistamehr et al., 2014). Sendo assim, a utilização da estimulação elétrica mostra-se mais satisfatória, sendo considerada uma alternativa mais funcional para pacientes após AVC que apresentam pé caído (Bethoux et al., 2014; Bethoux et al., 2015). A contração muscular gerada pela

FDS associada ao ciclo da marcha contribui para a normalização das atividades motoras reflexas, o relaxamento da musculatura espástica - mesmo após a interrupção do estímulo - ativação de áreas motoras corticais (Barbeau and Visintin, 2003; Thompson et al., 2006) além de agir na neuroplasticidade, aumentando o número de unidades motoras ativas (Stein et al., 2006; Thompson et al., 2009).

Figura 4. Figura e foto representativa do posicionamento da *Foot Drop Stimulation.*



(Foto: autor; Figura adaptada de anual de configuração do sistema WalkAide)

A literatura fornece evidências de que a FDS associada à fisioterapia pode resultar em benefícios clinicamente significativos, mesmo em indivíduos crônicos pós-AVC (Bae et al., 2014; Hwang et al., 2015). Os efeitos do uso de FDS podem ser divididos em três condições: efeitos imediatos, de treinamento e terapêuticos. O efeito imediato ocorre quando o indivíduo é introduzido ao dispositivo e esse modifica subitamente a biomecânica da marcha, devido ao estimulo produzido pelo FES (Everaert et al., 2013). O efeito do treinamento ocorre quando o FDS é usado por um período específico de tempo, sendo que os efeitos são avaliados enquanto o indivíduo está usando o dispositivo (Kluding et al., 2013). Por outro lado, o efeito terapêutico pode ocorrer após o uso prolongado da FDS. Os efeitos terapêuticos incluem plasticidade neural (Everaert et al., 2010), aumento da velocidade de caminhada (Kottink et al., 2007; Stein et al., 2010) e amplitude de movimento articular (Bae et al., 2014; Sheffler et al., 2015). Essas adaptações positivas estariam presentes mesmo quando o dispositivo fosse desligado (Kluding et al., 2013). A literatura

disponível não estabelece um período recomendado e/ou uma intensidade padrão de estimulação para atingir os efeitos terapêuticos e de treinamento nos indivíduos após o AVC. A frequência elétrica a estimulação definida pelo FDS é de 25 Hz, a duração do pulso em 150 a 300 μs e a intensidade entre 60 e 150 V, que devem ser ajustada de acordo com tolerância do participante e do nível de estimulação necessária para provocar a dorsiflexão do tornozelo e eversão do pé (Hwang et al., 2015).

3 OBJETIVOS

3.1 OBJETIVO GERAL:

Avaliar o efeito da tDCS e do FDS na reabilitação do membro inferior de indivíduos com hemiparesia crônica após o AVC.

3.2 OBJETIVOS ESPECÍFICOS:

- Verificar se a FES aplicada no nervo peroneal parético em combinação ou não com a terapia convencional poderia melhorar a velocidade da marcha em indivíduos pós-AVC com pé caído. Secundariamente, investigar o efeito desta terapia na mobilidade ativa de dorsiflexão do tornozelo, equilíbrio e mobilidade funcional (ARTIGO 1).

- Explorar os efeitos de duas semanas de uso de FDS combinado com fisioterapia na amplitude de movimento ativa do tornozelo - avaliada durante a locomoção com a órtese em modo ON (efeito de treinamento) e modo OFF (efeito terapêutico). Secundariamente, avaliar as mudanças na amplitude de movimento (ADM) do joelho e quadril, os parâmetros espaço-temporais da marcha e a distância total percorrida durante o treinamento em esteira (ARTIGO 2).

- Verificar os efeitos de duas semanas da combinação de tDCS e FDS sobre a mobilidade funcional em indivíduos com hemiparesia crônica pós-AVC. Além disso, investigar os efeitos desse protocolo na espasticidade dos membros inferiores, qualidade de vida e distância total caminhada durante o tratamento (ARTIGO 3).

- Investigar os efeitos da combinação de tDCS e FDS sobre os níveis séricos de BDNF em indivíduos com hemiparesia crônica pós-AVC. Além disso, avaliar os efeitos desse protocolo nos níveis séricos de IGF-1, IGFBP-3, IL-6, IL-10 e TNF-α e no comprometimento motor, mobilidade funcional e nível de participação social (ARTIGO 4).

- Verificar se a combinação de tDCS e FDS poderia melhorar a velocidade da marcha em indivíduos com hemiparesia crônica pós-AVC. Além disso, investigar os efeitos desse protocolo em outros parâmetros espaço-temporais da marcha (cadência, comprimento do passo, fase de apoio simples e fase de balanço), nas alterações da amplitude de movimento (ADM) do membro inferior parético e simetria da marcha (ARTIGO 5).

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5 ARTIGOS

5.1 Functional electrical stimulation on the peroneal nerve improves post-stroke gait speed when combined with physiotherapy - A Systematic Review and Meta-Analysis

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Review

Functional electrical stimulation of the peroneal nerve improves post-stroke gait speed when combined with physiotherapy. A systematic review and meta-analysis

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ABSTRACT

Background: Functional electrical stimulation (FES) applied to the paretic peroneal nerve has positive clinical effects on foot drop secondary to stroke.
Objective: To evaluate the effectiveness of FES applied to the paretic peroneal nerve on gait speed, active ankle dorsiflexion mobility, balance, and functional mobility.
Methods: Electronic databases were searched for articles published from inception to January 2020. We included randomized controlled trials or crossover trials focused on determining the effects of FES combined or not with other therapies in individuals with foot drop after stroke. Characteristics of studies, participants, comparison groups, interventions, and outcomes were extracted. Statistical heterogeneity was assessed with the I^2 statistic.
Results: We included 14 studies providing data for 1115 participants. FES did not enhance gait speed as compared with conventional treatments (i.e., supervised/unsupervised exercises and regular activities at home). FES combined with supervised exercises (i.e., physiotherapy) was better than supervised exercises alone for improving gait speed. We found no effect of FES combined with unsupervised exercises and inconclusive effects when FES was combined with regular activities at home. When FES was compared with conventional treatments, it improved ankle dorsiflexion, balance and functional mobility, albeit with high heterogeneity for these last 2 outcomes.
Conclusions: This meta-analysis revealed low quality of evidence for positive effects of FES on gait speed when combined with physiotherapy. FES can improve ankle dorsiflexion, balance, and functional mobility. However, considering the low quality of evidence and the high heterogeneity, these results must be interpreted carefully.

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1. Introduction

Foot drop is a common impairment after stroke. This condition is related to high degrees of motor impairment, weakness or lack of voluntary control of ankle dorsiflexors and increased spasticity of plantar flexors [1–3]. Foot drop interferes with the initial foot contact at the beginning of the stance phase and hinders ankle dorsiflexion during the swing phase of gait [4]. Consequently, foot drop contributes to disruption in weight acceptance and weight transfer; reduces walking speed, efficiency and stability of gait [5] and increases the risk of falling [6].

Electrical stimulation is a therapeutic method able to reduce post-stroke walking dysfunctions [7–9]. These benefits have been demonstrated for some types of stimulation: transcutaneous electrical nerve stimulation (TENS) [9], functional electrical stimulation (FES) on the peroneal nerve and FES on tibialis anterior muscle [8]. However, some evidence suggests that FES is more effective than TENS [10]. FES is able to stimulate voluntary muscle activity, reduce foot drop, decrease spasticity, and lead to long-term sensorimotor

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cortical reorganization [11,12]. When FES is applied on the peroneal nerve and synchronized with gait phases [13], it allows for a more precise ankle dorsiflexion/eversion during gait [13] as compared with FES applied on the tibialis anterior. FES of the peroneal nerve could also facilitate hip and knee flexion during the swing phase of gait and lead to a walking pattern closer to the normal [11,14]. The stimulus can be applied with conventional electrical stimulation equipment used in current clinical practice or by foot drop stimulator devices with tilt sensors or foot switches. Several foot-drop stimulators are commercially available [14,15].

Some studies have demonstrated that FES applied to the paretic peroneal nerve has positive clinical effects on foot drop secondary to stroke [16–18]. A previous systematic review showed that FES could increase gait speed in post-stroke individuals as compared with ankle foot orthoses (AFO) [13]. However, this study included only one randomized controlled trial (RCT). A more recent systematic review included 6 RCTs and showed that both foot drop stimulation devices and AFO seem to be effective and "equivalent" for increasing gait speed after stroke [19]. These authors argue that probably a combination of physiotherapy and devices would be necessary to improve gait speed in this population. From the available literature and considering the lack of a meta-analysis exploring the effects of FES combined with conventional therapy, we cannot make evidence-based inferences about the clinical benefits of FES of the peroneal nerve to treat foot drop after stroke. New data from RCTs that applied a stimulus on the peroneal nerve by conventional equipment or implanted electrodes [17,18,20–22], combined or not with a conventional therapy, must be considered. These data must be synthesized in a systematic review with meta-analysis to add value to the previously published studies and explore the effectiveness of FES on the peroneal nerve in post-stroke individuals.

For this purpose, we performed a systematic review of RCTs and crossover trials to verify whether FES applied to the paretic peroneal nerve, combined or not with conventional therapy, could enhance gait speed in post-stroke individuals with foot drop. Second, we investigated the effect of this therapy on active ankle dorsiflexion mobility, balance, and functional mobility. Our findings may provide solid evidence to empower post-stroke individuals and support clinicians in their decision-making when dealing with post-stroke gait rehabilitation.

2. Methods

2.1. Protocol and registration

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [23]. The protocol was registered at the International Prospective Register of Systematic Reviews, PROSPERO (No. CRD42019127552) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019127552.

2.2. Literature search

The following electronic databases were searched for articles published from inception to January 2020: MEDLINE via PubMed, Embase, Cochrane Central Register of Controlled Literature Search Trials (CENTRAL) and Physiotherapy Evidence Database (PEDro). In addition, we screened studies from reference lists of manuscripts included in this review and checked unpublished or ongoing studies in clinical trial registries (ClinicalTrials.gov). The search strategy was adjusted to each database. Appendix 1 shows the complete search strategy.

2.3. Study selection

Inclusion criteria were reports of RCTs or crossover trials focused on determining the effects of FES applied to the paretic peroneal nerve of post-stroke individuals with foot drop. The stimulus could be applied using FES conventional equipment or foot drop stimulators with implanted or non-implanted electrodes. For crossover trials, we analyzed only data from the first period and considered them a parallel-group trial.

We included articles that combined or did not combine FES with other therapies (supervised exercises, gait training, treadmill training, AFO, unsupervised exercises, regular activities at home and others). Studies must have investigated the effect of FES on gait speed, active ankle dorsiflexion mobility, balance and functional mobility.

Comparator groups were sham FES, combined or not with other therapies, and conventional physiotherapy (treadmill gait training, robot-assisted gait training, gait re-education, neurodevelopmental treatment, proprioceptive neuromuscular facilitation, conventional walking devices such as AFO and orthopedic shoes).

We included studies written in English, Spanish and Portuguese. We excluded studies that enrolled infant stroke survivors as well as theses or articles published only as abstracts, including conference proceedings.

Two reviewers (MJC and KDR) independently screened studies based on title and abstracts. The same reviewers deleted duplicates and independently assessed the full texts. When different assessments from the same trial were reported in separate publications, we considered them as a single publication. Disagreements were solved by consensus or with a third reviewer (APS).

2.4. Data extraction and assessment of characteristics of trials

We extracted data on methodological characteristics, number of participants, comparison groups, interventions and outcomes by using standardized forms. When studies did not have enough data available or we needed clarification, we contacted authors by e-mail.

2.5. Outcomes

Our primary outcome was gait speed, which was assessed during the 10-m Walk Test (10MWT) with stopwatches, inertial sensors or optoelectronic systems. Gait speed was calculated as the ratio between distance and time spent (seconds) to walk 10 m. When authors presented data as the "time to complete the test", we transformed values in meters per seconds (m/s) by using the ratio of distance to time.

Secondary outcomes were:

- active ankle dorsiflexion mobility (data collected during gait assessment by using optoelectronic systems);
- balance assessed by the Berg Balance Scale (BBS) and;
- functional mobility assessed by the Timed Up and Go test (TUG).

Although authors also collected data from the time participants were receiving the FES stimulation, we analyzed data collected only when stimulation was off.

2.6. Quality assessments

PEDro scores from the Physiotherapy Evidence Database were used to assess the quality of studies (www.pedro.org.au). The PEDro scale contains 11 items and, except for item one, pertaining to external validity, each satisfied item contributes one point to the total score (range 0–10) [24]. Scores 9 or 10 were considered

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excellent quality; 6 to 8 good quality; 4 or 5 fair quality; and < 4 poor quality. Scores 0 to 5 correspond to high risk of bias and 6 to 10 low risk of bias [25]. We used the grading of recommendation, assessment, development and evaluation (GRADE) system to assess the quality of the body of evidence [26].

2.7. Data analysis

Between-group meta-analyses were conducted for quantitative analysis. Data were obtained by comparing the change from post- to pre-intervention. Data were pooled by using a random effects model for quantitative synthesis [27]. Outcomes are presented as the weighted mean difference (MD) or standardized mean differences (SMD) with 95% confidence intervals (95% CIs). Statistical heterogeneity was assessed with the I^2 statistic, with values classified as low heterogeneity (I^2 < 25%), moderate heterogeneity (I^2 25% to 50%) and high heterogeneity (I^2 > 50%) [27]. $P < 0.05$ was considered statistically significant. Considering that studies had varied types of protocols, a sensitivity analysis was conducted to reduce the statistical heterogeneity. We considered the time after stroke (acute/subacute and chronic) and the type of protocol applied (FES combined with supervised or unsupervised exercises and regular activities at home). All analyses were conducted with R v3.3.3 (package metaphor v2.0-0) [28].

3. Results

Table 1 depicts all information about outcomes, measurement tools and characteristics of participants such as age, sex and time after stroke.

3.1. Flow of articles in the review

Fig. 1 shows the flow of articles in the review. The electronic search strategy identified 2328 studies. After titles and abstracts screening, 46 manuscripts were considered relevant and 14 trials met the eligibility criteria and were included. Thirteen studies were included in the meta-analysis, providing data from 1115 participants. Eleven studies reported data on gait speed and expressed data in m/s. One study [18] described gait speed as time spent to walk 10 m. We contacted the author and performed the procedure to estimate data, converting them to the same scale (m/s). One study was not included in the meta-analysis [29] because it used the same sample presented by Bethoux (2014) [30]. Another 2 studies presented outcome data from the same trial, and we considered them as a single publication [16,22]. These studies published by Kottink and colleagues in 2007 and 2012 described data on gait speed from the same participants. Thus, we considered data from only Kottink and colleagues (2007) because they reported the complete sample.

3.2. Participants

Mean age of participants ranged from 45 [17] to 72 years [31]. The mean time since stroke ranged from < 1 month [32] to almost 108 months. Twelve studies included post-stroke individuals in the chronic phase [16–18,22,29,30,33–37]. Three trials included participants in both acute and subacute phases [31,32,38]. Six studies included both ischemic and hemorrhagic stroke [17,18,31,35,37,38]. Other trials did not describe the type of stroke.

3.3. Interventions

Twelve studies used peroneal nerve devices [16–18,22,30–35,37,38] and 2 used conventional FES on the peroneal nerve [20,21]. Only one study used implanted electrodes to stimulate the peroneal nerve [16,22].

In 3 studies, participants did not perform specific exercises while wearing the stimulation devices. They were instructed simply to follow their regular activities at home (such as regular walking activities throughout the day) [22,30,34]. Four studies prescribed a routine of exercises focusing on gait training while using the stimulation devices [31,33,35,37]. In these studies, the authors compared FES stimulation with AFO devices.

In 3 studies, FES was associated with conventional physiotherapy and compared with AFO [32] or with other types of stimulation

Table 1
Summary of included studies.

Study	Design	Participants	Protocol		Outcome measures
			Frequency and duration for the different groups	Characteristics	
Bae et al., 2014	RCT	n = 20 Age (year) IG: 45.4 ± 19.7 CG: 52.0 ± 16.1 Sex: 13M/7F Type of stroke: I/H Severity: N/S Time since stroke: >6 mo (chronic) Follow-up: not reported	IG 30 min a day, 3 days/wk, during 5 wks + 30 min a day, 3 days/wk, during 5 wks CG 30 min a day, 3 days/wk, during 5 wks + 30 min a day, 3 days/wk, during 5 wks	IG Robot-assisted gait training plus FES to stimulate the peroneal (device) + Conventional physiotherapy CG Robot-assisted gait training + Conventional physiotherapy	Tempo-spatial gait parameters Dynamic angular gait parameters Modified Motor Assessment Scale TUG BBS Timing: 0; 5 wks
Bethoux et al., 2014 Bethoux et al., 2015[a]	RCT	n = 495 Age (year) IG: 63.87 ± 11.33 CG: 64.3 ± 12.01 Sex: 304M/191F Type of stroke: N/S Severity: N/S Time since stroke: > 6 mo (chronic) Follow-up: 26 weeks	IG All day at home during 6 mo CG All day at home during 6 mo	IG Participants used the FES to stimulate the peroneal (device) at home CG Participants used the AFO device at home	10M Walk Test Activities of Daily Living Stroke Impact Scale Serious adverse event 6-Min Walk Test GaitRite Functional Ambulation Profile Modified Emory Functional Ambulation Profile BBS TUG Gait quality Stroke-Specific Quality of Life Timing: 0; 24; 48[a] wk

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Table 1 (*Continued*)

Study	Design	Participants	Protocol		Outcome measures
			Frequency and duration for the different groups	Characteristics	
Burridge et al., 1997	RCT	n = 32 Age (year) IG: 52.3 ± 14.3 CG: 61.3 ± 8.6 Sex: 23M/9F Type of stroke: N/S Severity: N/S Time since stroke: >6 mo (chronic) Follow-up: 6 wks	IG All day at home during 6 wks CG 10 physiotherapy sessions during the first month of the trial. Each session lasted for 1 h	IG Participants used the FES to stimulate the peroneal (device) on a full-time basis for all walking activities throughout the day + Conventional physiotherapy CG Conventional physiotherapy	Gait speed Physiological Cost Index Timing: 0; 4; 12 wks
Everaert et al., 2013	Cross-over RCT	n = 69 Age (year) IG: 57.1 ± 12.9 CG: 55.6 ± 11.9 Sex = 51M, 18F Type of stroke = n/s Severity: not reported Time since stroke: >6 mo (chronic) Follow-up: not reported	IG All day at home during 6 wks CG All day at home during 6 wks	IG Participants used the FES to stimulate the peroneal (device) daily at home and for walking in the community CG Participants used the AFO daily at home and for walking in the community	Figure-of-8 Walking Speed Physiological Cost Index 10M Walk Test Mobility Index Perceived Safety Level Device Preference Timing: 0; 6 wks
Hwand et al., 2015	RCT	n = 30 Age (year) IG: 50.0 ± 7.55 GC: 49.47 ± 5.01 Sex: 17M/13F Type of stroke: I/H Severity: not reported Time since stroke: >6 mo (chronic) Follow-up: not reported	IG 30 min a day/4 wks + 30 min twice per day/4 wks CG 30 min a day/4 wks + 30 min twice per day/4 wks	IG Treadmill training plus FES to stimulate the peroneal (device) + Conventional physiotherapy CG Treadmill training plus placebo of FES to stimulate the peroneal (device) + Conventional physiotherapy	TUG BBS 10M Walk Test Muscle structure of the tibialis anterior Timing: 0; 4 wks
Kluding et al., 2013	RCT	n = 197 Age (year) IG: 60.71 ± 12.24 CG: 61.58 ± 10.98 Sex: 118M/79F Type of stroke: I/H Severity: N/S Time since stroke: >6 mo (chronic) Follow-up: not reported	IG All day at home during 30 wks + 8 sessions during the first 6 wks CG All day at home during 30 wks + 8 sessions during the first 6 wks	IG Participants used the FES to stimulate the peroneal (device) at home + Physical therapy focused on education on device use, gait training, and an individualized home exercise program CG Participants used the AFO at home + Physical therapy focused on education on device use, gait training, and an individualized home exercise program Participants received surface sensory stimulation with TENS device	10M Walk Test comfortable/fast speed Fugl-Meyer Assessment-Lower Limb TUG 6-min Walk Test BBS Functional reach test Stroke Impact Scale Activity monitoring Timing: 0; 6; 12; 30 wks
Kottink et al., 2012	RCT	n = 23 Age (year) IG: 55.6 ± 13.16 CG: 53.31 ± 10.55 Sex: 15M/8F Type of stroke: N/S Severity: N/S Time since stroke: >6 mo (chronic) Follow-up: not reported	IG All day at home during 26 wks CG All day at home during 26 wks	IG Participants used the FES to stimulate the peroneal (implantable) at home CG Participants used the conventional device at home	Tempo-spatial gait parameters Dynamic angular gait parameters Timing: 0; 4; 8; 12; 26 wks
Kottink et al., 2007	RCT	n = 29 Age (year) IG: 55.2 ± 11.36 CG: 53.31 ± 9.87 Sex: 20M/9F Type of stroke: N/S Severity: N/S Time since stroke: >6 mo (chronic) Follow-up: N/S	IG All day at home during 26 wks CG All day at home during 26 wks	IG Participants used the FES to stimulate the peroneal (implantable) at home CG Participants used the conventional device at home	6-min Walk Test 10M Walk Test Physical activity Timing: 0; 4; 8; 12; 26 wks

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Table 1 (Continued)

Study	Design	Participants	Protocol		Outcome measures
			Frequency and duration for the different groups	Characteristics	
Morone et al., 2012	RCT	n = 20 Age (year) IG: 53.3 ± 14.6 CG: 61.2 ± 16.2 Sex: no report Severity: N/S Type of stroke: N/S Time since stroke: < 1 mo (acute) Follow-up: N/S	IG 40 min a day, 5 days/wk during at 12 wks + 40 min a day, 5 days/wk during at 12 wks CG 40 min a day, 5 days/wk during 12 wks + 40 min a day, 5 days/wk during 12 wks	IG Walking training plus FES to stimulate the peroneal (device) + Conventional physiotherapy CG Walking training plus AFO + Conventional physiotherapy	10M Walk Test Functional Ambulation Classification Barthel Index Mobility Index Medical Research Council Canadian Neurological Scale Ashworth scale Timing: 0; 4; 8; 12 wks
Mitsutake et al., 2019	RCT	n = 23 Age (year) IG: 61.45 ± 11.51 CG: 68.75 ± 10.59 Sex: 18M, 5F Severity: moderate Type of stroke: I/H Time since stroke: < 6 mo (sub-acute) Follow-up: N/S	IG 20 min a day, all days during 2 wks + 40 min a day, all days during 2 wks CG 20 min a day, all days during 2 wks + 40 min a day, all days during 2 wks	IG Walking plus FES to stimulate the peroneal (device) + Conventional physiotherapy plus NMES (20 min) CG Training plus NMES + Conventional physiotherapy	10M Walk Test Timing: 0; 2; wks
Salisbury et al., 2013	RCT	n = 16 Age (year) IG: 72.9.3 ± 13.9 CG: 52.6 ± 17.2 Sex = 6M, 10F Severity: N/S Type of stroke = I/H Time since stroke: > 1 < 3 mo (sub-acute) Follow-up: N/S	IG All day during 12 wks + 20 min a day, 5 days/wk during 12 wks CG All day during at 12 wks + 20 min a day, 5 days/wk during 12 wks	IG Participants used the FES to stimulate the peroneal (device) at home + Routine gait re-education CG Participants used the AFO at home + Routine gait re-education	10M Walk Test Functional Ambulation Classification Stroke Impact scale Perception of change in walking Timing: 0; 12 wks
Sheffler et al., 2015	RCT	n = 110 Age (years) IG: 52.8 ± 12.2 CG: 53.2 ± 10.1 Sex = 67M, 43F Severity: N/S Type of stroke = I/H Time since stroke: > 6 mo (chronic) Follow-up: 12 and 24 wks	IG All day during 12 wks + 1 h functional training (first 5 wks) + 8 h per day device usage 2 h functional training (last 7 wks) + 8 h per day device usage CG All day during 12 wks + 1 h functional training (first 5 wks) + 8 h per day device usage 2 h functional training (last 7 wks) + 8 h per day device usage	IG Participants used the FES peroneal nerve at home + Functional training GC Participants used the AFO at home + Functional training	Tempo-spatial gait parameters Dynamic angular gait parameters Timing: 0; 12; 24; 36 wks
Park et al., 2017	RCT	n = 30 Age (year) IG: 64.2 ± 9.7 CG: 63.5 ± 8.6 Sex = N/S Type of stroke = N/S Severity: N/S Time since stroke: > 6 mo (chronic) Follow-up: N/S	IG 30 min, 1 day CG 30 min, 1 day	IG FES on peroneal nerve + Conventional physiotherapy CG TENS on sural nerve + Conventional physiotherapy	Tempo-spatial gait parameters Timing: 0; 4 days
Sharif et al., 2017	RCT	n = 38 Age (year): N/S Sex: N/S Type of stroke: N/S Severity: N/S Time since stroke: > 6 mo (chronic) Follow-up: not reported	IG 30 min a day, 5 days/wk during 6 wks CG 10 min a day, 5 days/wk during 6 wks	IG FES on peroneal nerve during swing phase of walking + Physiotherapy and occupational therapy CG Conventional electrical stimulation on peroneal nerve + Physiotherapy and occupational therapy	Fugl-Meyer Assessment-Lower Limb Modified Ashworth Scale BBS TUG Gait Dynamic Index Timing: 0; 3; 6 wks

RCT: randomized controlled trial; N/S, not stated; IG: intervention group; CG: control group; M: male; F: female; I: ischemic; H: hemorrhagic; wk(s): weeks; mo: months; FES: functional electrical stimulation; AFO: ankle foot orthosis; TENS: transcutaneous electric nerve stimulation; TUG: Time Up and Go; BBS: Berg Balance Scale.

[a] Study included only in the systematic review and not in the meta-analysis.

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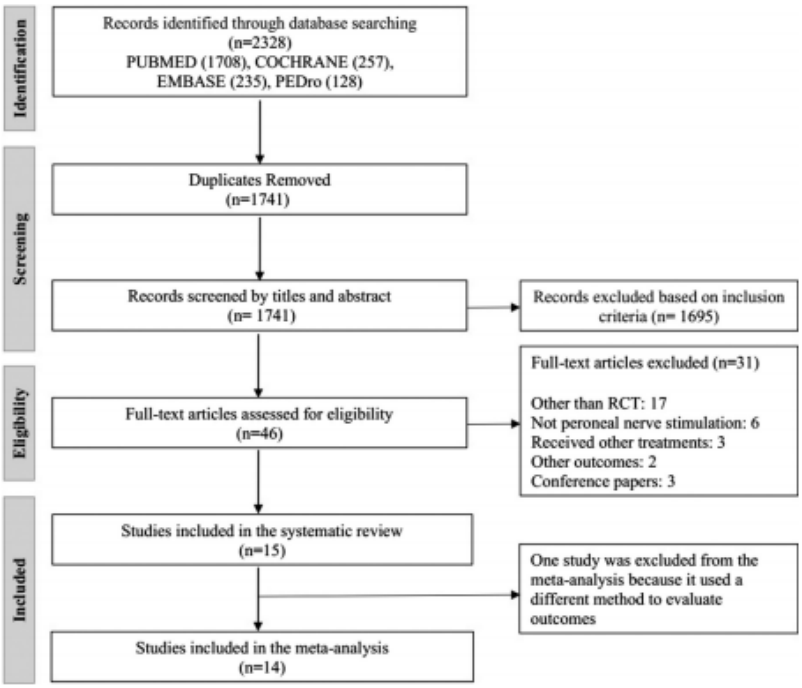

Fig. 1. Flow of articles in the study. RCT: randomised controlled trial.

(TENS and neuromuscular electrical stimulation [NMES]) [20,21,38]. Two studies combined FES with treadmill gait training and compared to sham plus treadmill gait training [17,18].

The duration of sessions ranged from 20 to 60 min [17,18,31,37,38]. In some studies, participants received the stimulation at home during the entire day [16,22,29–31,33–35,37].

Frequency of FES stimulation ranged from 1 [21] to 5 [20,31,32,38] days per week or every day at home for 4 to 30 weeks. The intervention period studied ranged from 2 weeks [38] to 30 weeks [35] or just 1 day.

3.4. Quality of studies

The median PEDro score was 5 (range 4 to 7), so studies presented fair quality and high risk of bias (Table 2). All trials were randomized, showed between-group differences, and reported

Table 2
PEDro scores of included studies.

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	Adequate follow-up	Intention-to-treat analysis	Between-group difference reported	Point estimate and variability reported	Total (0 to 10)
Bae et al., 2014	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Bethoux et al., 2014	Y	N	Y	N	N	N	N	Y	Y	Y	5
Bethoux et al., 2015[a]	Y	N	Y	N	N	N	N	Y	Y	Y	5
Burridge et al., 1997	Y	Y	N	N	N	N	Y	N	Y	Y	5
Everaert et al., 2013	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Hwang et al., 2015	Y	N	Y	N	N	Y	Y	N	Y	Y	7
Klulding et al., 2013	Y	N	N	N	N	Y	N	Y	Y	Y	5
Kottink et al., 2007	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Kottink et al., 2012	Y	Y	Y	N	N	N	N	N	Y	Y	5
Mitsutake et al., 2019	Y	N	Y	N	N	Y	Y	N	Y	Y	6
Morone et al., 2012	Y	N	Y	N	N	Y	N	N	Y	Y	5
Park et al., 2017	Y	N	Y	N	N	N	N	N	Y	Y	4
Salisbury et al., 2013	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Sharif et al., 2017	Y	N	Y	N	N	N	N	N	Y	Y	4
Sheffer et al., 2015	Y	Y	Y	N	N	N	N	Y	Y	Y	6
Median (min-max)											5 (4–7)

[a] This study was not included in the meta-analysis because the follow-up was higher than in other studies.

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Table 3
Quality Assessment (GRADE).

Quality assessment (GRADE)							Summary of findings		
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%) With conventional therapy	Study event rates (%) With FES on peroneal nerve	Risk difference with FES on peroneal nerve
Gait speed									
1077 (12 RCTs)	Serious [a,b,c]	Serious	Not serious	Not serious	None	⨁⨁◯◯ LOW	540	537	SMD 0.06 SD higher (0.4 lower to 0.52 higher)
Ankle dorsiflexion angle									
151 (3 RCTs)	Serious [a,e]	Not serious	Not serious	Serious [d]	None	⨁⨁◯◯ LOW	78	73	MD 3.3 higher (1.48 higher to 5.12 higher)
Balance (assessed with Berg Balance Scale)									
780 (5 RCTs)	Serious [a,f]	Serious	Not serious	Not serious	None	⨁⨁◯◯ LOW	395	385	MD 2.76 higher (0.64 higher to 4.88 higher)
Functional mobility (assessed with Time Up and Go)									
780 (5 RCTs)	Serious [a,h]	Serious [g]	Not serious	Not serious	None	⨁⨁◯◯ LOW	395	385	MD 3.19 lower (5.76 lower to 0.62 lower)

CI: confidence interval; SMD: standardized mean difference; MD: mean difference. [a]Studies did not blind assessors. *2 of 4 studies did not use intention-to-treat analysis.
[a] Studies did not blind participants and therapists.
[b] 9 of 11 studies did not blind assessors.
[c] 6 of 11 studies did not use intention-to-treat analysis.
[d] Insufficient number of studies.
[e] Assessor was not blinded. Not all studies used intention-to-treat analysis.
[f] 2 of 5 studies did not blind assessors and did not use intention to treat analysis.
[g] High heterogeneity and the confidence intervals do not overlap.

point estimate and variability. Thirteen studies had similar groups at baseline [17,18,20,21,29–32,34,37,38]. Seven trials concealed allocation lists [16,17,22,31,33,34,37] and 7 had adequate follow-up [17,18,22,31,33,34,38]. Only 4 studies blinded assessors [18,32,35,38], and 6 studies used intention-to-treat analysis [22,29–31,35,37]. No study blinded therapists or participants. Quality of evidence was low for all outcomes. Table 3 presents the evidence profile according to the GRADE system.

3.5. Outcomes measures

3.5.1. Gait speed

Twelve studies (n = 1077) evaluated gait speed and were included in the meta-analysis. FES did not enhance gait speed as compared with conventional treatment [SMD = 0.092 (95% CI: −0.34 to 0.53; I^2 89%, P = 0.68)] (Fig. 2A). Sensitivity analysis was performed considering the time after the stroke. Groups did not differ in gait speed: 11 studies included chronic post-stroke individuals (n = 1008) [SMD = 0.013 (95% CI: −0.49 to 0.52; I^2 91%, P = 0.96)] and only 3 studies included participants in the acute/subacute phase (n = 69) [SMD = 0.41 (95% CI: −0.073 to 0.89; I^2 0%, P = 0.096)].

Considering that studies included in this review applied varied types of protocols, we conducted other sensitivity analyses. Four studies combined FES with supervised programs of exercise (i.e., physiotherapy). A sensitivity analysis showed that FES combined with physiotherapy could increase gait speed as compared with physiotherapy alone (n = 133) [SMD = 0.51 (95% CI: 0.16 to 0.86; I^2 0%, P = 0.0042)] (Fig. 3). Four studies combined FES with unsupervised home exercises (n = 355), and 3 studies used FES in regular activities at home (n = 589). A sensitivity analysis did not reveal a significant difference between groups [SMD = 0.02 (95% CI: −0.23 to 0.19; I^2 0%, P = 0.849) and SMD = −0.28 (95% CI: −1.53 to 0.96; I^2 95%, P = 0.653)] (Fig. 3).

3.6. Active ankle dorsiflexion mobility

Three studies (n = 151) assessed the effect of FES on active ankle dorsiflexion mobility of the paretic limb and were included in the meta-analysis [16,17,37]. These studies applied FES combined or not with supervised exercises. FES could improve active ankle dorsiflexion as compared with conventional treatment [MD = 3.30 (95% CI: 1.48 to 5.12; I^2 0%, P = 0.0007)] (Fig. 4A).

3.7. Balance and functional mobility

Five studies (n = 780) were included in this meta-analysis [17,18,20,30,35]. These studies applied FES combined or not with supervised exercises. FES could improve balance (evaluated by the BBS) as compared with conventional treatments [MD = 2.76 (95% CI: 0.64 to 4.88; I^2 90%, P = 0.011)]. However, the heterogeneity was high (Fig. 4B).

The same 5 studies (n = 780) evaluated functional mobility, assessed by the time to complete the TUG test, and were included in the meta-analysis [17,18,20,30,35]. FES induced functional mobility improvements as compared with conventional treatments [MD = −3.19 (95% CI: −5.76 to −0.62; I^2 84%, P = 0.015)]. However, the heterogeneity was high (Fig. 4C).

4. Discussion

This systematic review with meta-analysis aimed to determine the effectiveness of FES applied to the paretic peroneal nerve of post-stroke individuals with foot drop. We analyzed the effect of FES combined or not with other therapies on gait speed, active ankle dorsiflexion mobility, balance, and functional mobility. Regardless of the duration of electrical stimulation, FES could improve gait speed only if it was associated with supervised exercises (i.e., physiotherapy).

Some evidence indicates that FES can induce electrophysiological modifications over time (e.g., increase maximal voluntary contraction and motor-evoked potential), so FES could improve voluntary motor control [11,39]. However, changes in walking speed may be smaller than electrophysiological modifications because walking requires synchronized activities of several muscles [11]. When combined with physiotherapy, FES could improve gait speed, stability, and functional mobility [40,41].

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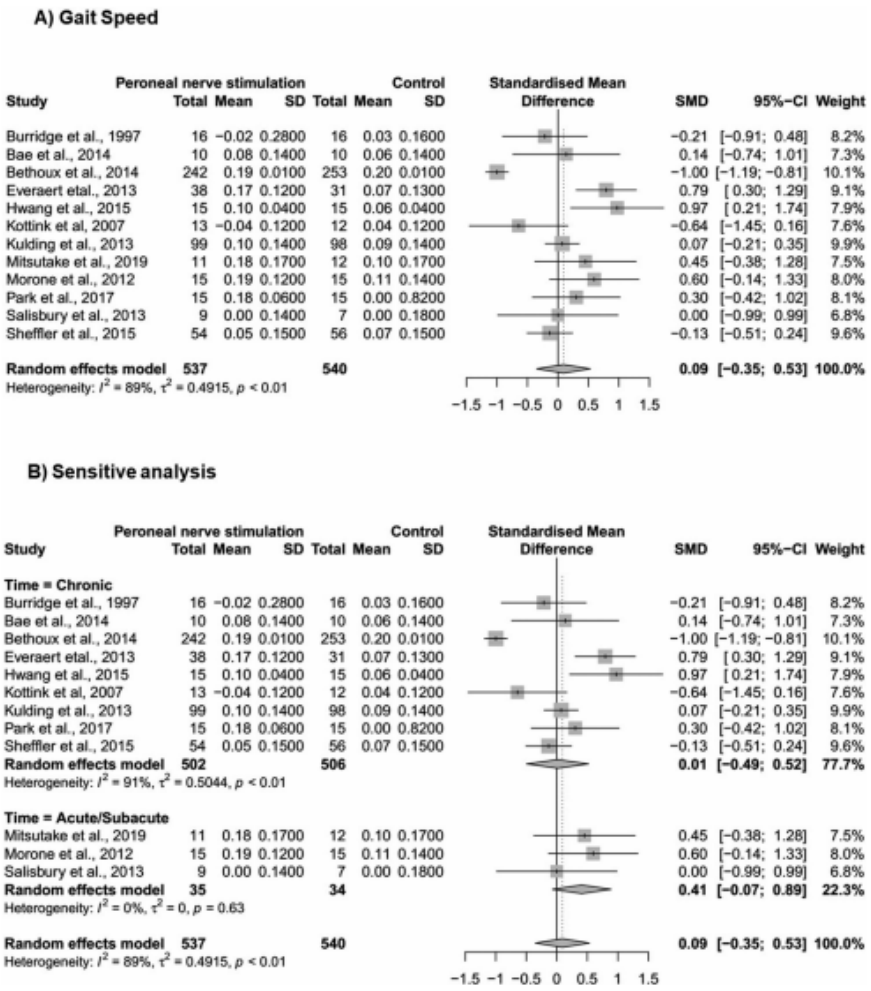

Fig. 2. Effect of functional electrical stimulation (FES) of the peroneal nerve on gait speed (A). Sensitivity analysis considering acute/subacute and chronic stroke (B).

A possible explanation for this result is the improvement in ankle dorsiflexion movement. Once the ankle mobility increases, the initial foot contact on the ground changes from anterior to posterior [42,43]. The improvement in foot clearance would ameliorate the forward progression and stability during locomotion and could also improve gait speed.

Gait speed is the leading indicator of function, level of disability, and survival and is used to classify ambulation status after stroke [44,45]. The literature reports minimal clinically significant changes for gait speed of 0.10 to 0.18 m/s [46,47]. Most studies that associated FES with physiotherapy reached a mean difference of 0.08 to 0.19 m/s. Studies that combined FES with unsupervised exercises and regular activities at home were ineffective in improving gait speed, and most reported minimal clinical changes < 0.10 m/s. Furthermore, the high heterogeneity of treatments may have influenced the results. Studies used an imprecise control of the volume of unsupervised exercises and regular activities at home, but supervised exercises (i.e., physiotherapy) included strategies to improve posture, gait, balance and functional mobility — outcomes assessed in this review.

Additional critical points are noteworthy when we analysed between-group differences in the studies. For instance, we need to consider the control groups. In 7 studies, FES was compared with AFO [16,22,29–32,34,35,37]. Two studies compared FES with treadmill gait training [17,18] and 2 compared it with conventional stimulation (TENS and NMES) [20,21,38]. Only 1 study compared

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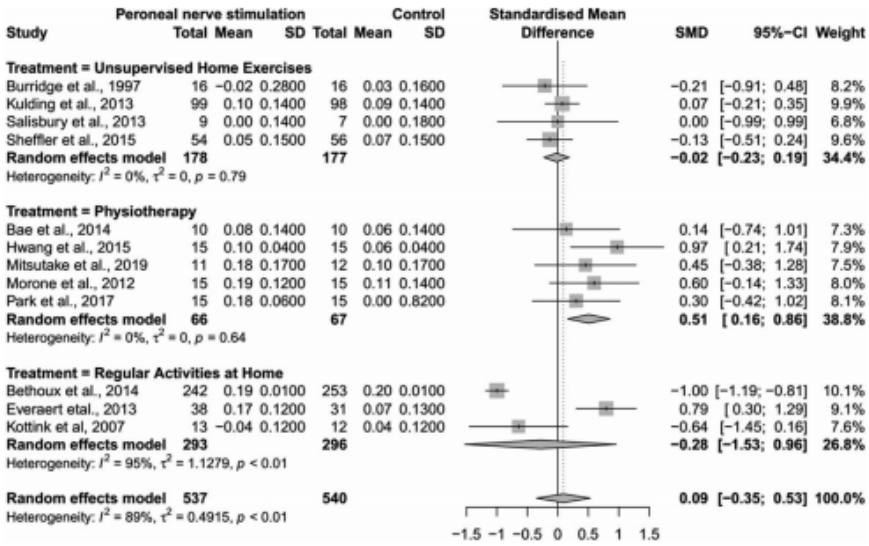

Fig. 3. Sensitivity analysis of protocols of treatment: unsupervised home exercises, physiotherapy, and regular activities at home.

FES with conventional physiotherapy [33]. Thus, differences in therapy delivered to the control group may have influenced the results of gait speed.

Post-stroke individuals usually present reduced or absent dorsiflexion during the heel strike and mid-swing phases of gait due to the loss of motor control [48]. Our results showed that FES improved the active ankle dorsiflexion angle during gait. Of note, 2 studies included in the meta-analysis compared FES with AFO [16,37]: 1 study used a custom-molded hinged AFO with plantar flexion blocker and was fabricated with conventional techniques [37] and the other study did not specify the type of device [16]. AFO is commonly used as standard care to promote mobility and independence [49]. This type of orthosis holds the ankle in neutral position, maintains the foot in the swing phase of gait and avoids the forefoot contact on the floor. AFO corrects the foot drop via a passive mechanism and does not involve neuromuscular, spinal or brain circuits [32,50]. For this reason, FES may be more effective than AFO in increasing active ankle dorsiflexion mobility.

Impaired balance and functional mobility are also common after stroke and may interfere in the performance of daily life activities [51,52]. FES had positive effects on balance, as evaluated by the BBS. The BBS is a good tool to assess static and dynamic aspects of balance and provides quantitative information about equilibrium and risk of falls [53]. Additionally, our meta-analysis showed that FES was more effective than conventional treatments in improving functional mobility. All studies included in this review assessed functional mobility by the TUG test. The TUG test is a complex task, comprising several elements, including gait performance, mobility, and balance. By repetitive muscle contractions, FES could increase sensory inputs to the brain and contribute to the motor relearning [11,13]. This reasoning could explain in part the improvements in balance and functional mobility. Additionally, improvements in ankle mobility and tibialis anterior activity would facilitate the ankle strategy necessary to keep the standing to sitting, turning and transferring movements, as assessed by the BBS. Another hypothesis is that FES ameliorates forward progression and stability during gait [42,43] and increases gait speed [13,19], and these improvements would also affect the time to complete the TUG test. Minimal clinically significant changes expected in the time to complete the TUG test range from 4 to 9 s [54]. Five studies were included in the meta-analysis for this outcome. Three studies reported a mean difference between pre- and post-treatment greater than 4 s [17,18,20]. However, the heterogeneity was high in BBS and TUG analyses (90% for BBS and 84% for TUG). Also, 3 studies included in the TUG analysis included gait training as part of the physiotherapy treatment [17,18,20]. Considering that part of the TUG performance depends on gait velocity, this type of task-specific training [19] may have skewed the results of functional mobility.

To the best of our knowledge, this is the first up-to-date and comprehensive systematic review with meta-analysis that assessed FES applied to the peroneal nerve and investigated its effect on gait performance, active ankle dorsiflexion mobility, balance and functional mobility. This study has some limitations. For example, the diversity in time since the stroke, motor impairment, protocols of treatment, and outcomes cannot be ignored. All these elements can increase the heterogeneity and decrease the validity of our results. Although we stipulated extensive and specific eligibility criteria, the GRADE showed a high risk of bias of the studies included in the review. The PEDro score was 5, reported as low-quality evidence. Most studies did not conduct intention-to-treat analyses, adequate follow-up or blinding. However, blinding participants and therapists is difficult because the electrical stimulus promotes visible ankle dorsiflexion. Another important limitation is the significant heterogeneity in gait speed, balance, and functional mobility meta-analyses. Possibly, the high heterogeneity is due to differences in protocols and sample characteristics. Furthermore, most studies did not present detailed information on the type of stroke and its severity.

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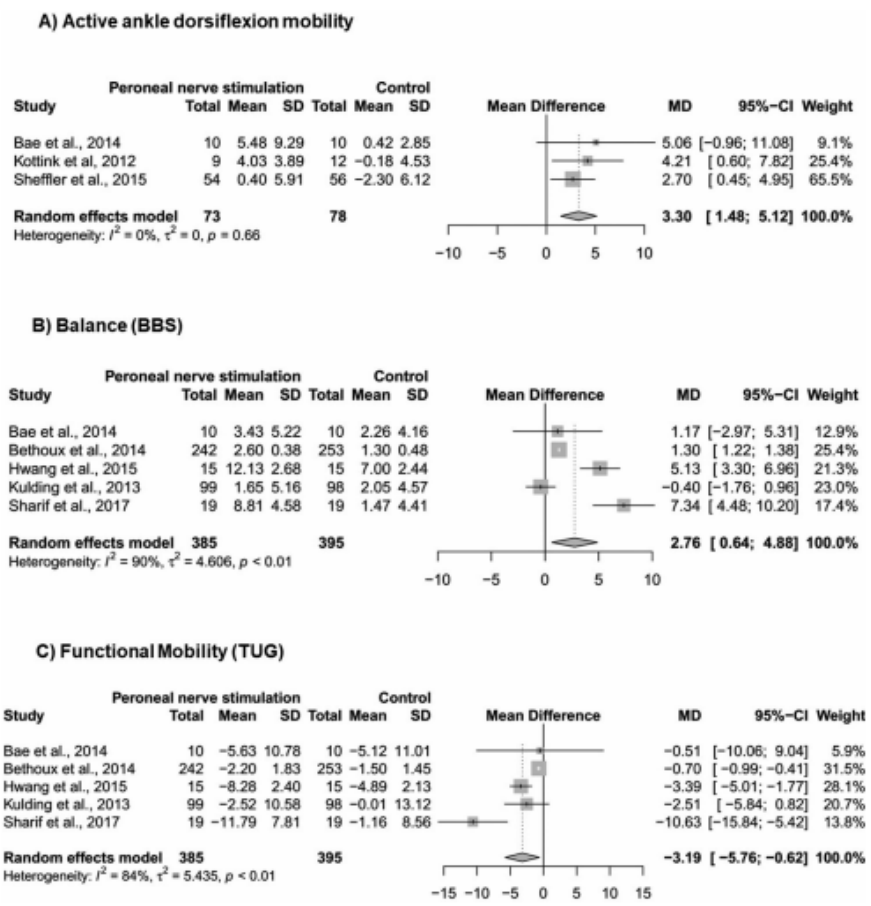

Fig. 4. Effect of FES of the peroneal nerve on active ankle dorsiflexion mobility (A), balance (B), and functional mobility (C).

5. Conclusions

Our meta-analysis showed positive effects of FES on the peroneal nerve to improve gait speed when combined with supervised exercises (i.e., physiotherapy). FES combined with unsupervised home exercises had no effect on gait speed. However, taking into account the high heterogeneity in our analysis, we could not determine the benefits of FES combined with regular activities at home for improving gait speed. Additionally, our findings showed a low quality of evidence for positive effects of FES on active ankle dorsiflexion mobility, with high heterogeneity for balance and functional mobility.

Future studies may emphasize gait training and other challenging activities during physiotherapy combined with FES in order to obtain better outcomes. Further research with adequate methodological quality is still necessary to determine the exact effects of FES on gait speed, ankle dorsiflexion mobility, balance, and functional mobility.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rehab.2020.03.012.

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5.2 Combining foot drop stimulation devices with gait training improves gait active ankle movement of chronic post-stroke individuals

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ORIGINAL RESEARCH ARTICLE

Combining Foot Drop Stimulation Devices with Gait Training Improves Gait, Active Ankle Movement of Chronic Poststroke Individuals

Maira Jaqueline da Cunha, PhD, Camila Pinto, MSc, Bruna Zanfir, PT, Veronica Cimolin, PhD, Aline Souza Pagnussat, PhD

ABSTRACT

Introduction: Foot drop stimulator (FDS) devices induce positive clinical effects on foot drop secondary to stroke. Literature does not establish a recommended period or a standard intensity of stimulation to achieve training and therapeutic effects in individuals after stroke.

The objective of this study was to evaluate the training and therapeutic effects of 2 weeks of FDS use combined with intensive treadmill gait training in chronic poststroke individuals.

Materials and Methods: The study design was a quasiexperimental clinical trial. Participants underwent gait training on a treadmill associated with FDS stimulation for 20 minutes, five times a week for 2 weeks. Gait analysis was measured at pre-training and 2 weeks after the training with FDS off/on mode.

Results: Sixteen chronic poststroke individuals were included. One participant was excluded from the analysis due to data processing fault. After the period of training, and with the orthosis on mode on, individuals ameliorated the active dorsiflexion and increased the distance covered, that is, positive training effect of FDS use. Training and therapeutic effects were not observed in other outcomes.

Conclusions: Our results demonstrated a positive training effect on ankle active movement during gait. FDS combined with gait training is able to increase the total distance walked after 2 weeks of treatment.

Clinical Relevance: FDS ameliorated the active dorsiflexion and increased the distance covered in people with chronic poststroke. Our results suggest a positive training effect of FDS that can guide physiotherapists in their clinical practice. (*J Prosthet Orthot.* 2022;34:213–222)

KEY INDEXING TERMS: stroke, stroke rehabilitation, lower extremity, electric stimulation, neurologic gait disorders

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Ankle dorsiflexion is a fundamental movement to promote toe clearance during locomotion. The efficient use of some muscles depends on ankle dorsiflexion, such as the hip and knee flexors during the swing phase of the gait for promoting lower-limb advancement.[1] Poststroke individuals often present a clinical condition referred to as "foot drop." This condition may be due to weakness of the tibialis anterior and/or spasticity of the ankle invertors/plantarflexors muscles.[1,2] During locomotion, the foot drop results in decreased ability to clear the paretic lower limb and causes the need to create compensatory motor strategies during the swing phase of gait.[3] These compensatory movements generate biomechanical adaptations that may result in inefficient ambulation, decreased gait speed, asymmetries, instability, increased risk of falls, and dependency in activities of daily living.[4–7]

Foot drop stimulator (FDS) devices have been used as an alternative to ankle-foot orthoses (AFOs) to treat foot drop after stroke.[8] FDS corrects the ankle movement using functional electrical stimulation (FES) applied on the peroneal nerve and synchronized with the swing phase of gait. This stimulus allows the foot to clear the ground and results in a safe initial loading response during the stance phase of gait.[9] FDS could stimulate voluntary muscle activity, reduce foot drop, decrease spasticity, and lead to long-term sensorimotor cortical reorganization in nonprogressive and progressive neurological disorders.[10,11] This

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stimulation allows for a more precise ankle dorsiflexion/eversion[9] and could facilitate hip and knee flexion—necessary for foot clearance during the swing phase of gait. These benefits would lead to a walking pattern closer to normality.[4,10]

Results of FDS use may be divided into three conditions: immediate, training, and therapeutic effects. The immediate orthotic effect occurs when initially wearing the device and improvement in gait biomechanics is due to the FES-induced ankle dorsiflexion.[12] The training effect occurs when FDS is used for a specific period, and the effects are evaluated while the individual is using the device.[13] On the other hand, the therapeutic effect may occur after long-term use of FES delivered using conventional equipment, surface, or implanted channels for peroneal stimulation. Therapeutic effects include neural plasticity,[10] increase of walking speed,[4,14] and joint range of motion (ROM).[15,16] These positive adaptations would be present even when the device is turned off.[13]

In clinical practice, some clinicians introduce the FDS with instructions of use, but without a period of physiotherapist-supervised exercises. Besides, the available literature does not establish even a recommended period or a standard intensity of stimulation to achieve training and therapeutic effects in individuals after stroke. Literature provides evidence that FDS associated with physiotherapy may result in clinically meaningful benefits, even for chronic poststroke individuals.[15,17] These findings are based on long training protocols (intensive and interval training) and show only the therapeutic effect of FDS. Recently, we reported positive therapeutic effects of FES on the peroneal nerve on gait speed and active dorsiflexion movement when it is associated with physiotherapy or gait training.[18] However, studies included in our review presented a high heterogeneity regarding the treatment protocols. The exercise intensity is a crucial parameter related to gait poststroke rehabilitation. However, to define the intensity of exercises is sometimes a challenge in clinical practice. Ideal rehabilitation involves repetitive and intensive training according to the tolerance of the patient.[19] Following this reasoning, we hypothesized that training and therapeutic effects of FDS would be enhanced if associated with short periods of intensive physiotherapy and gait training.

To evaluate gait abnormalities and the effects of FDS, it is essential to conduct a detailed gait analysis. Traditionally, gait is analyzed using discrete parameter statistics, which quantifies the entire cycle of gait and does not allow the examination of individual gait phases.[20] The statistical parametric mapping (SPM) analysis has been used in kinematic data as a complement to the discrete analysis. SPM continuously investigates kinematic data, taking into account the interdependence of the data points.[21,22] Therefore, SPM provides a better understanding of movement strategies throughout the task and reduces the risk of type I error.[21]

Literature has a lack of studies evaluating training and therapeutic effects achieved using FDS combined with intensive gait training in chronic poststroke individuals. For this reason, the main objective of this study was to explore the effects of 2 weeks of FDS use combined with physiotherapy on active ankle ROM, assessed during locomotion with the orthosis in on (training effect) and off mode (therapeutic effect), and quantified by means of discrete analysis and SPM. Secondarily, we evaluated changes on knee and hip ROM, spatiotemporal gait parameters, and total distance covered during the treadmill training.

MATERIALS AND METHODS

STUDY DESIGN

This quasiexperimental clinical trial was registered at ClinicalTrials.gov (NCT04077814, no primary study) and approved by the Ethics and Research Committee of the Santa Casa de Misericórdia de Porto Alegre Hospital (CAAE 64819617.0.0000.5335). Procedures were conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[23]

PARTICIPANTS

Volunteers were recruited through a database of the Santa Casa de Misericórdia Neurology Service in Porto Alegre, institutional sites, and social media. Those individuals who met the following criteria were included for convenience: We included individuals with diagnosis of cortical or subcortical unilateral cerebrovascular accident confirmed by imaging (tomography or magnetic resonance imaging) at least 6 months before recruitment; aged 20 to 80 years; foot drop as result of the stroke (reduction or absence of dorsiflexion and eversion movements of ankle and foot); with severe (0 to 19), moderate, or mild (≥29 points) motor compromise according to Fugl-Meyer Assessment of the lower limb (FMA-LL)[24,25]; minimum score of 20/30 points (illiterate) or >24/30 points (literates) in the Mini-Mental State Examination (MMSE)[26]; and ability to walk at least 10 m with or without assistive device. Participants were excluded if they presented any contraindication for electrical stimulation (electric or metallic implant; skin lesions appearing at or near the site of FDS stimulation; pregnant women) and ankle joint mobility restrictions (ankle contracture fixed to at least 10° of plantarflexion with the knee extended). Furthermore, we also excluded individuals with lower-limb musculoskeletal disorders that could interfere in gait, significant visual impairment, and low response to FDS electrical stimulation (no response to the highest stimulation intensity provided by the FDS device). All participants signed a free and informed consent form.

PROCEDURES

Procedures were conducted at the Movement Analysis and Rehabilitation Laboratory of the Federal University of Health Sciences of Porto Alegre (UFCSPA). The study was divided in a habituation (3 days) and intensive training period, as depicted in Figure 1. All clinical assessments were applied by the same researcher at pre-treatment (1 day after the habituation period) and post-treatment (1 day after the last session of the treatment period). Training effects were assessed with participants wearing the FDS on mode on. Therapeutic effects were evaluated with FDS on mode off.

INTERVENTION

The WalkAide (Innovative Neurotronics, Austin, TX, USA) was used to stimulate the peroneal nerve on the affected side. The orthosis stimulates the peroneal nerve through a tilt sensor,

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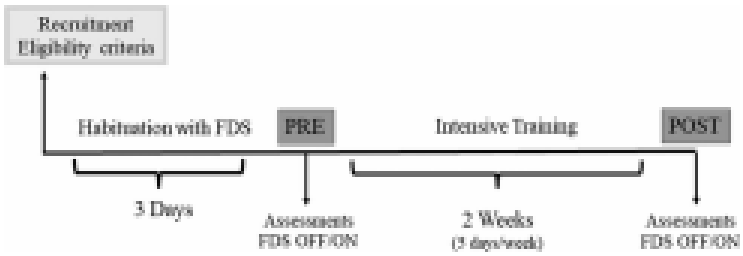

Figure 1. Timeline of study. FDS, foot drop stimulator; off/on mode of foot drop stimulator; pretraining assessment = 3 days after starting the study (1 day after habituation with foot drop stimulator); posttraining assessment = after 10 sessions of intensive training with FDS.

which detects the affected leg tilt when foot contact on the ground changes from posterior to anterior (preswing phase). Stimulus stops when the leg is tilted forward on foot strike.[12,27] FDS parameters were adjusted to each participant using the WalkAnalyst software. The intensity of stimulation was painlessly controlled by allowing sufficient dorsiflexion and eversion during the swing phase of the gait cycle.

First, volunteers underwent a 3-day habituation period using the FDS device for an hour a day. In this period, participants used the FDS in on mode and walked on a flat surface, went upstairs and downstairs, and finally walked on a treadmill. During the habituation period, the most appropriate intensity of the stimulus was adjusted for each participant. Then, 3 days after finishing the habituation period, participants underwent 10 sessions of gait training with FDS stimulation for 20 minutes, five times a week for 2 weeks (excluding weekends). Participants received gait training on a treadmill (Athletic advanced-720EE) with a self-selected comfortable velocity. During gait training, participants were allowed to hold the treadmill bars. They could stop walking at any time. However, the chronometer was not stopped.

At the beginning of each session, participants received a protocol of lower-limb stretching and passive ankle mobilization for approximately 15 minutes. Heart rate and blood pressure were periodically monitored. Treatment was conducted by the same licensed physiotherapist who had received training and competency assessment in the use of FDS. Total time of treatment sessions was approximately 50 minutes.

GAIT ANALYSIS

Gait was assessed using a 3D motion analysis system (BTS Bioengineering, Italy) composed of six infrared cameras. Twenty-two retroreflective spherical markers were placed on anatomic landmarks, as described by the Davis protocol.[28] Participants were asked to walk at a self-selected speed, barefoot, along an 8-m flat pathway. They were allowed to take a rest break after each trial. Gait evaluations were performed after the habituation period (pretreatment evaluation) and 1 day after finishing the 10 sessions of training (posttreatment evaluation). During gait analysis (off/on condition FDS or pretreatment and posttreatment), individuals were wearing the FDS device and were allowed to use assistive walk devices (e.g., cane) if needed. We recorded at least three trials in each condition FDS off/on, and we calculated the mean of them. The order of acquisitions was randomly defined to avoid bias related to the effect of the device use and fatigue. Raw data were processed using the SMART analyzer software (Version 1.10.458.0; BTS Bioengineering, Italy). Subsequently, data were imported into a custom-made MATLAB software tool to evaluate the joints angles of ankle, knee, and hip during stance and swing phases of gait in the sagittal plane.

PRIMARY OUTCOME

Primary outcome was active ankle ROM computed by the difference between maximum and minimum values in degrees of ankle plantarflexion/dorsiflexion (Ankle-PD) and quantified by means of discrete analysis and SPM.

SECONDARY OUTCOMES

Secondary outcomes included active ROM computed by the difference between the maximum and minimum values in degrees of knee flexion/extension (Knee-FE) and hip flexion/extension (Hip-FE); and spatiotemporal gait parameters were as follows: gait speed (m/s), cadence (steps/min), step length (m), and swing phase (% of cycle) and stance phase (% of cycle). Considering that some individuals stopped walking during the 20 minutes of training, we also recorded the distance covered during the FDS training sessions. We believed that this measure would represent an indirect estimation of walking endurance.

STATISTICAL ANALYSIS

Sample size was determined based on a previous study[29] using the G-Power 3.0 software. Adopting a power of 80% and α value of 0.05 to detect the minimum effect size of 0.70% in maximum ankle dorsiflexion, a sample size of 15 participants was estimated as necessary to this study.

Statistical analysis was conducted using the generalized estimating equation (GEE) to compare the effect of time (pre-treatment/post-treatment), condition (FDS off/on), and time × condition interaction. Bonferroni post hoc tests were used when appropriate. Data are presented as mean and confidence interval/standard deviation.

IBM SPSS Statistics software v.20.0 was used for analysis. The significance level was set at $P < 0.05$.

A customized MATLAB program (The MathWorks Inc, Natick, MA, USA) was used to conduct one-dimensional SPM analyses using the open-source *spm1d code* (version 0.4, http://www.spm1d.org) as described by Pataky (2014).[26,30] SPM1D uses the single inference method to calculate significance of temporal

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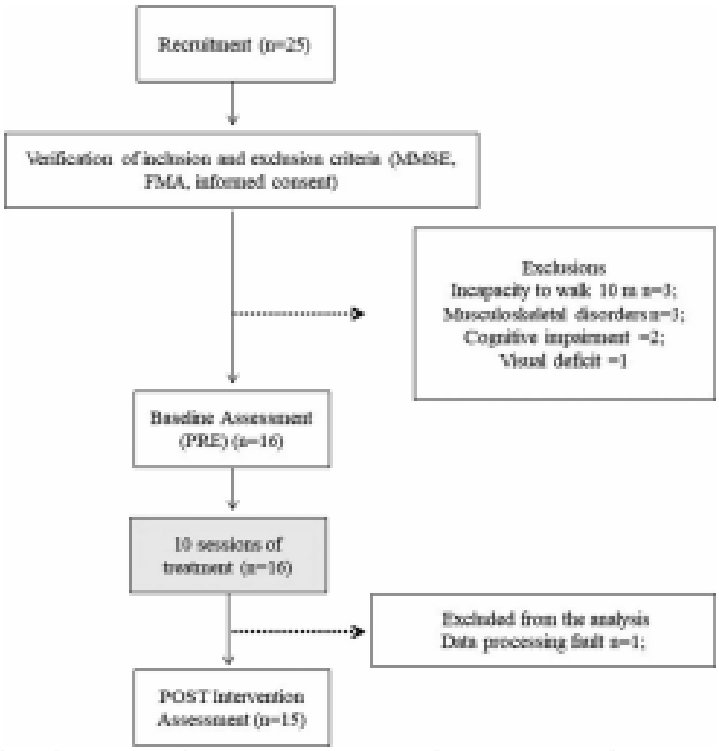

Figure 2. Flow diagram of the study. FMA-LL, Fugl-Meyer Assessment–Lower Limb; MMSE, Mini-Mental State Examination; FDS, foot drop stimulator; pretraining assessment = 3 days after starting the study; posttraining assessment = after 10 sessions of intensive training with FDS.

clusters, or regions of next values for which the statistic test exceeds the significance critical threshold (t critical), which are called as suprathreshold clusters. A two-sample *t*-test was used to compare the kinematic data of the ankle, knee, and hip ankle movement of the paretic leg during the gait cycle for each time-normalized phase between the FDS offon pretreatment and posttreatment ($\alpha = 0.05$).[20]

RESULTS

Twenty-five individuals with chronic hemiparesis after stroke were recruited. Nine participants failed to meet the eligibility criteria and were excluded: incapacity to walk 10 m (n = 3), musculoskeletal disorders (n = 3), cognitive impairment (n = 2), and significant visual deficit (n = 1). Thus, 16 participants were included. After data collection, one participant was excluded due to data processing fault. The flow diagram is shown in Figure 2. Demographic and clinical characteristics are depicted in Table 1.

Figure 3 shows the SPM analysis for active ankle ROM. SPM did not report significant differences when FDS on was compared with FDS off in pre-treatment. On the other hand, there was a significant increase in ankle dorsiflexion when FDS on was compared with FDS off in post-treatment. The critical threshold was exceeded among 0% to 20%, 20% to 25%, and 70% to

Table 1. Demographic characteristics

Sex, n (%)	
Male	11 (68.8)
Age, mean ± SD, yrs	58.25 ± 9.75
Height, m	1.68 ± 0.09
Body mass, kg	72.56 ± 12.57
Time since stroke, median (min-max), mo	36.50 (6–87)
Stroke type, n (%)	
Ischemic	13 (81.3)
Hemorrhagic	3 (18.7)
Affected hemisphere, n (%)	
Right	10 (62.5)
Left	6 (37.5)
AFO/orthopedic shoe user	2 (12.5)
Assistive device (cane)	2 (12.5)
FMA-LL (0–34), median (min-max)	19.88 (13–30)
MAS, frequency (0/1/1+/2/3/4)	
Plantiflexors	0/2/0/2/6/6
Knee extensors	3/4/3/1/3/2
Adductors	3/1/2/6/4/0

FMA-LL, Fugl-Meyer Assessment–Lower Limb; MAS, Modified Ashworth Scale; max, maximum; min, minimum; n, number of participants; SD, standard deviation.

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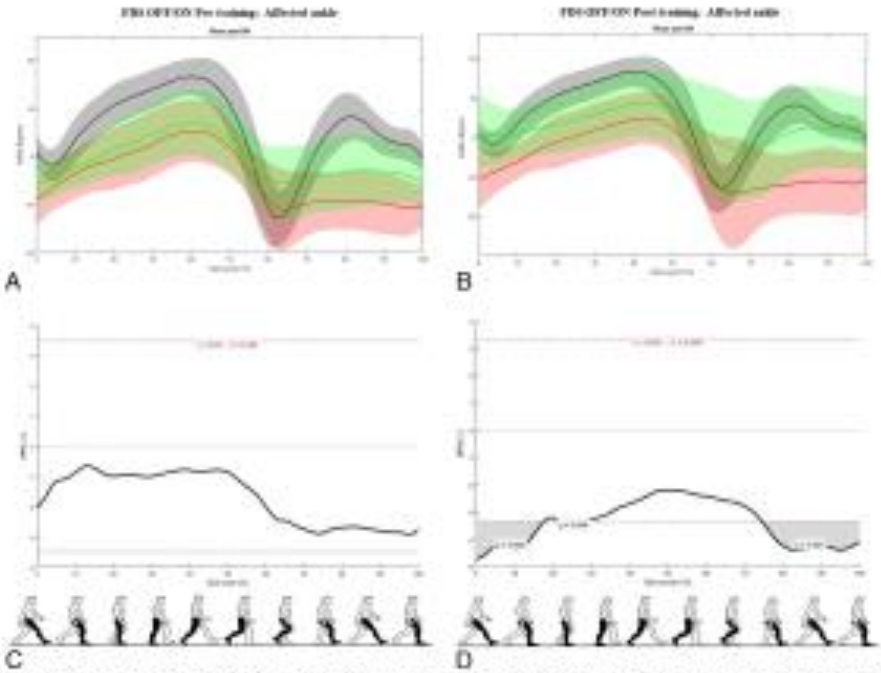

Figure 3. Statistical parametric mapping analysis of active ankle movement during the gait cycle. Upper graphs (A and B) show kinematic trajectories of the affected ankle angle in the sagittal plane. The black line represents the reference group; red line, the FDS in off mode; and the green line, the FDS in on mode. Solid lines represent mean, and the shaded bands represent ±SD. In (A) pretraining and (B) posttraining. The black bar on the lower graphs (C and D) represents the significant differences between FDS off and on occurrences, indicated by the SPM *t* statistic. Shaded gray areas indicate significant differences, FDS off to on condition. Dotted line indicates the significant threshold ($P < 0.05$).

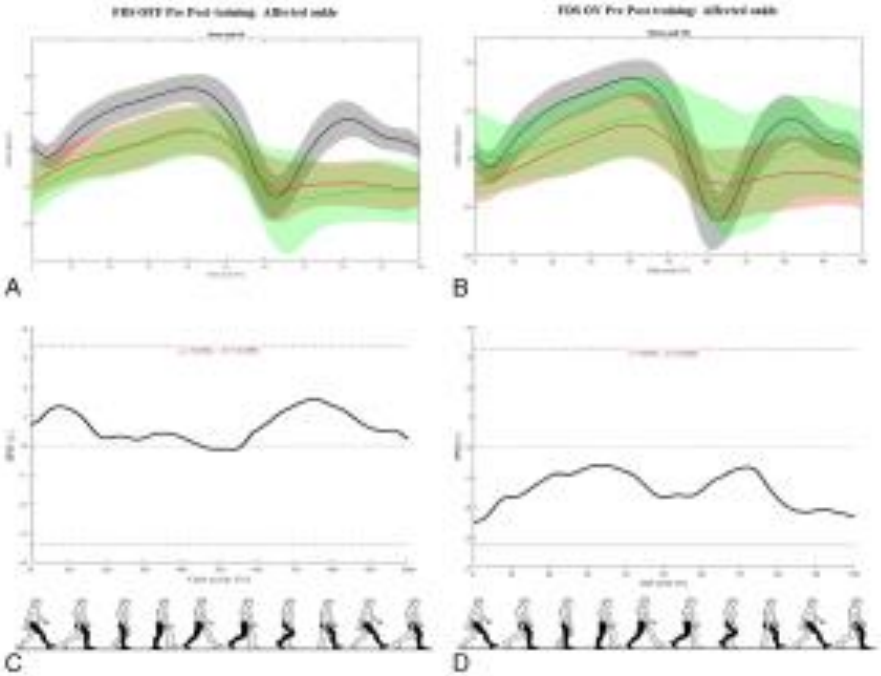

Figure 4. Statistical parametric mapping analysis of active ankle movement during the gait cycle. Upper graphs (A and B) show kinematic trajectories of the affected ankle angle in the sagittal plane. The black line represents the reference group; red line, the pretraining; and the green line, the posttraining. Solid lines represent mean, and the shaded bands represent ±SD; (A) off mode and (B) on mode. The black bar on the lower graphs represents the differences between pretraining and posttraining in off mode (C) and on mode (D).

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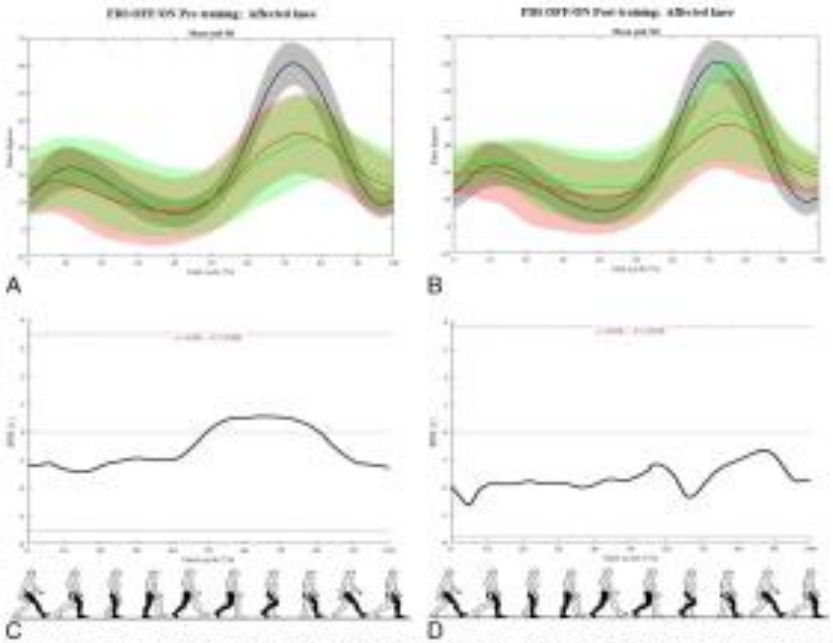

Figure 5. Upper graphs show kinematic trajectories of the affected knee angle in the sagittal plane. The black line represents the reference group; red line, the FDS in off mode; and the green lines, the FDS in on mode. Solid lines represent mean, and the shaded bands represent ±SD for knee joint. In (A) pretraining and (B) posttraining. The black bar on the below graphs represents the differences between FDS off and on.

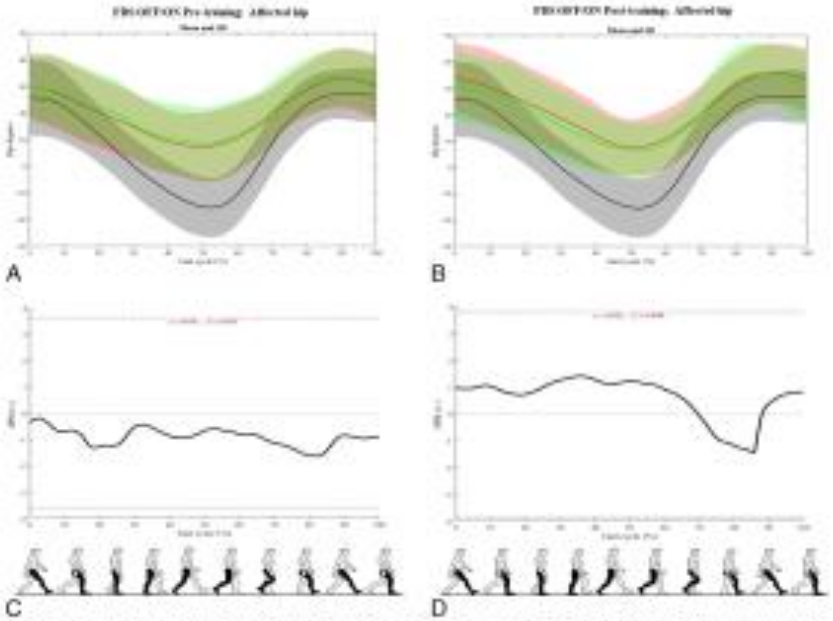

Figure 6. Upper graphs show kinematic trajectories of the affected hip angle in the sagittal plane. The black line represents the reference group; red line, the FDS in off mode; and the green lines, the FDS in on mode. Solid lines represent mean, and the shaded bands represent ±SD for hip joint. In (A) pretraining and (B) posttraining. The black bar on the below graphs represents the differences between FDS off and on.

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Table 2. Joint angles in sagittal plane of paretic limb

	Pre (n = 15)		Post (n = 15)		Time		Condition		Time × Condition Interaction	
	FDS Off	FDS On	FDS Off	FDS On	Wald χ^2	P	Wald χ^2	P	Wald χ^2	P
ROM										
Ankle-PF	18.5° (15.57°–22.2°)	16.3° (13.9°–19.12°)	21.5° (17.7°–26.2°)	17.5° (13.6°–21.86°)	1.93°	0.165°	8.98°	0.003°	1.96°	0.168°
Knee-FE	30.7° (25.15°–37.64°)	28.9° (23.03°–36.5°)	31.6° (24.63°–38.63°)	31.5° (24.9°–38.94°)	2.11°	0.146°	0.19°	0.663°	1.67°	0.206°
Hip-FE	30.1° (23.7°–38.31°)	31.01° (24.27°–39.62°)	31.5° (24.31°–40.0°)	34.3° (25.9°–45.62°)	0.81°	0.368°	3.36°	0.067°	1.47°	0.225°

Data are mean and 95% confidence intervals.
n, number of participants; Pre, pretraining after habituation with FDS; 3 days/Post, posttraining (after 10 sessions of intensive training with FDS); ROM, range of motion; FDS, foot drop stimulator; Ankle-PF, ankle plantarflexion/dorsiflexion; Knee-FE, knee flexion/extension; Hip-FE, hip flexion/extension.

Table 3. Spatiotemporal gait parameters

	Pre (n = 15)		Post (n = 15)		Time		Condition		Time × Condition Interaction	
	FDS Off	FDS On	FDS Off	FDS On	Wald χ^2	P	Wald χ^2	P	Wald χ^2	P
Gait speed, m/s	0.61 (0.49–0.75)	0.6 (0.48–0.73)	0.63 (0.52–0.76)	0.61 (0.5–0.73)	0.62	0.430	2.41	0.121	0.23	0.630
Cadence, steps/min	87.82 (60.02–95.62)	86.78 (79–94.58)	88.59 (80.79–96.39)	88.71 (80.91–96.51)	0.88	0.348	0.33	0.568	1.53	0.216
Affected step length, m	0.46 (0.41–0.51)	0.45 (0.41–0.5)	0.46 (0.41–0.51)	0.46 (0.42–0.51)	0.75	0.383	0.01	0.956	0.34	0.561
Unaffected step length, m	0.38 (0.31–0.46)	0.38 (0.31–0.46)	0.38 (0.31–0.46)	0.36 (0.3–0.44)	0.22	0.637	0.11	0.741	0.47	0.491
Affected stance phase, %	62.57 (61.34–65.88)	63.54 (60.95–66.24)	64.44 (61.82–67.16)	63.22 (61.2–65.31)	0.17	0.683	1.02	0.313	1.39	0.239
Unaffected stance phase, %	74.33 (71.41–77.37)	74.33 (71.72–77.03)	72.85 (69.72–76.13)	74.06 (71.57–76.63)	1.80	0.179	1.60	0.205	1.19	0.275
Affected swing phase, %	25.95 (23.7–28.35)	25.82 (23.1–28.76)	25.68 (23.29–28.29)	25.64 (23.67–28.71)	0.15	0.700	0.33	0.565	0.67	0.412
Unaffected swing phase, %	25.61 (22.35–28.71)	25.48 (22.77–28.51)	25.48 (22.77–28.51)	25.88 (23.51–28.49)	0.65	0.421	0.09	0.774	0.02	0.891

Note: Data are mean and 95% confidence intervals.
n, number of participants; Pre, pretraining (after habituation with FDS); 3 days/Post, posttraining (after 10 sessions of intensive training with FDS); FDS, foot drop stimulator.

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	n (16)		Paired Sample test		
	1st Day	10th Day	t	df	p-value
Distance (m)	555.62 ± 202.22	624.37±164.23	3.44	15	0.004

Note: Data are mean and SD=standard deviation, m=meters, 1st Day = First session of training 10th Day = Last session of training, * Significant values, -student test , p<0.05

Figure 7. Distance covering during the training. Data are presented as mean and SD.

100% of the gait cycle ($P = 0.005$, $P = 0.039$, and $P < 0.001$, respectively, Figure 2D). These phases corresponding to the initial contact, loading response, midstance, and mid/terminal swing phase of the gait. These differences evidence the effect of FDS training.

Figure 4 shows the SPM analysis to investigate the pre-treatment/post-treatment (with FDS on mode on) and therapeutic effects (with FDS on mode off). Although the visual analysis revealed an increase in ankle dorsiflexion when pre-treatment and post-treatment were compared with the FDS on mode on (training effect), no significant training or therapeutic effect was found.

Figure 5 and Figure 6 shows SPM analyses for knee and hip, respectively. SPM did not identify any differences comparing FDS on with FDS off in pre-treatment or post-treatment for both knee and hip joints. We also did not find differences regarding the therapeutic effects (FDS on mode off, graphics not shown).

Table 2 depicts discrete data analysis of ROM: ankle (plantarflexion/dorsiflexion), knee, and hip (extension/flexion). We found a significant main effect of FDS off/on condition in ankle plantarflexion/dorsiflexion movement ($P = 0.003$). Ankle ROM with FDS on mode off was higher compared with FDS on mode on, because in off mode, participants started the locomotion with ankle with increased plantarflexion. Regarding the ROM of knee and hip, the discrete analysis did not evidence any difference ($P > 0.05$).

Table 3 presents gait spatiotemporal parameters. No differences were found in gait speed, cadence, affected and unaffected step length, stance phase, and swing phase duration either between pretreatment and posttreatment or FDS off and on ($P > 0.05$). In these parameters, we also did not find differences when therapeutic effects were investigated ($P > 0.05$).

The distance covered during each gait training session is presented in Figure 7. At the end of treatment period, participants significantly increased the total distance covered ($P = 0.004$). This analysis was done with FDS on mode on and evidences a training effect of FDS use.

DISCUSSION

This experimental clinical trial aimed to determine the effects of 2 weeks of FDS use combined with physiotherapy and intensive gait treatment in chronic poststroke individuals with foot drop. Here, we analyzed gains on active ankle ROM assessed during locomotion with the orthosis in on (training effect) and off mode (therapeutic effect) and quantified by means of discrete analysis and SPM. We also evaluated changes on knee and hip ROM, spatiotemporal gait parameters, and distance covered during treadmill treatment. Our results showed that after the period of treatment, and with the orthosis on mode on, individuals ameliorated the active dorsiflexion and increased the distance covered, that is, positive training effect of FDS use. Training and therapeutic effects were not observed in other outcomes.

Poststroke individuals present reduced dorsiflexion during swing phases of gait that interferes on initial foot contact at the beginning of the stance phase. This condition may be due to poor motor control of ankle dorsiflexors,[30] reduced intermuscular coordination,[32] and/or increased spasticity of plantarflexors.[2,3,33] FDS stimulation could be able to increase sensory inputs to the brain, improve tibialis anterior muscle activity,[17] and decrease spasticity.[10,11] Our results demonstrated a positive training effect on ankle active movement during the initial contact, loading response, midstance, and mid/terminal swing phases of gait. Reducing the plantarflexion during initial contact and loading response allows for a more controlled impact deceleration, eccentric activity of pretibial muscles for shock absorption, and limb progression.[34] In addition, an improvement in ankle dorsiflexion during midstance and mid/terminal swing phases allows for foot clearance and preparation for the next initial contact. Improvements

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in ankle mobility would facilitate forward progression and stability,[8,20] and these improvements would also impact gait performance and may be related to the greater distance covered at the end of the treatment period.

Our discrete analysis showed that ankle ROM with FDS on mode on was significantly lower than that with FDS on mode off. Lower initial plantarflexion caused by the device explains this result, that is, reduction of foot drop condition at the beginning of the gait cycle.[29] For this reason, we consider the SPM analysis more precise to identify real differences between FDS off and on.

Our initial hypothesis that FDS could facilitate hip and knee flexion was not confirmed. Previous studies reported that FES on the peroneal nerve could assist hip and knee flexion during the swing phase of gait and lead to a walking pattern closer to the normality.[4,10] In addition, intensive gait training with FDS was unable to improve spatiotemporal gait parameters. A previous study reported that association between FDS and gait training could improve gait and balance.[17] Unlike our protocol, these authors applied a progressive increment of speed in gait training sessions of 30 minutes, once a day, for 4 weeks. Gait training was also combined with conventional physiotherapy to improve the function of affected limbs.[17] Decrease in speed and other gait parameters may result from weakness of other muscles, which are not stimulated by the FDS.[4] Thus, possibly better results in these outcomes could be reached if FDS training is combined with global trunk and lower-limb muscle strengthening.

In addition, we highlight that the participants had severe motor compromise with increased muscle tone, which may contribute to compensatory motor patterns[35] and reduced walking ability.[36] Although compensatory movements may be used as a strategy of movement, their use can induce maladaptive plasticity, thereby creating a movement pattern that may limit the functional recovery.[37] Previous studies suggest that the long-term use of FDS devices induces improvement on maladaptive motor patterns and increases speed and stability of gait, even when the stimulation is turned off (therapeutic effects).[9,10] However, intensive but shorter treatments may not be enough to induce therapeutic effects on spatiotemporal gait parameters. In this view, chronic poststroke individuals probably need longer intervention periods to exhibit substantial improvements on gait performance. Notwithstanding, we must mention that the short intensive treatment with FDS could be enough to achieve training effects in gait performance. These results highlight the importance of the adaptation period to achieve therapeutic effects with FDS.

This study has some limitations that need to be highlighted and may limit the generalizability of findings. We included only chronic poststroke individuals with important motor impairment. Furthermore, our gait training protocol was short and of low intensity, and these parameters might have some impact on our results. Other limitations are the study design and the lack of a control group. Future randomized clinical trials aiming to investigate other outcomes as balance, kinematic modifications and symmetry,[7] and outdoor locomotion must be conducted.

CONCLUSIONS

Our study showed positive effects of FDS training on active ankle dorsiflexion movement during the gait cycle. Although FDS combined with intensive gait treatment did not improve either knee and hip kinematics or spatiotemporal gait parameters, it was able to increase the total distance covered at the end of treatment. Future studies including chronic poststroke individuals with severe motor compromise may combine FDS and gait training with speed variation or other challenging activities to obtain better results.

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5.3 Bi-cephalic transcranial direct current stimulation does not add benefits to foot drop stimulator for improving functional mobility in chronic post-stroke: A double-blind randomized controlled trial

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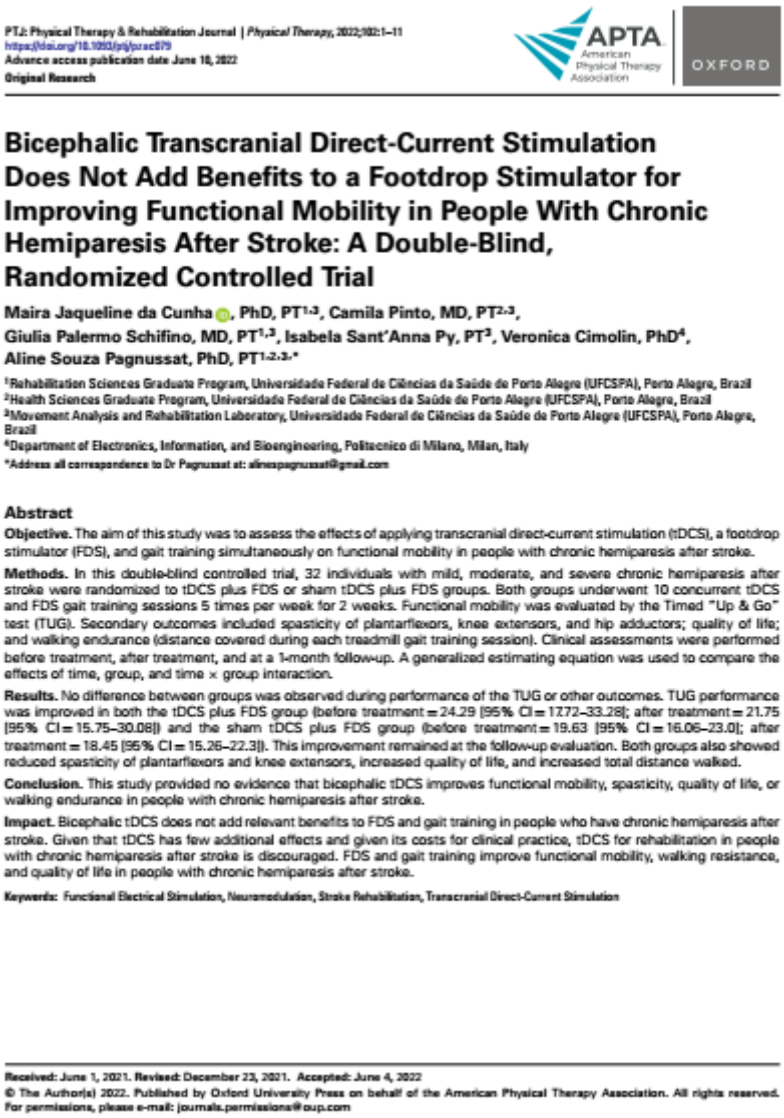

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Original Research

Bicephalic Transcranial Direct-Current Stimulation Does Not Add Benefits to a Footdrop Stimulator for Improving Functional Mobility in People With Chronic Hemiparesis After Stroke: A Double-Blind, Randomized Controlled Trial

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Abstract

Objective. The aim of this study was to assess the effects of applying transcranial direct-current stimulation (tDCS), a footdrop stimulator (FDS), and gait training simultaneously on functional mobility in people with chronic hemiparesis after stroke.

Methods. In this double-blind controlled trial, 32 individuals with mild, moderate, and severe chronic hemiparesis after stroke were randomized to tDCS plus FDS or sham tDCS plus FDS groups. Both groups underwent 10 concurrent tDCS and FDS gait training sessions 5 times per week for 2 weeks. Functional mobility was evaluated by the Timed "Up & Go" test (TUG). Secondary outcomes included spasticity of plantarflexors, knee extensors, and hip adductors; quality of life; and walking endurance (distance covered during each treadmill gait training session). Clinical assessments were performed before treatment, after treatment, and at a 1-month follow-up. A generalized estimating equation was used to compare the effects of time, group, and time × group interaction.

Results. No difference between groups was observed during performance of the TUG or other outcomes. TUG performance was improved in both the tDCS plus FDS group (before treatment = 24.29 [95% CI = 17.72–33.28]; after treatment = 21.75 [95% CI = 15.75–30.08]) and the sham tDCS plus FDS group (before treatment = 19.63 [95% CI = 16.06–23.0]; after treatment = 18.45 [95% CI = 15.26–22.3]). This improvement remained at the follow-up evaluation. Both groups also showed reduced spasticity of plantarflexors and knee extensors, increased quality of life, and increased total distance walked.

Conclusion. This study provided no evidence that bicephalic tDCS improves functional mobility, spasticity, quality of life, or walking endurance in people with chronic hemiparesis after stroke.

Impact. Bicephalic tDCS does not add relevant benefits to FDS and gait training in people who have chronic hemiparesis after stroke. Given that tDCS has few additional effects and given its costs for clinical practice, tDCS for rehabilitation in people with chronic hemiparesis after stroke is discouraged. FDS and gait training improve functional mobility, walking resistance, and quality of life in people with chronic hemiparesis after stroke.

Keywords: Functional Electrical Stimulation, Neuromodulation, Stroke Rehabilitation, Transcranial Direct-Current Stimulation

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Introduction

Stroke is the primary cause of long-term disability in adults.[1] Although the substrates underlying functional recovery after a stroke are not entirely understood, the asymmetry in interhemispheric inhibition may play an important role. In stable conditions, both hemispheres work equally by exerting mutual inhibitory control.[2] It has been proposed that the dynamics of inhibition change from one hemisphere to the other after a stroke.[3] These abnormal patterns of cortical control may imply cortical reorganization after stroke.[4] Although the neural changes concerning motor performance after stroke are not fully elucidated, the functional recovery would be tightly linked to the ipsilesional and contralesional hemispheres' motor system reorganization.[5]

More than 20% of people who have had a stroke cannot walk independently.[6] A common problem after a stroke is footdrop. This condition may result from the weakness or lack of voluntary control of the ankle dorsiflexors and/or increased spasticity of the tibialis posterior/plantarflexor muscles. Footdrop compromises ankle dorsiflexion and eversion movements during the swing phase of the gait. Footdrop also contributes to the disruption in weight acceptance and weight transference in the initial foot contact and stance phases.[7,8] Consequently, individuals who have had a stroke may have slower and less efficient walking,[9] a higher risk of falling, and reduced functional mobility.[10] All these impairments interfere with daily living activities and reduce the quality of life.[11]

Neurorehabilitation methods have been developed to treat unbalanced interhemispheric inhibition and footdrop. Transcranial direct-current stimulation (tDCS) has been used in research studies as a therapeutic alternative to restore motor performance in stroke survivors.[12,13] The weak direct current delivered by tDCS seems to normalize the excitatory and inhibitory corticospinal networks.[14] The way tDCS modulates cortical excitability is polarity specific, with several models for electrode application. Anodic tDCS increases the excitability on the affected motor area (M1) by decreasing the excitability threshold; this montage model is applied to the affected motor area. Cathodic tDCS decreases the excitability by increasing the threshold; the cathodic electrode is placed on the nonaffected area.[15] Bicephalic stimulation is applied by electrodes placed over the scalp when using anodic tDCS and cathodic tDCS simultaneously.[16] Previous studies have reported positive effects of tDCS on the mobility of individuals in the subacute stage after stroke[17–19] and on lower limb motor function in the chronic stage.[20,21] However, evidence of the positive effects of tDCS in individuals with chronic hemiparesis after stroke remains inconclusive.[22] Despite the benefits of tDCS, it has been proposed that combining rehabilitation approaches, such as tDCS and sensorimotor activities, could optimize neuronal plasticity and functional performance.[12,13]

Functional electrical stimulation of the peroneal nerve delivered by footdrop stimulator (FDS) devices can improve spasticity[23] and gait performance after a stroke.[24,25] FDS devices facilitate ankle dorsiflexion during the swing phase of gait. Once the device facilitates ankle mobility and tibialis anterior contraction, the center of pressure during the initial foot contact on the ground changes from anterior to posterior.[26] These improvements could ameliorate forward progression and stability during gait[26] and impact functional mobility.[24] The use of functional electrical stimulation has increased, and there is evidence of positive effects of functional electrical stimulation devices on walking speed and functional mobility when associated with physical therapy or gait training.[24]

Individuals with chronic hemiparesis after stroke usually achieve modest results under traditional methods of rehabilitation. Even when conducted for a short period—such as 5 consecutive days—the task-specific training can induce the remapping of the cortical function.[27] Thus, we hypothesized that combining central and peripheral stimulation could maximize rehabilitation gains in this condition. To the best of our knowledge, no study has combined concurrent tDCS with FDS and treadmill gait repetitive training in individuals with chronic hemiparesis after stroke. The main objective of this study, therefore, was to verify if this combination—applied simultaneously—could improve functional mobility. In addition, we investigated the effects of this protocol on lower limb spasticity, quality of life, and total distance walked after treatment.

Methods

Study Design

We conducted a double-blind randomized trial with concealed allocation and intention-to-treat analysis at the Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil, between September 2019 and March 2020. The study was approved by the Ethics and Research Committee of the Santa Casa de Misericórdia Hospital of Porto Alegre (CAAE 64819617.0.0000.5335) and conducted according to the 1964 Declaration of Helsinki principles. The data of this study were collected as part of a more extensive randomized clinical trial, and data are being published separately. This study was registered at clinicaltrials.gov (number identifier: NCT04077814) and followed CONSORT guidelines.[28] According to the Mini-Mental State Examination score (Tab. 1), all participants were presumed competent for decision-making, and, for this reason, written informed consent was obtained from all participants before the procedures started.

Participants

Participants were recruited through a database of the Santa Casa de Misericórdia neurology service in Porto Alegre, Brazil, institutional sites, and social media, and those who met the following criteria were included for convenience: age between 18 and 80 years; a diagnosis of cortical or subcortical unilateral cerebrovascular accident confirmed by imaging (tomography or magnetic resonance imaging) at least 6 months before recruitment; a history of a single stroke or more than 1 stroke in the same hemisphere; no history of seizures; footdrop as a result of the stroke (reduction in or absence of dorsiflexion and eversion movements of the ankle and foot), with severe (0–19 points), moderate (20–28 points), or mild (≥29 points) motor compromise according to the Fugl-Meyer Assessment of the lower limb[29,30]; a minimum score of 20 of 30 points (illiterate) or more than 24 of 30 points (literate) on the Mini-Mental State Examination[31]; and the ability to walk at least 10 m with or without assistive devices. Exclusion criteria were as follows: any contraindication to electrical stimulation (electric or metallic implant, skin problems or lesion close to the site of FDS stimulation, or being pregnant); an inadequate response to FDS electrical stimulation (no response to the highest stimulation intensity); irreversible ankle

Table 1. Demographic Characteristics[a]

Characteristic	tDCS + FDS Group (n = 16)	Sham tDCS + FDS Group (n = 16)	P
No. (%) men[b]	11 (68.7)	11 (68.7)	1.000
Age, mean (SD), y[c]	55.44 (8.47)	58.25 (9.75)	.391
Height, mean (SD), m[c]	1.71 (0.75)	1.68 (0.99)	.311
Body mass, mean (SD), kg[c]	77.69 (10.97)	72.56 (12.57)	.229
MMSE score, median (minimum–maximum)[d]	29 (27–30)	29 (21–30)	.146
Prior disease/risk factors[b]			
Hypertension	14 (87.5)	10 (62.5)	.096
Diabetes mellitus	4 (2.5)	2 (12.5)	.361
Smoking	7 (43.7)	8 (50)	.934
Stroke type[b]			
Ischemic	11 (68.7)	13 (81.2)	.412
Hemorrhagic	5 (31.2)	3 (18.7)	
Time since stroke, median (minimum–maximum), mo[d]	37 (6–96)	31 (6–87)	.474
Affected hemisphere[b]			
Right	9 (56.2)	10 (62.5)	.719
Left	7 (43.7)	6 (37.5)	
Lesion localization[b]			
Anterior cerebral artery	1 (6.2)	5 (31.2)	.158
Medial cerebral artery	8 (50)	5 (31.2)	
Internal capsule	7 (43.7)	6 (37.5)	
Motor impairment measured with FMA-LL, median (minimum–maximum)[d]	19 (11–32)	18 (13–30)	.910
Spasticity, no. of participants with MAS value of 0/1/1+/2/3/4[b]			
Plantarflexors	0/1/2/2/5/6	0/2/0/2/6/6	.524
Knee extensors	2/3/3/3/5/0	3/4/3/1/3/2	.458
Hip adductors	2/3/2/6/3/0	3/1/2/6/4/0	.846

[a]Data are reported as number (percentage) of participants unless otherwise indicated. FDS = footdrop stimulator; FMA-LL = Fugl-Meyer Assessment of the lower limb (scored from 0 to 34: 20–34 = mild/moderate motor compromise; <19 = severe motor compromise); MAS = Modified Ashworth Scale; MMSE = Mini-Mental State Examination; tDCS = transcranial direct-current stimulation. [b]Likelihood ratio χ^2 analysis. [c]Student *t* test. [d]Mann-Whitney *U* test.

restriction (ankle contracture at 10 degrees of plantarflexion in the hemiplegic leg with the knee extended); a lower limb musculoskeletal disorder that compromised locomotion; or significant visual impairment.

Procedures

This study was conducted at the Movement Analysis and Rehabilitation Laboratory at UFCSPA. Each participant underwent a clinical and documented evaluation session. The clinical assessments were applied by the same researcher at baseline (before intervention, after 3 days of habituation with FDS), after intervention (1 day after the last session), and follow-up (1 month after finishing the treatment), as depicted in the study time line (Fig. 1). The researcher (M.J.C) determined a person's eligibility. Another researcher (G.P.S.) conducted the Timed "Up & Go" Test (TUG) analyses and clinical evaluation (spasticity), and yet another researcher (I.S'A.P.) applied the quality-of-life questionnaire. Participants and researchers who conducted the evaluations were masked with regard to the treatment condition—real or sham tDCS.

Randomization

Participants were stratified according to the level of motor impairment (according to the Fugl-Meyer Assessment of the lower limb score) and randomized in block sizes of 4 individuals with a computer-generated random number of sequences by a tool available at https://www.random.org. Participants were allocated into 2 groups: tDCS plus FDS and sham tDCS plus FDS. An investigator (A.S.P.) who was not involved in the assessment, treatment, or statistical analysis conducted the randomization. On the first day of treatment, a second investigator (M.J.C) verified the participant's allocation and was responsible for applying the treatment to all participants. This researcher was not masked with regard to the treatment condition—real or sham tDCS.

Intervention

Participants underwent 10 concurrent tDCS and FDS gait training sessions 5 times per week for 2 weeks (excluding weekends). The therapy sessions lasted 30 minutes and were subdivided into 3 parts: the participants received tDCS (or placebo) while sitting in a comfortable position for the first 5 minutes. Then they performed 20 minutes of walking training on a treadmill while wearing the FDS device and receiving the tDCS/placebo stimulation (the combination of both treatments). They returned to the sitting position in the last 5 minutes and received only tDCS (or placebo).

During gait training, participants were allowed to hold the treadmill bars. They could stop walking at any time, but the stopwatch did not stop. Participants walked on the treadmill at a self-selected and comfortable velocity. The gait speed was set during the FDS habituation period, and the speed did not change over the gait training. Heart rate, blood pressure, and distance covered during the 20 minutes of walking were registered. Before each session, participants received lower limb stretching and passive ankle mobilization for approximately 15 minutes to normalize muscle tone and facilitate active ankle movements during gait training.

Transcranial Direct-Current Stimulation

Individuals allocated to the tDCS plus FDS group received a combination of bicephalic tDCS, FDS, and treadmill

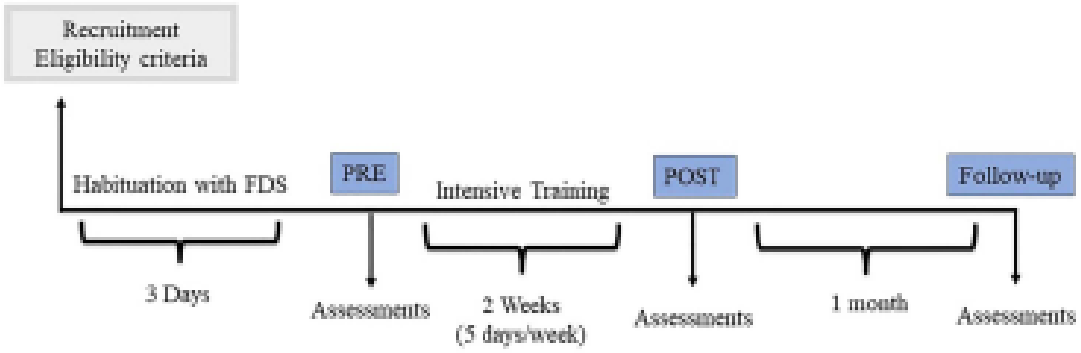

Figure 1. Time line of the study. Preintervention = 3 days after starting the study (1 day after habituation with the footdrop stimulator); postintervention = 1 day after the last session (10 sessions); follow-up = 1 month after finishing the treatment. FDS = footdrop stimulator.

gait training. Anode electrodes were positioned over the ipsilesional M1 area on the participant's scalp according to the electroencephalogram 10–20 system,[32] and cathode electrodes were placed over the contralesional M1 area.[21] Before positioning of the electrodes, the hair was separated to reveal the area to be stimulated; the skin was cleaned with saline to remove creams, dirt, or grease. tDCS was delivered by a TCT neurostimulator (Research Version; TransCranial Research Ltd, Hong Kong, China) via a pair of 5-cm saline-soaked sponge surface electrodes. The applied current was set to deliver 2 mA of bicephalic tDCS,[13,22] with a relative current density of 0.08 mA/m^2, for 30 minutes.[24] The sham tDCS modality was delivered using the same electrode montage as that used for real tDCS. However, the stimulation stopped after a ramp-up and ramp-down period of 30 seconds to provide an equivalent scalp sensation.[24] If the participant reported some discomfort, the treatment was suspended, and, if necessary, we referred the participant for a medical evaluation.

Footdrop Stimulator

A WalkAide orthosis (Innovative Neurotronics, Austin, TX, USA) stimulated the peroneal nerve on the affected side. This device stimulates the peroneal nerve through a tilt sensor that detects the affected leg tilt when foot contact on the ground changes from posterior to anterior (pressing phase). Stimulus stops when the leg is tilted forward on foot strike.[33] FDS parameters were adjusted according to each individual using WalkAnalyst Software (Innovative Neurotronics, Austin, TX, USA). The stimulation intensity was painlessly controlled by allowing sufficient dorsiflexion and eversion during the swing phase of the gait cycle. FDS adjustment was conducted by a licensed physical therapist who had received training and competency assessment in the use of the FDS device. Participants underwent a 3-day habituation period using the FDS device for 1 hR. In the habituation period, participants used the FDS device, walked on a flat surface, went up and down stairs, and finally walked on a treadmill. We set the best intensity of stimulation for each participant during this period. The intensity of FDS stimulation was enough to induce a comfortable ankle dorsiflexion/eversion movement. The frequency of electrical stimulation was set at 25 Hz, the pulse duration was set at 150 μs, and the intensity was set between 60 and 150 V.

Outcomes Measures

Instrumented TUG

Functional mobility was assessed using the instrumented TUG with an inertial sensor device (G-Walk; BTS Bioengineering, Milano, Italy). Individuals were instructed to walk as fast as possible, safely, without running and turning toward their paretic side.[26] Test latency and acceleration data were recorded using the inertial sensor attached to the participants' waists with a semielastic belt covering the L2 segment. Time to complete the TUG was subdivided into 5 phases: lift from the chair; walk 3 m (going phase); turn around; walk 3 m back to the chair (returning phase); and sit down.[17] Each participant performed this test 3 times, and an average of 3 trials was used in the analysis.

Modified Ashworth Scale

The modified Ashworth scale (MAS) was used to evaluate the resistance to passive movements. This measure corresponds to an indirect assessment of spasticity[38] and consists of 6 ordinal values ranging from 0 (no tonus increase) to 4 (stiffness).[39] Participants were evaluated lying in a supine position and were instructed to remain relaxed during the test. Spasticity of plantarflexors, knee extensors, and hip adductors was tested.

Stroke-Specific Quality of Life Scale

The validated version of the Stroke-Specific Quality of Life scale (SS-QOL) questionnaire was used to assess the quality of life.[40] The SS-QOL questionnaire consists of 49 questions bundled into 12 fields; each involves 3 to 10 items averaged to generate an overall score. SS-QOL scoring is rated on a 5-point Likert scale, with a minimum value of 1 (indicating the worst outcome) and a maximum value of 5 (indicating the best outcome). The interview questionnaire has psychometric characteristics, and answers are related to a reference point from the previous week.[41] SS-QOL scores range from 49 to 245, with higher scores indicating better function.[40,41]

Total Distance Walked

We recorded the distance covered during each 20 minutes of treadmill gait training. This measure would represent an indirect estimation of walking endurance.

Adherence and Safety

Adherence to the treatment was measured by the number of participants who finished the 2-week treatment course and completed all assessments. We assessed treatment safety by asking about possible undesirable effects during each stimulation session (tingling, burning, headache, sleepiness, muscle pain, and others).

Data Analysis

The sample size was determined using G-Power 3.0 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) on the basis of the mean time described as necessary to complete the TUG (20 seconds).[25] We estimated that 32 participants would be needed to detect a difference of 4 seconds[42,43] (20%) in the TUG, with an effect size of 0.5, 90% power, and an alpha value of .05.

Intention-to-treat analysis was applied to compare all outcomes. Shapiro-Wilk tests were used to evaluate the normality of the continuous variables. Parametric Student *t* tests, nonparametric Mann-Whitney *U* tests, and chi-square tests were used to compare demographic characteristics between groups. A generalized estimating equation[44,45] was used to compare the effect of time (before intervention, after intervention, and at follow-up), the effect of group (tDCS plus FDS and sham tDCS plus FDS), and the time × group interaction. Analyses were adjusted, adding time since stroke and motor impairment (mild/moderate and severe) covariates. Bonferroni post hoc tests were used to identify differences for time, groups, and the group × time interaction. The preintervention-postintervention delta variance (Δ) was analyzed for TUG time and SS-QOL and walking endurance, and it was calculated with the following formula: Δ = %(postintervention − preintervention)/preintervention. Correlations were tested using the Spearman correlation coefficient. We interpreted the strength of correlation as follows: 0.19 to 0.39 = weak; 0.40 to 0.69 = moderate; 0.7 to 0.89 = strong; and 0.9 to 1.0 = very strong.[46] Data are presented as mean and 95% CIs. We used Statistical Package for the Social Sciences (SPSS; IBM SPSS, Chicago, IL, USA) software v.20.0 for all analyses. The significance level was set at a *P* value of <.05. Effect sizes were calculated using G-Power 3.0 software and classified according to Cohen as small (0.2), moderate (0.5), and large (0.8).[47] Effect sizes greater than 0.4 were considered clinically relevant.[47]

Role of the Funding Source

The funders played no role in the design, conduct, or reporting of this study.

Results

Forty-four individuals with chronic hemiparesis after stroke were screened for eligibility between September 2019 and March 2020. Thirty-two individuals matched the inclusion criteria and were enrolled in the study and randomized into the tDCS plus FDS (n = 16) or sham tDCS plus FDS (n = 16) group. A flowchart depicts participant recruitment and the reasons for ineligibility and losses (Fig. 2).

The groups displayed similar baseline demographic and clinical characteristics, which are depicted in Table 1. In general, our sample presented severe motor compromise (Fugl-Meyer Assessment of the lower limb scores of 18 and 19 for the tDCS plus FDS and sham tDCS plus FDS groups, respectively). The mean (SD) age, time since stroke, and percentage of men for the tDCS plus FDS and sham tDCS plus FDS groups were 55.44 (8.47) and 58.25 (9.75) years, 37 and 31 months, and 68.7% and 68.7% men, respectively.

Timed "Up & Go" Test

Table 2 presents the effects of time, group, and group × time interactions for the TUG. According to the Mann-Whitney *U* test analysis, baseline TUG variables were similar for the tDCS plus FDS and sham tDCS plus FDS groups: the mean (SD) TUG times were 24.29 (16.13) and 21.75 (8.31) seconds ($U_2 = 121.0$; $P = .792$), respectively; the mean (SD) times for sit-to-stand were 1.6 (0.4) and 1.61 (0.41) seconds ($U_2 = 114.0$; $P = .597$), respectively; the mean (SD) times for stand-to-sit were 1.78 (0.53) and 1.9 (0.52) seconds ($U_2 = 125.5$; $P = .895$); the mean (SD) times for the going phase were 5.5 (5.27) and 4.7 (2.53) seconds ($U_2 = 115.5$; $P = .638$), respectively; and the mean (SD) times for the returning phase were 3.9 (3.91) and 3.97 (2.47) seconds ($U_2 = 102.0$; $P = .638$), respectively.

Statistical analysis evidenced a time effect for the total time to perform the TUG ($P < .001$), the going phase ($P = .035$), and the returning phase ($P = .027$). When postintervention and follow-up evaluations were compared with the baseline evaluation, both groups showed significant decreases in the total time and time spent to complete the going and returning phases. No effect of group or time × group interaction was observed for TUG variables.

Motor impairment was the only covariate that influenced TUG parameters (TUG total time and going and returning phases). Table 3 shows the interaction between time and motor impairment ($P < .001$). When postintervention and follow-up evaluations were compared with the baseline evaluation, individuals with mild/moderate impairment showed reductions in the time to perform the TUG; the same did not occur for individuals with severe motor impairment.

Modified Ashworth Scale

Table 4 presents the results for the MAS. We found a main effect of time for plantarflexors and knee extensors on MAS scores ($P < .05$). Both groups showed decreases in resistance to passive movements at follow-up compared with those before the intervention and after the intervention. No effect of group or time × group interaction was observed for the MAS.

Stroke-Specific Quality of Life Scale

The statistical analysis reported an effect of time for the SS-QOL ($P < .001$). Thus, both groups showed increased quality of life scores when postintervention and follow-up evaluations were compared with the baseline evaluation. Group did not affect the SS-QOL. We did not find an effect of group or time × group interaction for SS-QOL scores (Suppl. Tab. 1). SS-QOL domain analysis showed a time effect for language ($P = .04$), social roles ($P = .024$), and memory ($P = .027$). Scores of both groups increased when the postintervention evaluation was compared with the baseline evaluation. Statistical analysis also revealed an increase in the mobility domain for the tDCS plus FDS group ($P = .034$) when the postintervention and follow-up evaluations were compared with the baseline evaluation. The self-care ($P = .034$) domain score increased only in the follow-up evaluation. The covariates time since

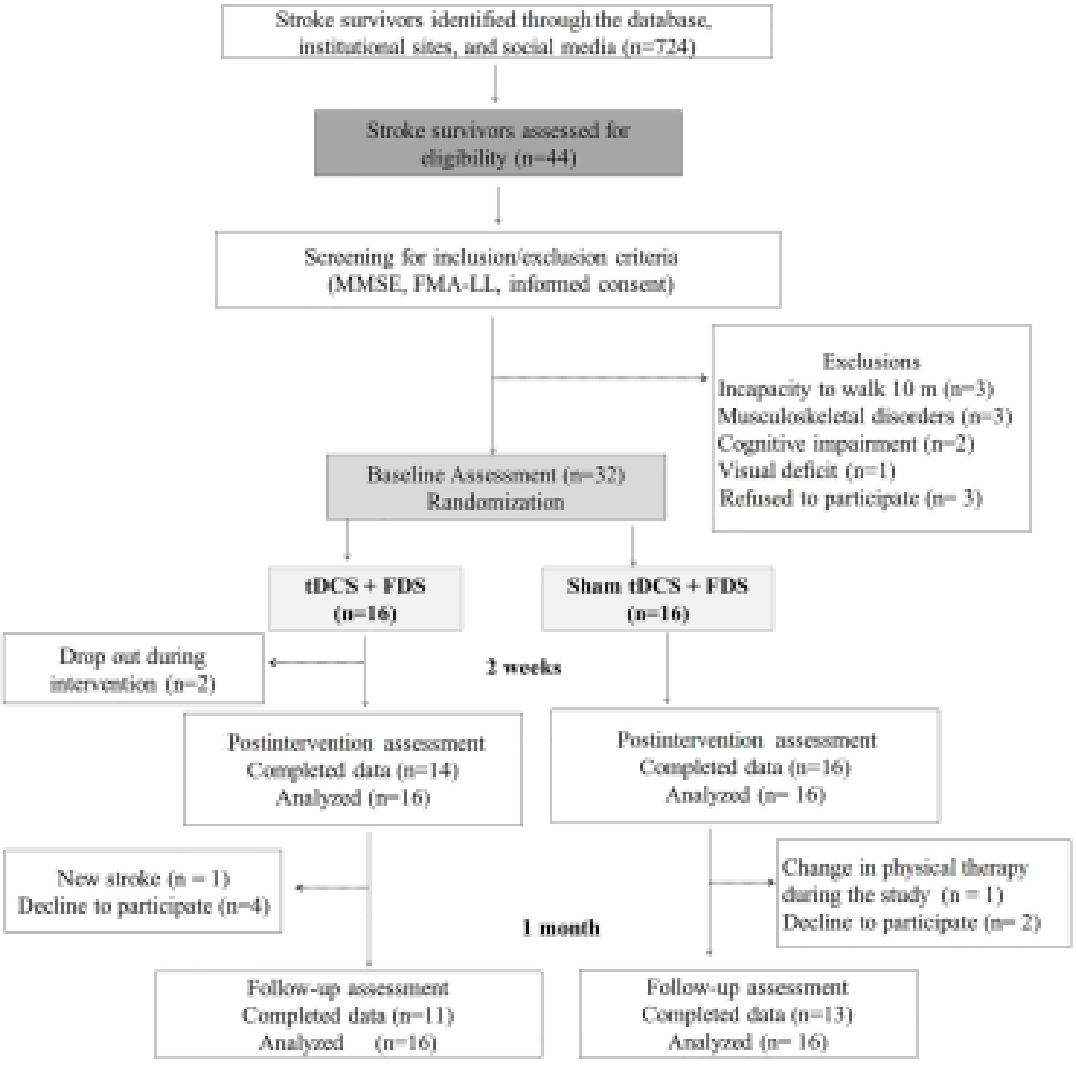

Figure 2. Flow diagram of the study. FDS = footdrop stimulator; FMA = Fugl-Meyer Assessment of the lower limb; MMSE = Mini-Mental State Examination; tDCS = transcranial direct-current stimulation.

stroke and motor impairment did not influence SS-QOL scores.

Total Distance Walked

The total distance covered during each gait training is presented in the Supplementary Figure. Statistical analysis evidenced a main effect of time ($P = .001$) but no effect of group or time × group interaction. Both groups showed increases in the total walking distance at the end of the treatment compared with the first training session. The mean improvement in walking distance was 76 m; this value, from a clinical standpoint, indicates a significant clinical improvement.[48,49] The covariates time since stroke and motor impairment did not influence this parameter.

Correlations

We found weak correlations between the total TUG time delta range and the SS-QOL ($rs = 0.451$; $P = .012$). No correlation was observed between the total TUG time delta range and walking distance.

Adherence and Safety

Treatment adherence was 93.75%, because 30 participants completed preintervention and postintervention assessments, and 24 participants (75%) completed the entire study (treatment and all evaluations). Twenty-five participants (78%) received all 10 stimulation sessions during the 2-week intervention period. Two participants from the tDCS plus FDS group discontinued the study after 1 week, and 6 participants

Table 2. Timed "Up & Go" Test (TUG) Results[a]

Parameter[b]	Mean (95% CI) for:		Time Effect			Group Effect		Time × Group Interaction	
	tDCS + FDS Group (n = 16)	Sham tDCS + FDS Group (n = 16)	Wald χ^2	*P*	Effect Size	Wald χ^2	*P*	Wald χ^2	*P*
TUG total time, s									
Preintervention	24.29 (17.72–33.28)[c]	19.63 (16.06–23.0)[c]	21.74	.0001		0.86	.352	1.19	.551
Postintervention	21.75 (15.75–30.08)	18.45 (15.26–22.3)			0.16[d]				
Follow-up	19.87 (14.06–28.09)	16.83 (12.76–2.17)			0.31[e]				
Time for sit-to-stand, s									
Preintervention	1.6 (1.44–1.78)	1.61 (1.45–1.82)	0.77	.680		0.02	.898	1.91	.384
Postintervention	1.48 (1.26–1.73)	1.57 (1.41–1.75)							
Follow-up	1.65 (1.42–1.93)	1.51 (1.34–1.69)							
Time for stand-to-sit, s									
Preintervention	1.78 (1.6–1.99)	1.9 (1.68–2.16)	0.49	.784		0.08	.772	0.49	.884
Postintervention	1.94 (1.67–2.24)	1.95 (1.74–2.18)							
Follow-up	1.87 (1.54–2.26)	1.89 (1.63–2.18)							
Going phase, s									
Preintervention	5.50 (3.5–8.67)[c]	4.7 (3.64–6.07)[c]	6.68	.035		0.27	.606	0.18	.914
Postintervention	4.56 (2.94–7.05)	4.13 (3.06–5.58)			0.21[d]				
Follow-up	4.67 (2.69–8.12)	3.97 (2.82–5.59)			0.21[e]				
Returning phase, s									
Preintervention	3.90 (2.44–6.23)[c]	3.97 (2.95–5.33)[c]	7.209	.027		0.157	.692	1.332	.514
Postintervention	3.08 (2.06–4.6)	3.75 (2.87–4.91)			0.17[d]				
Follow-up	3.06 (1.89–4.94)	3.36 (2.37–4.78)			0.25[e]				

[a]Values in bold type are significant. FDS = footdrop stimulator; tDCS = transcranial direct-current stimulation. [b]Preintervention = baseline; postintervention = after 10 sessions of treatment; follow-up = 1 month after treatment. [c]Significant values in Wald χ^2 test. [d]Effect size of difference between preintervention and postintervention. [e]Effect size of difference between preintervention and follow-up.

Table 3. Timed "Up & Go" Test (TUG) and Motor Impairment[a]

Parameter[b]	Mean (95% CI) for:		Time × Motor Impairment Interaction			Motor Impairment Effect		
	Group With Mild/Moderate Impairment (n = 16)	Group With Severe Impairment (n = 16)	Wald χ^2	*P*	Effect Size	Wald χ^2	*P*	Effect Size
TUG total time, s								
Preintervention	15.61 (13.62–17.88)[c]	27.56 (21.56–35.56)	30.83	.0001		25.65	.0001	1.32
Postintervention	13.25 (12.28–14.30)	25.90 (20.76–32.30)			0.66[d]			
Follow-up	12.27 (11.39–13.22)	25.26 (19.50–33.04)			0.67[e]			
Going phase, s								
Preintervention	3.10 (2.54–3.79)	6.88 (4.96–9.54)	5.24	.264		29.47	.0001	1.25
Postintervention	2.49 (2.10–2.95)	6.03 (4.52–8.06)						
Follow-up	2.37 (1.9–2.95)	6.57 (4.58–9.42)						
Returning phase, s								
Preintervention	2.43 (1.82–3.27)	5.26 (3.80–7.29)	4.38	.357		19.33	.0001	1.12
Postintervention	2.29 (1.86–2.82)	4.53 (3.45–5.94)						
Follow-up	2.01 (1.62–4.90)	4.66 (3.31–6.56)						

[a]Values in bold type are significant. FDS = footdrop stimulator; tDCS = transcranial direct-current stimulation. [b]Preintervention = baseline; postintervention = after 10 sessions of treatment; follow-up = 1 month after treatment. [c]Significant values in Wald χ^2 test. [d]Effect size of difference between preintervention and postintervention for group with mild/moderate impairment. [e]Effect size of difference between preintervention and follow-up for group with mild/moderate impairment.

missed at least 3 sessions. During treatment, there were no serious adverse effects. Five participants from the real tDCS group reported moderate tingling, which persisted for the first 1 minute of stimulation. Two participants from the sham group reported mild tingling, and 1 participant from the sham group reported mild headaches after the treatment session.

Discussion

This study aimed to investigate the effects of tDCS and FDS devices on functional mobility, spasticity, and quality of life of individuals with chronic hemiparesis after stroke. Additionally, we measured walking endurance during the gait training, adherence, and treatment safety. As a result, we did not confirm the preliminary hypothesis that central stimulation through bicephalic tDCS could benefit FDS and gait training.

Results showed that both groups improved functional mobility and decreased latency to complete the entire test, both the going and returning phases. Because the TUG performance depends, at least partly, on walking performance, gait training with FDS devices seems to improve gait velocity and functional mobility. However, these data must be carefully

Table 4. Spasticity[a]

Parameter[b]	Median (No. of Participants With MAS Value of 0/1/1+/2/3/4) for:		Time Effect		Group Effect		Time × Group Interaction	
	tDCS + FDS Group (n = 16)	Sham tDCS + FDS Group (n = 16)	Wald χ^2	*P*	Wald χ^2	*P*	Wald χ^2	*P*
MAS for plantarflexors								
Preintervention	3 (0/1/2/2/5/6)	3 (0/2/0/2/6/6)	6.75	.034	0.01	.904	0.11	.945
Postintervention	3 (1/1/1/1/7/3)	3 (0/2/2/5/4/5)						
Follow-up	3 (2/0/0/2/5/2)[c]	3 (1/2/1/0/6/3)[c]						
MAS for knee extensors								
Preintervention	2 (2/1/3/3/5/0)	1+ (3/4/3/1/3/2)	7.24	.027	0.10	.746	0.71	.699
Postintervention	2 (3/2/1/6/2/0)	1+ (3/3/3/3/4/0)						
Follow-up	1+ (2/3/2/3/0/1)[c]	1 (3/2/1/3/2/0)[c]						
MAS for hip adductors								
Preintervention	2 (2/1/2/6/3/0)	2 (3/1/2/6/4/0)	3.97	.137	0.18	.670	2.78	.249
Postintervention	1+ (2/1/5/4/2/0)	1+ (3/3/4/4/2/0)						
Follow-up	2 (1/2/2/5/3/0)	1+ (1/4/4/1/3/0)						

[a]FDS = footdrop stimulator; MAS = Modified Ashworth Scale; tDCS = transcranial direct-current stimulation. [b]Preintervention = baseline; postintervention = after 10 sessions of intensive treatment; follow-up = 1 month after treatment. [c]Follow-up difference between preintervention and postintervention.

interpreted because the minimal clinically relevant change for the TUG ranges from 4 to 9 seconds.[42] The results evidenced a difference of approximately 2 seconds, and the benefits attained seem small considering the effect size. This study also demonstrated that individuals with severe compromise are more resistant to improving functional mobility when compared with those with mild/moderate impairment. Of course, individuals with severe compromise have increased muscle tone and lower walking ability.[50] Thus, perhaps these individuals need more treatment time with FDS devices to modify TUG parameters.

tDCS was unable to add benefits to FDS and gait training in any assessed outcomes. The lack of surviving brain tissue in the chronic phase after stroke could explain this result. More surviving brain tissue and the increase of neurotrophic factors in the acute/subacute phase could allow better responses to tDCS.[51] Previous studies have reported that bicephalic stimulation can improve balance and functional mobility in the acute and subacute phases after stroke.[17,52]

Studies have reported the positive effects of tDCS on functional recovery of the upper limb in individuals with chronic hemiparesis after stroke.[34,53] However, there is no consensus about the positive effects of tDCS on inducing motor improvements and functional recovery in patients with chronic hemiparesis after stroke.[22,54] Meta-analysis demonstrated that tDCS might have beneficial effects on improving functional ambulation, walking independence, and the muscle strength of lower limbs in individuals who have had a stroke.[18,22] These positive findings are not consistent across all the included studies, possibly because of the heterogeneity of stimulation protocols. Furthermore, studies have not reported significant positive effects on walking speed, walking endurance, and balance function.[18,22] Our study contributes to the knowledge in this area because it supports the idea that bicephalic tDCS is not recommended as a primary treatment choice for individuals in the chronic phase after stroke.

Nevertheless, the lower limb representation has a more profound and vertical orientation than the upper limb area and, therefore, could be less responsive to tDCS.[55] Although the electrode montage over the M1 leg area is adequate for eliciting modulation in the lower limbs,[22] the low specificity of the bicephalic montage might have attenuated the current. Inhibitory or excitatory stimulation by surface electrodes occurs because of current flow from the anode to the cathode.[55] The role of polarity and current flow direction is crucial for developing tDCS approaches targeting the different cortical areas.[56] The distance between electrodes might influence cortical current flow through the target region.[57] Thus, we could suppose that when using a bicephalic electrode montage, the current would not penetrate deeply enough, would be attenuated, and would be less effective.[21] A previous study showed improvement of knee extensor force of the paretic limb after only unilateral tDCS stimulation (anode upon affected hemisphere).[58] Anodal tDCS stimulation on the motor cortex for the leg affected by the hemisphere containing a lesion can increase motor excitability during walking[59] and improve motor control of the hemiparetic ankle.[60,61] Comparisons of electrode positions are rare, and the underlying mechanisms are still unclear; further research with different electrode montages is needed to answer this question.

This study reported a mean change of approximately 18 points in SS-QOL total score after treatment. A minimal difference of 4.7 points in SS-QOL represents a clinically relevant improvement.[62] After treatment, the domains that changed were language, social roles, memory, and mobility. These findings could relate to the physical and mental benefits of exercise.[63] SS-QOL presents significant correlations with neurological function.[64] Thus, we suppose that improving functional mobility, spasticity, and walking resistance through FDS and gait training, could improve the quality of life of stroke survivors.[65]

Limitations

This study has some limitations that need to be highlighted. First, we did not control the specific cortical areas activated by tDCS and FDS devices through assessing neural excitability and interhemispheric interactions. Furthermore, the sample size calculation was conducted without considering the loss percentage. Even though more than 90% of the sample completed the 2 weeks of intervention, follow-up losses exceeded 20%, and we cannot specify how these losses might have impacted the interpretation of the long-term effects of treatment. Other factors might also be responsible for the lack of positive results using tDCS, such as the variability

of the sample regarding the stroke severity, site of lesion, and time after stroke. There is evidence that lesion location might have a crucial impact on the response to stimulation,[66] and this points toward a need for individual patient stratification to individually tailored stimulation protocols. We hypothesize that patient stratification in terms of the clinical deficit, lesion location, lesion size, and comorbidities could be crucial.

In terms of the dose of treatment, we set a short and repetitive treatment regimen considering that some studies report that training of low volume (duration) can result in satisfactory motor function rehabilitation[67] and induce the remapping of cortical functions.[27] Although the dose of locomotor training seems small, we found a mean improvement in functional mobility and walking distance, and bicephalic tDCS did not add any effect. Furthermore, the optimal number of tDCS sessions and the optimal duration of the session has not yet been well defined, with conflicting reports in the literature.

Conclusion

On the basis of the results of this study, there is no evidence for bicephalic tDCS to enhance FDS gait training in improving functional mobility, spasticity, quality of life, and walking endurance in individuals with chronic hemiparesis after stroke. We consider these findings to be relevant because they could inform a clinical decision to use bicephalic tDCS for this population.

Author Contributions

Concept/idea/research design: M.J. da Cunha, LS'A. Py, A.S. Pagnussat
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Ethics Approval

The study was approved by the Ethics and Research Committee of the Santa Casa de Misericórdia Hospital of Porto Alegre (CAAE 64819617.0.0000.5335).

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Clinical Trial Registration

This study was registered at clinicaltrials.gov (NCT04077814).

Disclosures

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5.4 Bi-cephalic brain stimulation has no additional effect on brain neuroplasticity biomarker and motor impairment in chronic post stroke: Double-blind randomized clinical trial

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Abstract

Background: Transcranial direct current stimulation (tDCS) and foot drop stimulator device (FDS) are widely used strategies in stroke rehabilitation, however, their combined effects on chronic post-stroke subjects are still unknown. Objective: To investigate the effects of the combination of tDCS and FDS on the brain-derived neurotrophic factor (BDNF) serum levels. A secondary aim was to evaluate the effects of this protocol on the insulin-like growth factor 1 (IGF-1), insulin growth factor–binding proteins -3 (IGFBP-3), IL-6, IL-10 and TNF-α levels and on motor impairment, functional mobility and social participation levels. *Material and Methods:* Thirty-two individuals with mild, moderate, and severe chronic hemiparesis after stroke were randomized to tDCS plus FDS or sham tDCS plus FDS groups. Both groups underwent ten sessions of gait training using FDS device - with real or sham tDCS five times a week, for two weeks. Blood and clinical evaluations were performed before and after intervention. *Results*: Both groups of treatment increased the BDNF and IL-10 levels, decreased Cortisol, IL-6 and TNF-α serum levels, and improved the motor impairment, functional mobility and social roles; after the training period. There was a weak correlation between the delta value of BDNF and motor impairment. *Conclusion:* tDCS does not induce additional effect to FDS gait training in improving motor plasticity in chronic post-stroke.

Keywords: transcranial direct current stimulation, stroke rehabilitation; lower extremity; electric stimulation, neurologic gait disorders, brain-derived neurotrophic factor, glucocorticoids, neuronal plasticity.

Introduction

Chronic post-stroke individuals frequently have gait impairments that interfere in functional mobility, cause of long-term disability and decrease the social participation [1]. These characteristics are associated with motor impairment in the lower limbs [2], and the individuals usually present foot drop, reduced motor control, muscle weakness, and increase in spasticity [3,4]. Recovery in motor function in chronic post-stroke can be modest with neurophysiological methods of rehabilitation and are often not the target of clinical research because they are more difficult to rehabilitate [5]. Hence it is needed to investigate new therapeutic strategies with technologies that may enhance the effectiveness of rehabilitation therapies in post-stroke patients at different recovery stage.

The functional electrical stimulation on peroneal nerve by foot drop stimulator device (FDS) has positive clinical effects on foot drop in chronic post-stroke 6. There is evidence of the positive effects of FDS for improving walking speed and functional mobility when it is associated with gait training [7]. In such a way, the transcranial direct current stimulation (tDCS) has been used as a therapeutic alternative that could help to restore motor performance in subjects with stroke [8,9]. Believed that tDCS stimulates the bi-hemispheric rebalancing, induces the plasticity, and contributes to motor improvement [10-12]. Previous studies reported that tDCS associated with peripheral sensorimotor activities in chronic post-stroke could optimize the motor recovery [8,13,14]. tDCS can hyperpolarize or depolarize the resting neural membrane potential and recruit intact ipsilesional regions [15] modulating the brain excitability [16]. The peripheral training increases afferent inputs to the cortex [9], and its combination with tDCS may has the potential to enhance functional performance and neuronal plasticity. Despite its increasing use in clinical, the studies assess mostly functional outcomes but the cellular and molecular mechanisms underlying tDCS remain unknown; however, believed that tDCS could increase neurotrophins, such as brain-derived neurotrophic factor (BDNF) secretion [17].

Neuroplasticity could be related to the ability of the nervous system to respond to stimulus and mainly recovery the motor function [18], and BDNF makes an important function in neuroplasticity post-stroke [19] and it is involved in the

learning process. It can be secreted in response to physical activity, and they be able to promote neural plasticity [20]. It is known that cortisol, a glucocorticoid secreted in stress situations, can suppress both the synthesis and the release of BDNF [21]. The cortisol level can be augmented in chronic post-stroke individuals due to factors such as functional and cognitive impairment and depression [22]. In some chronic neurological diseases, BDNF levels decrease while there is an increase of pro-inflammatory substances [23]. Besides, BDNF improvement the anti-inflammatory effect through the upregulation of expression of IL-10 and downregulation of TNF-α [24].

In this sense, neuroinflammation may have a central role in pathogenesis and functional recovery in post-stroke. Furthermore, there is a link between the recruitment of immune cells, the levels of proinflammatory mediators and the blood-brain barrier disruption that causes neuronal loss [25]. Indeed, tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) are proinflammatory cytokines involved in the acute phase of the systemic inflammation and its concentration remains high in chronic inflammatory conditions, such as stroke, contributing to the amplification of the size and severity of the lesion [25].

The BDNF serum levels are measured as a biomarker of motor functional recovery [26]. Since BDNF molecules can cross the blood-brain barrier, through bidirectional transport [27], the BDNF blood levels may be considered an indirect measure of neuroplasticity and may be associated with BDNF brain levels [28]. A previous study found lower serum BDNF levels associated with the worst motor function in chronic phase post-stroke [29]. Evidence in the literature reported that one session of bi-cephalic tDCS stimulation improves knee extension and flexion force in poststroke hemiparetic subjects [30] the authors believed that the increase in motor plasticity obtained by stimulating the affected motor hemisphere, enhance the interhemispheric balance.

Insulin-like growth factor 1 (IGF-1) also is a hormone with strong anabolic effects, such as increases in muscle mass, that have some neurotrophic properties associated with synaptogenesis in the central nervous system [31], and it even can cross the blood-brain barrier in the central nervous system in response to exercise and muscle hypertrophy [32]. The insulin growth factor–

binding proteins (IGFBPs) tightly control the activity of IGF-1 [32]. Besides, serum concentrations of IGF-1 and IGFBP-3 in post-stroke have been investigated due to their positive correlation with the physical performance [33], and negative association with muscle atrophy in chronic post-stroke [34].

Based on previous studies, FDS has positive effects for improving walking speed when it is associated with gait training. Thus, it hypothesized that the combination of central and peripheral stimulation could maximize the plasticity and gains in motor impairment in chronic post-stroke. Then, the main objective of this double-blinded controlled study was to investigate the effects of the combination of tDCS and FDS on BDNF serum levels. Additionally, this study aimed to evaluate the effects of this protocol on the IGF-1, IGFBP-3, IL-6, IL-10 and TNF-α levels and on motor impairment, functional mobility and social participation levels.

Material and Methods

Study Design

Double-blinded randomized trial with concealed allocation and intention-to-treat analysis was conducted at the Universidade Federal de Ciencias da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil. The study was approved by the Ethics and Research Committee of the Santa Casa de Misericórdia Hospital of Porto Alegre (CAAE 64819617.0.0000.5335) and conduced according to the principles of the 1964 Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (number identifier: NCT04077814) and conducted according to the CONSORT guidelines for randomized clinical trials[35]. All participants signed the informed consent after an explanation about the objectives and possible complications of the study. According to the Mini-Mental State Examination (MMSE) score, all participants were presumed competent for decision-making and, for this reason, signed the informed consent (Table 1).

Participants

Participants were recruited through a database of the Santa Casa de Misericórdia Neurology service in Porto Alegre, institutional sites and social media, and selected according to eligibility criteria. Inclusion criteria were: Age between 18 and 80 years; with ischemic or hemorrhagic stroke confirmed by imaging (tomography or magnetic resonance imaging) at least six months before recruitment; history of a single or more than one stroke as long as in the same hemisphere; no history of seizures; with severe, moderate or mild motor impairment - according to Fugl-Meyer Assessment of the lower limb (FMA-LL) [36,37]; minimal cognitive ability on MMSE [minimum score of 20/30 points (illiterates) or > 24/30 points (literates)] [38]; furthermore, participants had to able to walk at least 10 meters with or without assistive devices. Exclusion criteria were: contraindication for electrical stimulation (electric or metallic implant, skin problems or lesion close to the site of FDS stimulation, pregnant); low response to FDS electrical stimulation (no response to the highest stimulation intensity); fixed ankle contracture at 10 degrees of plantar flexion in the hemiplegic leg with the knee extended; lower limb musculoskeletal disorder that compromised locomotion; significant visual impairment.

Procedures

This study was conducted at the Movement Analysis and Rehabilitation Laboratory of the Federal University of Health Sciences of Porto Alegre (UFCSPA). Each participant performed a clinical and documented evaluation session. All clinical assessments were applied by the same researcher at baseline (pre-intervention - after three day of habituation with FDS) and post-intervention (one day after the last session).

Indirect assessment of spasticity done of Modified Ashworth Scale (MAS) [39] that consists of 6 ordinal values ranging from 0 (no tonus increase) to 4 (stiffness) [39]. Participants were evaluated lying in a supine position and were instructed to remain relaxed during the test. Spasticity of plantar flexors, knee extensors, and hip adductors was tested. The sleep disturbances may interfere with BDNF signaling and cortisol levels, for this reason all the participants underwent the evaluation of the quality of sleep through the Pittsburgh Sleep

Quality Index (PSQI). PSQI differentiates “poor” from “good” sleep by measuring seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month [40]. The subjects self-rates each of these seven areas of sleep. Scoring of the answers is based on a 0 to 3 scale, whereby 3 reflects the negative extreme on the Likert Scale. A global sum of “5” or greater indicates a “poor” sleep [40].

Randomization

Participants were stratified according to the level of motor impairment (according to the FMA-LL score) and randomized in block sizes of four individuals by an investigator who was not involved in the assessments, recruitment or data analysis. By means of the tool available at https://www.random.org, volunteers were allocated into two groups: tDCS plus FDS or Sham tDCS plus FDS.

Intervention

Participants underwent ten sessions of concurrent tDCS and gait training with FDS stimulation, five times a week for two weeks (excluding weekends).

The therapy sessions lasted thirty minutes and consisted of three steps: at the beginning, participants received tDCS (or placebo) for five minutes when sitting in a comfortable position and, then, they performed twenty minutes of gait training on a treadmill (Athletic advanced-720EE- Brazil) at a self-selected comfortable speed, wearing the FDS device, and receiving the tDCS/placebo stimulation (the combination of both treatments). In the last five minutes, they returned to the sitting position and received only the tDCS. Gait speed was set during the FDS habituation period. The speed did not change over the gait training. During gait training, participants were allowed to hold the treadmill bars. They could stop walking at any time, but the stopwatch did not stop. Heart rate, blood pressure, and distance covered during the 20 minutes of walking were

registered. Before each session, volunteers received lower limb stretching and passive ankle mobilization for approximately 15 min - to normalize the muscle tone and facilitate ankle active movements during the gait training.

Transcranial direct current stimulation

Individuals allocated to the tDCS plus FDS group received bi-cephalic tDCS and treadmill gait training with FDS at the same time. tDCS was delivered by a TCT neurostimulator (Research Version) developed by TransCranial Research Ltd. (Hong Kong, China) via a pair of 5- 5 cm saline-soaked sponge surface electrodes [41.] Anode electrodes placed on the participant's scalp over the ipsilesional M1 are and cathodes over the contralesional M1[30], according to the electroencephalogram 10–20 system [42]. Before positioning the electrodes, the hair was separated to reveal the area to be stimulated; the skin was cleaned with saline to remove creams, dirt, or grease. The applied current was set to deliver 2 mA bi-cephalic tDCS [9,43], with a relative current density of 0.08 mA/m2, for 30 min [44]. The ShamtDCS modality involved the same electrode montage used for active tDCS. The stimulation stopped after a ramp-up and ramp-down period of 30 s each to provide an equivalent scalp sensation [44].

Foot Drop stimulator

The WalkAide orthosis (Innovative Neurotronics, Austin, TX, USA) was used to stimulate the peroneal nerve on the affected side. This device stimulates the peroneal nerve through a tilt sensor that detects the affected leg tilt when foot contact on the ground changes from posterior to anterior (pre-swing phase). Stimulus stops when the leg was tilted forward on foot strike [45,46]. FDS parameters were adjusted according to each participant using the WalkAnalyst Software. Device adjustments was conducted by a licensed physical therapist who had received training and competency assessment in the use of FDS. The FDS device was set at enough intensity to induce a comfortable ankle dorsiflexion/eversion movement during the swing phase of the gait cycle. The frequency of electrical stimulation was set at 25 Hz, the pulse duration at 150 µs,

and the intensity between 60 and 150 V. Participants underwent a three-days habituation period using FDS device for one hour a day. In the habituation period, volunteers used the FDS device and walked overground on a flat surface, went up and downstairs and finally walked on a treadmill.

Outcomes

Blood measure

Blood samples (approximately 5 mL) were collected from antecubital vein into tubes without anticoagulant, between 7:00 a.m. and 9:00 a.m., at baseline (Pre) and 24-h after the last session (Post). Blood samples from the control group were processed likewise. Tubes were centrifuged at 1048 g for 10 min. Serum samples were then divided into several aliquots and stored at –20◦C for further analysis. Serum BDNF levels was set as primary outcomes. Serum BDNF levels were determined using the enzyme-linked immunosorbent assay (ELISA) method, using the specific kit (Promega, EUA). Serum cortisol levels were measured by Enzyme Immunoassay (EIA) as per the manufacturer's instructions (Accubind, EUA). All samples were measured in duplicate by microplate reader SpectraMax M2e (Molecular Devices, EUA). Intra-assay coefficients of variation were always <5.0%, 3.8% for BDNF and cortisol, respectively. The detection limits of the BDNF and cortisol assays are 7.8 – 500.0 pg/mL and 0.366 – 50.0 g/dL, respectively.

Serum IGF-1 (Human IGF-1 ELISA Kit PicoKine) and IGFBP-3 (Human IGFBP-3 ELISA Kit PicoKine) were determined by ELISA according to the manufacturer's recommendation using a microplate spectrophotometer adjusted to 450 nm (Molecular Devices, EUA). The detection limits of the IGF-1 and IGFBP-3 assays are: 156 – 10.000 pg/mL with sensitivity of 50 pg/mL; and 156.2 – 16.000 pg/mL with sensitivity of 10 pg/mL, respectively.

The plasma concentrations of IL-6, IL-10 and TNF-α (all from eBioscience, EUA), were quantified by ELISA in microplate reader (EzReader, EUA). The detection limits of each cytokine were TNF-α, 4-500 pg/mL, IL-6, 2-200 pg/mL; IL-10, 2-300 pg/mL.

Clinical measures

Lower limb motor impairment

Fugl-Meyer Assessment (FMA) [36] was used to assess motor impairment of the lower limb (LL). This scale measures voluntary movement, velocity, coordination, and reflex activity. Each item has three possible scores, 0 (cannot be performed), 1 (partially performed) and 2 (performed entirely). The maximum score for the LL is 34 points. According to the FMA-LL score, the participants were classified to their motor impairment: severe (0 to 19), moderate (20-28) or mild (≥29 points) [37].

Timed Up and Go (TUG)

Functional mobility was assessed by means time to complete the TUG test. Individuals were instructed to walk as fast as they could, in a safe way, without running and turn towards their paretic side [47]. Each participant performed this test three times and the average of three trials was used in the analysis.

Social participation levels.

The Stroke Specific Quality of life Scale (SSQOL) questionnaire contains 12 subscales [48], that included: Mobility, energy, upper extremity function, social roles, work/productivity, mood, self-care, family roles, vision language, thinking and personality. SS-QOL scoring is rated on a 5-point Likert scale, with a minimum value of 1 (meaning the worst outcome) and a maximum value of 5 (meaning the best outcome) [48,49]. As a result, only the subscales related to social participation: social roles (defined by patients as relationships with friends and activities outside the home) and work/productivity (defined by patients as necessary tasks done within or outside the home) were reported.

Statistical Analysis

The sample size was determined by G-Power 3.0 software based on previous study [50], considered an effect size of 0.5, adopting the power of 90% and an alpha value of 0.05 to detect the minimum difference of 25% in BDNF levels. A final sample size of 32 participants was estimated as necessary for this study.

Intent-to-treat analysis was applied to compare the outcomes. Shapiro-Wilk tests were used to evaluate the normally of the continuous variables. Parametric Student t-tests, nonparametric Mann -Whitney, and Chi-square tests were used to compare demographics characteristics between groups. To statistical analysis used the Generalized Estimation Equation (GEE), to compare: Effect time (Pre and Post) and effect of group (tDCS plus FDS and Sham tDCS plus FDS) and time x group interaction. Analyses were adjusted, adding ‘‘time since stroke’’, “motor impairment” (Mild/Moderate and Severe), “lesion localization” and “diabetes mellitus” as covariates. A Bonferroni post-hoc was used to identify the differences between groups and times and the group x time interaction. The delta variance [= % outcome by the formula (Post - Pre)/Pre] was analyzed for primary and secondary outcomes. Correlations were tested by means of the Spearman’s correlation coefficient. It interpreted the strength of correlation as follows: 0.26-0.49= weak; 0.5-0.69 =moderate; 0.7-0.89=strong; and 0.9-1.0 = very strong.

The data are presented in mean and 95% confidence interval and were analyzed with the Statistical Package for Social Science (SPSS) software v.20.0, with a significance level of $p < 0.05$. Effect sizes were calculated (G-Power) and classified according to Cohen as small (0.2), moderate (0.5), and large (0.8). An effect size > 0.4 is considered clinically relevant [51].

Results

Forty-three potential stroke survivors were screened, of whom eleven failed to meet inclusion and exclusion criteria, and finally, thirty-two individuals

were included (Figure 1). The baseline demographic and clinical characteristics of participants are in Table 1.

Table 2 shows the effects of time, group, and group x time interactions for the blood analysis. There was a time effect for the BDNF ($p = 0.003$) cortisol ($p=0.005$), IL-6 ($p=0.022$) TNF-α ($p<0.001$), and IL-10 ($p=0.048$). Both groups showed a significant increase in BDNF and IL-10 concentrations and a reduction in cortisol, IL-6 and TNF-α levels after the intervention period. There wasn't difference over the time in both groups in IGF-1 and IGFBP-3 levels ($p>0.05$). Group did not affect any blood analysis; The covariates "time since stroke", "motor impairment", "lesion localization" and "diabetes mellitus" did not influence any of the parameters evaluated.

Table 3 presents the results of FMA-LL, TUG test, social participation (social roles and work/productivity). Statistical analysis evidenced a time effect for FMA-LL ($p=0.010$), total time to perform the TUG test ($p<0.001$), and social roles ($p=0.006$). Thus, both groups significantly increased the score of motor impairment and social roles and decreased the total in TUG test comparing pre with post-intervention assessments. Data were collected as part of a larger randomized clinical trial. The TUG and social roles results have been presented in Cunha et al (in press).

Motor impairment and lesion localization were the only covariates that influenced TUG and FMA-LL, respectively. When the post was compared with the baseline evaluation, individuals with mild/moderate impairment reduced the time to perform the TUG test. Individuals with internal capsule lesion localization presented lower FMA_LL score improvement.

The spearman's correlation showed weak correlations between BDNF delta range and FMA-LL ($rs = 0.375$, $p = 0.041$). No correlation was observed between BDNF delta range and IGFB-3, IGF-1 IL-6, IL-10, TNF-α, TUG, social roles and work/productivity delta range.

Discussion

This double-blind controlled study aimed to investigate the effects of tDCS associated with FDS training on BDNF serum levels. Also, this study examined the connection between BDNF and Cortisol serum levels with IGF1, IGFB3, IL-6, IL-10 and TNF-α levels and on motor impairment, functional mobility social roles in chronic post-stroke. The results demonstrated that both groups of treatment increased the BDNF and IL-10 levels, decreased Cortisol, IL-6 and TNF-α serum levels, and improved the motor impairment, functional mobility and social roles; There weren't observe differences between groups. Moreover, a weak correlation between the increase of BDNF levels and FMA-LL it was observed. tDCS does not seem to add effect to FDS gait training in improving motor plasticity in chronic post-stroke. These findings are clinically relevant since they contribute to understanding the mechanism straightforward of bi-cephalic tDCS and FDS on stroke rehabilitation.

The increase of circulating BDNF may represent a relevant reserve for brain cells and promote a neuroplasticity effect in stroke. The results of this clinical study demonstrate a significant improvement in motor impairment in both groups post treatment, and tDCS did not affect this clinical outcome. This result would be related to an increase of BDNF levels. Studies suggested that exercise increases BDNF levels [52,53] which has been identified as an important factor in motor learning and post-stroke rehabilitation. Gait training is characterized by a repetitive and active movement, focused on functional activity that can affect motor learning by providing a favorable environment for neural plasticity [54,55]. Nevertheless, a rehabilitation program based on the gait training with FES to peroneal nerve represents an important approach for the gait rehabilitation and functional mobility of stroke [7]. It has been hypothesized that the increase of BDNF and changes in motor impairment caused by FDS gait training would be related to the functional mobility improvement and a better social participation level.

It is well known that neuroinflammation may suppress the synthesis and action of BDNF [24]. This study found a decrease in proinflammatory cytokines (TNF alfa and IL-6) and an increase in IL-10 level (an anti-inflammatory cytokine). In the presence of inflammatory mediators, neutrophils and monocytes generate reactive oxygen species, thus facilitating oxidative damage and decrease the

BDNF levels [23]. In this study, the FDS gait training seems to modify the level of inflammation can influence serum BDNF level in chronic post-stroke. Furthermore, the upregulation in TNF- α concentrations are fundamental to stroke pathogenesis and leads to brain injury progression, apoptosis of neurons, worsening of stroke symptoms and muscle wasting [56,57]. Thus, the effects of lower TNF-α concentrations may be a link between chronic effects of these interventions on functional capacity and inflammatory biomarkers.

Chronic stroke can be associated with long-term disabilities, and individuals have lower serum concentrations of IGF-I and IGFBP-3 that may be correlated to muscle weakness and neuromuscular impaired [34]. The elevate levels of serum could be associated with neuroprotective actions, neurological recovery and functional gains [31,58]. Identification of the changes in IGF-1 and IGFBP-3 serum concentrations in post stroke has been associated with neuromuscular performance could help explain the neuromuscular adaptations to treatment [34]. However, in this study the treatment does not change the IGF-I and IGFBP-3 levels. The patient's severity could have influenced on IGF-I and IGFBP-3 results. Individuals with severe compromise have increased muscle tone, muscle weakness and lower walking ability [59]. Thus, maybe these individuals need more time of treatment to modify these parameters.

As mentioned before tDCS does add effect on FDS gait training. While the electrode montage over the leg area in the primary motor cortex is adequate for eliciting modulation in lower limbs [43], the low specificity of bi-cephalic montage may have attenuated the current penetrated deep enough to affect the leg area. Considering that inhibitory or excitatory brain effect by surface electrodes stimulation occurs due to run current flow from the anode to the cathode [60]. It could be therefore speculated that using bi-cephalic electrodes montage, the current could be more superficial and less effective in facilitating inhibitory or excitatory leg motor area. Further experiments where electrode position is modified are needed to resolve these issues.

This study has some limitations that need to be highlighted. First, the specific cortical areas activated by tDCS through the neural excitability and interhemispheric interactions assessment did not evaluate. Other factors might

also have influenced the results, such as stroke severity and cortical connections integrity.

Therefore, bi-cephalic tDCS did not influence BDNF, cortisol, IGFB-3, IGF-1, IL-6, TNF-α and IL-10 levels and motor impairment. Considering that tDCS effects remain uncertain, to further confirm it, additional clinical trials with different montage of stimulation are warranted to verify the effectiveness of tDCS on lower limb rehabilitation in chronic post-stroke. In conclusion, FDS with gait training may be used as an alternative complementary therapy to induce neuroplasticity and motor impairment in subjects with stroke. These results contribute to the understanding of rehabilitation strategies for subjects with chronic post stroke.

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Conflict of interests

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Figure Legends

Figure 1. Flow diagram of study. FMA: Fulg Meyer Assessment - Lower Limb; MMSE: Mini-mental state examination; tDCS: transcranial direct electrical stimulation; FDS: Foot drop stimulator.

Table 1. Demografic characteristics

	tDCS plus FDS (n=16)	**Sham tDCS plus FDS** (n=16)	*p=value*
Gender, n (%) ¥			
Male	11 (68.7)	11 (68.7)	1.000
Age, years, mean ±SD #	55.44 ± 8.47	58.25 ± 9.75	0.391
Height, mean ±SD (m) #	1.71± 0.73	1.68 ± 0.99	0.311
Body Mass (kg) #	77.69 ± 10.97	72.56 ± 12.57	0.229
MMSE score, median (min-max)*	29 (27-30)	29 (21-30)	0.146
Prior disease/risk factors, n (%)¥			
Hypertension	14 (87.5)	10 (62.5)	0.096
Diabetes mellitus	4 (25)	2 (12.5)	0.361
Smoking	7 (43.75)	8 (50)	0.934
Stroke type, n (%)¥			
Ischemic	11 (68.7)	13 (81.2)	0.412
Hemorrhagic	5 (31.3)	3 (18.8)	
Time since stroke, month, median (min-max)*	37 (6-96)	31 (6-87)	0.474
Affected hemisphere, n (%)¥			
Right	9 (56.2)	10 (62.5)	0.719
Left	7 (43.8)	6 (37.5)	
Lesion localization, n (%)¥			
Anterior Cerebral Artery	1(6.25)	5 (31.3)	0.158
Medial Cerebral Artery	8 (50)	5 (31.3)	
Internal Capsule	7 (43.75)	6 (37.5)	
Motor impairment, median (min-max)*			

FMA-LL (0-34)	19 (11-32)	18 (13-30)	0.910
Spasticity, MAS, frequency (0/1/1+/2/3/4) ¥			
Plantar Flexors	0/1/2/2/5/6	0/2/0/2/6/6	0.524
Knee Extensors	2/3/3/3/5/0	3/4/3/1/3/2	0.458
Hip Adductors	2/3/2/6/3/0	3/1/2/6/4/0	0.846
PSQI, median (min-max)*	5 (1-15)	5 (1-10)	0.791

Note: tDCS = transcranial direct current stimulation; FDS = foot Drop stimulator; n = number of participants; SD, standard deviation; max, maximum; min, minimum; MMSE = Mini-Mental State Examination; FMA-LL = Fugl Meyer Assessment - Lower Limb; Mild/Moderate = FMA-LL scores of 20-34; Severe = FMA-LL scores below than 19; PSQI = Pittsburgh Sleep Quality Index.
#t-Student, *U-Mann-Whitney, ¥ Likelihood Ratio Chi-Square analysis

Table 2. Blood measure

	tDCS plus FDS (n=16)	**ShamtDCS plus FDS (n=16)**	Time effect			Group effect		Time X group interaction	
			Wald χ2	*p-value*	*Effect Size*	Wald χ2	*p-value*	Wald χ^2	*p-value*
BDNF (pg/mL)									
Pre	114.29 (101.64 - 128.52)	117.61 (108.99 - 126.9)	9.13	**0.003**	0.52	0.20	0.658	0.01	0.921
Post	129.62 (115.14 - 145.91)*	134.52 (115.59 - 156.55)*							
Cortisol (µg/dL)									
Pre	33.78 (32.54 - 35.07)	33.77 (32.75 - 34.82)	7.75	**0.005**	0.47	0.10	0.750	0.33	0.565
Post	32.82 (31.26 - 34.45)*	32.31 (31.16 - 33.51)*							
IGF-1 (pg/mL)									
Pre	521.47 (428.14 - 635.14)	501.65 (413.77 - 608. 17)	1.03	0.309	-	0.32	0.568	0.60	0.440
Post	513.62 (396.56 - 665.22)	449.0 (349.23 - 577.28)							
IGFBP-3 (ng/mL)									
Pre	9.38 (7.95 - 11.08)	8.23 (7.44 - 9.11)	0.03	0.865	-	0.242	0.623	0.313	0.576
Post	9.23 (7.97 - 10.69)	8.84 (7.0 - 9.78)							
IL-6 (pg/mL)									
Pre	8.65 (7.7 - 9.73)	9.43 (7.38 - 12.03)	4.61	**0.032**	0.20	0.46	0.494	0.02	0.879
Post	7.94 (7.25 - 8.7)*	8.74 (6.77 - 11.29)*							
IL-10 (pg/mL)									
Pre	12.41 (7.21 - 21.35)	15.1 (10.24 - 22.26)	5.53	**0.019**	0.11	0.50	0.478	0.433	0.510
Post	13.43 (8.17 - 22.05)*	17.38 (12.36 - 24.46)*							
TNF-α (pg/mL)									
Pre	14.33 (12.68 - 16.19)	13.62 (12.81 - 14.49)	15.8	**<0.001**	0.51	0.13	0.717	0.75	0.384
Post	12.41 (10.92 - 14.11)*	12.43 (11.43 - 13.51)*							

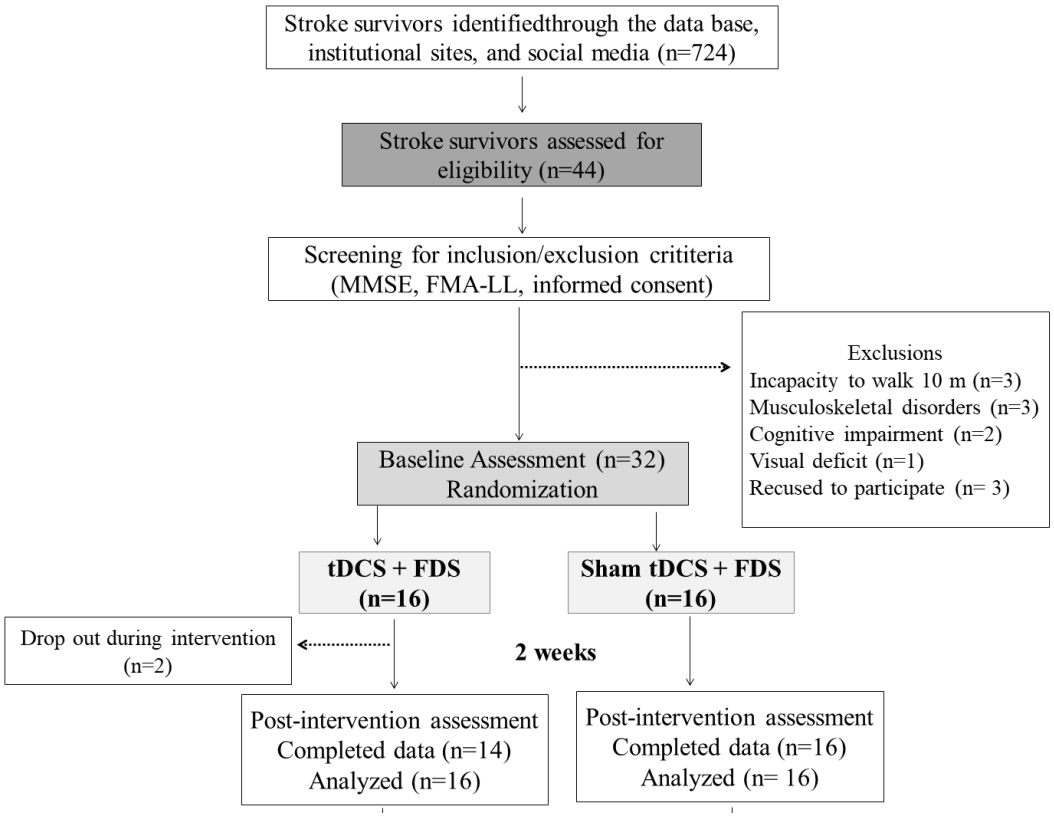
Note: Data are mean and 95% confidence intervals; tDCS= transcranial direct current stimulation; FDS: foot Drop stimulator; n=number of participants; Pre= pre intervention (baseline); Post = post intervention (after 10 session of intensive treatment). * Significant values compared to pre-evaluation Wald χ2: Wald Chi Square.

	tDCS plus FDS (n=16)	**ShamtDCS plus FDS (n=16)**	Time effect			Group effect		Time X group interaction	
			Wald χ2	*p-value*	*Effect Size*	Wald χ2	*p-value*	Wald χ^2	*p-value*
Motor impairment, FMA-LL (score)									
Pre	19.37 (16.85 - 22.27)	19.87 (17.35 - 22.75)	8.97	**0.003**	0.34	0.48	0.827	1.81	0.179
Post	22.57 (19.35 - 26.33)*	21.06 (17.99 - 24.65)*							
TUG (total time)									
Pre	24.28 (17.72 - 33.28)	19.63 (16.06 - 23.0)	14.68	**<0.001**	0.16	0.99	0.319	1.11	0.291
Post	21.76 (15.74 - 30.08)*	18.45 (15.26 - 22.3)*							
Social roles (Domain n = 5, min-max = 5-25)									
Pre	11.38 (8.72 - 14.84)	11.38 (8.89- 15.55)	7.44	**0.006**	0.39	0.072	0.789	0.35	0.552
Post	14.43 (11.49 - 18.11)*	13.25 (10.57 - 16.61)*							
Work/productivity (Domain n = 5, min-max = 5-25)									
Pre	8.62 (6.69 - 11.12)	8.31 (6.66 - 10.38)	3.62	0.164	-	0.37	0.540	1.58	0.454
Post	10.07 (8.28 - 12.25)	8.44 (6.71 - 10.6)							

Note: Data are mean and 95% confidence intervals; tDCS= transcranial direct current stimulation; FDS: foot Drop stimulator; n=number of participants; Pre= pre intervention (baseline); Post = post intervention (after 10 session of intensive treatment).

* Significant values compared to pre-evaluation Wald χ2: Wald Chi Square.

Figure 1.


Stroke survivors identifiedthrough the data base, institutional sites, and social media (n=724)
Stroke survivors assessed for eligibility (n=44)
Screening for inclusion/exclusion crititeria (MMSE, FMA-LL, informed consent)
Exclusions
Incapacity to walk 10 m (n=3)
Musculoskeletal disorders (n=3)
Cognitive impairment (n=2)
Visual deficit (n=1)
Recused to participate (n= 3)
Baseline Assessment (n=32)
Randomization
tDCS + FDS (n=16)
Sham tDCS + FDS (n=16)
Drop out during intervention (n=2)
2 weeks
Post-intervention assessment
Completed data (n=14)
Analyzed (n=16)
Post-intervention assessment
Completed data (n=16)
Analyzed (n= 16)

5.5 Bi-cephalic tDCS combined with foot drop stimulator does not improve gait speed in chronic post-stroke individuals: A double-blind randomized controlled trial

Submetido ao periódico Disability and rehabilitation
(Fator de impacto: 2.22)

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Abstract

Abstract

Background: Stroke survivors often present changes in spatiotemporal parameters that cause limitations in walking performance. Transcranial direct current stimulation (tDCS) and Foot drop stimulator (FES) are widely used strategies for gait stroke rehabilitation. However, the effects of combining these two therapies to rehabilitate individuals with chronic post-stroke are still unknown. Objective: Primary aim was to evaluate if bi-cephalic tDCS add significant clinical benefit to FDS gait training on gait speed. Secondary aim was to verify the effects of the combined therapies on other spatiotemporal gait parameters, lower limb range of motion and gait symmetry. Material and Methods: Thirty-two individuals with mild, moderate, and severe chronic hemiparesis after stroke were randomized to tDCS plus FDS or sham tDCS plus FDS groups. Both groups underwent ten sessions of treadmill gait training wearing an FDS device - with real or sham tDCS five times a week, for two weeks. Clinical assessments were performed before, after the treatment and in one-month follow-up. Results: After treatment, tDCS plus FDS increased the percentage of the swing phase on the affected leg. It did not observe any difference between groups in other outcomes. Both groups increased step length and swing phase on the unaffected leg and single support phase on the affected leg and ameliorated the symmetry of single support phase. Conclusion: In chronic post-stroke individuals, bi-cephalic tDCS does not add benefits to FDS training to improve gait performance.

Trial registration: ClinicalTrials.gov (NCT04077814).

Keywords: Transcranial direct current stimulation; stroke rehabilitation; lower extremity; electric stimulation; neurologic gait disorders; neuromodulation; functional electrical stimulation.

Introduction

Individuals with hemiparesis often have limitations in walking and the most common post-stroke pattern of impairment is the foot drop [1]. This motor impairment is associated with the weakness or lack of voluntary control of ankle dorsiflexors and/or increased spasticity of plantar flexor muscles [2-4]. Foot drop interferes on ankle dorsiflexion during the swing phase of gait and contributes to disruption in weight acceptance and weight transfer in the initial foot contact of

the stance phase [5]. Consequently, post-stroke individuals may demonstrate classic changes in spatiotemporal and kinetic parameters, such as slower gait velocity with higher duration in paretic swing phases and reduced paretic single stance phase duration, cadence, and stride length [1, 6].

Lower limb movement is controlled by bilateral motor pathways from both lesioned and non-lesioned hemispheres [7]. In normal conditions, both hemispheres work in balanced mutual inhibitory actions [8]. After a stroke, this balance is disrupted, increasing the excitability in the contralesional hemisphere and reducing the activity in the affected hemisphere. This imbalance negatively affects functional recovery [9]. Thus, it is crucial to investigate whether restoring the balance between both hemispheres plays the dominant role in gait rehabilitation following a stroke.

Transcranial direct current stimulation (tDCS) modulates cortical excitability [10], and induces plasticity through long-term potentiation or long-term depression [11]. tDCS consist of a weak electrical direct current passing through the cortical tissue altering cortical excitability by hyperpolarizing or depolarizing resting neurons membrane potentials. This device has different physiological effects, depending on its configuration montage over brain sides. Bi-cephalic tDCS emerges as an attractive model to normalize excitatory and inhibitory corticospinal networks. The anodal tDCS (a-tDCS) up-regulate activity in the affected hemisphere, while simultaneously cathodal tDCS (c-tDCS) down-regulate activity in the non-affected hemisphere [12, 13]. Randomized clinical trials have investigated the effect of transcranial direct current stimulation (tDCS) for gait rehabilitation in acute/subacute [14, 15] and chronic post-stroke subjects [16]. tDCS seems to be a promising therapeutic modality to improve walking ability in patients with stroke by enhancing the effects of conventional rehabilitation strategies. Therefore, evidence about the effects of tDCS on gait speed in chronic post-stroke remains inconclusive and is not well established [17]. For this reason, it is still necessary to clarify the tDCS effects on walking abilities.

Combining rehabilitation approaches have been proposed to improve functional recovery after stroke [18]. Functional electrical stimulation (FES) of the peroneal nerve delivered by foot drop stimulator (FDS) devices has been used as an alternative to correct the ankle movement after stroke [19]. The FES stimulation

through FDS is synchronized with the swing phase of gait and could stimulate voluntary muscle activity, reduce foot drop, and decrease spasticity [20]. This stimulus allows the foot to clear the ground, results in a safe initial loading response during the stance phase of gait [21] and could facilitate hip and knee flexion - necessary for foot clearance during the swing phase of gait [22-24]. There is evidence about the positive effects in improving the walking speed when using FES on the peroneal nerve combined with physiotherapy or gait training [25].

Gait impairment is identified as a significant functional deficit after a stroke. However, it remains a challenge regarding the rehabilitation of chronic post-stroke survivors. Given the necessity of proposing novel approaches and treatment combinations to rehabilitate gait, it is hypothesized that central and peripheral stimulation could maximize the rehabilitation gains in this condition. There is no study combining concurrent tDCS, FDS, and treadmill gait training in chronic post-stroke individuals to the best of our knowledge. Therefore, the main objective of this study was to verify if this combination could improve gait speed. Additionally, this study investigated the effects of this protocol on other spatiotemporal gait parameters (cadence, step length, single stance phase, and swing phase), changes in the paretic lower limb range of motion (ROM), and gait symmetry.

Materials and Methods

Study Design

A double-blinded randomized trial with concealed allocation and intention-to-treat analysis was conducted in the Universidade Federal de Ciencias da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil. The study was approved by the Ethics and Research Committee of the Santa Casa de Misericórdia Hospital of Porto Alegre (CAAE 64819617.0.0000.5335) and conduced according to the principles of the 1964 Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (number identifier: NCT04077814) and conducted according to the CONSORT guidelines for randomized clinical trials [26]. According to the Mini-Mental State Examination (MMSE) score, all participants were presumed competent for decision-making and, for this reason, signed the informed consent (Table 1).

Participants

Participants were recruited through a database of the Neurology Service of Santa Casa de Misericórdia Hospital in Porto Alegre, institutional sites, and social media, and those who met the following criteria were included for convenience. Inclusion criteria were: age between 18 and 80 years; history of a single or more than one cerebrovascular accident as long as in the same hemisphere at least six months before recruitment; no history of seizures; with severe, moderate, or mild motor compromise; the presence of foot drop as a result of the stroke (reduction or absence of dorsiflexion and eversion movements of ankle and foot); minimum score of 20/30 points (illiterates) or > 24/30 points (literates) in the MMSE [27]; ability to walk at least 10 meters with or without assistive devices. Exclusion criteria were: any contraindication for electrical stimulation (electric or metallic implants, skin problems or lesion close to the site of FDS stimulation, being pregnant); inadequate response to FDS electrical stimulation (no response to the highest stimulation intensity); irreversible ankle restriction (ankle contracture at 10 degrees of plantar flexion in the hemiplegic leg with the knee extended); lower limb musculoskeletal disorder that compromised locomotion; significant visual impairment.

Procedures

This study was conducted at the Movement Analysis and Rehabilitation Laboratory at UFCSPA. Each participant underwent a clinical and documented evaluation session.

Modified Ashworth Scale (MAS) [28] was used for indirect assessment of spasticity; it consists of 6 ordinal values ranging from 0 (no tonus increase) to 4 (stiffness) [28]. Participants were evaluated lying in a supine position and were instructed to remain relaxed during the test. Spasticity of plantar flexors, knee extensors, and hip adductors was tested. Lower limb motor impairment was evaluated by Fugl-Meyer Assessment of lower limb (FMA-LL) [29]. The maximum score is 34 points. According to the FMA-LL score, the participants were classified to their motor impairment: severe (0 to 19), moderate (20-28), or mild (≥29 points) [30].

All clinical assessments were applied by the same researcher at baseline (pre-intervention - after three days of habituation with FDS), post-intervention (one day after the last session) and follow-up (one month after finished the treatment), as depicted in Figure 1. Participants and researchers who conducted the evaluations were blinded to the treatment condition - real or sham tDCS.

Randomization

Participants were stratified according to the level of motor impairment (according to the FMA-LL score) and randomized in block sizes of four individuals by an investigator who was not involved in the assessments, recruitment or data analysis. By means of the tool available at https://www.random.org, volunteers were allocated into two groups: tDCS plus FDS or Sham tDCS plus FDS. Another researcher checked the participant's allocation and applied the treatment in both groups. This researcher was not blinded to the treatment condition (real or sham tDCS) and did not participate in the assessment sessions.

Intervention

Participants underwent ten concurrent tDCS and FDS gait training sessions five times a week for two weeks (excluding weekends). The therapy sessions lasted thirty minutes and consisted of three steps: during the first five minutes, the participants received tDCS (or placebo) when sitting in a comfortable position; followed, they performed twenty minutes of gait training on a treadmill (Athletic advanced 720EE Brazil), wearing the FDS device on the paretic side, and receiving the tDCS/placebo stimulation (the combination of both treatments). They returned to the sitting position in the last five minutes and received only the tDCS (or placebo). Gait speed was set during the FDS habituation period. The speed did not change over the gait training. Participants could hold the treadmill bars if they needed and stop walking at any time; however, the stopwatch did not stop. Before each session, heart rate and blood pressure were checked, and all volunteers received lower limb stretching and passive ankle mobilization for approximately 15 min - to normalize the muscle tone and facilitate active ankle movements during the gait training.

Transcranial direct current stimulation

Individuals allocated to the tDCS plus FDS group received a combination of bi-cephalic tDCS, FDS and treadmill gait training. Anode electrodes were placed on the participant's scalp at the ipsilesional M1 and cathodes over the contralesional M1 area [31], according to the electroencephalogram 10–20 system [32]. Before positioning the tDCS electrodes, the hair was separated to reveal the area to be stimulated; the skin was cleaned with saline to remove creams, dirt, or grease. tDCS was delivered by a TCT neurostimulator (Research Version - TransCranial Research Ltd.; Hong Kong, China) via a pair of 5- 5 cm saline-soaked sponge surface electrodes. The applied current was set to deliver 2 mA bi-cephalic tDCS [10, 33], with a relative current density of 0.08 mA/m2, for 30 min [34]. The ShamtDCS modality was delivered using the same electrode montage used for real tDCS; however, the stimulation stopped after a ramp-up and ramp-down period of 30s to provide an equivalent scalp sensation [34]. If the participant reported some discomfort, the treatment was suspended and, and if necessary, they could be referred then for medical evaluation.

Foot Drop stimulator

FDS device used to stimulate the peroneal nerve on the affected side was the WalkAide orthosis (Innovative Neurotronics, Austin, TX, USA). This device stimulates the peroneal nerve on the affected side through a tilt sensor that detects the leg tilt when foot contact on the ground changes from posterior to anterior (pre-swing phase). Stimulus stops when the leg is tilted forward on foot strike [35]. Participants underwent a three-day habituation period using an FDS device for one hour a day. In the habituation period, volunteers used the FDS device, walked on a flat surface, went up and downstairs, and finally walked on the treadmill. During this period, the device adjustments have been performed to provide the best stimulus intensity for each participant. The intensity of FDS stimulation was enough to induce a comfortable ankle dorsiflexion/eversion movement during the swing phase of the gait cycle. The frequency of electrical stimulation was set at 25 Hz, the pulse duration at 150 μs, and the intensity between 60 and 150 V. FDS adjustment was conducted by a licensed physical therapist who had received training and competency assessment in the use of FDS.

Outcomes measures

Gait analysis

Gait was assessed using a 3D motion analysis system (BTS Bioengineering, Italy) composed of 6-infrared cameras. Twenty-two retro-reflective spherical markers were placed on anatomic landmarks described by the Davis protocol [36]. Participants were asked to walk at a self-selected speed, barefoot, without FDS, along an eight-meter flat pathway, with the assistive walking devices (e.g., cane) if used regularly. They were allowed to take a rest break after each trial. Gait evaluations were performed after the habituation period (baseline evaluation), one day after finished the ten sessions of training (post-training evaluation), and in follow-up (one month after finished the intensive treatment). It recorded at least three trials and calculated the mean of them. Raw data were processed using the SMART analyzer software (Version 1.10.458.0 - BTS Bioengineering, Italy).

The spatiotemporal gait parameters were analyzed: gait speed (m/s), cadence (steps per min), step length (m), single stance phase (% of cycle), and swing phase (% of cycle). Paretic lower limb ROM was computed by the difference between the maximum and minimum values in degrees of ankle plantar/dorsiflexion (Ankle-PD), knee flexion/extension (Knee-FE), and hip flexion/extension (Hip-FE).

Gait symmetry was calculated according to the Robinson method [37] as follows: SI=2(x non-paretic - x paretic)/(x non-paretic + x paretic)*100. The symmetry index (SI) is calculated by quoting the difference between measures for paretic and non-paretic limb and the mean of these measures. The symmetry index should be zero, reflecting a perfectly symmetrical gait pattern. Higher symmetry index values correspond to greater gait asymmetry [37, 38].

Statistical Analysis

Sample size was determined using the G-Power 3.0 software based on previous studies [22, 39, 40], considering 90% power and alpha value of 0.05 to detect a minimum clinical difference of 20% in gait speed. Thirty-two participants were estimated as necessary for this study.

Intent-to-treat analysis was applied to compare all outcomes. Shapiro-Wilk tests were used to evaluate the normally of the continuous variables. Parametric Student t-tests, nonparametric Mann-Whitney, and Chi-square tests were used to compare demographics characteristics between groups. Generalized Estimation Equation (GEE) was used to compare: effect of time (Pre, Post and Follow-up), effect of group (tDCS plus FDS and Sham tDCS plus FDS) and time x group interaction. Data are presented as mean and 95% confidence intervals. Statistical Package for Social Science (SPSS) software v.20.0 was used to all analyses. Significance level was set at $p < 0.05$. Effect sizes were calculated using the G-Power 3.0 software and classified according to Cohen as small (0.2), moderate (0.5), and large (0.8). Effect sizes > 0.4 were considered as clinically relevant [41].

Results

Forty-three potential participants were screened, of whom eleven failed to meet inclusion and exclusion criteria. Thus, 32 individuals were included (Figure 1). Baseline demographic and clinical characteristics of participants are depicted in Table 1.

Table 2 presents the effects of time, group, and group x time interactions for the spatiotemporal gait parameters. Statistical analysis evidenced a group x time interaction for the swing phase in the affected limb ($p=0.022$). According to post-hoc analysis, tDCS plus FDS effectively increased the time of swing phase on the affected leg post and follow-up compared with baseline. It observed a time effect for step length and swing phase on an unaffected limb and single support on the affected limb. When post and follow-up evaluations were compared with the baseline, both groups significantly increased the step length ($p=0.037$ and $p=0.026$ respectively) and single support phase in the affected leg ($p=0.001$ and $p=0.05$ respectively). Also, when post evaluations were compared with the baseline, both groups significantly increased the swing phase in the unaffected leg ($p=0.01$). It found an effect of group in cadence ($p=0.042$). tDCS plus FDS group presented a lower cadence compared with the sham group. No other effects of group or time x group interaction were observed for spatiotemporal gait parameters.

Table 3 depicts discrete data analysis of the paretic lower limb ROM: ankle (plantar-dorsiflexion), knee, and hip (extension-flexion). No differences were found in ROM of the ankle, knee, and hip between PRE, POST-training, and follow-up ($p>0.05$).

The Symmetry index (Step length, single stance duration phase, ROW of ankle-PD, knee-FE, and hip-FE) is presented in Table 4. Time effect in symmetry of single support phase ($p=0.049$) was found. When post and follow-up were compared with the baseline evaluation, both groups improved the symmetry of the single support phase. No effect of time, group, or time x group interaction was observed for other symmetry indexes.

Discussion

This study aimed to investigate the effects of tDCS and FDS combined with treadmill gait training on gait speed. Additionally, the other spatiotemporal gait parameters, paretic lower limb angular kinematics (ankle, knee, and hip joint), and gait symmetry were assessed in chronic post-stroke individuals. The findings of this study reveal that the combination of the central stimulation through bi-cephalic tDCS was unable to add significant clinical benefit to FDS and treadmill training for improving gait performance in chronic post-stroke individuals, and thus raise doubts about a meaningful clinical benefit of these interventions combined.

It was expected that tDCS to balance the excitability between the hemispheres after the brain lesion[42] and contribute to post-stroke motor recovery. However, the preliminary hypothesis was not confirmed, and bi-cephalic tDCS had no additional effect of restoring walkability in chronic post-stroke. According to the literature, it is feasible to stimulate the leg area even if it is in the more profound and vertical cortical orientation [33]. The unilateral anodal tDCS stimulation on the leg motor cortex of the affected hemisphere during walking was proven to increase motor excitability of the motor cortex [43]. Besides, a smaller electrode may result in more focal and more superficial stimulation[44]. In fact, in the present study, a bi-cephalic montage with relatively small electrodes was adopted. So, tDCS intervention may have failed to modulate activity in the leg motor cortex deep. Since that, the low specificity of bi-cephalic montage may

have attenuated the current flow through the target region. Since the position of electrodes seems to be crucial to the direction of current flows and stimulation effects [45]. future studies, different electrode montages, and larger electrodes are needed to answer this question.

FDS training was unable to improve some temporospatial gait parameters. Post-stroke individuals present reduced dorsiflexion during swing phases of gait that interfere with initial foot contact at the beginning of the stance phase due to poor motor control of ankle dorsiflexors [46], reduced intermuscular coordination[47] and/or increased spasticity of plantar flexors [2-4]. Through repetitive muscle contractions, FDS could be able to increase sensory inputs to the brain, improve tibialis anterior muscle activity [24], decrease spasticity [20, 48] and contribute to motor relearning [48, 49]. FDS training ameliorates stability during gait [19, 21] and could partially explain the improvements on spatiotemporal gait parameters and symmetry between affected e non-affected body sides without the need of tDCS association.

A difference in gait speed ($p=0.052$) was observed only in the follow-up period. This difference had minor clinical relevance and effect size. Considering that this study had losses after the follow-up period, these results could be insufficient to infer positive effects of treatment protocol upon the walking speed. A previous study reported that the association between FDS and gait training could improve gait speed [24]. Unlike the protocol of this study, these authors applied a progressive increment of speed in gait training sessions of 30 minutes, once a day, for four weeks. Gait training was also combined with conventional physiotherapy (based on the neurodevelopmental treatment concept and proprioceptive neuromuscular facilitation) to improve the function of affected limbs [24]. Thus, possibly better results in gait speed could be reached if FDS was combined with gait training with slight speed incremental between sections and the inclusion of global muscle strengthening.

Previous studies reported that FDS stimulus could assist ankle, knee, and knee flexion during the swing phase of gait and lead to a walking pattern closer to the normality [48, 50]. However, the results did not evidence a difference in ROM of the paretic ankle, hip, and knee. It is worth noting that post-stroke included in this study had a severe compromise with higher lower limb muscle tone, affecting walking ability. Thus, less affected post-stroke subjects may show more

significant benefit, and maybe severe individuals need more intervention to modify these parameters.

This study has some limitations that need to be highlighted. The study did not control the specific cortical areas activated by tDCS through the neural excitability and interhemispheric interaction assessment. Besides, even though more than 90% of the sample completed two weeks of intervention, follow-up losses exceeded 20%, and it can not make unable to specify how these losses could impact the interpretation of long-term effects of treatment. Other factors may also be responsible for the lack of positive results using tDCS, such as the variability of the sample regarding the stroke severity, site of lesion, and time after stroke.

Based on results showed, bi-cephalic tDCS does not seem to add effect to FDS gait training to improve gait performance in chronic post-stroke individuals. These findings were considered quite relevant because they can support the clinical decision of not using bi-cephalic tDCS when treating stroke patients with treadmill gait rehabilitation and FDS.

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Conflict of interests

Authors declare that the Össur Brazil/Porto Alegre company provided the WalkAide (Innovative Neurotronics, Austin, TX, USA) orthosis for this study. Authors did not receipt any additional financial support for this research, authorship, and/or publication of this article.

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Figure Legends

Figure 1. Timeline of study. FDS = Foot drop stimulator; Pre- intervention assessment:3 days after started the study (1 day after habituation with Foot drop stimulator); Post-intervention: one day after the last session (10 sessions) and follow-up: one month after finished the treatment.

Figure 2. Flow diagram of study. FMA: Fulg Meyer Assessment - Lower Limb; MMSE: Mini-mental state examination; tDCS: transcranial direct electrical stimulation; FDS: Foot drop stimulator.

Table 1. Demografic characteristics

	tDCS plus FDS (n=16)	**Sham tDCS plus FDS** (n=16)	*p=value*
Gender, n (%) ¥			
Male	11 (68.7)	11 (68.7)	1.000
Age, years, mean ±SD #	55.44 ± 8.47	58.25 ± 9.75	0.391
Height, mean ±SD (m) #	1.71± 0.73	1.68 ± 0.99	0.311
Body Mass (kg) #	77.69 ± 10.97	72.56 ± 12.57	0.229
MMSE score, median (min-max)*	29 (27-30)	29 (21-30)	0.146
Prior disease/risk factors, n (%)¥			
Hypertension	14 ()	10 ()	0.096
Diabetes mellitus	4 (25)	2 (12.5)	0.361
Smoking	7 (43.75)	8 (50)	0.934
Stroke type, n (%)¥			
Ischemic	11 (68.7)	13 (81.2)	0.412
Hemorrhagic	5 (31.3)	3 (18.8)	
Time since stroke, month, median (min-max)*	37 (6-96)	31 (6-87)	0.474
Affected hemisphere, n (%)¥			
Right	9 (56.2)	10 (62.5)	0.719
Left	7 (43.8)	6 (37.5)	
Lesion localization, n (%)¥			
Anterior Cerebral Artery	1(6.25)	5 (31.3)	0.158
Medial Cerebral Artery	8 (50)	5 (31.3)	
Internal Capsule	7 (43.75)	6 (37.5)	

Motor impairment, median (min-max)*			
FMA-LL (0-34)	19 (11-32)	18 (13-30)	0.910
Spasticity, MAS, frequency (0/1/1+/2/3/4) ¥			
Plantar Flexors	0/1/2/2/5/6	0/2/0/2/6/6	0.524
Knee Extensors	2/3/3/3/5/0	3/4/3/1/3/2	0.458
Hip Adductors	2/3/2/6/3/0	3/1/2/6/4/0	0.846

Note: tDCS = transcranial direct current stimulation; FDS = foot Drop stimulator; n = number of participants; SD, standard deviation; max, maximum; min, minimum; MMSE = Mini-Mental State Examination; FMA-LL = Fugl Meyer Assessment - Lower Limb; FMA-LL scores below than 19 severe; 20-28 moderate and ≥29 points mild motor compromise.

#t-Student, *U-Mann-Whitney, ¥ Likelihood Ratio Chi-Square analysis

Table 2. Gait Analysis

	tDCS plus FDS (n=15)	ShamtDCS plus FDS (n=15)	Time effect			Group effect		Time X group interaction		
			Wald χ2	*p-value*	*Effect Size*	Wald χ2	*p-value*	Wald χ2	*p-value*	*Effect Size*
Walk speed (m/s)										
Pre	0.49 (0.38 - 0.62)	0.61 (0.49 - 0.74)	5.93	0.052		1.52	0.271	0.85	0.655	
Post	0.51 (0.41 - 0.65)	0.62 (0.51 - 0.74)								-
FU	0.56 (0.43 - 0.72)	0.65 (0.54 - 0.80)			0.24¥					-
Cadence (steps/min)										
Pre	73.68 (63.02 - 86.13)	87.82 (80.23 - 96.13)	3.58	0.166		4.14	**0.042**	1.47	0.477	
Post	76.66 (66.77 - 87.98)	88.59 (81.45 - 96.36)			-					-
FU	76.92 (65.98 - 89.68)	91.97 (84.14 - 100.55)			-					-
Affected step length (m)										
Pre	0.40 (0.36 - 0.47)	0.45 (0.40-0.50)	4.41	0.110		0.48	0.487	2.42	0.298	
Post	0.43 (0.38 - 0.48)	0.45 (0.41 - 0.50)			-					-
FU	0.44 (0.38 - 0.52)	0.46 (0.40 - 0.52)			-					-
Unaffected step length (m)										
Pre	0.32 (0.26-0.39)	0.37 (0.31-0.44)	8.81	**0.012**	0.23#	0.19	0.662	5.50	0.064	
Post	0.37 (0.31-0.45)*	0.37 (0.31-0.44)*			0.31¥					-
FU	0.39 (0.30-0.46)*	0.39 (0.32-0.48)*								-
Affected single stance phase (%)										
Pre	22.26 (18.67 - 26.54)	25.26 (22.63 - 28.20)	11.51	**0.003**		0.66	0.415	5.52	0.063	
Post	25.47 (22.11 - 9.35)*	25.90 (23.35 - 28.73)*			0.28#					-
FU	25.11 (22.25 -28.34)*	26.84 (23.99 - 30.05)*			0.35¥					-
Unaffected single stance phase (%)										
Pre	33.03 (28.69 - 38.04)	36.55 (34.28 - 38.98)	4.68	0.096		0.79	0.598	5.52	0.063	

Post	35.82 (31.79 - 40.36)	36.36 (34.04 - 38.83)								-
FU	36.74 (32.36 - 41.72)	36.51 (33.55 - 39.73)								-
Affected swing phase (%)										
Pre	33.59 (29.40 - 38.38)	36.46 (34.15 - 38.93)	3.09	0.214		0.12	0.730	7.67	**0.022**	
Post	35.96 (32.18 -40.19)*	35.99 (33.67 - 38.46)			-					0.31[#]
FU	36.14 (31.13 - 1.96)*	35.70 (33.26 - 38.32)			-					0.33[¥]
Unaffected swing phase (%)										
Pre	23.06 (19.63 - 27.10)	25.38 (22.75 - 28.32)	8.15	**0.017**	0.23[¥]	0.366	0.545	5.27	0.071	
Post	25.82 (22.68 -29.40)*	25.72 (23.15 - 28.57)*			0.23[§]					-
FU	24.81 (21.59 - 28.51)	26.42 (23.52 - 29.67)								-

Note: Data are mean and 95% confidence intervals; tDCS= transcranial direct current stimulation; FDS: foot Drop stimulator; n=number of participants; Pre= pre intervention (baseline); Post = post intervention (after 10 session of intensive treatment); FU = Follow up (one month after finish the treatment).

* Significant values compared to pre-evaluation Wald $\chi 2$: Wald Chi Square;

#Effect size of difference Pre to Pos; ¥ Effect size of difference Pre to FU; §Effect size of difference Pos to FU

Table 3. Joint angles in sagittal plane of paretic limb

	tDCS plus FDS (n=16)	ShamtDCS plus FDS (n=16)	Time effect		Group effect		Time X group interaction	
ROM (degrees)						*p-value*	Wald $\chi 2$	*p-value*
Ankle-PD								
Pre	17.67 (14.21 - 21.97)	17.59 (15.25 - 20.18)	2.30	0.317	0.66	0.417	2.64	0.266
Post	17.76 (13.69 - 23.05)	20.47 (16.78 - 24.96)						
FU	17.43 (13.21 - 23.0)	21.80 (16.80 - 28.29)						
Knee-FE								
Pre	33.93 (26.44 - 43.54)	30.66 (25.36 - 37.07)	0.66	0.719	0.19	0.666	4.45	0.108
Post	29.81 (19.80 - 44.87)	31.70 (25.39 - 39.26)						
FU	26.69 (15.92 - 44.73)	36.71 (28.47 - 47.34)						
Hip-FE								
Pre	26.19 (19.44 - 35.30)	29.43 (23.27 - 37.22)	4.02	0.134	0.64	0.423	0.68	0.709
Post	25.62 (16.18 - 40.58)	30.42 (23.36 - 39.61)						
FU	27.98 (18.24 - 42.92)	36.52 (26.36 - 50.61)						

Note: Data are mean and 95% confidence intervals; tDCS= transcranial direct current stimulation; FDS: foot Drop stimulator; n=number of participants; Pre= pre intervenion (baseline); Post = post intervention (after 10 session of intensive treatment); FU = Follow up (one month after finish the treatment); ROM= Range of motion; Ankle-PD= ankle plantar/dorsiflexion; Knee-FE= knee flexion/extension; Hip-FE=hip flexion/extension.

Table 4. Symmetry index (SI) for gait parameters

	tDCS plus FDS (n=16)	ShamtDCS plus FDS (n=16)	Time effect			Group effect		Time X group interaction	
						Wald $\chi 2$	*p-value*	Wald $\chi 2$	*p-value*
Step length (m)									
Pre	28.41 (19.59 - 41.20)	26.56 (15.63 - 45.14)	1.34	0.511		0.07	0.786	0.19	0.906
Post	26.40 (17.42 - 40.02)	25.36 (15.29 - 42.05)			-				
FU	25.85 (17.94 - 37.26)	22.35 (12.57 - 39.73)			-				
Single stance phase (%)									
Pre	46.12 (36.04 - 59.02)*	37.84 (28.46 - 50.41)*	6.02	**0.049**		0.83	0.363	0.05	0.976
Post	40.78 (30.45 - 54.61)	34.42 (24.46 - 48.44)			0.19 #				
FU	37.95 (27.33 - 52.69)	31.15 (20.83 - 46.59)			0.34 ¥				
Ankle-PD ROM									
Pre	49.36 (29.34 - 83.03)	42.46 (27.81 - 64.84)	0.391	0.823		1.54	0.214	2.98	0.225
Post	52.0 (35.09 - 77.04)	40.61 (23.53 - 70.09)			-				
FU	59.45 (39.04 - 90.54)	29.55 (16.10 - 54.25)			-				
Knee-FE ROM									
Pre	51.80 (37.89 - 70.82)	42.17 (26.97 - 65.95)	5.65	0.059		2.24	0.134	3.53	0.171
Post	75.42 (55.15 - 103.15)	43.44 (27.58 - 68.43)			-				
FU	64.31 (41.11 - 100.61)	36.92 (20.22 - 67.41)			-				
Hip-FE ROM									
Pre	36.35 (24.91 - 53.07)	30.88 (16.85 - 56.57)	2.15	0.341		0.91	0.340	0.89	0.639
Post	47.83 (29.55 - 77.42)	32.07 (18.99 - 54.17)			-				
FU	40.70 (23.74 - 69.79)	27.25 (13.62 - 54.50)			-				

Note: Data are mean and 95% confidence intervals; tDCS= transcranial direct current stimulation; FDS: foot Drop stimulator; n=number of participants; Pre= pre intervention (baseline); Post = post intervention (after 10 session of intensive treatment); FU = Follow up (one month after finish the treatment). SI = Symmetry index; ROM= Range of motion; Ankle-PD= ankle plantar/dorsiflexion; Knee-FE= knee flexion/extension; Hip-FE=hip flexion/extension.

* Significant values compared to pre-evaluation Wald χ2: Wald Chi Square; #Effect size of difference Pre to Pos; ¥ Effect size of difference Pre to FU.

Figure 1.

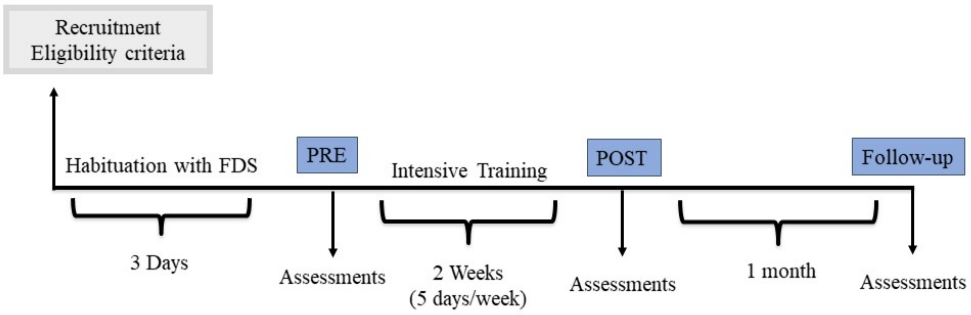
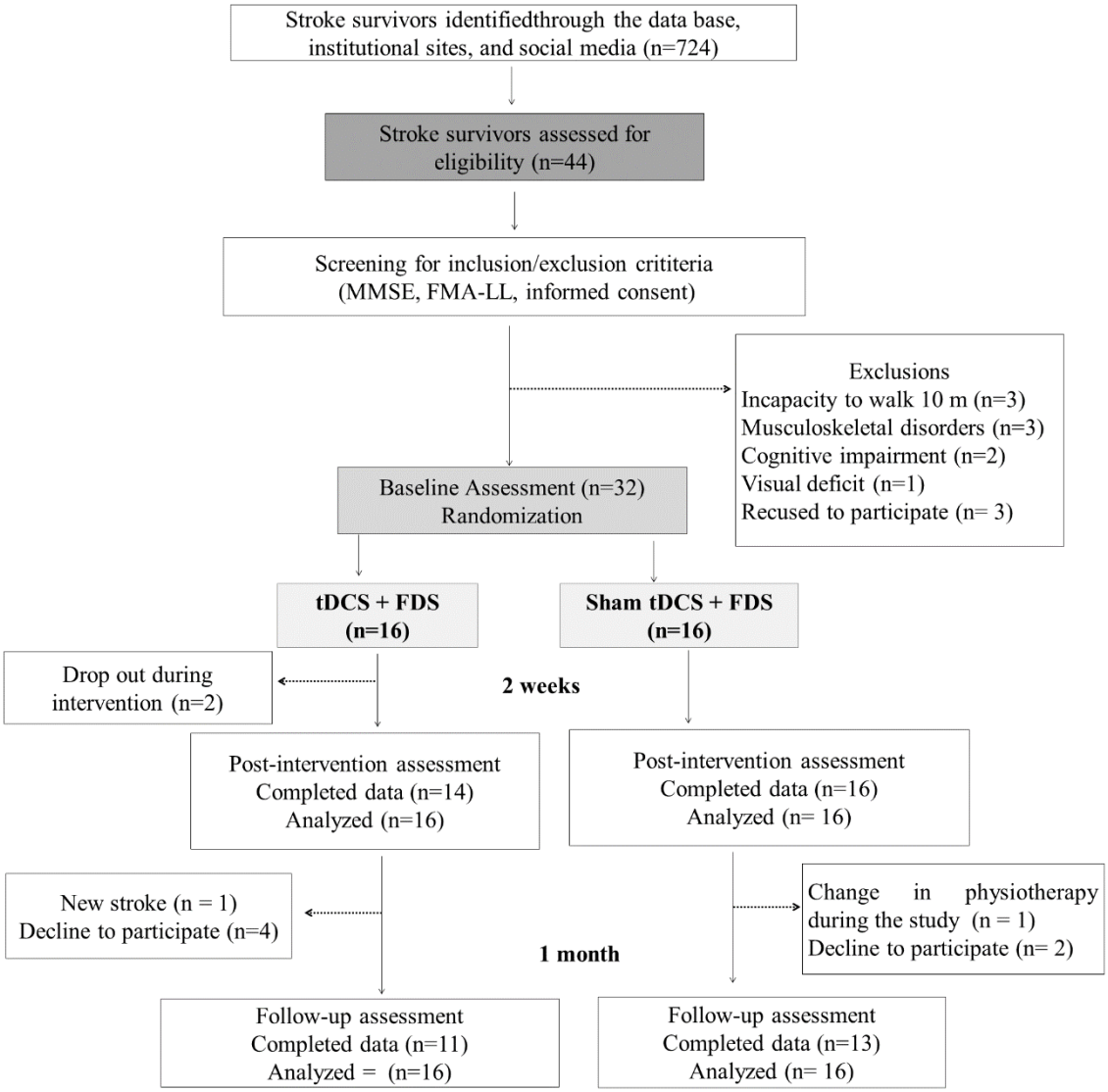


Figure 1.

Figure 2.


Stroke survivors identifiedthrough the data base, institutional sites, and social media (n=724)
Stroke survivors assessed for eligibility (n=44)
Screening for inclusion/exclusion crititeria (MMSE, FMA-LL, informed consent)
Exclusions
Incapacity to walk 10 m (n=3)
Musculoskeletal disorders (n=3)
Cognitive impairment (n=2)
Visual deficit (n=1)
Recused to participate (n= 3)
Baseline Assessment (n=32)
Randomization
tDCS + FDS (n=16)
Sham tDCS + FDS (n=16)
Drop out during intervention (n=2)
2 weeks
Post-intervention assessment
Completed data (n=14)
Analyzed (n=16)
Post-intervention assessment
Completed data (n=16)
Analyzed (n= 16)
New stroke (n = 1)
Decline to participate (n=4)
Change in physiotherapy during the study (n = 1)
Decline to participate (n= 2)
1 month
Follow-up assessment
Completed data (n=11)
Analyzed = (n=16)
Follow-up assessment
Completed data (n=13)
Analyzed (n= 16)

6 CONCLUSÃO GERAL

Com esta tese, buscou-se estudar os efeitos da tDCS e da FES sobre o nervo peroneal comum na reabilitação de pacientes com hemiparesia crônica após AVC. Com o primeiro artigo desta tese, mostramos que existe uma baixa qualidade de evidência de efeitos positivos da FES na melhora da velocidade da marcha quando combinado com fisioterapia. FES pode ser capaz de melhorar a mobilidade ativa de dorsiflexão do tornozelo, a mobilidade funcional e equilíbrio.

No segundo artigo, visamos determinar os efeitos de duas semanas de uso de FDS combinado com treino intensivo de marcha em indivíduos após AVC com queda do pé. Avaliamos os ganhos na amplitude de dorsiflexão ativa do tornozelo durante a locomoção com a órtese em modo ON (efeito de treino) e OFF (efeito terapêutico), quantificados por meio de análise discreta e SPM. Também avaliamos alterações na amplitude de movimento de flexão e extensão do joelho e quadril, parâmetros espaço-temporais da marcha e distância percorrida durante os treinos. Nossos resultados mostraram que, após duas semanas de uso da FDS combinado com treino intensivo de marcha e com a órtese em modo ON, os indivíduos melhoraram a dorsiflexão ativa de tornozelo e aumentaram a distância percorrida durante os treinos.

O terceiro estudo realizado durante esta tese, teve o objetivo de verificar os efeitos da utilização simultânea da tDCS e da FDS na mobilidade funcional, espasticidade e qualidade de vida dos indivíduos após AVC. Além disso, também medimos a resistência da marcha durante o treino de marcha, a aderência e a segurança do tratamento. O tDCS parece não acrescentar efeito ao treino de marcha com FDS na melhoria da mobilidade funcional, espasticidade, qualidade de vida, e resistência à marcha em indivíduos após o AVC.

No quarto artigo, nosso objetivo foi investigar os efeitos da associação do tDCS ao treino com FDS sobre os níveis de BDNF no soro. Também examinamos a ligação entre os níveis de BDNF no soro com os níveis de IGF1, IGFB3, IL-6, IL-10 e TNF-α, comprometimento motor, participação social e mobilidade funcional em indivíduos após AVC na fase crônica. Nossos resultados demonstraram que ambos os grupos de tratamento aumentaram os

níveis de BDNF e IL-10, diminuíram os níveis séricos de Cortisol e IL-6 e melhoraram o comprometimento motor, a mobilidade funcional e a participação social. No entanto, não observamos diferenças entre os grupos. O tDCS foi capaz de induzir uma diminuição do TNF-α. Além disso, observamos uma fraca correlação entre o aumento dos níveis de BDNF e o comprometimento motor. O tDCS parece não acrescentar efeito ao treino de marcha do FDS na melhoria da plasticidade em indivíduos após AVC.

O quinto e último estudo desta tese teve como objetivo verificar os efeitos do tDCS combinados com o treino de marcha com FDS sobre velocidade de marcha. Além disso, avaliamos os parâmetros espaço-temporal da marcha, cinemática angular do membro inferior parético (articulação de tornozelo, joelho e quadril) e simetria da marcha de indivíduos crônicos após AVC. Nossas descobertas revelam que a combinação da estimulação central através do tDCS bi-cefálico não foi capaz de acrescentar efeito significativo no desempenho da marcha quando combinada com FDS. Sendo assim, levanta dúvidas sobre um benefício clínico dessa intervenção em indivíduos pós AVC crônico.

A hipótese inicial deste estudo era que o tDCS equilibrasse a excitabilidade entre os hemisférios após a lesão cerebral e contribuísse para a recuperação motora pós-AVC. O tDCS não conseguiu adicionar benefícios ao FDS e ao treinamento da marcha em nenhum dos resultados avaliados. Embora estudos relatem que a estimulação bi-cefálica é capaz de melhorar o equilíbrio e a mobilidade funcional nas fases aguda e subaguda após o acidente vascular cerebral. Acreditamos que a maior extensão de tecido cerebral sobrevivente e aumento de fatores neurotróficos envolvidos com a neuroplasticidade nessas fases podem permitir melhores respostas à tDCS. Sendo assim a falta de tecido cerebral sobrevivente na fase crônica após o AVC poderia explicar nossos resultados.

A representação cortical do membro inferior ter uma orientação mais profunda e vertical em comparação com a área do membro superior, portanto, acreditamos ser menos responsiva ao tDCS. Embora a montagem do eletrodo sobre a área da perna M1 seja adequada para provocando modulação nos membros inferiores, a baixa especificidade da montagem bi-cefálica pode ter atenuado a corrente. A estimulação inibitória ou excitatória por eletrodos de superfície ocorre devido ao fluxo de corrente do ânodo para o catodo. Assim,

poderíamos supor que, usando a montagem de eletrodos bi-cefálicos, a corrente não penetrasse fundo o suficiente, fosse atenuada e menos eficaz. Pesquisas adicionais, com diferentes montagens de eletrodos, são necessários para responder a essa pergunta.

Outro fator que pode ter influenciado nos resultados é em que momento deve-se aplicar a estimulação - antes ou durante o treino de marcha. É possível que os estímulos aplicados ao mesmo tempo, como os que usamos em nosso estudo, possam estar competindo entre si e influenciando os resultados.

Nosso estudo possui algumas limitações que precisam ser destacadas. Não controlamos as áreas corticais específicas ativadas pelo tDCS através da avaliação da excitabilidade neural e das interações inter-hemisféricas. Além disso, embora mais de 90% da amostra tenha completado as duas semanas de intervenção, as perdas de acompanhamento excederam 20% - e não podemos especificar como essas perdas podem impactar a interpretação dos efeitos do tratamento a longo prazo. Outros fatores também podem ser responsáveis pela falta de resultados positivos com o tDCS, como a variabilidade da amostra em relação à gravidade do AVC e ao tempo após o AVC.

De modo geral, verificou-se que a tDCS bi-cefálica não adiciona benefícios ao treino de marcha com FDS na reabilitação de indivíduos pós AVC crônico. Consideramos essas descobertas bastante relevantes porque podem apoiar a decisão clínica sobre a utilização do tDCS nesta população. Considerando que não encontramos efeitos no modo de estimulação, como perspectivas, sugerimos ensaios clínicos com diferentes montagens e protocolos de aplicação para verificar se o tDCS é eficaz na reabilitação de membros inferiores em após AVC. Também sugerimos a utilização de protocolos mais longos de tDCS tanto simultânea quanto previamente à FDS na mesma sessão de tratamento. Avaliações da eficácia fisiológica de técnicas de neuromodulação através da estimulação magnética transcraniana, da ressonância magnética funcional e da eletroencefalografia também são recomendadas.

De modo geral, a FES no nervo fibular comum pode ser usada como uma terapia complementar para reabilitação de indivíduos com hemiparesia crônica após AVC. No entanto, nossos resultados apresentaram uma diferença clínica muito pequena. Considerando que o tratamento fisioterapêutico deve ser

baseado nas necessidades e nos níveis de comprometimento de cada sujeito, sugere-se que novos estudos sejam feitos, utilizando o treino de marcha com o FDS com variação de velocidade ou outras atividades desafiantes para obter melhores resultados.

7 ANEXOS

ANEXO A - Parecer consubstanciado do CEP

IRMANDADE DA SANTA CASA DE MISERICORDIA DE PORTO ALEGRE - ISCMPA

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Associação entre neuro-órtese e estimulação transcraniana por corrente continua na reabilitação do paciente com sequela de Acidente Vascular Cerebral

Pesquisador: ALINE DE SOUZA PAGNUSSAT

Área Temática:

Versão: 3

CAAE: 64819617.0.0000.5335

Instituição Proponente: Irmandade da Santa Casa de Misericordia de Porto Alegre - ISCMPA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.850.833

Apresentação do Projeto:

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 afeta o equilíbrio inibitório inter-hemisférico, gerando um padrão anormal de atividade entre os hemisférios cerebrais e provocando um desajuste na inibição inter-hemisférica. Devido às perdas do controle

neuromotor, dentre outras alterações, a marcha apresenta alterações em sua velocidade, cadência, tempo e comprimento de passos, desajustes

quanto à postura, equilíbrio e reações de proteção. De forma geral, o indivíduo não realiza adequadamente a tomada de peso durante a fase de

apoio, além de ser observada a fraqueza dos músculos dorsiflexores e aumento da espastiticidade dos plantiflexores. A limitação da caminhada gera

um impacto direto na mobilidade funcional e qualidade de vida desses indivíduos. Acredita-se que tratamentos que promovam plasticidade no cérebro lesado possam promover a recuperação funcional. Nesse sentido, o uso da eletroestimulação funcional (FES) e da estimulação transcraniana por corrente contínua (tDCS) têm sido estudadas como parte da reabilitação neurofuncional. O FES pode ser aplicado de forma funcional durante a marcha por meio da órtese de sistema "foot drop stimulators" (FDS). A FDS é uma órtese que realiza uma estimulação funcional sobre nervo fibular comum fornecendo padrões de movimento de tarefas específicas que

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resultam em atividade funcional dinâmica durante a
deambulação. Por outro lado, a tDCS atua no bloqueio ou na redução da plasticidade "mal adaptativa" podendo reduzir a competição interhemisférica,
promovendo 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). Ambas as formas de terapia têm sido investigadas na literatura, e resultados promissores têm sido apontados. Entretanto, há carência de informações precisas sobre a modificação no padrão da marcha com a utilização das órteses FDA, e também sobre sua associação com mecanismos de eletroestimulação central. Desse modo, os objetivos do presente estudo são: (1) avaliar o efeito da utilização FDS sobre a modificação no padrão da marcha de indivíduos com hemiparesia; (2) verificar o efeito da associação entre FDS e tDCS sob a reabilitação do membro inferior e da marcha de pacientes com hemiparesia crônica após AVC.

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar o efeito da utilização FDS sobre a modificação imediata no padrão da marcha de indivíduos com hemiparesia crônica pós AVC. Verificar o efeito da associação entre tDCS e FDS sob a reabilitação do membro inferior e da marcha de indivíduos com hemiparesia crônica após AVC.

Avaliação dos Riscos e Benefícios:

Riscos:

Os possíveis riscos ou desconfortos decorrentes da participação na pesquisa são irritação (vermelhidão) ou coceira da pele na região onde forem posicionados os eletrodos. Eventualmente, você poderá sentir dor de cabeça. Algum desconforto poderá ser sentido na perna em função da utilização da neuro-órtese ou associados à coleta de sangue, como dor, hematoma ou outro desconforto no local da coleta. Salientamos que a coleta
será realizada por profissional experiente e habilitado, portanto, os riscos e desconfortos tendem a ser mínimos. Caso qualquer um desses desconfortos aconteça, o tratamento será interrompido e, se necessário, você será encaminhado para avaliação médica. Os tratamentos que você irá receber são técnicas conhecidas, testadas e estudadas em seres humanos há vários anos, são consideradas seguras e capazes de trazer
benefícios para as pessoas que as utilizam. Nós asseguramos que todas as normas e recomendações de segurança para a utilização dos dois tratamentos propostos serão rigorosamente seguidos, de acordo com a orientações.

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Benefícios:

Os possíveis benefícios decorrentes da participação na pesquisa são de melhorar os movimentos dos músculos que são importantes para acaminhada e que estão prejudicados. Dessa forma, você poderá realizar melhor suas atividades do dia-a-dia.

Comentários e Considerações sobre a Pesquisa:

Solicitação de correção do parecer emitido pelo CEP Nº.: 3722486, devido ao erro da Plataforma Brasil, nos textos apresentados.

Considerações sobre os Termos de apresentação obrigatória:

Apresentados e adequados.

Conclusões ou Pendências e Lista de Inadequações:

Emenda apresentada:

1) Modificação dos grupos experimentais - na primeira versão do projeto ambos os grupos experimentais receberiam a estimulação transcraniana por corrente continua. No entanto, apenas o grupo tDCS+FDS receberá esta estimulação, enquanto que o grupo ShamtDCS+FDS receberá o estimulo placebo. Em vista disso foram feitas modificações no TCLE no campo que descreve os grupos de tratamento, cuja redação passa a:

I- tDCS sham + FDS: Você utilizará a neuro-órtese com moderada intensidade de estimulação, associada à caminhada em uma esteira elétrica em velocidade confortável. Junto com a neuro-órtese, serão posicionados eletrodos na cabeça sem que sejam conduzidas correntes elétricas significativas, não produzindo efeitos de melhora, exclusivamente para fins de comparação com o grupo que teve a região afetada pelo AVC realmente estimulada.

II- tDCS + FDS: Você utilizará a neuro-órtese com moderada intensidade de estimulação, associada à caminhada em uma esteira elétrica em velocidade confortável. Junto com a neuro-órtese você receberá estimulação no cérebro por meio de uma corrente elétrica contínua aplicada por meio de eletrodos posicionados na cabeça (tDCS), a fim de estimular a região do cérebro que foi afetada pelo AVC.

2) Inclusão de um grupo referência no estudo – Grupo de indivíduos saudáveis, pareados por sexo e idade,os quais serão submetidos a uma avaliação da caminha e da mobilidade funcional utilizando os mesmos testes já descritos no projeto. Essa coleta tem por objetivo adquirir valores normativos de comparação. Foi elaborado novo termo de consentimento específico para indivíduos

do grupo referência.

3)Tendo em vista a modificação dos grupos experimentais, bem como a inclusão de um grupo referência foi necessário alterar o cronograma do presente projeto. Com novas datas para a coleta de dados, análise de dados, elaboração e submissão do(s) artigo(s) científicos e a elaboração da tese.

Considerações Finais a critério do CEP:

Após a avaliação da solicitação da correção ao Parecer Consubstanciado do CEP, referente ao estudo acima descrito, o presente Comitê não encontrou óbices quanto à implementação das mesmas.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1503086_E2.pdf	04/02/2020 08:41:58		Aceito
Outros	JUSTIFICATIVA_DA_EMENDA_PARECER.pdf	04/02/2020 08:36:25	Maira Jaqueline da Cunha	Aceito
Parecer Anterior	PB_PARECER_CONSUBSTANCIADO_out2019.pdf	28/01/2020 11:08:03	Maira Jaqueline da Cunha	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_amostrareferencia.pdf	16/10/2019 05:08:35	Maira Jaqueline da Cunha	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	16/10/2019 05:08:22	Maira Jaqueline da Cunha	Aceito
Brochura Pesquisa	FORMULARIODEINSCRICAODEPROJETOSDEPESQUISACOMITEDEETICAEMPESQUISISCMPA.pdf	15/02/2017 11:31:46	Maira Jaqueline da Cunha	Aceito
Projeto Detalhado / Brochura Investigador	Projeto.pdf	06/02/2017 11:23:42	Maira Jaqueline da Cunha	Aceito
Folha de Rosto	FOLHADEROSTO.pdf	02/02/2017 00:55:51	Maira Jaqueline da Cunha	Aceito
Declaração de Instituição e Infraestrutura	TERMODEANUENCIADORESPONSAVELPELOSETOROUINSTITUICAOONDESERAREALIZADAAPESQUISA.pdf	02/02/2017 00:51:19	Maira Jaqueline da Cunha	Aceito
Declaração de Instituição e Infraestrutura	DECLARACAODEAUTORIZACAODACHEFIARESPONSAVEL.pdf	02/02/2017 00:47:13	Maira Jaqueline da Cunha	Aceito

Declaração de Pesquisadores	DECLARACAODEUTILIZACAODEDADOSDEPRONTUARIOSEUSODEPUBLICACAO.pdf	02/02/2017 00:44:32	Maira Jaqueline da Cunha	Aceito
Declaração de Pesquisadores	DECLARACAODECONFIDENCIALIDADEDOSUJEITONOESTUDO.pdf	02/02/2017 00:42:48	Maira Jaqueline da Cunha	Aceito
Declaração de Pesquisadores	DECLARACAODEISENCAODEONUSAINSTITUICAO.pdf	02/02/2017 00:42:00	Maira Jaqueline da Cunha	Aceito
Orçamento	ORCAMENTO.pdf	02/02/2017 00:38:54	Maira Jaqueline da Cunha	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	DECLARACAODEMANUSEIODEMATERIAISBIOLOGICOS.pdf	02/02/2017 00:36:25	Maira Jaqueline da Cunha	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 20 de Fevereiro de 2020

Assinado por:
Claudio Marcel Berdún Stadñik
(Coordenador(a))