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Flávio Taira Kashiwagi

Non-invasive brain stimulations for unilateral spatial neglect after stroke: a systematic review and meta-analysis of randomized and non-randomized controlled trials

Dissertação apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Mestre em Clínica Médica.

Orientador: Prof. Dr. RODRIGO BAZAN

Botucatu
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Palavras-chave: Acidente Vascular Cerebral; Cérebro; Estimulação; Não-invasiva; Negligência.

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À Faculdade de Medicina da Universidade Estadual Paulista pela oportunidade.

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SUMÁRIO

RESUMO

Objetivo: Uma revisão sistemática para investigar o impacto da estimulação cerebral não-invasivas (i.e., estimulação transcraniana de corrente direta (ETCC), estimulação magnética transcraniana repetitiva (EMTr) e Theta-Burst (TBS)) em comparação com placebo para negligência espacial unilateral após acidente vascular encefálico (NEU).

Bases de dados: Pesquisas na MEDLINE, EMBASE, CENTRAL, CINAHL e LILACS até julho de 2017.

Seleção de estudos: Ensaios controlados randomizados (ECRs) e não-ECRs.

Extração de dados: Dois pares de revisores examinaram de forma independente artigos potencialmente elegíveis, extraíram dados dos estudos incluídos sobre populações, intervenções e resultados e avaliaram seu risco de viés. Utilizamos a abordagem GRADE para avaliar a certeza geral da evidência por resultado.

Síntese de dados: 12 ensaios randomizados, incluindo 273 participantes, e quatro não-ECRs, incluindo 94 participantes, mostraram ser elegíveis. Os resultados fornecidos pelos ECR sugerem um benefício no NEU geral medido pelo Teste de Bissecção de Linhas com estimulação cerebral não invasiva em comparação com placebo (SMD –2,35, IC 95% -3,72, -0,98; p = 0,0001; I2 = 85%); particularmente a EMTr produziu resultados que foram consistentes com a meta-análise geral (SMD -2,82, IC 95% -3,66, -1,98; p = 0,09; I2 = 0%). Os resultados de dois ECRs que comparam o EMTr com placebo também sugeriram um benefício no NEU geral medido pelo Motor Free Perception Test com EMTr 1Hz(SMD 1,46, IC 95% 0,73, 2,20; p <0,0001; I2 = 0%). Houve também um benefício no NEU global medido pelo Teste de Albert e Teste de Cancelamento de Linha com rTMS de 1 Hz em comparação com placebo (SMD 2,04, IC 95% 1,14, 2,95; p <0,0001; I2 = não aplicável). Os resultados também sugerem um possível melhora nas atividades da vida diária com EMTr de 10 Hz em comparação com

placebo (SMD 1,83, IC 95% 0,68, 2,97; p = 0,002; I2 = não aplicável).

Conclusões: Evidências de qualidade moderada mostram que o EMTr, com 1 Hz é mais eficaz que o placebo para negligência espacial unilateral após o AVC medido pelo Motor Free Perception Test. Além disso, evidências de baixa qualidade também sugerem um benefício da estimulação cerebral não-invasiva, particularmente com o uso de EMTr, para o NEU medido pelo Teste de Bissecção de Linha, Teste de Albert e Teste de Cancelamento de Linha. Esses achados devem ser explorados ainda mais no contexto da prática clínica entre neurologistas e fisioterapeutas.

ABSTRACT

Objective: A systematic review to investigate the impact of non-invasive brain stimulations (i.e., transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and theta-burst (TBS)) compared to sham for unilateral spatial neglect after stroke.

Data sources: Searches of MEDLINE, EMBASE, CENTRAL, CINAHL, and LILACS up to July 2017.

Study selection: Randomized controlled trials (RCTs) and non-RCTs.

Data extraction: Two pairs of reviewers independently screened potentially eligible articles, extracted data from included studies on populations, interventions and outcomes, and assessed their risk of bias. We used the GRADE approach to rate overall certainty of the evidence by outcome.

Data synthesis: 12 randomized trials including 273 participants, and four non-RCTs including 94 participants proved eligible. Results provided by RCTs suggest a benefit in overall USN measured by Line Bisection Test with non-invasive brain stimulations in comparison to sham (SMD -2.35, 95% CI -3.72, -0.98; p = 0.0001; I^2=85%); particularly the rTMS yielded results that were consistent with the overall meta-analysis (SMD -2.82, 95% CI -3.66, -1.98; p = 0.09; I^2=0%). Results from two RCTs comparing rTMS with sham also suggested a benefit in overall USN measured by Motor Free Visual Perception Test with 1 Hz (SMD 1.46, 95% CI 0.73, 2.20; p < 0.0001; I^2=0%). There was also a benefit in overall USN measured by Albert test and Line crossing test with 1 Hz rTMS compared to sham (SMD 2.04, 95% CI 1.14, 2.95; p <0.0001; I^2=not applicable). Results also suggest a possible increase in daily life functions with 10 Hz rTMS compared to sham (SMD 1.83, 95% CI 0.68, 2.97; p =0.002; I2=not applicable).

Conclusions: Moderate-quality evidence shows that rTMS, with 1 Hz, is more

efficacious compared to sham for unilateral spatial neglect after stroke measured by Motor Free Visual Perception Test. Furthermore, low-quality evidence also suggests a benefit of non-invasive brain stimulation, particularly with the use of rTMS, for overall USN measured by Line Bisection Test, Albert test and Line crossing test. These findings should be explored further in the context of the clinical practice among neurologists and physiotherapists.

1 BACKGROUND

Stroke is the second leading cause of death worldwide and the primary cause of chronic disability in adults [1]. In the United States, it is the fourth leading cause of death overall [2]. Among people who survive a stroke, unilateral spatial neglect (USN) is the most frequent disorder for right hemisphere lesions [3].

The incidence of USN varies widely from 10% to 82% [4-6]. USN is characterized by the inability to report or respond to people or objects presented on the side contralateral to the lesioned side of the brain and has been associated with poor functional outcomes and long stays in hospitals and rehabilitation centers.

Pharmacological interventions such as dopamine and noradrenergic agonists or pro-cholinergic treatment, have been used in people affected by USN after stroke, but the evidence derived from a Cochrane systematic review which included only two available RCTs was very low and inconclusive [7].

Other non-pharmacological rehabilitation techniques have been explored for USN with the aim to facilitate the recovery of perception and behavior which include right half-field eye-patching [8], mirror therapy [9], prism adaptation [10], left-hand somatosensory stimulation with visual scanning training [11], contralateral transcutaneous electrical nerve stimulation and optokinetic stimulation [12], trunk rotation [13], repetitive transcranial magnetic stimulation [14], galvanic vestibular stimulation [15], and dressing practice [16]. However, their results do not support use of these techniques in isolation for improvement of secondary outcomes such as performance and sensorimotor functions, activities of daily living (ADLs), or quality of life [9,14,17].

Non-invasive brain stimulations (transcranial Direct Current Stimulation (tDCS) and repetitive Transcranial Magnetic Stimulation (rTMS)) have already shown their

ability to modify cortical excitability [18]. The tDCS is a non-invasive method used to modulate cortical excitability by applying a direct current to the brain [19,20] which is less expensive than repetitive transcranial magnetic stimulation (rTMS). The latter is an electric current that creates magnetic fields penetrate the brain and can modulate cortical excitability by decreasing or increasing it and potentially improve cognitive abilities (including spatial neglect).

A previous Cochrane systematic review [21] summarized results about the effects of tDCS versus control (sham/any other intervention) in activities of daily living (ADLs) among stroke survivors. The authors included 32 randomized controlled trials (RCTs), and concluded that tDCS might enhance ADLs, but upper and lower limb function, muscle strength and cognitive abilities should be further explored [21]. Another Cochrane systematic review [22] assessed the efficacy of repetitive transcranial magnetic stimulation (rTMS) compared to sham therapy or no therapy for improving function in people with stroke. The 19 included trials showed that rTMS was not associated with a significant increase in ADLs neither on motor function, therefore the authors do not support the use of rTMS for the treatment of stroke, and they claimed for further trials to confirm their findings [22].

Previous reviews were, however, limited in that they did not include non-RCTs studies neither evaluated the newest non-invasive brain stimulation – thetaburst. We therefore conducted a systematic review of RCTs and non-RCTs studies that assessed the impact of tDCS, rTMS, and TBS for unilateral spatial neglect after stroke.

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Undertaking searches: Erica A. Suzumura (EAS)

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Organizing retrieval of papers: FTK and GL

Screening retrieved papers against inclusion criteria: FTK, HG, NG and RB

Appraising quality of papers: FTK, HG, NG and RB

Extracting data from papers: FTK and EAS

Writing to authors of papers for additional information: GL

Providing additional data about papers: GL

Obtaining and screening data on unpublished studies: GL

Managing data for the review: FTK and RB

Entering data into Review Manager (RevMan): FTK and RB

Analyzing RevMan statistical data: FTK and RB

Interpreting data: FTK, HG, NG, EAS, GL and RB

Making statistical inferences: FTK, HG, NG, EAS, GL and RB

Writing the review: FTK and RB

Taking responsibility for reading and checking the review before submission: FTK, HG, NG, EAS, GL and RB

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Non-invasive brain stimulations for unilateral spatial neglect after stroke: a systematic review and meta-analysis of randomized and non-randomized controlled trials

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Short title: Non-invasive brain stimulations for unilateral spatial neglect.

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Data sharing statement: No additional data available.

Key words: non-invasive brain stimulation; tDCS; rTMS; theta burst; spatial neglect; stroke; systematic review; GRADE.

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