

Brief Communication
Comunicação Breve

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What are the barriers to participation in a neuromodulation pilot trial for aphasia after stroke?

Quais são as barreiras para a participação em estudo piloto de neuromodulação para afasia após acidente vascular cerebral?

ABSTRACT

Purpose: Aphasia is a common and debilitating manifestation of stroke. Transcranial electrical stimulation uses low-intensity electric currents to induce changes in neuronal activity. Recent evidence suggests that noninvasive techniques can be a valuable rehabilitation tool for patients with aphasia. However, it is difficult to recruit patients with aphasia for trials, and the reasons for this are not well understood. This study aimed to elucidate the main difficulties involved in patient's recruitment and inclusion in a randomized clinical study of neuromodulation in aphasia. **Methods:** We evaluated the reasons for the exclusion of patients in a pilot, randomized, double-blinded clinical trial in which patients diagnosed with motor aphasia after stroke were recruited from March to November 2018. A descriptive statistical analysis was performed. **Results:** Only 12.9% (4) of patients with ischemic stroke were included in the clinical trial. A total of 87.1% (27) of the 31 recruited patients were excluded for various reasons including: sensory aphasia (32.2%), dysarthria (25.8%), spontaneous clinical recovery (16.1%), previous stroke (6.4%), and death or mutism (3.2%). **Conclusion:** The presence of other types of aphasia, dysarthria, spontaneous recovery, deaths, and mutism were barriers to recruiting patients evidenced in this neuromodulation study.

RESUMO

Objetivo: A afasia é uma manifestação comum e debilitante do acidente vascular cerebral (AVC). A estimulação elétrica transcraniana por corrente contínua oferece uma corrente elétrica de baixa intensidade que induz alterações na atividade neuronal e evidências recentes sugerem que técnicas não invasivas podem servir como uma ferramenta benéfica para a reabilitação de pacientes afásicos. No entanto, é muito difícil recrutar esses pacientes para estudos clínicos e as razões não são claras. O objetivo do estudo foi identificar as principais dificuldades envolvidas no recrutamento e inclusão de pacientes em ensaio clínico piloto randomizado sobre neuromodulação em pacientes com afasia. **Método:** Foram avaliadas as razões para a exclusão e não inclusão de pacientes em um ensaio clínico piloto, randomizado, duplo-cego no qual foram incluídos pacientes diagnosticados com afasia motora após AVC no período de março a novembro de 2018. Análise estatística descritiva foi realizada. **Resultados:** Apenas 12,9% (4) dos pacientes com AVC isquêmico foram incluídos no estudo. Um total de 87,1% (27) dos 31 pacientes recrutados foram excluídos por apresentarem afasia sensorial (32,2%), disartria (25,8%), recuperação clínica espontânea (16,1%), AVC prévio (6,4%) e óbito ou mutismo (3,2%). **Conclusão:** A presença de outros tipos de afasia, disartria, recuperação espontânea, óbitos e mutismo foram as principais barreiras ao recrutamento de pacientes evidenciadas nesse estudo de neuromodulação.

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INTRODUCTION

A stroke is characterized by a focal acute neurological deficit of vascular origin. It often results in diverse functional impairments, such as language disorders, which are denominated aphasias. Aphasia affects more than 38% of stroke survivors and can be defined as a language disorder resulting from a brain injury that leads to alterations in the content, form, and use of language and its underlying cognitive processes^(1,2).

Aphasia can incapacitate and compromise quality of life and daily life activities. Currently available therapies show limited success in terms of execution, results, and short- and long-term prognoses. For these cases, rehabilitation seeks to achieve better day-to-day patient adaptation and generally restore affected functions (both language and non-language). There is no specific therapeutic method for all patients with aphasia. Thus, the therapy can be carried out in many ways as long as it meets the specific needs of each subject⁽³⁾.

The literature suggests that noninvasive techniques for brain stimulation may benefit patients with aphasia by improving their language abilities. Transcranial electrical stimulation by direct current (tDCS) uses low-intensity electrical currents to induce changes in neuronal activity, probably by modulating the intensity of synaptic transmission. The effects of tDCS persist after the stimulation period^(4,5).

Over the last decade, there have been an increasing number of aphasia rehabilitation studies. The majority of these studies are conducted in high-income countries. Difficulties with patient recruitment represent a great barrier to advances in the field of aphasia. Probable reasons for the scarcity of studies in low- and medium-income countries include lack of financial resources and qualified staff for research; however, the local conditions and characteristics of stroke patients in these areas are equally important. Strategies to improve recruitment must target economic aspects and be deliverable within a specific social context^(6,7).

To develop rehabilitation treatments based on evidence that are adapted to specific contexts, it is crucial to understand the obstacles for including patients with stroke in aphasia rehabilitation protocols in developing countries. Due to the questions described above, we acquired in-depth data on patient profiles and recruitment characteristics for a randomized clinical trial on neuromodulation-based language rehabilitation after stroke to obtain a better picture of the barriers to participation in rehabilitation studies.

METHODS

We prospectively evaluated the reasons for the exclusion of patients with motor aphasias post-stroke in a clinical, randomized, double-blinded pilot study. The study was conducted in an adult language outpatient clinic of Botucatu Medical School

(UNESP). Patients with aphasia received anodic transcranial electrical stimulation or sham stimulation in combination with language rehabilitation.

We recruited patients with ischemic stroke who were admitted to the institution's stroke unit between March and November 2018 and were referred to the adult language outpatient clinic. The patients were at least 18 years old, Brazilian Portuguese native speakers, right-handed, and diagnosed with motor aphasia due to left-hemisphere lesions, as confirmed by computed tomography scans or magnetic resonance imaging. The individuals were assessed initially to confirm the diagnosis of motor aphasia by a speech therapist using the *Montreal-Toulouse Language Assessment Battery* (MTL-BR)⁽⁸⁾.

The exclusion criteria were as follows: any metal in the cephalic segment, lesions in the cutaneous area, pacemaker use, sensory aphasia, clinical instability, severe cognitive impairment, auditory and/or visual alterations prior to the stroke, previous stroke or convulsions in the last 12 months or other associated neurological diseases, dysarthria, severe difficulty in verbal comprehension, and oral or verbal apraxia as confirmed by the Token Test and the Protocol for Evaluation of Speech Apraxia^(9,10).

A descriptive statistical analysis was performed. The results are expressed as numbers, percentages, means, and standard deviations.

The study was approved by the Research Ethics Committee of Botucatu Medical School (reference number 2.554.242). All patients signed an informed consent form.

RESULTS

The availability of speech therapy care in the adult language outpatient clinic was restricted to patients who presented with alterations of speech or language originating from acquired neurological injuries, such as stroke or traumatic brain injury.

In this study, a total of 58 patients diagnosed with aphasia were admitted to the institution's stroke unit during the recruitment period and were referred to the outpatient clinic: 14 patients were lost follow-up after hospital discharge and 44 were followed up in outpatient care. Of these 44 patients, 31 had an ischemic stroke and were recruited for the study.

The mean age of the 31 patients screened for the protocol was 64.7 ± 8.7 years, 54.8% ($n = 17$) were male, 38.7% ($n = 12$) were Afro-Brazilians, 54.84% ($n = 17$) were Caucasian, and 6.5% ($n = 2$) were Asians.

Twenty-seven (87.1%) patients were excluded. One (3.2%) died, 10 (32.2%) displayed severe difficulties in oral comprehension or characterizing sensory aphasia, eight (24.8%) presented with dysarthria, two (6.4%) had histories of prior stroke, one (3.2%) exhibited mutism, and five (16.1%) patients recovered spontaneously. Therefore, only four patients fulfilled the requirements of the study. A flowchart of patient recruitment is displayed in Figure 1.

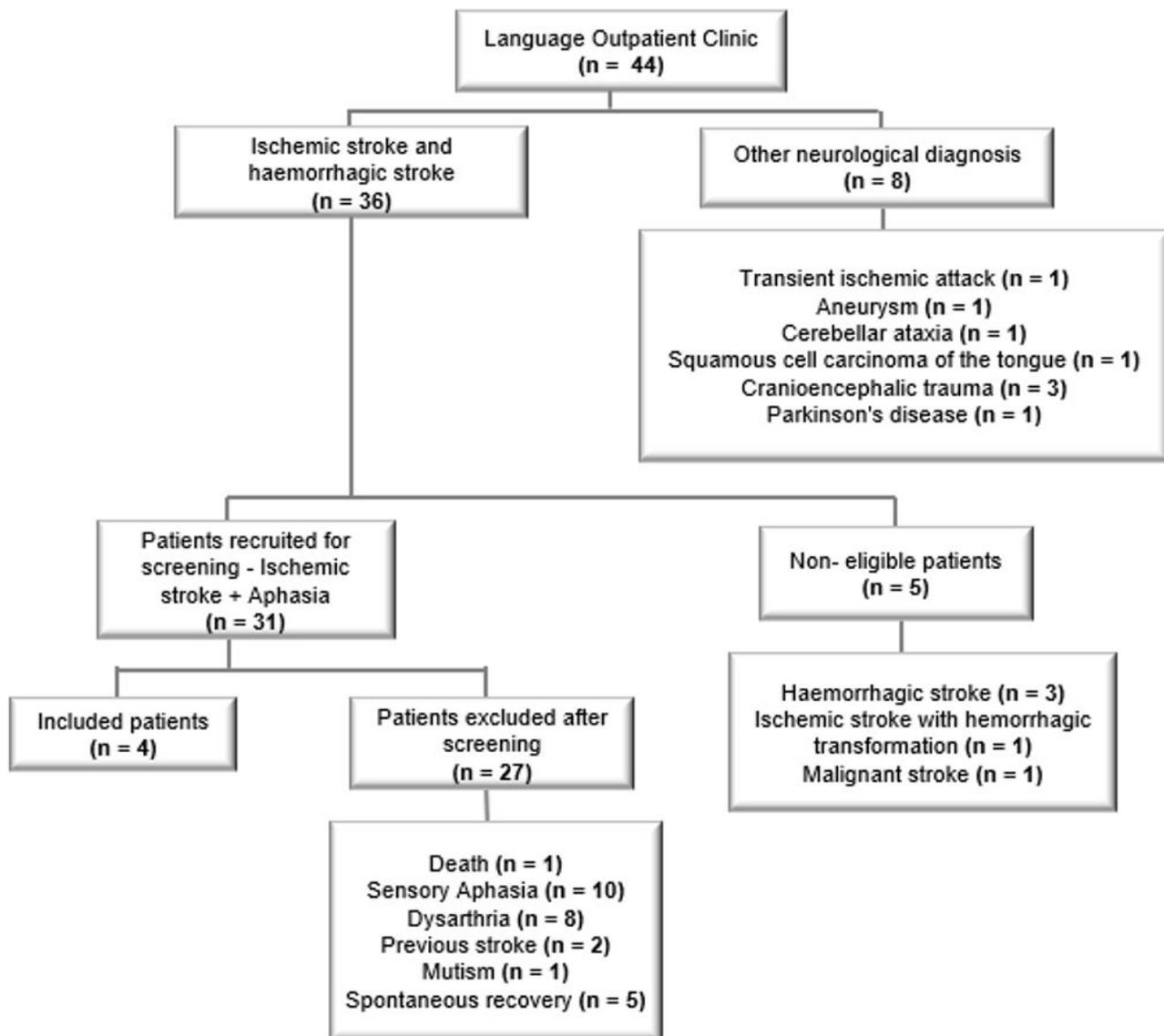


Figure 1. Study recruitment flowchart.

DISCUSSION

More than two-thirds of the patients in this study who fulfilled the inclusion criteria were excluded because of sensory aphasia, dysarthria, or spontaneous recovery of aphasia. The literature showed, the primary reasons for exclusion were related to apraxia, dysarthria, and others causes, the use of medications, and the inclusion criteria for transcranial stimulation. In other studies, reported neuroplasticity-related spontaneous recovery of aphasia or motor impairments after stroke, reactivation of impaired areas, and resolution of cerebral diaschisis, mainly among less-severe clinical cases⁽¹¹⁻¹³⁾. In our study, an important criterion for exclusion was spontaneous recovery of aphasia between the time of recruitment and the start of the protocol.

The recruitment rate of patients in this study (n = 31) over an eight-month period was considered low for international

clinical trial protocols, even given adequate referral to the outpatient clinic. In our study, 14 patients were lost to follow-up after hospital discharge. Clinical trials conducted in developing countries have specific challenges related to patient recruitment and inclusion⁽¹⁴⁾.

In our study, most patients came from remote, rural regions with poor public transport. This made access to the treatment center difficult. Unfortunately, the location of patients' homes is a limitation to the inclusion of participants, even with the tireless efforts of the institution's social service team to facilitate access and treatment adherence. Patients with aphasia usually have considerable communication difficulties and need the support and availability of a companion for traveling.

In addition, we realized that in our service, many patients have poor educational, socioeconomic, and cultural backgrounds. This can make it difficult for them to understand their own

treatment and how important professional follow-up after hospital discharge is to the rehabilitation process after stroke.

May studies have used tDCS in patients with aphasia, however, the main reasons for not including patients remain unclear. Similar studies conducted in the USA, Germany, Poland, and Korea found that the main reasons for exclusion were use of anti-depressives, apraxia, dysarthria, non-native speakers, use of pacemakers, dementia, epilepsy, depression, previous stroke, seizure, and multiple stroke lesions. In these studies, the exclusion rate ranged from 16.8–86.3%⁽¹¹⁻¹³⁾. Unfortunately, many studies do not mention the number of patients screened and excluded, making it difficult to compare our results with prior studies⁽¹¹⁻¹³⁾.

Generally, clinical trials require methodological rigor and high applicability of the intervention to the population. While descriptive studies aim to identify mechanisms, pragmatic clinical trials are conducted to evaluate viable interventions. In many developing countries, the need for clinically relevant trials requires adaptation of protocols to local needs and the cultural characteristics of the population⁽¹⁵⁾.

Conducting a clinical trial with patients with aphasia is a major challenge, particularly in developing countries. However, although challenges in including aphasia patients in these types of studies are known, only a few studies have described and defined these challenges in detail.

CONCLUSION

The presence of other types of aphasia, dysarthria, spontaneous recovery, deaths, and mutism were barriers to recruiting patients evidenced in this neuromodulation study.

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Author contributions

MLA and RDG contributed with data curation, investigation and writing; JTS, PWR, RDMC, TRS, FCW, KFA and GPM contributed with writing (review and editing); PTHF, SGZB and LEGGB contributed with supervision in data collection and writing; and RB and GJL participated in the conceptualization, methodology, supervision and writing (review and editing).