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Effects of Neuromuscular Electrical Stimulation in Patients with Post-Stroke Related Dysarthria: A Double-Blinded, Phase-II Randomized Sham-Controlled Trial Protocol - ULYSSES Trial

Mustafa Reha Dodurgali[1,2*], Roser Coll-Fernández[2,3], Fernanda Queiroz Petrus[2,4], Márcio Kawano[2,5], Franziska Schreiber[2,6], Nayara de Lima Froio[2,7], Guilherme Jose Machado Lacerda[1,2,8], Edilin Lopez[2,9], Adrielly Martins[2,10], Angélica Flores-Flores[2,11], Belen Machado[2,12], Bethânia Soares dos Santos[2,13], Bianca Parron[2,4], Christiany Marilinn Tapia Argudo[2,14], Claudia Renata dos Santos Barros[2,15], Cristina Stephan[2,16], Daniela Bouzas Rodeiro[2,17], Gustavo Mucci[2,18], James Alfonso Carvajal Acosta[2,19], Larrie Rabelo Laporte[2,20], Laura De Leon Benedetti[2,21], Luis Morales Ojeda[2,22], Paula Raso Bastos[2,23], Regina Villalobos[2,24], Vinicius Trindade Gomes da Silva[2,25,26], Abdul Haseeb[2,27], Mariana Gasparoto Pereira Valério[2,28], Renata Junqueira Moll-Bernardes[2,29], Roseanne Ferreira de Freitas Euzébio[2,30], Gabriel Rangel Olivera[2,31], Caio Cesar dos Santos Kasai[2,4], Fathima Minisha[2,32], Juan Carlos Silva Godinez[2,33]

[1] Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [2] Principles and Practice of Clinical Research (PPCR), Harvard T.H. Chan School of Public Health - ECPE, Boston, MA, USA; [3] Department of Rehabilitation, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [4] Pontifícia Universidade Católica do Paraná (PUCPR), Londrina Brazil; [5] Clinical Oncology, São Camilo Mooca (IBCC Oncologia) and Hospital da Santa Casa de São Paulo, São Paulo, Brazil; [6] Institute of Pathology, Ludwig-Maximilians-University Munich, Germany; [7] State Government Employee Medical Assistance Institute (IAMSPE) and Federal University of São Paulo (UNIFESP), São Paulo, Brazil; [8] Universidade de São Paulo (HC-FMUSP), São Paulo, Brazil; [9] Department of Neurosurgery, Lahey Hospital and Medical Center, Burlington, MA, USA; [10] Hospital Cárdio Pulmonar and Hospital Aliança - Rede D'Or São Luiz, Salvador, Bahia, Brazil; [11] Laboratory of Immunopharmacology, Instituto Nacional de Enfermedades Respiratorias "Ismael Cosío Villegas", Mexico City, Mexico; [12] Clinical Pharmacology Department, University of Sabana, Bogotá, Colombia; [13] Clinical Oncology, Rede D'Or Rio de Janeiro, Brazil; [14] Department of Cardiovascular, Internal Medicine, YALE Cardiovascular Research Group, New Haven, CT, USA; [15] Butantan Institute, São Paulo, Brazil; [16] Step Medical Affairs Consulting, São Paulo, Brazil; [17] Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, Brazil; [18] Retina Department, Evangelico Hospital and Luvere Clinic, Belo Horizonte, Brazil; [19] Fundacion Clinica Abood Shaio (FCS), Surgery Department, Bogotá, Colombia; [20] Escola Bahiana de Medicina e Saúde Pública, Salvador, Brazil; [21] Children's Hospital of Philadelphia, Philadelphia, PA, USA; [22] Department of Female Pelvic Medicine and Reconstructive Surgery, Institute of Urology, Keck School of Medicine USC, Los Angeles, CA, USA; [23] Dermatology, IRDA Santa Casa RJ, Rio de Janeiro, Brazil; [24] Division of Pulmonary and Critical Care, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; [25] Division of Neurosurgery, University of Sao Paulo Medical School, São Paulo, Brazil; [26] AC Camargo Cancer Center, São Paulo, Brazil; [27] Department of Clinical Pharmacy, College of Pharmacy, Umm Al-Qura University, Makkah, Saudi Arabia; [28] Hôpitaux Universitaires de Genève, Service des Maladies Infectieuses, Unité VIH/SIDA, Geneva, Switzerland; [29] D'Or Institute for Research and Education, Rio de Janeiro, Brazil; [30] Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada; [31] Hospital General ISSSTE Tláhuac, Mexico City, Mexico; [32] Women's Wellness and Research Centre, Hamad Medical Corporation, Doha, Qatar; [33] Hospital de Oncología, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico.

Abstract

Introduction: *Post-stroke individuals with dysarthria experience difficulties in producing speech due to muscle dysfunction. Neuromuscular electrical stimulation (NMES) can stimulate motor units and enhance their functionality. The objective of this study is to investigate the effects of NMES on speech intelligibility in patients with persistent dysarthria 3-6 months post-ischemic stroke.*

Methods: *This study will be designed as a phase II, double-blinded, randomized, two-arm, parallel-group, superiority trial conducted at a single center. The target population will consist of post-stroke individuals with dysarthria, who will undergo randomization to receive either neuromuscular electrical stimulation (NMES) or sham-NMES. Both intervention groups will receive treatment sessions 5 days a week over a 4-week period. The sample size for this study will be 154 patients, recruited exclusively from a Rehabilitation Unit located in the United States. The primary outcome measure will focus on determining the mean difference in the FDA-2 intelligibility score between the two treatment groups. Secondary outcomes will involve evaluating the mean difference in the full FDA-2 score, as well as various subsets of the score, alongside an assessment of the participants' health-related quality of life, utilizing the Stroke Impact Scale (SIS).*

Conclusion: *To the best of our knowledge, this will be a comprehensive assessment of the potential benefits of NMES for post-stroke patients with dysarthria. Considering the positive impact of NMES on enhancing muscle functionality, it is plausible to anticipate its potential benefits in improving speech outcomes as well. Despite early studies indicating the safety and tolerability of NMES for various motor muscle conditions, there is limited data on its use in patients with dysarthria.*

Introduction

Background

Stroke represents a significant global burden in terms of both mortality and disability worldwide (Tsao et al., 2022). Dysarthria, characterized by impaired speech muscle function, manifests as one of the main consequences of stroke and is typically related to lesions of the cerebellum, basal ganglia, and cranial nerves. Its prevalence ranges from 25% to 70%, and it is the third most common residual disability, with an estimated persistence of 42% after three months of stroke (De Cock et al., 2021). Communication disorders resulting from dysarthria are a considerable barrier to activity and participation in social and civil life (Wray et al., 2019; Brady et al., 2011). Consequently, improving dysarthria is an essential step in the rehabilitation of stroke survivors. Orofacial muscle exercises, breathing training, behavioral changes, and psychological support are the most frequently used interventions for this purpose. However, the application of these interventions during the acute phase of the stroke can vary according to the type of dysarthria, its severity, and the resources available in each healthcare service. Unfortunately, there is currently no well-defined standard treatment for dysarthria. While many patients improve with these therapies, some may persist with the condition. Therefore, having a therapeutic option for patients who do not respond well to current treatments would be beneficial.

Neuromuscular electrical stimulation (NMES) has been used in post-stroke rehabilitation since the early 1960s (Ijzerman et al., 2009). This therapeutic modality operates by delivering peripheral nerve stimulation, activating the motor units, and maintaining their trophism and functionality. Additionally, it brings up modulation over the sensorimotor cortex and spinal motor neurons (Maffiuletti et al., 2010). NMES has been utilized for diverse stroke sequelae, including flexor synergy of the wrist, hand, and fingers; hemiplegic shoulder subluxation; plantar spasticity, and foot drop (Nussbaum et al., 2017; Hong et al., 2018; Lee et al., 2017) as well as other types of spasticity (Stein et al., 2015). Some studies have shown that NMES can improve dysphagia by facilitating muscular contraction, motor unit recruitment, and muscle strength. It can also enhance laryngeal elevation and tongue base retraction during swallowing (Oh et al., 2017; Oh et al., 2020; Alamer et al., 2020; Park et al., 2016). This is particularly relevant in the context of the present study considering the anatomical similarities between the muscles involved in dysphagia and dysarthria, and it is not uncommon for patients with dysphagia to also have dysarthria as they can result from the same stroke. Another deficit that can coexist with dysarthria is central facial palsy in which NMES can strengthen facial muscles and prevent muscle atrophy (Choi et al., 2016).

The existing literature on the use of NMES for dysarthria is limited, with few studies specifically investigating its effectiveness in improving speech impairment. Peng et al. (2015) conducted a study on 32 patients with spastic dysarthria within one month of experiencing a stroke. Those who underwent NMES showed significant improvements in the modified Barthel index and Frenchay Dysarthria Assessment (FDA) after four weeks of treatment. In a separate study, Ko et al. (2016) investigated the effect of laryngopharyngeal NMES therapy on phonation in a group of 28 post-stroke and traumatic brain injury patients with dysphonia and dysphagia. NMES added to conventional swallowing training, demonstrated a positive effect on phonation after two and four weeks of treatment, possibly due to improvements in vocal fold vibration/tension and restoration of muscle function for laryngeal elevation. More recently, Berenati et al. (2021) reported a case of severe dysarthria after anoxic-ischemic encephalopathy who underwent NMES for four weeks, resulting in moderate improvement in speech impairment severity.

Objectives

Considering the existing gap regarding the utilization of NMES in the treatment of dysarthria, this study aims to investigate the effects of a four-week daily NMES intervention on speech intelligibility in individuals with unresolved dysarthria following a stroke. The study will follow up with participants between 3 to 6 months after the completion of the intervention. The primary outcome measure will involve comparing the mean difference in the intelligibility section score of the FDA-2 between baseline and one week after the intervention in the fifth week. Secondary outcomes will be assessed through the Stroke Impact Scale (SIS), which quantifies the health-related quality of life (HRQoL), as well as additional subsets of the FDA-2 and the overall FDA-2 score. This research aims to address the current knowledge gap and contribute to the academic understanding of the efficacy of NMES in the management

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of dysarthria.

Materials and Methods

Trial Design

This study is a phase II, superiority randomized controlled clinical trial, designed as a two-arm, parallel-group, double-blinded trial conducted at a single center aiming to address the hypothesis that the effect of NMES on dysarthria is different from the effect of sham intervention.

Study Setting

The study will be conducted in a single rehabilitation center with specialized post-stroke rehabilitation units. This facility, situated within a hospital offering comprehensive stroke management capabilities and specialized neurology and rehabilitation departments, is equipped to handle speech disorders. The rehabilitation center will be located in an urban area of a large city in the United States of America, where approximately 250 patients are admitted each year for stroke rehabilitation programs. The study protocol will be presented to the Institutional Review Board, and informed consent will be obtained from all participating patients.

Eligibility Criteria

Participants aged 18 years and older with a dysarthria diagnosis three to six months post-ischemic stroke event, who meet the study's inclusion and exclusion criteria, will be recruited. Inclusion criteria will encompass medically stable outpatients without any acute illness within the past 14 days prior to recruitment and no worsening of neurological symptoms since hospital discharge. Participants must have an FDA-2 intelligibility score of less than 8, assessed by a certified healthcare provider. Participants must be native English speakers or fluent in the English language and able to comprehend the informed consent.

Individuals who have been diagnosed with co-existing aphasia or apraxia of speech as determined by a neurologist and speech therapist will be deemed ineligible. Additional exclusion criteria will include participants with pre-existing dementia, neuromuscular disorders, or mental abnormalities assessed by the Mini-Mental State Examination with a score of less than 20. Pregnant individuals or those who have previously undergone NMES therapy for any reason or have contraindications to NMES, such as having a pacemaker or other implanted electronic systems, metal implants in the head and neck, lesions or infections in the treatment site, or a history of seizures, will also be excluded from the study.

Recruitment Strategy

The study timeline is depicted in Figure 1. The researchers will actively identify potential candidates at the rehabilitation center. Ischemic stroke patients that sign up for rehabilitation in the clinic will be screened for eligibility. In the event that the screened patient is diagnosed with dysarthria and is still not 3 months apart from the stroke, the patient will be followed and re-screened. Three-month post-stroke will be an appropriate time to evaluate eligibility to ensure a more uniform severity of dysarthria by excluding cases that might naturally improve during the acute phase and maximize the value of investing in NMES as it targets more severe cases. Invitation letters will be distributed to physicians working at the unit to help recruit their patients for the study. To enhance the recruitment process, advertisements in the form of flyers and print materials will be distributed in the hospital and digital versions will be published on the hospital's website.

Interested patients will be requested to complete a screening questionnaire based on the eligibility criteria. Candidates will be informed by phone call, text/SMS, or email about their eligibility and invited to a screening consultation with a certified healthcare specialist, to complete the screening process and undergo the FDA-2 assessment. If the intelligibility score in the FDA-2 is less than 24 and all other eligibility criteria are met, the patient will be taken through the informed consent and randomization process on the same visit.

Randomization

This study will employ a blocked randomization method utilizing block sizes of 4 and 6. The sample will be allocated into two groups with a balanced ratio of 1:1. An automatic central web-based randomization program will generate the allocation sequence. This information will be held in the secure institutional server and will be password protected, requiring double authentication and not accessible to those involved in the recruitment process to ensure allocation concealment.

The recruited patients will be allocated to the intervention groups after completing the informed consent. The assignment of participants to the intervention will be done via a centralized telephone-based method. Researchers will have access to a secure telephone number line. This telephone line

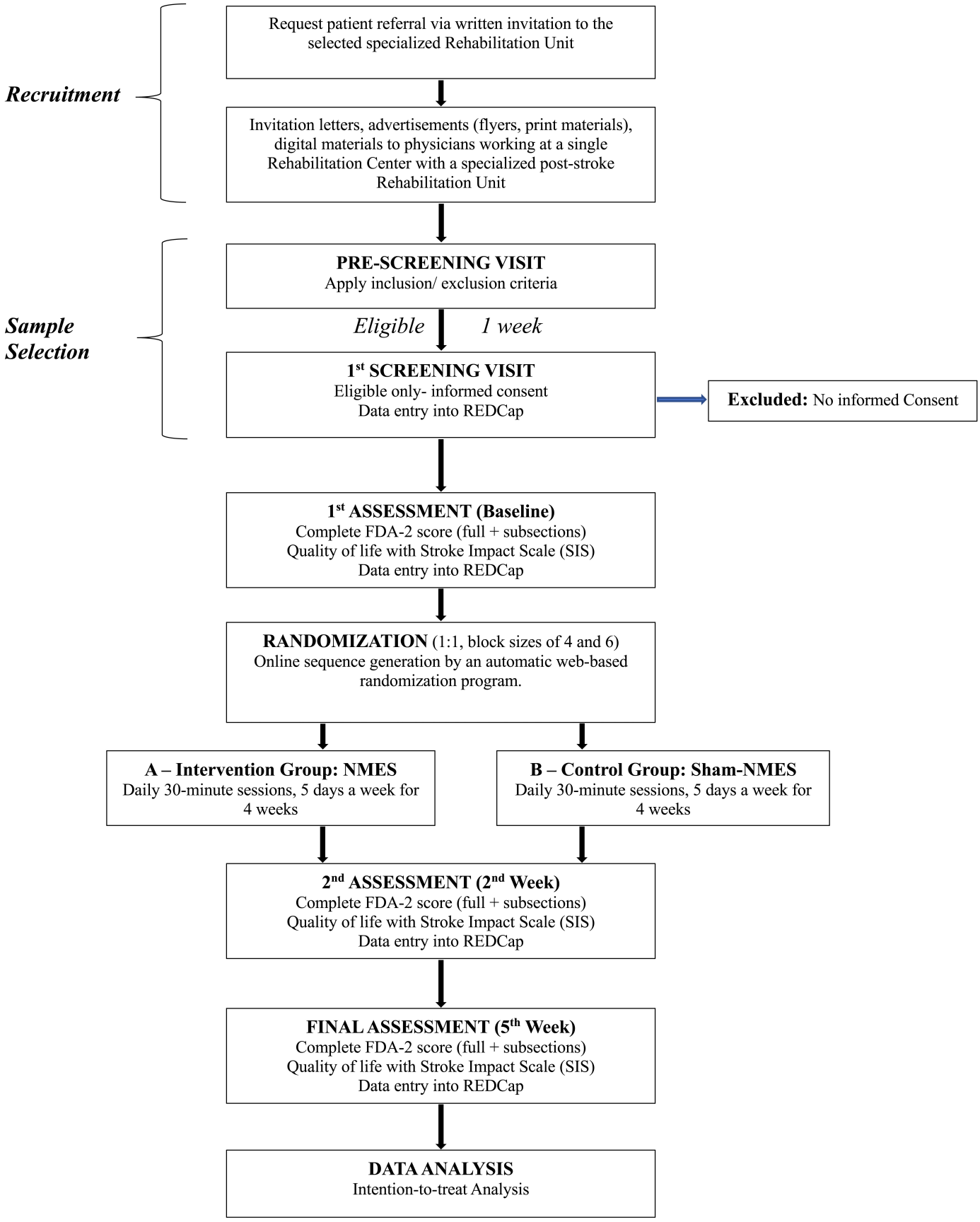

Figure 1: *Flowchart of the study.*

will go directly to a previously determined group that will reveal the patients' allocation during the session. The allocation will be locked to each patient even if the patient decides to withdraw from the study. Each researcher will have access to a secret code they will use to ensure the adequate use of the telephone line and confidentiality.

Blinding

This study will implement blinding procedures for both participants and outcome assessors. However, due to the nature of the intervention, it is impractical to blind the researcher responsible for administering either the NMES or sham-NMES to the patients. To ensure participant blinding, identical devices will be utilized, with displays and indicators operating in a similar manner. Moreover, the sham protocol will involve electric stimulation that does not lead to muscle contraction, allowing participants to experience a sensation without a therapeutic effect. Participant blinding is crucial to promote adherence and minimize dropout rates. Additionally, blinding of the outcome assessors will be implemented to ensure objective evaluation of the outcomes, reducing potential bias.

In the event of an unexpected serious adverse event, a designated site monitor will be promptly notified through the toll-free helpline established for the emergency unblinding procedure. Allocation information will not be disclosed to the patient or study personnel. Following notification of the event, a comprehensive assessment will be conducted to determine whether treatment should be discontinued.

Interventions

The study participants will be allocated to two groups: the intervention arm (NMES) and the control arm (sham-NMES). Both groups will use VitalStim® devices (VitalStim® Therapy; Chattanooga Group, Chattanooga, TN, USA), which cycle automatically "on-off" for 1 second every minute. Patients in the intervention arm will receive NMES on the masseter, orbicularis oris, risoris, buccinators, and depressor anguli oris muscles, which are involved in shaping the sound and air stream into speech. NMES is a transcutaneous electrical stimulation that will be administered by placing electrodes bilaterally on each side of the facial musculature in a random order (Berenati M, 2021). The intervention group will be stimulated at a motor level with a frequency of 80Hz, starting at an intensity of 7mA, which will be gradually increased with each session to a maximum tolerable level without pain or perceived muscle contraction, with an impulse time of 700 μs during 30 minutes (Diéguez-Pérez et al., 2020; Berenati et al., 2021).

In contrast, the sham-NMES group will receive NMES using the same device and electrode placement but at a sensory threshold level insufficient to produce muscle contractions. This group will be stimulated at a frequency of 80Hz, intensity of 5mA, which will remain the same throughout all the sessions, and an impulse time of 700 μs during 30 minutes (Ludlow et al., 2007).

The sessions for both groups will be administered by experienced speech therapists trained in NMES management, with interventions administered between 9 AM and 5 PM, 5 days a week for 4 consecutive weeks to balance adherence and potential dropouts associated with longer durations. The interventions will be administered in addition to the standard dysarthria management protocol existing in the rehabilitation center.

Modification/Discontinuation

While NMES is generally well tolerated, there are some side effects reported such as headache, skin irritation or allergy at the electrode sites, pain during treatment if the current amplitude is not properly adjusted based on patient feedback, difficulty concentrating, acute mood changes, and nausea (Nussbaum et al., 2017). To ensure patient safety, the intervention will be discontinued if certain criteria are fulfilled. These include the development of mild to severe skin irritation due to allergic factors, chemical burns resulting from the buildup of acids and bases, electrical burns caused by excessive current density, patient refusal to continue with the research, missing more than 20% of the intervention sessions, or worsening of symptoms. Any adverse events will be closely monitored until they resolve or stabilize, prioritizing the safety of the participants.

Adherence

To ensure and enhance adherence to the study protocol, a comprehensive written document, outlining the dates and times of all visits, including the name and location of the healthcare professional they will see during each visit will be provided to all patients. The physician's appointment will be optimized to align with the intervention. Participants will be given the option to choose their appointment time and preferred way of contact, whether email, text/SMS, or phone, and visit reminders will be sent based on their choice for the upcoming appointments.

A consent form will be provided to participants

and caregivers outlining all risks and benefits and supplementary information to ensure they fully comprehend their rights and responsibilities. Furthermore, financial support will be provided to increase adherence, such as reimbursement of travel expenses and a complete meal voucher for both participants and caregivers.

Outcomes

The primary outcome of the study will be the mean difference in FDA-2 (Enderby et al., 2008) intelligibility score (score at one week after completion of intervention i.e., week-5 score minus baseline score) between the NMES and sham-NMES groups. The intelligibility score will be treated as a continuous outcome, ranging from 0 to 27 for the intelligibility section, with up to 9 points for each of the three sections: word, sentence, and conversation intelligibility. Higher scores indicate better performance.

The secondary outcomes will include the following:

- Assessments of the FDA-2 intelligibility score mean difference after 2 weeks of intervention- investigating an additional time point can aid in evaluating the magnitude and duration of the treatment effect and guide decisions for future clinical research.
- Assessment of the comprehensive FDA-2 score encompassing 26 sections, with a total score range of 0 to 234- the mean difference in the full FDA-2 score between groups pre- and post-intervention (week-5 score minus baseline score) will be examined, along with differences in the score subsections, namely reflexes (total range: 0 to 27; including cough, swallow, dribble/drool), respiratory (total range: 0 to 18; at rest, in speech), lips (total range: 0 to 45; at rest, spread, seal, alternate, in speech), palate (total range: 0 to 27; fluids, maintenance, in speech), laryngeal (total range: 0 to 36; time, pitch, volume, in speech), and tongue (total range: 0 to 54; at rest, protrusion, elevation, lateral, alternate, in speech).
- Changes in the participants' health-related quality of life measured using the self-reported Stroke Impact Scale (SIS) - the SIS 3.0 assesses 59 items within eight domains related to the self-reported quality of life after stroke (Mulder et al., 2016): strength (4 items), communication (7 items), emotion (9 items), hand function (5 items), mobility (9 items), physical and instrumental activities of daily living (10 items), memory and thinking (7 items), and social participation (8 items). The scores for each domain will be noted from 0 to 100, with higher scores representing better health-related quality of life. Additionally, the SIS 3.0 includes a question to assess the patient's overall perception of recovery since the onset of the stroke. The answer will be rated on a visual analog scale from 0 to 100, with higher scores indicating better-perceived recovery. The change in pre- and post-intervention (week 5) scores will be compared between the groups.

Data Collection and Management

REDCap™electronic data capture will be used to collect all trial data starting from the draft of the data management plan to the end of the trial. All data will be input electronically and secured with a password-protected system. Identification of each subject will be determined by assigning numbers to protect their confidentiality. Participant records will be kept in numerical order and in a safe and accessible location. Only the principal investigator, Data Monitoring Committee (DMC), data analysis team, and research personnel will have access to the database.

An independent Data Monitoring Committee (DMC) will be established to monitor recruitment, overall data accuracy, and the safety of patients on a weekly basis. DMC members will consist of experts in the field of neurology, speech, and language therapy, and statistics. They will not be directly involved in the study or have any conflict of interest. In addition, DMC will manage unmasking treatment allocation in case of adverse health issues for patients. Previous reports state a low risk of adverse events that might require early trial interruption with NMES. Moreover, the trial is of short duration with a low expected dropout rate. Since there are no major life-threatening safety concerns for the participants, no interim analysis will be performed.

Sample Size Calculation

Based on the meta-analysis by Tan et al. (2013) for dysphagia in post-stroke patients, where the treatment group who underwent NMES had a mean Swallowing Function Scale score of 2.96 (SD=3.25), while the control group had a mean score of 1.4 (SD=2.92) on the same scale, and after careful evaluation of previous reports on the NMES effect for dysarthria using the FDA-2 score in post-stroke patients, we expect to detect a difference of 0.5 the SD between groups. Both methods lead to a numerically similar sample size. Thus, for a significance level of 0.05, a power of 0.80, and a dropout rate of 20%, the required sample size is 77 participants per group, a total of 154 participants.

Statistical Analysis

The demographic variables of the participants, such as age, biological gender, duration since the stroke, other medical comorbidities, baseline FDA-2, and SIS scores in the two groups, will be reported. Continuous variables will be reported as mean +/- SD or median +/- interquartile range depending on the distribution of the variable. Categorical variables will be reported as frequencies and percentages within each group.

An intention-to-treat analysis will be conducted for all outcomes. The primary statistical analysis will consider the intelligibility domain of the FDA-2 as a continuous outcome measured before and after the treatments. The difference between pre- and post-measurement scores will be calculated as the primary outcome variable. The normality of the data will be assessed using the Shapiro-Wilk test. If a normal distribution is confirmed, the Student's T-test will be employed to compare the mean differences between groups in the FDA-2 intelligibility domain.

As a secondary analysis, the same analytical procedure will be applied to examine whether there are differences between groups regarding the FDA-2 week-2 intelligibility score and FDA-2 total score. Additionally, an evaluation of the FDA-2 intelligibility score mean difference over time (baseline, week 2, week 5) will be performed using a two-way repeated measures ANOVA test; the independent variables will be treatment groups and time-repeated measures, and the dependent variable being continuous FDA-2 intelligibility domain scores. The SIS 3.0, which assesses changes in participants' health-related quality of life, will be evaluated at baseline and after the intervention period by considering the summative scores in the eight included domains as continuous variables. The change in SIS 3.0 scores between groups will be analyzed using Student's t-test.

In case normal distribution is not met, analyses to evaluate the mean differences between the two different treatment groups will be performed using a paired bootstrapping and a mixed effects model with robust estimators.

All statistical analysis will be performed using Stata 17 BE (StataCorp LLC, College Station, Texas, USA). The intention-to-treat principle will be followed for all outcomes. A p-value of <0.05 will be considered statistically significant and as evidence against a null hypothesis of no difference between the groups.

Missing Data

The potential mechanisms of missing data are anticipated to fall under the categories of missing completely at random or missing at random. Consequently, an intention-to-treat analysis will be applied. In accordance with these assumptions, a regression imputation technique will be used to replace data. To assess the robustness and plausibility of this process, a per-protocol approach will be utilized for a sensitivity analysis.

Discussion

Study Impact

Despite the considerable impact of post-stroke dysarthria on the social life and overall well-being of patients, no intervention so far has demonstrated significant improvement in this impairment. However, NMES has been described successfully as a management option in other post-stroke sequelae of similar mechanisms such as dysphagia and dysphonia (Oh et al., 2020; Schreiber et al., 2023). Therefore, the potential for the success of NMES in dysarthria is promising. Even in the event of negative outcomes from the study, we believe that the trial would still yield valuable information regarding post-stroke dysarthria patients, FDA-2 scores, and important insights into participants' quality of life.

Strengths and Limitations

This study aims to evaluate the effectiveness of an intervention that has shown efficacy in conditions sharing similar pathophysiology with dysarthria. The intervention is known to be well-tolerated and safe for patients. The results of this study will be essential to bridge the gap that currently exists in the literature, providing robust evidence of the efficacy of NMES in post-ischemic stroke dysarthria patients. We propose a randomized clinical trial, which is one of the best methods to evaluate treatment effects of therapeutic significance while reducing selection bias.

To reduce observer bias, the investigators responsible for reporting primary outcomes will be independent of the recruitment process and blinded to participant allocation. Participant blinding will also be implemented, aiming to reduce drop-out rates and reporting bias for the self-reported secondary outcome (SIS-3 score). Moreover, to establish a fair comparison and reduce the possibility of bias, which could ultimately alter the results, NMES will be compared with sham NMES.

Another important consideration is that it is essential to ensure that participants in the control group are not disadvantaged and have access to the currently standard treatment plans for dysarthria. Considering the interventions will be administered in addition to the standard protocols for the manage-

ment of dysarthria, participants in the control group will not be at a disadvantage and will have access to existing standard treatment plans. Furthermore, after the trial, should NMES prove to be effective, we will offer the treatment to the patients in the control group as well. On the other hand, it is important to mention that some potential weaknesses of the trial should be acknowledged. It is possible that blinding may not be feasible for some patients with prior experience with any electric stimulation therapy. Those patients may differentiate the active and sham stimulation. The enrollment period may last up to 3 years due to budget constraints and the limited availability of stimulation devices and research personnel. Despite the short intervention period of 4 weeks, patient and caregiver adherence may also be a challenge as they are required to visit the research center daily. Moreover, the study is being conducted at a single specialized post-stroke rehabilitation unit, which may lead to sampling bias as the sample might not be representative of all post-stroke patients. However, we plan to conduct a phase-2 study for which a more homogenous sample from a single center is more feasible and desirable. If the results are in favor of NMES, this study will serve as an important foundation for subsequent larger multicenter phase-3 studies in a wider population.

Registration

This trial will be registered on ClinicalTrials.gov, after approval by the local ethics and research committee.

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Conflicts of Interest

The authors declare no conflict of interest.

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