Peer-review Comments and Author Responses

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

Reviewer 1

Some points I would like to emphasize are:

1. Is 4 weeks of treatment enough?

Response: Thank you for bringing this to our attention. When we were designing this protocol, we discussed alternatives such as 6-8 weeks of treatment. However, our justification for choosing 4 weeks of treatment was that the effects of neuromuscular electrical stimulation (NMES) have been shown in literature after 4 weeks of therapy. Additionally, we also considered adherence: more weeks would increase dropouts and decrease adherence. Therefore, we found that 4 weeks of NMES therapy will fit our protocol considering the pros and cons of different lengths of intervention.

2. The time period from which the patient had the stroke and started the intervention could influence the result and be a confounder since early intervention could possibly have better results, and not all patients will start treatment at the same time post-stroke.

Response: Thank you for your valuable feedback. We decided to start intervention 3-6 months post-stroke. If recruited within three months of diagnosis, some patients will have a natural recovery. Therefore, it will be difficult to determine if the improvement is because of natural recovery or because of NMES. Additionally, after six months, it will be more difficult to recruit subjects. Therefore, we decided that a 3–6-month period is suitable for our study. As this is a randomized controlled trial, our aim is to achieve a balance between the treatment groups concerning the time elapsed since the stroke diagnosis, and this will be one of the variables listed in Table 1.

3. In the recruitment strategy section, it says, "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 at the appropriate moment to check for eligibility." if I was to reproduce this study I don't think enough information about when is this appropriate time for re-screening for eligibility is mentioned, so as a researcher, I would know when to do this.

Response: We appreciate for bringing this to our attention. Dysarthria is a common symptom after a stroke. In the acute phase, its incidence varies between 25% and 70%, but most tend to improve within the first 3 months. About 42% of patients persist with dysarthria after 3 months, and residual disability may decrease to 27% in the following 6 months [1,2,3,4]. Nevertheless, the persistent cases refer to more severe dysarthria, which can be very disabling for daily activities, both professional and personal, causing social and emotional disturbances. In view of the above, we consider that the appropriate moment to check for eligibility is 3 months after the stroke for the following reasons:
- the severity of dysarthria would be more homogeneous, excluding milder cases that would improve regardless of treatment during the acute phase;
- investment in NMES would not be futile as cases are more severe;
- patients with persistent dysarthria may have significant losses in performing everyday tasks.
Thus, a new rehabilitation tool could indeed be of great value. Then, as soon as 3 months after the stroke, we would check if the patient met all the eligibility criteria.

1. Ali M, Lyden P, Brady M; VISTA Collaboration. Aphasia and Dysarthria in Acute Stroke: Recovery and Functional Outcome. Int J Stroke. 2015 Apr;10(3):400-406. doi: 10.1111/ijs.12067
2. 2. De Cock E, Batens K, Hemelsoet D, Boon P, Oostra K, De Herdt V. Dysphagia, dysarthria and aphasia following a first acute ischaemic stroke: incidence and associated factors. Eur J Neurol. 2020 Oct;27(10):2014-2021. doi: 10.1111/ene.143853
3. Geddes JM, Fear J, Tennant A, Pickering A, Hillman M, Chamberlain MA. Prevalence of self reported stroke in a population in northern England. J Epidemiol Community Health. 1996 Apr;50(2):140-3. doi: 10.1136/jech.50.2.140
4. De Cock E, Oostra K, Bliki L, Volkaerts AS, Hemelsoet D, De Herdt V, Batens K. Dysarthria following acute ischemic stroke: Prospective evaluation of characteristics, type and severity. Int J Lang Commun Disord. 2021 May;56(3):549-557. doi: 10.1111/1460-6984.12607

4. In the statistical analysis section, they mentioned using Shapiro-Wilk to test for normality,

but there are more than 50 observations, so wouldn't a Kolmogorov Smirnov be more appropriate? And they mentioned that if the normality is confirmed, they will use a t-test, but what statistical test would be used if normality is not confirmed? This could be of benefit to mention.

Response: Thank you for pointing out this. Although Shapiro-Wilk is more suitable for a sample size of less than 50 subjects, it can be used for larger ones [1,2] and is the most commonly used test. Regarding the second question, we believe a parametric test should be used because our sample size is large enough to consider normal distribution according to Central Limit Theorem. But if normality is not confirmed, we will consider the use of robust estimators, which are known to be stable, consistent, and resistant to outliers in case normality of data assumption is not met, considering the two different treatment groups.

1. Rahman MM, Govindarajulu Z. A modification of the test of Shapiro and Wilk for normality. J Appl Stat. 1997;24(2):219-236. doi:10.1080/02664769723828
2. Royston P. Approximating the Shapiro-Wilk W-test for non-normality. Stat Comput. 1992;2(3):117-119. doi:10.1007/BF01891203

Reviewer 2

The clinical trial, "Effect of neuromuscular electrical stimulation in patients with poststroke related dysarthria: A double-blinded, phase-II randomized sham-controlled trial protocol - ULYSSES Trial" is a well-written study research. The topic and object of the trial is really interesting, and at the same time, it is necessary information in the medical field because of the high prevalence of this pathology.

The title is really descriptive and identifies the study design, population, and interventions. In the abstract, the authors did a good job summarizing everything. The background is well done by describing the research question and justification for undertaking the trial, including a summary of relevant studies, examining the benefits and harms of each intervention.

Objectives are well explained. A good option for study design because as post-stroke dysarthria does not have a standard intervention, authors won't have ethical concerns, and is more practical for the aim of the study in proving the efficacy of the new intervention. Authors describe the study settings, relevant dates, including the process of recruitment, exposure, follow-up, data collection and how it will be managed, interventions for each group with sufficient detail to allow replication, including how and when they will be administered, also, criteria for discontinuing or modifying allocated interventions for a given trial participants like changes in response to harms, strategies to improve adherence to intervention protocol. It is mentioned the primary and secondary outcomes, including the specific measurement variable analysis metric and method of aggregation. Correct description of the time schedule for enrollment and interventions. As a clinical trial study, they clearly describe the eligibility and exclusion criteria, the population was well-defined and authors knew what they were looking for.

They did a good option for the sampling method estimating the number of participants needed to achieve study objectives, based on previous reports considering a significance level of 0.05, a power of 0.80, avoiding errors and loss of power. Also, description of Method in generating the allocation sequence and how it will of implementing the allocation sequence. The correct description of statistical methods for analysis depending on primary and secondary outcomes. In ethics, it reports who and how will obtain informed consent from potential trial participants. Also, how personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial. Give a cautious overall interpretation of possible limitations and biases that can occur.

5. From my point of view, overall is an excellent research study, but it has some weaknesses. For example, the authors did not describe any potential source of confounders like age and did not use any method to control them, like propensity score or outcome regression.

Response: Thank you for bringing this to our attention. As our protocol is a randomized controlled trial, we felt that the discussion about potential confounding variables like age in the protocol is not necessarily a cause for concern. In RCTs, the randomization process is designed

to minimize the impact of confounding variables, including age, on the study outcomes. We are confident that the randomization process will balance any possible confounders between the groups, giving us unbiased estimators in the analysis.

6. Also, the population they chose can lead to possible bias because they are recruiting patients with persistent dysarthria 3-6 months post-ischemic stroke, this timeframe can lead to differences between patients who have 3 months and patients who have 6 months.

Response: Thank you for bringing this to our attention. Dysarthria is a common symptom after a stroke. In the acute phase, its incidence varies between 25% and 70%, but most tend to improve within the first 3 months. About 42% of patients persist with dysarthria after 3 months, and residual disability may decrease to 27% in the following 6 months [1,2,3,4]. We decided to start intervention 3-6 months post-stroke. If recruited within three months of diagnosis, some patients will have a natural recovery. Therefore, it will be difficult to determine if the improvement is because of natural recovery or because of NMES. Additionally, after six months, it will be more difficult to recruit subjects. Therefore, we decided that a 3–6-month period is suitable for our study based on published reports.

1. Ali M, Lyden P, Brady M; VISTA Collaboration. Aphasia and Dysarthria in Acute Stroke: Recovery and Functional Outcome. Int J Stroke. 2015 Apr;10(3):400-406. doi: 10.1111/ijs.12067
2. 2. De Cock E, Batens K, Hemelsoet D, Boon P, Oostra K, De Herdt V. Dysphagia, dysarthria and aphasia following a first acute ischaemic stroke: incidence and associated factors. Eur J Neurol. 2020 Oct;27(10):2014-2021. doi: 10.1111/ene.143853
3. Geddes JM, Fear J, Tennant A, Pickering A, Hillman M, Chamberlain MA. Prevalence of self reported stroke in a population in northern England. J Epidemiol Community Health. 1996 Apr;50(2):140-3. doi: 10.1136/jech.50.2.140
4. De Cock E, Oostra K, Bliki L, Volkaerts AS, Hemelsoet D, De Herdt V, Batens K. Dysarthria following acute ischemic stroke: Prospective evaluation of characteristics, type and severity. Int J Lang Commun Disord. 2021 May;56(3):549-557. doi: 10.1111/1460-6984.12607

7. On the other hand, the authors explained that it is possible that blinding may not be feasible for some patients with prior experience with any electric stimulation therapy. I think this can be included in the exclusion criteria and avoid this type of bias. Despite everything mentioned, I think it is a good manuscript for publication.

Response: Thank you for your feedback. It's true that the previous experience of patients with neuromuscular electric stimulation (NMES) can impact the study's blinding. As a result, we have decided to exclude patients who have had previous NMES therapy for any reason. This information is stated in the eligibility criteria section: **"**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."

Reviewer 3

8. Great manuscript. I read it, and everything was clear. I like the novelty of the subject. No plagiarism, and you definitely take the ethics committee into account. The study's limitations may have already been addressed in the manuscript.

Response: We appreciate the positive feedback.

Reviewer 4

Overall the text is very good and clear.
Below I attach specific suggestions to further improve its quality and readability.

9. I would change "Effect" to "Effects" and keep the rest the same.

Response: Thank you for your suggestion. We have changed this part.

10. At the end of the first paragraph, I would change "regrettably" to "unfortunately".

Response: Thank you for your suggestion. We have revised this part.

11. In the first sentence of the second paragraph, I would change "has been employed" to "has been used".

Response: Thank you for your suggestion. We have revised this part.

12. In the first sentence of the third paragraph, I would suggest changing "ameliorating" to "improving."

Response: Thank you for your suggestion. We have revised this part.

13. Study setting, in the first sentence, I would change "housing" to "with".

Response: Thank you for your suggestion. We have revised this part.

14. I believe it would be more appropriate to use a random block randomization strategy of 4 to 6 patients in each group instead of fixed blocks in order to preserve allocation concealment and decrease the chance of bias.

Response: We appreciate that you pointed out this important issue. It is true that using block randomization with variable block sizes such as 4 and 6 will allow us to preserve the allocation concealment and decrease the chance of bias. Therefore, we have changed it from a block size of 4 to block sizes of 4 and 6.

15. I verified the sample size calculation you performed with STATA 18, and I didn't obtain the same numbers. Additionally, if supposedly 77 participants are required in each arm, the total sample size would be 154, not 148, as you mentioned.
I think you should review the sample size calculations and mention which statistical program or tool you used to perform these calculations.

Response: We appreciate your checking our sample size calculation. We have added a reference meta-analysis for dysphagia in post-stroke patients and made a revision in our calculation. Our final sample size calculation includes 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.

16. Study impact, In the first sentence of the first paragraph, I would change "thus far" to "so far."

Response: Thank you for your suggestion. We have revised this part.

17. The third sentence of the first paragraph seems to be redundant because the word "currently" is used 2 times. Therefore, I would change "The results of this study will be instrumental in filling the current gap that currently exists in the literature, providing robust evidence for the efficacy of NMES in post-ischemic stroke dysarthria patients" to "The results of this study are 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."

Response: Thank you for your suggestion. We have revised this part.

18. In the third sentence of the second paragraph, "Neurological conditions are often noted to recover at different rates and often spontaneously- hence the importance of comparing NMES with a sham procedure," I would say that the comparison of NMES with a sham procedure is performed in order to have a fair comparison and to decrease the chance of bias which could ultimately affect the final results.

Response: Thank you for your suggestion. We have revised this paragraph based on your review.

19. I believe the last sentence of the second paragraph, "Considering the interventions will be administered in addition to the standard protocols for the management of dysarthria, participants in the control group will not be at a disadvantage and will have access to existing

standard treatment plans" is a very important consideration to take into account once the protocol is finished, but unfortunately isn't related to the previous sentence. I would surely include this phrase but probably place it in another paragraph and develop this idea more exhaustively.

Response: Thank you for your suggestion. Indeed, it is essential that the sham group's subjects will not be disadvantaged in having access to their treatments. We have added another paragraph addressing this issue.