PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect and safety of C7 neurotomy at the intervertebral foramen in patients with chronic post-stroke aphasia: A multicentre, randomised, controlled study protocol
AUTHORS	Li, Tie; Feng, Juntao; Hu, Ruiping; Lv, Minzhi; Chang, Wenshuo; Ma, Xingyi; Qi, Wenjun; Zhang, Ying; Chen, Xiuen; Ding, Ling; Gu, Yudong; Xu, Wendong

VERSION 1 – REVIEW

REVIEWER	Hillis, Argye E Johns Hopkins University School of Medicine, Department of Neurology
REVIEW RETURNED	13-Oct-2022

GENERAL COMMENTS	The authors present a protocol for evaluating the effectiveness and safety of C7 neurotomy on aphasia. The protocol is well-written, and the study is well-designed. Outcome measures are justified. My main concern is that the study was designed on the basis of weak preliminary data indicating that people who had the procedure for motor recovery reported (subjectively) improvements in language. They state, "Therefore, we speculate that the clinical phenomenon of language function improvement is due to the stimulation inducing neuroplasticity of the "language centre", that is, "Reconstructing the peripheral nerve changes the central nervous system." They admit that this mechanism is speculative, and I find it implausible. If they see improvement, they will not be able to support the mechanism. They will use fMRI and EEG to evaluate "reorganization" but they need to acknowledge that changes might reflect improvement irrespective of the mechanism of improvement. So, for example, if patients in the treated group improve more than those in the untreated group simply because of a placebo effect, they might still show greater changes on fMRI and EEG. They should therefore modify the last phrase of the paper,"... which may provide a novel perspective on aphasia treatment and the interaction with peripheral between central nervous system." They should add that a limitation is that the study is not "double blind" - patients may improve because of a strong placebo effect (in general, the more invasive the treatment, the larger the placebo effect). Blinded outcome evaluators do not overcome this limitation. They plan for 15% "lost to follow up", but they may well have other reasons for attrition, such as new medical problems that interfere with continuing therapy, drop out, etc.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Argye E Hillis, Johns Hopkins University School of Medicine

COMMENTS TO THE AUTHOR:

Comment 1: The authors present a protocol for evaluating the effectiveness and safety of C7 neurotomy on aphasia. The protocol is well-written, and the study is well-designed. Outcome measures are justified.

Reply:

Thank the reviewer for her high evaluation.

Comment 2: My main concern is that the study was designed on the basis of weak preliminary data indicating that people who had the procedure for motor recovery reported (subjectively) improvements in language. They state, "Therefore, we speculate that the clinical phenomenon of language function improvement is due to the stimulation inducing neuroplasticity of the "language centre", that is, "Reconstructing the peripheral nerve changes the central nervous system." They admit that this mechanism is speculative, and I find it implausible. If they see improvement, they will not be able to support the mechanism. They will use fMRI and EEG to evaluate "reorganization" but they need to acknowledge that changes might reflect improvement irrespective of the mechanism of improvement. So, for example, if patients in the treated group improve more than those in the untreated group simply because of a placebo effect, they might still show greater changes on fMRI and EEG. They should therefore modify the last phrase of the paper,"... which may provide a novel perspective on aphasia treatment and the interaction with peripheral between central nervous system."

Reply:

We appreciate the reviewer's comment. This interesting clinical finding comes from more than 1000 Contralateral C7 to C7 Cross Nerve Transfer (CC7) surgeries we have completed in the past five years. The purpose of CC7 surgery is to improve the sensory-motor function of upper extremity of hemiplegic patients, while the improvement of language function in patients with post-stroke aphasia after surgery was beyond our expectation.

To begin with, after continuous reporting of improvements in language and speech function by patients and their families, we conducted retrospective observation study and prospective observation study (phase Ⅰ clinical trial, these results have been submitted to a professional journal and now

under revision), and after obtaining credible results of phase I clinical trial, we designed this phase Ⅱ clinical trial to confirm the effect and safety. The sample size of this trial was also derived from the primary data. Therefore, we think the basis on this trial we designed is solid.

Secondly, reviewer expressed concern about the possible mechanism we described, "They admit that this mechanism is speculative, and I find it implausible." Indeed, the corresponding brain regions and circuits involved in human language function are still unsolved mysteries, which is one of the 125 scientific questions raised by “Science” in 2021, “How did speech evolve and what parts of the brain control it?”(https://www.science.org/content/resource/125-questions-exploration-and-discovery, Page 34, Chapter Neuroscience, Q3).

Therefore, we fully understand and accept the reviewer’s comments, we made modifications according to the reviewer’s opinion. We deleted the two sentences mentioned by reviewer. ~~"Therefore, we speculate that the clinical phenomenon of language function improvement is due to the stimulation inducing neuroplasticity of the "language centre", that is, "Reconstructing the peripheral nerve changes the central nervous system.~~" and "~~... which may provide a novel perspective on aphasia treatment and the interaction with peripheral between central nervous system."~~

The two parts are now described in the manuscript as follows：

“The mechanisms of language production are complex. The corresponding brain regions and circuits involved in human language function are still unsolved mysteries, “How did speech evolve and what parts of the brain control it?” listed in the 125 scientific questions by “Science” journal (https://www.science.org/content/resource/125-questions-exploration-and-discovery, Page 34, Chapter Neuroscience, Q3). Based on the anatomy of brain functional areas, we hypothesized that, since the sensory-motor centre is adjacent to the language centre, if the sensory-motor centre can be changed artificially by NCT at the intervertebral foramen, then it is possible to induce the language centre and produce related functional changes. It may also be that NC7 leads to a change in the interhemispheric balance, thus, affecting the functional neural circuits of language. We designed this trial to evaluate the surgical effect of NC7 at the intervertebral foramen on underlying neuroplasticity in patients with chronic post-stroke aphasia. Meanwhile, the iSLT is selected as the control method, we will assess the effect of intensive intervention (SLT) after 3 weeks and the maintenance of the effect after 6 months in both groups. Meanwhile, we use neuroimaging methods to provide objective data as evidence to support our hypothesis.” (As in the manuscript mark copy, Page 6, line 157-160.)

“…Once our hypothesis is confirmed, this trial will provide important evidence for supporting neurotomy of C7 nerve at intervertebral foramen as a novel treatment approach for chronic aphasia. A limitation of this study…” (As in the manuscript mark copy, Page 19, line 425-432.)

In conclusion, this is the first RCT to evaluate the surgical effect in patients with chronic post-stroke aphasia for whom there is no effective treatment available.

Comment 3: They should add that a limitation is that the study is not "double blind" - patients may improve because of a strong placebo effect (in general, the more invasive the treatment, the larger the placebo effect). Blinded outcome evaluators do not overcome this limitation.

Reply:

This suggestion is helpful, and we appreciate it. As a strong invasive intervention, surgery does have a placebo effect, as the reviewer said. To offset the short-term placebo effect after surgery, we conducted a secondary endpoint assessment at 6 months, at which time the patient 's placebo effect due to invasive interventions will be greatly reduced. We agreed with the reviewer 's opinion and added this limitation to the discussion.

This part is described in the manuscript as follows：

"…A limitation of this study is that it is not double-blind but evaluator-blind, and the experimental group may involve a minor placebo effect. To offset the short-term placebo effect after surgery, we conducted a secondary endpoint assessment at 6 months. At that time, at which time the patient 's placebo effect due to invasive interventions will be greatly reduced." (As in the manuscript mark copy, Page 19, line 428-432.)

Comment 4: They plan for 15% "lost to follow up", but they may well have other reasons for attrition, such as new medical problems that interfere with continuing therapy, drop out, etc.

Reply:

We appreciate the reviewer's comment. Indeed, the subjects will withdraw from the clinical trial due to the interference of various factors. For this reason, we have formulated corresponding measures to ensure that the rate of "lost to follow up" is within the expected range. For example, in the exclusion criteria, we take " 6)-Ability to fully understand and agree with the doctor's treatment plan and sign the informed consent (As in the manuscript mark copy, Page 8, line 206-207.)" as the entry criteria, and " 6)-Unable to complete the assessments and rehabilitation required by the study design (As in the manuscript mark copy, Page 8, line 217.)" as the exclusion criteria to ensure that the subjects can complete all therapy programme and assessments well. Second, the subjects we selected were stroke patients in the plateau period (over 12 months after single onset), who were relatively stable and had little chance of developing new medical problems. Even if that occurred, each centre we selected had the ability to deal with routine medical problems. Of course, there will be some unpredictable factors, such as the impact of the COVID-19 pandemic. However, we have rich experience in conducting clinical trials to complete this trial.