PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Transcutaneous auricular vagus nerve stimulation prevents postoperative delirium in elderly patients (VNSTAR): protocol for a multicenter, randomized controlled trial

Authors

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Gesso , A.S.**
Affiliation	**Addis Ababa University College of Health Sciences, Anesthesia and critical care**
Date	**31-Mar-2025**
COI	**None**

Fist and for most, I would like to thank the editorial teal for inviting me to review the above referenced trail protocol, then I appreciate the authors for their different view and trying to add something interesting perspective to the existing body of knowledge. But, unfortunately I am not in a position to declare the decision of acceptance to this article at this point in time for the following reasons.

1. Even if the trail protocol has a merit, it is a study that is going to be concluded in 2027.

2. It would be better to see at least interim analysis

3. There is no result displayed

4. The discussion cannot be applied directly from current study

5. Conclusion and recommendations should only be drawn from results

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Reviewer	**2**
Name	**Jing, Jiyong**

Affiliation	**People's hospital of Hangzhou medical college**
Date	**01-Apr-2025**
COI	**None**

Thank you for submitting the manuscript titled "Transcutaneous Auricular Vagus Nerve Stimulation Prevents Postoperative Delirium in Elderly Patients (VNSTAR): Protocol for a Multicenter, Randomized Controlled Trial."

Overall, this is an engaging and clinically relevant study that explores transcutaneous auricular vagus nerve stimulation (taVNS) as a non-invasive neuromodulation method for preventing postoperative delirium in elderly patients. However, there are a few points that warrant further consideration to enhance the study design and contextual clarity.

1. Since the primary aim of this study is to investigate the efficacy of taVNS in preventing postoperative delirium, rather than comparing the effects of different stimulation intensities, the addition of a blank control group in the experimental design may be more appropriate.

2. A similar study titled "Effects of Transcutaneous Auricular Vagus Nerve Stimulation on Postoperative Delirium in Older Patients with Hip Fracture: Protocol for a Randomised Controlled Trial" appears to be underway. The authors should clarify how their study differs from this ongoing research to highlight its unique contributions.

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

1. Even if the trail protocol has a merit, it is a study that is going to be concluded in 2027.

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Response: Thank you for your insightful comments. This manuscript is currently submitted as a research protocol. Our intention is to demonstrate the significant work we are undertaking and to encourage more research centers to participate in our study. This is a large - scale, multicenter study with a sample size of approximately 1,776 cases, which is why it will take until at least 2027 to complete. We have incorporated interim analysis into the study design, thereby preventing the unnecessary expenditure of resources. The data from the interim analysis will be evaluated by an independent Data and Safety Monitoring Board (DSMB). The research team will not have access to the interim analysis data, and thus, we cannot report on it unless the study is terminated prematurely. Since no research results are available at present, the discussion section of this article primarily focuses on the study's feasibility and limitations, without delving into the research hypothesis. Once again, we sincerely appreciate your review of our manuscript and the valuable suggestions you have provided.

Reviewer: 2

1. Since the primary aim of this study is to investigate the efficacy of taVNS in preventing postoperative delirium, rather than comparing the effects of different stimulation intensities, the addition of a blank control group in the experimental design may be more appropriate.

Response: We sincerely appreciate your insightful comments. In this study, the control group will receive low - frequency stimulation instead of blank control. This choice is based on the frequency - dependent nature of taVNS. Published research has widely recognized the 20–30 Hz range as the safe and effective frequency band for taVNS. Functional magnetic resonance imaging (fMRI) studies observing the therapeutic effects of vagus nerve stimulation (VNS) have shown that higher stimulation frequencies lead to more extensive and intense activation of brain functional areas. In contrast, frequencies below 5 Hz exhibit limited activation of brain functional areas compared to 20 Hz. As a result, some previous studies have used 1 Hz as the control group and 25 Hz as the intervention group for taVNS, and significant differences were observed between the two groups.

Compared with sham interventions that place electrodes on non - standard stimulation sites, such as the earlobe, using different frequencies (1 Hz as control) better enables researcher blinding. Additionally, sham interventions with electrodes on non - standard sites may still activate the vagus nerve due to current diffusion under high - intensity electrical conditions. Therefore, our study selects a stimulation frequency of 1 Hz for the control group. (Detailed explanations can be found in the discussion section of the original article.)

2. A similar study titled "Effects of Transcutaneous Auricular Vagus Nerve Stimulation on Postoperative Delirium in Older Patients with Hip Fracture: Protocol for a Randomised Controlled Trial" appears to be underway. The authors should clarify how their study differs from this ongoing research to highlight its unique contributions.

Response: ① The study population selected in Zhou's study consisted of elderly patients undergoing hip surgery. In contrast, our study does not limit surgical modality. In actual clinical practice, elderly patients do not just undergo fixed orthopedic surgeries. Hence, the setting of our study protocol is more realistic and has greater clinical generalizability.

② Zhou's study had a sample size of 154 cases. Our study, however, utilizes a large multicenter sample size of 1778 cases, making the findings more reliable. Additionally, to avoid the waste of resources due to negative results, our study is designed with an interim analysis. If the intervention is effective and reaches the preset superiority boundaries, the trial can be terminated early because of its effectiveness.

③ In Zhou's study, the blinding was set up as a blank control, resulting in insufficient comparisons between the two groups, a potential for patients to see through the blinding, and a high selection bias. In our study, different stimulation frequencies are employed to ensure standard blinding. All patients

receive current stimulation, but only the built-in frequency of the instrument varies and is not visible to the public. Previous studies have shown that transcutaneous auricular vagus nerve stimulation (taVNS) is frequency-dependent. Some studies have used 1 Hz as the control group for taVNS and 25 Hz as the intervention group, and significant differences were observed in both groups. This makes our method more conducive to blinding the researchers in our study.

In line with the suggestions, we have added relevant descriptions in the discussion section to highlight the differences between our ongoing study and emphasize its unique contributions. (Details are explained in the discussion section of the original article, Page 14, Line 7)
