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Vagus nerve stimulation to improve post-stroke motor function and activity

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Abstract

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effectiveness and safety of VNS as an add-on treatment to rehabilitate poststroke motor function and activity.

Background

Description of the condition

Stroke is defined as “an episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥ 24 h or until death” (Hankey 2017; Sacco 2013). Stroke is the second leading cause of death and third leading cause of disability (GBD 2021). Individuals with hypertension, cardiac diseases, diabetes, hypercholesterolemia, cigarette smoking, excessive alcohol consumption, drug abuse, obesity, and a lack of physical activity face an increased risk of stroke (GBD 2021).According to recent predictions, one of four people will suffer a stroke during their lifetime (Gorelick 2019). Brain damage attributed to the loss of neurons caused by stroke can result in motor, sensory, and cognitive deficits. About half of individuals with stroke present with upper limb motor impairment and cognitive disorders (Fekadu 2019). These disabilities may limit functional independence, reduce quality of life, and affect mental health (Gil-Salcedo 2022).

Description of the intervention

Current Canadian guidelines recommend the implementation of exercise therapy programs to improve poststroke motor function (Teasell 2020). However, despite rehabilitation, half of individuals remain permanently impaired (Lee 2015). To promote recovery, interventions that enhance brain plasticity were developed (Su 2020). Evidence has shown that the improvement of brain plasticity, characterized by an increased neural activity and connectivity, is an excellent predictor of motor recovery (Stinear 2010). In this context, to enhance outcomes of stroke rehabilitation, treatments involving vagus nerve stimulation (VNS) have been recently developed.

VNS includes any neuromodulation treatment that alters the activity of cranial nerve X. VNS typically involves surgical implementation of a pulse generator, leads, and electrodes under the skin of the left pectoral and neck regions while the person is under general anesthesia (Howland 2014). This subcutaneous system is coupled with an external programmable device that serves to set up the parameters of the electrical stimulation (Afra 2021). When set up, the electrical signal is transmitted from the pulse generator to the VN through the leads

(Wheless 2018). VNS is generally regarded as safe and well tolerated. Adverse events, when they occur, are commonly associated with either the surgical procedure or the stimulation process itself. Adverse events related to stimulation encompass voice alteration, cough, dyspnea, paresthesia, headache, and local pain (Wheless 2018). Notably, the frequency of these adverse events tends to diminish over time with continued treatment. Signal amplitude may vary from 0 to 3.5 mA, current frequency from 1 to 30 Hz, and pulse width from 100 to 1000 µs (Wheless 2018). More recently, studies have described the use of non-invasive VNS treatment using a handheld stimulator over the skin covering the VN (in the carotid triangle region) (Arsava 2022) or in the auricular cavum conchea (Li 2022). Transcutaneaous VNS is also considered as safe and well tolerated. Skin irritation stands out as the most prevalent adverse event (Redgrave 2018).

How the intervention might work

Overall, neurological recovery may be improved by enhancing the brain's ability to reorganize poststroke residual networks (brain plasticity) (Engineer 2019; Krakauer 2004; Nudo 2006). While the precise mechanism of VNS remains unknown, this treatment is thought to promote neuroplasticity by driving the rapid activation of neuromodulatory networks (cholinergic, serotoninergic, and noradrenergic systems) thanks to the nucleus tractus nerve solitarius projection of the VN (Ma 2019). Through this projection, the VN modulates the release of serotonin, acetylcholine, and norepinephrine from the dorsal raphus nucleus, nucleus basali, and locus coeruleus to different brain regions (Gu 2002; Manta 2009). Recent evidence suggests that the predominant mechanism may be cholinergic reinforcement. The heightened noradrenergic activity induced by VNS is proposed to influence the trisynaptic circuit in the hippocampus, a relay system involved in synaptic plasticity (Olsen 2023). VNS-induced alterations in the locus coeruleus are closely tied to adrenergic signaling and can potentiate perforant path-dentate gyrus evoked potentials and enhance perforant path-CA3 field excitatory post-synaptic potentials (Shen 2012). This cascade of events is associated with long-term potentiation, a form of synaptic plasticity linked to enhanced learning and memory (Kandel 2014). Additionally, VNS boosts the excitability and spontaneous spiking in the CA1 region and enhances synaptic transmission (Olsen 2022). Furthermore, VNS induces lasting changes in synaptic plasticity by influencing mediators such as growth factors, immediate early genes, and proteins critical for long-term potentiation (Olsen 2023). This includes an increase in the expression of brain-derived neurotrophic factor (BDNF) and activation of tropomyosin receptor kinase B, the receptor for BDNF (Furmaga 2012). Fibroblast growth factor expression is also augmented by VNS, along with enhanced expression of adrenergic receptors and proteins crucial for long-term potentiation, such as GluN2B (NMDA receptor subunit) and its downstream signaling target calcium/calmodulin-dependent protein kinase II (Olsen 2023). These comprehensive changes induced by VNS contribute to long-term alterations in plasticity and memory consolidation in the hippocampus, highlighting the multifaceted mechanisms through which VNS may enhance cortical reorganization. The activation of neuromodulatory networks through the vagus nerve is thus expected to have neuroprotective effects as it limits oxidative stress and neuroinflammatory activation, and enhances cortical map reorganization by strengthening synapse efficacy and triggering neurogenesis (Engineer 2019; Ma 2019).

Although existing literature indicates that VNS enhances hippocampal synaptic plasticity in healthy individuals and demonstrates improvements in attention and memory for epileptic patients when utilized as an antiepileptic intervention (Olsen 2023), there is currently no documented evidence supporting the efficacy of VNS in influencing neuroplasticity among individuals with stroke. Nevertheless, animal studies have provided evidence supporting the positive effects of VNS on neuronal and corticospinal plasticity (Ay 2009; Biggio 2009; Meyers 2018) therefore underlining its potential effect to improve neurological recovery after a stroke. These outcomes reinforce the perspective that VNS is contingent on neuroplasticity, a phenomenon that unfolds over time and is sensitive to temporal dynamics. We may therefore expect differences between VNS effect during the acute and chronic phases of individuals with stroke. The purpose of starting in the acute phase is to prevent motor function or other disabilities to develop by protecting the neurons from breaking down. Recent findings strongly indicate that VNS could be an appealing approach to mitigate the adverse effects of spreading depolarization waves in acute brain disorders (Cheng 2022;Lindemann 2020), therefore underling its potential to preserve the penumbra and restrict the extent of the infarct core in individuals with acute stroke (Dreier 2011;Nakamura 2010;Hartings 2017). During the chronic phase, the treatment goal is to promote neuroplasticity and induce neurogenesis in order to improve disabilities. A study conducted among rats with chronic stroke, showed that VNS did not diminish the size of the lesion but instead, improved the recovery process by enhancing neuroplasticity (Khodaparast 2016).

The positive effects of VNS on mood may also play a role in the context of stroke rehabilitation. Prior research has indicated that mood symptoms following an acute stroke are correlated with a lower quality of life at one year (Donnellan 2010). Importantly, this study also reveals that depression symptoms exert a more pronounced influence on functional recovery. In this context, the mood-enhancing benefits of VNS may not only contribute to an improved quality of life but could also potentially have a positive impact on functional recovery, underscoring the broader rehabilitative potential of VNS interventions in poststroke care.

When combined with motor training, animal studies reveal that VNS results in the reorganization of cortical motor maps, affirming the capacity of VNS to foster synaptic plasticity when a targeted timing approach is employed (Tseng 2020). In adults with stroke, the combination of VNS and high-repetition, functional and progressive exercise therapy has shown promising results on upper limb motor function (Dawson 2021). A pivotal randomized sham-controlled trial, involving 108 individuals with ischemic stroke, showed that VNS paired with rehabilitation significantly improved upper limb motor control and activity. These changes were maintained at 3

months postintervention. The number of people achieving clinically significant improvement in upper limb control was greater in the VNS group than in the control group.

Why it is important to do this review

VNS may be a potential adjunctive treatment for rehabilitation in individuals with stroke. Therefore, it remains important to assess the effectiveness and safety of VNS to improve poststroke motor function and activity and aid future guidance for VNS implementation in stroke survivors. While six meta-analyses reviewed the effectiveness and safety of VNS in individuals after stroke (Ananda 2022; Liu 2022; Ramos-Castaneda 2022; Xie 2021; Zhang 2020; Zhao 2021), none of them used a GRADE approach to analyze the body of evidence. Since the publication of the last meta-analysis, new and large randomized controlled trials (RCTs) assessing the effect and safety of VNS among individuals with stroke have been published (Arsava 2022; Li 2022). These recent RCTs enrolled 60 and 69 individuals, respectively, which represent about 62% of the total sample size of the last meta-analysis. In addition, all participants were treated during the subacute phase (in contrast to 85% of participants in previous RCTs) and new outcomes were evaluated (magnetic resonance imaging [MRI] outcomes, National Institute of Health Stroke Scale [NIHSS] score, and lower limb motor function). Lastly, in Li 2022, authors assessed participants with severe motor impairments and evaluated their outcomes at the 1-year follow-up. Also, the number of studies on non-invasive VNS is increasing.

Currently, despite the findings of recent meta-analyses, several factors remain unknown that potentially influence the effectiveness of VNS, such as impairment severity and time since stroke onset. In addition, some authors have questioned whether motor changes induced by VNS could be clinically important (Kwakkel 2021). If so, there is the possibility of extrapolating such therapies in other individuals suffering from brain injury. Importantly, to date, the distribution of VNS effects in the population and the implications in terms of health equity remain underexplored. With the addition of new RCTs to the field and the elaboration of subgroup analyses, it is worthwhile to synthesize the current evidence.

Objectives

To assess the effectiveness and safety of VNS as an add-on treatment to rehabilitate poststroke motor function and activity.

Methods

Criteria for considering studies for this review

Types of studies

We will include only RCTs as they are the strongest study design to evaluate efficacy of interventions (see Cochrane Handbook 3.3.1.) (McKenzie 2023). We will include parallel, cluster and crossover trials. We will not include quasi-RCTs.

Types of participants

We will include studies reporting on adults (age > 18 years old) diagnosed with a first-ever stroke (ischemic or hemorrhagic) as defined by the American Heart Association (Sacco 2013). We will include participants in the hyperacute (0–24 h since stroke onset), acute (1–7 days), early subacute (7 days to 3 months), late-subacute (3–6 months), or chronic phases (>6 months) (Bernhardt 2017). Studies of participants with mixed pathologies (for example, studies that involved adults with a stroke and adults with dementia) will be excluded.

Types of interventions

Experimental interventions

The experimental group received any VNS intervention, paired with usual care (as defined by the authors) or conventional rehabilitation (intervention during which a clinician provides and supervises the rehabilitation tasks; therapy recommended by the most recent guidelines). In this review, we will consider VNS intervention to be any technique involving the use of a device (either invasive [placed under] or non-invasive [over the skin]) to stimulate the VN with pulses of electrical energy (Howland 2014). While signal amplitude of VNS usually varies from 0 to 3.5 mA, current frequency from 1 to 30 Hz, and pulse width from 100 to 1000 µs, we will consider all VNS interventions, irrespective of their signal amplitude, current frequency and pulse width. In addition, there will be no restriction in terms of treatment intensity, duration and number of sessions, length and frequency of treatment for both VNS and usual care interventions. Lastly, we will consider all types of coupling between VNS and motor training (VNS provided before, during or after the trials).

Control interventions

The control group received the usual care (as defined by the authors), conventional rehabilitation or any other active intervention (aiming to promote the motor recovery and activity of the individual's affected limb). We will

also include studies in which the control group received sham VNS or minimal VNS stimulation. There will be no restriction in terms of treatment intensity, duration and number of sessions, length and frequency of treatment for sham VNS, conventional rehabilitation or usual care interventions. We will consider all types of coupling between sham VNS and motor training (sham VNS provided before, during or after the trials).

Types of outcome measures

We will select eligible studies that reported at least one of the following outcome measures:

Primary outcomes

Regarding the effectiveness of VNS, we will select the upper limb motor function as the primary outcome.

- Upper limb motor function: Upper Extremity Fugl-Meyer Assessment (UE-FMA), a scale ranging from 0 to 66 points with a minimal clinically important difference (MCID) of 6.6 points (Fugl-Meyer 1975).

We will assess the safety of VNS by comparing the proportion of serious adverse events (SAEs) reported by the authors at the completion of the intervention and follow-up for the experimental and control groups.

- Number of people with at least one SAE; SAEs include any event that result in death, is life threatening, requires or prolongs hospitalization, leads to significant or permanent disability, causes congenital anomalies or birth defect (Cook 2008). We will therefore consider events such as infection, dysphagia, and vocal cord paresis as SAE.

Timing of outcome assessment

We will consider the short-term, middle-term and long-term time points for the analysis of outcomes.

- Short term (post-intervention outcome within a timeframe that is closest to six weeks but does not exceed 12 weeks). We will use the short-term time point as the primary time-point of interest.
- Medium term (outcome closest to six months)
- Long term (outcome closest to 12 months)

Secondary outcomes

Regarding the effectiveness of VNS, we will select upper limb activity, spasticity, manual dexterity, lower limb motor function, quality of life, anxiety, stroke severity improvements, and relative infarct growth as secondary outcomes. For studies using more than one scale to measure a given outcome, we will use hierarchical order of preference as per recommended guidelines (Van Criekinge 2023; Prange-Lasonder 2021; Pohl 2020; Kwakkel 2017; Lanctôt 2020; Winstein 2016). In this section, we present the prioritized scales first. The others are enclosed in parentheses and listed in order of preference.

- Upper limb activity: Action Research Arm Test (ARAT), a scale ranging from 0 to 57 points with an MCID of 5.5 points (Yozbatiran 2008) (Wolf Motor Function Test, a scale ranging from 0 to 5 points with an MCID of 0.4 points (Lin 2009; Wolf 2001)).
- Spasticity: modified Ashworth Scale, a scale ranging from 0 to 4 points (Gregson 1999) (modified Tardieu Scale, a scale ranging from 0 to 4 points for each joint (Morris 2002); upper limb Brunnstorm stage, a scale ranging from 1 to 7 points (Brunnstrom 1966)).
- Manual dexterity: Box and Block Test, a functional measure ranging from 0 to 150 points (Mathiowetz 1985) (Nine Hole Peg Test, an average time measure ranging from 0 to 300s (Mathiowetz 1985a)).
- Lower limb motor function: Lower-Extremity Fugl-Meyer Assessment (LL-FMA), a scale ranging from 0 to 34 points (Fugl-Meyer 1975).
- Quality of life: Stroke Impact Scale (SIS), a scale ranging from 0% to 100% (Duncan 1999) (EuroQol 5 Dimension 5 Level (Rabin 2001), a multidimensional scale).
- Anxiety: Hospital Anxiety and Depression Scale, a scale ranging from 0 to 21 points (Zigmond 1983) (General Anxiety Disorder scale, a scale ranging from 0 to 21 points (Spitzer 2006)).
- Stroke severity improvement: NIHSS, a scale ranging from 0 to 42 (Brott 1989).
- Relative infarct growth: an MRI measure based on diffusion-weighted imaging and computed as: ([post-intervention lesion volume-baseline lesion volume]/baseline lesion volume) × 100 (Arsava 2022; Dávalos 2004).

Regarding the safety of VNS, our secondary outcomes will include the proportion of dropouts and adverse events (AE) reported at the completion of the intervention and follow-up in both experimental and control groups.

- Number of people that discontinued the intervention (due to any reason related to the intervention).
- Number of people with at least one AE; AEs include pain, fall, injury, etc.

Timing of outcome assessment

As for the primary outcomes, we will consider the short-term, middle-term and long-term time points for the analysis.

Search methods for identification of studies

Electronic searches

We will search published trials from the following databases using systematic search strategies:

- Cochrane Central Register of Controlled Trial in Cochrane Library
- MEDLINE (via PubMed; inception date: 1971)
- Scopus (via Elsevier; inception date: 2004)
- Embase (via Elsevier; inception date: 2007)
- PsychINFO (via Ovid; inception date: 1967)
- CINAHL (via EBSCO; inception date: 1977)
- PEDro (inception date: 1999)

We developed a systematic search strategy for PubMed using MeSH terms and free terms. We then adapted this systematic search strategy for the other databases. All search strategies are presented in Appendix 1. To avoid any publication bias, we will not restrict the searches by language, date, or article type (see Cochrane Handbook 4.4.2 and 4.4.7) (Lefebvre 2023).

Searching other resources

We will search ongoing and unpublished trials in opengrey.eu, clinicaltrial.gov, the World Health Organisation International Clinical Trials Registry Platform, and strokecenter.org/trials. We will perform handsearching by reading the reference lists of all included studies, relevant scoping and systematic reviews, and conference papers covering the use of VNS for stroke rehabilitation (see Cochrane Handbook 4.3.5) (Lefebvre 2023). We will also contact review authors of the included studies to collect information about ongoing or unpublished studies.

In addition, review authors will perform searches on Google scholar, looking for studies that could have been missed or that were not published in the above-mentioned databases.

Data collection and analysis

Selection of studies

We will download all references resulting from the search strategies and store them in Covidence systematic review software (Covidence) (see Cochrane Handbook 4.6.6.1.) (Lefebvre 2023). After removal of duplicates, two independent review authors (GE and IS) will perform a first selection based on titles and abstracts. This process will be followed by a meeting to resolve any conflicting selections between review authors. If no agreement is reached, another review author will make the final decision (GEB and/or BL). Next, the review authors (GE and IS) will make a second selection by reviewing the full text of all remaining articles. Lastly, another meeting will be held to resolve any conflicting selection and a third review author (GEB and/or BL) involved in case of discrepancy. During the selection process, we will record a brief list of excluded studies (after full-text review) that, on appearance, seemed to meet the eligibility criteria. For each of these studies, we will document the primary cause of exclusion (see Cochrane Handbook 4.6.5.) (Lefebvre 2023). We will also search potential errata statements of the included studies. Author retraction, fraud suspicion, or important limitations (calling into question the validity of the results) will lead to exclusion of the study (see Cochrane Handbook 5.2) (Li 2023).

Data extraction and management

Two independent reviewers (GE and IS) will extract the following data of each study using a data collection form (see Cochrane Handbook 5.4.1.) (Li 2023): number of individuals randomized, number of drop-out, age, sex, time since stroke onset (or stroke stage classification), degree of severity of arm impairment (according to baseline score of UE-FMA), design of the intervention (type of VNS treatment, VNS modalities, area targeted by VNS, coupling method, type of add-on therapy, dose, duration, intensity, frequency), design of the control intervention (type of sham-VNS treatment, sham-VNS modalities, area targeted by sham-VNS, coupling method, type of usual care, dose, duration, intensity, frequency), length of follow-up assessment, primary and secondary outcome scores at baseline, postintervention and follow-up, main findings of the study, country where the study was conducted, funding of the study and COI of authors. This form was pilot tested (by GE and IS) using a representative sample of the studies to be reviewed. For multiarm studies, we will only extract data from relevant intervention groups (see Cochrane Handbook 5.3.6.) (Li 2023). Disagreements will be resolved through discussion. One review author (GE) will export all the data into the RevMan web application (RevMan Web 2022) and another review author (IS) will check that the data have been exported correctly.

Assessment of risk of bias in included studies

Two review authors (GE and IS) will independently evaluate the methodological quality of each included study using the last version of the Cochrane Risk of Bias tool (RoB 2) (Sterne 2019) (see Cochrane Handbook 7.1.2 and 7.3.2.) (Boutron 2023). This tool enables the assessment of risk of bias for each outcome. We will evaluate

the impact of assignment to the intervention for the short-term outcomes of the following outcome measures: upper limb motor function (assessed with the UE-FMA), upper limb activity (assessed with the ARAT), quality of life (assessed with the SIS), and SAE. The risk of bias assessment covers the following domains: bias arising from the randomization process (domain 1a), bias due to deviations from intended interventions (domain 2), bias due to missing outcome data (domain 3), bias in measurement of the outcome (domain 4), and bias in selection of the reported result (domain 5). We will use specific variants of the RoB 2 to handle the risk of bias assessment for crossover (see Cochrane Handbook 23.2.3) and cluster-RCTs (see Cochrane Handbook 23.1.2) (Higgins 2023). These specific variants of RoB 2 also include additional domains such as bias arising from period effect and carryover effect (domain S) for crossover RCTs and bias arising from the identification or recruitment of participants into cluster (domain 1b) for cluster RCTs.

For each domain, we will qualify the risk of bias for a certain outcome as low, high, or unclear. In the case of uncertainty or disagreement between review authors, a third reviewer will be involved (GEB and/or BL) and the authors of the included study eventually contacted. At the end of the process, we will determine an overall risk of bias (low, some concerns, or high) based on the following:

- Low: for all domains, the risk of bias is qualified as low.
- Some concerns: for some domains, the risk of bias is unclear but all others are qualified as low.
- High: for one or several domains, the risk of bias is qualified as high.

We will use the Excel tool (available on the riskofbiasinfo.org website) to record and manage RoB 2 assessments and provide all support for the judgements as well as the sources of information for risk of bias assessments (see Cochrane Handbook 7.3.1. and 7.3.2.) (Boutron 2023). We will use the RevMan web software to store the risk of bias outcomes and create summary graphs.

Measures of treatment effect

We will report dichotomous outcomes such as the presence of dropouts, AE, or SAEs using a risk ratio (RR) and 95% confidence interval (CI). For continuous outcomes, if the included studies used the same scale to measure the outcome, we will report the treatment effect using mean differences (MDs and 95%CI) between VNS and control intervention. If different scales were used for the same outcome, we will measure treatment effectiveness by computing a standardized mean difference (SMD) between VNS and control intervention (see Cochrane Handbook 6.5.1.2.) (Higgins 2023a). For each group, we will compare postintervention outcomes at the end of treatment and follow-up. We will check the accuracy of numerical data by comparing the direction of effect between the RR, MD, or SMD and findings of the included studies (see Cochrane Handbook 5.4.3.) (Li 2023).

Unit of analysis issues

If individuals underwent more than one intervention (due to a crossover design), we will consider performing analyses only on the data that were reported before the crossover (first phase) since there is a risk of carryover due to the potential persistence of effect of the first intervention (see Cochrane Handbook 23.2.3. and 23.2.6.) (Higgins 2023). For three-arm studies where all intervention groups were relevant, we will give priority to the splitting approach (Rücker 2017) (see Cochrane Handbook 16.5.4.) (Welch 2023). This method consists of dividing the 'shared' group into different subgroups of equal sample size. If the study compared two types of VNS interventions to a conventional therapy program, the 'shared group' will be the conventional therapy one. Conversely, if the study compared a VNS intervention to a conventional therapy program and no intervention, the shared group will be the VNS group. This method allows for an effect comparison between all participants' first group and half of the participants' shared group, and between all participants' second group and the other half of the participants' shared group.

In the case of cluster RCTs, we will determine the effective sample sizes for both the intervention and control groups. This will involve computing a ratio between the original sample size and the design effect. We will approximate the design effect by adjusting the average cluster size (M) through the intraclass correlation coefficient (ICC) (see Cochrane Handbook 23.1.4) (Higgins 2023). In cases where studies do not provide the ICC, we will impute this information based on comparable studies. Subsequently, we will conduct a sensitivity analysis to assess the impact of the imputation.

Dealing with missing data

In case of missing data (going from full-text unavailability to missing statistical information), we will contact the corresponding authors of the included studies. For continuous data, if authors of the included studies are unable to provide the mean and standard deviations (SDs), we will convert the medians and their quartiles to means and SDs using Wan's approach (Wan 2014). Similarly, we will convert CIs and standard errors of the mean to SDs following the methods described in the Cochrane Handbook (see section 7, chapter 7.3.2) (Boutron 2023).

Assessment of heterogeneity

We will quantify between-study statistical heterogeneity using the Higgins I^2 test (Higgins 2002; Higgins 2023a) and interpret it as low (for an I^2 between 0% to 40%), moderate (for an I^2 between 40% and 60%), substantial (for an I^2 between 50% and 90%), or considerable (for an I^2 between 75% and 100%) (see Cochrane Handbook

10.10.2) (Deeks 2023). We will also assess heterogeneity by visual inspection of forest plots and through chi-square tests.

We will assess clinical heterogeneity using descriptive tables for characteristics of population, intervention, comparison and outcomes. This assessment will take place before we decide to pool the data. If the studies are sufficient similar, we will pool the data. We also anticipate subgroup analysis based on the stroke phase (acute-early-subacute versus late-subacute-chronic) to investigate clinical heterogeneity.

We will assess methodological heterogeneity using sensitivity analysis to see whether the inclusion of high risk of bias studies affects our conclusions.

Assessment of reporting biases

We will evaluate reporting biases by comparing the information described in each trial's published protocol (on clinical trials registers) to the methods and results sections of the publication. In case of uncertainty or inconsistency between protocols, we will contact the authors. We will also use a funnel plot to check for small study effects which may suggest publication bias (through symmetry visual analyses) if we find more than 10 studies that reported the same outcome. In case of asymmetry or outlier result, we will perform the Egger regression test to assess the influence of publication bias on each result (Egger 1997).

Data synthesis

If the studies are sufficient similar (based on the clinical heterogeneity assessment), we will synthesize VNS treatment safety (proportion of dropouts, AEs, and SAEs) and effectiveness on poststroke upper limb motor function, activity, spasticity, manual dexterity, quality of life, and anxiety using a meta-analysis. This meta-analysis will include all eligible studies. We will use RevMan web software for all statistical analyses and forest plots. We will employ a random-effects model as we expect some heterogeneity between studies. If the number of studies is insufficient ($n < 2$), or the heterogeneity considerable (I^2 between 75% and 100%), even after outlier removal, we will summarize the results using a narrative synthesis (according to Synthesis Without Meta-analysis guidelines) instead of a pooled statistical synthesis (Campbell 2020).

Subgroup analysis and investigation of heterogeneity

If a sufficient number of studies ($n \geq 10$) and data are available, we will perform subgroup analyses using the formal Test for Subgroup Differences in RevMan Web. Given that post-lesional neuroplasticity is supposed to be at its greatest within the first 3 months of brain injury, we will first realize subgroup analyses to compare the findings collected in the (hyper-)acute and early subacute, from those collected in the late subacute and chronic phases. In addition, we will assess the influence of impairment severity (low-moderate vs. severe motor impairments) and VNS device set-up (invasive vs. non-invasive) on poststroke motor and activity outcomes. We will also assess health equity by determining whether the effect of VNS may change according to the location of studies. To this end, we will conduct subgroup analyses comparing VNS effect on individuals with stroke from high- to middle- and low-income countries (Hawe 2004; Pope 2007).

Sensitivity analysis

We will conduct the following sensitivity analysis to assess the robustness of the decision we made in our analysis:

- Risk of bias: analyses limited to studies at low risk of bias and with some concerns.

Summary of findings and assessment of the certainty of the evidence

We will realize a summary of findings table for the following comparison:

1. VNS as an add-on therapy versus no training or usual care (either with or without sham VNS) in individuals with stroke.

We will only include the short-term outcomes of these results in each summary of findings table:

- upper limb motor function (assessed with the UE-FMA)
- upper limb activity (assessed with the ARAT)
- quality of life (assessed with the SIS)
- SAE

This summary of findings table will comprise a brief description of the population and settings, a brief description of the experimental and comparison intervention, a list of the most important health outcomes, the measure of each outcome (RR, MD, or SMD), the magnitude of effect, the numbers of participants and studies, and the overall certainty of the body of evidence (Cochrane Handbook 14.1.3.) (Schünemann 2023). If subgroup analyses reveal a significant difference between outcomes collected among individuals with stroke in the acute-early-subacute phase, and these in the late-subacute-chronic phase, we will realize two different summary of findings tables (one for outcomes collected among individuals in the acute-early-subacute phase and another for outcomes collected among individuals in the late-subacute-chronic phase).

For each analysis of treatment effectiveness and safety, two review authors (GE and IS) will determine the quality of the body of evidence using the GRADE approach (GRADEpro GDT) (see Cochrane Handbook 14.2.1.) (Schünemann 2023). This method rates the certainty of evidence for a certain outcome (classified as very low, low, moderate, or high) according to the study design, overall risk of bias, inconsistency, indirectness, imprecision and publication bias (Brożek 2009). After the rating of certainty of evidence by the two independent review authors, we will arrange a meeting involving one or more additional review authors (including GEB) to address any disagreements, ultimately reaching a consensus.

We will decrease the grading for the following rationale, fed by the overall RoB 2 judgement:

- Serious (-1) [some concerns] or very serious (-2) [high risk of bias] overall risk of bias is suspected.
- Serious (-1) or very serious inconsistency (-2)
- Serious (-1) or very serious (-2) indirectness (assessed as the correspondence between population, intervention, control, and outcome research question and included studies).
- Serious (-1) or very serious imprecision (-2).
- Publication bias is strongly suspected (-1).

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Contributions of authors

GE created the search strategies under the supervision of GEB. All authors (GE, IS, JD, DET, SA, HMT, BOL and GEB) contributed to the conception and design, drafting, revision, and final approval of the version of the protocol manuscript to be published.

Declarations of interest

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Ita Daryanti Saragih: works as a health professional in Kaohsiung Medical University (Taiwan)

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Appendices

Appendix 1. Search strategies

Cochrane Stroke Group Trials Register :

"Vagus Nerve Stimulation"

OR "Vagus Nerve"

OR "10th cranial nerve"

OR "cranial nerve X"

OR "non-invasive vagus nerve"

OR "transcutaneous auricular vagus nerve"

OR "transcutaneous auricular nerve"

OR "VNS" OR "ta-VNS"

OR "pneumo-gastric nerve"

OR "pneumo gastric nerve"

OR "pneumogastric nerve"

OR "stimulation of the vagus nerve"

OR "tenth cranial nerve"

Cochrane Central Register of Controlled Trial in Cochrane Library :

Title Abstract Keyword : "Vagus Nerve Stimulation" OR "Vagus Nerve" OR "10th cranial nerve" OR "cranial nerve X" OR "non-invasive vagus nerve" OR "transcutaneous auricular vagus nerve" OR "transcutaneous auricular nerve" OR "VNS" OR "ta-VNS" OR "pneumo-gastric nerve" OR "pneumo gastric nerve" OR "pneumogastric nerve" OR "stimulation of the vagus nerve" OR "tenth cranial nerve"

AND

Title Abstract Keyword : "stroke" OR "cva" OR "accident cerebrovascular" OR "acute cerebrovascular lesion" OR "brain vascular accident" OR "cerebral stroke" OR "cerebro vascular accident" OR "cerebrovascular accident"

PubMed search strategy :

("Vagus Nerve Stimulation"[MeSH Terms] OR "Vagus Nerve Stimulation"[Title/Abstract] OR "Vagus Nerve"[Title/Abstract] OR "10th cranial nerve"[Title/Abstract] OR "cranial nerve X"[Title/Abstract] OR "non-invasive vagus nerve"[Title/Abstract] OR "transcutaneous auricular vagus nerve"[Title/Abstract] OR "transcutaneous auricular nerve"[Title/Abstract] OR "VNS"[Title/Abstract] OR "ta-VNS"[Title/Abstract] OR "pneumo-gastric nerve"[Title/Abstract] OR "pneumo gastric nerve"[Title/Abstract] OR "pneumogastric nerve"[Title/Abstract] OR "stimulation of the vagus nerve"[Title/Abstract] OR "tenth cranial nerve"[Title/Abstract])

AND

("stroke"[MeSH Terms] OR "stroke, lacunar"[MeSH Terms] OR "embolic stroke"[MeSH Terms] OR "thrombotic stroke"[MeSH Terms] OR "stroke rehabilitation"[MeSH Terms] OR "stroke"[Title/Abstract] OR "cva"[Title/Abstract] OR "accident cerebrovascular"[Title/Abstract] OR "acute cerebrovascular lesion"[Title/Abstract] OR "acute stroke"[Title/Abstract] OR "brain vascular accident"[Title/Abstract] OR "cerebral stroke"[Title/Abstract] OR "cerebro vascular accident"[Title/Abstract] OR "cerebrovascular accident"[Title/Abstract]

Scopus :

(TITLE-ABS-KEY("Vagus Nerve Stimulation") OR TITLE-ABS-KEY("Vagus Nerve") OR TITLE-ABS-KEY("10th cranial nerve") OR TITLE-ABS-KEY("cranial nerve X") OR TITLE-ABS-KEY("non-invasive vagus nerve") OR TITLE-ABS-KEY("transcutaneous auricular vagus nerve") OR TITLE-ABS-KEY("transcutaneous auricular nerve")

OR TITLE-ABS-KEY("VNS") OR TITLE-ABS-KEY("ta-VNS") OR TITLE-ABS-KEY("pneumo-gastric nerve") OR TITLE-ABS-KEY("pneumo gastric nerve") OR TITLE-ABS-KEY("pneumogastric nerve") OR TITLE-ABS-KEY("stimulation of the vagus nerve") OR TITLE-ABS-KEY("tenth cranial nerve"))

AND

(TITLE-ABS-KEY("stroke") OR TITLE-ABS-KEY("cva") OR TITLE-ABS-KEY("accident cerebrovascular") OR TITLE-ABS-KEY("acute cerebrovascular lesion") OR TITLE-ABS-KEY("acute stroke") OR TITLE-ABS-KEY("brain vascular accident") OR TITLE-ABS-KEY("cerebral stroke") OR TITLE-ABS-KEY("cerebro vascular accident") OR TITLE-ABS-KEY("cerebrovascular accident"))

Embase :

('cerebrovascular accident'/exp OR 'cva':ti,ab,kw OR 'accident, cerebrovascular':ti,ab,kw OR 'acute cerebrovascular lesion':ti,ab,kw OR 'acute stroke':ti,ab,kw OR 'brain vascular accident':ti,ab,kw OR 'cerebral vascular accident':ti,ab,kw OR 'cerebral vascular insufficiency':ti,ab,kw OR 'cerebro vascular accident':ti,ab,kw OR 'cerebrovascular accident':ti,ab,kw OR 'cerebrum vascular accident':ti,ab,kw OR 'stroke':ti,ab,kw)

AND

('vagus nerve'/exp OR '10th cranial nerve' OR 'cranial nerve x' OR 'cranial nerve, tenth' OR 'nerve, tenth cranial' OR 'nerve, vagal' OR 'nervus vagus' OR 'pneumo-gastric nerve' OR 'pneumogastric nerve' OR 'tenth cranial nerve' OR 'vagal nerve' OR 'vagus nerve' OR 'vagus nervus' OR 'vagus nerve stimulation'/exp OR 'vagal nerve stimulation':ti,ab,kw OR 'vagus nerve stimulation':ti,ab,kw OR 'implanted vagus nerve stimulator'/exp OR 't-vns':ti,ab,kw OR 't-vns stimulator cm02':ti,ab,kw OR 'vns therapy system':ti,ab,kw OR 'implantable vagus nerve stimulator':ti,ab,kw OR 'implanted vagus nerve stimulator':ti,ab,kw OR 'vagus nerve electrical stimulation system lead':ti,ab,kw OR 'vagus nerve electrical stimulation system programmer':ti,ab,kw OR 'vagus nerve electrical stimulators/stimulation systems':ti,ab,kw OR vns:ti,ab)

PsychINFO :

Title/Abstract : "Vagus Nerve Stimulation" OR "Vagus Nerve" OR "10th cranial nerve" OR "cranial nerve X" OR "non-invasive vagus nerve" OR "transcutaneous auricular vagus nerve" OR "transcutaneous auricular nerve" OR "VNS" OR "ta-VNS" OR "pneumo-gastric nerve" OR "pneumo gastric nerve" OR "pneumogastric nerve" OR "stimulation of the vagus nerve" OR "tenth cranial nerve"

AND

Title/Abstract: "stroke" OR "cva" OR "accident cerebrovascular" OR "acute cerebrovascular lesion" OR "acute stroke" OR "brain vascular accident" OR "cerebral stroke" OR "cerebro vascular accident" OR "cerebrovascular accident"

CINAHL :

Abstract : "Vagus Nerve Stimulation" OR "Vagus Nerve" OR "10th cranial nerve" OR "cranial nerve X" OR "non-invasive vagus nerve" OR "transcutaneous auricular vagus nerve" OR "transcutaneous auricular nerve" OR "VNS" OR "ta-VNS" OR "pneumo-gastric nerve" OR "pneumo gastric nerve" OR "pneumogastric nerve" OR "stimulation of the vagus nerve" OR "tenth cranial nerve"

AND

Abstract: "stroke" OR "cva" OR "accident cerebrovascular" OR "acute cerebrovascular lesion" OR "acute stroke" OR "brain vascular accident" OR "cerebral stroke" OR "cerebro vascular accident" OR "cerebrovascular accident"

PEDro :

Abstract/Title : "Vagus Nerve Stimulation Stroke" (Matched any search term (OR))

OR Abstract/Title : "VNS Stroke" (Matched any search term (OR))

OR Abstract/Title : "Vagus Nerve Stimulation cva" (Matched any search term (OR))

OR Abstract/Title : "VNS cva" (Matched any search term (OR))

OR Abstract/Title : "Vagus Nerve Stimulation cerebrovascular accident" (Matched any search term (OR))

OR Abstract/Title : "VNS cerebrovascular accident" (Matched any search term (OR))

OR Abstract/Title : "Cranial Nerve Stroke" (Matched any search term (OR))

OR Abstract/Title : "Cranial Nerve cva" (Matched any search term (OR))

OR Abstract/Title : "Cranial Nerve cerebrovascular accident" (Matched any search term (OR))

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