Effect of vagus nerve stimulation paired with rehabilitation for upper limb function improvement after stroke: a systematic review and meta-analysis of randomized controlled trials

Kehong Zhao[a,b,c,*], Jiaen Yang[a,b,c,*], Jiapeng Huang[a,b,c], Ziqi Zhao[a,b,c] and Yun Qu[b,c]

Vagus nerve stimulation (VNS) could potentially facilitate arm function recovery after stroke. The aim of this review was to evaluate the effect of VNS paired with rehabilitation on upper limb function recovery after stroke. We considered randomized controlled trials (RCTs) that used VNS paired with rehabilitation for the improvement of upper limb function after stroke and were published in English. Eligible RCTs were identified by searching electronic databases, including MEDLINE, Web of Science, Embase, CENTRAL and PEDro, from their inception until June 2021. Quality of included studies was assessed using PEDro score and Cochrane's risk of bias assessment. A meta-analysis was performed on the collected data. Five studies with a total of 178 participants met the inclusion criteria. Overall, the present meta-analysis revealed a significant effect of VNS on Fugl–Meyer Assessment for Upper Extremity (FMA-UE, MD = 3.59; 95% CI, 2.55–4.63; $P < 0.01$) when compared with the control group. However, no significant difference was observed in adverse events associated with device implantation between the invasive VNS and control groups (RR = 1.10; 95% CI, 0.92–1.32; $P = 0.29$). No adverse events associated with device use were reported in invasive VNS, and one was reported in transcutaneous VNS. This study revealed that VNS paired with rehabilitation can facilitate the recovery of upper limb function in patients with stroke on the basis of FMA-UE scores, but the long-term effects remain to be demonstrated. *International Journal of Rehabilitation Research* 45: 99–108 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Stroke is the leading cause of death and years lived with disability globally [1]. Upper limb impairment is one of the most prevalent dysfunctions after stroke, which results in poor health-related quality of life [2,3]. Approximately, 80–85% of patients with acute stroke present with upper limb motor impairment, and 60% of the stroke survivors still experience persistent impaired upper limb function 6 months after stroke [4,5]. Improving upper limb function is a priority for both stroke survivors and caregivers [6]. However, recent studies have revealed that the effects of current interventions for improving upper limb impairment are not satisfactory [3,7,8]. Therefore, novel and more effective methods are required to maximize upper limb recovery and ensure a high quality of life among stroke survivors [9].

Vagus nerve stimulation (VNS), which has been used for the treatment of epilepsy, headache and depression [10–12], can potentially enhance and facilitate the reorganization potential of cortical networks [13–15]. Several studies have investigated the efficacy of VNS paired with rehabilitation for upper limb function improvement in adults with stroke, but the results were conflicting and controversial. A meta-analysis of VNS and stroke published previously reported the potential effect of VNS on stroke [16]. The authors stated that additional high-quality studies, with large sample sizes, were required to validate their findings. Furthermore, the authors did not distinguish between invasive VNS and noninvasive VNS (transcutaneous VNS, tVNS), and the adverse events associated with device implantation and stimulation [16]. A previous study with a large sample size investigated

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the role of VNS in adults with stroke and was published in the Lancet recently [17]. Consequently, the present systematic review and meta-analysis of randomized controlled trials (RCTs) aimed to integrate new evidence presented in recent years to evaluate the efficacy and safety of VNS paired with rehabilitation for upper limb function improvement and to compare its effect with that of rehabilitation only or with sham VNS in adults with stroke.

Methods

The present systematic review and meta-analysis were performed and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement (PRISMA 2020), and *Cochrane Handbook for Systematic Reviews of Interventions* [18,19]. In addition, the present systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42021268269.

Data sources and search strategy

We systematically searched for relevant articles available in English in electronic databases, including MEDLINE (via PubMed), Web of Science, Embase (via Ovid), CENTRAL (Cochrane library) and Physiotherapy Evidence Database (PEDro) from their inception until June 2021. Search terms included keywords associated with stroke, VNS and the upper limb. The specific search strategy of MEDLINE used is presented in Table 1 (see Supplementary Table, Supplemental digital content 1, *http://links.lww.com/IJRR/A21* which presents the search strategies of the other four databases). Furthermore, manual screening of reference lists of the articles was performed to identify additional relevant studies. No ethical approval or patient consent was required because all analyses were on the basis of previously published studies.

Table 1 Search strategy of MEDLINE

MEDLINE (via PubMed)
1. Stroke [mh] or Cerebrovascular disorders [mh] or Basal ganglia cerebrovascular disease [mh] or Brain ischemia [mh] or Carotid artery diseases [mh] or Cerebral small vessel diseases [mh] or Intracranial arterial diseases [mh] or Intracranial embolism and thrombosis [mh] or Intracranial hemorrhages [mh] or Brain infarction [mh] or Stroke, lacunar [mh] or Vasospasm, intracranial [mh] or Vertebral artery dissection [mh] or Hemiplegia [mh] or Paresis [mh] or Brain injuries [mh] or Brain injury, chronic [mh]
2. Stroke* [tiab] or Poststroke [tiab] or Post-stroke [tiab] or Cerebrovasc* [tiab]
3. 1 or 2
4. Vagus nerve [mh]
5. Vagus nerve [tiab] or Vagal nerve [tiab] or Vagus nerve stimul* [tiab] or Vagal nerve stimul* [tiab]
6. 4 or 5
7. Upper extremity [mh]
8. Upper limb* [tiab] or upper extremit* [tiab] or arm* [tiab] or shoulder* [tiab] or hand* [tiab] or elbow* [tiab] or forearm* [tiab] or wrist* [tiab] or finger* [tiab] or axilla* [tiab]
9. 7 or 8
10. 3 and 6 and 9

Study selection

Endnote software was used to check for duplicated studies. Two investigators reviewed the studies independently and selected studies on the basis of the predetermined criteria. All potentially relevant articles were retrieved from the databases for the assessment of their full text on the basis of titles and abstracts. Studies that did not meet the inclusion criteria were excluded. Discrepancies between two reviewers were resolved through discussions with a third reviewer and a consensus was reached. The included studies were required to meet the following criteria: (1) studies were RCTs published in English, (2) patients were diagnosed with ischemic or hemorrhagic stroke by computerized tomography or MRI, (3) intervention treatments were VNS (transcutaneous VNS or invasive VNS) paired with rehabilitation versus rehabilitation only and (4) with regard to outcome measures, at least one outcome associated with function of the upper limb was measured.

Data extraction and quality assessment

Two reviewers independently extracted relevant data onto a predeveloped data extraction sheet, and disagreements were adjudicated by a third reviewer. The data extracted from selected studies included basic information (first author, year of publication), study design, demographic characteristics of patients (sample size, age, sex, time from stroke), details of interventions applied to the experimental and control groups, relevant outcome measures and time of evaluation.

Eligible articles were scrutinized for methodological quality by two independent reviewers using PEDro scale. The PEDro scale comprises 11 items with a total score ranging from 0 to 10 (except for item 1). The methodological quality of studies scoring 9–10 was considered to be of 'excellent' quality, studies scoring 6–8 were considered to be of 'good' quality, studies scoring 4–5 were considered to be of 'fair' quality, and studies scoring below 4 were considered to be of 'poor' quality [20]. Discrepancies between two reviewers were resolved through discussions with a third reviewer. Additionally, risk of bias assessments was performed using the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* [19]. The evaluation entries included the following aspects: random sequence generation, allocation concealment, masking, incomplete outcome data and selective outcome reporting among others. The included articles were evaluated as 'low risk', 'high risk' or 'unclear risk'. Quality assessment was not used as a selection or exclusion criterion.

Data synthesis and analysis

The results of all included studies were pooled using standard meta-analytic methods to estimate the effect of VNS paired with rehabilitation versus rehabilitation only for upper limb function improvement after stroke. On the basis of the nature of extracted data, we assessed the mean differences (MDs) and 95% confidence intervals

(CIs) for continuous outcomes, and risk ratios (RRs) at 95% CIs for adverse events. A P value <0.05 (two-sided) was considered statistically significant in the estimation of effects. Statistical heterogeneity was evaluated using chi-square test and I^2 statistic. P value <0.05 or I^2 value >50% was considered high heterogeneity. A fixed-effects model was used when P value was >0.05; otherwise, a random-effects model was used. Sensitivity analyses were performed by excluding each study from the analysis when heterogeneity was detected, and the subgroup analyses were performed on the basis of the different methods of VNS (tVNS or invasive VNS). Publication bias was not assessed due to the limited number of included studies (fewer than ten). All statistical analyses were performed using RevMan software (Version 5.3; Cochrane Collaboration, Copenhagen, Denmark).

Results

Search results

The initial electronic search resulted in a total of 278 studies, of which 175 unique articles were retrieved after duplicates were removed. After screening the titles, abstracts and full text of the articles on the basis of the inclusion and exclusion criteria, five studies [17,21–24] with a total of 178 participants were identified as eligible for the systematic review. The five studies were also used for the meta-analysis. A detailed flowchart of the search process for the studies is included in the systematic review and meta-analysis Fig. 1.

Description of studies

The studies included in the analysis were published between 2016 and 2021. The sample size ranged from 12 to 108 participants. The primary characteristics of the selected studies, including study design, baseline characteristics of enrolled participants, details of interventions and outcomes are summarized in Table 2.

The studies included in the current systematic review and meta-analysis satisfied specific inclusion and exclusion criteria. All participants in the selected studies were diagnosed with different stages of stroke [25]. One study reported subacute or chronic phase of stroke [23], one study reported acute or subacute phase of stroke [24] and three studies reported the chronic phase of stroke [17,21,22].

All experimental groups received VNS paired with rehabilitation. Two studies used tVNS [22,24] and three studies used surgically implanted VNS [17,21,23]. The intervention period ranged from 10 days to 6 weeks. One study compared VNS paired with rehabilitation to rehabilitation only [21], one study compared tVNS combined with robotic-assisted therapy to sham tVNS combined with robotic-assisted therapy [22], two studies compared VNS paired with rehabilitation to sham VNS combined with rehabilitation [17,23] and one study compared tVNS paired with rehabilitation to sham tVNS combined with rehabilitation [24].

Outcomes were measured at baseline and at the end of the intervention. The Fugl-Meyer Assessment for Upper Extremity (FMA-UE) Score was the main outcome in the evaluation of the effect of intervention and it was measured in five studies [17,21–24]. Additionally, three trials employed the Wolf Motor Function test (WMFT) [17,23,24] and Stroke Impact Scale (SIS) [17,21,23]; two trials used the Box and Block test and Nine-Hole Peg test [21,23], and five trials reported adverse events [17,21–24].

Quality

PEDro scores of the included studies ranged from 6 to 10, with a mean score of 8. The methodological quality of two studies was considered to be of 'excellent' quality [17, 23], while that of three studies was considered to be of 'good' quality [21,22,24]. A detailed evaluation of the PEDro scores is presented in Table 3. All included studies reported adequately with regard to their methods of blinding outcome assessors and random sequence generation, except for one study [22]. Only two studies satisfied the concealed allocation criterion. Subject blinding was satisfied in three of the selected studies [17,22,23]. Risk of bias assessment of the studies included in the present systematic review and meta-analysis is illustrated in Figs. 2, 3.

Effect of intervention

Fugl–Meyer assessment for upper extremity scores

A fixed-effects model was used for the analysis of FMA-UE scores. The variations in FMA-UE scores before and after intervention in five studies [17,21–24] indicated that FMA-UE scores increased significantly as a result of VNS paired with rehabilitation when compared to rehabilitation with or without sham VNS (MD = 3.59; 95% CI, 2.55–4.63; $P < 0.01$). On the basis of subgroup analyses, three studies [17,21,23] reported that the variations in FMA-UE scores between invasive VNS paired with rehabilitation and the control groups were significantly different (MD = 3.62; 95% CI, 1.75to–5.48; $P < 0.01$). Furthermore, two studies [22, 24] revealed that the variations in FMA-UE scores between tVNS paired with rehabilitation and control groups were significantly different (MD = 3.58; 95% CI, 2.33–4.82; $P < 0.01$). No heterogeneity was detected among the studies ($I^2 = 0\%$; $P = 0.78$; Fig. 4).

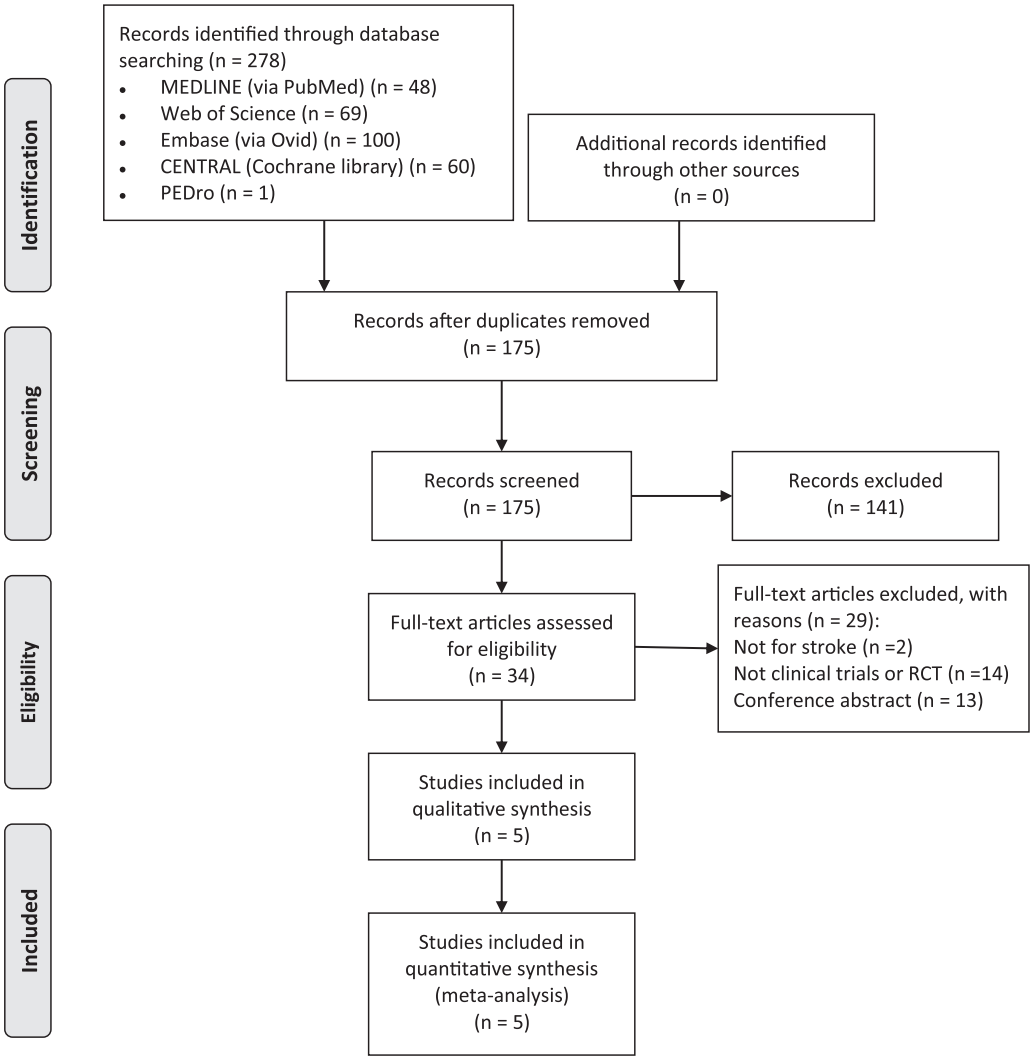
Wolf motor function test scores

A fixed-effects model was used to analyze WMFT scores. Two studies [17,23] revealed a significant difference in the variations of WMFT scores between invasive VNS and control groups (MD = 0.30; 95% CI, 0.18–0.43; $P < 0.01$), and no heterogeneity was observed among the studies ($I^2 = 0\%$; $P = 0.88$; Fig. 5). One study [24] revealed a significant difference in the variations of WMFT scores between the tVNS and control groups (MD = 3.59; 95% CI, 1.97–5.21; $P < 0.01$; Fig. 5).

Stroke impact scale (hand function)

Pooling data from two studies in the fixed-effects model [17,23] revealed no significant difference in SIS (Hand

Fig. 1



PRISMA flow diagram.

function) scores between the invasive VNS and control groups (MD = 1.07; 95% CI, −6.06 to 8.20; P = 0.77). Pooled studies were homogenous (I^2 = 0%; P = 0.83; Fig. 6).

Box and block test

No significant difference was observed between invasive VNS and control groups on the basis of Box and Block test scores (MD = −0.31; 95% CI, −3.48 to 2.87; P = 0.85) in the fixed-effects model when data from two studies were pooled [21,23]. Pooled studies were homogenous (I^2 = 0%; P = 0.94; Fig. 7).

Nine-hole peg test

No significant difference was observed in the Nine-Hole Peg test scores between invasive VNS and control groups (MD = 2.77; 95% CI, −31.40 to 36.95; P = 0.87) in the fixed-effects model when data from two studies were pooled [21,23]. Pooled studies were homogenous (I^2 = 38%; P = 0.20; Fig. 8).

Adverse events

The invasive VNS and control groups did not differ significantly in terms of adverse events associated with device implantation (RR = 1.10; 95% CI, 0.92–1.32; P = 0.29) in the fixed-effects model when data from three studies were pooled [17,21,23]. Pooled studies were homogenous (I^2 = 0%; P = 0.43; Fig. 9). Moreover, no adverse events associated with device use were reported in three studies with regard to invasive VNS [17,21,23]. One study [22] regarding tVNS did not report adverse events, while one study [24] reported that one patient in the tVNS group developed skin redness at the point of contact of the auricular skin with electrodes.

Table 2 Characteristics of included studies

Study	Design	Participants	Interventions	Outcomes
Dawson [21], 2016	RCT	*N* = 20 EG (*n* = 9) Age: 57.9 ± 17.2 years Onset: 1.8 ± 1.0 years CG (*n* = 11) Age: 60.7 ± 10.7 years Onset: 1.7 ± 1.3 years	EG: VNS paired with rehabilitation. (VNS: 0.8 mA, 100 μs, 30 Hz, lasting 0.5 s) CG: Rehabilitation alone (the rehabilitation-only group did not have a device implanted). Both groups: All participants received a 6-week course of 2-h therapy sessions 3× per week.	FMA-UE ARAT Grip and pinch strength SIS Box and Block test Nine-hole peg test At pre-, and post-Tx (6 weeks)
Capone [22], 2017	RCT	*N* = 12 EG (*n* = 7) Age: 53.71 ± 5.88 years Onset: 93.91 ± 38.81 months CG (*n* = 5) Age: 55.60 ± 7.12 years Onset: 46.00 ± 21.85 months	EG: tVNS and robotic-assisted therapy. Electric stimulator was placed in the left external acoustic meatus at the inner side of the tragus. tVNS was delivered as trains lasting 30 s and composed by 600 pulses (pulse frequency = 20 Hz; pulse duration = 0.3 ms) repeated every 5 min for 60 min. CG: Sham tVNS and robotic-assisted therapy. Both groups: Robotic treatment was delivered daily for 10 consecutive working days, immediately after the end of real or sham tVNS.	FMA-UE At pre-, and post-Tx (10 days)
Kimberley [23], 2018	RCT	*N* = 17 EG (*n* = 8) Age: 59.5 ± 7.4 years Onset: 18 (11-43) months CG (*n* = 9) Age: 60.0 ± 13.5 years Onset: 18 (6.3–53) months	EG: VNS paired with rehabilitation. VNS (0.8 mA). CG: Sham VNS paired with rehabilitation. VNS (0 mA) Both groups: Both groups were surgically implanted with the VNS device. All participants received 6-week in-clinic rehabilitation (≈3×a week for 6 weeks) followed by a home exercise program.	FMA-UE WMFT Box and Block test Nine-hole peg test SIS Motor Activity Log At pre-, and days 1, 7, 30, and 90 days after in-clinical therapy
Wu [24], 2020	RCT	*N* = 21 EG (*n* = 10) Age: 64.50 ± 9.97 years Onset: 36.30 ± 9.23 days CG (*n* = 11) Age: 61.82 ± 10.63 years Onset: 35.55 ± 6.47 days	EG: tVNS paired with rehabilitation. Parameters: 600 pulses (pulse frequency = 20 Hz; pulse duration = 0:3 ms), lasting 30 s each time, stimulating once every 5 min. CG: Sham tVNS paired with rehabilitation. Both groups: Rehabilitation training, lasting approximately 30 min, was performed immediately after the end of real or sham tVNS per day for 15 days.	FMA-UE WMFT FIM BS At pre-, and post-Tx.
Dawson [17], 2021	RCT	*N* = 108 EG (*n* = 53) Age: 59.1 ± 10.2 years Onset: 3.1 ± 2.3 years CG (*n* = 55) Age: 61.1 ± 9.2 years Onset: 3.3 ± 2.6 years	EG: VNS paired with rehabilitation (VNS: 0.8 mA, 100μs, 30 Hz stimulation pulses, lasting 0.5 s). CG: Sham VNS paired with rehabilitation. Both groups: Both groups were surgically implanted with the VNS device. Participants received 6 weeks of in-clinic therapy (three times per week; total of 18 sessions) followed by a home exercise program.	FMA-UE WMFT SIS

ARAT, arm research arm test; SIS, Stroke Impact Scale; BS, Brunnstrom stage; CG, control group; EG, experimental group; FIM, functional independence measurement; FMA-UE, Fugl-Meyer Assessment for Upper Extremity scale; Tx, treatment; VNS, vagus nerve stimulation; WMFT, Wolf motor function test.

Table 3 PEDro assessment quality results of included studies

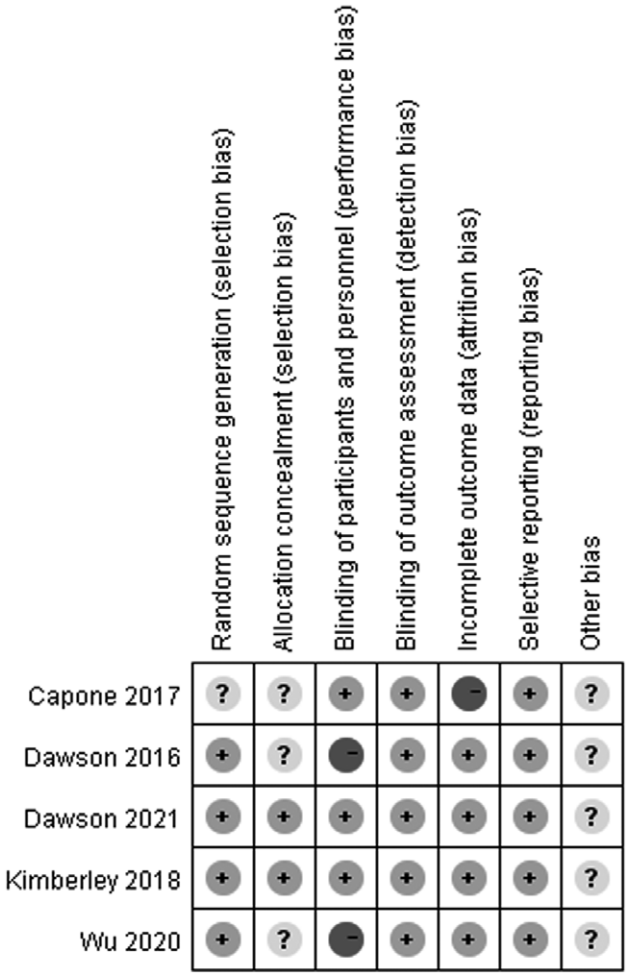
Study	Eligibility*	Random allocation	Concealed allocation	Baseline comparability	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up	Intention-to-treat analysis	Between-group comparisons	Point estimates and variability	Total score	Quality
Dawson [21], 2016	YES	1	0	1	0	0	1	1	1	1	1	7	GOOD
Capone[22], 2017	YES	1	0	1	0	1	1	0	0	1	1	6	GOOD
Kimberley [23], 2018	YES	1	1	1	1	1	1	1	1	1	1	10	Excellent
Wu [24], 2020	YES	1	0	1	0	0	1	1	1	1	1	7	GOOD
Dawson [17], 2021	YES	1	1	1	1	1	1	1	1	1	1	10	Excellent

*Eligibility criteria is not included in the scoring of PEDro scale.

Discussion

The present systematic review and meta-analysis reviewed the findings of previous studies to evaluate the safety and determine the effect of VNS paired with rehabilitation on upper limb function recovery in patients with stroke. The outcome measures were evaluated on the basis of the difference in performance between the baseline and immediately after the intervention. The results of the present meta-analysis revealed that the increases in FMA-UE and WMFT scores of patients in the VNS group were significantly greater than those in the control group. However, the increases in SIS (hand function), Box and Block test and Nine-Hole Peg test scores were similar in both groups. The results are consistent with the findings of a previous review [16]. Our findings have presented moderate statistical evidence

Fig. 2



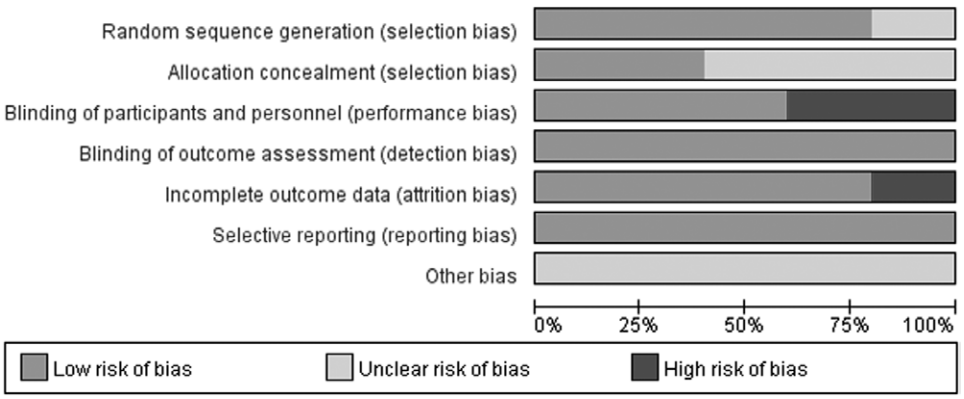
Risk of bias summary according to the Cochrane risk of bias tool: '–', '+' and '?' indicate high, low and unclear risk of bias, respectively.

for improved efficacy of VNS paired with rehabilitation when compared to the efficacy of convenient rehabilitation on the basis of FMA-UE and WMFT scores.

With regard to the FMA-UE, an increase of 3.59 was recorded across all included trials on average. One study revealed that the clinically important difference (CID) for FMA-UE in individuals with minimal to moderate impairment due to chronic stroke ranged from 4.25 to 7.25 points [26]. However, the variations in scores observed in the present systematic review were lower than the CID threshold, which suggest that there was no clinical significance. One study that investigated invasive VNS defined a clinically meaningful response as a 6-point or greater improvement in FMA-UE score and reported that more participants in the VNS group reached a threshold of clinically meaningful response when compared with the control group (23 [47%] of 53 vs. 13 [24%] of 55, $P = 0.0098$) [17]. Similarly, an increase of 0.3 was observed in invasive VNS on average on the basis of WMFT scores and an increase of 3.59 was observed in tVNS on average. Lin *et al.* reported that the CID of WMFT in patients with stroke varied from 0.2 to 0.4 points [27]. Both variations reached the CID threshold, which indicated a clinical significance.

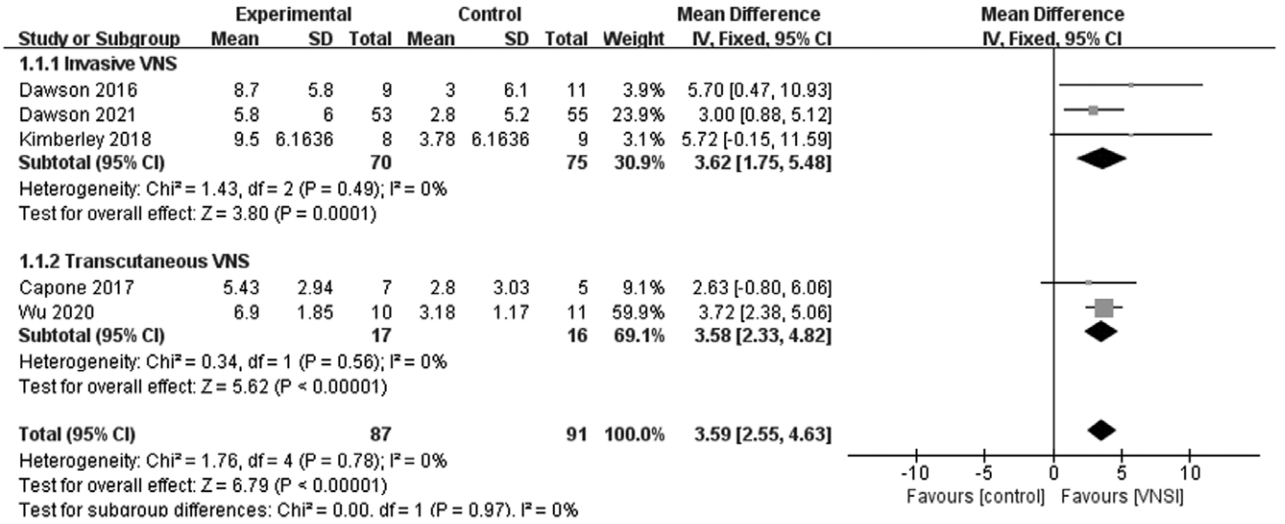
The primary safety outcome measure was the number of adverse events associated with device implantation or stimulation. The results of the present meta-analysis revealed no significant difference in adverse events associated with device implantation between the invasive VNS and control groups. Only one study reported that one patient in the tVNS group developed skin redness at the point of stimulation [24]. In addition, no adverse events associated with therapy were reported. tVNS is a relatively safe intervention as a result of surgical-related complications caused by invasive VNS, such as left vocal cord palsy and dysphagia; however, no study has compared the effect

Fig. 3



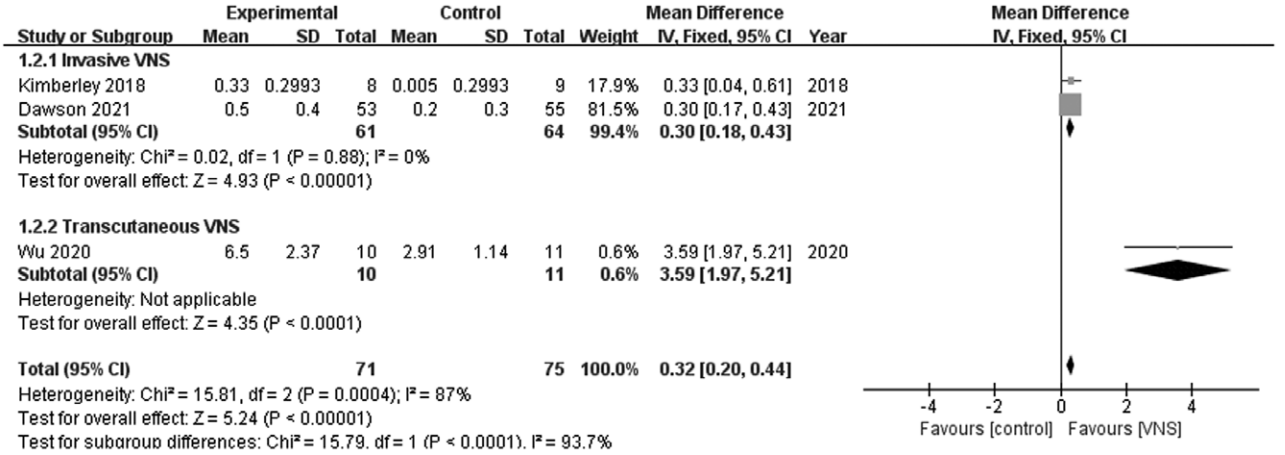
Risk of bias graph according to the Cochrane risk of bias tool.

Fig. 4



Fugl–Meyer assessment for upper extremity scores.

Fig. 5



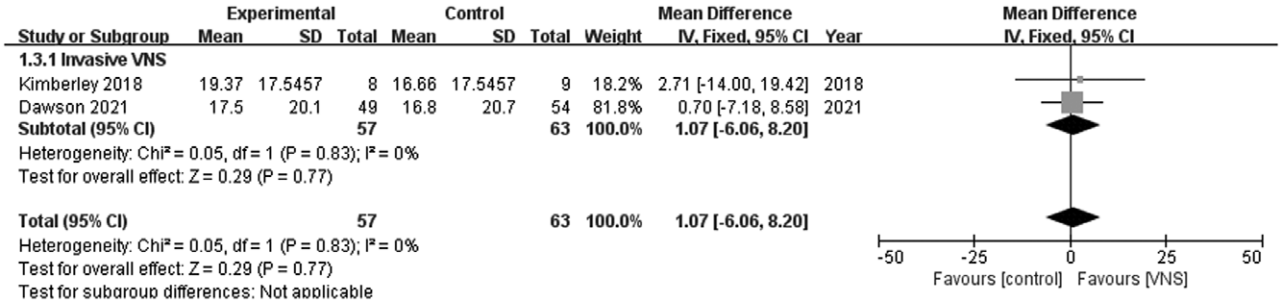
Wolf motor function test scores.

of invasive VNS to that of tVNS. Although there is increasing interest in tVNS, concerns regarding the degree of activation of vagal fibers, optimal stimulation site and stimulation parameters, and potential effects of stimulation on other nerves in the region have been raised.

The patients in the selected studies were diagnosed with stroke in the subacute or chronic phase, which suggests that the mechanism of VNS improvement occurs through the upregulation of neuroplasticity. Furthermore, VNS could have a potential benefit in improving acute stroke performance due to its participation in pathophysiological processes associated with anti-glutamate effects, anti-inflammatory activity, attenuating spreading depolarizations and decreasing intracranial pressure [28]. Further studies are required to elucidate the mechanisms and therapeutic effects of VNS.

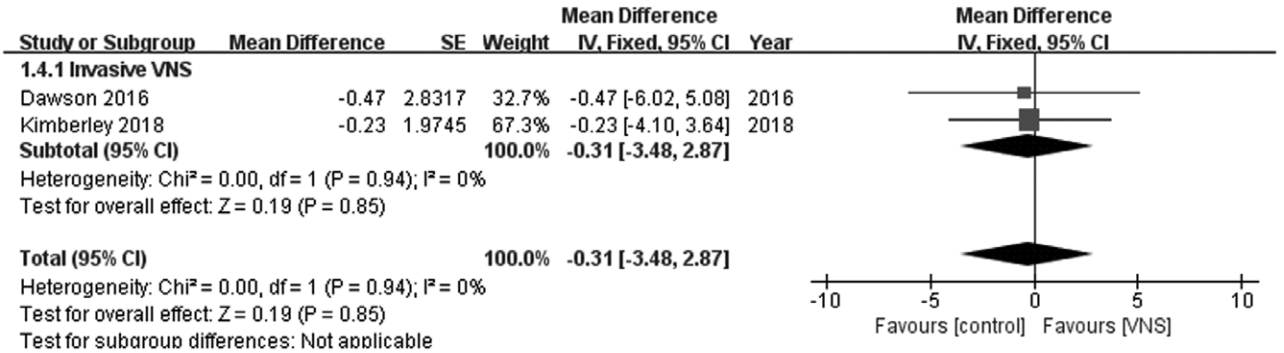
The stimulation parameters of invasive VNS for three studies that were included in the present systematic review and meta-analysis were the same; that is, burst of 500 ms with a constant current of 0.8 mA, pulse duration of 100 μs, and frequency of 30 Hz, which were derived from hypothesis-driven research in human and animal models [14,15,29,30]. The stimulations of invasive VNS

Fig. 6



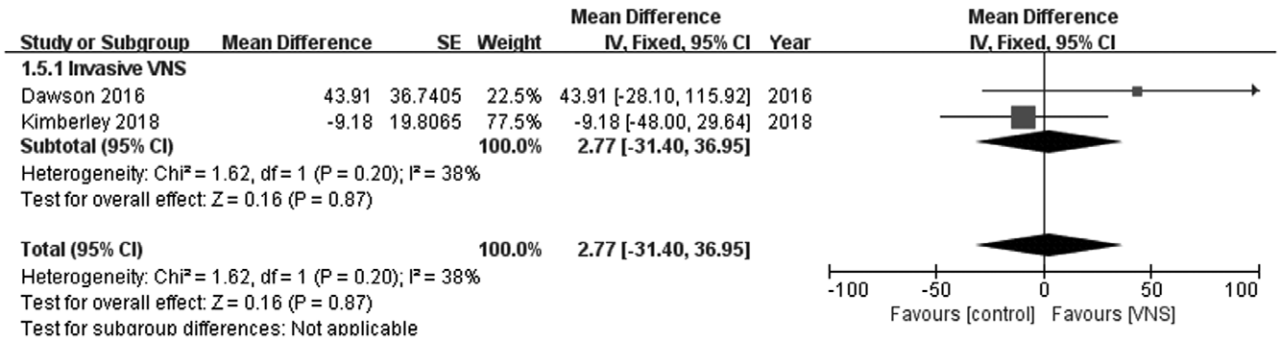
Stroke Impact Scale (hand function).

Fig. 7



Box and Block test.

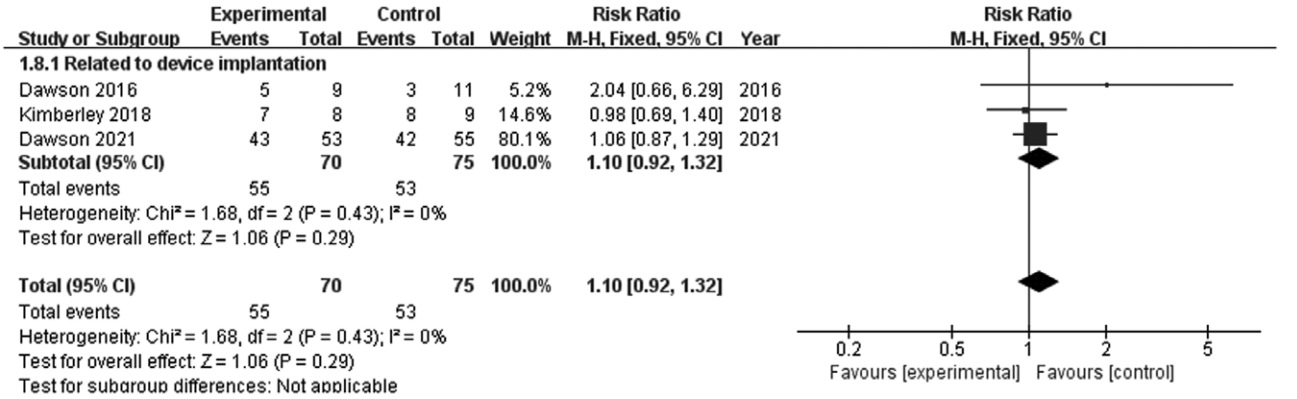
Fig. 8



Nine-Hole Peg test.

were delivered to the left vagus nerve to avoid activation of the sinoatrial node. The stimulation site for tVNS was the left external acoustic meatus on the inner side of the tragus, and the stimulation intensities for two studies were adjusted independently (above the detection threshold and below the pain threshold) to a pulse duration of 0.3 ms and frequency of 20 Hz repeated every 5 min for 60 min. However, there was no relevant basis for the stimulation parameters of tVNS, and the specific range of parameters that influence cortical plasticity remain unknown. Therefore, further studies regarding tVNS should be conducted.

Fig. 9



Adverse events.

Consequently, on the basis of the evidence provided by the current systematic review and meta-analysis, invasive VNS and tVNS paired with rehabilitation are effective in improving upper limb performance in patients with stroke. VNS could be used as adjuvant therapy for patients with subacute or chronic stroke in clinics. However, further research regarding the adverse events associated with device implantation in invasive VNS should be conducted.

Study limitations

The limitations of the current systematic review and meta-analysis were as follows. First, studies published in languages other than English were excluded. Second, quality assessment was not used as a selection or exclusion criterion. Third, the lack of concealed allocation and blinding in a few of the studies selected could have influenced the results. Fourth, outcomes of selected studies were measured immediately after treatment without any long-term follow-up. Finally, the number of included studies and patients were relatively small and may not provide sufficient statistical power to support the results.

Conclusion

VNS paired with rehabilitation is a promising strategy to promote upper limb function recovery for patients with stroke. The results of this systematic review and meta-analysis indicate that VNS paired with rehabilitation could improve upper limb function in patients with stroke on the basis of FMA-UE and WMFT scores. More studies with a focus on the long-term effect are needed.

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Conflicts of interest

There are no conflicts of interest.

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