Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial

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Summary

Background Long-term loss of arm function after ischaemic stroke is common and might be improved by vagus nerve stimulation paired with rehabilitation. We aimed to determine whether this strategy is a safe and effective treatment for improving arm function after stroke.

Methods In this pivotal, randomised, triple-blind, sham-controlled trial, done in 19 stroke rehabilitation services in the UK and the USA, participants with moderate-to-severe arm weakness, at least 9 months after ischaemic stroke, were randomly assigned (1:1) to either rehabilitation paired with active vagus nerve stimulation (VNS group) or rehabilitation paired with sham stimulation (control group). Randomisation was done by ResearchPoint Global (Austin, TX, USA) using SAS PROC PLAN (SAS Institute Software, Cary, NC, USA), with stratification by region (USA *vs* UK), age (≤30 years *vs* >30 years), and baseline Fugl-Meyer Assessment-Upper Extremity (FMA-UE) score (20–35 *vs* 36–50). Participants, outcomes assessors, and treating therapists were masked to group assignment. All participants were implanted with a vagus nerve stimulation device. The VNS group received 0·8 mA, 100 μs, 30 Hz stimulation pulses, lasting 0·5 s. The control group received 0 mA pulses. Participants received 6 weeks of in-clinic therapy (three times per week; total of 18 sessions) followed by a home exercise programme. The primary outcome was the change in impairment measured by the FMA-UE score on the first day after completion of in-clinic therapy. FMA-UE response rates were also assessed at 90 days after in-clinic therapy (secondary endpoint). All analyses were by intention to treat. This trial is registered at ClinicalTrials.gov, NCT03131960.

Findings Between Oct 2, 2017, and Sept 12, 2019, 108 participants were randomly assigned to treatment (53 to the VNS group and 55 to the control group). 106 completed the study (one patient for each group did not complete the study). On the first day after completion of in-clinic therapy, the mean FMA-UE score increased by 5·0 points (SD 4·4) in the VNS group and by 2·4 points (3·8) in the control group (between group difference 2·6, 95% CI 1·0–4·2, p=0·0014). 90 days after in-clinic therapy, a clinically meaningful response on the FMA-UE score was achieved in 23 (47%) of 53 patients in the VNS group versus 13 (24%) of 55 patients in the control group (between group difference 24%, 6–41; p=0·0098). There was one serious adverse event related to surgery (vocal cord paresis) in the control group.

Interpretation Vagus nerve stimulation paired with rehabilitation is a novel potential treatment option for people with long-term moderate-to-severe arm impairment after ischaemic stroke.

Funding MicroTransponder.

Introduction

Approximately 80% of people with acute stroke have upper limb motor impairment and 50–60% of these survivors still have persistent impaired upper limb function 6 months later.[1,2] Persistent arm impairment is linked with poorer quality of life and reduced wellbeing.[3] Identifying new treatments to improve upper limb function after stroke is a research priority for both stroke survivors and caregivers.[4]

There are few effective treatments to enhance upper limb recovery after stroke. Trials of increased rehabilitation therapy dose and of adjuvant drug or brain stimulation therapies have not been effective.[5–8] Constraint-induced movements therapy has been shown to improve measures of upper limb impairment and function in selected people with stroke, possibly through helping them to relearn how to use intact motor pathways.[9]

One potential method to enhance the reorganisation potential of the brain following stroke is via cholinergic and monoaminergic modulation of motor cortex neurons.[10,11] This method can be achieved by vagus nerve stimulation. Vagus nerve stimulation paired with sensory input or motor training has been shown to result in

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Research in context

Evidence before this study

We searched PubMed, with terms "ischemic stroke or ischaemic stroke" and "(VNS or vagus nerve stimulation)", for studies published up to April 6, 2021, without language restrictions. 46 articles were retrieved. Evidence from rodent models suggests that vagus nerve stimulation paired with rehabilitation improves forelimb function after experimental stroke and can enhance task-specific plasticity. Two pilot clinical studies of invasive vagus nerve stimulation paired with upper extremity rehabilitation have been done in patients who have suffered stroke. These studies were small and no large adequately powered clinical studies of this technique had been done when our study began.

Added value of this study

To our knowledge, VNS-REHAB is the first multicentre trial with adequate statistical power to compare active vagus nerve stimulation and sham stimulation, both paired with rehabilitation. Participants treated with vagus nerve stimulation had clinically meaningful improvements in

measures of upper limb function and impairment on the first day after completion of in-clinic therapy and similar improvements 90 days later after a period of home exercise. The clinical response rate with active vagus nerve stimulation was double that of sham stimulation on both the Fugl-Meyer Assessment-Upper Extremity and Wolf Motor Function Test-Functional scores, and almost 50% of participants treated with active vagus nerve stimulation achieved a clinical response.

Implications of all the available evidence

The results of this trial support the use of vagus nerve stimulation paired with rehabilitation for the treatment of selected people with upper limb impairment at least 9 months after ischaemic stroke. Further research should explore how to implement this approach in clinical practice and whether vagus nerve stimulation can be used to improve other impairments after stroke, including more severe degrees of arm impairment.

input-specific reorganisation of rat cortical neurons.[12,13] In rodent models of ischaemic stroke, vagus nerve stimulation combined with movement training significantly improved forelimb motor recovery and tripled the synaptic connectivity of motor cortex neurons compared with movement training alone.[14] Two pilot studies of vagus nerve stimulation paired with intensive upper limb rehabilitation have been done in people with long-term moderate-to-severe arm weakness after stroke.[15,16] Participants treated with vagus nerve stimulation had greater improvement in the total Fugl-Meyer Assessment-Upper Extremity (FMA-UE) score than participants who received intense rehabilitation alone.

We did a trial comparing active vagus nerve stimulation paired with rehabilitation versus sham stimulation paired with rehabilitation in people with moderate-to-severe arm impairment after ischaemic stroke. The purpose of this trial was to determine whether vagus nerve stimulation paired with rehabilitation is a safe and effective treatment for improving arm function after stroke.

Methods

Study design and participants

This pivotal, randomised, triple-blinded, sham-controlled trial was done in 19 stroke rehabilitation services in the UK and the USA (appendix p 2). Further details regarding the design of the trial have been published previously.[17] The study was approved by the review boards at each institution and subject to appropriate regulatory approvals (US Food and Drug Administration Investigational Device Exemption, number G170031, and UK Medicines and Healthcare products Regulatory

Agency, number CI/2017/0031). The study was done according to the Declaration of Helsinki and written informed consent was obtained from all participants.

Study participants were adults between 22 years and 80 years, with a history of unilateral supratentorial ischaemic stroke that occurred between 9 months and 10 years before enrolment. People with moderate-to-severe arm impairment defined as an FMA-UE score of 20–50 were eligible for inclusion. Full inclusion and exclusion criteria are provided in the appendix (p 3).

Randomisation and masking

At the time of vagus nerve stimulation implant surgery, participants were randomly assigned (1:1) to either rehabilitation paired with active vagus nerve stimulation (VNS group) or rehabilitation paired with sham stimulation (control group). Randomisation was done by ResearchPoint Global (Austin, TX, USA) using SAS PROC PLAN (SAS Institute Software, Cary, NC, USA), with stratification by region (USA vs UK), age (≤30 years vs >30 years), and baseline FMA-UE score (20–35 vs 36–50). The randomisation allocation was sent via email to an unmasked clinical engineer at each site who tested and programmed the device with the appropriate stimulation settings according to the group assignment during implantation. Participants, outcomes assessors, and treating therapists were masked to group assignment. To maximise masking of treatment allocation, all participants were implanted with the vagus nerve stimulation device. In addition, participants from both treatment groups received five stimulations in reducing strengths (starting at 0·8 mA and then reducing by 0·1 mA each step) at the beginning of each therapy session

followed by stimulation according to randomised allocation. This strategy was designed to minimise risk of participants being able to infer treatment allocation by exposing all participants to the same stimulation parameters at the start of each session. After the primary endpoint assessment, participants were asked to rate their certainty regarding group allocation by selecting one of five options: knew they had received vagus nerve stimulation; thought they received vagus nerve stimulation; knew they were in the sham stimulation group; thought they were in the sham stimulation group; or did not know which treatment group they were allocated.

Procedures

A presurgery assessment was done. Device (Vivistim System, MicroTransponder, Austin, TX, USA) implantation was done under general anaesthesia. A horizontal neck crease incision was created left of the midline at the level of the cricoid cartilage. After the vagus nerve was identified, the stimulation lead was wrapped around the vagus nerve. The lead was then tunnelled subcutaneously to the pulse generator device, which was contained in a subcutaneous pocket in the pectoral region.[18]

Baseline assessments were done 1 week after device implantation. Stimulation was tested in increments of 0·1 mA to assess the level at which participants felt and tolerated stimulation. This process was done in both groups regardless of treatment allocation.

In-clinic rehabilitation therapy began the next day and was provided three times per week for 6 weeks (total of 18 sessions). Details about the upper limb rehabilitation delivered in the trial have been reported previously.[16] Briefly, in-clinic rehabilitation consisted of high-repetition, task-based, functional, individualised, and progressive upper limb exercises. All participants received the same goal-oriented and intense upper limb rehabilitation following specific guidelines.[16] Therapy tasks were divided into six categories: reach and grasp, gross movement, object flipping, simulated eating tasks, inserting objects, and opening and closing containers. For a given task, the object, movement direction, and environment factors were adjusted to maintain difficulty level and subject motivation. Since participants had varying degrees of impairment and functional deficit, the exact number of repetitions and tasks per session varied. However, it was expected that six tasks would be done in the same order at each session and that approximately 30–50 repetitions would be done for each task (>300 repetitions per session). The therapist timed the vagus nerve stimulation pulse with each repetition of movement (appendix p 10). The VNS group received 0·8 mA (or lower if required for comfort), 100 μs, 30 Hz stimulation pulses, lasting 0·5 s, during each movement repetition. The control group received 0 mA pulses.

Following the six weeks of in-clinic therapy, all participants began daily therapist-prescribed home exercises. The home therapy session lasted 30 min and included tasks following the same principles as the in-clinic therapy. During home exercises, participants activated the vagus nerve stimulation device via a single magnet swipe over the device and 30 min of either active or sham vagus nerve stimulation was then delivered according to their randomised allocation. The stimulation output current was kept the same as during in-clinic therapy. Bi-monthly telephone calls between the therapist and participant were conducted to ensure compliance and adequate exercise intensity.

Outcome assessments were done on days 1 and 90 after the completion of the 6-week in-clinic therapy. Assessments were the FMA-UE, Wolf Motor Function Test (WMFT; function and time score), Motor Activity Log (MAL), Stroke Impact Scale (SIS) score, Stroke Specific Quality of Life (SS-QOL), EQ-5D, and the Beck Depression Inventory (BDI). The WMFT and FMA-UE were also assessed at day 30 following completion of in-clinic therapy. A description of each of the measures is provided in the appendix (p 4). Assessments were done by the same assessor at baseline and at follow-up.

Data on all adverse events and serious adverse events were recorded prospectively at each therapy session and at all outcome assesments. Events were coded with the use of the Medical Dictionary for Regulatory Activities, version 22. Adverse events were rated as mild, moderate, or severe. Severity and causality or relationship to study treatment (rehabilitation and vagus nerve stimulation) or implant surgery was assigned by the site principal investigator. The BDI was assessed at baseline and the final outcome assessments to explore changes in depressive symptoms.

Outcomes

The primary outcome was change in FMA-UE score from baseline to the first day following completion of in-clinic therapy.[19,20] The secondary outcomes measures were clinically meaningful response on FMA-UE score at day 90; change in day 90 WMFT-Functional score relative to pretreatment (baseline); and change in day 90 FMA-UE score relative to baseline. We defined a clinically meaningful response as a 6-point or greater improvement in FMA-UE score based on previous research showing that a 5·25-point change was associated with an excellent improvement (greater than 50%) in arm function.[21]

Tertiary outcome measures were the MAL score, SIS score, SS-QOL score, and EQ-5D score.

Statistical analysis

The a-priori sample size calculation was based on data from our pilot studies.[15,16] A sample size of 100 participants (50 per group) was determined to provide 80% power (α 0·05) to detect a mean FMA-UE difference of 2·3 (SD 4) points between the two treatment groups. We enrolled 108 participants to allow for dropouts.

An independent data safety monitoring board (DSMB) reviewed adverse events, safety information, and the

planned futility analysis. The predefined futility analysis was done based on data from the first 40 participants. The criteria for futility were not met and DSMB determined that the trial could continue.

All efficacy and safety analyses were done on the intention-to-treat population, defined as all participants who have any surgical portion of the implant procedure attempted, regardless of the treatment to which they are assigned, and regardless of the amount of intervention completed. A per-protocol population was defined a priori to include participants who completed at least 12 sessions without major protocol violations, which could affect or compromise the safety or efficacy of the treatment.

For the primary outcome measure, an analysis of covariance (ANCOVA) model was used, with the FMA-UE change from baseline to day 1 following completion of in-clinic therapy as the dependent variable, and treatment arm, region (UK or USA), treatment by region interaction as factors, and with age and baseline FMA-UE score as covariates. A significance level of 0·05 was used. The region by treatment interaction was to be removed from the final model if it was not significant (p>0·1). For the comparison of clinically important response rate at day 90 after completion of therapy, we used a logistic regression model with treatment arm, region, age, and baseline FMA-UE score as factors. An ANCOVA model, with the change from baseline as the dependent variable, and treatment and randomisation strata as factors was used for the analysis of the WMFT-Functional change and the FMA-UE change at day 90 following completion of in-clinic therapy. The three secondary outcomes measures were tested for significance in a hierarchical manner in the order listed. Significance was declared for the first secondary outcome at 0·05, and each subsequent outcome only if all higher ranked endpoints were significant at 0·05. A number needed to treat to achieve an additional clinically meaningful response was calculated. Between group differences for all primary and secondary outcome measures were assessed using the *t* distribution. For the post-hoc outcome measure of WMFT response rate at day 90, we used Fisher's Exact test to assess the between group difference. We added change in WMFT between baseline and day 1 and WMFT response rate as a post-hoc outcome measure. A clinically meaningful response was defined as a greater than 0·4-point change in WMFT-Functional score at day 90 relative to baseline.[22] In additional post-hoc analyses we compared response rates on the FMA-UE score at 3 additional levels (≥4 points, ≥5 points, and ≥7 points). We also compared the proportion who guessed they received vagus nerve stimulation and who correctly guessed their treatment allocation. Summary statistics for tertiary measures were tabulated but formal statistical analysis was not done.

A last observation carried forward approach was used if an assessment was missing after baseline. We assessed the effect of missing data (sensitivity analysis) by first performing a mixed model for repeated measures test (SAS PROC MIXED) on the full dataset. We then did multiple imputation with missing at random assumptions (SAS PROC MI).

All statistical analyses were independently done by ResearchPoint Global using SAS, version 9.4 or higher. The study was registered on ClinicalTrials.gov (NCT03131960).

Role of the funding source
The funder participated in the study design and writing of the manuscript, but had no role in data collection, data analysis, data interpretation, or the decision to submit the manuscript. The decision to submit the manuscript was the responsibility of JD, TJK, and CYL.
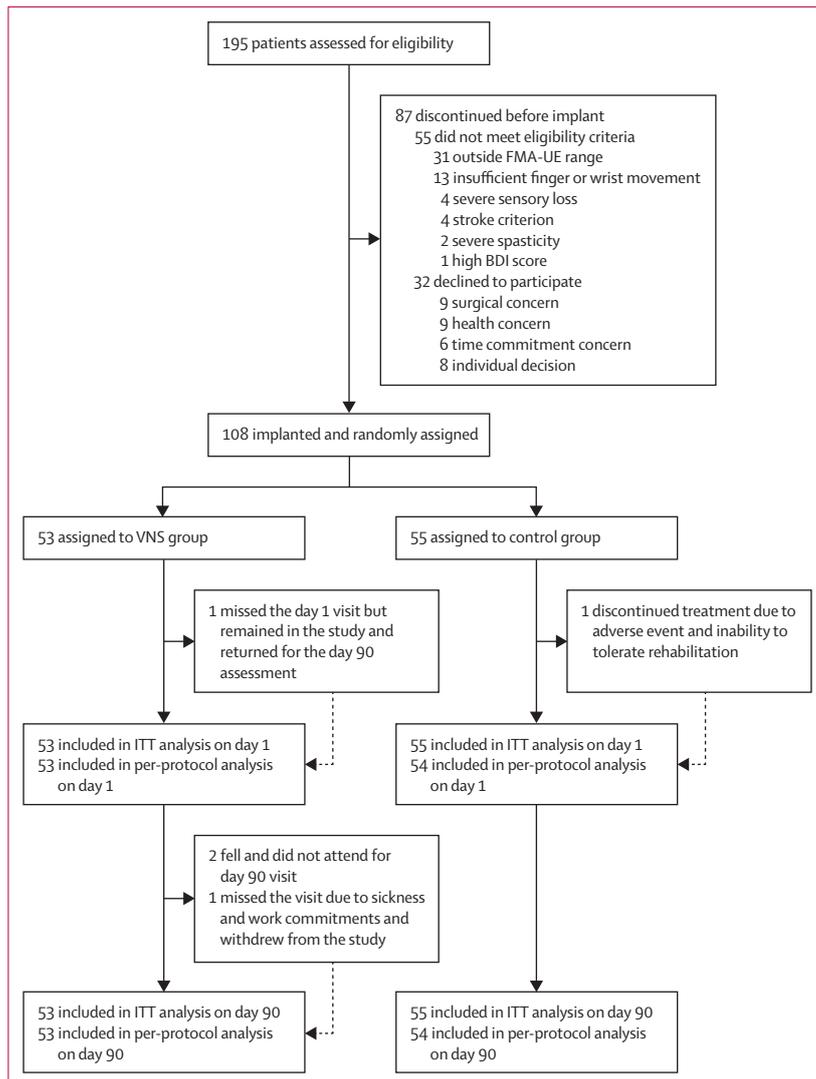

***Figure 1:* Trial profile**
FMA-UE=Fugl-Meyer Assessment-Upper Extremity. BDI=Beck Depression Inventory. VNS=vagus nerve stimulation. ITT=intention to treat.

	VNS group (n=53)	Control group (n=55)
Age, years	59·1 (10·2)	61·1 (9·2)
Sex		
Male	34 (64%)	36 (65%)
Female	19 (36%)	19 (35%)
Race*		
White	42 (79%)	43 (78%)
African American	9 (17%)	9 (16%)
Asian, Indian, or other	1 (2%)	4 (7%)
Not reported	1 (2%)	1 (2%)
Time since stroke, years	3·1 (2·3)	3·3 (2·6)
Handedness		
Right	48 (91%)	50 (91%)
Left	4 (8%)	5 (9%)
Ambidextrous	1 (2%)	0
Side of paresis		
Right	25 (47%)	26 (47%)
Left	28 (53%)	29 (53%)
FMA-UE baseline score	34·4 (8·2)	35·7 (7·8)
WMFT-Functional score	2·71 (0·70)	2·83 (0·65)

Data are n (%) or mean (SD). Some percentages can add up to more than 100% due to rounding. VNS=vagus nerve stimulation. FMA-UE=Fugl-Meyer Assessment-Upper Extremity. WMFT=Wolf Motor Function Test. *Participants could select more than one option for race.

Table: **Baseline demographics and characteristics of the intention-to-treat population**

Figure 2: **Response and change in FMA-UE and WMFT scores**
(A) Change in FMA-UE score between baseline and day 1 after completion of in-clinic therapy (primary endpoint). (B) Change in FMA-UE score between baseline and day 90 after completion of in-clinic therapy (secondary endpoint). (C) FMA-UE response rate (≥6-point change from baseline) at day 90 after completion of in-clinic therapy (secondary endpoint). (D) Change in WMFT score between baseline and day 1 after completion of in-clinic therapy. (E) Change in WMFT score between baseline and day 90 after completion of in-clinic therapy (secondary endpoint). (F) WMFT response rate (≥0·4-point change from baseline) at day 90 post completion of in-clinic therapy (post-hoc outcome). The circle is the mean group value and the vertical lines denote 95% CIs. FMA-UE=Fugl-Meyer Assessment-Upper Extremity. WMFT= Wolf Motor Function Test-Functional. VNS=vagus nerve stimulation. *p<0·05 for the between group difference.

Results

Between Oct 2, 2017, and Sept 12, 2019, 195 participants were screened for eligibility (figure 1). 55 did not meet eligibility criteria and 32 withdrew before device implantation and randomisation. Of the 108 participants randomly assigned (intention-to-treat population) to treatment, 53 were assigned to the VNS group and 55 to the control group. A total of 107 completed the study intervention and were included in the per-protocol population. One participant received fewer than 12 therapy sessions so was excluded from the per-protocol analysis.

There were no significant protocol deviations that affected the rights, safety, or wellbeing of participants or the scientific integrity of the study (appendix p 5). Baseline demographics are shown in the table. Groups were well matched at baseline.

Participants in the VNS and control groups received a similar mean number of stimulations per therapy session (VNS group 422 stimulations [SD 99], control 419 stimulations [86]). The mean duration of each in-clinic rehabilitation session was 90 min (SD 16) in the VNS group and 91 min (16) in the control group. In two participants in the VNS group, stimulation intensity was lowered to 0·7 mA and 0·6 mA.

The primary outcome, change in FMA-UE score from baseline to the first day after in-clinic therapy, was significantly higher in the VNS group than in the control group (mean change 5·0 [SD 4·4] in the VNS group
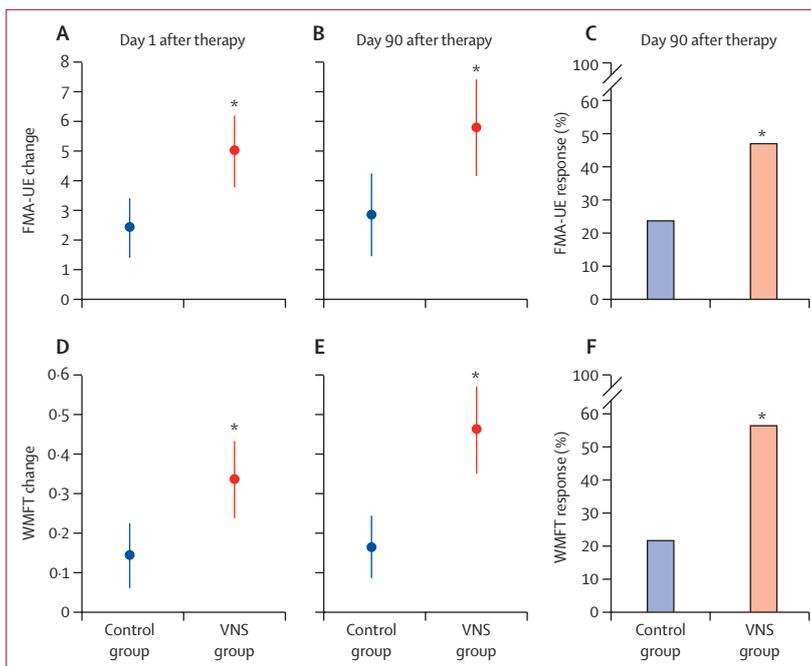
vs 2·4 [3·8] in the control group; between group difference 2·6 [95% CI 1·0–4·2], p=0·0014; figure 2, appendix p 6). Geographical region was related to outcome (p=0·036), but age (p=0·47) and baseline FMA-UE (p=0·32) were not.

The FMA-UE score was significantly increased in the VNS group compared with the control group at 90 days after in-clinic therapy (5·8 [SD 6·0] vs 2·8 [5·2]; between group difference 3·0, 95% CI 0·8–5·1, p=0·0077). A clinically meaningful response on the FMA-UE score occurred in more participants in the VNS group than in the control group at day 90 following completion of in-clinic therapy (23 [47%] of 53 vs 13 [24%] of 55, between group difference 24%, 6–41, p=0·0098), resulting in a number needed to treat of 4·3 for vagus nerve stimulation. In a post-hoc analysis, response rates defined as a 4-point or higher, or 5 point or higher increase on the FMA-UE score were higher with vagus nerve stimulation, although response rate of 7 point or higher was not significantly different (appendix p 6). The WMFT-Functional score was significantly increased in the VNS group compared with the control group at 90 days after the end of in-clinic therapy (0·5 [SD 0·4] vs 0·2 [0·3]; between group difference 0·30, 95% CI 0·16–0·43; p<0·0001). In a post-hoc analysis, a clinically meaningful response on the

WMFT-Functional test occurred in significantly more participants in the VNS group than in the control group (30 [57%] of 53 participants *vs* 12 [22%] of 55, p<0·0001), resulting in a number needed to treat of 2·8 with vagus nerve stimulation.

Data for the tertiary outcomes is shown in the appendix (p 8). Results for all outcomes were similar on the per-protocol analysis and sensitivity analyses showed no significant effect of missing data (appendix p 9).

In a post-hoc analysis, 103 participants (49 in the VNS group and 54 in the control group) rated their certainty regarding treatment allocation (appendix p 6). Nine (18%) participants in the VNS group and nine (18%) in the control group believed they received vagus nerve stimulation (p>0·99). Nine (18%) in the VNS group and 13 (24%) in the control group inferred their treatment allocation correctly (p=0·63).

43 (81%) of 53 patients in the VNS group and 42 (76%) of 55 patients in the control group had at least one adverse event (total of 163 events *vs* 171 events, appendix p 6). There were no deaths. There were three severe adverse events in two (4%) participants in the VNS group (one each of urinary tract infection, hyponatraemia, and insomnia) and two severe adverse events in two (4%) participants in the control group (one headache and one syncope). None of the severe events were reported as related to the trial device. 21 (40%) participants in the VNS group and 24 (55%) in the control group reported an adverse event assessed as either possibly, probably, or definitely related to device implantation. These events were mostly due to postoperative pain. 13 (25%) of 53 participants in the VNS group and nine (16%) of 55 participants in the control group reported an adverse event assessed as either possibly, probably, or definitely related to device use. The number of events, the number of participants reporting at least one event, and the number of severe events were similar in both groups (appendix p 7). There were no unexpected adverse events or serious adverse events reported associated with the device. There was one case of vocal cord palsy following device implantation in a control participant, which resolved after 5 weeks.

Discussion

In our trial involving participants with moderate-to-severe arm impairment after chronic ischaemic stroke, participants who were assigned to vagus nerve stimulation paired with rehabilitation showed clinically meaningful improvements in motor impairment and function compared with participants assigned to rehabilitation and sham stimulation. The number of participants achieving a clinically meaningful improvement in upper limb impairment in the VNS group was approximately double that of the control group, with nearly half of the participants in the active VNS group achieving a clinically meaningful response. Notably, the responder rate was also significantly higher in the VNS group for the WMFT,

a measure of arm function, and was consistent across different FMA-UE score thresholds. The greater improvement in the VNS group was consistent across the primary outcome measure and all secondary outcome measures.

All participants had had the stroke at least 9 months earlier, with a mean time from stroke longer than 3 years. Treatment options for people with arm impairment at this stage typically focus on treatment of complications, rather than concerted efforts to improve function. Our data show it is possible to achieve meaningful improvements many years after stroke. Any improvements are unlikely to be attributable to spontaneous or expected recovery; indeed, many stroke survivors have functional decline at this timepoint.[23] Many large clinical trials in the past 5 years have not found additional clinically important improvements in arm impairment or function with intensive rehabilitation treatment, despite the use of rehabilitation devices, when compared with usual care.[5,24] We observed a small improvement of arm function in the control group, consistent with other trials. However, the improvement was 2–3 times higher across multiple measures of arm function in participants who received vagus nerve stimulation paired with therapy. These findings are consistent with improvements reported in numerous experimental studies of motor recovery after stroke and in our clinical pilot studies (appendix p 11).[10,15,16,25]

In our study, nearly half of participants receiving vagus nerve stimulation had a clinically meaningful improvement assessed by the FMA-UE score. We found a similar rate of clinically meaningful response rate for the WMFT. In addition, tertiary outcome measures, including the MAL,[26] SIS-Activities of Daily Living,[27] and SS-QoL,[28] suggested greater improvement in the VNS group. The consistency of findings across WHO outcome dimensions provides further evidence that the vagus nerve stimulation-related improvements shown are important to stroke survivors. Further, responses were maintained at 90 days after completion of in-clinic therapy.

In preclinical models of ischaemic and haemorrhagic stroke, vagus nerve stimulation paired with task-specific rehabilitation significantly enhanced poststroke recovery compared with rehabilitation alone.[10] When vagus nerve stimulation was dissociated from rehabilitation or when rehabilitation was delivered alone, rats showed relatively less motor improvement, suggesting that task-specific rehabilitation paired with vagus nerve stimulation is key to driving plastic changes in the motor cortex.[29] Pairing vagus nerve stimulation with rehabilitation has been shown to triple the synaptic connectivity in the corticospinal tract networks controlling the impaired forelimb compared with rehabilitation alone.[14] This task-specific neuroplasticity is believed to result from molecular and neuronal mechanisms induced by vagus nerve stimulation that include activation of noradrenergic, cholinergic, and serotonergic systems.[30] It is possible that vagus nerve stimulation-mediated heterosynaptic

neuromodulation facilitates long-term synaptic changes in motor neurons during a temporal learning window for spike-timing dependent plasticity.[31,32] This preclinical evidence would suggest that heterosynaptic neuro-modulation as used in this clinical human trial might exploit similar neuroplastic mechanisms,[33] although this effect remains to be verified.

This intervention requires surgical device implantation. Vagus nerve stimulation devices are used for the treatment of epilepsy and depression, and more than 100 000 devices have been implanted worldwide for such clinical indications. The risk of implantation and side-effects of stimulation have been well described.[34,35] We found a similar low rate of vocal cord palsy, as has previously been documented,[34,35] suggesting that the risk of vocal cord palsy is not substantially increased in well selected people with a history of chronic ischaemic stroke. No serious adverse events associated with the device were reported in our study. The stimulation parameters of 0·8 mA, 100 μs, 30 Hz, and 0·5 s duration were used in all our preclinical stroke studies and in our two pilot studies of vagus nerve stimulation for poststroke rehabilitation.[10] These settings have been shown to cause desynchronisation of the rat cortical electroencephalogram[12] suggesting activation of cholinergic and noradrenergic neurons[36,37] and to be associated with cortical plasticity and motor recovery.[38,39] Non-invasive methods of stimulating the vagus nerve are now available.[40] However, it is unclear whether non-invasive vagus nerve stimulation activates the nerve to the same degree as with cervical implantable vagus nerve stimulation.[41] The optimum site to deliver non-invasive vagus nerve stimulation and which, if any, stimulation parameters cause task-specific plasticity remain unclear.

In this trial, the risk of bias was low and groups were well matched at enrolment. All participants were implanted with a vagus nerve stimulation device, and masking of therapists, participants, and outcome assessors was achieved. There was no evidence of expectation bias or unmasking of participants. Most participants were uncertain or incorrect regarding their treatment allocation and there was no difference between groups in the number who inferred they received vagus nerve stimulation or who inferred treatment allocation correctly. These findings suggest that the study was well blinded. Randomisation was done by an independent service with allocation concealment. The outcome measures used here are common in stroke rehabilitation trials and are valid, reliable, and sensitive to change. There were low numbers of missing data and all but two participants completed the study to day 90. Although the long-term data from this study are not yet available, our earlier pilot study suggests that benefits of paired vagus nerve stimulation therapy are maintained over time.[42]

Our study has some limitations. We cannot generalise our findings to people who do not meet trial eligibility criteria or to people with other types of stroke or other neurological disorders. In particular, it is unclear whether vagus nerve stimulation paired with rehabilitation improves motor outcomes in people with a more severely affected upper limb, spasticity, and severe sensory loss. Although improvements were maintained for at least 90 days, we cannot be certain that the benefits of vagus nerve stimulation paired with rehabilitation will be maintained in the longer term and these benefits should be investigated in future research. The sample size of our study limits our ability to assess the effect of vagus nerve stimulation treatment in different subgroups and two-thirds of participants in our study were men.

Participants with arm impairment, an average of 3 years after ischaemic stroke, who received rehabilitation showed clinically meaningful improvements in impairment and function that were 2–3 times greater with vagus nerve stimulation compared with sham stimulation. Improvements with paired vagus nerve stimulation therapy were also reflected in quality-of-life measures. Vagus nerve stimulation combined with rehabilitation is a novel strategy to help people achieve improvement in arm and hand function after stroke.

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