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Published version

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TITLE

Transcutaneous Auricular Vagus Nerve Stimulation with Upper Limb Repetitive Task Practice May Improve Sensory Recovery in Chronic Stroke

RUNNING TITLE

Transcutaneous VNS and Sensory Recovery in Stroke

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KEY WORDS

Stroke; Vagus Nerve Stimulation; Rehabilitation; Neuroplasticity

TABLE COUNT

1

FIGURE COUNT

1

SOURCES OF FUNDING

This is a summary of independent research funded by Sheffield Hospital Charity and carried out at the National Institute for Health Research (NIHR) Sheffield Biomedical Research Centre (Translational Neuroscience)/NIHR Sheffield Clinical Research Facility.

ABSTRACT

***Background* -** Sensory impairment is associated with reduced functional recovery in stroke survivors. Invasive vagus nerve stimulation (VNS) paired with rehabilitative interventions improves motor recovery in chronic stroke. Non-invasive approaches e.g. transcutaneous auricular VNS (taVNS) are safe, well-tolerated and may also improve motor function in those with residual weakness. We report the impact of taVNS paired with a motor intervention, repetitive task practice, on sensory recovery in a cohort of patients with chronic stroke.

***Methods* –** Twelve participants who were > 3 months post-ischaemic stroke with residual upper limb weakness received 18 x 1 hour sessions over 6 weeks with an average of at least 300 repetitions of functional arm movements per session concurrently with taVNS at maximum tolerated intensity. Light touch and proprioception were scored as part of the Upper Limb Fugl-Meyer (UFM) assessment at baseline and post-intervention (score range for sensation 0-12).

***Results* –** 11 participants (92%) had sensory impairment at baseline of whom 7 (64%) regained some sensation (proprioception n = 6 participants, light touch n = 2, both modalities n =1) post intervention. The maximal increase in UFM sensation score (3 points) was seen in the patient with the greatest improvement in motor function.

***Conclusions* –** taVNS paired with motor rehabilitation may improve sensory recovery in chronic stroke patients. The relative contribution of motor and sensory rehabilitation to overall functional recovery in chronic stroke needs further characterisation in a larger, phase 2 study.

INTRODUCTION

The global economic and social costs of chronic disability attributable to stroke [1] necessitates the development and characterisation of novel methods to induce and potentiate neuroplasticity in stroke recovery. Vagus nerve stimulation (VNS) is an established treatment in medication-resistant epilepsy and depression whilst there is also emerging evidence of a potentially therapeutic effect of VNS in a range of other disorders including migraine and chronic pain [2]. The repetitive pairing of short bursts of electrical activation of vagal nerve afferents with motor rehabilitative tasks, has been shown to improve limb strength in both a rodent stroke model [3] and chronic stroke patients [4][5].

VNS has classically required the implantation of a programmable device and electrodes that directly stimulate afferents of the vagus nerve. This is performed under general anaesthesia, requiring a neck incision and blunt dissection down to the vagus nerve (where it lies between the common carotid artery and the internal jugular vein) where three electrodes are implanted. A subcutaneous pocket is then created in the thoracic wall through which a stimulator lead is connected to the electrodes and a battery is implanted in the subcutaneous thoracic pocket and secured to the pectoralis muscle [6]. However, with the development of a non-invasive method of VNS via transcutaneous stimulation of the peripheral auricular branch of the vagus nerve (taVNS), there is now a potentially safer, better-tolerated method for delivering VNS [7]. Our group has previously published a pilot study in which taVNS was paired with therapist-directed repetitive upper limb movements in 12 chronic stroke patients with residual weakness. We found significant improvements in upper limb function as measured by the Upper Limb Fugl-Meyer assessment (UFM). UFM is a composite score primarily used to measure hemiplegia but which also incorporates measures of proprioception and light touch sensation [4].

Subsequently, Kilgard *et al* reported sensory improvements in a stroke survivor who received VNS (via a surgically implanted stimulator) paired with a sensory stimulus (‘tactile therapy’) of the upper limb [8]. The individual was asked to localise, identify and explore a variety of everyday objects (e.g. sandpaper, paintbrush) whilst blindfolded. The authors subsequently hypothesised that pairing VNS with sensory stimulation may be a novel way of promoting neuroplasticity and sensory recovery in chronic stroke survivors. However, this conclusion was based on data from only one patient.

In the current post-hoc analysis, we report sensory improvements in a larger series of patients (n=12) who received taVNS paired with a motor-specific task rather than dedicated sensory training.

MATERIALS AND METHODS

Participants, Outcome Measures and Intervention

Study methods have been reported previously [4]. Patients with a history of ischaemic stroke more than three months prior and moderate-severe upper limb weakness were recruited between October-December 2016. The intervention consisted of 18 x 1 hour sessions over six weeks where repetitive upper limb task training, a motor intervention, was paired with concurrent transcutaneous stimulation of the left auricular branch of the vagus nerve. A taVNS earpiece (NEMOS by Cerbomed; https://nemos.t-vns.com/en/) was fitted to the concha of the participant's left ear and pulses of the stimulator (pulse width of 0.1 millisecond, pulse frequency of 25 Hz and pulse amplitude as maximally tolerated by the participant) were initiated when the participant began the repetitive task movement and stopped when the active arm movement had ceased. A minimum of 300 repetitions per session was targeted. Tasks included included the handling and manipulation of different objects e.g. turning cards and lifting objects. Participants were asked not to undergo any other rehabilitative treatments during this 6 week period.

The Upper Limb Fugl-Meyer (UFM) scores were assessed at baseline and at the end of the intervention. The UFM is a composite assessment of sensorimotor function (66 points for motor elements, 12 for sensation (includes 8 points for proprioception and 4 points for light touch), 24 for passive joint motion and 24 for joint pain during passive motion) with a reported minimum clinically important difference for the overall score of 4.25-7.25.[9] In the UFM, proprioception is assessed with a three-point scale in the shoulder, elbow, wrist and thumb (maximum score of 8) and perception of light touch is assessed with a three-point scale in the arm and the hand (maximum score of 4).

Data Analysis

The statistical difference between UFM scores for proprioception and light touch sensation before and after intervention were determined using the Wilcoxon Signed Rank Test. Spearman's rank correlation co-efficient was used to assess the relationship between improvements in UFM sensory and motor scores. Data analysis was performed using IBM SPSS Statistics software (Version 25).

Ethical Approval

This was a single-group pre-post intervention study. The protocol was approved by Sheffield Research Ethics Committee (reference 15/YH/0397). The study design conformed to the CONSORT-statement extension for pilot and feasibility studies (http://consort-statement.org). The study was registered at ClinicalTrials.gov (reference NCT03170791). All participants gave written informed consent for the study.

RESULTS

12 participants (10 male, mean [SD] age 64.2 [7.1], median [IQR] 1.29 [0.7-3.4] years since ischaemic stroke, mean [SD] baseline UFM score 71.2 [25.3]) completed a total of 210 therapy sessions. The mean [range] intensity of taVNS delivered was 1.4 [1 – 3.2] mA and the mean [SD] number of arm movements per session was 464 [70] with all participants completing at least 300 arm movements per session.

All participants showed improvements in the UFM motor score (mean increase 10.1 points, SD 5.5) [Table 1]. 11 participants (92%) had an impairment in UFM-rated sensation at baseline. Of these, 7 participants (64%) showed an improvement in UFM-sensation post-intervention, 3 (27%) showed no change and 1 (9%) showed a 1-point reduction [Figure 1A].

Considering the sensory modalities individually, 9 participants had impaired UFM-proprioception scores at baseline of whom 6 (67%) improved post-intervention with a mean [SD] increase of 0.78 [0.97] points (p = 0.053) [Table 1, Figure 1B]. One participant (Participant 6) had a 1 point decrease in their UFM-proprioception score from a baseline of mild impairment. 8 participants had impaired UFM-light touch scores at baseline of whom 2 (25%) improved post-intervention with a mean [SD] increase of 0.38 [0.74] points (p = 0.180) [Table 1, Figure 1C].

The individual with the greatest increase in UFM-motor score also demonstrated the greatest improvement in UFM-sensation (Participant 4). However, amongst all participants, there was no significant correlation between the degree of motor improvement and the degree of sensory improvement (Spearman rank correlation co-efficient 0.287, p = 0.37).

DISCUSSION

The present study demonstrates improvements in upper limb sensation following taVNS paired with motor training in the majority of a cohort of chronic stroke survivors. This effect was seen despite there being no intervention targeted specifically aimed at improving sensation.

Importance of Sensory Recovery

The ability to optimally perform goal-directed movements relies on the successful integration of sensory and spatial information with functioning motor pathways [10]. Chronic sensory impairment is a common sequelae of stroke with abnormalities in tactile sensation, proprioception, stereognosis and inattention contributing to disability [11]. Most intuitively, the recognition of light touch, pain and heat is necessary for interacting with the environment and for the avoidance of noxious stimuli. Lack of such sensation may discourage stroke survivors from using the affected limb in daily tasks thereby providing a barrier to rehabilitation.

The influence of proprioception on long term function in chronic stroke survivors is more complex. The integration of somatosensory feedback from joint position sense with cortical networks facilitates motor planning and the effective recovery of goal-directed movements [10].

In a recent study of 102 chronic stroke patients, mild-moderate impairment in upper limb proprioception, as assessed by the thumb localisation test, was associated with less active movement and functional ability of the limb [12]. Whilst this result may be confounded to some extent by the initial severity of stroke, focussed rehabilitation of proprioception in chronic stroke patients has been shown to improve performance in somatosensory and sensorimotor tasks and is an established aspect of current stroke rehabilitation protocols [13].

taVNS and Sensory Rehabiitation

A possible explanation for the improvements in proprioception in 6 subjects is through taVNS-facilitated improvements in the strength and range of movements achieved by upper limb tasks. It is possible that the greater range of active joint movement increased sensory feedback from the affected limb and contributed towards neuroplasticity in cortical sensory maps. Taken together with the aforementioned link between sensory feedback and improvements in motor function, it may be hypothesised that motor and sensory recovery reciprocally enhance one another in a positive feedback loop.

Light touch sensation improved in a proportion of patients, which could be explained by tactile feedback from the handling of objects during the repetitive task practice indirectly providing somatosensory training to the affected limb. A recent anecdotal study by Kilgard *et al* [8] demonstrated that daily multimodal tactile therapy training paired with VNS significantly improved measures of tactile threshold, joint position sense and stereognosis in a single chronic stroke survivor over a 20 day period. Moreover, this was associated with a 15-point improvement in the participant's UFM score, further consolidating the notion that sensory rehabilitation may impact on overall functional recovery.

The precise mechanisms by which paired VNS influences cortical plasticity have not been fully elucidated. It is thought that VNS may mediate its effects through noradrenergic transmission from the locus coeruleus and cholinergic transmission from the basal forebrain which, when combined with a specific stimulus or task, drives localised and specific neuroplasticity for that task [3]. For example, Hulsey *et al* showed that a selective lesion of the cholinergic nucleus basalis in rats prevented the increased cortical motor representation of the proximal forelimb that was seen after VNS was paired with motor training [14]. Whilst animal studies have shown that the temporal pairing of VNS with rehabilitative exercises is necessary for promoting neuroplasticity [3] (i.e. VNS alone has no effect), the precise timing of VNS in relation to the task (i.e. whether it needs to be given continuously during the task or once at the beginning of the task) is not clear. For example, a cumulative effect from multiple VNS stimuli, as in this study with more than 300 pulses of stimulation per session, may create a neurohormonal mileu which favours cortical plasticity for some time after the physiotherapy session has ended. Further studies are required to elucidate whether significant neuroplasticity can be achieved with repeated VNS, of the order of magnitude achieved in the present study, and training events which are more temporally distinct.

Limitations

The present study was not prospectively designed to characterise and monitor changes in sensory recovery in chronic stroke survivors. The UFM is predominantly designed to measure motor recovery and as such, does not incorporate all individual sensory modalities such as stereognosis and two-point discrimination. Furthermore, the three point grading system does not convey the impact of smaller incremental improvements in sensation which may still be clinically significant. A comprehensive assessment of sensory function, such as the Nottingham Sensory Assessment [15], could provide more detailed information about the nature and degree of sensory recovery.

The study was designed as a feasibility study and there was no control group. As such it is not possible to conclude whether the taVNS, repetitive task practice or both contributed to the sensory gains. It is also possible that improvements may have occurred naturally. Nevertheless, all the participants in the study began the taVNS intervention at least three months after their stroke, all having persistent neurological deficits.

SUMMARY

Chronic stroke patients receiving taVNS paired with repetitive task practice improved not only their motor function (the primary outcome) but also, in a substantial majority, their sensory function, taVNS may provide a non-invasive method to supplement and potentiate rehabilitative therapy to promote functional recovery in chronic stroke. A phase 2 clinical study, with a larger patient cohort, assessing taVNS paired with an integrated post-stroke rehabilitation programme consisting of motor and sensory therapy, is warranted to determine the relative contribution of motor and sensory rehabilitative therapies, with and without VNS, to overall functional recovery post-stroke.

ACKNOWLEDGEMENTS

This research was supported / funded by the NIHR Sheffield Biomedical Research Centre (BRC) / NIHR Sheffield Clinical Research Facility (CRF).

CONFLICTS OF INTEREST/DISCLOSURES

The views expressed are those of the authors and not necessarily those of the Sheffield Hospital Charity, NHS, the NIHR, or the Department of Health.

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