Stroke

EMERGING THERAPY CRITIQUES

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Vagus Nerve Stimulation for Upper Limb Function

Significant Difference, but Clinically Important?

Gert Kwakkel, PhD; Bruce H. Dobkin, MD

Cohort studies suggest that impairments in motor function and limitation in purposeful activity of the most affected upper extremity occur in over 80% of patients with stroke,[1] restricting quality of life.[2] Most randomized controlled trials (RCTs) have not found statistically significant differences in upper extremity recovery of motor impairment between an experimental rehabilitation intervention and another active, more conventional control therapy provided at the same intensity and duration[3] when measured with the Fugl-Meyer Upper Extremity (FM-UE) scores, as well as in upper limb capacity by the Action Research Arm Test or Wolf Motor Function Test. In addition, only a few trials have measured the impact of an experimental intervention on the actual amount and quality of movement of the upper paretic limb after stroke.[4] All these recent RCTs, along with many that preceded them, rarely achieved an agreed upon clinically meaningful improvement (CMI) in motor impairment or in daily use of the arm and hand. Unfortunately, there is no clear consensus on a definition for CMI, otherwise called a clinically important difference, in part, because the concept may be defined from different perspectives, including clinicians, patients, statisticians, health care economists, and stakeholders.[5] Thus, the outcome measurement tools that might best define a CMI for the most affected upper extremity (UE) pose a persistent confounder to allowing accurate interpretation of treatment effects of stroke rehabilitation for RCTs.

A well designed and performed RCT from Dawson et al[6] called VNS-REHAB recently showed that vagus nerve stimulation (VNS), requiring surgical placement of an electrode over the left cervical vagal nerve, then paired with exercise and skills practice, may be a novel treatment option for people with long-term, moderately severe UE paresis after chronic ischemic stroke (mean 3 years duration). Vagal afferent input during practice had improved motor learning and outcomes for several tasks in preclinical studies[7] that matched important treatment aspects of this RCT. Cortical reorganization in primary motor cortex, release of key neurotransmitters, Hebbian plasticity with synaptic strengthening, and up- and downregulation of other molecules are possible mechanisms of action.[7]

The VNS-REHAB trial (Vagus Nerve Stimulation Paired With Rehabilitation) included 108 subjects from 19 rehabilitation sites and was triple blinded; well powered to detect a mean difference of a modest seeming 2.3 (SD, 4) points on the 66-point FM-UE scale; did not suffer from protocol deviations; and the only serious adverse event was vocal cord paresis after surgical placement of the VNS wire in one subject.[6] Of note, the FM-UE is an ordinal scale of requested movements executed within and beyond patients' preferred pattern of coactivation and scored as 0 (cannot perform), 1 (partially performs), or 2 (fully performs each of its 22 subtests). The stimulation parameters of the vagus nerve were supported by a number of preclinical[7] and pilot clinical studies.[8,9] The possibility of gains was built into the protocol in that the entry criteria included only participants with some potential for improvement at baseline (excluded FM-UE <21) and by preventing ceiling effects (excluded FM-UE >50).

The authors found a statistically significant between-group difference of 2.6 points (≈4% [95% CI, 1.0–4.2]; $P<0.001$) for the FM-UE in favor of paired VNS compared with an equal dose of 6 weeks of in-clinic training combined with sham VNS stimulation. After another 5 to 6 weeks of 30 minutes of daily stimulation and practice

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at home, this between-group difference rose to 3.0 points ([95% CI, 0.8–5.1] *P*=0.007) at 90 days follow-up from the first VNS session. The authors acknowledged, however, that a minimal change of 6 points (equivalent to about 10% improvement) is necessary to exceed the 95% CI limits of measurement error for the FM-UE score.[10,11] Subsequently, the VNS-REHAB authors performed a post hoc analysis showing that the proportion of subjects who could be classified as responders (having improved ≥6 points) was significantly higher in the VNS group at 90 days compared with sham stimulation (ie, 25 of 53 versus 13 of 55, respectively).[6] Of interest, had the analysis tested a slightly more conservative estimate using a threshold of 7 points or higher on the FM-UE, the difference in the proportion of responders would have failed to show significance by lack of sufficient power (18 of 53 versus 12 of 55, respectively).[6] Overall, Dawson et al[6] interpreted their findings as being clinically meaningful and concluded that VNS is a "novel potential treatment option for those subjects with a moderate-to-severe arm impairment after ischemic stroke."

Some may disagree with this conclusion. The between-group absolute difference of 2.6 points (4%) on the FM-UE after 18 sessions, increasing to 3.0 points at 90 days, may be statistically significant, but did this small gain enable additional effective daily use of the UE, that is, a CMI from the perspective of the hemiparetic patients? The claim of the VNS-REHAB trial to have shown a CMI was only based on a post hoc analysis of the difference in the proportion of responders. An analysis of responders can be helpful not only to look for predictors of responsiveness to a new therapy but to give the reader a sense of individual rather than only group responses.[12] However, to place this trial in the context of the literature, between-group differences of 2.5 to 3 points on FM-UE scores are not exceptional in participants with chronic stroke treated at similar intensities as the VNS-REHAB groups. A variety of RCTs have found the same or higher gains when their primary analysis revealed equivalence between the experimental and control interventions. For example, the single-blinded, neutral EVEREST trial (Epidural Electrical Stimulation for Stroke Rehabilitation; n=164) found a between-group effect of 2.3 points on the FM-UE in favor of electrical epidural motor cortex stimulation by using an implantable pulse generator for 6 weeks,[13] whereas the neutral RATULS trial (Robot Assisted Training for the Upper Limb After Stroke; n=770) showed an adjusted mean between-group difference of 2.79 points (98.3% [CI, 0.66–5.01]) in favor of upper limb robotics for 12 weeks.[14] Also, the mean within-group improvement for real VNS was 5.0 points (SD, 4.4) after 6 weeks, followed by an incremental 0.8 points to the maximal gain of 5.8 (SD, 6.0) at 90 days. This change is in line with many other neutral trials in chronic stroke, ranging from 4% to 14% of the FM-UE score.[3] For example, the EVEREST trial showed a mean improvement of 4.4 points after 4 weeks of electrical stimulation, which was not statistically significant,[13] whereas the neutral NICHE trial (Navigated Inhibitory Repetitive Transcranial Magenetic Stimulation to Contralesional Hemisphere; n=199) that investigated the effects of 18 sessions of repetitive transcranial magnetic stimulation when combined with upper limb training over 6 weeks, showed mean within-group improvements of 5.6 points at the end of treatment.[15] Even more impressive, in a pre-post designed study, Ward et al[16] reported a significant gain of 8 points on the FM-UE, just by offering 224 chronic subjects 90 hours of an upper limb training program for 3 weeks.

How the CMI was originally estimated for the FM-UE adds to our concerns about the interpretation of the between-group and within-group changes in the VNS-REHAB trial. Although there is broad consensus how trialists should establish statistical significance, estimating clinical significance remains elusive for neurorehabilitation trials. Several attempts to define CMI for the FM-UE were developed from distribution-based models assuming that 6 to 10 points is the minimum.[10,11] In a frequently referenced study, Page et al[11] used a global ratings of change scale as the anchor for the FM-UE score. They asked the occupational and physical therapists in the EVEREST brain stimulation trial whether they perceived improvement in the participants at the end of treatment. This seems like a practical method but only encompasses the therapists' appreciation of change in movement capacity, not necessarily a clinically meaningful gain. Indeed, the VNS-REHAB trial found a mean nonsignificant, between-group difference of 5.1 points (≈5%) on the self-reported activities of daily living score of the stroke impact scale and 0.7 points (<1%) on its hand domain.[6]

To further understand whether the results of VNS-REHAB are truly robust enough to forge ahead with VNS as an adjunct to UE training, we suggest the following to help focus future proof-of-concept trials. A histogram of the initial and final scores for the two outcome measures (ie, FM-UE) for each subject would enable a deeper understanding about, for example, whether a modest number of responders accounted for the majority of mean gains in each group. Further insight may be achieved by exploring the mean scores for the hand and arm tasks of the FM-UE or of other tools separately to reveal what changed in selective motor control. If movements of the hand improve enough to restore effective pinch and grasp after VNS, the reader may more easily assess the potential for a CMI. In addition, some of the initial gains with training with or without VNS in subjects with chronic stroke may be due to relative nonuse of the affected extremity over the previous 3 years. This potential noise, in which any sort of therapy might induce 1 to 3 points of rapid recovery on the FM-UE, may be reduced by a brief bout of formal UE

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reach-and-grasp type therapy and then repeating the performance test at baseline, before starting the trial's interventions.[12] Also, any adjunct benefit of VNS could be ascertained, in part, by crossing over the control group with its responders and nonresponders to VNS plus targeted therapy for an additional 4 to 6 weeks to look for further gains and determine whether a plateau in gains had been reached at 90 days, as originally suggested in the protocol of the VNS-REHAB study.[9] As the authors note, a phase III RCT should test longer term outcomes at 6 or 12 months. In the near future, merging commonly deployed motor impairment scales with key changes in measured kinematics, as well as using corticospinal tract biomarkers to improve stratification of subjects at baseline,[4] could strengthen trial designs. In addition, anchoring impairment, activity, and participation-related scales to continuous measures of purposeful use of the affected UE with wearable sensors[17] may better ascertain the actual gain required to establish a CMI.[12]

In summary, the VNS-REHAB RCT shows a rather weak signal that is heavily based on a post hoc analysis and a distribution-based definition of responders but not by showing robust between-group differences or within-group improvements on its primary outcome measurement. The authors' interpretation of clinically meaningful effects seems too optimistic, in our opinion, to label VNS as a novel treatment option. This remarkably designed trial, however, is an important step forward to develop evidence for CMIs induced by VNS.

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REFERENCES

1. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol.* 2009;8:741–754. doi: 10.1016/S1474-4422(09)70150-4
2. Morris JH, van Wijck F, Joice S, Donaghy M. Predicting health related quality of life 6 months after stroke: the role of anxiety and upper limb dysfunction. *Disabil Rehabil.* 2013;35:291–299. doi: 10.3109/09638288.2012.691942
3. Stinear CM, Lang CE, Zeiler S, Byblow WD. Advances and challenges in stroke rehabilitation. *Lancet Neurol.* 2020;19:348–360. doi: 10.1016/S1474-4422(19)30415-6
4. Kwakkel G, van Wegen EEH, Burridge JH, Winstein CJ, van Dokkum LEH, Alt Murphy M, Levin MF, Krakauer JW; ADVISORY Group. Standardized measurement of quality of upper limb movement after stroke: consensus-based core recommendations from the second stroke recovery and rehabilitation roundtable. *Neurorehabil Neural Repair.* 2019;33:951–958. doi: 10.1177/1545968319886477
5. Keefe RS, Kraemer HC, Epstein RS, Frank E, Haynes G, Laughren TP, McNulty J, Reed SD, Sanchez J, Leon AC. Defining a clinically meaningful effect for the design and interpretation of randomized controlled trials. *Innov Clin Neurosci.* 2013;10(5-6 suppl A):4S-19S.
6. Dawson J, Liu CY, Francisco GE, Cramer SC, Wolf SL, Dixit A, Alexander J, Ali R, Brown BL, Feng W, DeMark L, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. *Lancet.* 2021;397:1545–1553. doi: 10.1016/S0140-6736(21)00475-X
7. Khodaparast N, Kilgard MP, Casavant R, Ruiz A, Qureshi I, Ganzer PD, Rennaker RL II, Hays SA. Vagus nerve stimulation during rehabilitative training improves forelimb recovery after chronic ischemic stroke in rats. *Neurorehabil Neural Repair.* 2016;30:676–684. doi: 10.1177/1545968315616494
8. Kimberley TJ, Pierce D, Prudente CN, Francisco GE, Yozbatiran N, Smith P, Tarver B, Engineer ND, Alexander Dickie D, Kline DK, et al. Vagus nerve stimulation paired with upper limb rehabilitation after chronic stroke. *Stroke.* 2018;49:2789–2792. doi: 10.1161/STROKEAHA.118.022279
9. Kimberley TJ, Prudente CN, Engineer ND, Pierce D, Tarver B, Cramer SC, Dickie DA, Dawson J. Study protocol for a pivotal randomised study assessing vagus nerve stimulation during rehabilitation for improved upper limb motor function after stroke. *Eur Stroke J.* 2019;4:363–377. doi: 10.1177/2396987319855306
10. Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. *Phys Ther.* 1993;73:447–454. doi: 10.1093/ptj/73.7.447
11. Page SJ, Fulk GD, Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. *Phys Ther.* 2012;92:791–798. doi: 10.2522/ptj.20110009
12. Dobkin BH. Progressive staging of pilot studies to improve Phase III trials for motor interventions. *Neurorehabil Neural Repair.* 2009;23:197–206. doi: 10.1177/1545968309331863
13. Levy RM, Harvey RL, Kissela BM, Winstein CJ, Lutsep HL, Parrish TB, Cramer SC, Venkatesan L. Epidural electrical stimulation for stroke rehabilitation: results of the prospective, multicenter, randomized, single-blinded EVEREST trial. *Neurorehabil Neural Repair.* 2016;30:107–119. doi: 10.1177/1545968315575613
14. Rodgers H, Bosomworth H, Krebs HI, van Wijck F, Howel D, Wilson N, Aird L, Alvarado N, Andole S, Cohen DL, et al. Robot assisted training for the upper limb after stroke (RATULS): a multicentre randomised controlled trial. *Lancet.* 2019;394:51–62. doi: 10.1016/S0140-6736(19)31055-4
15. Harvey RL, Edwards D, Dunning K, Fregni F, Stein J, Laine J, Rogers LM, Vox F, Durand-Sanchez A, Bockbrader M, et al; NICHE Trial Investigators *. Randomized sham-controlled trial of navigated repetitive transcranial magnetic stimulation for motor recovery in stroke. *Stroke.* 2018;49:2138–2146. doi: 10.1161/STROKEAHA.117.020607
16. Ward NS, Brander F, Kelly K. Intensive upper limb neurorehabilitation in chronic stroke: outcomes from the Queen Square programme. *J Neurol Neurosurg Psychiatry.* 2019;90:498–506. doi: 10.1136/jnnp-2018-319954
17. Dobkin BH, Dorsch AK. The evolution of personalized behavioral intervention technology: will it change how we measure or deliver rehabilitation? *Stroke.* 2017;48:2329–2334. doi: 10.1161/STROKEAHA.117.016620