Transcutaneous VNS

A new therapeutic approach in epilepsy

Dr Schulze-Bonhage reviews a new transcutaneous vagus nerve stimulation (VNS) device, analysing its effectiveness and side-effects compared with standard VNS systems
Vagus nerve stimulation (VNS) has become a standard treatment for patients with insufficient response to presently available antiepileptic drugs. Even though more than 100,000 epilepsy patients have been using this device, the step to undergo a device implantation is considered a hurdle by many patients, and the lack of well-established predictors of efficacy in the individual patient limits its use in the view of many physicians.

Furthermore, despite good overall tolerability and positive effects on vigilance, mood and quality of life, there are some frequent unwanted side effects of standard VNS like hoarseness of the voice or a pressure to cough during the stimulation periods, which can limit its up-titration for optimal efficacy.

A new concept arises based on the notion that the vagus nerve not only supplies internal organs via its main descending trunk but also innervates the skin in a certain part of the auricle, the so-called ‘cymba conchae’, above the earhole. Both studies using labelling of the nerve and stimulation of the nerve show that the fibers terminate in the brainstem at the nucleus tractus salutarii, which is the target of the majority of afferent vagus nerve fibers. Transcutaneous vagus nerve stimulation (t-VNS) uses the non-invasive activation of this nucleus via electrical impulses applied to the skin of the auricle.

**The t-VNS device**

The CE-certified device manufactured by cerbomed® consists of a generator unit in the shape of a smartphone and lead connecting the generator to the auricle. The generator has a graphical user interface which allows the patient to program the stimulation intensity for an individual adaptation of well tolerated current amplitudes. In contrast to standard VNS, stimulation is performed intermittently for a total of four hours a day; the real daily time under stimulation is indicated to the user and documented by the device. Stimulation occurs using an electrode resembling an earphone, with a flexible, open ring placed into the left external ear canal for fixation and two small titanium iridium electrodes positioned at the cymba conchae above (fig 1).

The stimulation intensity can be adjusted by the patient, caregiver or treating physician. It is increased at steps of 0.1 mA until the perception threshold of the electrical stimulation is reached; stimulation intensity may be further increased but should remain below the range when any painful sensation occurs. The stimulation frequency is predefined at 25 Hz, the pulse width at 250 µs.

**Tolerance and effectiveness**

Safety and efficacy of this t-VNS device has been assessed in two studies, one of which, with a small pilot patient cohort, was published in 2012 in Epilepsia. In this first pilot study by Stefan et al, seven adult patients underwent repeated in-hospital video-EEG monitoring for one week every three months; three of them showed a reduction in seizure frequency.
frequency by 25-50% within nine months. Stimulation was well tolerated in most patients.

Recently, a multicenter two-arm, parallel group, prospective, double-blind study was conducted at multiple sites in Europe with either a 25 Hz (‘high level’) t-VNS or a 1 Hz (‘low-level’, presumably sub-therapeutic dose) t-VNS as an active control group. Stimulation was performed for four hours daily for a period of 20 weeks.

In this study, 76 adult epilepsy patients with a broad range of epilepsy syndromes uncontrolled by one to three currently applied anti-epileptic drugs were treated with either 25 Hz or 1 Hz t-VNS stimulation following a baseline period of two months. The aims of this study were to compare add-on therapy with high-level versus low-level t-VNS in reducing the monthly seizure-frequency in patients with drug-resistant epilepsy and to assess the tolerability of t-VNS.

The full results of this study are yet to be published. Preliminary data from the manufacturer cerbomed® provide evidence for excellent handling and adherence with t-VNS application, with a median compliance rate of 96% in the 25 Hz-stimulation group and 93% in the 1 Hz-stimulation group. In the 25 Hz-stimulation group, adverse effects occurring in >5% of patients were headaches (18.9%), ear pain (16.2%), local erythema (8.3%) and vertigo (8.1%).

At the last visit, the patient group stimulated at 25 Hz had a significant reduction in seizure frequency compared to baseline, but not compared to the 1 Hz-stimulation control group. The mean reduction in seizure frequency was -22.9% with 25 Hz stimulation versus +2.4% with 1 Hz-stimulation, resulting in a total difference between high and low stimulation of 25.3%. In prospective studies of standard with active control, differences between high stimulation and control groups were 18.4% (E03) and 12.7% (E05); due to higher patient numbers in those studies, these smaller differences were statistically significant.

Responder rates with t-VNS were similar in 25 Hz- and 1 Hz-stimulation groups (27%/26%), whereas in studies on standard VNS, the active control groups had lower responder rates (31%/13% in E03, statistically significant difference, 23%/16% in E05 (not statistically significant)). Thus, whereas differential effect of applying 25 Hz stimulation versus 1 Hz stimulation on seizure frequency showed a tendency of t-VNS to be at least as effective as standard VNS, responder rates were similar in the active control group (fig 3a,b). This may either suggest an anti-epileptic efficacy of its own of the low frequency stimulation arm, a major placebo effect or a regression to the mean following the baseline period.

A modified Chinese device was used in a study by He et al (2013), who applied t-VNS bilaterally to treat epilepsy in children aged two to 12 years. These patients had very high baseline seizure frequencies and showed a gradual increase in seizure reduction over 24 months, with 5/14 patients being seizure free and 3/14 patients having a reduction >50% at the end of the study period. Treatment was well tolerated, the only noted adverse effects were small skin ulcerations in 2/14 patients.

Recently, a larger study confirmed the efficacy of this device applying
bilateral transcutaneous stimulation of the ears at relatively high intensities (6mA); notably, differences between stimulation at the cymba conchae and at the earlobe serving as an active control became statistically significant only after 12 months of treatment (Aihua et al, 2014).

**Preliminary conclusions**

Transcutaneous vagus nerve stimulation is an interesting new approach for a non-invasive activation of the brainstem systems conveying the efficacy of the well-established standard VNS. It avoids both risks associated with the standard VNS implantation procedure and specific side effects of VNS related to the stimulation site at the neck.

Standard VNS implantation is associated with risks of infection (~3%), often leading to device explantation, and of vocal cord paralysis when harming the laryngeal recurrent nerve (~5%).

Side-effects specific to the implantation at the neck comprise hoarseness of the voice during the stimulation periods (depending on the stimulus intensity), pressure to cough, dyspnea, local and irradiating pain, and local muscle contractions. Device failures in particular include lead breakages (11.9% in a recently published series) and disconnections (2.8%).

In contrast, side effects of t-VNS have so far only been reported to result in local skin irritation at the auricle, and possibly in headaches when high stimulation intensities are used. T-VNS thus may offer a low threshold option for patients with insufficient response to anti-epileptic drugs who are interested in non-pharmacological treatment options but are hesitating to undergo a device implantation, and a treatment option for patients in whom future MR imaging is planned.

So far it has not been investigated if a positive response to t-VNS correlates to an anti-epileptic efficacy of the implanted device; if so, t-VNS might serve to be the first step to enrich the patient population for responders who undergo long-term therapy with an implanted device. This could save economic resources by using the less expensive transcutaneous stimulator in a larger population and the costly implants in patients with a high chance of profiting in terms of seizure reduction.

Beyond these practical aspects, the application of stimulation for short, intermittent periods only for the treatment of epilepsy is conceptually interesting. Whereas a long-term neuromodulatory effect of standard VNS and also of deep brain stimulation (DBS) for epilepsy patients beyond the immediate anti-epileptic response has often been discussed, t-VNS mostly relies on a neuromodulatory effect with only 4/24 hours of stimulation a day. Showing a statistically significant response of its efficacy would thus be the first evidence for almost purely neuromodulatory anti-epileptic efficacy of a stimulation treatment. Whereas a good tolerability of t-VNS is well established based on the mode of application and available experiences, its efficacy has so far prospectively been investigated only in relatively small patient cohorts and in retrospective case series; additional large-scale studies are thus desirable.

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**Further reading**