



Lessons learned from transcutaneous vagus nerve stimulation (tVNS)

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ABSTRACT

Transcutaneous vagus nerve stimulation (tVNS) is a newly developed method which intends to overcome the disadvantage of surgical implantation of the stimulation device. The tVNS device is designed to stimulate the auricular branch of the vagus nerve via a bipolar electrode attached to the skin of the left ear conch. A randomized, double-blind controlled trial assessed efficacy and safety over 20 weeks of tVNS (n = 39) vs. active control tVNS (n = 37) in patients with drug-resistant epilepsy. While the mean seizure reduction per 28 days at end of treatment (2.9% reduction from baseline in the control group vs 23.4% in the active group) did not reach statistical significance, there was a significant reduction in seizure frequency (34 %) in patients in the tVNS group at the end of the treatment period (20 weeks). TVNS was well-tolerated. The results justify further trials with longer observation periods and possibly at earlier stages of epilepsy.

1. Introduction and rationale for development

Various brain stimulation therapies are currently available. VNS is the stimulation method which is most frequently applied and is associated with the longest experience in clinical practice. It requires implantation of a stimulator and an electrode which connects to the left vagal nerve. Long-term VNS reduced seizure frequency during initial treatment by roughly 30%–40% (Handforth et al., 1998; Morris and Mueller, 1999). The treatment effect usually increases over time (Morris and Mueller, 1999). Transcutaneous vagus nerve stimulation (tVNS) is a newly developed method which intends to overcome the disadvantage of surgical implantation of the stimulation device.

2. Technical and functional characteristics

The auricular branch of the vagus nerve supplies the cyma conchae (Peuker and Filler, 2002). It can be stimulated using an external device with a bipolar electrode attached to the skin of the left ear conch (Fig. 1). Typical settings are: stimulation frequency 25 Hz, pulse width 250 μ s, 30 s on/30 s off, application time 4 h per day, resulting in 180.000 stimuli per day. Active control stimulation can be performed with 1 Hz, resulting in 7.200 stimuli per day. Pilot studies showed responder rates and mean seizure reduction of up to 55% (Stefan et al., 2012; He et al., 2013).

3. Results

One randomized, double-blind controlled trial has been performed to assess efficacy and safety over 20 weeks of tVNS in patients with drug-resistant epilepsy (Bauer et al., 2016). Primary objective was to demonstrate superiority of add-on therapy with tVNS (stimulation frequency 25 Hz, n = 39) versus active controls (1 Hz, n = 37) in reducing seizure frequency over 20 weeks. The primary efficacy variable was the relative change of seizure-frequency per 28 days over the treatment period. Analysis of covariance (ANCOVA) was performed with treatment as factor and baseline seizure frequency per 28 days as covariate, calculating treatment differences in least square means and 95% confidence intervals. Responder rates were compared between the two treatment groups using a logistic regression model with treatment as factor and the log-transformed baseline seizure-frequency per 28 days as covariate.

With treatment adherence of > 80% in both groups, the difference in mean seizure reduction per 28 days at end of treatment (2.9% reduction from baseline in the 1 Hz group vs 23.4% in the 25 Hz group) was not significant (p = 0.146). However, there was a significant reduction in seizure frequency in patients in the 25 Hz group at the end of the treatment period, i.e. at 20 weeks (n = 26, 34.2%, p = 0.034) (Fig. 2).

Responder rates (25%, 50%) were similar in both groups (Fig. 3). The study failed to show superiority of 25 Hz tVNS over 1 Hz tVNS

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Fig. 1. tVNS device NEMOS®. Left side: programmable stimulation device and ear electrode. Right side: placement of ear electrode in the ear conch; taken from (Bauer et al., 2016).

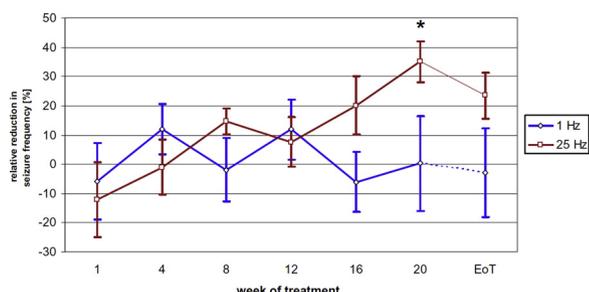


Fig. 2. Mean relative reduction in seizure frequency at each study visit as compared to baseline seizure frequency. LS-means, *p < 0.05. Error bars: SEM; taken from (Bauer et al., 2016).

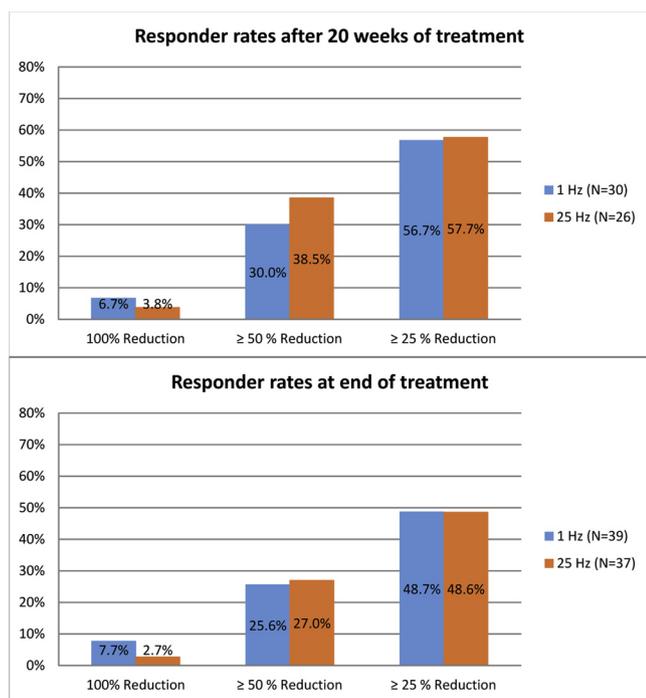


Fig. 3. Responder rates after 20 weeks of tVNS treatment and at end of treatment (including patients who did not complete the full 20 weeks of treatment).

in the intention-to-treat study population. However, there was a

moderate but significant seizure reduction rate of 23.4% within the 25 Hz per-protocol group.

4. Tolerability and safety

Adverse events were usually mild or moderate and comprised headache (1 Hz: 35.9%; 25 Hz:32.4%), ear pain 1 Hz: 7.7%, 25 Hz: 16.2%), application site erythema (1 Hz:2.6%; 25 Hz: 8.1%), vertigo (1 Hz: 7.7%; 25 Hz: 10.8%), fatigue (1 Hz: 12.8%; 25 Hz: 2.7%), and nausea (1 Hz: 7.7%; 25 Hz: 8.1%). One sudden unexplained death in epilepsy (SUDEP) occurred in the 1 Hz group.

5. Further studies

The results justify further trials in larger patient populations. The following lessons have to be learnt:

- Since treatment effect appeared to increase after 20 weeks of treatment, longer observation periods are necessary when assessing potential neuromodulatory effects.
- Future trials should include comparisons of tVNS and standard VNS: patients who benefited from tVNS treatment could be considered for implantation of standard or responsive VNS. Positive responses to tVNS could allow personalization of neuromodulatory treatments, while negative responses could avoid unnecessary implantations.
- Due to its favorable safety profile and non-invasive nature, tVNS in contrast to VNS, could be considered for treatment studies at early stages of epilepsy.
- Because numerous parameters of brain stimulation therapies (e. g. stimulation target, frequency, pulse patterns, intensity, duration) can be adjusted within wide ranges, the “optimal” stimulation settings remain unclear. Hence, there is a strong need for comparative studies.

In conclusion, the clinical value of tVNS cannot be finally evaluated at this point and the results of further trials must be awaited (Boon et al., 2018).

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