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BRIEF COMMUNICATION

Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: A proof of concept trial

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Summary

To elucidate, in a pilot-study, whether noninvasive transcutaneous vagus nerve stimulation (t-VNS) is a safe and tolerable alternative treatment option in pharmacoresistant epilepsy. t-VNS was applied to 10 patients with pharmacoresistant epilepsies. Stimulation via the auricular branch of the vagus nerve of the left tragus was delivered three times per day for 9 months. Subjective documentation of stimulation effects was obtained from patients' seizure diaries. For a more reliable assessment of seizure frequency, we carried out prolonged outpatient video–electroencephalography (EEG) monitoring. In addition, computerized testing of cognitive, affective, and emotional functions was performed. Three patients aborted the study. Of the remaining seven patients, an overall reduction of seizure frequency was observed in five patients after 9 months of t-VNS. The noninvasive t-VNS stimulation is a safe and well-tolerated method for relatively long periods, and might be an alternative treatment option for patients with epilepsy.

KEY WORDS: Transcutaneous vagus nerve stimulation, Pharmacoresistant epilepsies, Outpatient monitoring, Automatic seizure quantification, Computerized cognitive testing in epilepsy, Neuromodulation, Neurostimulation, EEG.

Pharmacoresistance is diagnosed in 20–40% of patients with epilepsy (Crawford, 2000; Kwan & Brodie, 2000). Many of the patients being treated with antiepileptic polytherapy have side effects of cognitive impairment or depression, which may also be due to epilepsy comorbidity (Shorvon & Reynolds, 1979; Kwan & Brodie, 2001).

Epilepsy surgery provides an effective option (Wiebe et al., 2001) but can be performed in only a limited number of patients. In very difficult-to-treat patients, invasive stimulation of the vagus nerve (Handforth et al., 1998) or deep brain stimulation (Fisher et al., 2010) might be an alternative treatment option. Very recently, animal studies showed that there was no significant difference between invasive vagus nerve stimulation (VNS) and transcutaneous VNS (t-VNS) with respect to the anticonvulsive effect (He et al., 2009). To determine whether t-VNS offers a treatment option in drug-resistant epilepsy, we initiated a pilot study concerning safety and tolerability.

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Methods

Patients

Ten patients with pharmacoresistant epilepsies (eight focal, two generalized, mean age 37.7 years and range 18–55 years, six female, four male) were enrolled in the study. For study inclusion, a minimal seizure frequency of four seizures per month was required. The dose of medication was to be kept constant for the whole study period. Exclusion criteria were the same as used for invasive vagus nerve stimulation. The study was approved by the local ethics committee. The patients were informed about the procedures to be used in the study provided their written consent.

Stimulation

Transcutaneous stimulation was performed by means of electrical stimulation of the auricular branch vagus nerve (ABVN) at the left ear. Intensity of t-VNS was individually selected by the patient according to tolerance; pulses were biphasic, stimulus frequency was 10 per s, pulse width was 300 μsec, applied voltage was 25 V on average, and stimulated area was approximately 2 cm^2. After individual training, patients applied t-VNS by themselves as part of daily routine. Stimulation was performed for 1 h in the morning, 1 h at noon, and 1 h in the evening over a period of 9 months.

Documentation

For seizure documentation during the study, patient diaries were used. The patients were asked to report their seizures as well as the tolerability, side effects, and practicability of the t-VNS device using a standardized questionnaire. For a more reliable determination of the actual seizure frequency and seizure semiology, prolonged outpatient video–electroencephalography (EEG) monitoring was performed for 1 week in a hotel very close to the clinic. This outpatient monitoring was done for each patient for the baseline period and then every 3 months after t-VNS was starting.

Data acquisition

The video-EEG recording (10-20 system) was employed using a portable system (Natus Europe GmbH, Munich, Germany) that included a laptop computer and an infrared capable pan/tilt camera. The scalp electrodes were glued to provide good recording conditions. Each day a medical assistant went to the hotel and serviced the electrodes and the system. The video-EEG data from the previous day were transferred via an external hard disk to the main database in the hospital (Stefan et al., 2011).

Data analysis

First, the entire set of EEG data were analyzed using an automated seizure detection program (Hopfengärtner et al., 2007). Second, a visual inspection and analysis of the video-EEG was carried out by experienced electroencephalographers. The duration of generalized spike-waves (GSWs) were automatically determined (Stefan & Hopfengärtner, 2009). In addition, the detected GSWs were checked visually. This analysis was carried out for each time period.

Computerized testing of cognitive and affective functions

For assessment of cognitive and emotional functions, a computerized testing system was used (Kurzbuch et al., 2010). Cognitive domains of working memory, attention, cognitive speed, and verbal and visuospatial memory were assessed by the test battery. For assessing depressive symptoms, the Beck Depression Inventory (BDI) was used. Furthermore, patients completed the Quality of Life in Epilepsy Inventory-89 (QOLIE-89), a questionnaire about perceived quality of life in patients with epilepsy. The neuropsychological tests were completed immediately before the outpatient video-EEG monitoring started at the hotel.

Results

From the 10 patients enrolled in this study, 7 patients remained for the whole 9 months. Three patients aborted the study for various reasons. In Figure 1 we present the results for the averaged number of seizures per week, according to the patients' seizure diaries. A comparison of seizure frequency during baseline and after 9 months revealed a reduction of seizures in five of seven patients (Patients 2, 3, 4, 7, and 8). Patients 9 and 10 showed an increase of the number of seizures per week; this increase remained constant during the whole study period.

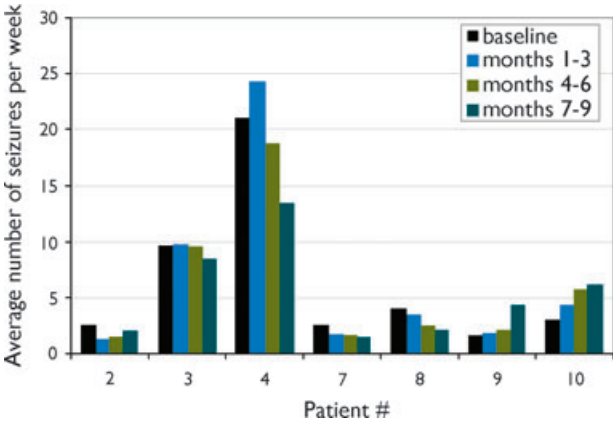

Figure 1.
Average number of seizures per week according to the patient's seizure diary (Patients 1, 5, and 6 aborted the study). The average of three consecutive months is shown, respectively.
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A survey of all findings of the video-EEG monitoring sessions is summarized in Table 1. Patients 2, 7, 8, and 9 showed no clinical seizures at all during baseline monitoring. Therefore, only relative changes of duration and number of seizures obtained from monitoring sessions at month 3 and 9 have been considered. Patients 3 and 10 also exhibited no seizure during video-EEG monitoring. In the case of patient 4, the relative changes of months 3 and 9 with respect to baseline are shown. Patients 2 and 8 showed a significant reduction of seizure number (29% and 50%, respectively), reflecting the overall trend of the results found for these patients in their seizure diaries (Fig. 1). Patient 4 showed a significant increase of the seizure number compared to baseline (175% after 3 months; 100% after 9 months). This increase is contrary to what was reported in the patient's seizure diary (Fig. 1). Patient 7 exhibited mainly simple partial seizures without clear seizure pattern in the EEG; the number of seizures was identical during sessions at months 3 and 9.

In all video-EEG monitoring sessions, Patient 3 exhibited only GSWs. The relative changes of GSW duration for the different recordings showed first a slight increase after 3 months (7%) compared to baseline, followed by a decrease after 9 months (29%). Patient 10 showed continuous periodic, high-amplitude spike-waves in baseline EEG resembling a discontinuous nonconvulsive status epilepticus. An indirect measure for occurrence of these

Table 1. A summary of findings of the seven patients investigated in the t-VNS study during the different outpatient video-EEG monitoring sessions

Patient	Video EEG		Tolerance	Cognition/Affect		
	Duration (↑↓ in %)	Number (↑↓ in %)		Quality of life	Cognition	Depression
				↑/=/↓ : improved/stable/deteriorated		
2	no seizures in baseline ③→⑨ ↓29%	③→⑨ ↓29%	good, stimulation sometimes painful	③ ↑ ⑥ ↑ ⑨ =	③ 2/4/1 ⑥ 0/6/1 ⑨ 1/5/1	③ = ⑥ = ⑨ =
3	GSWs ③ ↑7% ⑨ ↓29%	number of GSWs not determined, summarized in duration	very good, no side effects	③ = ⑥ = ⑨ =	③ 1/4/2 ⑥ 1/5/1 ⑨ 1/5/1	③ = ⑥ = ⑨ =
4	③ ↓241% ⑨ ↑133%	③ ↑175% ⑨ ↑100%	acceptable	③ = ⑥ = ⑨ =	③ 1/5/1 ⑥ 1/6/0 ⑨ 0/7/0	③ ↓ ⑥ = ⑨ ↑
7	no seizures in baseline ③→⑨ ?%(SP)	③→⑨ = 0%	good after getting used to	③ ↓ ⑥ = ⑨ =	③ 0/7/0 ⑥ 1/6/0 ⑨ 3/4/0	③ = ⑥ = ⑨ =
8	no seizures in baseline ③→⑨ ↓46%	③→⑨ ↓50%	very good, no side effects	③ = ⑥ = ⑨ =	③ 0/7/0 ⑥ 0/7/0 ⑨ 1/6/0	③ = ⑥ = ⑨ =
9*	no seizures in baseline ③→⑨ 0″→1′11″	③→⑨ 0→1	good	③ ↑ ⑥ = ⑨ =	③ 1/6/0 ⑥ 0/7/0 ⑨ 0/7/0	③ = ⑥ = ⑨ =
10**	interictal activity quantified by integrated power analysis		very good, no side effects	③ = ⑥ ↑ ⑨ =	③ 2/4/1 ⑥ 4/3/0 ⑨ 2/5/0	③ ↑ ⑥ ↑ ⑨ =
	* no verifyable events in EEG or video; seeks to acquire disability status ** in the beginning fronto contro temporal discontinuous nonconvulsive status epilepticus			1/2/3 = number of cognitive subtests (out of 7) which were improved/stable/deteriorated compared to baseline		
	③/⑥/⑨ = change compared to baseline after 3/6/9 months ↑↓xx% = total change during study period					

Patients 1, 5, and 6 aborted the study. ③/⑨/⑥ indicates the results found in months 3, 6, and 9, respectively. The relative changes (↑ increase, ↓ decrease) are presented in %. Patient 3 showed only GSWs (generalized spike-waves) during consecutive monitoring; the number of GSWs has been summarized in the total duration. Patient 9 exhibited no seizure during baseline and month 3, so no relative changes could be calculated (only one seizure in month 9). Patient 10 showed no seizures, only continuous high-amplitude spike-waves have been recorded all the time. Measures of cognition, depression, and quality of life were stable for the greater part. For further details see text.

spike-waves was extracted from the integrated power, and showed a marked decrease after 3 and 6 months, leveling off after 9 months.

The majority of cognitive functions were stable over the course of three examinations in all patients; slight improvement could be found in two patients. Measures of quality of life and depression were stable or improved over the examinations in all patients except one who showed deterioration in quality of life, and another whose depression scores worsened but then improved again at the last examination.

Discussion

This pilot study of t-VNS for pharmacoresistant epilepsies indicates that t-VNS is safe, well tolerated, and practicable for long-term treatment. Some subjective complaints such as hoarseness occurred but are not easily explained by auricular nerve stimulation.

Three patients discontinued participation in the study due to one or more of the following reasons: (1) difficulties with integrating the highly demanding study protocol into their daily life; (2) technical problems (e.g., electrodes had to be replaced as a result of mechanical breakage); and (3) side effects (hoarseness, headache, or obstipation).

A reduction of seizure frequency, as determined from patients' seizure diaries, was observed in five of the seven patients remaining in the study, indicating a possible inhibitory effect. A 50% response rate was not reached, but two Patients (patients 7 and 8) had a decrease in seizure frequency of 45% and 48% (comparison of baseline to months 7–9), respectively. Concerning the possibility that patients may tend to show higher seizure rates during baseline than placebo, one should consider that patients after recruitment directly entered the treatment phase; the typical baseline phase was missing in our pilot study. Because this pilot study was noncontrolled, a reversion to the mean cannot be ruled out, but all patients had pharmacoresistant epilepsies over many years. Therefore, we assume that a spontaneous reduction of seizure frequency of all these patients is not likely.

Major discrepancies between subjective patient reports and quantified video-EEG were seen in patient 4, who reported a 37% reduction of seizure frequency (baseline: 21 seizures per week; average of months 7–9: 13.3 seizures per week) but an increase in seizures was recorded during

video-EEG monitoring. Patient 9 reported a significant increase of simple partial seizures with subjective signs (baseline: 1.6 seizures per week; average of months 7–9: 4.2 per week), but no changes were seen on EEG recording.

In addition to study of ictal frequency, interictal EEG analysis may show treatment- induced changes if the EEG is recorded in repeated long-term monitoring sessions over weeks, as shown in Patient 10. Emotional and cognitive functions were stable or improved in two patients, and no major and/or permanent impairment was observed.

The noninvasive and reversible t-VNS approach may offer new options for improving patient care by use of well-tolerated adjunctive epilepsy treatment. In this pilot study, primary outcomes were safety and tolerability, and secondary outcome was seizure reduction.

We are aware that our study has serious limitations: (1) no randomized and controlled (sham) stimulations were performed; (2) only a small number of patients were enrolled; and (3) an inhomogeneous patient group (focal, generalized epilepsies) was selected. Given the results of this proof of concept pilot study, further studies are encouraged.

Acknowledgments

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Disclosure

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest related to this paper to disclose.

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