Seizure: European Journal of Epilepsy 60 (2018) 115–119

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Transcutaneous vagal nerve stimulatio (t-VNS): An adjunctive treatment option for refractory epilepsy

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ARTICLE INFO

Keywords:
Transcutaneous vagal stimulation (t-VNS)
Medically refractory epilepsy
Palliative treatment
Seizure severity

ABSTRACT

Purpose: The aim of this trial was to investigate the efficacy and safety of transcutaneous vagal nerve stimulation (t-VNS) in the palliative treatment of drug resistant epileptic patients ineligible for surgery.
Methods: Twenty adult patients received four hours of t-VNS per day for six months (T1), followed by a two-month washout period (T2). The frequency and type of seizures recorded at T1 and T2 were compared with those occurring in the three months preceding study entry (T0). Responders ($\geq$30% reduction in the total number of seizures) subsequently received two hours of t-VNS per day for further six months (T3). All patients underwent electroencephalography (EEG) and completed the Quality of Life in Epilepsy questionnaire at baseline and T1.
Results: At T1 six patients were considered responders. In these patients, at T3 the average reduction in seizure frequency was 60% compared to T0 ($p = 0.043$), and 51% compared to T2 ($p = 0.043$). Responders had more often seizures with falls (5 of 6; 83.3%) compared with non-responders (3 of 14; 21.4%) ($p = 0,010$) and t-VNS reduced their frequency by a percentage ranging from 47.5 to 100%. There was no change in responders' EEG findings after stimulation. At the end of the trial, three responders continued t-VNS, one implanted VNS.
Conclusions: t-VNS had no or minimal side effects and significantly reduced seizures in about one third of the enrolled patients. Further studies should be planned to assess whether t-VNS is a suitable tool to predict the efficacy of implanted VNS.

1. Introduction

Epilepsy is a common neurological disorder with an estimated prevalence of 4–10/1000 people per year [1].Drug treatment of epilepsy is symptomatic and is intended to suppress seizures with minimal side effects, although 33% of patients have drug-resistant epilepsy (defined as the failure of at least two tolerated and appropriately chosen and scheduled antiepileptic drugs [AEDs]) [2], mainly because of genetic modification of drug targets [3]. As adding more drugs is unlikely to make them seizure free, resective surgery is the treatment of choice for patients with medically refractory partial epilepsy. ome patients are ineligible for surgery for various reasons (unidentifiable seizure focus, presence of multiple foci, location of seizure focus within eloquent cortex, or patient refusal).

There are alternative palliative treatments: one approach is to use electrical neurostimulation to decrease the excitability of specific brain structures and, consequently, seizure frequency or duration. The most widely used neurostimulation techniques are deep brain stimulation (DBS), responsive cortical stimulation (RCS), and vagal nerve stimulation (VNS) [4,5].

VNS directly stimulates left vagus nerve, then the stimulation reaches brainstem nuclei and diffusely affects the excitability of the cortex [6]. Indeed, the stimuli activate the neurons of the solitary tract nucleus (NTS) and the neural network of the prefrontal cortex, thalamus, hypothalamus, cingulate gyrus, and hippocampus [7–9]. The effectiveness of VNS has been demonstrated by numerous studies, even if there are no definite indications concerning the most responsive type of epilepsy or seizure [10–12].

Abbreviations: t-VNS, transcutaneousvagal nerve stimulation; EEG, electroencephalography; AEDs, antiepilepticdrugs; DBS, deepbrain stimulation; RCS, responsivecortical stimulation; VNS, vagalnerve stimulation; NTS, solitarytract nucleus; ABVN, auricularbranch of the vagus nerve; QoLIE-31-P, Qualityof Life in Epilepsy-31-P questionnaire

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https://doi.org/10.1016/j.seizure.2018.06.016
Received 22 February 2018; Received in revised form 14 June 2018; Accepted 15 June 2018

The use of a transcutaneous vagal stimulation (t-VNS) is a development of implantable VNS. The auricular branch of the vagus nerve (ABVN) is a mixed nerve consisting of the vagus, glossopharyngeal and facial nerves; anatomical studies have shown that it is distributed to the posterior wall of the external auditory canal. A projection from the ABVN and the NTS has recently been demonstrated in animal models [13], thus supporting t-VNS as an alternative treatment to implanted VNS in refractory epilepsies. Experimental data have revealed that VNS and t-VNS have equivalent effects on the EEG activity of epileptic rat models [14], functional magnetic resonance imaging (fMRI) studies of healthy volunteers and patients undergoing t-VNS or implanted VNS have shown the same pattern of activation, whereas the stimulation of parts of the ear lobe not innervated by the auricular nerve does not have the same brain activation pattern [9,15].

The aim of this prospective, open-label, single-center experimental trial was to investigate the efficacy and safety of t-VNS in the palliative treatment of drug-resistant epilepsy, with the working hypothesis that it may reduce seizure frequency, severity and improve patients' quality of life.

2. Material and methods

This study was carried out at the Fondazione Istituto Neurologico Carlo Besta, Milan, Italy, after being approved by the Institute's Ethics Committee.

Inclusion criteria were: age of ≥ 16 years; presence of at least two years long drug-resistant epilepsy with more than 10 monthly seizures, despite the administration of two or more AEDs; stable antiepileptic therapy for three months before starting the stimulation; ineligibility for surgical treatment after a pre-surgical evaluation, ineffective previous surgery, or unwillingness to undergo surgery.

Exclusion criteria were: progressive neurological disease and unreliability in seizure reporting or in using t-VNS. Informed Consent was obtained from patients or their parents/legal guardians before the start of the trial.

Twenty patients with refractory focal epilepsy (10 females and 10 males; mean age 38.6 years, range 16–57; mean disease duration 28.4 years, range 7–47), regularly followed at our outpatient clinic, were enrolled between May and July 2014; AEDs schedule was kept unchanged throughout the duration of the trial.

At the baseline visit we collected information including personal data, family history, epilepsy duration, seizure types, AEDs treatment and monthly seizure frequency in the previous three months. The number and type of seizures were recorded based on patients' diaries.

Patients or their caregivers completed the standardized Quality of Life in Epilepsy-31-P questionnaire (QoLIE-31-P) to assess patient's health-dependent quality of life [16].

All patients underwent a 60-minute awake video-EEG recording including 20 min without t-VNS, 20 min during subliminal (unperceived) t-VNS, and 20 min during perceived t-VNS. Electrodes were placed in accordance with the 10–20 System.

t-VNS intensity was adjusted to be perceived as a tingling sensation but below the pain threshold (0.6-0.8 mA).

During the first stimulation period, t-VNS was applied for six months four hours per day, divided into two-three sessions of at least one hour each. This timeframe was defined according to its correspondence with that applied daily for long cycle in implanted VNS(20 s on/ 5 min off).

At the end of the first stimulation period (T1), patients underwent a second video-EEG session, comparable to the first one, and completed the QoLIE-13-P again.

After a washout period of two months (T2), those patients having a reduction in seizure frequency ≥ 30% assessed at T1 (responders), underwent a second six-month period of stimulation for two hours a day (T3) to verify whether there was any difference in the effect depending on daily t-VNS stimulation period.

The primary aim of the study was to evaluate the percentage changes in seizure frequency and severity from baseline (T0) after six-month treatment (T1), after the washout (T2) and after the second six-month treatment of t-VNS (T3). For this purpose, we considered the seizure frequency at T0, T1, T2 and T3 and seizure severity, subjectively defined as the most disabling seizure type reported in patients' diaries. Changes in ictal and post-ictal severity were registered from patients' or caregivers' diaries.

At T1 the average seizure frequency during the first six months stimulation period was compared with the one assessed at T0. At T2 the average seizure frequency during the two washout months was compared with that assessed at T1 and at T0. At T3 the average seizure frequency during the second stimulation trial was compared with the one analysed at T0, T1 and T2. at T0, T1 and T2.

The classification proposed by McHugh et al. was used to describe seizure outcome in VNS [17]. This scale defines five classes, the first three include a reduced seizure frequency (I = 80–100%; II = 79-50%, III = less than 50%), while class IV indicates a benefit from external magnet use, and V no improvement. Each class was subdivided into A and B according to the reduction of more severe seizures.

Secondary endpoints were the number of seizure-free days assessed at T0, T1, T2 and T3, the QoLIE-31-P scores and the EEG signals at T0 and T1.

The effects of t-VNS on the epileptic interictal discharges (IED) recorded in both EEGs performed at T0 and T1,with subliminal and perceived stimulation, were compared by visual inspection.

2.1. Statistical analyses

To test differences between the mean seizures frequency and scores at the different time-points (T0, T1, T2, T3) the non-parametric Wilcoxon Signed-Rank test was applied. To compare demographic and clinical factors it was used the non-parametric Kruskall-Wallis. All the anamnestic factors that could predict positive outcome were investigated by means of multivariate logistic regression.

Statistical analyses were carried out using SPSS statistical software, version 14 (SPSS Inc., Chicago, IL, U.S.A.) and p-values of < 0.05 were considered statistically significant.

3. Results

Table 1 shows the main patients' demographic, electro-clinical and Magnetic Resonance (MR) data; Table 2 shows their outcomes using McHugh's classification.

The most frequent side effects of t-VNS were pain, small abrasions or eczema at the electrode contact point, which were reported by four patients. They couldn't change the point of stimulation as it a very small area, however patients never discontinued the study although they reported some break during daily sessions. One patient reported headache and one a sense of strangeness if the stimulation preceded a seizure. Even in the absence of significant side-effects, all patients complained about the duration of the daily stimulation period.

3.1. First trial epoch and washout

At T1, after the first six months of t-VNS period, seizure frequency was on average reduced, but, in the whole population, the difference with respect to T0 did not reach a statistical significance. None of the patients became seizure free, but six had a reduction in seizure frequency ≥ 30%, 47.5–100 %and were considered as responders (Class III A). Two of them felt more alert.

Among patients considered as non-responders, four had a reduction in seizure frequency of ≥ 30% (exceeding the 50% in one), but felt subjectively worse at the end of the first six months of stimulation and refused to go on with the trial. Two of them had an unchanged frequency of falls; one continued with tonic seizures at night; in the last

Table 1
Demographic and electro-clinical data. Values are shown as mean (min-max) or number of patients (percentage of the column total). Seizure type has been classified according to Fisher et al., 2017 [31].

	All patients (n = 20)	Responders (n = 6)	Non-responders (n = 14)
Sex (males/ females)	8/12	2/4	6/8
Age at T0 (years)	38,6 (16-57)	46.33 (33-53)	36 (16-57)
Age at epilepsy onset (years)	11.2 (0-43)	12.8 (3-43)	10.5 (0-30)
Epilepsy duration (years)	28.4 (7-47)	33.5 (8-44)	26.6 (7-47)
Previous epilepsy surgery	1 (5%)	1 (16%)	0
Normal Neurological	12 (60%)	3 (50%)	9 (64%)
Examination	8 (40%)	3 (50%)	5 (36%)
Neurological deficits			
Normal Cognitive Level	9 (45%)	3 (50%)	6 (43%)
Cognitive Disability	11 (55%)	3 (50%)	8 (57%)
Number of AEDs	2 (30%)	2 (33%)	2 (29%)
	3 (40%)	3 (0%)	3 (57%)
	4 (30%)	4 (67%)	4 (14%)
Seizure type			
Focal onset	20	6	14
Impaired awareness	14	5	9
Aware	4	1	3
Undefined	2	0	2
Motor signs at onset	13	5	8
Focal to bilateral	3	2	1
Seizures with falls	7	5	2
EEG interictal pattern			
Focal IED	11 (55%)	4 (67%)	7 (50%)
Multifocal IED	9 (45%)	2 (33%)	7 (50%)
MR data			
No detectable pathology	8 (40%)	3 (50%)	5(36%)
Abnormal	12 (60%)	3 (50%)	9(64%)
Cortical Malformation	6	2	4
Perinatal stroke	2	0	2
Others (gliosis, infection, hippocampal sclerosis)	4	1	3
Baseline seizure frequency	20.3 (11.3-162)	15 (11.3-36)	22.3 (12.3-162)
QoLIE-31 score at the baseline	44.3 (31-66)	42.33 (32-55)	45.1 (31-66)
QoLIE-31 score at the end of treatment	42.9 (24-63)	38.5 (24-49)	44.8 (31-63)
3-month stimulation intensity (mA)	0.7 (0.2-1.8)	0.65 (0.4-0.8)	0.8 (0.2-1.8)
6-month stimulation intensity (mA)	0.8 (0.2-2)	0.6 (0.4-0.8)	0.8 (0.2-2)

Table 2
Patient outcomes at T1: McHugh classification [17].

Class I	80-100% reduction in seizure frequency	IA IB	0
Class II	50-79% reduction in seizure frequency	IIA IIB	1
Class III	< 50% reduction in seizure frequency	IIIA IIIB	5 4
Class V	No improvement		10

one, seizure reduction was limited to the first 3 months, thereafter their frequency returned to baseline. They were classified as IIIB or IIB McHugh scale.

The QoLIE-31-P scores at T0 and T1 did not significantly change, in particular no changes were found in the section of “emotional well-being”.

Demographic data, focal or multifocal seizure onset, localization of EEG interictal activities, presence or absence of neurological or cognitive deficits did not show different distribution among responders and not-responders. The age at starting t-VNS was slightly higher in responders (p = 0.049).

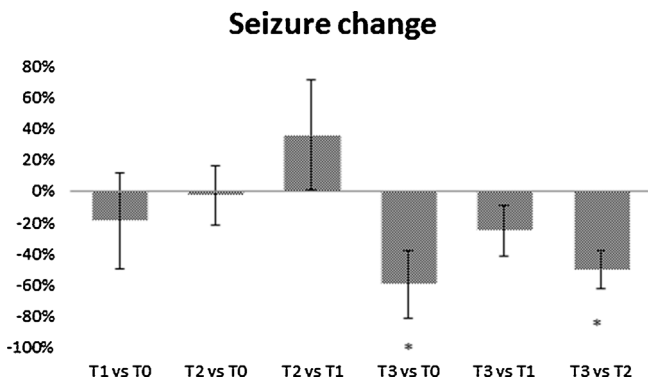

Fig. 1. Seizure change.

3.2. Second trial epoch

After the washout period (T2), responders increased their seizure frequency by 35.7% in comparison to T1 whereas non-responders did not change their seizure frequency. Five responders, after two-month washout period, entered the second phase of treatment (one responder refused to continue the trial). At the end of the second stimulation period (T3) seizure frequency significantly decreased compared to both T0 (p = 0.043) and T2 (p = 0.043) () In three patients seizures with fall were meanly reduced by 80%: in one patients they disappeared, in one were reduced by 83%, in one by 54%, in two they were unchanged but less disabling. All patients better tolerated the second trial shorter stimulation period.

The graph in Fig. 1 shows seizure change comparison at different time points in responders. A trend in seizure increase was observed between the first six months of stimulation (T1) and the end of washout (T2); a trend in seizure frequency reduction was observed between the short- lasting period of stimulation (T3) and T1. A significant seizure frequency reduction was observed between T3 and both T2 and T0. At the end of the first six months of stimulation (T1) no significant seizure reduction was observed. In addition at the end of washout period seizure frequency comes back to baseline one.

*= p < 0,05

3.3. Seizure free days

The mean increase of seizure-free days at T1 was greater in responders than in non-responders, even if this increase was not statistically significant. After the washout period, the mean of seizure-free days returned to T0 level. At the end of the second stimulation period responders still showed an increase of seizure-free days.

3.4. EEG assessment

The inspective evaluation of video-EEG recordings was performed at T0 and T1, but did not reveal any change in term of occurrence of interictal discharges; moreover, activation of t-VNS did not lead to any visible effect on IED.

Diffuse delta waves were detected at both T0 and T1 in five patients, four of whom were responders. In the second EEG recording we observed the presence of runs of monomorphic delta waves. This slow activity became almost continuous when t-VNS was ON in three of the six responders as well as in six of the 14 non-responders.

3.5. Outcome predictors

We evaluated the relationship between the condition of responders and not responders with age at epilepsy onset, disease duration, seizure with falls, number of AEDs, EON, cognitive impairment and QoLIE-31-P score before the treatment.

The test of the full model versus a model with intercept only was statistically significant, $X^2 = 6.97$, $p = 0.008$. The model correctly classified 80.0% of cases. Analysis indicated that the occurrence of falls (odds ratio 18.33, $p = 0.022$) was the only variable predicting better result, suggesting that patients with seizures determining falls had a better outcome.

Seizures with falls characterized five out of six responders (83.3%), but only three of 14 non-responders (21.4%) ($p = 0,01$). Among responders, seizures determining falls were quantitatively reduced and less disabling because in some cases they were preceded by some kind of aura. We found no correlation between the response to t-VNS and age at the time of epilepsy onset, duration of epilepsy, baseline seizure frequency, sex, etiology.

At the end of the trial three responders continued with t-VNS and one with implanted VNS. All the three patients with t-VNS retained the seizure improvement, with further reduction of seizures with falls in two and disappearance of focal to bilateral seizures in one. The patient in whom VNS was implanted, retained the improvement and had no more seizures with falls.

4. Discussion

Our study indicates that t-VNS was effective in treating about one third of patients with drug-resistant epilepsy.

Indeed, although seizure distribution over time did not substantially change during the trial and none reported an increased seizure number or seizure free days, about one third of patients had a seizure reduction exceeding 30% of the baseline seizure frequency and a reduction of seizure severity.

Patients defined as responders experienced an increase in seizure frequency during the washout period (T2) in comparison with the first treatment period and a significant decrease in seizure frequency after 14 months compared to baseline. This result is in line with other studies' findings applying VNS or t-VNS indicating an improved effect over time [4,10,18–20]. The use of t-VNS also proved to be effective in reducing more disabling seizures, in particular seizures with falls.

We used McHugh's classification as more appropriated to describe responders and non-responders to a palliative treatment as t-VNS and VNS, because it includes the judgment of seizure severity compared to the more commonly applied Engel scale [2,23,24]. In our study this allowed to distinguish seizure with falls as more responsive and predictive of a better response.

To our knowledge, this is the first study evaluating the efficacy of t-VNS in terms of seizures with falls, but our results are in line with previous studies performed with implanted VNS, that reported complete disappearance of seizures with falls in seven out of 26 children with Lennox-Gastaut syndrome [21] and a reduction of seizures with falls in 40% of 39 pediatric and adult patients [22].

In our observation, t-VNS had minimal side effects, however the four hours of stimulation per day performed during the first six-month trial was still rather challenging therefore we investigated the effect of shorter stimulation performed for two hours per day.

esults were similar for the two stimulation periods, suggesting the effectiveness of briefer daily stimulation, better tolerated by patients.

Using t-VNS, Aihua et al. [19] found a positive correlation between baseline seizure frequency and the duration of epilepsy, but others have not found any correlation with age, sex, seizure type or baseline seizure frequency [18,20,25]. Likewise, we did not find correlation between the response to t-VNS and age at epilepsy onset, duration of epilepsy, baseline seizure frequency, sex, etiology, but we found that patients had a positive correlation with age at t-VNS treatment.

Other studies of VNS or t-VNS found improvements of QoLIE in control and treated groups, suggesting that the quality of life is not necessarily related to an increase or decrease in seizure rates [18–20,25,26]. Also in our series quality of life scores in responders did not significantly correlate with their better outcomes. Actually 11 of our 20 patients (55%) were cognitively impaired and were therefore assisted in completing the questionnaire, thus inevitably reducing the reliability of the evaluation. Caregivers reported improved mood or a greater alertness in some patients with severe cognitive defects which would not have been picked up by the QoLIE-31-P.

Pre-clinical studies have demonstrated that VNS can desynchronize EEG activity and suppress epileptiform activity in animal studies [27,28]. However, its effect on EEG rhythms in humans is still uncertain, as resulting from previous studies with contradictory results [29]. Some clinical studies have shown a long-term effect: a pilot study with VNS reported decreased epileptiform activity in 15 children and changes in synchronization between ON and OFF phases of stimulation and between responders and non-responders, after nine months of VNS stimulation [30].

We did not perform a quantitative evaluation of the EEGs performed at T0 and T1. We found no changes in epileptiform activity and in its localization both in responder and non-responders. Moreover, we did not found any influence on epileptiform activity comparing the period with t-VNS ON and OFF. We observed the appearance of slow activity during the epochs of stimulation in three of the six responders, but also in six of the 14 non-responders. There is only one previous pilot study investigating the effect of t-VNS on EEG, which also found no significant changes [26].

A limitation of our study is the small number of enrolled patients and the unfeasibility of a double-blind trial with "sham" stimulation, since patients need to recognize the stimulation, that is not related to intensity and cannot be painful. We tried to overwhelm this problem including a washout after the first stimulation period, confirming the positive effect of t-VNS in responders.

5. Conclusions

Our findings indicate that t-VNS is effective in reducing seizure frequency and severity in patients with refractory epilepsy and namely in those presenting seizures with falls. About one third of patients may improve with very mild or no side effects. This method can therefore be suitable to treat patients with refractory severe epilepsy who are not candidates for, or unwilling to undergo surgery. Additional extensive trials are needed to confirm the usefulness of t-VNS as a non-invasive procedure that doesn't need hospitalization and is therefore appropriate also for severely impaired patients. Moreover, further evaluations are expected to clearly demonstrate the suitability of t-VNS in predicting the efficacy of implanted VNS.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical publication statement

We conform that we have read the Journal's position on issues involved in ethical publication, and affirm that this report is consistent with those guidelines.

Declaration of interest

None.

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