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

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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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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