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Short communication

External trigeminal nerve stimulation: A long term follow up study

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ABSTRACT

Purpose: External trigeminal nerve stimulation is an emerging noninvasive therapy for drug resistant epilepsy (DRE). The aim of this study is to describe the long-term outcome of a series of patients treated with eTNS.
Methods: We present a retrospective observational study of patients with DRE who received eTNS treatment, comparing the monthly seizure frequency during the 3-months period before eTNS initiation with the monthly seizure frequency at 6, 12, 24, 36 and 48 months after eTNS. We analyze the responder rate, the retention rate and the tolerability.
Results: 17 patients with highly drug-resistant epilepsy were included. Mean follow-up was 2194 [6–56] months. The responder rate was 35% at 6 months and 12 months, 23% at 24 months, 19% at 36 months, and 14% at 48 months. Retention rates at the same periods were 88%, 53%, 41%, 37.5% and 28.5%. There were no reports of serious adverse events. Four patients reported improvement in sleep and better mood.
Conclusion: The effectivity of eTNS is similar to some of the new treatments available, with a retention rate of 52% in the first year and 285% at 4 years. Tolerability is excellent with only mild effects reported by a minority of patients.

1. Introduction

Drug-resistant epilepsy (DRE) affects 30% of all people with epilepsy, and may lead to disability and death. Neurostimulation has emerged as a potential alternative to antiepileptic drug therapy for some of these patients who are not candidates for surgery. Since vagus nerve stimulation (VNS) became the first device approved by the FDA for epilepsy, several new therapies based on devices have been developed. The external Trigeminal Nerve Stimulation (eTNS) system is a new medical device developed by Neuro Sigma Inc. (Los Angeles, California) that provides bilateral external non-invasive electrical stimulation to the V1 branch of the trigeminal nerve. It has been approved for the adjunctive treatment of DRE and major depressive disorder (MDD) for patients over nine years old in Europe since 2012.

Initial clinical studies from DeGiorgio et al. [1–4] showed safety of this treatment with significant reductions in median seizure frequency at 12 months of long-term treatment. They reported compelling responder rates (30%) in range with other implantable devices for epilepsy, proposing eTNS as a promising alternative long-term treatment for drug-resistant epilepsy [1–4]. Since then, to our knowledge, there is only a recent clinical report on the outcome of eTNEs in 42 patients followed between 2013–2015, showing it is an easy to use therapy, well tolerated and with improvement in the quality of life. At the end of the audit period 45% of the patients were still using the device, including 11 who continued for more than 52 weeks, suggesting that eTNS is an additional option in patients with DRE [5].

Following these studies, our aim is to report our clinical experience and long-term outcome with eTNS therapy.

2. Methods

All patients treated with eTNS between May 2013 and June 2017 in our epilepsy center were retrospectively evaluated.

Treatment was offered to any patient who fulfilled the following criteria: intractable drug-resistant epilepsy, concurrent use of at least 1 AED, and sufficient cognitive abilities to understand the purpose of the device and how to use it (if not, a parent or care giver able to understand and use the device and the patient felt to be sufficiently cooperative for its use). Patients with a history of non-epileptic seizures, other serious or progressive medical or psychiatric illnesses, facial pain or trigeminal neuralgia, as well as patients previously treated with vagus nerve stimulation were excluded.

Patients and/or caregivers were trained in the use of the device. Stimulation was administered by an external electrode patch placed on

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Table 1
Clinical characteristics of 17 patients treated with eTNS.

Patient	Age (years)	Baseline Seizure frequency (per month)	Localization	Etiology	Duration (years)	Number of Prior AEDs	Number of AEDs at enrollement
1	25	70	Generalized/LG	Hipotalamic Hamathoma	25	11	5
2	16	20	Generalized/LG	Unknown	9	10	4
3	49	2	Parietal	Meningioma	3	5	3
4	13	45	Generalized/PME	Genetic	7	9	4
5	18	39	Indeterminated lobe	Unknown	5	7	2
6	38	17	Left temporal lobe	Encephalocele	7	12	3
7	47	3	Indeterminated lobe	Unknown	35	5	3
8	15	60	Indeterminated Epileptic encephalopathy	Unknown	8	16	2
9	25	188	Generalized/LG	Unknown	24	16	4
10	20	15	Multilobar	Lissencephaly	16	8	4
11	9	225	Generalized	Genetic	8	14	5
12	35	14	Occipital	Heterotopy	24	14	4
13	53	20	Indeterminated lobe	NF	39	13	3
14	12	220	Right Hemisphere	MCD	9	12	3
15	52	3	Occipital	Head Trauma	20	5	3
16	53	65	Generalized	Idiopathic	42	12	3
17	10	182	Temporal bilateral	Polymicrogyria	2	13	2

LG: Lennox-Gastaut syndrome, PME: progresive myoclonus epilepsy, MCD: malformation of cortical development, NF: neurofibromatosis.

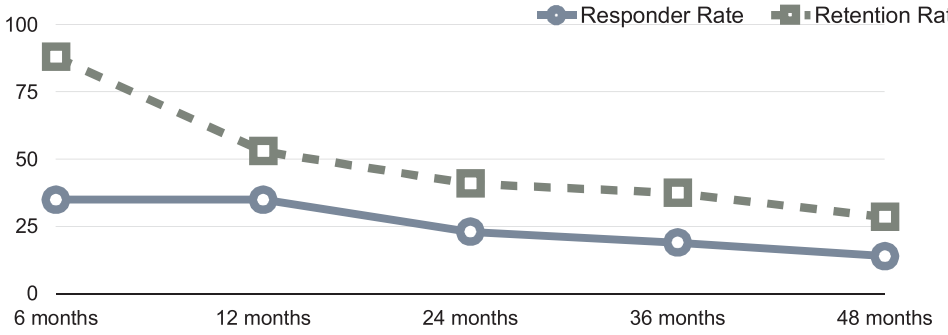

Fig. 1. Responder and Retention Rates during 6–48 months.

the forehead over the V1 branch of the trigeminal nerve.

Our protocol for eTNS includes follow-up visits with the same epileptologist at 4 week intervals, during which calendars were reviewed. Parameters were set according to clinical criteria (efficacy and tolerability). Only measurable seizures were accounted for in calendars. In patients with absence seizures, patients and/or caregivers counted days with and whithout seizures.

Parameters were set according to clinical criteria (efficacy and tolerability). In order to evaluate the effect of eTNS, antiepileptic drugs (AEDs) were modified only after a 6-month initial evaluation period. After this period AEDs were modified as required in clinical practice.

We performed an intention-to-treat analysis of the retention and responder rates at 6, 12, 24, 36 and 48 months of follow-up. Responders were defined as those patients who experienced a 50% or higher reduction in seizure frequency (considering all measurable seizures types together) compared to a baseline period of 3-months.

3. Results

Our series include 17 patients treated with eTNS for a period of 6–56 months. Table 1 summarizes clinical information of the subjects, including baseline seizure frequency, etiology of epilepsy, localization, and antiepileptic drug history.

Subjects were highly drug-resistant, with a mean duration of epilepsy of 16.6 [2–42] years and a very high seizure frequency (2–224 seizures per month). Most patients presented a combination of several seizure types (focal with or without awareness, tonic, atonic, generalized tonic-clonic seizures and absences). The most common seizure types were focal, generalized tonic-clonic, and absences. An average of 10.7 [5–16] antiepileptic drugs had failed before eTNS was started. Mean age at time of eTNS initiation was 28.8 [9–53] years. Stimulation was set at 2.8–5 mA s during 8–14 h/day at night, largely while the individual slept. Mean follow-up since the treatment was implemented was 21.9 [6–56] months.

Overall, eTNS was well tolerated. No serious adverse events or deaths occurred and no patient discontinued treatment due to side effects. One subject reported mild transient headache at the beginning of the treatment and another subject reported mild skin irritation (11%). Four patients reported improvement in time of sleep, better mood, and more energy.

The responder rates were 35% at 6 and 12 months, 23% at 24 months, 19% at 36 months, and 14% at 48 months. At the same evaluation periods retention rates were 88% (15/17), 53% (9/17), 41% (7/17), 37.5% (6/16) and 28.5% (4/14) (Fig. 1).

Patient number 2 subsequently underwent VNS after showing a good response to eTNSs, with good results for the moment.

At the end of the follow-up, 6 patients were still under eTNS therapy, 4 of them after more than 4 years of treatment. No clinical characteristics of these 4 patients could predict response.

4. Discussion

This study reports real-world safety and efficacy outcomes from a series of patients with long lasting and very DRE treated with eTNS for up to four years. The responder rates of our series are very similar to those reported by De Giorgio et al in the first year (30.6% vs 28% in our series), providing information for longer periods that show higher retention rates than responder rates in each measured period.

Both retention and responder rates drop with time of follow-up, as occurs with most AEDs in DRE patients, but are still comparable to most AEDs. Focussing in retention rate, as it is known to be a parameter that adequately reflects the effectiveness of a treatment, since both efficacy and tolerability have an impact on the probability of remaining on a therapy, we believe the retention rates here reported are competitive for a new non-invasive treatment.

Retention rates at 3 years of very well known AEDs such as lamotrigine and topiramate are 29% and 30% respectively, as reported by Lhatoo et al. [6], lower than those of eTNS in the same period evaluation (37.5%). Regarding real life studies on the latest AEDs, we have information of 6–12 months only. Our retention rate at 6 months (88%) was much higher than the 50% retention rate of Brivaracetam [7,8]. The 53% retention rate at one year was in the range of that of Perampanel (44–89% [9] and 60% [10]) and slightly lower than that of eslicarbazepine acetate (72% [11,12]).

In patients with DRE there is a higher risk of neurotoxicity with polytherapy, resistance to newer AEDs and/or interaction with other drugs. With similar retention rates, eTNS had less side effects, most of them transient and mild, and no interaction at all with other treatments.

Quality of life, depression, or sleep scales were not specifically assessed in this study, but 24% of the patients reported improvement in time of sleep, better mood, and more energy. This could explain why at least two patients continued with the therapy although their seizure frequency didn't decrease more than 50%, as we can deduce for the higher retention than responder rate in every period

5. Conclusion

We conclude that eTNS is a new, non-invasive, very safe and well tolerated treatment that can reduce seizure frequency in a number of patients, with improvement of quality of life in some of them. This therapy can be initiated in a few minutes, does not require surgery, is easy to use, and can be stopped immediately if not effective, being an additional option for the treatment of DRE.

In patients with a good response to eTNS an implantable device (under development) could be placed subcutaneously. However, larger controlled studies are required in order to establish the place of eTNS in the treatment of epilepsy.

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Ethical publication statement

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.

Disclosures

Laura Olivié has received honoraria for activities organized by Esteve, Beatriz G. Giráldez has received honoraria for activities organized by UCB, Esteve and Eisai Inc., José M Serratosa has received honoraria from UCB, Esteve, GW Pharma, Sanofi, Eisai Inc., Bial for participation in advisory boards or pharmaceutical industry sponsored symposia.

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