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# External trigeminal nerve stimulation for drug resistant epilepsy: A randomized controlled trial

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ABSTRACT

*Background:* External trigeminal nerve stimulation (ETNS) is an emergent, non-invasive neurostimulation therapy delivered bilaterally with adhesive skin electrodes. In previous studies, ETNS was associated to a decrease in seizure frequency in patients with focal drug-resistant epilepsy (DRE).
*Objective:* To determine the long-term efficacy and tolerability of ETNS in patients with focal DRE. Moreover, to explore whether its efficacy depends on the epileptogenic zone (frontal or temporal), and its impact on mood, cognitive function, quality of life, and trigeminal nerve excitability.
*Methods:* Forty consecutive patients with frontal or temporal DRE, unsuitable for surgery, were randomized to ETNS or usual medical treatment. Participants were evaluated at 3, 6 and 12 months for efficacy, side effects, mood scales, neuropsychological tests and trigeminal nerve excitability.
*Results:* Subjects had a median of 15 seizures per month and had tried a median of 12.5 antiepileptic drugs. At 12 months, percentage of responders was 50% in ETNS group and 0% in control group. Seizure frequency in ETNS group decreased by −43.5% from baseline. Temporal epilepsy subgroup responded better than frontal epilepsy subgroup (55.56% vs. 45.45%, respectively). Median stimulation intensity was 6.2 mA. ETNS improved quality of life, but not anxiety or depression. Long-term ETNS affected neither neuropsychological function, nor trigeminal nerve excitability. No relevant adverse events were observed.
*Conclusions:* ETNS is an effective and well-tolerated therapy for focal DRE. Patients with temporal epilepsy showed a better response than those with frontal epilepsy. Future studies with larger populations may define its role compared to other neurostimulation techniques.
*Classification of evidence:* This study provides Class II evidence that ETNS reduces seizure frequency in patients with focal DRE.


*Abbreviations:* AED(s), antiepileptic drug(s); BDI, Beck Depression Inventory; CMH, Cochran-Mantel-Haenszel; DBS, deep brain stimulation; DRE, drug resistant epilepsy; ETNS, external trigeminal nerve stimulation; HADS, Hospital Anxiety and Depression Scale; HCB, Hospital Clínic de Barcelona; ITT, intention to treat; mA, mili-Amperes; MMRM, Mixed Models for Repeated Measures; PP, per protocol; RCT, randomized controlled trial; TEAEs, treatment-emergent adverse events; VNS, vagus nerve stimulation.

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## Introduction

Drug resistant epilepsy (DRE) affects about 30% of patients with epilepsy and is associated with multiple complications, including increased mortality, psychiatric pathology, and social, work and stigma problems [1]. For this reason, therapies that can be offered to patients on antiepileptic drugs (AEDs) with incomplete seizure control and who cannot benefit from surgical treatment are needed. Neurostimulation is a very promising option for these patients. Some therapies, like vagus nerve stimulation (VNS) and deep brain stimulation (DBS), are expensive and considered palliative, with a response rate around 50% [2]. VNS is also approved for the treatment of depression and has been shown to improve mood and level of alertness in epileptic patients [3]. As a disadvantage, they are invasive (especially DBS) and not completely reversible, since in case of non-functioning there are parts of the implanted system that cannot be removed (VNS).

The stimulation of trigeminal nerve is an emerging non-invasive neurostimulation therapy that can be performed externally with adhesive skin electrodes, bilaterally and at low cost. It is approved for use in Europe, Canada, and Australia and is investigational in the United States. The trigeminal nerve has connections to the brainstem and other brain structures that have an important role in the inhibition of seizures, like the nucleus of the solitary tract, the locus coeruleus and the reticular formation [4-6]. Animal studies indicate that the stimulation of the trigeminal nerve and its related structures inhibits seizures [7].

In pilot studies and in a controlled study, external trigeminal nerve stimulation (ETNS) decreased seizure frequency in patients with DRE and improved the score on depression scales. A phase I trial in 13 subjects showed a 42% of responders at 6 and 12 months. In a phase II randomized controlled trial (RCT) in 50 subjects with DRE, ETNS improved the within-group responder rate to 40.5% at 18 weeks of treatment ($p = 0.01$); however, the between-groups difference did not achieve significance (40.5% for treatment group vs. 15.6% for control group, $p = 0.078$). This result was attributed to the relatively small sample size, the numerically different seizure frequencies between treatment groups, the number of seizures required for inclusion ($\geq 2$) and the active control settings (2 Hz). The stimulation was well tolerated. Side effects were mild and included anxiety (4%), headache (4%) and skin irritation (14%) [8–10]. In the prospective open-label study, subjects were offered a long-term follow-up for one year. Those originally randomized to control settings were crossed over to effective device parameters (30 s on, 30 s off, pulse duration of 250 μs, frequency of 120 Hz). Thirty-five of 50 subjects continued in the long-term study. For the original treatment group, the median seizure frequency decreased by −3.03 seizures per month (−34.8%) at 12 months ($p < 0.05$). The 50% responder rates at 12 months were 36.8% for the treatment group and 30.6% for all subjects combined [11].

Other research groups have not yet replicated these results. Trigeminal nerve stimulation is still not integrated in routine clinical practice, unlike VNS. So far, ETNS is not reimbursed. Moreover, it is not known if some specific types of epilepsy could benefit more from this therapy.

Therefore, the aim of our study was to determine the efficacy and tolerability of long-term ETNS in a group of patients with focal DRE not eligible for epilepsy surgery, to know whether ETNS has a different efficacy profile depending on the epileptogenic zone (frontal or temporal), and to find out the impact of this therapy on mood, cognitive function, quality of life and trigeminal nerve excitability.

## Material and methods

This was an unblinded RCT, including subjects aged ≥18 years with focal DRE, clinical history and EEG compatible with frontal or temporal epilepsy, seizure frequency of ≥6 seizures per month (focal impaired awareness seizures or focal to generalized), treated with at least one AED, and without any changes in their AED regimen during 30 days prior to entering the study. Exclusion criteria were cognitive or psychiatric disorders that prevent patients from following adequately the ETNS protocol and the corresponding visits, epilepsy secondary to a progressive or degenerative neurological disease, concomitant non-epileptic seizures, history of facial pain or trigeminal neuralgia, concomitant VNS, and pregnancy.

Patients seen consecutively at the outpatient epilepsy clinical that fulfilled eligibility criteria were proposed to participate in the study. They were randomized to receive either ETNS in addition to their usual medical treatment (treatment group) or just their usual medical treatment (control group), prescribed by their epileptologist. Changes in AEDs were not allowed.

Patients and caregivers were asked to complete seizure diaries. Compliance with antiepileptic treatment was ascertained following routine clinical practice: asking directly to patients and determining serum drug levels when considered appropriate by the treating epileptologist, but no pill counts were carried out. Similarly, patients and caregivers were required to report the days they had missed ETNS treatment.

Trigeminal nerve stimulation: an external pulse generator was used to deliver ETNS. Treatment device settings were intensity <10 mA, frequency 120 Hz, pulse duration 250 μs, and duty cycle 30 s on and 30 s off. A bipolar transcutaneous gel-based electrode was used, designed to contact the right and left branches of the ophthalmic and supratrochlear nerves to provide bilateral stimulation. Subjects were trained to use the device, including education on electrode placement and review of precautions and warnings. They were asked to use the stimulation for at least 8 h a day. Subjects were evaluated at 3, 6 and 12 months.

The ethics committee of Hospital Clínic de Barcelona (HCB) approved the study. Written informed consent was obtained from all participants.

## Objectives

Primary objective was to determine the percentage of responders to ETNS (patients achieving ≥50% reduction in seizure frequency) at 6 and 12 months.

Secondary objectives were to determine:

- the percentage of seizure reduction with the use of ETNS at 6 and 12 months
- if ETNS has a different efficacy profile depending on the epileptogenic zone (frontal or temporal)
- the tolerability of ETNS at 6 and 12 months
- whether ETNS is associated with changes in mood, measured by Hospital Anxiety and Depression Scale (HADS) and Beck Depression Inventory (BDI) at 6 and 12 months; quality of life, measured by QOLIE-31 scale, at 6 and 12 months; and cognitive function, assessed by changes in the neuropsychological test at 12 months compared to baseline. Neuropsychological evaluation included logical memory, visual memory, Rey auditory learning verbal test, trail making test, digit symbol, Boston naming test, block design and digit span (Table e–4).
- whether ETNS is associated with changes in trigeminal nerve excitability. In a subgroup of 10 patients undergoing ETNS, the

effect of repetitive stimulation on the excitability of trigeminal reflex circuits was evaluated using the blink reflex test. Single stimuli were applied at the supraorbital nerve, and reflex responses of the orbicularis oculi were recorded on both sides. A paired stimulation with a conditioning stimulus followed by a test stimulus at intervals of 250, 500 and 750 ms was done in order to measure the recovery curve of the excitability of the blink reflex. These examinations were performed at baseline and at 12 months. The excitability of the blink reflex was measured by calculating the area of response R2 to the test stimulus as a percentage of the response obtained by application of the conditioning stimulus in the three described intervals.

## Statistical analyses

Data collection notebooks were monitored by Clinical Trials Unit at HCB and were entered into a database by remote access (MACRO system of Infermed Limited) managed by the Medical Statistical Core Facility IDIBAPS-HCB. This system complies with the general good practice standards and the highest requirements for computer validation, with restricted user access, inconsistency detection filters and traceability of all information until the closure of the database.

The Medical Statistical Core Facility, a platform of research and clinical trials from the Spanish Clinical Research Network (SCReN), carried out the statistical analysis. All analyses were performed using SAS 9.4 Software (SAS institute, Cary, NC, USA) and the level of signification was established at two-sided 5%. The randomization list was generated from the PROC-PLAN module of SAS 9.4, in blocks (multiple size of 2), with a 1:1 probability of allocation to each group. The assignment was made loading directly the codes in the electronic database.

The main study population was intention-to-treat (ITT) population, defined as all randomized subjects with their initial treatment assignment. As a sensitivity analysis, per protocol (PP) population was defined as all randomized subjects who met the inclusion criteria, had a baseline efficacy measurement and at least one post-baseline efficacy measurement and did not present major violations of the protocol. The safety population was defined as all randomized subjects who received the study treatment.

The main and secondary efficacy analyses were performed using ITT population. The main analysis was also performed using PP population as a sensitivity analysis.

A specific handling of missing data (Imputed Data) was performed only for the variables number of responders and number of seizures: for the variable 'responders', a missing value was imputed at the worst case (non-responder), and for the variable 'number of seizures per month', a missing value was assumed as the Baseline Observation Carried Forward −seizure frequency at baseline-. The rest of analyses were performed using Available Data Only, all data available in database with or without missing values.

Categorical variables were summarized by counts and proportions, and continuous variables by mean (standard deviation) or median (interquartile range) as appropriate. The primary efficacy endpoint was the percentage of responders at 12 months, which was analysed by means of proportions and 95% confidence interval using exact methods based on binomial, Clopper-Pearson method and treatments comparisons using the Fisher exact test by time point (3, 6 and 12 months).

To test if ETNS has a different efficacy profile depending on the epileptogenic zone, a Cochran-Mantel-Haenszel test was performed.

Continuous variables were conducted by means of Mixed Models for Repeated Measures (MMRM) including the group, treatment and the baseline measurement for longitudinal continuous variables.

Number of seizures was analysed by means of non-parametric approaches: the median (95% CI) and median differences (95%CI) using the Hodges-Lehmann estimates were compared by means of the Mann-Whitney test by visit.

Time to response (at 50%) was analysed by survival function and the median [95% CI] by means of Kaplan-Meier method, and treatment effects were compared using the log-rank test. Hazard Ratios (95%CI) were taken from the Cox model.

For the rest of the variables: Fisher's exact test to compare categorical variables between-groups; for continuous or ordinal variables a non-parametrical Mann-Whitney *U* test was conducted.

The safety analyses were performed using the Safety population. Inferential tests were performed for the comparison between treatments of the number (%) of patients reporting one or more treatment-emergent adverse events (TEAEs) by means of the Fisher's exact test.

Analyses were adjusted by baseline. All statistical tests were applied with a 0.05 two-sided significance level.

## Results

Forty consecutive patients were included in the study, twenty of which were randomly assigned to ETNS group, whereas the other twenty were assigned to control group. All subjects (40) were included in ITT population, whereas 32 subjects (82.5%) were included in PP population: 17 patients in the ETNS group and 15 patients in the control group were analysed for the primary outcome (Fig. 1).

Eligible participants were recruited from July 2015 to July 2017. They attended clinic visits at 3, 6 and 12 months. The rate at which participants were recruited was 1.7 per month. The follow-up period finished in July 2018, when patient number 40 reached the 12-month follow-up and the trial ended.

BASELINE CHARACTERISTICS: Baseline characteristics are represented in Table 1.

### *Stimulation parameters*

In the ETNS group, patients received instructions to increase the stimulation intensity across the different visits until they reached the maximum tolerated intensity. The goals were 3–5 mA at 3 months, 5–7 mA at 6 months, and 7–10 mA at 12 months, unless it was not tolerated.

Median [IQR] stimulation intensity was 5.00 mA [4.00; 5.20] at 3 months, 5.10 mA [5.00; 6.40] at 6 months, and 6.20 mA [5.00; 7.00] at 12 months. Median daily time of use of ETNS was 9 h [8–11]. All patients used ETNS during night sleep hours, except one who used it during the day.

All patients reported good adherence to ETNS, and none reported more than one day of missed stimulation.

### *Primary outcome*

Percentage of responders at 6 and 12 months was higher in ETNS group, either in ITT population (50% vs. 0%, $p = 0.0004$) or PP population (58.82% vs. 0%, $p = 0.0003$). Results are summarized in Table 2.

### *Analysis of responders by epileptogenic zone*

Given that Cochran-Mantel-Haenszel (CMH) test gave statistically significant p-value (0.0004), there was an association between treatment, number of responders and type of epilepsy.

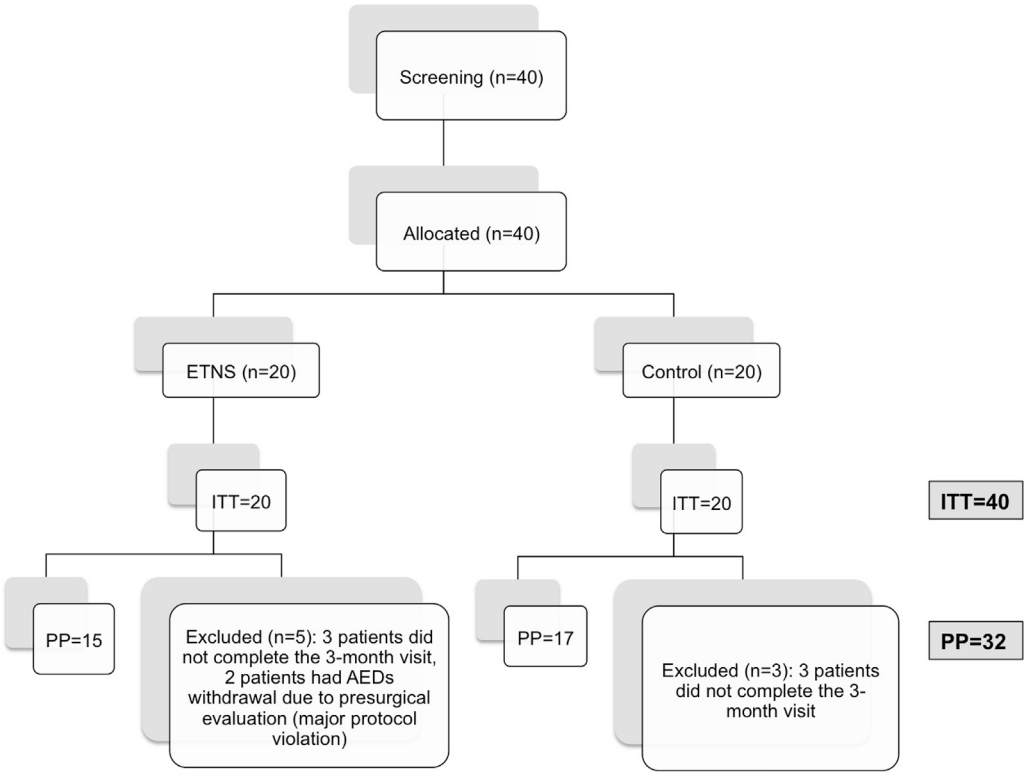


**Fig. 1.** Flow diagram.

Therefore, the same analyses were done at 12 months separately by epileptogenic zone (secondary outcome). These analyses showed statistically significant differences between treatment groups (ETNS and control) only in the temporal epilepsy subgroup. In the frontal epilepsy subgroup, these differences were not statistically significant (Table 3).

*Secondary outcomes*

*Number of seizures and percentage of seizure reduction*

For each subject, we calculated the relative difference of the number of seizures per month [(final-baseline)/baseline*100] and the median. The median of the relative difference of the number of seizures per month for the ETNS group decreased by −41.79% at 6 months and −43.50% at 12 months respectively, from the initial baseline ($p < 0.05$). Median relative differences compared to control group were 27.27% at 6 months ($p = 0.0203$) and 32% at 12 months ($p = 0.0013$) (Table 4).

*Number of seizures by epileptogenic zone.* Again, CMH test gave a statistically significant p-value (0.0008), so the same analyses were done at 12 months separately by epileptogenic zone, showing statistically significant differences between treatment groups (ETNS and control) only in the temporal epilepsy subgroup (Table 5).

**Table 1**
Demographic and baseline characteristics. ITT population.

| Demographics | Total (n = 40) | ETNS (n = 20) | Control (n = 20) |
|---|---|---|---|
| Mean age (SD), years | 40.65 (12.24) | 44.20 (10.95) | 37.10 (12.68) |
| Female, n (%) | 24 (60%) | 13 (65%) | 11 (55%) |
| Male, n (%) | 16 (40%) | 7 (35%) | 9 (45%) |
| Epilepsy-specific medical history | | | |
| Age of seizure onset | 16.02 (13.03) | 15.90 (15.31) | 16.15 (10.67) |
| Median duration of epilepsy, years (IQR) | 24.62 (13.45) | 28.30 (14.16) | 20.95 (11.94) |
| Seizure type, n (%) | | | |
| Focal aware and focal impaired awareness seizures | 6 (15%) | 4 (20%) | 2 (10%) |
| Focal impaired awareness seizures only | 16 (40%) | 7 (35%) | 9 (45%) |
| Focal impaired awareness to bilateral tonic-clonic seizures | 18 (45%) | 9 (45%) | 9 (45%) |
| Type of epilepsy | | | |
| Frontal epilepsy, n (%) | 17 (42.5%) | 11 (55%) | 6 (30%) |
| Temporal epilepsy, n (%) | 23 (57.5%) | 9 (45%) | 14 (70%) |
| Baseline monthly seizure frequency, median (IQR) | 15 (9–25) | 20 (8.5–25) | 13 (9–24.5) |
| Previous AEDs, median (IQR) | 12.5 (9–16) | 13.5 (11–16.5) | 12 (7.5–15) |
| Concomitant AEDs, median (IQR) | 3 (2.5–4) | 3 (2–4) | 3 (3–4) |
| Pathological brain MRI, n (%) | 32 (80%) | 13 (65%) | 19 (95%) |

**Table 2**
Number of responders. Proportion difference.

| Variable | Category | Control (N = 20) n (%)95%CI | ETNS (N = 20) n (%)95%CI | Control vs. ETNS Proportion difference [95%CI] p-value[a] |
|---|---|---|---|---|
| ITT population | | | | |
| Responders at 3 months Control n = 20; ETNS n = 20 | Yes | 2 (10.0%) [1.23; 31.70] | 8 (40.0%) [19.12; 63.95] | −30.0 [-58.74; 3.37] 0.0648 |
| Responders at 6 months Control n = 20; ETNS n = 20 | Yes | 0 (0.0%) [NE; NE] | 10 (50.0%) [27.20; 72.80] | −50.0 [-74.62; −17.61] **0.0004** |
| Responders at 12 months Control n = 20; ETNS n = 20 | Yes | 0 (0.0%) [NE; NE] | 10 (50.0%) [27.20; 72.80] | −50.0 [-74.62; −17.61] **0.0004** |
| PP population | | | | |
| Responders at 3 months Control n = 15; ETNS n = 17 | Yes | 2 (13.33%) [1.66; 40.46] | 8 (47.06%) [22.98; 72.19] | −33.73 [-63.16; 0.57] 0.0605 |
| Responders at 6 months Control n = 15; ETNS n = 17 | Yes | 0 (0.0%) [NE; NE] | 10 (58.82%) [32.92; 81.56] | −58.82 [-81.77; −26.59] **0.0003** |
| Responders at 12 months Control n = 15; ETNS n = 17 | Yes | 0 (0.0%) [NE; NE] | 10 (58.82%) [32.92; 81.56] | −58.82 [-81.77; −26.59] **0.0003** |

[a] Fisher exact test.

*Survival analysis for time to response*

Survival analysis for time to response between control and ETNS groups is shown in Fig. 2. The median of response in ETNS group is at 6 months, whereas in the control group the median cannot be estimated, since less than half of the patients responded: there were only 2 patients in the control group who were responders at 3 months, but not at 6 and 12 months.

In the ETNS group, the probability of being a responder is 6.816 times higher: OR (95% CI) 6.816 (1.52; 30.55), log rank test p = 0.0012.

*Mood scales*

There were no statistically significant differences between groups (ETNS and control) at any visit in BDI scores (p = 0.089, Table e−1).

There were no statistically significant differences between groups at any visit in HADS scores (p = 0.353, Table e−2), neither in its anxiety and depression subscales.

*Quality of life (QOLIE-31) scale*

There were statistically significant differences between groups (p = 0.024). Patients who received ETNS had better quality of life at 6 and 12 months (Table e−3). Comparing ETNS vs. control, QOLIE-31 scores were 8.37 points higher at 6 months (p = 0.045) and 14.02 points higher at 12 months (p = 0.008).

*Neuropsychological test*

There were no statistically significant differences between ETNS and control groups in any neuropsychological subtests at 12 months (Table e−4).

*Trigeminal nerve excitability: blink reflex*

Blink reflex was studied in 9 patients in the ETNS group in order to observe changes in trigeminal nerve excitability. The objective of 10 patients could not be reached because one of them did not complete the 12-month follow-up. No statistically significant changes were observed in neurophysiological parameters (p-

**Table 3**
Number of responders. Proportion difference by epileptogenic zone.

| Variable | Type of epilepsy | Category | Control (N = 20) n (%) 95%CI | ETNS (N = 20) n (%) 95%CI | Control vs. ETNS Proportion difference [95%CI] p-value[a] |
|---|---|---|---|---|---|
| **ITT population** (CMH p-value 0.0004) | | | | | |
| Responders at 12 months Control n = 20; ETNS n = 20 | Frontal | Yes | 0 (0.0%) [NE; NE] | 5 (45.45%) [16.75; 76.62] | −45.45 [-80.37; 6.75] 0.1023 |
| | Temporal | Yes | 0 (0.0%) [NE; NE] | 5 (55.56%) [21.20; 86.30] | −55.56 [-86.30; −13.72] **0.0037** |
| **PP population** (CMH p-value 0.0006) | | | | | |
| Responders at 12 months Control n = 15; ETNS n = 17 | Frontal | Yes | 0 (0.0%) [NE; NE] | 5 (62.50%) [24.49; 91.48] | −62.50 [-94.73; −4.74] 0.0754 |
| | Temporal | Yes | 0 (0.0%) [NE; NE] | 5 (55.56%) [21.20; 86.30] | −55.56 [-86.30;-8.58] **0.0108** |

[a] Fisher exact test.

**Table 4**
Number of seizures and percentage of seizure reduction. Median and median differences.

| Number of seizures per month | Control (N = 20) [Median 95% CI] | ETNS (N = 20) [Median 95% CI] | Median difference (N = 40) [Median 95% CI] | p-value[a] |
|---|---|---|---|---|
| ITT population | | | | |
| Median reduction, 3 months Control n = 20; ETNS n = 20 | 0.00% [-26.67; 0.00] | −16.23% [-66.67; 0.00] | 14.29% [0.00; 39.29] | **0.0272** |
| Median reduction, 6 months Control n = 20; ETNS n = 20 | 0.00% [0.00, 0.00] | −41.79% [-57.14, 0.00] | 27.27% [0.00, 57.14] | **0.0203** |
| Median reduction, 12 months Control n = 20; ETNS n = 20 | 0.00% [-20.00, 0.00] | −43.50% [-66.67, −10.00] | 32.00% [11.11; 60.26] | **0.0013** |

[a] Mann-Whitney test.

**Table 5**
Number of seizures and percentage of seizure reduction. Median and median differences by epileptogenic zone. ITT population.

| Type of epilepsy | Subjects (n) | | Observed values Median (95%IC) | | Treatment differences Median (95%CI) | p-value[a] |
|---|---|---|---|---|---|---|
| | Control | ETNS | Control | ETNS | | |
| Number of seizures per month at 12 months | | | | | | |
| Frontal | 6 | 11 | 18.50 (10.00; 22.00) | 18.00 (4.00; 25.00) | 0.00 (−64.00; 16.00) | 1.0000 |
| Temporal | 14 | 9 | 12.00 (8.00; 26.00) | 4.00 (2.00; 17.00) | −7.00 (−16.00;-2.00) | **0.0380** |

[a] Mann-Whitney test.

values > 0.05) in the blink reflex test suggesting an increase in trigeminal nerve excitability (Table e−5). We noticed that higher intensities were required to obtain adequate responses and appropriate R1, R2 and R2c curves. This was observed both in baseline and 12-month tests.

*Adverse events*

Sixteen of 40 patients (40%) had at least one treatment-emergent adverse event (TEAE). The rate of TEAEs was higher in the ETNS group (55% vs 25%). There was a total of 18 TEAEs reported. Regarding severity, 10/18 (55.6%) TEAEs were mild and 8/18 (44.4%), moderate. None was considered a serious adverse event.

In the ETNS group, TEAEs occurred in 11 of 20 patients (55%). Forehead skin irritation was observed in 3 patients (15%), headache in 4 (20%) and anxiety in 2 (10%). These effects resolved spontaneously during follow-up or decreasing time or intensity of stimulation. Some patients managed skin irritation with moisturizing cream, and headache with acetaminophen or ibuprofen. One patient experienced a change in seizure pattern at 9 months, from nocturnal to diurnal so she stopped using the stimulator. Nevertheless, the seizure pattern continued being diurnal despite having interrupted the stimulation. Another patient referred tiredness and also numbness of the upper extremities after one month that he attributed to stimulation, so he interrupted it.

In the control group, TEAEs occurred in 5 of 20 patients (25%). Two patients had an acute non-Q wave myocardial infarction during follow-up that required hospitalization. Other three patients experienced TEAEs related to their antiepileptic treatment: somnolence, blurred vision and dizziness. These events were not related to the study.

*Completion of the study*

In ITT population, 29 of 40 subjects (72.5%) completed the study according to the protocol. In PP population, 29 of 32 subjects (90.6%) completed the study according to the protocol. Causes for not completing the study were: major protocol violation (2 patients), lost to follow up (3), interruption of stimulation (4) and personal decision to abandon the study (2). A detailed description of patients lost to follow up per group is provided in Fig. 3.

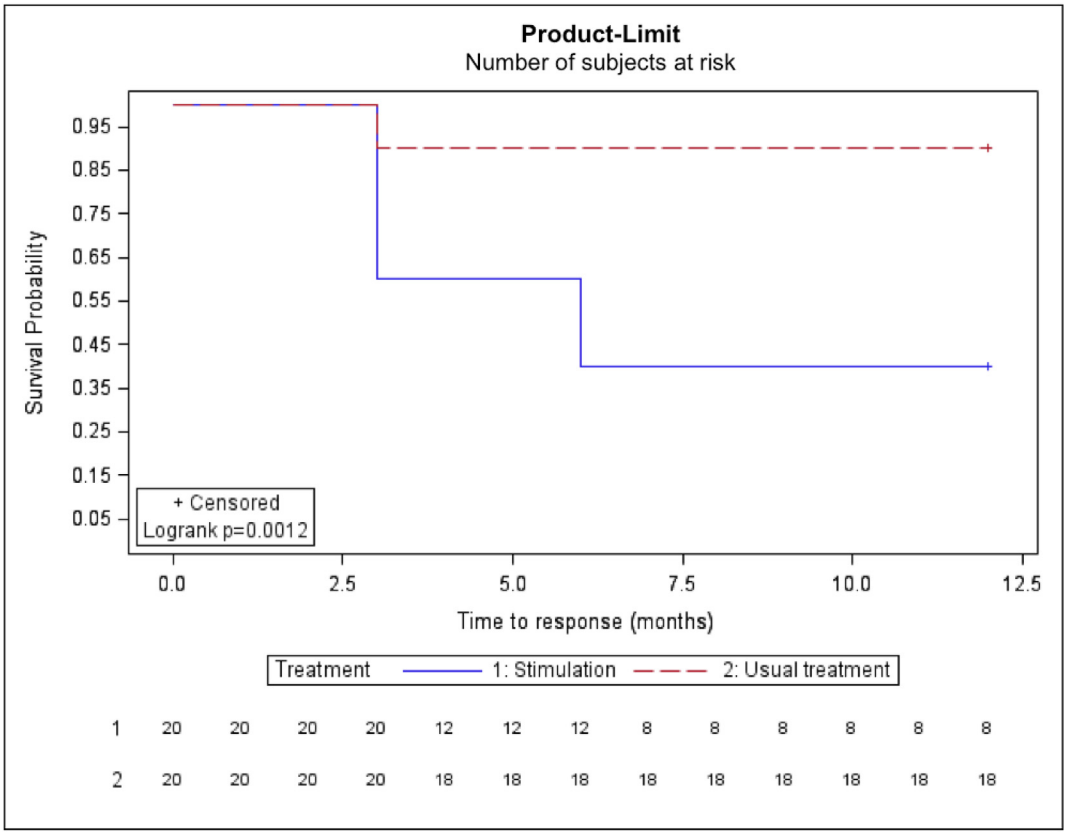


**Fig. 2.** Time to response. Survival analysis using log-rank test.

## Discussion

In the present study, ETNS was effective for the treatment of focal DRE. The percentage of responders was 50% at 6 and 12 months in ITT population (58.82% in PP population). The percentage of seizure reduction in ETNS group was 41.79% at 6 months and 43.50% at 12 months, with median relative differences compared to control group of 27.27% at 6 months and 32% at 12 months. These results were statistically significant. Considering the epileptogenic zone, both analyses (percentage of responders and percentage of seizure reduction) showed statistically significant differences between treatment groups (ETNS and control) at 12 months only in the temporal epilepsy subgroup, meaning that patients with temporal epilepsy are more likely to respond to ETNS than patients with frontal epilepsy.

The subjects used the device a minimum of 8 h per day. This was a shorter daily exposure than DeGiorgio's group in the first RCT of ETNS in DRE [8] (at least 12 h per day). Our study was longer in duration (12 months vs 18 weeks), so we needed a protocol that was patient friendly and improved long-term compliance. For this reason, we suggested the use of ETNS during night sleep hours, usually less than 12 h per day, and set the minimum stimulation time to 8 h. In fact, once the study began, most patients refused to wear the ETNS during the day, because they did not want the device to interfere with their routine. All patients except one used the device during night sleep hours. Median daily time of use of ETNS was 9 h (IQR 8–11). Yet, our study found differences with a much shorter daily exposure. This suggests that the exposure (dose) – response curve may reach a plateau, although the minimum effective number of hours per day of ETNS is still unknown and should be clarified in future studies. Moreover, the long-term use of the device might be more relevant to the efficacy than the total daily exposure, as seen with other neurostimulation techniques like VNS.

ETNS improved quality of life, as measured by QOLIE-31 scale scores (Table e–3), but no effects on mood, as measured by HADS and BDI scores, were detected (Tables e–1 and e–2), although a sample size effect cannot be ruled out. Improvement in quality of life is possibly related to seizure reduction. The same applies to neuropsychological scores. Again, we were not able to detect relevant changes after 12 months of stimulation.

Finally, we could not demonstrate an increase of trigeminal nerve excitability related to long-term stimulation. The intake of multiple AEDs possibly interfered with trigeminal nerve excitability, because higher intensities were required to obtain adequate responses and appropriate R1, R2 and R2c curves in both baseline and 12-month blink reflex tests.

ETNS was well tolerated: 16 patients (40%) had at least one adverse event, whose intensity was considered mild in 55.6% and moderate in 44.4%. Most frequent TEAEs were skin irritation (15%), headache (20%) and anxiety (10%). There was a theoretical concern about modifying the properties of the trigeminal nerve as a consequence of the chronic stimulation. In fact, one of our exclusion criteria was a history of facial pain or trigeminal neuralgia. Nevertheless, we did not observe any changes in neurophysiologic parameters of the trigeminal nerve after long-term stimulation.

### *Generalisability*

Patients in our study had a high seizure frequency (median 15, IQR 9–25). They had tried a median of 12.5 AEDs and were taking a median of 3 concomitant AEDs. All of them had been referred to the

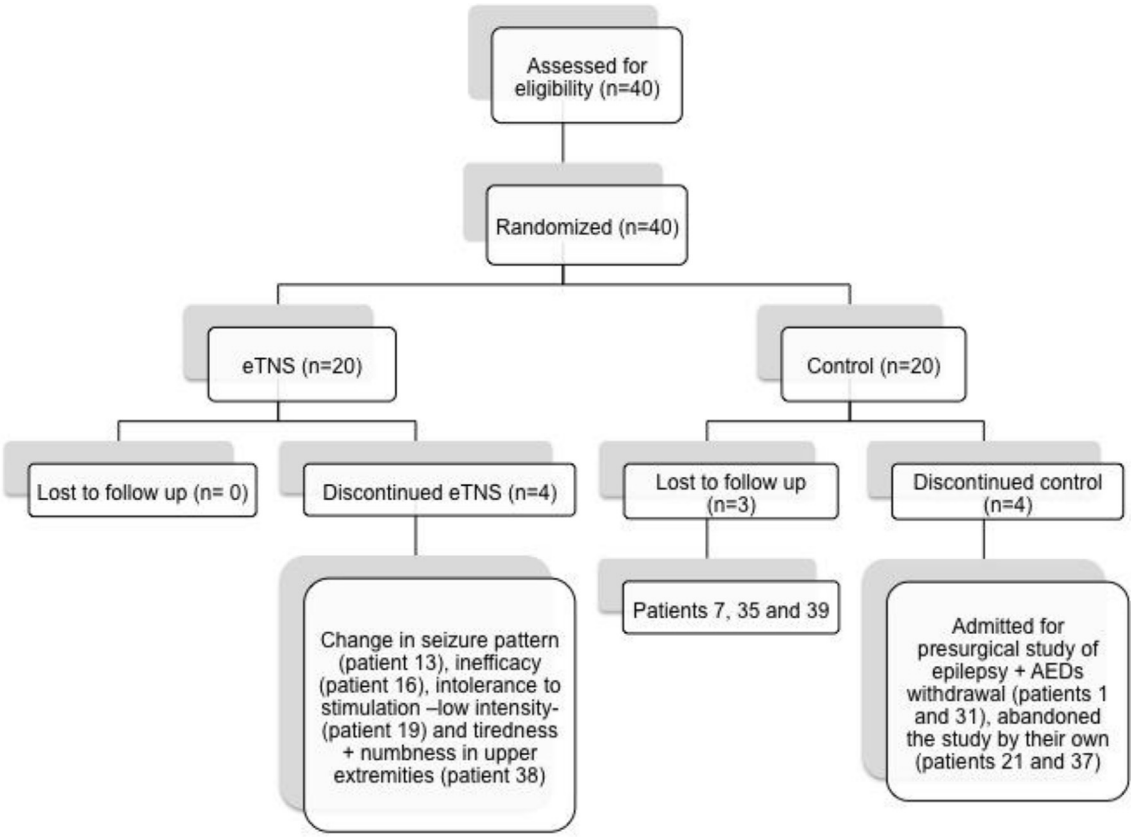


**Fig. 3.** Completion of the study.

epilepsy unit for presurgical evaluation and were not considered suitable for epilepsy surgery. Thus, our results can only be generalized to patients with focal DRE, but the fact that ETNS has proved being effective in such severe epilepsies suggests that it could be used also in less drug resistant patients. Future studies should explore the effect of ETNS in other less common types of focal epilepsy (parietal, occipital and insular) or even in generalized epilepsy.

Compared to previous studies [11], we found a higher percentage of responders at 12 months (50% vs. 36.8%). Our sample size, although small (40 patients), is similar to sample sizes used in previous studies [8,11], and in fact our population seems to be more drug resistant than the population in DeGiorgio's RCT [8]. For this reason, our 50% responder rate is clinically relevant in this very ill group of patients, especially given the fact that 0% of the control group responded.

We also analysed if the epileptogenic zone has an influence on the efficacy of ETNS, confirming that patients with temporal epilepsy seem to have a better response than patients with frontal epilepsy. Both types were equally represented in the ETNS group (11 frontal and 9 temporal), but not in the control group (6 frontal and 14 temporal), as shown in Table 1, because randomization was not stratified by type of epilepsy.

The mechanism of this better response to ETNS in temporal epilepsy remains unknown. In other modalities, such as DBS of the anterior nucleus of the thalamus, a better response is observed in bilateral temporal epilepsies (e. g. epilepsies of autoimmune origin), due to the participation of the anterior nucleus of the thalamus in the limbic circuit of Papez [12].

Nevertheless, the connections between trigeminal nuclei and the temporal lobes are not so evident. Trigeminal nuclei are connected with the thalamus, the nucleus of the solitary tract and the locus coeruleus.

In ETNS, we stimulate the supraorbital nerve bilaterally. The sensitive fibres of the ophthalmic branch of the trigeminal nerve have their end at the lower region of the spinal nucleus. The axons of these neurons cross the median plane and ascend as the trigeminal lemniscus to terminate in the ventral posteromedial nucleus of the thalamus. The axons of these cells now run through the internal capsule to the postcentral gyrus in the parietal lobe, and through the inferior thalamic radiation in the temporal lobe.

The most important nucleus connected with trigeminal nuclei is the locus coeruleus [13], located in front of the trigeminal accessory nucleus, in the pons triangle of the fourth ventricle floor. There are projections to both the dorsal and ventral hippocampus originated from the dorsal segment of the nucleus. This is probably the most evident connection with the temporal lobe.

In conclusion, the better response to ETNS in temporal lobe epilepsy has to be confirmed in future studies.

Our rate of adverse events is similar to previous studies [8], although we found a higher frequency of headache (20% vs. 4%) and anxiety (10% vs. 4%), without any other new concerns. Considering that one of our patients had a change in seizure pattern from nocturnal to diurnal, future research should clarify whether ETNS has the ability to modify seizure pattern, although clinical experience suggests that this effect may be seen either spontaneously or temporally related to the intake of a new antiepileptic drug.

Unlike previously published studies [8,14], we did not observe an improvement in mood associated to the use of ETNS. Nevertheless, there was a tendency to deterioration in the control group and improvement in the ETNS group (Table e−1), which is in line with the results observed in previous studies [8,14]. Contrarily, there was not a similar tendency in HADS scale scores.

In our study, BDI score at baseline (ETNS 14.5, control 11.6) was slightly inferior to that found in DeGiorgio's study [8] (ETNS 16.7, control 12.0) in both groups, but in our ETNS group the reduction seen in BDI score after ETNS treatment is less than DeGiorgio's (−3.39 vs. −8.13). Possibly we did not reach statistical significance because our patients were less depressed at baseline and their improvement was smaller. On the contrary, the patients in our control group experienced a worsening in BDI score (+6.11), whereas in DeGiorgio's control group, they experienced an amelioration (−3.95). This difference could be explained by the fact that in the study of DeGiorgio, the control group was an active control group. Hence, a positive effect of low-intensity stimulation (2 Hz) cannot be ruled out.

In the pilot study of Cook [14], evaluating the effect of ETNS in eleven adults with major depressive disorder after 8 weeks of treatment, symptoms of depression improved significantly, whether assessed with clinician- or self-rated scales ($p < 0.01$), including BDI, as did quality of life. Again, patients included in this study were more depressed at baseline (BDI 27.9) than ours.

No significant changes in neuropsychological function were observed after 12 months of stimulation. Again, the direction of change showed deterioration in the control group in the majority of measures, while the ETNS group showed improvement in the majority of measures, a pattern suggesting that sample size could have obscured the effects.

In studies performed in other conditions, ETNS has shown to improve attention. McGough et al. [15] randomized 62 children 8−12 years old with a diagnosis of attention-deficit/hyperactivity syndrome (ADHD), to 4 weeks of nightly treatment with active or sham ETNS, followed by 1 week without intervention. Assessments included weekly clinician-administered ADHD Rating Scales (ADHD-RS) and Clinical Global Impression (CGI) scales. A slightly more than half of those receiving therapy had clinically meaningful improvement in ADHD symptoms. In our study, the parameters included in the neuropsychological test (Table e−4) evaluated changes in different areas of cognition. Although some patients and their families had the clinical impression of an improvement of attention with ETNS, no significant differences were found in the subtests evaluating attention (e.g. digit span). This could be explained by the fact that epilepsy and ADHD are different pathologies and deserves further investigation in future studies.

Finally, an improvement in quality of life was observed in patients treated with ETNS (57.77 vs. 43.76 at 12 months) compared to control. Probably the improvement of quality of life is mainly related to the remarkable reduction in seizure frequency. It was not possible to evaluate whether the quality of life was dependent of the response due to the absence of responders at 12 months in the control group.

### *Limitations*

This is an open study. Double blind was not possible because the only ETNS device available on the market allows regulating the intensity but not the frequency of the stimulation. Therefore, we could not have a completely active control group. In the case of having an active control group, we would not know if a low-intensity stimulation is really ineffective. In a previous RCT [8], the authors could not rule out a positive effect of a presumably ineffective low-intensity stimulation (ETNS 2 Hz), which was used in the active control group. Thus, the lack of blinding could have inflated our results.

Despite having recruited 40 patients, which was considered to have enough statistical power, this is a small sample size if compared to other neurostimulation studies such as the ones performed with VNS or DBS of the anterior nucleus of the thalamus. Larger study populations are needed in future research.

Randomization was not stratified by type of epilepsy (frontal or temporal). Thus, both types were equally represented in the ETNS group, but not in the control group. The primary outcome was the percentage of responders, so in this analysis we explored the interaction between treatment and type of epilepsy, which is statistically significant, meaning that treatments (control vs. ETNS) have a different behaviour in the group of frontal epilepsy compared to temporal epilepsy. For this reason, the main variable was also analysed by type of epilepsy.

However, we believe our study provides interesting information due to the homogeneous patient population, the long-term follow-up and the concomitant neuropsychological and psychiatric tests performed. It may set the pathway for further studies in the future including larger patient populations.

## Conclusions

ETNS is an effective therapy for DRE, because it can considerably reduce seizure frequency and is not associated with serious side effects, in addition to being non-invasive and reversible. Future studies with larger populations may position ETNS in relation with other modalities of neurostimulation for epilepsy.

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## Declaration of competing interest

We used the Monarch ETNS system by NeuroSigma because it is the only external trigeminal nerve stimulation device available on the market.

Preliminary data from this study were previously presented at the Annual Meeting of the European Academy of Neurology in Amsterdam (2017) and also in the Annual Meeting of the Spanish Society of Epilepsy (SEEP) in Madrid (2017).

All authors report no disclosures.

## CRediT authorship contribution statement

**Francisco Gil-López:** Conceptualization, Validation, Formal analysis, Investigation, Resources, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Teresa Boget:** Methodology, Validation, Investigation, Writing - review & editing, Visualization, Supervision. **Isabel Manzanares:** Investigation, Resources, Writing - review & editing. **Antonio Donaire:** Investigation, Resources, Writing - review & editing, Supervision. **Estefanía Conde-Blanco:** Investigation, Resources, Writing - review & editing. **Eva Baillés:** Validation, Investigation, Writing - review & editing, Visualization, Supervision. **Luis Pintor:** Investigation, Writing - review & editing, Supervision. **Xavier Setoaín:** Writing - review & editing. **Núria Bargalló:** Writing - review & editing. **Judith Navarro:** Validation, Investigation, Writing - review & editing. **Jordi Casanova:** Validation, Investigation, Writing - review & editing, Supervision. **Josep Valls:** Methodology, Validation, Writing - review & editing, Visualization, Supervision. **Pedro Roldán:** Writing - review & editing. **Jordi Rumià:** Writing - review & editing. **Georgina Casanovas:** Software, Formal analysis, Writing - review & editing, Visualization, Supervision. **Gema Domenech:** Software, Formal analysis, Writing - review & editing, Visualization, Supervision. **Ferrán Torres:** Methodology, Software, Formal analysis, Writing - review & editing, Visualization. **Mar Carreño:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.06.005.

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