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Title: An audit of external trigeminal nerve stimulation (eTNS) in epilepsy

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Abstract

Purpose: External trigeminal nerve stimulation (eTNS) is a non-invasive neurostimulation treatment for drug refractory epilepsy. There is limited published data on the efficacy of eTNS and none relating to quality of life, mood or effect on sleep quality.

Methods: We audited its use in 42 patients with drug refractory epilepsy at a tertiary centre. Data was collected on seizure frequency, quality of life, mood and sleep quality before and after initiating treatment.

Results: 45% of patients continued to use eTNS at the end of the audit period. We observed a significant improvement in both quality of life and mood in those without intellectual disabilities. A decrease in seizures (-11.0%, min -60, max +65) was observed though this did not reach statistical significance with the relatively small numbers available for analysis.

Conclusion: Further controlled studies are required to confirm the efficacy of eTNS. However, as it is non-invasive, flexible and safe eTNS can be considered as an option in patients with drug refractory epilepsy.
Introduction

Neurostimulation for epilepsy includes both brain stimulation and extracranial stimulation of cranial nerves. Unilateral stimulation of the left vagus nerve is licensed as treatment for epilepsy and depression. Controlled studies showed short and long-term improvement in seizure control [1]. Although impact on seizure control, compared to resective surgery, is modest with low seizure freedom rates, a retrospective review based on Medicaid data in the United States of both adults and children showed significantly fewer hospitalizations and emergency department visits post-VNS with decreased resource use and cost savings [2]. VNS, however, is invasive, and although considered safe, is not without side-effects, limitations or complications [1]. Trigeminal nerve stimulation in an animal model showed bilateral stimulation to be more effective than unilateral [3]. Imaging showed BOLD (blood oxygen level-dependent) MRI activation in rat somatosensory cortex following trigeminal nerve stimulation [4]. The proposed mechanism by which cranial nerve stimulation reduces seizures is of a widespread effect on cortical arousal, perhaps mediated by the brainstem reticular-activating system [3]

Following an open study [5], non-invasive External Trigeminal Stimulation (eTNS), providing bilateral non-invasive electrical stimulation to the V1 branch, has shown some effect in a small randomised controlled trial of 50 patients with drug resistant focal epilepsy. Although the primary outcomes (median reduction in seizure frequency, time to 4th seizure and 50% or more reduction in seizure frequency during the 18 week trial period) were not statistically different between the treatment group and controls, after 18 weeks, 40.5% of the treatment group had a 50% or more reduction in seizure frequency compared to 15.6% in controls [6]. In a follow-up open-label long-term study, 35/50 subjects were followed up for one year providing evidence of experience with longer term treatment [7]. Small open studies also reported benefit in depression and posttraumatic stress disorder. ETNS use has also been explored in Attention Deficit Hyperactivity Disorder. In 2012, eTNS was approved in Europe as treatment for drug resistant epilepsy for those aged nine years and above and the Monarch device (NeuroSigma) gained a Class IIa CE (Conformité Européenne). This was followed in 2015 with approval for use in ADHD.

We audited eTNS use by patients with drug resistant epilepsy at a specialist centre.

Methods:

The audit was approved by the hospital’s New Clinical Procedures Committee. ETNS was offered to adult patients with drug-resistant epilepsy, previous multiple antiepileptic drugs (AEDs), concurrent AED use, patient or parent/carer able to understand and use the device and a patient likely to be co-operative with its use. We did not offer eTNS to pregnant patients or patients with non-epileptic seizures, other serious or progressive co-morbid medical or psychiatric illnesses, history of facial pain or trigeminal neuralgia, concurrent VNS or other neurostimulation.

A self-adhesive disposable electrode is placed on the forehead and attached via wires to the Monarch device (NeuroSigma, USA). The ophthalmic divisions of both trigeminal nerves are stimulated (120 Hz, for 7/30 seconds). Patients were provided with written and verbal information about the device then trained in its use. The current was set so that stimulation is noticeable but not uncomfortable (< 10 mA) aiming for a minimum of 8 hours’ use overnight.
The following assessments were performed at baseline, 4, 12 and 18 weeks: seizure diaries with a 12 week baseline where possible, record of use (time on/off, current setting, problems), quality of life (QOLIE-10P) [8], mood (Beck's Depression Inventory (BDI)) [9], sleep quality (Pittsburgh Sleep Scale) [10] and daytime somnolence (Epworth Score) [11]. For patients with intellectual disabilities (ID) unable to use self-reporting questionnaires, parents or carers completed the Epilepsy and Learning Disabilities Quality of Life Scale (ELDQOL) [12] which includes measures of seizure severity, side-effects, behaviour and mood.

Results:

The audit took place between 02/04/2013 and 14/08/2015, the last audited patient commencing eTNS on 03/08/2015. Table 1 outlines demographics, epilepsy classification and previous treatments. Mean current used, once established, was 4.1mA (min 2, max 8.6, SD 1.6, median 3.6). Mean hours of use per 24 hours were 9.2 (min 4, max 12, SD 1.8, median 9). Follow up data were analyzed at 18 weeks with the last observation carried forward. At the end of the audit period, 19 of 42 (45%) continued to use the device (mean duration 62 weeks, median 63 weeks, range 2-124 weeks) including 11 for more than 52 weeks. Twenty-three (55 %) stopped eTNS, eight in the first 15 weeks. Reasons included not liking the sensation (1), headache (3), skin redness at low current (1), a change in seizure pattern (from two absence clusters at either end of the day to absences spread over the day) as well as embarrassment at wearing the device (1) or no benefit discerned (2). Six additional patients discontinued at 18 weeks reporting no benefit. Eight of nine who discontinued use after 18 weeks (range 20-76 weeks) did so because of limited efficacy. The ninth who had used eTNS on three nights a week reported a change in seizure pattern from nocturnal to daytime on using eTNS daily. Three other patients, who continued use, reported side-effects: skin redness (1), slight rash when hot at the site of electrode placement (1) and headaches (1).

Seizure frequency:

In 12 insufficient baseline seizure frequency data were available. Two further cases had concurrent drug changes. Fourteen were thus excluded from analysis of seizure frequency. Ten of these chose to continue use beyond the audit period, only 6 of whom had reached 18 weeks of follow up. There were 28 with seizure frequency data and no drug changes shown in table 1. Mean percentage change in seizure frequency was -11.0% (minimum -60, maximum +65, SD 33.5, median -5.4). Four had 50% or more reduction in seizures (range 50-60%). Fifteen had less than 50% reduction in seizures. In nine an increase in seizures was recorded, largely within natural fluctuations observed. In two who discontinued use there was a reported change in pattern described above.

Quality of Life, Depression and Sleep Scales:

Data for QOLIE-10p, BDI, Pittsburgh Sleep Scale and Epworth score for patients without ID are shown in table 2, along with ELDQOL data for patients with ID. There were significant improvements in QOLIE-10P and BDI scores in these patients without ID, with no change in Pittsburgh Sleep Scale or Epworth score. There was no change in the ELDQOL for patients with ID.
Discussion

ETNS use was audited in adults with intractable epilepsy. At the end of the audit period, 19 of 42 (45%) were still using the device (mean duration 62 weeks, median 63 weeks, range 2-124 weeks) including 11 who continued for more than 52 weeks. Although 55% of patients stopped using the device, in those who continued the device was generally well tolerated and easy to use with reliable adhesive electrodes. Disconnections from the stimulator, an early model, could occur. Despite the need to apply this daily, reported adherence in those who chose to continue the device was generally good. A decrease in seizures was observed though this did not reach statistical significance with the relatively small numbers available for analysis.

There was a significant improvement in quality of life as measured using the QOLIE-10p scale, although not in the small number (12) of patients with ID measured with ELDQOL. We also observed a significant improvement in mood as measured by the BDI. This accords with the previous randomized controlled trial where an improvement in BDI was also observed [6]. However, as this is an open label audit without a control group and relatively high initial BDI scores (indicative of low initial mood), the possibility that some of this improvement could be attributable to regression towards the mean, rather than a treatment effect, needs to be considered.

Wearing the device at night did not result in significant changes in sleep quality or daytime sleepiness. This has not been shown before in previous studies of eTNS [5,6,7]

The advantage of eTNS is that it is not invasive which allows for flexibility of use compared to more invasive stimulation such as VNS. Despite the need for nightly application, patients with perceived benefit continued to use the device for prolonged periods. No cost assessment was carried out in this audit. The disposable electrodes are comparable in price to third generation antiepileptic drugs.

In our experience, eTNS is a flexible additional option in the treatment of difficult to control epilepsy. However, larger controlled studies are required to establish the place of eTNS in the treatment of epilepsy.
Table 1: Demographics and Epilepsy History

<table>
<thead>
<tr>
<th>Total:</th>
<th>42 patients, male 18 (43%), female: 24 (57%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age:</td>
<td>Mean 37 years (range 20-68, standard Deviation (SD) 12, median 36)</td>
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<tr>
<td></td>
<td><strong>Epilepsy age of onset in 40 patients (2 unknown):</strong></td>
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<tr>
<td></td>
<td>Mean 12 years (range 0-42, SD 11, median 9)</td>
</tr>
<tr>
<td></td>
<td><strong>Classification of the Epilepsy:</strong></td>
</tr>
<tr>
<td></td>
<td>Focal: 26 (temporal 14, frontal 6, occipital 1, unclassified 5)</td>
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<tr>
<td></td>
<td>Generalised: 15 (idiopathic/genetic 3, symptomatic 11, unknown 1)</td>
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<tr>
<td></td>
<td>Unclassified: 1</td>
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<td></td>
<td><strong>Intellectual disabilities:</strong></td>
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<td></td>
<td>16 were documented as having 4 of whom were considered mild</td>
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<td></td>
<td><strong>AEDs at the start of eTNS:</strong></td>
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<tr>
<td></td>
<td>Mean 3 (range 1-5, SD 1, median 3)</td>
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<tr>
<td></td>
<td><strong>Total AEDs tried:</strong></td>
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<tr>
<td></td>
<td>Mean 8 (range 3-17, SD 4, median 7)</td>
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<tr>
<td></td>
<td><strong>History surgery for epilepsy:</strong></td>
</tr>
<tr>
<td></td>
<td>Previous VNS 6</td>
</tr>
<tr>
<td></td>
<td>Right temporal lobectomy 3 (including one who had also tried VNS)</td>
</tr>
</tbody>
</table>
Table 2: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>On treatment</th>
<th>Paired Students t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure frequency/week</td>
<td>Mean 7.2 (min 0.3, max 70.2, SD 13.5, median 3.6, n=28*)</td>
<td>Mean 6.8 (min 0.2, max 71, SD 13.9, median 3.0, n=28*)</td>
<td>p=0.3562</td>
</tr>
<tr>
<td>QOLIE – 10p</td>
<td>Mean 30 (min 4, max 87, SD 25, median 19, n=23**)</td>
<td>Mean 19 (min 1, max 95, SD 23, median 11, n=23**)</td>
<td>p=0.0089</td>
</tr>
<tr>
<td>BDI</td>
<td>Mean 13.3 (min 0, max 57, SD 12.9, median 8, n=25†)</td>
<td>Mean 10.9 (min 0, max 55, SD 13.6, median 8, n=25†)</td>
<td>p=0.0492</td>
</tr>
<tr>
<td>Pittsburgh Sleep Scale</td>
<td>Mean 7.3 (min 2, max 16, SD 4.0, median 7, n=25†)</td>
<td>Mean 6.1 (min 1, max 14, SD 3.8, median 6, n=25†)</td>
<td>p=0.0819</td>
</tr>
<tr>
<td>Epworth Score</td>
<td>Mean 9.4 (min 0 max 22, SD 6.8, median 8, n=25†)</td>
<td>Mean 9.0 (min 0, max 22, SD 6.4, median 9, n=25†)</td>
<td>p=0.3104</td>
</tr>
<tr>
<td>ELDQOL</td>
<td>Mean 103 (min 64, max 151, SD 29, median 99, n=12‡)</td>
<td>Mean 97 (min 72, max 137, SD 21, median 94, n=12‡)</td>
<td>p=0.326</td>
</tr>
</tbody>
</table>

Notes: If data was missing the last observation was carried forward.
* There were 28 with seizure frequency data and no drug changes of whom 21 had follow up data to 18 weeks, 4 to 12 weeks and 3 to 6 weeks.
**QOLIE-10p data were available for 23/30 without ID, amongst whom 15 had data at 18 weeks, 5 at 12 weeks and 3 at 4 weeks.
† BDI, Pittsburgh Sleep Scale and Epworth Score data were available for 25, amongst whom 15 had data at 18 weeks, 6 at 12 weeks and 4 at 4 weeks.
‡ ELDQOL for 12 with epilepsy and ID were available for 9 at 18 weeks, 2 at 12 weeks and 1 at 4 weeks.
Acknowledgments

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SJS and LN planned and carried out the audit and wrote the manuscript. Analysis was carried out by SJS.
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[5] DeGiorgio CM, Shewmon DA, Murry D, Whitehurst T, Pilot study of Trigeminal nerve stimulation (TNS) for epilepsy: a proof of concept study, 2006 Neurology 47(7); 1213-1215


