King's College Hospital NHS
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External Trigeminal Nerve Stimulation (eTNS) for Epilepsy

Early Clinical Experience

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Introduction

The Monarch external Trigeminal Nerve Stimulation (eTNS) system is a new medical device from NeuroSigma that provides bilateral external non-invasive electrical stimulation to the V1 branch of the Trigeminal nerve. The device gained a Class IIa CE (Conformité Européenne) Marked Medical Device. As such it can be sold and used clinically in the United Kingdom and throughout the European Union. The approved indications for use are: Adjunctive therapy for treatment of epilepsy and depression in patients 9 years and older.

Only two small clinical trials of eTNS for drug resistant epilepsy have been published:

- An open label trial in which 12 patients with highly refractory epilepsy (baseline seizure frequency of 2.1 seizures/day) completed the first 3 months of the trial with a 66% seizure reduction. Seven patients completed 12 months of the trial, of whom 5 had a sustained decreased in seizure frequency of >50% [1].
- A double blind randomized controlled trial of eTNS. This study showed a 40.5% responder rate after 18 weeks in the active group vs. 15.6% in controls [2].
- There were no significant adverse events associated with the device in either of the trials.

Although only shown in small numbers, these studies are comparable to VNS effect in intractable epilepsy. The disadvantage of VNS is that if the treatment is not effective, and while it is relatively easy for the stimulator to be removed surgically, it is difficult for the wire to be removed; this carries a risk of local complications.

eTNS has also been shown to have a positive effect on mood[3] and a small trial in ADHD is underway in children[4].

We have introduced eTNS as a treatment option for our patients with refractory epilepsy. We present the data from the on-going service evaluation in our patients.

Methods

The use of the device was approved by King's College Hospital New Clinical Procedures Committee.

The treatment was offered to any patient in our epilepsy service who fulfilled the following criteria

- Age 9 plus
- Intractable drug-resistant epilepsy
- Adequate trials of multiple antiepileptic drugs (AEDs)
- Concurrent use of at least 1 AED
- Sufficient cognitive abilities to understand the purpose of the device and to use it; if not a parent or carer able to understand and use the device and a patient felt to be sufficiently co-operative in its use.

We did not offer the device to patients with:

- History of nonepileptic seizures
- Other serious or progressive medical or psychiatric illnesses
- History of facial pain or trigeminal neuralgia;
- Concurrent vagus nerve stimulation (VNS) or neurostimulation
- Pregnancy

Patients were provided with an information sheet about the device and given time to ask questions. They were then trained in the use of the device.

The following assessments were performed at baseline, 4, 12 and 18 weeks:

- Seizure diaries (aiming for a 12 week baseline prior to treatment)
- Use diaries (to record: time on/off, current, problems)
- Quality of life (QOLIE-10P)
- Mood (Beck's Depression Inventory: BDI)
- Sleep quality (Pittsburgh Sleep Scale)
- Daytime somnolence (Epworth)

Patient Demographics

#	Age	Sex	Classification	Seizure Types	Age onset	% Life	Med now	Med prev	Surgery	LD	Comments
1	27	F	IGE (JME)	GTCS, Absence, atonic, myoclonic	11	59	4	2	No	No	Daily myoclonus not recorded
2	34	F	Focal (likely TLE)	CPS	6	82	2	5	No	No	
3	29	M	Focal (TLE)	SPS, CPS	7	76	2	5	RTL	No	
4	23	F	IGE (JAE)	Absence, GTCS	18	22	3	1	No	No	Daily absences, unable to record but good days after 12 weeks of treatment
5	44	F	Focal (Likely frontal)	SPS, CPS	11	75	1	4	No	No	
6	58	M	Focal (TLE)	CPS, GCTS	40	31	1	5	RTL	No	Stopped using for 7 nights as camping – seizure day after stopped and when put back on
7	21	F	Generalised ? IGE or S'tomatic	Absence, GTCS	7	67	3	5	No	No	Daily absences, unable to record but good days after starting treatment. Stopped at 14 weeks as ran out of electrodes and did not want to continue.
8	25	M	S'tomatic Generalised (LGS)	GTCS, myoclonic absences CPS, atonic	2	92	3	6	No	Yes	
9	38	M	S'tomatic Generalised	Atonic, Atypical Absences	10	74	4	9	No	Mild	Missed a week due to problems with device Redness on forehead during hot weather
10	52	M	Focal	CPS, GTCS	32	38	2	5	No	No	Used Twice – first 4 nights, then second time 5 nights. Could not get his mind off the stimulus sensation, even though it was not painful.
11	45	F	Focal (TLE)	CPS, SPS	21	53	3	3	VNS[1]	No	Levetiracetam increased two weeks before starting
12	56	F	S'tomatic Generalised	GTCS, Drops	8	86	4	9	No	No	Patient started eTNS during a bad phase in her seizure cycle. She was admitted for a drug change soon after starting.
13	38	M	Focal (likely TLE)	CPS	7	84	2	1+	No	No	
14	31	M	S'tomatic Generalised	Absence, Myoclonus	0.5	97	2	11	No	Yes IQ 60	Daily absences. Only used for 12 days as recently moved into supported living and embarrassed to wear. Reported seizures less frequent but longer.
15	20	M	S'tomatic Generalised	Absence, myoclonus GTCS	11	55	4	6	No	Yes mild	Daily absences.
16	21	F	Focal (R temporo parietal)	SPS, CPS, GTCS	7	67	1	6	No[2]	Yes mild	Developed recurrent clusters of seizures during VT admission. eTNS started along side introduction of eslicarbazepine and perampanel as inpatient.

IGE: Idiopathic Generalised Epilepsy, JME: Juvenile Absence Epilepsy, TLE: Temporal Lobe Epilepsy, JAE: Juvenile Absence Epilepsy, LGS: Lennox-Gastaut Syndrome, GTCS: Generalised Tonic Clonic Seizure, SPS: Simple Partial Seizure, CPS: Complex Partial Seizure. Notes: [1] Patient did not tolerate so VNS removed. [2] Patient had intracranial recordings 6 weeks after eTNS started.
The shade colour in the first column is the same colour used to represent the same patient in the graphs below.

Results

Sixteen patients have been started with eTNS. The following patients have been excluded from further analysis:

- Patient 10 disliked the sensation of stimulation (see table)
- Patient 14 stopped after 12 days (see table)

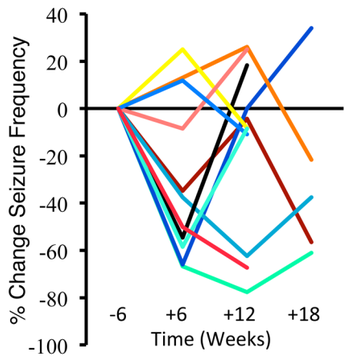
There were no serious adverse events and all other patients tolerated the device well. One patient had slight reddening of his forehead when the weather was very hot, but this resolved.

The device was worn between 6½ and 12 hours per night (median 10) with a median current of 5 mA (range 2.6-7.6). In only a few instances was contact lost overnight.

Patients 12 and 16 had significant changes in their medication regimens at the same time as or just after starting eTNS. However, both felt the device to be beneficial and have continued to use it.

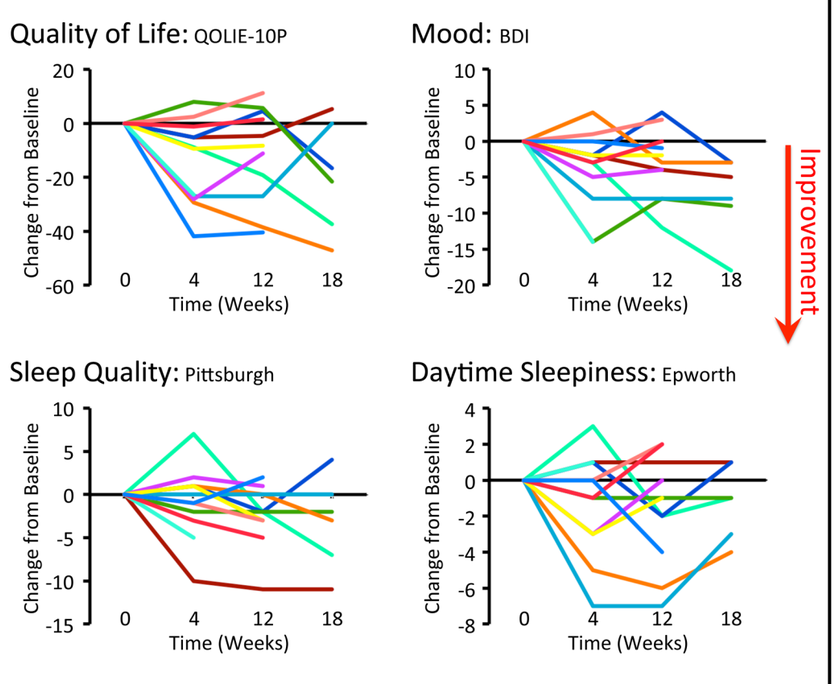
Two patients (4 and 7) had daily absences which they were unable to count. Patient 7 reported 2.3 good days (less than 5 absences) per week in the twelve weeks of treatment. Patient 4 reported 1.3 good days after 12 weeks. Prior to treatment, they both always had more than 10 absences per day.

The remaining 12 all had 12 weeks of treatment of whom 6 had 18. The mean seizure rate before treatment was 3.2/week (range 0.7-7.1), which reduced to 2.5/week (0.3-7.3) for the 12 weeks after treatment (n=11, data for patient 16 not available). Six patients had a 30% reduction in seizures and 4 a 50% reduction.



Graph showing the percentage change in seizure frequency for 6 weeks before starting and each 6 weeks thereafter.

Results: Non-Seizure Measures



Each graph shows the change from baseline. QOLIE-10P is scored out of 100, Beck's Depression inventory out of 63, Pittsburgh sleep scale out of 21 and the Epworth out of 24. In each case a lower number is better.

Discussion

Our early data from using eTNS in clinical practice confirms that it is safe and well tolerated. The device resulted in seizure reduction in a number of patients, without the side effects that can limit the use of medications.

eTNS reportedly shows similar responses to VNS, but has the advantage of not requiring an operation and being easy to remove if not effective or not tolerated.

In addition to the observed seizure reduction, we have also observed an improvement in quality of life, mood and sleep in some patients.

eTNS should be considered as an option in patients with refractory epilepsy.

An NHS funding stream has not yet been established.

We will continue to collect data on patients started on eTNS to help determine its place in the treatment of epilepsy.

Conclusion

eTNS is safe, well tolerated and easy to use.

eTNS can reduces seizure frequency without drug side effects.

eTNS can easily be stopped if not effective.

References

1) DeGiorgio CM, Murray D, Markovic D, et al. Trigeminal nerve stimulation for epilepsy: long-term feasibility and efficacy. Neurology. 2009;72:936-8.

2) DeGiorgio CM, Soss J, Cook IA, et al. Randomized controlled trial of trigeminal nerve stimulation for drug resistant epilepsy. Neurology. 2013; 80:786-91.

3) Schrader LM, Cook IA, Miller PR, *et* al. Trigeminal nerve stimulation in major depressive disorder: First proof of concept in an open pilot trial. Epilepsy & Behavior. 2011;22:475-478.

4) McGough J, Loo S, Leuchter A *et al.* Trigeminal Nerve Stimulation (TNS) for Attention-Deficit/Hyperactivity Disorder: A Pilot Feasibility Study. American Psychiatric Association Meeting, San Francisco 2013.

Declaration

The equipment and starting electrodes for this early introduction of eTNS were provided by NeuroSigma who had no further part in the collection or interpretation of these data.

ILAE British Chapter 2013 Annual Scientific Meeting

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