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Long-term outcome of vagus nerve stimulation therapy after failed epilepsy surgery

Fernando L. Vale [a,*], Amir Ahmadian [a], A. Samy Youssef [a], William O. Tatum [b], Selim R. Benbadis [c]

[a] University of South Florida, Department of Neurosurgery, Tampa, FL, United States
[b] Mayo Clinic, Department of Neurology, Jacksonville, FL, United States
[c] University of South Florida, Department of Neurology, Tampa, FL, United States

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ABSTRACT

Objective: Adequate control of intractable epilepsy continues to be a challenge. Little is known about the role of VNS therapy in intractable epilepsy in patients who failed to respond to surgical management. The objective of the present study is to determine the efficacy of vagus nerve stimulation therapy in patients with intractable epilepsy who have failed surgical and medical therapy.

Methods: All the patients who had persistent seizures after cranial surgery who subsequently underwent vagus nerve stimulator (VNS) placement at our institution from 1998 to 2008 were included in the study. Thirty-seven consecutive patients were enrolled and followed for the outcome measures of seizure burden, anti-epileptic drug (AED) burden and quality of life (QoL). Minimum follow-up was 18 months.

Results: Overall, 24 (64.9%), 9 (24.3%), 4 (10.8%) patients reported less than 30%, between 30% and 60% and greater than 60% reduction in seizure frequency after VNS placement, respectively at a mean of 5 years follow-up period. Post-VNS anti-epileptic requirement exhibited a decreasing trend. 17 patients (45.9%) report an improvement in QoL (better or much better).

Conclusion: VNS therapy in patients who have failed medical and surgical therapies only provides marginal improvement in seizure control but has greater likelihood to improve subjective QoL issues. In addition, VNS has the potential to reduce AED burden without adversely impacting seizure management. Given the low surgical risk of VNS placement, vagus nerve stimulation as a therapeutic modality should be individualized to achieve best clinical response and fewest side effects.

1. Introduction

Despite great advancement in surgery, localization techniques and pharmacological therapies adequate control of intractable epilepsy continues to be a challenge.[1] Current surgical approach to epilepsy relies heavily on localization of epileptogenic focus and encompasses a diverse set of approaches that include partial focal lobectomy, mesial temporal resection and corpus callosotomy amongst others.[2–5] Surgical treatment of intractable epilepsy can provide long-term seizure reduction/control in 70–90% of patients.[6–9] Adequate seizure control remains a persistent problem in patients who have failed initial surgical management.[10–12] Failure of surgery for epilepsy is multi-factorial with poor predictability of which patients are destined to fail.[8,13] Repeat surgery has however shown to be less effective than the initial attempt in addition to having increased surgical risk.[12,13]

Vagus nerve stimulator (VNS) is a FDA approved treatment approach to refractory epilepsy.[14] The VNS is an implantable device for peripheral stimulation of the vagus nerve in the neck. Though the exact mechanism of action is not fully elucidated, it is believed that it can provide seizure control via a retrograde global inhibitory effect on the central nervous system particularly through the thalamus.[15,16] Retrograde afferent stimulation of both the thalamus and other midbrain/limbic structures, as a relay to cortical modulation has been studied.[17,18] The modulation of both cortical electrical activity and possibly norepinephrine can effectively reduce seizures in select patients.[15,19] VNS has been shown to be efficacious in focal, generalized and syndromic forms of epilepsy (i.e. Lennox-Gastaut).[16,20,21] Historically it has served as a treatment option for patients with medically intractable epilepsy who are not surgical candidates. There are few studies on efficacy

* Corresponding author at: 2 Tampa General Circle, USF Health, 7th Floor, Department of Neurosurgery, University of South Florida, Tampa, FL 33606, United States.
Tel.: +1 813 259 0605; fax: +1 813 259 0858.
E-mail address: fvale@health.usf.edu (F.L. Vale).

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of VNS in failed surgery. The aim of the present study is to report the efficacy of vagus nerve stimulation in patients who continue to have intractable seizures after epilepsy surgery.

2. Methods

2.1. Patient selection

A prospective data registry was established in 1998 for all patients referred to our comprehensive epilepsy center for surgical evaluation. 37 consecutive patients with drug-resistant epilepsy who had unsatisfactory results from cranial surgery (lobectomy or corpus callosotomy) and subsequently underwent VNS placement at our institution between 1998 and 2008 were identified. Initial patient selection for surgery was based on phase I localization of epileptogenic foci, which consisted of video EEG and neuroimaging (MRI and in some cases PET/SPECT). If surface EEG and imaging were inconclusive then the patient underwent phase II localization that consisted of cortical grid/strips or depth electrode placement and video monitoring.

The patients who failed to respond to surgery were deemed nonsurgical candidates for repeat surgery if re-localization did not find an appropriate resectable focus. Modified Engel classification scale was used to determine and stratify surgical failures.[22] Engel class III (worthwhile seizure reduction) and class IV (no worthwhile improvement) outcomes were considered for VNS placement and enrollment in the present study. A total of 37 patients were enrolled in this study with a minimum follow up of one year (range: 18 months to 10 yrs). Demographic data are displayed in Table 1.

During the first few weeks after VNS implantation, the patients were seen in the clinic to confirm wound healing and assess proper pulse generator operation. Stimulation was started at a low current setting (0.25 mA) and the current was increased gradually to allow accommodation to the stimulation. For patient comfort, the output current was increased in 0.25 mA increments until a comfortable level was reached. Treatment parameters were individualized to achieve the best clinical response with the fewest side-effects. In addition, AEDs remained stable for the first three months of stimulation to assess clinical response.

Table 1
Patient population statistics.

No. patients	37
Age at VNS placement	
Mean	29.1
Median	27.4
Range	4.8–63.3 yrs
Range of follow up	18–127 months
Mean	61.7 months
Sex	
Male (%)	46%
Female (%)	54%
Type of surgery (*6 patients had two different surgical sites)	
Temporal	24
Frontal	12
Occipital	1
Corpus callosotomy	6
No. of AEDs pre-implantation (%)	
1	(2.7%)
2	(35%)
3	(46%)
4	(13.5%)
5	(2.7%)
No. of AEDs post-implantation (%) at most recent follow-up	
1	(13.5%)
2	(32.4%)
3	(24.3%)
4	(27%)
5	(2.7%)

2.2. Outcomes

Outcomes were measured via a questionnaire at the most recent scheduled follow up. Pre and post-operative management of anti-epileptic drugs was deferred to the patient's treating neurologist. Outcomes measured included seizure burden, AED burden and quality of life (QoL).

Seizure burden (% seizure reduction) was subjectively quantified as $<$30% reduction, 30–60% reduction and $>$60% reduction. Pre-VNS anti-epileptic drug burden was compared to the number of drugs the patient required at the most recent follow up. Finally, QoL was investigated via ordinal analysis where the patient or caregiver categorized his/her QoL as "much worst, worst, no change, better or much better" as compared to post-cranial/pre-VNS surgery.

3. Results

Individualization of treatment was the accepted treatment modality. Output current was adjusted as necessary. Mean current therapy was 2.5 mA (range: 1.5–3.0 mA) for the cohort. There were no major complications noted in this group of patients (such as infections or permanent vocal cord paralysis). Two patients complained of transient persistent hoarseness on activation of VNS. No patient was lost to follow-up. Patients and caregivers did report an increase in efficacy in the first year after implantation, but no significant clinical changes were noted after longer than one year follow-up period.

Retrospective analysis of the 37 patients who met the inclusion criteria of Engel class III/IV was performed. Outcome measures were analyzed individually as well as in combination via non-parametric analysis (Mann–Whitney U). In regards to seizure burden 24 (64.9%), 9 (24.3%), 4 (10.8%) patients reported less than 30%, between 30% and 60% and greater than 60% reduction in seizure frequency after VNS placement as compared to post craniotomy, respectively (Fig. 1). No patient was seizure-free following VNS in this cohort. The reported percent seizure reduction was determined by the patient/caregiver at the most recent follow up (18 months to 10 yrs post VNS placement).

Poly-pharmacy was encountered in 94.5% of our post-surgical patients with an Engel class III/IV outcome. Antiepileptic drug requirement prior to VNS placement was from 1 to 5 medications. 35%, 46% and 13.5% of patients were on 2, 3 or 4 anti-epileptic drugs with 2.7% (1/37) on either one or five at the time of preoperative evaluation. Post-VNS anti-epileptic requirement exhibited a decreasing trend with 13.5%, 32.4% and 24.3% of patients requiring 1, 2 and 3 AEDs, respectively (Fig. 2). Patients requiring only one AED increased from pre-VNS 2.7% to 13.5% post-VNS. However, 11 of 37 (29.7%) of patient required at least 4 or 5 AEDs as compared to 6 patients (16.2%) pre-VNS. Non-parametric analysis suggests that patients that reported less than 30% reduction were more likely to be on 3 or more AEDs as compared to those who reported between a 30-60% reduction (Mann–Whitney U, $p = 0.032$). No patient was on VNS monotherapy.

Qualify of life, a quantification of satisfaction, as reported by the patient or caregiver underwent non-parametric analysis with both AED requirement and seizure burden. QoL analysis demonstrated that 19/37 (51.3%) of the patients had no change in self-reported quality of life. No one reported getting "much worse" though one patient did report being worse off. 17 patients (45.9%) report an improvement in QoL (better or much better) (Fig. 3). Mann–Whitney U analysis did not suggest any individual significant correlation when comparing QoL to AED or seizure burden.

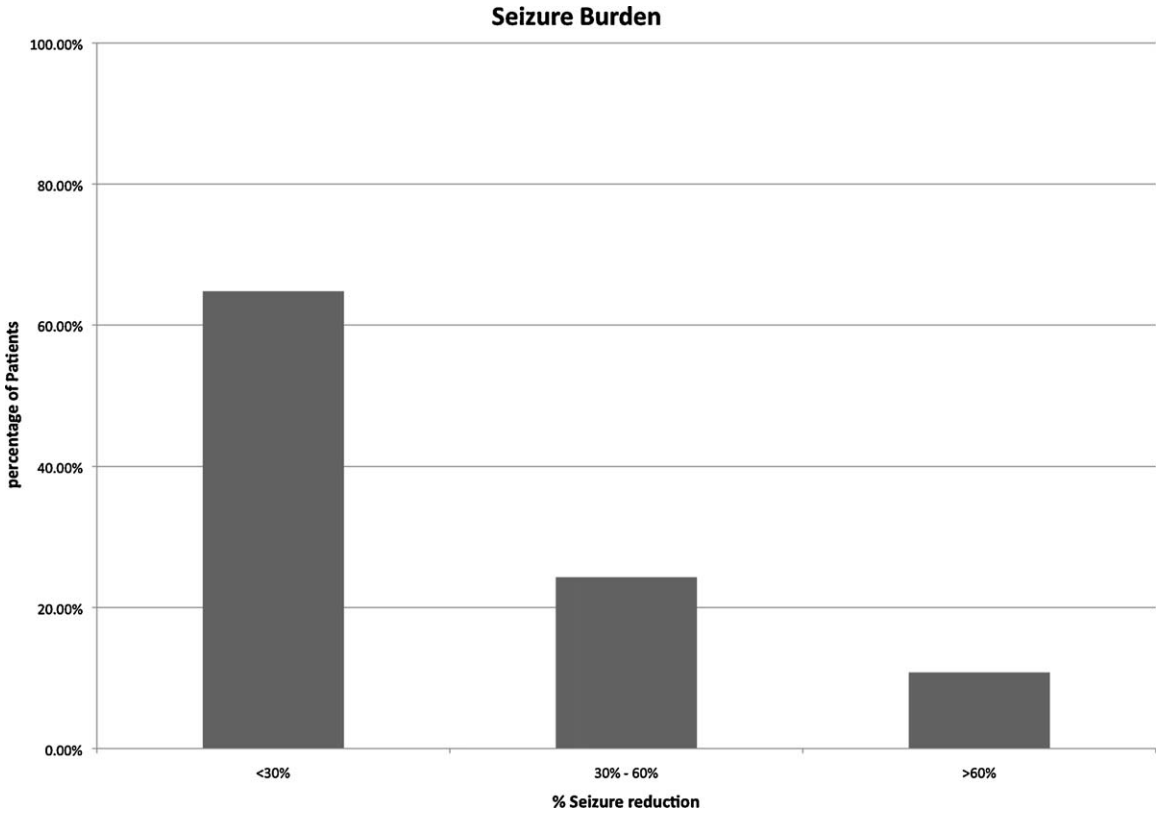

Fig. 1. Seizure burden.

A comparison between patients who underwent focal resections (FR) ($n = 31$) versus corpus collosotomy (CC) ($n = 6$) was also performed. There was no statistical difference between groups in terms of pre and post-VNS placement number of AEDs. However, >60% seizure reduction was only seen in the FR: 4/31 (13%). Between 30 and 60% seizure reduction was seen in 7/31 (23%) vs 2/6 (33%) in the FR and CC groups, respectively. QoL analysis demonstrated that 15/31 (48%) patients reported an improvement (better or much better) for the FR group versus 2/6 (33%) for CC patients. Furthermore, no significant difference in the stimulation parameters between groups was identified.

4. Discussion

Surgical management of intractable epilepsy is too often reserved as a last line of treatment particularly in patients who have failed medical management and who have a resectable lesion or epileptogenic zone.[23] Inevitably a certain subset of these patients will fail surgical treatment. This subset of patients is the most difficult to treat and exhibit a form of epilepsy that is refractory to conventional measures. Hence, in Engel class III/IV epileptics, other avenues of treatments need to be considered including but not limited to neuro-stimulation. Little is know about the efficacy of vagus nerve stimulation in this population of epileptic patients.

Few studies have investigated VNS in post surgical patients. Amar et al.[24] reported the findings from a subgroup analysis of a national registry data. They report a 45.7% and 50.5% median reduction in seizure frequency after 12 and 24 months, respectively. Their analysis of QoL (alertness, verbal communication, memory, school/professional achievement, mood, postictal state and seizure clustering) suggests a trend towards improvement overtime, though statistical significance was present only for greater alertness. As they note, the data in the national registry represents a nonconsecutive cohort that is susceptible to reporting and selection bias. This analysis of pre-marketing open label registry concluded that VNS therapy is a potential option for treatment of surgically failed intractable epilepsy even though the statistical significance of trends in efficacy over time cannot be verified (nonconsecutive data). A subgroup analysis of an outcome designed study by Ben-Menachem[25] of 18 Swedish patients showed decreased in seizure frequency in 6 patients (one with tumor) with reduction rates ranging from 20% to 75%.

Conversely, Koutroumanidis et al.[26] analysis of 16 post surgical patients suggests a limited efficacy in seizure burden after vagus stimulator placement. They report no change in 10 of the 16 patients (62.5%) in regards to both frequency and severity of seizures in a similar fashion to our results. Only 3 patients had up to a 50% reduction in frequency (18.75%). One patient's seizures had increased post VNS placement and hence had subsequently the device removed. Interestingly, Koutroumanidis et al. results also suggests positive psychotropic effect VNS in this patient population. Three of their patient elected to keep their vagus nerve stimulators for its positive psychotropic effect despite no change in seizure burden. Other patients in their study exhibited decrease in severity of psychosis and/or stabilization of mood.

Other clinical applications of VNS, which include major depression, Alzheimer, migraines, eating disorder and mood stabilization amongst others, have been investigated.[27,28] The positive psychotropic effects of VNS, particularly in regards to resistant depression, have been a particular point of interest.[29–32] Modulation of multiple neurotransmitters, neuro-modulators and amino acids is a hypothesized mechanism of the positive psychotropic side-effects of VNS.[33] This positive psychotropic effect of VNS must likely represent one of the many variables involved in quality of life analysis in patients with VNS. As seen in this study, subjective QoL determination was not associated with any one variable alone. It represents a conglomeration of variables

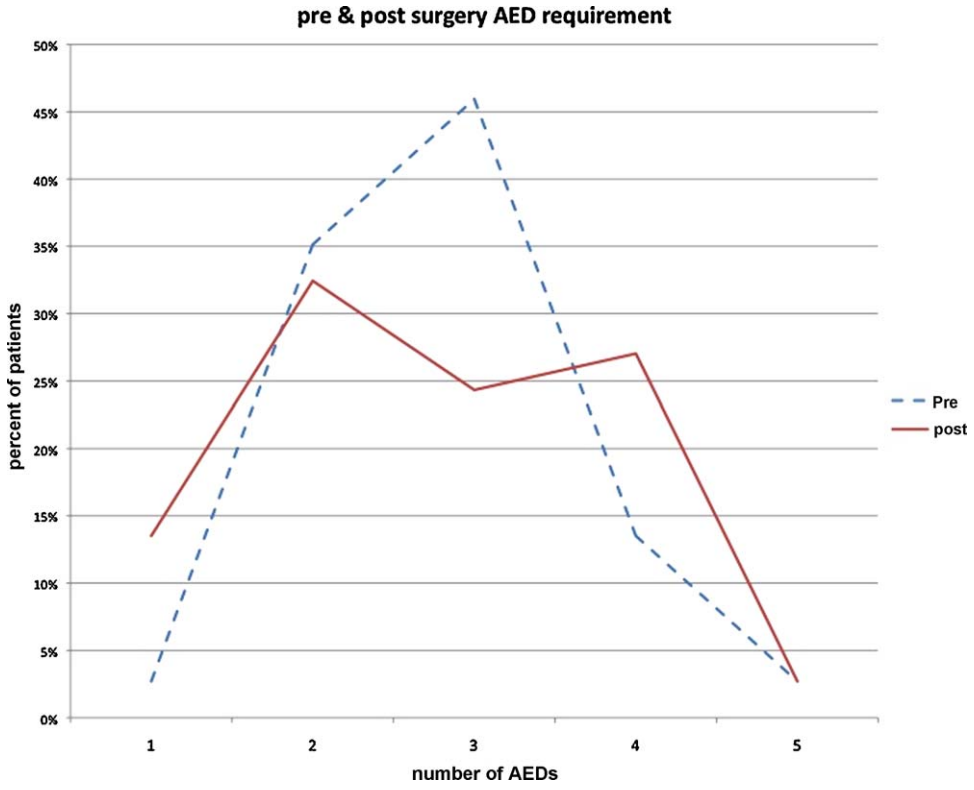

Fig. 2. AED requirement.

including seizure frequency, seizure severity, AED burden and mood amongst others.

In our experience, patients who pre-VNS implantation required more AEDs are more likely to have poorer outcomes than those who are on fewer AEDs. Patients that reported less than 30% reduction were more likely to be on 3 or more AEDs and only 10.8% patients reported a >60% reduction in seizure burden. Quality of life analysis does not directly correlate with seizure burden.

In regards to QoL, there is an approximate 50/50 split in regards to improvement vs. no improvement (45.9% vs 51.3%). QOL is multifactorial and may involve not only seizure burden but also medication burden amongst other psychosocial factors as suggested above. Subgroup analysis of patients who report "no change"/"got worse" in QoL versus those who report an improvement shows no significant inter-group difference either pre-VNS ($p = 0.326$) or post-VNS ($p = 0.125$). In regards to medication

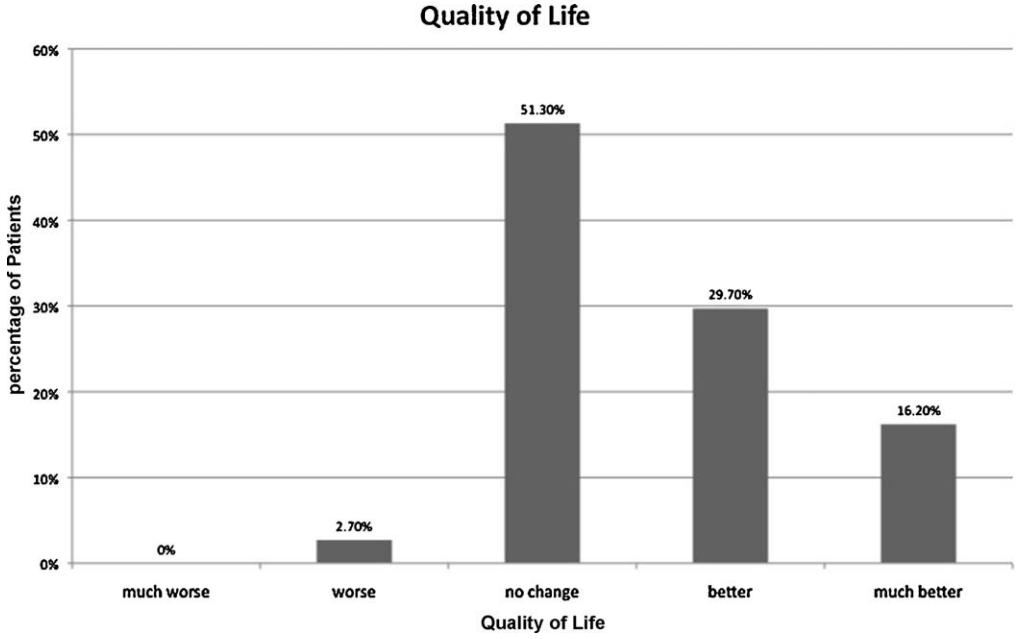

Fig. 3. Quality of life.

burden, no significant change between the pre and post VNS placement was seen in this group of patients as previously suggested in a case-controlled study.[34] Study design and patient selection may explain this finding.

When compared to national registry data our study suggest only a marginal improvement in seizure burden with VNS post cranial surgery. Approximately 65% of patient will have a less than 30% reduction in seizure frequency (Fig. 1). The true efficacy of VNS in intractable failed surgical epilepsy is unclear and controversial in current literature. Studies report a wide range of percent seizure reductions.[24,26,35] Based on our experience, VNS therapy in patients who have failed medical and surgical therapies only provides marginal improvement in seizure control but greater likelihood to improve subjective quality of life. These findings were independent of the type of intra-cranial procedure performed.

We acknowledge the limitations of a single center study and therefore recommend further studies to corroborate our clinical findings. In addition, this study includes a relatively small number of patients in the analysis, but due to severity of the disease, may still represent an accurate representation of this group of epileptic patients.

5. Conclusion

VNS therapy in patients who have failed surgical therapy seem to provide marginal improvement in seizure control but has greater likelihood to improve subjective quality of life. Further prospective studies to elucidate the true efficacy of VNS in epilepsy patients with a post-operative Engel class III/IV outcome are needed. Given the low surgical risk of VNS placement, its use as a therapeutic modality in intractable epilepsy should be left to the discretion of the surgeon and epileptologist with the potential benefit of drug reduction and improvement quality of life kept in mind.

Disclosure

Drs. Vale, Ahmadian, Youssef and Tatum have no conflict of interest to disclose in regards to the context of this manuscript. Dr. Benbadis is a member of the speaker bureau for Cyberonics. No grants from any government or private agencies were received for this research activity.

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