Seizure (2007) **16**, 579—585

SEIZURE

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Vagus nerve stimulation for medically refractory epilepsy: A long-term follow-up study

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Received 19 July 2006; received in revised form 17 April 2007; accepted 26 April 2007

KEYWORDS
Refractory epilepsy;
Vagus nerve stimulation;
Long-term evaluation

Summary

Introduction: Vagus nerve stimulation (VNS) is thought to have a cumulative effect in time on seizure frequency reduction. There also might be other variables than reduction of seizure frequency in order to determine VNS efficacy. In this study we describe the long-term outcome of the first group of vagus nerve stimulation patients with pharmacoresistant epilepsy at the Medisch Spectrum Twente, The Netherlands.
Methods: This long-term descriptive prospective study included 19 patients, 11 males and 8 females, aged 17—46 years with pharmacoresistant epilepsy. They had received 3—16 (mean 9) different anti-epileptic drugs and were not eligible for surgical resection of an epileptic focus. A vagus nerve stimulator was implanted in the period April 1999—October 2001. Follow-up ranges from 2 to 6 years (mean 4 years). Efficacy was measured as the percentage change in seizure rate during 1 year and then after each year follow-up of VNS compared to 5 months baseline before implantation.
Results: Mean seizure reduction at 1—6 years was, respectively, 14% (n = 19), 25% (n = 19), 29% (n = 16), 29% (n = 15), 43% (n = 9) and 50% (n = 7). Because of VNS two patients were able to start living without supervision. One patient died after 2 years of follow-up possibly as a result of SUDEP. Four patients had no apparent reduction in seizure frequency. Two of them had their stimulator removed. The other two patients however had significantly reduced post-ictal periods and seizure time and received a new pulse generator when the battery was depleted. One stimulator was switched off due to adverse effects, even though there was a positive effect on his seizure reduction. In six patients the medication regimen was changed during VNS by adding one anti-epileptic drug, however without significant change in seizure

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1059-1311/$ — see front matter
doi:10.1016/j.seizure.2007.04.005

reduction. Adverse effects were hoarseness and coughing during stimulation. One patient had a temporary paralysis of his left vocal cord.
Conclusion: We think that VNS is an effective treatment for pharmacoresistant epilepsy and its positive effect persists during the years of follow-up. Our results suggest that seizure reduction should not be considered as the only variable of importance to describe the outcome of VNS on epilepsy and it is worthwhile to look at other outcome measures.

Introduction

Early studies indicated that vagus nerve stimulation (VNS), used for medically refractory epilepsy, might have a cumulative effect in time on seizure frequency reduction.[1–3] In addition, a number of long-term VNS outcome studies reported an improved effect in seizure reduction over a period of time.[4–7] Furthermore, studies suggest other variables than reduction of seizure frequency to describe VNS efficacy, such as reduced post-ictal period, reduced seizure severity or an improved quality of life.[4,8] Evaluating VNS outcome is important because about 30% of patients with epilepsy have medically refractory epilepsy or have unacceptable side-effects from their anti-epileptic drug regimen at therapeutic dosage. Some of them will benefit from resective surgery.[9] For those who are not eligible for epileptic focus resection, VNS-therapy has been shown to be an effective alternative.

In response to the clinical outcome studies in the European community and the United States, VNS was introduced in our centre in 1999 as an add-on therapy for patients with medically refractory epilepsy. The primary objective of this study was to determine seizure frequency reduction in a long-term study in patients receiving VNS. Secondly, we investigated whether other relevant outcome measures could be identified in order to determine the effectiveness of VNS. We describe the experience in 19 patients in a long-term prospective study in a single centre in a period of up to 6 years.

Methods

Patient population

From April 1999 to October 2001, 19 patients with medically refractory epilepsy received a VNS system at Medisch Spectrum Twente Hospital, Enschede. There were 11 males and 8 females, with an average age of 33 years at the time of implantation. All had partial seizures. The average age at epilepsy onset was 11 years. Patients had a mean duration of refractory epilepsy of 23 years before VNS, and had received an average of 9 different anti-epileptic drugs. The average number of seizures before VNS was 28 per month (measured prospectively from baseline at 5 months before the implantation). None of them were eligible for surgical resection of an epileptic focus. Patients' characteristics are given in Table 1.

Study design

The primary objective was to study the outcome on seizure frequency of patients receiving VNS over a long-term period. In this long-term prospective analysis of patients, a VNS system (Cyberonics, Houston, TX, US) was implanted in patients between April 1999 and October 2001. We retrieved epilepsy seizure charts from November 1998 to September 2006. During the study period, all seizures were counted at the end of each year follow-up after implantation, and seizure frequency per month was then calculated. Clustering of seizures was counted as one seizure. Primary efficacy was defined as the percentage change in total seizure frequency for each year of follow-up compared to the seizure frequency per month from 5 months baseline. Ten days postoperative VNS-therapy was initiated. Gradual current ramp-up was done with steps of 0.25 mA every 3—4 weeks, according to tolerance of side effects. The first 3 months of VNS were excluded from analysis, because during this period the stimulator parameters had not reached settings which are believed to be therapeutic. Thus, efficacy over the first year was calculated over the last 9 months. During the total period of follow-up, stimulator parameters could be changed in order to reach the best optimal therapy for each individual patient. Furthermore, we retrospectively evaluated whether there was a change in seizure type, when patients reported different types of seizures. We also evaluated whether seizure reduction outcome is related to the length of medically refractory epilepsy period or the age of epilepsy onset and starting VNS. Retrospectively we also evaluated whether there was an increase in days without seizures per month.

Table 1 Patients' characteristics

Patient	Sex	Age at onset epilepsy (years)	Etiology	Seizure type	MRI findings	Number of AEDs	Years of epilepsy before VNS	Age at onset VNS (years)	Seizure frequency before VNS (per month)
1	M	14	Perinatal anoxia	CPS + aura	Normal	14	33	46	9
2	M	13	Head trauma	SPS + SGTC	Hyperintensity temporal left	7	10	23	2
3	M	1	Ischemia right medial artery	SPS	Ischemia right medial artery	8	24	25	21
4	M	1	Polio encephalitis	CPS + aura	Cortical dysplasia left fronto-parietal	10	40	41	6
5	F	14	Unknown	CPS + GTC	Normal	8	11	25	22
6	F	4	Arachnoid cyste	CPS + SGTC	Arachnoid cyste temporal right	7	26	30	45
7	M	6	Unknown	SPS	Normal	6	39	45	139
8	F	27	Unknown	CPS	Normal	3	11	38	7
9	F	5	Unknown	CPS + SGTC	Left temporal loss of tissue	12	23	28	21
10	F	13	Meningitis	SPS + SGTC	Left frontal gliosis	8	29	38	9
11	M	8	Encephalitis	SPS + CPS + SGTC	Normal	12	9	17	12
12	F	11	Unknown	GTC	Normal	16	25	40	58
13	F	13	Cortical dysplasia	CPS	Cortical dysplasia insula	9	23	36	17
14	F	26	Unknown	CPS + GTC	Normal	10	15	41	25
15	M	5	Haemolytic uremic syndrome	CPS	Multiple gliosis	7	20	25	10
16	M	10	Unknown	SPS	Normal	14	20	30	94
17	M	6	Meningitis	CPS	Atrophia right fronto-temporal	8	22	28	14
18	M	4	Unknown	SPS	Normal	9	36	40	3
19	M	26	Unknown	SPS + CPS	Atrophia right occipital	8	11	37	20

M: male, F: female, SPS: simple partial, CPS: complex partial, SGTC: secondary generalised tonic clonic, AED: anti-epileptic drug.

Our secondary objective was to evaluate whether there are other outcome variables to describe VNS efficacy. These second outcome variables were collected through retrospective record review. When patients came for periodic hospital visits, patients and caregivers were frequently asked to describe the effect of VNS on seizure severity and post-ictal period recovery. In addition, they were asked to evaluate the use of additional magnet activation on epilepsy pattern. Moreover, they were asked to report VNS related side effects, and to describe changes in the quality of life such as social, work or home related aspects.

During the first year of VNS patients had a stable anti-epileptic drug regimen. Thereafter medication adjustments were permitted. During the period of medication adjustments of VNS parameters did not change for several months in order to evaluate the effect of medication changes only.

For statistical analysis of this longitudinal data we used repeated measurements analysis (mixed models in SPSS 14.0). This analysis technique takes into account the correlation between intra-individual measures. It estimates what patients did in their years of follow-up and estimates their values in the future. For each year of follow-up, the frequency of seizures was calculated as a percentage of baseline. These percentages were entered into the repeated measurements analysis. The default value for the baseline visit is 100%, data outcome is statistical significant when the upper limit of the confidence intervals drops below 100%.

The study was approved by our Medical Ethical Board, and was not part of a sponsored clinical trial, nor were the authors connected with industry.

Results

Efficacy

Mean follow-up was 4 years (range 2—6 years). There were 23 VNS devices implanted. Four devices were replaced due to end of battery-life (all model 100 stimulators).

Mean device parameters during the years of follow-up were as follows: current output 1.50 mA, stimulation frequency, 30 Hz; pulse width, 250 ms; signal on time, 30 s; signal off time, 3 min. Mean magnet settings were as follows: current output 1.75 mA, pulse width 250 ms, and on-time 60 s.

Mean seizure reduction after 1—6 years was, respectively, 14% ($n = 19$), 25% ($n = 19$), 29% ($n = 16$), 29% ($n = 15$), 43% ($n = 9$) and 50% ($n = 7$). This is presented in Fig. 1. It shows that the reduction in the first year is not statistical significant, because the upper limit of the 95% confidence interval is 100%. Nevertheless, the positive effect of VNS persists during the years of follow-up, seizure frequency is decreasing and is becoming more significant as shown with the 95% confidence interval. A $\geq$ 50% seizure reduction was achieved in 12%, 33%, 31%, 36%, 38%, and 25% of patients at, respectively, 1—6 years of VNS. Six responders had an ongoing improvement in seizure reduction during their entire follow-up. One patient became seizure free. Three responders experienced an initial effect that gradually diminished after 2—3 years. There were four patients without any seizure frequency reduction. In fact, two of them experienced a mild increase in seizure frequency.

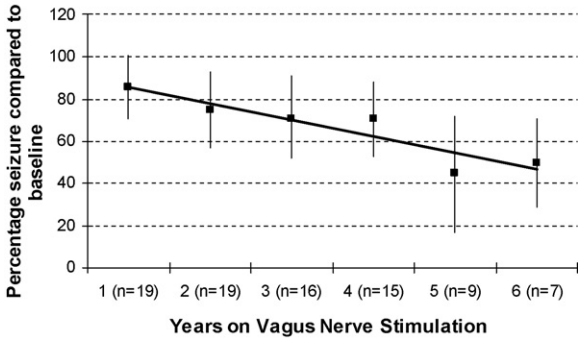

Figure 1 Seizure reduction over 6 years follow-up. The percentage seizures compared to 5 months baseline. The 95% confidence interval is integrated in the figure.

From eight patients we received seizure frequency charts differentiated to different types of seizures. There was no significant change in seizure type, only a general frequency reduction. We found no relation between the length of medically refractory epilepsy period before starting with VSN or the age of epilepsy onset and seizure reduction. There was no significant increase in seizure free days per month.

Eleven patients stayed on a stable anti-epileptic drug regimen. One patient stopped using topiramate when his seizure frequency was reduced by 50%, and remained stable in the follow-up. Another patient with 75% seizure frequency reduction after 1 year experienced a mild but gradual diminishing effect of VNS. After 5 years, when seizure frequency reduction was 58%, pregabaline was added. After 6 months, when seizure frequency did not change much, VNS was turned to the rapid cycle (7 s on, 18 s off) and the seizure frequency was reduced to 87%. Two patients started levetiracetam after 2 and 3 years of VNS. During a 6 months follow-up period in both patients no obvious decrease in seizure frequency were noticed. One patient, with an initial effect of 37% seizure reduction with VNS, started

Table 2 Side effects of vagus nerve stimulation

Side effects	Percentage
Hoarseness	84
Coughing	32
Paresthesia	16
Dyspnea on exertion	16
Pain	16
Paralysis vocal cord	11

oxcarbamazepine after 3 years of VNS, when seizures became more frequent. However, this had no effect on her epilepsy.

Side effects and serious adverse events

Main side effects were hoarseness (84%) and coughing (32%) during the stimulation ''on'' period or during the ''on'' period after additional magnet activation. An overview of the recorded side effects is given in Table 2. These side effects only occurred during the ''on'' period of stimulation. One patient had his stimulator temporarily switched off for 6 months, because of intolerable hoarseness and paresthesia during stimulation. One other patient used the magnet to halt VNS for limited periods of time during jogging, because of dyspnea on exertion during the ''on'' period of stimulation.

Few serious adverse events were recorded. Two patients experienced an intra-operatively paroxysmal bradycardia during device diagnostics (lead-test). At postoperative follow-up this was not recorded again. One patient experienced occasionally a choking sensation at which time the stimulation had to be discontinued for some weeks. During those ''off''-periods his seizure frequency increased to about one-third.

One patient had a temporary paralysis of his left vocal cord post-operatively, that was probably related to manipulation of the vagus nerve during surgery. After 6 months this paralysis had recovered spontaneously and VNS stimulation was initiated. Afterwards he experienced no further voice alterations due to VNS.

Deaths and discontinuations

During the study period five patients left the study. One patient who had a mild reduction in seizure frequency, died after 2 years of follow-up possibly as a result of SUDEP. The relationship of SUDEP and VNS in this patient is unknown. Two patients had their stimulator system removed on their request after, respectively, 2 and 6 years of VNS, because of a lack of effect on their epilepsy. Two patients were lost to follow-up. One moved to another part of the country, after 3 years of VNS. Another patient stopped using his seizure calendar after 2 years. Both are still using VNS.

Patients' evaluation of vagus nerve stimulation

In addition to a reduction in seizure frequency 9 out of 19 patients (47%) reported a reduction in seizure severity and post-ictal period. Of the earlier mentioned four patients without any seizure frequency reduction, two patients claimed to have a significantly reduced seizure severity and reduced post-ictal periods and therefore received a new pulse generator when the battery was depleted. One of these two was a patient with an increase in seizure frequency.

More than 50% of the patients and caregivers reported that magnet activation of the VNS system prevented the onset of a seizure or aborted a seizure. Some patients were able to activate the device with use of the magnet by themselves when having an aura. In other patients caregivers used the magnet to activate an extra magnet stimulation cycle in order to abort a seizure.

Two patients said that they were able to start living independently with the aid of VNS. Those two patients were in their mid-thirties and still living with their parents when VNS started. Before VNS they had many seizures, which were often so severe that they needed medical attention after falling, so it was not safe to live independently. During VNS seizure frequency and severity reduction was so impressive in these two patients that it became safe for them to start living alone. For the same reason two other patients were able to start working. Four patients felt more alert with VNS and in addition reported positive effects on their mood.

Discussion

In our study there was a gradual but significant reduction in seizures during 6 years of VNS. The overall effect of VNS on seizure frequency reduction amounted to about 50% after 5 years. We found that in almost half of the patients VNS also has a positive effect on seizure severity, seizure duration and post-ictal period time. There was no relation between seizure reduction and refractory epilepsy period or the age at onset of epilepsy.

The overall seizure reduction in our group is similar to that reported by others.[4,5,10] There is a possible correlation between the duration of VNS period and the effect on seizure reduction, as demonstrated by others.[3–5,11] Most of our responders had a gradual,

statistical significant improvement in seizure reduction over time. We found that patients could gradually reach a seizure frequency reduction of more than 50%, even after 2 years of VNS. Two patients had an initial effect that gradually diminished in time. This is also reported in a Norwegian study.[7]

There have been reports that show a significant seizure reduction in the first 3 months.[12,13] However, for our analysis we excluded the first 3 months of VNS, because our ramp-up period was longer, in contrast to other studies.[5,6,12] Hence, our results cannot confirm the conclusion of Salinsky et al.[13] who stated that the first 3 months might be an indicator for responders versus non-responders.

Our population is small and only 7 out of 19 have reached 6 years of follow-up, results should therefore be interpreted with caution. However, in our group there are only two discontinuations due to lack of efficacy (11% at 4 years on average), one of which was after 6 years of VNS. This shows a high compliance of our patients to VNS. Uthman et al.[5] describe a large population with 12 year follow-up. They had a discontinuation of 44% at 1.9 years on average. In that study most patients discontinued at depletion of battery, because of lack of efficacy in seizure reduction.

In our study, two patients who had no seizure reduction at all, received a new stimulator when the battery was depleted. They reported a reduced seizure severity and reduced post-ictal period. Furthermore, patients reported a better quality of life with the aid of VNS. This was also reported by Nakken et al.[7] In their study of 47 patients, there were two non-responders and five mild responders who claimed to have a better quality of life.

When asking patients to rate their quality of life with respect to work, social events and health we found encouraging results, especially in patients who were non- or mild-responders. Our results are descriptive, in contrast to Morrow et al.,[10] who used the Rank Health Scale, and reported no effect on quality of life. However, Dodrill and Morris[14] described a better quality of life using the Quality of Life in Epilepsy Inventory (QOLIE)-31.

We realise the limitations in our study in interpreting the patients' evaluation, because this was not done with standard questioners. However, we value our patients' own thoughts and experiences on VNS and their decision to continue or discontinue VNS. Therefore, we believe that seizure reduction should not be the only variable to measure outcome results, and thus agree with Schachter[8] and Spanaki et al.[4] who also suggest evaluating for other outcome standards. The effects of VNS on quality of life are currently being studied in more detail in a large Dutch study.

Main side effects were hoarseness and coughing during stimulation "on" period. These findings are similar to others.[3,15,16] No serious adverse events were seen, although there were two patients with intra-operative transient bradycardia. Although one patient died of SUDEP we believe that VNS is a safe therapy over a long period, even up to 6 years.

In conclusion, VNS is an effective long-term therapy to control a patients' seizure frequency. This positive effect persists during the years of follow-up. It also appears to be effective on seizure severity and post-ictal time. Our results suggest that seizure reduction should not be considered as the only variable of importance to describe the outcome of VNS on epilepsy and it is worthwhile to look at other outcome measures. A careful evaluation about termination of VNS should be considered because its effects gradually increase over some years, not only on seizure reduction but also on epilepsy in general.

Acknowledgements

We would like to thank professor O.F. Brouwer, MD, PhD, neurologist, for his valuable comments on this paper. We also would like to thank J. van der Palen, PhD, epidemiologist, for his help and advice with statistical analysis.

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