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Vagal nerve stimulation—the Norwegian experience

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The purpose of this open retrospective study was to analyze the efficacy and tolerability of vagal nerve stimulation (VNS) in a Norwegian cohort of referral patients with refractory epileptic seizures. A total of 47 patients have been assessed after a mean follow-up time of 2.7 years. Mean age was 34.4 years, mean duration of epilepsy was 25.3 years. Forty-two patients (89%) had localization-related epilepsy, 36 patients (77%) had daily seizures. The patients had tried on average 9.5 antiepileptic drugs, and 12 patients (26%) had undergone epilepsy surgery.

Sixteen patients (34%) had >50% reduction of seizure frequency with VNS, of which one patient became seizure free. The stimulation was generally well tolerated, but three patients requested the device removed because of troublesome side effects.

We conclude that VNS is an efficacious and safe mode of treatment that should be offered to patients with medically and surgically refractory seizures.

Key words: vagal nerve stimulation; refractory epilepsy; adults.

INTRODUCTION

During the last 10 years vagal nerve stimulation (VNS) has been utilized to an increasing extent as adjunctive therapy to patients with difficult-to-treat partial onset seizures. Despite an increasing amount of clinical data, it is still not possible to predict which patients will profit from VNS, and, moreover, the exact mechanisms by which VNS exerts its antiepileptic effect still remain unknown.

The purpose of this open, uncontrolled, retrospective study was to analyze efficacy and tolerability of VNS in a Norwegian epilepsy population. By characterizing the responders, would it be possible to find subgroups of patients most likely to respond to VNS? Do the results justify the costs and efforts associated with the treatment? Should VNS be an integral part of our future therapeutic armamentarium? And if so, how soon should patients be offered this treatment?

PATIENTS

From June 1993 to December 1999, a total of 47 patients have had a vagus nerve stimulator implanted at the National Hospital in Oslo. The clinical features of the patients are shown in Table 1. All the patients were recruited from those referred to the National Centre for Epilepsy in Sandvika. Most of these patients have refractory epilepsy, and those selected for VNS were considered particularly difficult-to-treat. This is illustrated by the fact that the patients still had weekly seizures, 3/4 had even daily seizures, despite having tried on average 9.5 antiepileptic drugs (AEDs) and that 1/4 had undergone epilepsy surgery. The patients had a mean seizure history of 25 years. The vast majority of the patients (89%) had a localization-related epilepsy with simple and/or complex partial seizures with or without secondary generalization. Eight of the patients were mentally retarded, three of whom had Lennox–Gastaut syndrome. Only five patients (11%) were fully employed, 36 patients (77%) received disablement benefit.

METHOD

Stimulation of the left vagal nerve was performed utilizing the Neurocybernetic Prosthesis (NCP)-system (Cyberonics Inc., Houston, TX). This system and the

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Table 1: Patients with vagus nerve stimulator[a].

Male/female	20/27
Mean age (range)	34.4 years (12–70 years)
Mean duration of epilepsy (range)	25.3 years (6–68 years)
Etiology	
Unknown	26 patients (55%)
Known	21 patients (45%)
CNS infection	7 patients
Cortical dysplasia	4 patients
Cerebrovascular insult	3 patients
CNS trauma	3 patients
Birth-related cerebral asphyxia	3 patients
AVM	1 patient
Epilepsy syndrome	
Localization-related	42 patients
Symptomatic	18 patients
Cryptogenic	24 patients
Generalized	5 patients
Symptomatic	3 patients (LGS: 2)
Cryptogenic	1 patient (LGS)
Idiopatic	1 patient (JME)
Seizure frequency in the baseline period	
>1 seizure per week	47 patients (100%)
>1 seizure per day	36 patients (77%)
Suffered SE	17 patients (36%)
Mean number of AEDs tried	9.53 (6–13)
Mean number of AEDs in use during baseline period	2.45 (1–5)
Undergone epilepsy surgery	12 patients (26%) (13 operations) 9 temporal lobectomy 2 extratemporal resections 1 MST 1 hemispherectomy
Mental retardation	8 patients (17%)
Permanent neurological sequela	12 patients (26%)

CNS: central nervous system; AVM: arteriovenous malformation; LGS: Lennox–Gastaut syndrome; JME: juvenile myoclonic epilepsy; SE: status epilepticus; AEDs: antiepileptic drugs; MST: multiple subpial transection.
[a] Clinical data ($n = 47$).

surgical procedure have previously been described[1–4]. Stimulation was initiated 1–2 weeks postoperatively, using parameters of current 0.5–1.25 mA, frequency 30 Hz, pulse width 500 microseconds, and on/off periods of 30 seconds/300 seconds. On subsequent visits the current was gradually increased to tolerance.

The patients were monitored at regular intervals, usually every 2–4 weeks during the ramping-up period. Later on they were monitored every 3–6 months. The magnet activation permitted stimulation on demand. The magnet output current was programmed at 0.25–0.5 mA, higher than the automatically delivered stimulation with a pulse width of 500 microseconds for a period of 60 seconds. Patients who had no seizure-reducing effect 1–1.5 years after implantation were offered a rapid cycling regimen, which consisted of on/off periods of 7 seconds/14 seconds.

All patients or their relatives were requested to keep seizure calenders. At every visit seizure frequency, seizure semiology, seizure duration, postictal state, prescribed AEDs, and dosages as well as side effects of VNS were recorded. The VNS effect was assessed by comparing the seizures in a 3-month baseline period prior to the implantation to the most recent seizure parameters. After 1–1.5 year post implantation, no restrictions were placed on changes of the concomitant AEDs. The mean follow-up time was 2.7 years (0.4–6.5 years).

On two occasions (April 1997 and January 2000) the patients or their relatives were asked to fill in a questionnaire aiming at getting the patients' perspective on the changes in seizure parameters, side effects, quality of life, and if they had benefited from use of the magnet.

RESULTS

The surgical procedure was uncomplicated, and the postoperative period was uneventful for all patients

Table 2: Effect of vagus nerve stimulation on seizure frequency and self-reported quality of life ($n = 47$).

	Number of patients (%)	Number of patients reporting a better quality of life post implantation (%)
Seizure free	1 (2)	1 (2)
>50% seizure reduction	15 (32)	11 (23)
<50% seizure reduction	11 (23)	4 (9)
No effect	20 (43)	2 (4)
Seizure aggravation	0 (0)	0 (0)

except for one who was explanted after 4 months due to a local infection at the implant.

The effect of VNS on seizure frequency is shown in Table 2. One patient became seizure free; a 31-year-old man, fully employed, with epilepsy onset at 14 years of age. He had a cryptogenic localization-related epilepsy with daily simple and complex partial seizures with occasionally secondary generalization in the pre-VNS period. After implantation his seizure frequency gradually decreased, but he was not seizure free until 1.5 years after the implantation. Furthermore, 15 patients had >50% reduction in seizure frequency, defined as responders. Thus, a total of 16 patients (34%) were responders. All the responders had localization-related epilepsies with an even distribution between symptomatic and cryptogenic forms. The responders did not differ from the non-responders with regard to etiology, localization of seizure onset, or ictal semiology. None of the patients with generalized epilepsy were responders. Among the three patients with Lennox–Gastaut syndrome, one had <50% reduction in seizure frequency, the other two had no change in seizure frequency.

The time interval between the implantation and onset of the seizure-reducing effect varied considerably among the responders. In some patients the effect was apparent after a few weeks, while in others the effect gradually emerged and increased over months and even years. Three of the patients had an initial effect that gradually disappeared after 3–9 months. Eight patients were switched to a rapid cycling regimen. Three patients gained by the switch, but did not reach >50% seizure reduction. The remaining five had no effect of rapid cycling regimen.

The side effects are shown in Table 3. Most of these were associated with the stimulation. They were easily tolerated, and the majority of the patients tended to habituate to the symptoms. Fourteen patients (30%) had their device removed after a mean of 2.2 years (0.3–4.3 years). The reasons for the explantation, as shown in Table 4, were mainly lack of efficacy. Three patients wanted to have the device removed, partly due to a moderate or no seizure-reducing effect and partly due to disabling side effects. Three patients were explanted due to device complications, i.e., a lead fracture.

Table 3: Vagus nerve stimulation[a].

	Number of patients (%)
Of the 47 patients 36 reported side effects	
Hoarseness during stimulation	30 (64)
Unpleasant feeling in the throat or left jaw during stimulation	11 (23)
Coughing, hawking, parestesia in the throat during stimulation	9 (19)
Feeling of being strangled during stimulation	5 (11)
Shortness of breath during stimulation	2 (4)
Sleep disturbances, snorelike sounds during sleep	2 (4)
Episodic stomach ache	1 (2)
Local chest pain	1 (2)
Menstrual disturbances	1 (2)
Oesophagitis	1 (2)

[a] Self-reported side-effects ($n = 36$).

Three patients died. One died from a heart disease, one was found drowned, and one suffered a probable SUDEP.

Sixteen patients (34%) reported that they had achieved a better quality of life as a consequence of VNS. Most of these were responders (11 patients). Unexpectedly, five patients claimed to have achieved a better life despite only moderate (three patients), or no (two patients) reduction in seizure frequency. Both their ictal and postictal symptoms were of shorter duration, they felt more alert, better concentrated, and were in a better mood. Some of the responders reported a decreased need of diazepam to stop ongoing seizures, fewer hospitalizations, and days off work. Eighteen patients (38%) would have chosen VNS again. However, three of the responders assessed the reduction in seizure frequency too little to justify

Table 4: Reasons for explantation of the device (n =14).

	Number of patients
Of the 47 patients 4 have been explanted	
Lack of efficacy	10
Embarrassing side effects	3
Lead fracture	3
Infection surrounding the device	1

another implantation. Twenty-two patients (47%) reported to have benefited from use of the magnet.

DISCUSSION

Both the efficacy and side effects achieved by VNS in this study in a very difficult-to-treat epilepsy population are comparable to the results from both short-term and long-term follow-up studies previously reported[4–10]. There is a current agreement that 1/3 of patients experience a seizure reduction of at least 50%, 1/3 experience a more moderate reduction of seizure frequency, and in the remaining 1/3 there is little or no effect of VNS[4]. This is also in accordance with the results in the present study, although the proportion of patients not responding to VNS was somewhat higher in our study (43%). As opposed to previous reports, three patients had an initial effect that gradually diminished after 3–9 months.

The time interval from the implantation to a seizure-reducing effect was achieved varied considerably among the responders. Our experience is in agreement with Uthman[4] who concluded that patients might be divided into three categories: those with a rapid onset of effect (weeks), those with a gradual onset of effect (months, even years), and those with no effect at all. In four of our patients, the improved seizure control was not only maintained but also increased over time. This is also in agreement with previous reports[7, 11].

While VNS seems to reduce the occurrence and severity of several seizure types, it was our clinical impression that secondary generalized tonic–clonic seizures responded more often than other seizure types.

In open clinical trials, in patients with refractory epilepsy, it is often difficult to avoid adjusting some of the patients' AEDs. In the present study, the medication was altered in 19 patients (40%) compared to the baseline period. However, only three of these patients were among the responders, and we believe that these alterations only had marginal influence on their seizure frequency. Nevertheless, it may be difficult to interpret the results in such open trials: The observed reduction in seizure frequency may be a result of a true effect of chronic intermittent VNS, a synergistic effect between VNS and the AEDs, a reflection of the natural history of the epilepsy, or of a placebo effect.

The number of patients in this study, like in some other studies[12, 14, 15], is too small to evaluate efficacy of VNS in patients with generalized epilepsy.

Most of the reported side effects in the present study were mild and transient, but three patients demanded explantation partly due to troublesome side effects. Deaths have occurred during VNS treatment. In a group of 791 patients with VNS followed for 2 years, 15 deaths were reported, of which six were considered to be SUDEP. The mortality rate was comparable to those seen in studies of new AEDs in a population with severe epilepsy. No increased mortality risk could be attributed to VNS[13]. None of the three deaths that occurred in this study had any apparent relation to the VNS treatment. When 1/3 of the patients in the present study reported a better quality of life, felt more alert, were in a better mood, as a consequence of VNS, this is in agreement with the results in another recent study[16].

In a very difficult-to-treat epilepsy population VNS offers a >50% reduction in seizure frequency in about 1/3, comparable to that of some of the new AEDs[17], but lower than for temporal lobectomy[18]. Compared to AEDs, VNS may appear advantageous, as there are no compliance problems, no risk of idiosyncratic or central nervous side effects, and no need for regular blood monitoring. Moreover, the magnet may give some patients a feeling that they are able to control their seizure disorder. The patients may also turn off the stimulation at any time. The treatment is reversible as the NPC system, both the device and the electrodes, can safely be removed[19]. This should be considered in those patients in whom VNS has offered little or no effect 2–3 years post implantation.

Before considering VNS, it is important to rule out the possibility of epilepsy surgery. As the treatment is invasive and associated with relatively high initial costs, approximately US $10,000, it should, in our opinion, only be offered those unable to tolerate or benefit from AEDs, and those in whom a partial reduction of seizure frequency will significantly improve their quality of life.

It is still a problem that VNS is not associated with physiological markers which allow us to monitor and adjust stimulation individually. In addition, there are currently no patient- or epilepsy-related variables that can be used prospectively to identify responders. However, the latter problem may also be applied to AEDs.

CONCLUSION

Although VNS appears to be an efficacious and safe mode of treatment, it should, in our opinion, only be offered to patients with medically and surgically refractory seizures.

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