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Evolution in VNS therapy for refractory epilepsy, experience with Demipulse devices at Ghent University Hospital

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ABSTRACT

Rationale: Vagus nerve stimulation (VNS) is a frequently used treatment for patients with refractory epilepsy who are unsuitable candidates for epilepsy surgery. There has been a steady evolution in VNS technology, as generators' volumes have become smaller and battery life expectancy longer. This pilot study is an open-label retrospective study that describes our experience with the latest commercially available generator, i.e. the VNS Therapy™ Demipulse Model 103. Treatment efficacy and side effects, as well as technical and practical enhancements useful for the patient and for the medical staff are discussed in this study.

Methods: Twenty patients (11F/9M) with a mean age of 40 years (range 8–61), who were considered unsuitable candidates for resective surgery, were implanted with a VNS Therapy™ Demipulse Model 103. Mean monthly seizure frequency reduction and side effects were evaluated 1 year after implantation.

Results: Mean monthly seizure frequency decreased significantly from 54 seizures/month (SEM 30; range 1–555) before treatment to 33 (SEM 24, range 0–445) following 12 months of treatment ($p < 0.05$). Seven patients (39%) were considered responders with a reduction in seizure frequency of more than 50%. One of those seven patients became seizure free. Side effects were stimulation-related tingling sensation in the throat and/or hoarseness, a painful sensation in the left neck or ear region and a lead breakage In addition; one case of SUDEP was reported.

Conclusion: Patients treated with VNS Therapy™ Demipulse generators proved to have a significant decrease in seizure frequency. In this patient group, VNS was well tolerated. The main technical advances are the decrease in size and improved options for battery life follow-up.

1. Introduction

Vagus nerve stimulation (VNS) is indicated in patients with medically or surgically refractory epilepsy. More than 50,000 patients worldwide have been implanted with VNS therapy™ devices since 1989. Initially, efficacy of VNS for refractory epilepsy was studied in the randomised double-blind placebo-controlled E03 and E05 studies, which included 114 and 198 patients with a follow-up of 3 months.[1,2] In these studies, seizure frequency reduction was compared between a high, so-called effective stimulation group and a low, so-called placebo stimulation group. The E03 study found a decrease in seizures of 24% in the high stimulation group versus 6% in the low stimulation group, while the E05 study found a 28% decrease in seizure frequency in the high stimulation group versus 15% in the low stimulation group.[1,2] Prospective and retrospective long-term open-label studies confirmed VNS efficacy and safety in adults and children with refractory epilepsy.[3–11]

In parallel with the increasing amount of clinical data, there has been a steady evolution in VNS technology, as the size of the generator has become smaller (Fig. 1) and battery life expectancy has increased at each new generator release.

This pilot study is an open-label retrospective study that describes our experience with the latest commercially available generator, i.e. the VNS Therapy™ Demipulse Model 103. Treatment efficacy and side effects, as well as technical and practical enhancements useful for neurologists, neurosurgeons and for the patient, are discussed in this study. This study is the first to date to report clinical experience with Demipulse generators.

2. Patients and methods

2.1. Patient population and presurgical evaluation

Between 1/6/2007 and 1/12/2009, 40 patients were implanted with a VNS device (Cyberonics®, Houston, USA) at the Ghent

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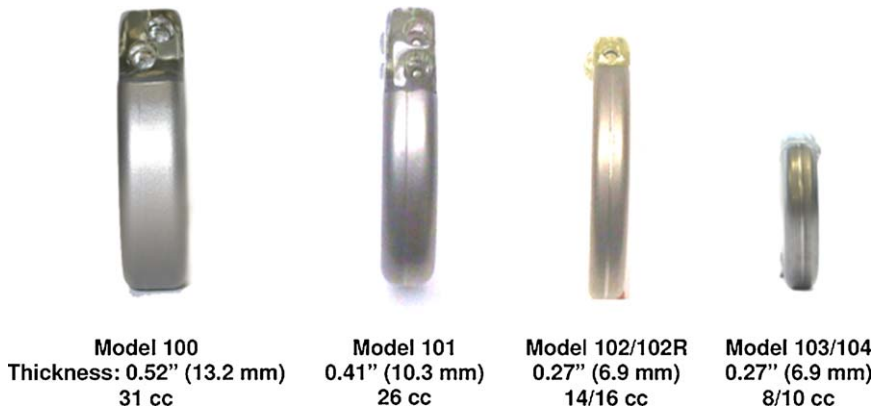

Fig. 1. Volume reduction of VNS generators over time.

University Hospital. All patients were diagnosed with refractory epilepsy and underwent long-term video-EEG monitoring for seizure detection, 3 T brain MRI and PET scan as part of the presurgical evaluation. All patients were considered unsuitable candidates for resective surgery, either because the epileptic focus remained unidentified, or because it was located in functional cortex. Subsequently they were offered treatment with VNS. For the purpose of this study, medical records of patients implanted with a VNS therapy™ Demipulse Model 103 were evaluated. Patients with a post-implantation follow-up of at least 1 year were included in this study. Additionally, a documentation of seizure frequency before implantation and at maximal follow-up was required.

2.2. Implantation procedure

The system was implanted under general anaesthesia via two short incisions. The first incision was placed in a skin fold at the left base of the neck, about 3 cm above the clavicle and across the medial border of the sternocleidomastoid muscle. The left vagus nerve was searched for between the common carotid artery and the internal jugular vein, and exposed over a distance of 3 cm. Using optical magnification, the helical tether and the two helical electrodes were wrapped around the nerve. The lead was carried to the surface in smooth loops and anchored twice, both to the deep and to the superficial cervical fascia. Through a second, also transverse, incision below the left clavicle on the mamillary line, a small epifascial pouch was shaped in which the pulse generator (Cyberonics Demipulse, model 103 or 104) was placed. The lead was subcutaneously tunneled from the first to the second incision and plugged into the pulse generator. The system was telemetrically verified before the pulse generator was anchored to the pectoral fascia and the wounds were closed.

2.3. Ramping-up procedure and stimulation parameters

Stimulation was initiated 2–4 weeks after surgery at the epilepsy clinic. Stimulation intensity was gradually increased over the next months with steps of 0.25 mA until seizure control was reached or side effects appeared. The other stimulation parameters were programmed as follows: pulse width 250–500 μs; frequency 20–30 Hz; on/off cycle 30 s on/10 min off or 30 s on/5 min off. As part of normal clinical practice in patients treated with VNS at the Ghent University Hospital, antiepileptic drug (AED) treatment was preferably left unchanged during the first 12 months of follow-up.

2.4. Outcome measures

The clinical data collected for this study included: gender and age at time of implantation; type of epilepsy; mean monthly seizure frequency before implantation and at maximal follow-up; number of antiepileptic drugs taken before implantation and at maximal follow-up; stimulation intensity at maximum follow-up. In addition, properties of the surgical implantation procedure as well as user friendly characteristics for neurologist and patients were assessed.

Monthly seizure frequency pre-VNS was based on seizure frequency reported 1 month before date of surgery. Mean monthly seizure frequency post-VNS resulted from an average of two to three consecutive months at maximum follow-up.

Type of epilepsy was based on clinical semiology of the seizures and ictal and interictal electroencephalographic recordings.

Primary outcome measures included reduction in mean monthly seizure frequency and the percentage of patients with a seizure frequency reduction of 50% or more (responder rate). Secondary outcome measures were the changes in number of concomitant AEDs taken at maximum follow-up compared to before stimulation and stimulation output at maximum follow-up.

Outcome measures were first calculated for the entire study group. Subsequently, the study population was divided into two groups: responders (seizure frequency reduction of 50% or more) and non-responders (seizure frequency reduction between of less than 50%). Outcome parameters were assessed for the two groups separately.

2.5. Ethical approval

This retrospective study was approved by the Ethical Committee of Ghent University Hospital (EC 2005/238 and EC 2009/604). Informed consent was obtained from all patients.

2.6. Statistical analysis

Group mean differences in percentage of reductions in seizure frequency and differences in mean monthly seizure frequencies were tested non-parametrically. Statistical significance was set on $p < 0.05$. All calculations were performed using SPSS 15.0.

3. Results

3.1. Patient population

Twenty patients (11 females, 9 males) with a mean age of 40 years (range 8–61) were included in the study. Sixteen patients had localised epilepsy with complex partial seizures with or without secondary generalisation. Four patients had generalised epilepsy with tonic clonic seizures, absences or myoclonic seizures. Two patients had a follow-up of 6 and 8 months due to early discontinuation of VNS therapy (1 sudden unexplained death in

Table 1
Overview of primary and secondary outcome parameters in patient population.

	Seizure reduction ≥ 50% $N = 7$	Seizure reduction ≤ 50% $N = 11$
Mean age at implantation (years)	34 (range 21–56)	32 (8–49)
Mean follow-up (months)	12	12
Mean seizure frequency/month pre-VNS (*n*)	42 (range 7–150)	62 (1–555)
Mean seizure frequency/month post-VNS (*n*)	4 (range 0–12.5)	51 (1–445)
Mean seizure reduction (%)	84	13
Number of AED before (*n*)	3 (2–5)	3 (3–4)
Number of AED after (*n*)	3 (2–5)	3 (2–5)
Mean stimulation output (mA)	1.64 (0.75–2.25)	1.88 (1.5–2.5)
Epilepsy type		
Focal	5	10
Generalised	2	1

epilepsy (SUDEP) and 1 lead breakage, respectively). They were excluded from further statistical analysis.

3.2. Seizure frequency reduction and responder rate (Table 1)

Mean monthly seizure frequency before implantation was 54 seizures/month (SEM 30, range 1–555), mean monthly seizure frequency at maximum follow-up was 33 seizures/month (SEM 24, range 0–445) (Wilcoxon Signed Ranks test, <0.05).

Seven patients (39%) were considered responders with a reduction in seizure frequency of more than 50%. One of those seven patients became seizure free. Eleven patients (61%) were non-responders (reduction in seizure frequency of less than 50%). In the non-responder group, three patients (16%) responded with a seizure frequency reduction between 30 and 50%, two patients (11%) responded with a seizure frequency reduction of less than 30%, five patients (28%) experienced no change in seizure frequency and one patient reported a small increase in seizure frequency. Responders started to respond to their VNS treatment at month 7 after date of implantation, while no effect was seen over time in the non-responder group (see Fig. 2) (Wilcoxon Signed Ranks test, $p < 0.05$).

3.3. Comparison between responders, partial responders and non-responders

There were no significant differences regarding seizure frequency before VNS, mean age at time of implantation and number of AEDs before implantation, between the responder and non-responder group (Table 1).

The mean stimulation output current at maximal follow-up was 1.79 mA (range 0.75–2.5 mA) (Fig. 3). Responders had a lower mean stimulation output at maximal follow-up (1.64 mA, range 0.75–2.25 mA) in comparison to non-responders (1.88 mA, range 1.5–2.5 mA), although these differences were not statistically significant. Mean number of AEDs before and after implantation in the responder and non-responder was 3 (range of 2–5 for the responders and 2–4 for the non-responders). These results, although based on small amount of patients, are in accordance with data in the literature in which these variables did not appear to be independent predictors of outcome.[7,14–19]

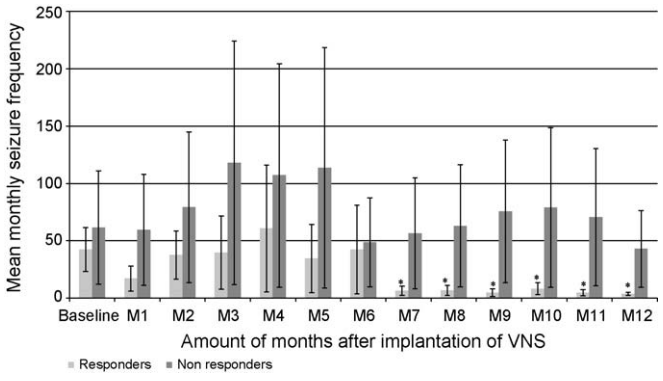

Fig. 2. Evolution of mean monthly seizure frequency in responders and partial responders compared to non-responders over time. Responders started to respond to their VNS treatment at month 7 after date of implantation.

3.4. Reported side effects

All patients reported a stimulation-related tingling sensation in the throat and/or hoarseness, especially during the ramping-up period. Two patients reported a painful sensation in the left neck or ear during stimulation at 2 and 2.25 mA, respectively. Other stimulation parameters for both patients were: 20 Hz, 500 μs, 30 s on/5 min off. One of those patients also complained of a light dyspnoea when lying on her left side. The dyspnoea was not continuously present over time, even though stimulation parameters were not adjusted.

One mentally retarded patient, which was considered as a partial responder at 6 months of follow-up, had a habit to frequently rotate his generator subcutaneously, which resulted in a corkscrew shaped lead and finally to a lead breakage. Consequently, at 8 months of follow-up, interrogation of his VNS device showed a very low lead impedance ($<200\ \Omega$), which indicated a short-circuit of his VNS system. Subsequently, the output current was programmed at 0 mA. As seizure frequency did not increase in the following months, it was decided not to replace the VNS device.

3.5. SUDEP

One patient died suddenly at the age of 62 after 6 months of follow-up. She was found at home in asystole with bilateral light-

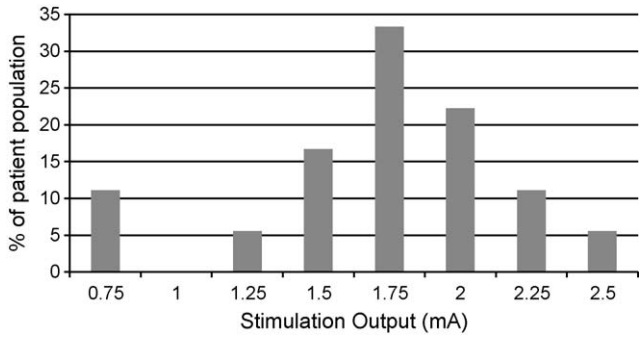

Fig. 3. Percentage of patients programmed at different stimulation outputs at maximal follow-up.

rigid pupils. The patient was transported to an intensive care unit after receiving emergency care at home, but she died shortly after. No specific cause of death was identified on autopsy. This case was considered as a 'sudden unexpected death in epilepsy' (SUDEP).

4. Discussion

In this retrospective study we evaluated the efficacy, safety and practical enhancements of the latest commercially available VNS device, the VNS Therapy Demipulse 103 Model (Cyberonics®, Houston, USA), in the treatment of patients with refractory epilepsy.

Demipulse generators seem to have similar efficacy as previous generators in the treatment of refractory epilepsy. We evaluated VNS therapy with Demipulse generators after 12 months of stimulation. Our study yielded a responder rate of 39%. This result is comparable to the results obtained with previous models of VNS generators, such as the study by Morris and Mueller, who described responder rates of 23% at 3 months and 37% at 1 year.[12] Other retrospective and prospective studies reported similar or slightly higher responder rates after at least 1 year of stimulation, such as 26%,[10] 48%,[7] 50%[11] or 54%.[3] In our study, mean stimulation output in the responder group was 1.79 mA range (0.75–2.5), which is similar to results reported by DeGiorgio et al.[13]

Besides equivalent efficacy, Demipulse generators appeared to have similar tolerability as previous generators, as no new side effects were described in our study.[1–3,12,13] We report 1 case of SUDEP and one case in which VNS therapy was stopped due to a lead breakage. The relationship between VNS and SUDEP has been subject of research, although no correlations between VNS treatment and SUDEP were found.[8,20–22] Lead breakages were also reported in previous studies, especially in children en mentally retarded patients.[23,24]

Due to reduced generator volume, Demipulse generators are more easily implanted, which reduces considerably possible surgery related complications. Earlier versions of the VNS pulse generator required larger incisions and larger pouches for implantation; they also brought about more distinct skin eminences in the pectoral region and some tension on the wound edges. In order to avoid unaesthetic scars the insertion of the pulse generator was often performed via an incision on the anterior axillary line (and in some cases underneath the pectoralis muscle), which implicated a longer and broader range of dissection and, hence, more frequent problems of pouch hematoma and pain after surgery. The pulse generators n° 103 and 104, in virtue of their small size and weight, do not require such coping strategies. The short skin incision can be placed directly over the site of insertion in the pectoral region, and can be aesthetically closed with a running intradermal suture or with glue. Problems of pouch hematoma or pain have become virtually eliminated. Moreover, in our study no single infection of generator or lead implantation site was reported, although this is the most common observed surgical complication in published trials with older devices with an incidence varying around 3%.[23,25] Even though cosmetic advantages are not a priority in health care in general, it is worthwhile noting that epilepsy patients often deal with a lot of prejudice, which indirectly affects their social and economic integration in our society. Discrete scars enhance their well being and ameliorate their daily social life. For this reason cosmetic advantage of Demipulse must be emphasized.

Besides the surgical and esthetical advantages of smaller generator volume, Demipulse generators also enhance treatment and clinical follow-up of patients. First of all, the generator life projection system displays the end of life (EOL) in exact amount of years and months in function of programmed parameters and warns the clinician 6 months ahead to foresee generator replacement. This is of particular value, as postponing generator replacement may result into permanent loss of seizure control.[26] Battery life depends on many factors including the generator model, stimulation parameters, lead impedance and magnet use. The first model developed for human use, Model 100 (2002), had an expected battery life of 4–8 years. For the second generation of generators, i.e. Model 101 (2003) battery life increased to 8–12 years. Model 102 and models 103/104 (2007, Demipulse) have similar life expectancies as model 101. Ideally, future technology development will allow transcutaneous battery recharge and render generator replacements unnecessary. This will further ameliorate quality of life of patients and reduce health care costs.

Another important feature useful for clinicians is the fact that Demipulse generators are capable of measuring lead impedances in Ohms, while older models only delivered DC–DC converter codes. This gives the clinician more accurate information about the good functioning of the VNS device. Lead impedance should vary between 200 Ω (low impedance) and 7 kΩ (high impedance). If high impedance is discovered upon interrogation of the device, a discontinuity of the lead or fibrosis between the nerve and the lead may be the reason. To check whether a lead breakage is present, a radiography or CT scan of the neck can be performed. In other cases a surgical revision of the device may be needed. Demipulse generators are able to measure lead impedance every 24 h. If the impedance has reached "high" or "low" values between interrogations at office visits, a warning message will be displayed when interrogating the device. For the moment, the device does not inform the clinician about the exact date/h on which lead impedance changed. This element could be useful to correlate with certain potentially harmful events, such as an important head or neck trauma which could explain breakage of the lead. In our study, one mentally retarded patient, showed a very low impedance (<200 Ω), which indicated a short-circuit of his VNS device.

Despite the fact that VNS therapy as a treatment for epilepsy has proven to reduce significantly health care utilisation and its related costs.[27,28] Demipulse generators are not reimbursed in all countries. In addition to equal efficacy and tolerability in comparison with older devices, Demipulse generators have better surgical characteristics and improve clinical follow-up of patients treated with VNS. Future studies with larger amount of patients are needed to confirm improved capacities of Demipulse VNS devices, which hopefully will lead to reimbursements of the new model 103 in all concerned countries.

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