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Vagus Nerve Stimulation in the Treatment of Patients with Pharmacoresistant Epilepsy: Our Experiences

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A B S T R A C T

Vagus nerve stimulation (VNS) for the treatment of refractory partial epileptic seizures with or without secondary generalisation in patients older than 12 years was approved in Europe in 1994 and in the United States in 1997. We have studied the efficacy of VNS in patients with pharmacoresistant epilepsy hospitalized in the Neurology Department of the University Hospital Centre Zagreb. From 1997 do 2001 we have implanted VNS in 11 patients with pharmacoresistant epilepsy, who were magnetic resonance imaging (MRI) negative and from May 2007 to May 2009 in 11 patients with pharmacoresistant epilepsy, 9 of them were MRI positive, and were inoperable due to localisation of the pathomorphologic changes (ganglioglioma, hamartoma, various types of cortical dysplasia, porencephalic cysts), 2 were MR negative. In the group of MRI negative patients 1 patient had complex partial seizures (CPS), 6 patients had CPS with secondary generalisation, 2 patients had primary generalized epilepsy (PGE) including myoclonic, absence, atonic and tonic-clonic seizures, one patient had PGE and CPS, and 3 patients had Lennox-Gastaut syndrome (LGS). In the group of MRI positive patients one patient had elementary partial seizures (EPS) and CPS, two patients had EPS and CPS with secondary generalisation, one patient had CPS, 3 patients had CPS with secondary generalisation, and 2 patients had CPS with secondary generalisation as well as atonic seizures. After continuous follow-up of 11 MRI negative patients during 5 years and 2 MRI negative patients during one year there was decrease in mean-seizure frequency of 51.67%. After continuous follow-up of 9 MRI positive patients during 2 years there was decrease in mean-seizure frequency of 61.9 %. The most frequent side effects were hoarseness, throat pain and cough in the »on phase« of the VNS, but they were mild and transitory. We can conclude that VNS was effective mode of therapy in our group of patients with pharmacoresistant epilepsy.

Key words: *epilepsy, pharmacoresistancy, neurosurgical treatment, vagus nerve stimulator*

Introduction

Many patients with epilepsy suffer from persistent seizures despite optimal antiepileptic therapy (AET). Surgical resection, such as temporal lobectomy for mesial temporal sclerosis, can result in a dramatic reduction in seizure frequency (chances of seizure-free results are high – 70–90%), but only in selected patients[1]. Generally, complication rates of epilepsy surgery are relatively low and thought to be acceptable, with approximately 1 to 2% permanent morbidity[1,2]. Chronic, intermittent vagus nerve stimulation (VNS) has proven to be a safe, effective option for patients suffering from refractory seizures who are not candidates for surgical resection. Although only a small minority of patients will be entirely seizure-free, VNS as an adjunct to medical therapy does appear to provide a significant amount of improvement in the quality of life. The neurocybernetic prosthesis (NCP) system developed by Cyberonics (Webster, TX) for the treatment of refractory partial epileptic seizures with or without secondary generalisation in patients aged 12 years or older was approved in Europe in 1994 and in the United States in 1997[3,4].

VNS consists of a pulse generator, bipolar electrodes, programator with software for IBM compatible computers, guide and magnetic plate for autoregulation. The

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generator is surgically placed in a pocket formed under the skin, below the left collarbone. Bipolar electrodes are wrapped around the left vagus nerve (middle cervical part). The generator is set to 0mA initially followed by an increase in the output current. Beginning parameter settings of 30-Hz signal frequency, 500-μs pulse width, 30 seconds on-time, and 5 minutes off-time have been found to be effective in double-blind, controlled studies, although these parameters may vary considerably in practice (from the literature data off-time could be set from 5 to 180 minutes). In addition, a hand-held magnet can be used by patients or caregivers to activate VNS in response to an aura or seizure onset[5–7]. Cardiac arrhythmias are a potential theoretical risk with VNS, for this reason, electrodes are implanted around the left vagus nerve only[8].

Patients and Methods

We have studied the efficacy of VNS in patients with pharmacoresistant epilepsy hospitalized in the Department of Neurology of the University Hospital Zagreb.

From 1997 do 2001 we have implanted VNS in 11 patients with pharmacoresistant epilepsy (6M, 5F), mean age 26.62±4.93, who were magnetic resonance imaging (MRI) negative and from May 2007 to May 2009 in 11 patients with pharmacoresistant epilepsy (5M, 6F), mean age 30.61±12.76; 9 of them were MRI positive (4M, 5 F), mean age 26.89±8.45, and were inoperable due to localisation of the pathomorphologic changes (ganglioglioma, hamartoma, various types of cortical dysplasia, porencephalic cysts, see details on Table 1), 2 were MR negative (1M, 1F), mean age 50±22.63.

TABLE 1
BRAIN MRI FINDINGS IN MRI POSITIVE PATIENTS

	Number of patients
Periventricular nodular heterotopia and hamartoma (parietal)	1
Polymicrogyria (frontal and parietal)	1
Polymicrogyria (frontal)	1
Polymicrogyria (occipital)	1
Frontoparietal ganglioglioma (precentral and postcentral)	1
Focal cortical dysplasia (frontal)	1
Bilateral frontoparietal porencephalic cysts (after perinatal stroke)	1
Bilateral frontal cortical atrophy	1
Focal cortical dysplasia (frontal and temporal)	1

From 2001 to 2007, due to financial reasons, we were not in the possibility to perform implantations. In the group of MRI negative patients 1 patient had complex partial seizures (CPS), 6 patients had CPS with secondary generalisation, 2 patients had primary generalized epilepsy (PGE) including myoclonic, absence, atonic and tonic-clonic seizures, one patient had PGE and CPS, and 3 patients had Lennox-Gastaut syndrome (LGS). In the

TABLE 2
MAIN CHARACTERISTICS OF PATIENTS WHO WERE CANDIDATES FOR VNS IMPLANTATION

2a. Characteristics of MRI negative patients

Seizure type	Number of patients	Mean disease duration (years)	Mean number of AEDs
		before VNS, $\overline{X}$±SD	$\overline{X}$±SD
CPS	1	19	4
CPS+SG	6	19.34±14	4.17±0.75
PGE	2	18±7.78	3
PGE+CPS	1	22	5
Lennox-Gastaut syndrome	3	22.33±12.09	4±1

2b. Characteristics of MRI positive patients

Seizure type	Number of patients	Mean disease duration (years)	Mean number of AEDs
		before VNS, $\overline{X}$±SD	$\overline{X}$±SD
EPS+CPS	1	33	4
EPS+CPS+SG	2	13.5±0.7	3.5±0.7
CPS	1	30	3
CPS+SG	3	22.34±12.42	4.34±0.58
CPS+SG+atonic	2	14±6.65	4

SG – secondary generalisation (periodically, i.e. grand mal seizure did not follow every partial seizure)
PGE – myoclonic + absence + atonic + tonic-clonic seizures

group of MRI positive patients one patient had elementary partial seizures (EPS) and CPS, two patients had EPS and CPS with secondary generalisation, one patient had CPS, 3 patients had CPS with secondary generalisation, and 2 patients had CPS with secondary generalisation as well as atonic seizures. Tables 2a and 2b in details summarize main characteristics of patients, including data about epilepsy classification (seizure type), mean disease duration and mean number of failed antiepileptic drugs (AEDs). Except one patient with asthma, there were no other comorbidities.

We have divided patients into two groups – MRI negative and MRI positive patients, because we wanted to compare the effectiveness of this surgical method of treatment in relation to certain brain patomorphologic changes.

Number of seizures was obtained retrospectively during follow up visits, that were organized in the first year after operation every month, and in the next years every 3 months. We calculated mean number of seizures on a monthly basis during follow-up period.

Intensity of the stimulation

One week after implantation we began stimulation with the lowest current (0.25 mA). The stimulation was being increased gradually in the next months. VNS parameters were adjusted according to a clinical response in an individual patient – we increased the intensity of the stimulation till we achieved the satisfactory reduction in the number of seizures. The final intensity of the stimulation in the group od MRI negative patients was from 0.75 to 2 mA: in one patient with CPS 0.75 mA, in 6 patients with CPS with secondary generalisation from 1.5 to 2 mA, in 2 patients with PGE from 1.25 to 2 mA, in one patient with PGE and CPS 0.75 mA, and in 3 patients with Lennox-Gastaut syndrome 2 mA. In the group of MRI positive patients the final intensity of the stimulation was from 0.25 to 2 mA: in one patient with EPS and CPS 1.25 mA, in 2 patients with EPS and CPS with secondary generalisation 0.75 and 1.50 mA, in one patient with CPS 2 mA, in 3 patients with CPS with secondary generalisation from 0.75 to 1.75 mA, and in 2 patients with CPS with secondary generalisation as well as atonic seizures from 1.5 to 2mA.

The duty cycle was on the basis of controlled clinical trials set to 30-Hz signal frequency, 500-μs pulse width, 30 seconds on-time, and 5 minutes off-time. After VNS implantation there was no reduction in the dose and number of AEDs, patients stayed on stable AED regimen.

Statistics

The results were expressed by mean values and standard deviation. The differences between groups were tested by Student t-test. The value of $p<0.05$ was considered statistically significant.

Side effects and complications of the procedure

In the group of MRI negative patients one patient died 3 years after VNS implantation (most probably as a consequence of suffocation after grand mal seizure), one patient experienced transient asystole during device implantation that was successfully treated with atropine (1 mg i.v.), other patients complained about transient mild hoarseness, throat pain and cough in the »on phase« of the VNS.

In the group of MRI positive patients one patient experienced serial EPS at the intensity of the stimulation of 0.50 mA, this patient also experienced worsening of asthma and had muscular pain on the place of implanted generator and was operated again due to pulse generator dislocation in the left pectoral region. It is important to mention that this patient was a woman of asthenic constitution. One patient experienced transitory hypotension at the intensity of stimulation of 0.50 mA, other patients complained about transient mild hoarseness, throat pain and cough in the »on phase« of the VNS.

Results

In all our patients overall seizure control continued to improve with time, and except the decrease in seizure frequency seizures became shorter and less intensive.

After continuous follow-up of 11 MRI negative patients during 5 years and 2 MRI negative patients during one year there was decrease in the mean-seizure frequency of 51.67% (Table 3). Reduction in the mean seizure frequency after first three months was 33.3%, after first year 42.4%, after second year 50.7%, after third year 51.5%, and after fourth year 51.88%.

After continuous follow-up of 9 MRI positive patients during 2 years there was decrease in the mean-seizure frequency of 61.9% (Table 4). Reduction in the mean seizure frequency after first three months was 38.4%, and after first year 56.7%.

We have observed improvement of mood and the general quality of life in all patients.

TABLE 3
COMPARATION OF MONTHLY NUMBER OF SEIZURES BEFORE AND AFTER VNS IMPLANTATION IN MRI NEGATIVE PATIENTS (FOLLOW UP: 5 YEARS FOR 11 PATIENTS AND ONE YEAR FOR TWO PATIENTS)

Seizure type	Monthly number of seizures before implantation, $\overline{X}$±SD	Monthly number of seizures after implantation, $\overline{X}$±SD
CPS	8	4
CPS+SG	12±5.22	5.83±3.71; p=0.01
PGE	18±2.83	4.5±0.71; p=0.07
PGE+CPS	30	20
Lennox-Gastaut syndrome*	26.67±5.77	13.34±2.88; p=0.02

* One of the patients with Lennox-Gastaut syndrome was completely seizure free after VNS implantation

TABLE 4
COMPARATION OF MONTHLY NUMBER OF SEIZURES BEFORE AND AFTER VNS IMPLANTATION IN MRI POSITIVE PATIENTS (FOLLOW UP: 2 YEARS)

Seizure type	Monthly number of seizures before implantation, $\bar{X}$±SD	Monthly number of seizures after implantation, $\bar{X}$±SD
EPS+CPS	16	8
EPS+CPS+SG	45±21.21	15±7.07 (only EPS); p=0.2
CPS	16	8
CPS+SG	6.67±4.16	2±1.73 (only CPS); p=0.1
CPS+SG+atonic	35±7.07 (serial seizures)	9.5±0.71 (only CPS); p=0.03

Discussion

It is agreed that 1% of the general population is affected with epilepsy and close to 30% of epilepsy patients are pharmacoresistant. In spite of a recent increase in the number of new medications that are available on the market, many patients continue to have seizures or their seizures are controlled at the expense of intolerable side effects. Resection epilepsy surgery is an alternative. Improvements in imaging resulted in an increased ability for preoperative identification of intracerebral and potentially epileptogenic lesions. High resolution MRI plays a major role in structural and functional imaging; other functional imaging techniques (e.g., positron emission tomography and single-photon emission computed tomography) provide complementary data and, together with corresponding electroencephalographic findings, result in a hypothesis of the epileptogenic lesion, epileptogenic zone, and the functional deficit zone[1]. However, not every pharmacoresistant patient is a good candidate for neurosurgical treatment. Additionally, it is only offered to a small fraction of those patients due to the lack of an adequate number of comprehensive epilepsy programs and financial support for such surgeries. In other patients with pharmacoresistant epilepsy we can offer vagus nerve stimulation (VNS), whose efficacy is well established in adults and adolescents with partial epilepsy with or without secondary generalisation. In several small studies that included patients with LGS, 37–73% of patients had a >50% decrease in seizures[9].

Side effects in our patients – hoarseness, throat pain, cough and dyspnea, usually occurring in association with stimulation, coincide with the side effects formerly described in the literature[10,11]. However, transitory hypotension noticed in our patient was not, to our knowledge, described in the literature as a side effect of VNS so far. Ventricular asystole due to complete atrioventricular nodal block has been reported as a rare but potentially serious complication of initial intraoperative testing during the device implantation[12,13]. Ventricular asystole is transient and generally of brief duration (<15 seconds), although one case lasted 45 seconds. The mechanism is unknown, but may be related to direct activation of the parasympathetic pathway to the heart (the left vagus nerve has a greater chronotropic effect on the atrioventricular node, while the right vagus nerve affects mostly the sinoatrial node) or to activation of afferent vagal pathways via the nucleus of the tractus solitarius affecting cardiovascular reflexes. Only one of our patients experienced transient asystole during device implantation. Other common adverse events of VNS, that were not present in our group of patients, include bleeding and infection from the surgery, pharyngitis, dyspepsia, dysphagia, nausea, vomiting, headache, paresthesia in the neck, and psychosis[13].

Unlike chronic treatment with antiepileptic medication, the benefit of VNS therapy is maintained during prolonged stimulation, and overall seizure control (percentage change from baseline and response rates) continues to improve with time. We have also observed progressive decrease in seizure frequency in our group of patients with implanted VNS. Preliminary results of pilot studies demonstrated significant reduction in the frequency, intensity, and duration of seizures with chronic, intermittent VNS[14,15], which led to subsequent multicenter, double-blinded, randomized controlled trials in adults with medically refractory epilepsy[16,17]. These trials demonstrated a mean or median seizure frequency reduction of 24 to 31% over 3 months of follow-up in patients receiving the VNS treatment paradigm. Response during the first 3 months of treatment is predictive of long-term response[18], which has also been shown in our group of patients – we noticed significant mean seizure reduction in the first three months after VNS implantation.

According to the literature data, after 2 years of treatment, patients achieve an overall average of 40 % reduction in seizure frequency. In 40 to 50 % of the patients, the frequency of seizures can even be decreased by 50%. Moreover, even in the absence of a significant reduction of seizures, patients subjected to this treatment have reported the improvement in their quality of life[19]. Other authors report in their series decrease in mean seizure frequency by 26% after 1 year, by 30% after 5 years, and by 52% after 12 years with VNS treatment[20]. Results in our series were even better – our MRI negative patients experienced decrease in mean-seizure frequency of 51.67% during 5 years and our MRI positive patients had better results and experienced decrease in mean-seizure frequency of 61.9 % during 2 years. Considering the fact that, according to the literature, the best seizure reduction frequency is achieved after 5 years of VNS[21], results in our group of patients were even better, because the significant decrease in mean seizure frequency was noticed in the early follow-up period.

It is also important to emphasize that we had good results in decreasing seizure frequency with VNS in patients with primary generalized epilepsy, although the primary indication of this mode of therapy is partial epilepsy.

Limitations of the study

We followed most of our MRI negative patients (11 of them) during five years, but two of them were operated recently and were followed only for one year. We described the results of VNS efficacy in all 13 MRI negative patients together, although there were not followed in the same period of time, because we divided our patients in two groups – MRI positive and MRI negative.

Intensity of the stimulation of VNS was not the same in every patient, but this was dependent on the clinical response and mean-seizure frequency in an individual patient.

Conclusion

VNS was effective mode of therapy in our group of patients with pharmacoresistant epilepsy, including both partial and generalized epilepsy. Decrease in mean seizure frequency was achieved in the early follow-up period and stayed stable in the later period. In all patients in whom treatment with three medications in monotherapy or combination therapy has failed, VNS may be considered as a viable option at this stage. VNS is associated with a low rate of perioperative complications, and the majority of side effects are stimulation-dependent and thus reversible.

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STIMULACIJA VAGUSNOG ŽIVCA U LIJEČENJU BOLESNIKA S FARMAKOREZISTENTNOM EPILEPSIJOM: NAŠA ISKUSTVA

SAŽETAK

Stimulator vagusnog živca (engl. Vagus nerve stimulator – VNS) odobren je za liječenje refraktornih parcijalnih epileptičkih ataka s ili bez sekundarne generalizacije u bolesnika starijih od 12 godina u Europi 1994. godine i u SAD-u 1997. godine. U našem smo istraživanju pratili učinkovitost VNS-a u bolesnika s farmakorezistentnom epilepsijom koji su hospitalizirani u Klinici za neurologiju Kliničkog bolničkog centra Zagreb. Od 1997. do 2001. godine VNS je ugrađen u 11 bolesnika s farmakorezistentnom epilepsijom, koji su bili MR (magnetska rezonanca) negativni, a od svibnja 2007. do svibnja 2009. godine u 11 bolesnika s farmakorezistentnom epilepsijom, od kojih je 9 bilo MR pozitivno, i nisu bili kandidati za resektivno neurokirurško liječenje zbog lokalizacije patomorfoloških promjena (gangliogliomi, hamartomi, različiti tipovi kortikalne displazije, porencefalične ciste), a 2 bolesnika bilo je MR negativno. U grupi MR negativnih bolesnika jedan bolesnik je imao kompleksne parcijalne epileptičke atake (engl. complex partial seizures - CPS), 6 bolesnika imalo je CPS sa sekundarnom generalizacijom, 2 bolesnika imalo je primarno generaliziranu epilepsiju (PGE) uključujući mioklone, absence, atoničke i toničko-kloničke epileptičke napadaje, jedan bolesnik imao je PGE i CPS, a 3

bolesnika imalo je Lennox-Gastautov sindrom (LGS). U grupi MR pozitivnih bolesnika jedan bolesnik imao je elementarne parcijalne epileptičke atake (engl. elementary partial seizures - EPS) i CPS, dva bolesnika imala su EPS i CPS sa sekundarnom generalizacijom, jedan bolesnik imao je CPS, 3 bolesnika imala su CPS sa sekundarnom generalizacijom, a 2 bolesnika imala su CPS sa sekundarnom generalizacijom kao i atoničke atake. Nakon kontinuiranog praćenja 11 MR negativnih bolesnika tijekom 5 godina te 2 MR negativna bolesnika tijekom godine dana nađeno je smanjenje u prosječnoj učestalosti epileptičkih ataka za 51,67%. Nakon kontinuiranog praćenja 9 MR pozitivnih bolesnika tijekom 2 godine nađeno je smanjenje u prosječnoj učestalosti epileptičkih ataka za 61,9%. Najčešće nuspojave bile su promuklost, bol u grlu i kašalj u »on-fazi« rada stimulatora. Navedene nuspojave bile su blagog intenziteta i prolaznog karaktera. Stimulacija vagusnog živca pokazala se kao učinkovit način liječenja u našoj grupi bolesnika s farmakorezistentnom epilepsijom.