Vagus nerve stimulation for the treatment of refractory epilepsy

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Abstract: Vagus nerve stimulation (VNS) represents one of the main surgical options for the treatment of the refractory epilepsy in pediatric and adult patients. There are several mechanism involved in vagal nerve stimulation which could influence the pathophysiology of seizures like neuromodulation of the thalamic and subthalamic nuclei involved in seizure initiation and the modulation of the neurotransmitters pattern norepinefrin, GABA, and serotonin. The VNS system is composed of the implanted components (the generator, the lead with the electrodes attached) and the programming system components (programming wand and handheld computer). The authors present their experience with 81 patients diagnosed with refractory epilepsy, investigated, selected and implanted with vagal neurostimulators between December 2012 and January 2015 in Neurosurgery Clinic, "Bagdasar-Arseni" Emergency Hospital. The surgical technique and the potential pitfalls are described in detail. There were 20 children (24,7%) and 61 (75,3%) adults in this series. There was no death in this series and no intraoperative incidence. One patient presented dysphagia postoperatively which completely remitted after two months of follow-up. The outcome in term of seizure frequency and severity was better for patients under 30 years compared with patients older than 30 years. VNS represents now a safe, quick and efficient surgical procedure with a minimum period of hospitalization and a short recovery period. The good results on long term improve the quality of life of the patients and facilitate the social and professional reinsertion.

Key words: refractory epilepsy, vagus nerve stimulation

Introduction

Refractory epilepsy represents a severe clinic entity which involves a significant number of patients and has important economic and social implications. The consequences for the patients are numerous and severe and include: adverse effects with long-term AED use (1, 2-5), increased seizure severity (3), depression and anxiety (4),

increased mortality and morbidity (6-8), seizure-related injuries, and increased healthcare utilization (eg, ER visits, hospitalizations) (9-11). For all these patients the drug therapy fails and the epilepsy surgery remains the only option. One of the surgical techniques employed in the management of refractory epilepsy is vagus nerve stimulation. Bremmer at al in 1938 were the first to investigate the use of vagus nerve stimulation and they recorded evoked response in thalamus after the nerve stimulation. The first effects of vagal nerve stimulation in animal models of chemical induced epilepsy were demonstrated in 1985 (12), this method relieving the subject from seizures by desynchronizing the cortical activity and decreasing the length and frequency of the seizures. There are several mechanism involved in vagal nerve stimulation which could influence the pathophysiology of seizures (13-23). First it should be underlined that vagus nerve contains an important contingent of afferent fibers to the dorsal nucleus of the vagus nerve located at the level of medulla oblongata. These inputs are directed to the locus coeruleus located in pons. This structure has multiple connections with several important cerebral structures. One important connection is with thalamic nuclei. Another important connection is with amygdala and hippocampus. From the thalamus the nervous inputs are directed through the entire subcortical and cortical structures of the brain. Therefore, in the end the vagus nervous stimuli are able to modulate the electric activity through the entire brain and to induce the desynchronization of the EEG rhythms (21, 22). Also, it was demonstrated that vagus nerve stimulation works by neuromodulation of the thalamic and subthalamic nuclei involved in seizure initiation and by modifying the neurotransmitters pattern like norepinefrin (13,14, 19), GABA (15, 17, 18), serotonin and aspartate (16, 17). The neurotransmitters pattern is regulated in hippocampus through the over expression of brain derived neurotrophic factor and fibroblast growth factor (24). Another important mechanism of action of vagus nerve stimulation is represented by the influence of the cerebral blood flow in thalamus and brain cortex, which indirectly may influence diffusely the electric activity of the entire brain cortex (20, 23).

The VNS system is composed of the implanted components (the generator, the lead with the electrodes attached (Figure 1a)) and the programming system components (programming wand and handheld computer) (Figure 1b).

There are three electrodes which are attached to the vagus nerve: one positive, one negative and a neutral (tethered) electrode (Fig. 1c). The electrodes are connected to the generator through a lead. The lead and the generator are placed subcutaneously. The generator can be interrogated wireless using a special emitter called wand. The wand is connected to a handheld computer. Using these tools the doctor can turn on, turn off and more important can interrogate the generator to see the status of the battery and the impedance. This parameter is very useful to verify intraoperatively and postoperatively if

the electrodes are properly placed. Postoperatively it can be checked if there is any discontinuity of the system. Another important parameters which can be set up using the computer programmer and the wand are: intensity of the current, pulse width, the duty cycle (signal on/off time) and the frequency. Tabel.1 shows the range of these parameters.

Figure 1a - Implanted components of the VNS system. 1b. Programming system components. 1c. The electrodes of the VNS system

TABEL 1

The parameters of the VNS stimulation

Parameters	Units	Range	Typical
Output current	Milliamps (mA)	0 – 3.5	**1 - 2**
Signal frequency	Hertz (Hz)	1 – 30	**20 - 30**
Pulse width	Microseconds (μsec)	130 – 1000	**250 - 500**
Signal ON time	Seconds (sec)	7 – 60	**30**
Signal OFF time	Minutes (min)	0.2 – 180	**5**

Intraoperatively the system is checked to see the proper function of it, and the impendence is measure to verify the correct placement of the electrodes around the vagus nerve, then the system is turned off. The system will be turned on at approximately two weeks after operation, in order to be sure that there is no risk of infections. Then, the patients will be periodically called for follow-up (usually every two weeks) to progressively increase the parameters of stimulation until they reached the typical values showed in Tabel 1. The authors present here the first series of patients with refractory epilepsy operated and implanted with vagal neurostimulators in Romania, and describe the surgical technique and the preliminary results.

Patients and methods

Our study includes 81 patients diagnosed with refractory epilepsy, investigated, selected and implanted with vagal neurostimulators between December 2012 and January 2015 in Neurosurgery Clinic, "Bagdasar-Arseni" Emergency Hospital. We have implanted in all patients the latest model of vagal neurostimulator (model 103), excepting two patients operated in December 2012, for whom the previous model (model 102) was used. We perform in all cases a standard left latero-cervical surgical approach. We use an horizontal incision in the left latero-cervical region in one of the skin crest, located at approximately the midway between the sternum and mastoid tip (Figure 2).

After skin incision and platysma muscle division, we identify the anterior border of sternocleidomastoid muscle and the omohyoid muscle (Figure 3)

Depending of the individual anatomy, we traction the omohyoid muscle out of the surgical corridor, or we divide it. The cervical left vasculo-nervous complex (common carotid artery and internal jugular vein) is identified and then we perform a microsurgical dissection of the left vagus nerv (Figure 4).

At that level, the vagus nerve is usually located between the common carotid artery (medially located) and the internal jugular vein (laterally located), but in deeper location. The surgical dissection is directed with great care to the connective tissue between the great vessels, using the microsurgical technique and optic magnification until the vagus nerve is identified. There are several principles which guide the vagus nerve dissection. First, we have to perform a minimum 3 cm long dissection of the nerve (ideally 5 cm). It is very useful to use two rubber pieces two anchor the nerve at the both ends of the portion of the nerve which is dissected (Figure 5).

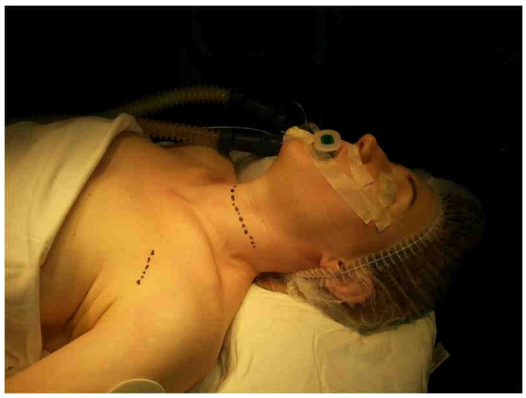


Figure 2 - The position of the skin incisions

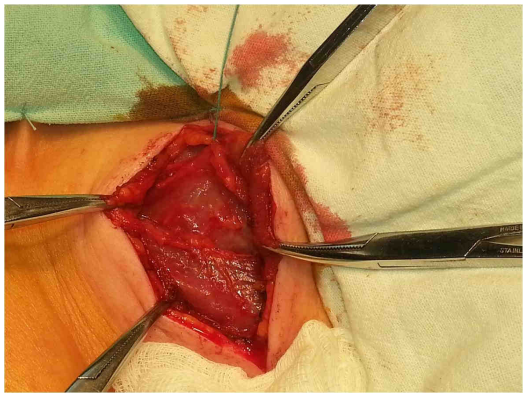


Figure 3 - Intraoperative view of the platysma muscle dissection

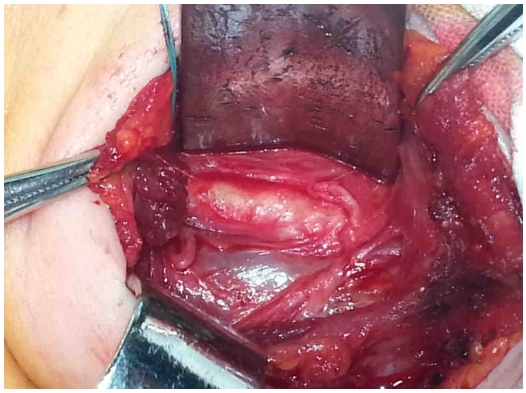


Figure 4 - The intraoperativ view of the common carotid artery and the internal jugular vein

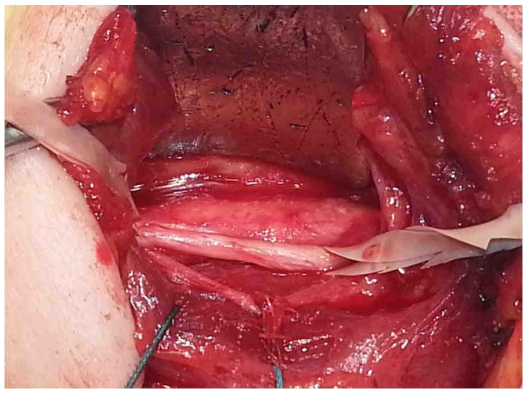


Figure 5 - The intraoperative view of the left vagus nerve

Applying gently a moderate tension on the nerve, we keep the portion of the nerve above the common carotid artery and internal jugular vein. Second, in order to obtain a proper contact between electrodes and vagus nerve it is necessary to completely remove the connective tissue which surround the nerve. Third, it is very important to not allow the nerve to dry out. Therefore, the surgical field should be continuously irrigated with saline serum. After a minimum of 3 cm of the vagus nerve is dissected (ideally 5 cm), the electrodes can now be connected to the vagus nerve. A second incision is performed, usually located at the pre-pectoral area, then the leads is tunneled between this second incision and the latero-cervical incision in a way that the electrodes' end of the lead is placed at the level of the cervical incision .

Then, the electrodes are placed on the vagus nerve. There are, from proximal to distal, one anchor tether and two electrodes: one positive electrode and one negative electrode (Figure 6).

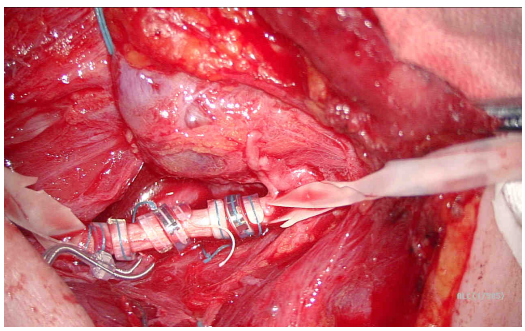
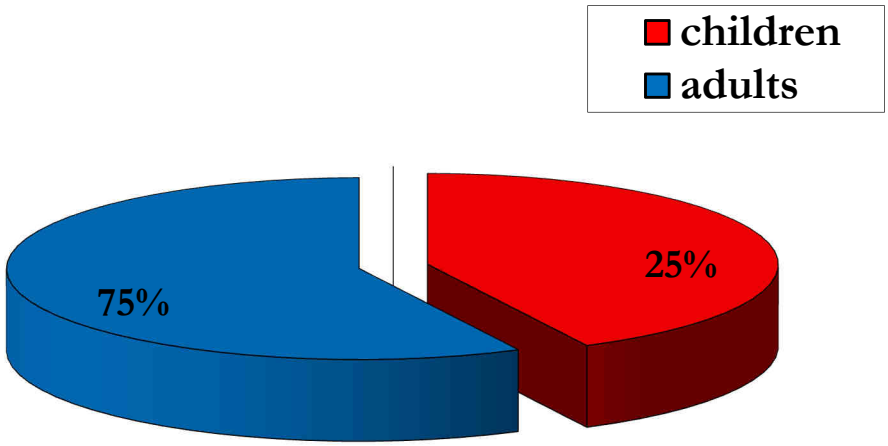


Figure 6 - Intraoperative view of the electrodes placed on the left vagus nerve

The order of electrodes placement depends on the surgeon's preference. The electrodes can be connected either from proximally to distally, or distally to proximally. After connecting the electrodes, a loop is made using the extra-length of the lead and the generator is inserted together with the extra-length of the lead in the subcutaneous pocket. At the end of the surgical procedure, before removing the sterile drapes, the system is checked to assure the proper function of it and also the correct positioning of the electrodes.

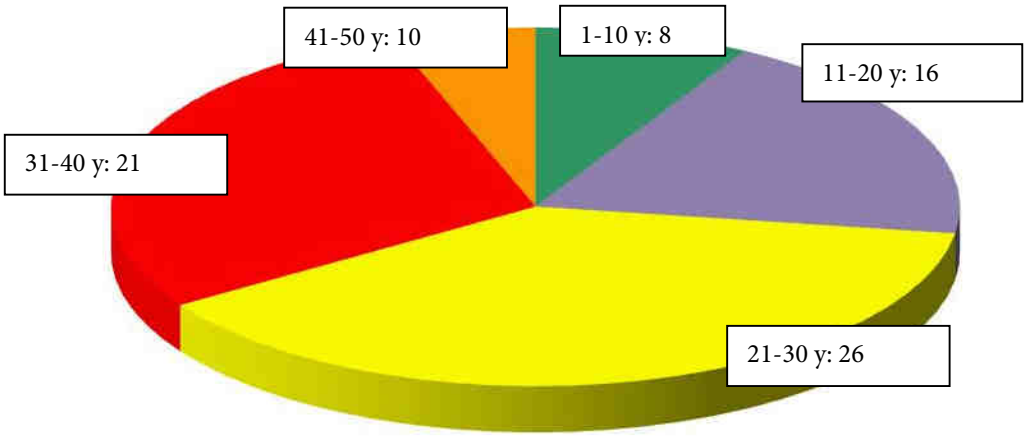
Results

There were 20 children (24,7%) and 61 (75,3%) adults in this series (Graphic 1).



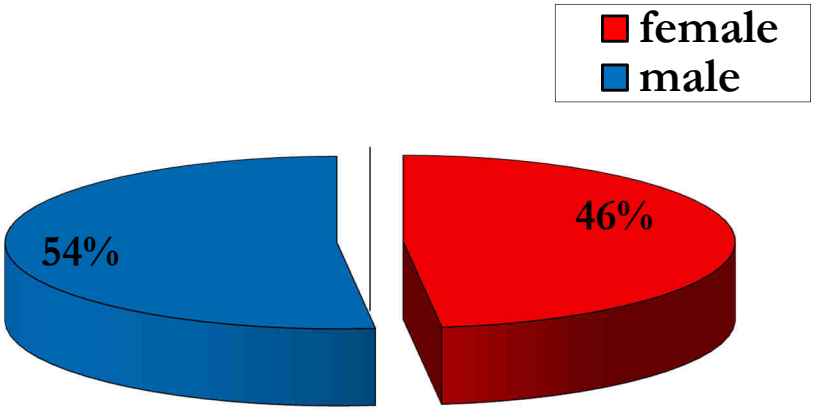
Graphic 1: The percents of the children and the adults of the cohort

The medium age was 25,2 years. The age distribution is represented in the graphic 2.



Graphic 2: Age distribution of the patients in our series

The gender distribution was: 39 females (48,1%) and 42 males (51,9%) (Graphic 3).



Graphic 3: Gender distribution of the patients in our series

The average period of hospitalization was 3 days. The medium follow-up period was 11,5 months and the minimum follow-up period was 3 months postoperatively for all patients. There was no death in this series and no intraoperative incidence. One patient presented dysphagia postoperatively which completely remitted after two months of follow-up. Eleven patients (13,5%) experienced for several days postoperatively hoarseness, which remitted completely within one week postoperatively. There were 50 patients under 30 years (61,7%) and 31 patients over 30 years (38,3%) in our series. We noticed that the percent of patients with 50% seizure frequency reduction was 58% (29 patients) at the end of the follow-up period in patients under 30 years compared with 48,4% (15 patients) in patients older than 30 years. Seven patients (8,6%) were seizure free at 6 months postoperatively.

Discussions

VNS therapy was first approved for clinical use in 1994 in European Union and Canada, followed by the FDA approval in 1997 for USA market. It should be noticed that this therapy is approved to be used for all kind of drug refractory epilepsy, both partial and generalized seizures (especially for partial seizures with secondary generalization). In order to be selected for this form of therapy the patients should fulfill two major requirements: 1. to be correctly diagnosed with drug refractory epilepsy (according with ILAE consensus definition) and 2. do not have a surgically resectable epileptic focus/foci. According with ILAE definition (published in 2010) the drug refractory epilepsy is "absence of complete seizures control of a properly diagnosed epilepsy syndrome, for a period of at least 12 months, following an adequate trial of two tolerated and appropriately chosen antiepileptic drugs" (25). The second condition is that patients, after a complete evaluation (including video EEG and cortical and deep electrodes monitoring) should not have a surgically resectable focus/foci. This means that it cannot be accurately identified the surgical focus/foci, or this/these are identified, but there are situated in eloquent areas of the brain. When the patients fulfills these criteria, they could be considered candidates for vagus nerve stimulation. Because more than 80% of the parasimpatic fibers which innervate the cord are part of the right vagus nerve, the left nerve is targeted for vagus nerve stimulation, in order to reduce to the minimum the cardiac side effects. Presently, the use of VNS goes beyond intractable epilepsy, its use for depression being well spread in USA. Since the FDA approval of vagal nerve stimulation in 1997 the refractory epilepsy gained a valuable treatment tool. Even if the cost is prohibitive for individuals, the efficacy of this treatment was proved in large scale trials. One of the largest meta-analysis in USA including 3321 patients from 74 clinical trials reported 50% reduction in seizures in half of the patients one year after the VNS surgery (26). Other series have communicated better results, with up to 10% becoming free of seizures at one year follow-up in pediatric population (27). These data underline the importance of a correct surgical pre-evaluation of the patients and a correct

selection in order to obtain a better outcome. We also find that children and young adults (under the age of 30 year-old) have a better response to VNS therapy compared with older patients (over 30 year-old).

A more recent meta-analysis included all the devices (51,882) implanted in USA from 1997 to 2012 and studied a rare complication, vocal cord paralysis, found in 193 cases (28). In our series we noticed only one case of temporary vocal cord paralysis, which remitted after two months of follow-up. There are several side effects related with VNS therapy, and includes: dysphonia, dysphagia, hoarseness, cough and tingling sensation in the throat and all are related with stimulation. It is important to mention that the intensity of these side effects decrease in time and they are related with the parameters of the stimulation (29).

Conclusions

VNS represents now a safe, quick and efficient surgical procedure with a minimum period of hospitalization and a short recovery period. The outcome of the patients is better, in term of the frequency and severity of the seizures, for children and young adults (under the age of 30 year-old) compared with older patients. The good results on long term improve the quality of life of the patients and facilitate the social and professional reinsertion.

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