Intractable childhood epilepsy: vagal nerve stimulation is it an option of treatment?

Epilepsia infantil intractable: ¿la estimulación del nervio vagal es una opción de tratamiento?

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Abstract

Introduction: Although the vagal nerve stimulation has been described significant results in the management of medically intractable seizures, it still remain a question regarding its applicability in pediatric patients. **Objective:** To analyse and to discuss the risks, complications, results as well de prognosis of vagal nerve stimulation in pediatric patients. **Methods:** It was performed bibliographical consultation, using the databases MEDLINE, LILACS, SciELO, utilizing language as selection criteria, choosing preferably recent articles in Portuguese, Spanish or English. **Results:** The vagal nerve stimulation has been described associated to a low technical difficulty, short surgical time and enhance of control of seizures. Vagal stimulation has been demonstrated a significant effect in the reduction of seizures frequency and drop attacks' intensity and duration, as well as the improvement in quality of life in pediatric patients. **Conclusion:** In spite of the results described in childhood epilepsy, it is still initial surgical approach of epilepsy and needs more clinical studies to verify the impact of this procedure in these patients in the long term.

Key words: Neurosurgery, vagal nerve stimulation, epilepsy, childhood.

Resumen

Introducción: Aunque la estimulación del nervio vago ha sido descrita como resultados significativos en el tratamiento de las convulsiones médicamente intratables, sigue siendo una cuestión con respecto a su aplicabilidad en pacientes pediátricos. **Objetivo:** Analizar y discutir los riesgos, las complicaciones, los resultados y el pronóstico de la estimulación del nervio vago en pacientes pediátricos. **Métodos:** Se realizó consulta bibliográfica, utilizando las bases de datos MEDLINE, LILACS, SciELO, utilizando el idioma como criterio de selección, eligiendo preferiblemente artículos recientes en portugués, español o inglés. **Resultados:** La estimulación del nervio vagal se ha descrito como una dificultad técnica baja, un tiempo quirúrgico corto y un mejor control de las convulsiones. La estimulación vagal ha demostrado un efecto significativo en la reducción de la frecuencia de los ataques y en la intensidad y duración de los ataques de caída, así como en la mejora de la calidad de vida en pacientes pediátricos. **Conclusión:** A pesar de los resultados descritos en la epilepsia infantil, sigue siendo un abordaje quirúrgico inicial de la epilepsia y necesita más estudios clínicos para verificar el impacto de este procedimiento en estos pacientes a largo plazo.

Palabras clave: Neurocirugía, estimulación del nervio vago, epilepsia, niñez.

Introduction

The epileptic patients represents 1% of the population and is intractable to current antiepileptic drug treatment in 20-25%. Regarding to childhood epilepsies, it occurs in 3-5% of children, stressing that 60% of epilepsy cases starts in childhood and most of the clinically significant sequelae of the disease occurs during childhood[1,2]. In order that, there are many childhood epilepsies, and seizures are the commonest pediatric neurological symptom[1-3].

Tradicionally, the childhood epilepsies are divided in neonatal seizures, benign syndromes and malignant syndromes[1,3]. Such that, the malignant neonatal seizures presents an overall poor prognosis for both survival, as well as future impairments (largely cognitive and motor) like the malignant syndromes of epilepsy, as West syndrome, Lennox-Gastaut Syndrome and Landau-Kleffner syndrome[1,3].

The vagal nerve stimulation (VNS) is a reversible, adjustable and nondestructive surgical approach that aims to control harmful seizures, for instance, myoclonic or drop seizures, preventing the genesis of epileptic electrical activity[4-12]. Such that, its first description happened in 1938 by Bailey[7], whose paper showed that the VNS changed the EEG patterns in cats. After this description, it has been showed a many essays about this approach that culminate in 1990 in a efficient antiepileptogenic effect in humans, whose paper described the use of this technique in 4 patients and it showed none mortality rates associated to control of seizures considered excellent by the standards of the time[8]. And, in 1993, Howard at al[9], demonstrated that the efficacy of VNS depends of stimulation parameters (frequency, wave amplitude, duration, voltage, current, time off and time) and it presents a accumulative effect.

This article aims to clarify the indications, risks, complications and prognosis related to treatment of childhood epilepsy described in the literature at moment, emphasizing the results of VNS regarding to the control of seizures and quality of life of patients.

Casuistic and Methods

It was performed bibliographical consultation from 1990 to 2016, using as keywords “epilepsy”, “vagal nerve stimulation”, “childhood”, “pediatric patient” in the databases MEDLINE, LILACS, SciELO, PubMed, utilizing language as selection criteria, choosing preferably recent articles in Portuguese, Spanish or English and only articles based in humans studies. Stressing that, the references were reviewed aiming the selection of relevant papers to be included in this critical review.

Selection of patients to epilepsy surgery

The selection of the patients directly implies in the success of the VNS, once different factors have to be considered, such as the intractability of the patient’s epilepsy, the etiology of the seizures, the type and localization of seizures, the age of the patient, the age at the surgery, the radiological and neurological findings[5,11,13,14]. Such that, although thousands of adult and pediatric patients have already been implanted with VNS, the best candidates for the procedure have not yet been adequately defined, once the inclusion of heterogeneous patient populations within the different studies and highly uncontrolled protocols made it very difficult to analyze the results[14].

At the moment, based on the literature and authors experience, the patients being indicated for VNS needs to comply with theses criterias:

- Patients with medical intractability of seizures[4,10,11,13-17].
- Patients who did not achieve appropriate seizures control after another epilepsy surgery, principally myoclonic seizures[11,13].
- Children affected by complex partial epilepsy (level I of ==evidence) or generalized secondary multifocal (level II of evidence), especially those with nonspecific findings on magnetic resonance image, like Lennox-Gastaut or Lennox-like syndrome[10-17] - for example, the male patient of 13 year-old affected by refractory epilepsy due to Lennox Gastaut like syndrome caused by Tuberous Sclerosis disease (Figures 1, 2, 3, 4, 5).
- Neurodevelopment retardation is usually present due to the interference of frequent seizures on the developing normal neural tissue. So that, this would therefore be a relative prerequisite for VNS[13,15,16].

Regarding to the indications of VNS in childhood, moreover this indications it is necessary to evaluate a few considerations:

- That is necessary to be considered the noxious effects of frequent uncontrolled seizures, the plasticity of the brain and the high doses of antiepileptic medications on the developing brain[18-21].
- That is necessary to be considered the social implications of a debilitating disease and the lost time at schooling due to the disease[15,16,20-22].
- That is necessary to be considered the morbidity of a major surgery at a young age and the possibility of increased neurological deficits in some cases needs to be well appreciated and weighed against the

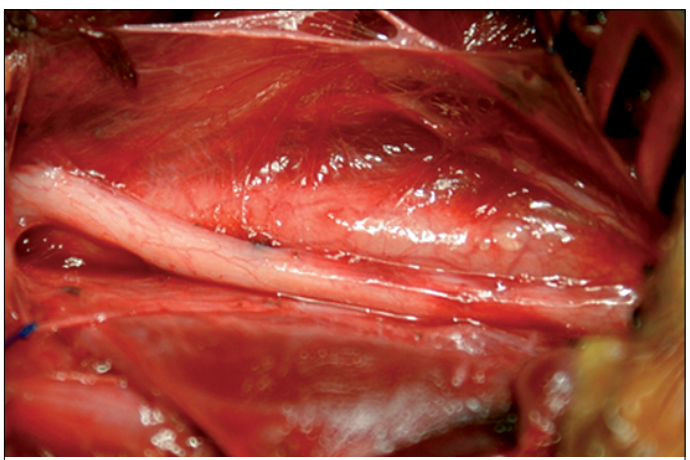

Figure 1. Dissection of vagal nerve in the anterior triangle of neck

substantial gains offered by surgery towards seizure relief and long-term functional outcome[13,15,16].

Epileptogenic evaluation for surgery

Regarding to the preoperative evaluation of epilepsy, it should be included in the evaluation of epileptogenic activity for surgery. In order that, the interictal electroencephalogram, interictal spect, magnetic resonance imaging and age-appropriate neuropsychological/developmental assessment may be include. Stressing that, the intracranial EEG may be imperative in localization of the correct focus of seizure, indicating a complementary surgery after a VNS[10,12,14,23]. Furthermore, Functional MRI, video-EEG and EEG may be useful and should be included actually in the protocols of seizure foci investigation[10,23,24].

Combined approaches

Although the VNS has been described as a efficient and palliative procedure in treatment of epilepsy since 1990 (Figure 3), it reduces the dose of anticonvulsant medication, increases the asymptomatic interval between seizures, reduces the intensify and duration of crisis, as well as the post-ictal becomes shorter[4,10,13,14,25,26].

The association of VNS and anothers surgical procedures should be considered aiming the better or total control of seizures. This combination of procedures depending on the kind of preoperative epileptogenic evaluation, such that the VNS may associated with callosotomy, anterior and posterior comissurotomy, selective amygdalohippocampectomy, anterior temporal lobectomy, hemispherotomy and others[6,10,14].

Risks and complications

Although lasting complications rates VNS are very variable on this type of epilepsy surgery, the presence transient tingling sensation in the throat, transient irritant cough, transient lower facial weakness, transient hoarseness, transient vocal cord paresis, dyspnoea, obstructive sleep apnea, infections in surgical size of generator implantation (Figure 4), peritracheal hematoma, pain, swallowing difficulties, depression, headache, bradycardia and rarely complete heart block, ischemic strokes, persistence of seizures, deaths and ventricular asystole are risks to be considered during and after the surgical act in pediatric and adults patients[5,6,10,15,16,17,22,23,25-35].

Regarding to the reason for VNS failure, it should be highlighted that it is not always apparent for an individual case. So, among the reasons persistence of the seizures in outpatients follow-up of VNS surgery include: 1) technical error implying in the failure to adequately dissection the vagal nerve causing lesions in the nerve (Figure 1) or inadequately installation of VNS (Figure 2, 3, 4); 2) the progression of disease implying in the development of a new seizure focus; 3) the misdiagnosis of seizures type, once the VNS has been described as ineffective in atonic seizures[6,14,25,26,34,35]. Such that, regarding to precautions of VNS complications, the use of bipolar rather than monopolar electrocautery imply in the reduction in the risk of damage to the device (Figure 1), as well as the magnetic resonance imaging of body is also not recommended for patients who have implantable VNS devices, as heat can cause thermal injury to the vagus nerve, surrounding structures, and the device itself[6,22,36]. Stressing that, it is advisable that after any surgical procedure or MRI, the physician should have a low threshold to interrogate and reprogram the device for maximal utility if the device is turned off to accommodate the procedure (Figure 5)[6,22,36].

The most frequent surgical complication of VNS is the presence of bradycardia, such that currently the bradycardia limit causing interruption of vagal stimulation was set at 55 bpm[37,38]. However, in spite of this complication was mainly described in the literature when the system was implanted on the right cervical vagus[37,38]. Ardesch et al.[32], reported the presence of bradycardia resulting from left vagus stimulation retrograde stimulation of the sinoatrial node in 3 of 111 patients who received VNS device placement. Furthermore, delayed arrhythmias inclusive of second degree heart blocks and asystole have been reported in pediatric and adult patients, but these resolved on device removal[37,38,39,40].

Morris et al.[15], in 1999, described the results of VNS in follow-up of 3 years in pediatric patients. Such that, it showed the presence of paraesthesias, cough, and hoarseness became less common

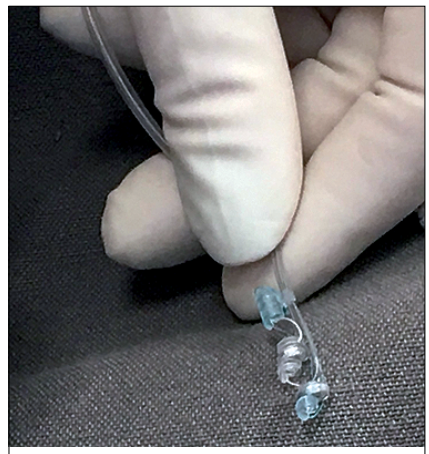

Figure 2. VN electrode before implantation.

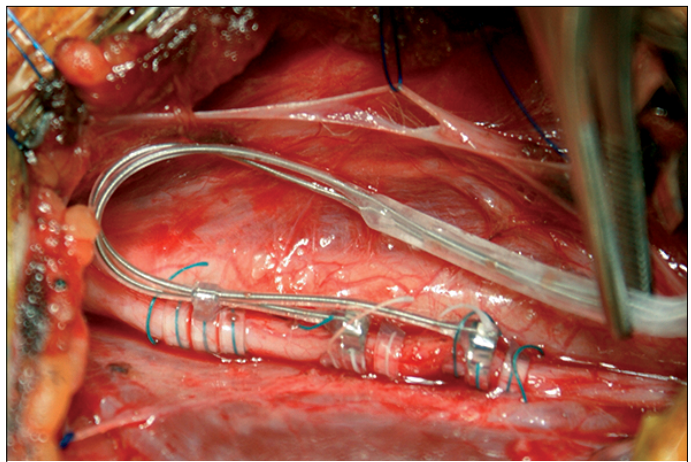

Figure 3. Electrode implanted in vagal nerve. Note that the 2 poles above.

Figure 4. Cervical and thoracic incision, and final pocket to implant the generator.

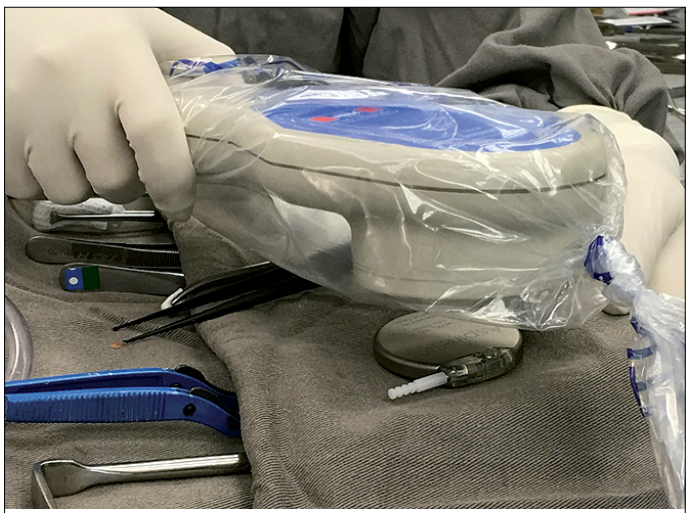

Figure 5. Program tool to modulate the parameters.

with time, as well as it demonstrated that dyspnoea was the most common adverse event reported at 3 years (3.2%). Moreover, it was described 3 serious events of respiratory difficulties, and 9 deaths. However, no changes in Holter monitor or lung function tests or blood chemistries that could be attributed to VNS were noted by authors.

Annegers and colleagues[41], in 2000, reviewed all deaths in 1819 patients with VNS, whose follow-up during 3 years from implantation and 25 deaths were reported. It showed that the rates of sudden unexplained death in epilepsy (SUDEP) were 4.1 per 1,000 in patients treated with VNS and 4.5 per 1000 for a control population with refractory epilepsy. Moreover, after stratification for duration of VNS use, the prevalence of SUDEP was 5.5 per 1,000 for the first 2 years and then dropped to 1.7 per 1,000 for the subsequent years. In order that, this essay concluded that the excessive death rates have not been seen in patients with epilepsy treated with VNS, as well as there was a tendency for SUDEP rates to be lower than in similar groups of patients not treated with VNS.

Another paper, in a 5 year follow-up of 64 patients, Ben-Menachem and co-workers[42], in 1999, reported mainly mild side-effects almost all related to stimulation. It showed that 1.56% (n = 1) of patients complained about device placement and had it moved twice without satisfaction, as well as 1.56% (n = 1), 18.7% (n = 11), 4.7% (n = 3) and 9.3% (n = 4) of patients referred paraesthesia (from whom the device and the electrodes were removed because the side-effect was severe), hoarseness, throat pain and deaths because of SUDEP (n = 1) and status epileptics (n = 3), which 33% (n = 2) was caused by infection, respectively.

In 2002, Ben-Menachem et al.[30], described the review results of VNS, and it demonstrated that the postoperative infections rates ranging from 3 to 6% of patients[44,45,46], however the most were treated with oral antibiotics and rarely were the generator or electrodes removed or culminate in death of patient**.**

Regarding the differences of pediatric and adults patients, there has been more reports of swallowing difficulties in children with VNS when compared to VNS implanted in adults[30,46,47]. Such that, while Lundgren et al.[46], demonstrated an increase in aspiration when the device was on, Schallert et al.[47], tested swallowing in 8 children with VNS in both the on and off phases and did not observe tracheal aspiration.

Dissussion and results in epilepsy surgery

Henry et al.[12], in 1998, described the results of the use of VNS and changes in cerebral blood flow in a case series (n = 10) of adults patients affected by idiopathic complex partial seizures. The patients was divided in underwent to low- and high-stimulation groups during VNS. Such that, it showed in both of groups increase in cerebral blood flow in the rostral, dorsal-central medulla, right postcentral gyrus, hypothalamus, thalami, insular cortex and cerebellar hemispheres inferiorly bilaterally. However, this paper showed the presence of bilateral reduction in hippocampus, amygdala and posterior cingulate gyri. Stressing that, the high-stimulation group had greater volumes of activation and deactivation sites.

Eggleston et al.[28], in 2014, described the review results of 34 articles that reported the prevalence of ictal tachycardia in patients with epilepsy. Such that, the authors concluded that the occurrence of significant increases in heart rate associated with ictal events in a large proportion of patients with epilepsy (82%) using concurrent electroencephalogram and electrocardiogram. Moreover, it showed that the average percentage of seizures associated with significant heart rate changes was similar for generalized (64%) and partial

onset seizures (71%), as well as intra-individual variability was noted in several articles, with the majority of studies reporting significant increase in heart rate during seizures originating from the temporal lobe.

In order that, based in the results of Eggleston et al.[28], Fisher et al.[29], described in 2016 the results of the Automatic Stimulation Mode (AutoStim), whose VNS therapy system stimulates the left vagus nerve on detecting tachycardia. It is a prospective, unblinded, multisite study in subjects with drug-resistant partial onset seizures and history of ictal tachycardia. This essay was constituted by 20 implanted subjects (ages 21-69) and, it showed that 73.7% (28/38) of complex partial and secondarily generalized seizures exhibited higher than 20% increase in heart rate change. Moreover, 34.8% (31/89) of seizures were treated by Automatic Stimulation on detection and 61.3% (19/31) seizures ended during the stimulation with a median time from stimulation onset to seizure end of 35 seconds. Mean duty cycle at six-months increased from 11% to 16%.

Englot et al.[13], in 2011, described the meta-analysis results of VNS efficacy in epilepsy treatment in adults and childhood, identifying 3,321 patients that suffering from intractable epilepsy in 74 clinical studies. This paper included 3 blinded, randomized controlled trials (Class I evidence); 2 nonblinded, randomized controlled trials (Class II evidence); 10 prospective studies (Class III evidence); and numerous retrospective studies, whose the minimum of 3 months postoperative follow-up was adopted to inclusion. Such that, it showed that after the VNS the frequency of seizures was reduced by an average of 45%, with a 36% reduction in seizures at 3-12 months after surgery and a 51% reduction after 1 year of therapy. Furthermore, it showed that patients with generalized epilepsy and children benefited significantly from VNS despite their exclusion from initial approval of the device.

Majoie et al.[26], in 2001, is a prospective, longitudinal and observational cohort analysis (n = 16) that described the results of VNS in patients affected by Lennox-Gastaut syndrome. This essay presented 12 months of follow-up and was constituted by 13 boys and 3 girls, whose mean and median age was, respectively, 11.05 years and 11.15 years (ranging from 6 to 17 years-old) and the mean duration of epilepsy was 7,9 years old (ranging from 4 to 14.3 years). It demonstrated that the frequency and severity of seizures were significantly reduced after the VNS, such that the patients referred a reduction in seizure frequency of 50% or greater in 25% (n = 4) of patients and the overall seizure reduction was estimated in 26.9%. Moreover, the measures of neuropsychological outcome showed a moderate improvement in mental functioning, behavior, and mood, stressing that the scores for mood and mental age improve independently of seizure control. Majoie et al.[25], in 2005 in 2 years of follow-up of this patients, and others authors[5,14,22,36,48,49,50], showed the same results.

Cukiert et al.[14], in 2013, described the results of callosotomy and VNS in a cohort (n = 44 - 24 of callosotomy and 20 VNS) of patients affected by Lennox-Gastaut syndrome after 2 years of postoperative follow-up. The mean age at surgery was 11.2 ± 3.3 and 8.6 ± 3.2 years for callosotomy and VNS groups, respectively. It showed that the final mean stimuli intensity was 3.0mA in the patients underwent to VNS. Furthermore, this essay demonstrated the presence of seizure-free patients accounted for 10% in callosotomy and none in VNS group, and it showed that ten and sixteen percent of patients of the callosotomy group and VNS group, respectively, were non-responders. However, it was described improvements in attention and quality of life were noted in 85% of both groups patients, as well as both procedures were effective regarding the control of atypical absences and generalized tonic-clonic seizures despite both procedures were not effective in controlling tonic seizures. Stressing that, the authors concluded that the callosotomy was very effective in reducing the frequency of atonic seizures, while VNS was effective in reducing myoclonic seizures.

Murphy and colleagues[35], in 2003, described the results of the outcome of intermittent left VNS in a cohort (n = 100) of pediatric patients, whose average age, duration of epilepsy, total number of antiepileptic therapies and median monthly seizure frequency was 10.4 years, 8.5 years, 8.4 and 120, respectively. It showed that 45% (n = 45) of patients achieved greater than 50% reduction and 18% (n = 18) had had no seizures for the last 6 months, stressing that the response was similar in patients with more than 7 years of refractory epilepsy as compared with patients with a shorter history. Regarding to complications, it was showed the presence of generator infections in 3% (n = 3) of patients, 24% (n = 24) of patients had their generators removed and 2% (n = 2) of these patients died.

Klinkenberg et al.[51], in 2012, described the results of the implantation of VNS in a cohort (n = 41) affected by intractable epilepsy, whose paper was constituted by 19 weeks of follow-up of 23 males and 18 females; mean age at implantation was 11.2 years; duration of epilepsy until the implantation was 4.2 years - ranged from 3.9 years to 17.7 years. Furthermore, 85.3% (n = 35) of patients had localization-related epilepsy (25 symptomatic; 10 cryptogenic), while 14.6% (n = 6) of patients had generalized epilepsy (4 symptomatic; 2 idiopathic). Regarding to the VNS adjust, half of the participants received high-output VNS (maximally 1.75 mA) and the other half received low-output stimulation (0.25 mA). This essay was the first randomized active controlled trial of VNS in children and showed reduction of seizure frequency in 50% or more occurred in 16% of the high-output stimulation group and in 21% of the low-output stimulation group.

Zamponi et al.[50], in 2011, described the results of the use of VNS in a cohort (n = 39) of patients with drug resistante epilepsy characterized by multiple seizures and drop attacks, whose paper was constituted by patients (n = 25) were affected by severe epilepsy with multiple independent spike foci (SE-MISF) and patients (14) by Lennox–Gastaut syndrome. It showed that the VNS produced a mean seizure rate reduction of 41% at six months, 50% at twelve months, and 54% at thirty-six months. Such that, after one year of stimulation, 52% (n = 13) of patients with SE-MISF and 21% (n = 3) of patients with Lennox-Gastaut syndrome showed a reduction above 50% in all seizures frequency rate. Furthermore, as for drop attacks, 20% (n = 8) of patients gained a reduction above 50%, while 17% (n = 7) of patients showed a reduction only in intensity and duration. Lastly, the authors concluded that the cognitive level and adaptive behavior were unchanged, while a better quality of life was reported in half out of the patients.

Considerations about the others use of VNS

Although the benefits of VNS has been described widely in epilepsy surgery, this procedure has been described associated to a satisfactory results in the treatment of severe chronic tinnitus[52], chronic heart failure[37,38], chronic pain management[6], reducing the risk of ischemic stroke[12,26], major depression[53], motor recovery of function after traumatic brain injury[54], cases of treatment-resistant depression[55,56], headache[57,58] Alzheimer's disease (VNS has been described associated to cognition-enhancing effect)[59].

Cost-effectiveness

Majoie et al.[26], in 2001, is a prospective, longitudinal and observational cohort analysis (n = 16) that described the cost-effectiveness of the use of VNS in patients affected by Lennox-Gastaut syndrome, whose evaluation addressed the direct medical costs, direct nonmedical costs, and indirect costs. Stressing that, the costs was expressed in monetary terms (1 Euro is the equivalent of approximately $1), the effects were measured in natural values (seizures) and 187 (97.4%) of the cost diaries were available for analysis. In order that, it showed that the total cost of VNS was 13,024 Euros (including the cost of the device, the surgical procedure, and all necessary preoperative investigations) and the assessed cost-effectiveness ratio was 16.93 Euros per reduction of one seizure. Such that, this ratio can be understood as follows: the costs of reducing seizure frequency by one seizure using VNS is 16.93 Euros and, consequently, the total reduction of costs in the postoperative period of 6 months as compared to the preoperative period is 2,876.06 Euros.

Aburahma et al.[60], in 2015, is a retrospective review of all children (n = 28) who underwent VNS implantation at King Abdullah University Hospital, and Jordan University Hospital. This study was constituted by 16 males and 12 females, whose mean age at implantation and mean duration of epilepsy prior implantation was 9.4 years (range from 2 to 19 years) and 6.5 years, respectively. It showed that the VNS implantation therapy in Jordan costs an average of 12,000 USD per patient. However, the total costs savings from decreased emergency room visits and intensive care unit admissions was 104,900 USD after the VNS implantation, soon after it had divided by the total number of patients, there was a savings of 3,885 USD per patient.

Conclusions

Based on literature and authors experience, VNS is an initial and controversial procedure that it has been demonstrated an effective adjunctive therapy in patients with medically refractory (focal and/or generalized) epilepsy not amenable to resection. Furthermore, because of its non-pharmacologic nature this therapy is devoid of the frequent adverse and interactive effects encountered with antiepileptic drugs polypharmacy in the vulnerable pediatric population.

However, although thousands of adult and pediatric patients have already been implanted with VNS, the inclusion of heterogeneous patient populations within the different studies and highly uncontrolled protocols made it very difficult to analyze the results. Furthermore, there are few clinical studies to verify the impact of this procedure in these patients in the long term.

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