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ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Efficacy of Vagus Nerve Stimulation in Patients with Drug Resistant Epilepsy

Dirençli Epilepsilerde Vagal Sinir Stimülasyonu Etkinliği

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Summary

Objectives: Vagal nerve stimulation (VNS), is an adjunctive therapy approved for use in patients with refractory epilepsy, based on stimulation of the exctracranial part of the vagus nerve. In this study, we provide an analysis of seizure outcomes after VNS implantation for pharmacologically resistant epilepsy patients.

Methods: We reviewed all patients who had VNS implantation in our center from 2005 to June 2013. Patient outcomes were evaluated using the VNS-specific outcome scale.

Results: This study consisted of 35 patients (24 males, 11 females; mean age 13.7±8.2 years, range 7 to 40 years). The mean age at VNS implantation was 17.17±8.4 years (range 4 to 35 years). The mean duration of VNS therapy was 26±19.2 months (range 3 to 84 months). The 80% of our patients were in the responders, 20% of them were in the nonresponders group.

Conclusion: Vagal nerve stimulation, is an alternative treatment approach. Given the potential for cognitive, behavioural improvement with or without improved seizure control, VNS may be considered in the course of treatment of refractory epilepsy.

Key words: Refractory epilepsy; vagal nerve stimulation; VNS.

Özet

Amaç: Vagal sinir stimülasyonu (VNS), tedaviye dirençli epilepsi hastalarında uygulanan, vagal sinirin ekstrakraniyal bölümünün uyarımına dayanan, alternatif bir tedavi yöntemidir. Bu çalışmada, ilaç tedavisine dirençli olup VNS uygulanan hastalar gözden geçirilerek sonuçlar değerlendirildi.

Gereç ve Yöntem: 2005 yılından Haziran 2013 tarihine kadar kliniğimizde takip edilen VNS uygulanmış hastalar değerlendirildi. Hastaların demografik ve klinik özellikleri ve VNS sonrası nöbet sonlanımı gözden geçirildi.

Bulgular: Vagal sinir stimülasyonu uygulaması yapılan 35 hasta (24 erkek, 11 kadın; ort. yaş 13.7±8.2 yıl; dağılım 7-40 yıl) çalışmaya alındı. Ortalama VNS takılma yaşı 17.17 ± 8.4 yıl (dağılım, 4-35 yıl), VNS uygulanması sonrası ortalama takip süresi 26 ± 19.2 ay (dağılım, 3-84 ay) olarak hesaplanmıştır. Hastaların %48.5'i parsiyel nöbetler geçirmektedir. Hastaların %80'i tedaviye yanıtlı, %20'si yanıtsız grupta yer almaktadır.

Sonuç: Vagal Sinir Stimülasyonu, dirençli epilepsi hasta grubunda nöbet sıklığı ve şiddetinin hafifleyebilmesi, kognitif ve davranışsal iyileşme sağlayabilmesi ile hastaların yaşam kalitelerini artırabilen alternatif bir tedavi yöntemidir.

Anahtar sözcükler: Dirençli epilepsi; vagal sinir stimülasyonu; VNS.

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Introduction

Epilepsy is a common neurological disease, affecting 0.2-4% of the population, that has been known since antiquity.[1] Many patients with epilepsy suffer from persistent seizures despite appropriate antiepileptic therapy. Uncontrolled seizures are associated with many detrimental effects, including cognitive impairment, affective disorders like depression, reduced quality of life and lower lifetime income and higher mortality rates. For drug resistant epilepsy there are, non-pharmacological treatment options such as epilepsy surgery, the ketogenic diet and vagus nerve stimulation therapy (VNS).[2,3]

Vagal Nerve Stimulation is an adjunctive therapy approved for use in patients with refractory epilepsy.[4] VNS is used in patients with focal seizures with or without secondary generalization as well as generalized seizures which are refractory to antiepileptic drugs.[5] The first VNS implant for epilepsy was performed in 1988.[6] Since then more than 60.000 patients worldwide have been treated with VNS; 30.4% were under 18 years and 8.8% were under 12 years age. VNS therapy was approved in Europe in 1994 and by the US Food and Drug Administration in 1997 (data on file, Cyberonics, Inc., Houston , TX).[7,8] First VNS implantation was applied in 1998 in Turkey.[9] Currently used implantation conditions were determined by Social Insurance Institution in 2009.[10]

Vagus nerve stimulation therapy is a method based on stimulation of the extra cranial part of the vagus nerve. The neurobiological mechanisms of VNS in epilepsy is not clearly understood yet. Studies suggest that the vagal stimulation may desynchronize activity and decrease abnormal spiking patterns on electroencephalography.[11] Putative targets of VNS activity have included multiple thalamic and brainstem sites proposed to desynchronize thalamocortical circuitry involved in seizure propagation.[3,12]

In this study, we provide an analysis of seizure outcomes after VNS implantation for pharmacologically resistant epilepsy patients. Clinical response to VNS, patient age, duration of epilepsy, predominant seizure type, etiology, surgical complications were investigated as potential prognostic indicators of a favorable outcome.

Materials and Methods

We reviewed all patients who had VNS implantation in our center from 2005 to June 2013. Patients with a post-implantation follow-up of at least 3 months and those which had a capture of background and follow-up seizure frequency were included. Seizure frequency was expressed as a composite of all seizure types experienced by a patient in a given month. For each patient gender, onset age of epilepsy, age at VNS implantation, ictal semiology, seizure type according to the 2010 classification of the International League Against Epilepsy,[13,14] underlying etiology (or predisposing factors for epilepsy), medications, seizure frequency before and after VNS implantation, duration of epilepsy prior to VNS, prior intracranial epilepsy surgery were collected from the patients' medical records. Adverse events were recorded throughout the study in order to evaluate the safety of VNS.

Patient outcomes were evaluated using the VNS-specific outcome scale proposed by McHugh et al. in 2007.[15] In this classification, patients are divided into five classes according to the percentage of seizure reduction (classes 1-5). Patients experiencing a reduction in seizure frequency between 80-100% were included in class 1, between 50-79% in class 2, <50% in class 3, magnet benefit only class 4 and patients who had no improvement were added in class 5. Then the first three classes are further subdivided into two distinct subgroups (A and B) in relation to the improvement of duration and severity of ictal and postictal period.[2,15] All outcomes (seizure frequency, the number of antiepileptic drugs, the quality of life), were compared between the pre (6 months before VNS implantation) and post VNS period (up to 5 years). The evaluation was based on patients', parents' or the caregivers' observations which included noticeable changes. Change in quality of life was questioned but not qualified, so this information was depending on the verbal reports.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL, U.S.A.). Descriptive analysis was conducted to summarize patient characteristics. Means were used to describe continuous variables, whereas frequency and proportions were used to describe categorical variables. For the comparison of VNS effect in different age groups (18> and 18≤) a chi-square test was used. The relationship between VNS effect and age, age at VNS implantation, age at seizure onset, the duration of epilepsy prior to VNS, the duration after VNS implantation was evaluated using Mann- Whitney U-test. The value of $p<0.05$ was considered statistically significant.

Table 1. The seizure outcomes according to the McHugh classification

	Class 1a	Class 1b	Class 2a	Class 2b	Class 3a	Class 3b	Class 4	Class 5
Number of patients (n)	0	2	7	7	2	11	1	5
Percentage (%)	0	5.7	20	20	5.7	31.4	2.9	14.3

Table 2. Distribution of patients data according to the McHugh classification

	Class 1	Class 2	Class 3	Class 4	Class 5
Number of patients = n (%)	2 (5.7)	14 (40)	13 (37.1)	1 (2.9)	5 (14.3)
Gender	1F, 2M	7F, 7M	2 F, 11 M	1 M	1 F, 4 M
Etiology	1 E, 1 MTS	1 NMD, 3PH, 3U, 5LGS, 1DS, 1E	3 PH, 1 NMD, 5 U, 1 MTS, 1 MNG, 1 ICH, 1 DDMS	1 PH	1 NMD, 1 LGS, 1 WS, 1PH, 1U
Seizure type	2 FC	6 FC, 6 G, 2 FC&G	8 FC, 2 G, 3 FC&G,	1 FC	3 FC&G, 1 G
Reduction of antiepileptic drugs	1 yes 1 no	6 yes 8 no	2 yes 11 no	1 yes	5 no

F: Female; M: Male; FC: Focal; G: Generalized; FC&G: Both focal and generalized seizure types occurring in the same patient; NMD: Neuronal migration disorders; PH: Perinatal hypoxia; U: Unknown; LGS: Lennox-Gastaut syndrome; DS: Dravet syndrome; E: Encephalitis; MTS: Mesial temporal sclerosis; WS: West syndrome; ICH: Intracerebral hemorrhage; DDMS: Dyke-Davidoff Masson syndrome; MNG: Meningitis.

Results

This study consisted of 35 patients; 24 male (68.57%) and 11 females (31.42%). The mean age of patients was 13.7±8.2 years (7-40 years). The mean age at seizure onset was 5 years 3±5.1 months for our patient group (newborn-18 years). Among patients with known underlying etiologies, the most common causes included perinatal hypoxia in 7 (20%), Lennox-Gastaut syndrome in 6 (17.1%), neuronal migration disorders in 3 (8.5%), infections like encephalitis and meningitis in 3 (8.5%), mesial temporal sclerosis in 2 (5.7%) patients, West syndrome, Dravet syndrome, Dyke-Davidoff Masson syndrome, sequelae of ischemia, sequelae of intracerebral haemorrhage in 1 (2.9%) patient each. Nine patients (25.7%) had unknown etiologies for their epilepsy. Focal seizures were the most common type of seizures in 17 patients (48.5%) followed by generalized seizures in 10 patients (28.6%). Also 8 patients (22.9%) had both partial and generalized seizures simultaneously.

The mean age at VNS implantation was 17.17±8.4 years (4-35 years). The mean duration of VNS therapy was 26±19.2 months (3- 84 months). The seizure outcomes at last follow-up visit according to the McHugh classification is shown in the Tables 1, 2 and Figure 1.

The mean number of antiepileptic drugs used in our patient group was 3.4±0.77 for the pre-VNS period while the number decreased to 3.08±0.88 in the post-VNS period. Ten patients (28.6%) had reduction in the dose or the number of antiepileptic drugs after VNS implantation taken over time. We have also observed improvement of quality of life in some our patients, who had reduction in the frequency of seizures, the severity, the duration of the seizures and the postictal period.

According to the comparison between well-responders (classes 1 and 2) and the others' (classes 3, 4, and 5) groups;

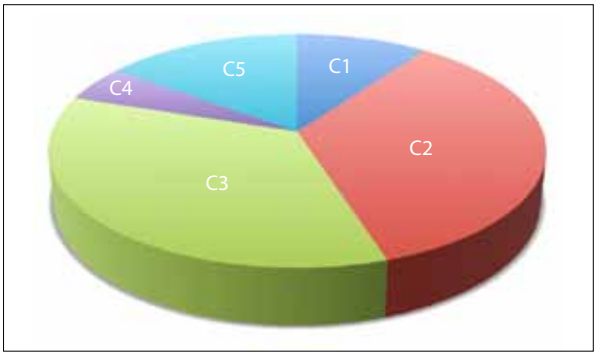

Figure 1. Distribution of percentages of classes according to the McHugh classification.

Table 3. The seizure outcomes according to the VNS implantation age

	Well-responders (Classes 1 and 2)		Others (Classes 3, 4 and 5)	
	n	%	n	%
Number of patients <18 years (n)	9	56.2	11	57.9
Number of patients ≥18 years (n)	7	43.8	8	42.1

there was no significant difference for recent age, age at VNS implantation, age at seizure onset, the duration of epilepsy prior to VNS, the duration after VNS implantation (p values were as follows: p=0.909; p=0.683; p=0.961; p=0.317; p=0.523). Also, there was no significant difference between well-responders and others group for patients under the age of 18 and above 18 years at VNS implantation (p=0.922). The number of patients according to this groups were summarized in Table 3.

Adverse events considered to be specific for VNS was reported in 9 patients (25.7%). Intermittent couch occurred in 8.5%, localized neck pain and/or paresthesias in 11.4%, intermittent hoarseness in 5.8% of them. Twenty six patients (74.3%) did not have side effects.

Three patients (8.5%) had underwent failed epilepsy surgery procedures before implantation of VNS. One patient had temporal lobectomy, one had selective amigdalohippocampectomy and the other one had fronto- insular resection, all without success.

Discussion

Vagal nerve stimulation, is an alternative treatment approach for the epilepsy patients refractory to antiepileptic medications. It is getting a widespread usage because it does not have interactions with antiepileptic drugs. Based on clinical observations, effects of treatment varies and VNS decreases the frequency and severity of seizure.[7,8] Here, in this study we investigated the effects of VNS treatment in patients with phamacoresistant epilepsy.

Uncontrolled seizures are associated with many other consequences including cognitive impairment, reduced lifetime income, higher risk of accidental injuries and higher rates of depression.[16] Vagal Nerve Stimulation, not only decreases the frequency of seizures but may also decrease the severity, duration of the seizures and also the postictal period. That may explain why we have observed improvement of quality of life in our patients.

According to the McHugh classification, patients experiencing a >50% seizure frequency reduction in respect to the baseline were considered as well-responders (classes 1 and 2), <50% seizure frequency reduction were considered as less responsive (classes 3 and 4) and nonresponders (class 5). In our patient population nearly 80% of them were responders (well and less responsive totally=classes 1, 2, 3 and 4) and almost 46% of them were in the well-responders (class 1 and 2) group. In the previous reports the >50% seizure control rate was notified as differing between range 23.4% and 63.8%.[17,18] Although most of the patients in our sample were in responders group, still 20% were nonresponders.

Various studies compared clinical response to VNS therapy in children and adults. Bao et al. have noticed better prognosis in adults than children.[2] According to the data obtained from the VNS patient outcome report provided by the manufacturer of the device, clinical response to VNS therapy was better, in patients under the age 18 when compared the adults over 18 years.[19] In our study there was no significant difference between children and adults for this statement (p>0.05).

In our study, 10 patients (28.6%) had reduction in the dose or the number of antiepileptic drugs after VNS implantation. A slight decrease of antiepileptic drugs was reported in another study by Majkowska-Zwolińska et al.[7] whereas no significant reduction after VNS implantation over one year follow up was stated by Elliott et al.[20] The reduction in usage of antiepileptic drugs is very important from clinical point of view, since chronic use of these drugs may cause several side effects which contributes the impairment of quality of life in these patients.

Side effects observed due to VNS in our patients were

hoarseness, throat pain and cough, as formerly described in the literature.[17,21] Other common adverse events of VNS, that were not present in our group of patients include bleeding and infection from the surgery, dyspnea, transitory hypotension, ventricular asystole, dyspnea, dyspepsia, dysphagia, vomiting, pharyngitis, headache and psychosis. Nearly two thirds of 57 patients in the study of Majkowska-Zwolińska et al.[7] experienced no adverse events specifically related to VNS. So we agree that this treatment is a safe option with minor side effects and injuries.

Main limitation of similar VNS studies is also valid for ours. First, the information before VNS implantation is obtained retrospectively therefore the seizure frequency and severity were defined with crude measures by patients or caregivers and this is subject to error. QoL scales were also not applied to the patients due to the difficulty of communication in many of them because of their low IQ, at this point a scale is needed to be developed for parents to quantify their observation. Furthermore, we were not able to identify alterations in seizure frequency for specific seizure subtypes in our results as many of the patients suffer from several types of seizures occurring several times a day which makes it difficult for the caregivers to record them correctly.

Vagal nerve stimulation is safe and can be an effective alternative option for adult and pediatric patients with medically refractory epilepsy. It seems that frequent changes in antiepileptic drug regimens and VNS together may play synergistic roles in seizure control. Other factors affecting the prognosis of VNS treatment remains unclear and we expect to acquire more information with increasing number of cases. Given the potential for cognitive, behavioural improvement with or without improved seizure control, VNS may be considered in the course of treatment of refractory epilepsy.

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References

1. Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy-a review. Epilepsy Res 2009;85(1):31-45.
2. Bao M, Zhou J, Luan GM. Treatment of drug-resistant epilepsy with vagus nerve stimulation - review of 45 cases. Chin Med J (Engl) 2011;124(24):4184-8.
3. Connor DE Jr, Nixon M, Nanda A, Guthikonda B. Vagal nerve stimulation for the treatment of medically refractory epilepsy: a review of the current literature. Neurosurg Focus 2012;32(3):E12.
4. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. Neurology 1995;45(2):224-30.
5. Bek S, Erdoğan E, Gökçil Z. Vagal sinir stimülasyonu ve hasta seçimi. Epilepsi 2012;18(Ek 1):63-7.
6. Ben-Menachem E. Modern management of epilepsy: Vagus nerve stimulation. Baillieres Clin Neurol 1996;5(4):841-8.
7. Majkowska-Zwolińska B, Zwoliński P, Roszkowski M, Drabik K. Long-term results of vagus nerve stimulation in children and adolescents with drug-resistant epilepsy. Childs Nerv Syst 2012;28(4):621-8.
8. Helmers SL, Duh MS, Guérin A, Sarda SP, Samuelson TM, Bunker MT, et al. Clinical and economic impact of vagus nerve stimulation therapy in patients with drug-resistant epilepsy. Epilepsy Behav 2011;22(2):370-5.
9. Yalnızoğlu D, Turanlı G, Açıkgöz D, Bilginer B, Oğuz KK, Erbaş B. Çocukluk çağında ilaca dirençli epilepside vagal sinir stimülasyonu. Epilepsi 2008;14(1):69-96.
10. T.C. Sosyal Güvenlik Kurumu Genel Sağlık Sigortası Genel Müdürlüğü İlaç ve Tıbbi Malzeme Mevzuatı Daire Başkanlığının B.13.2.SGK.0.11.00.00/769 ve 07/09/2009 tarihli genelgesi.
11. Koo B. EEG changes with vagus nerve stimulation. J Clin Neurophysiol 2001;18(5):434-41.
12. Fisher RS, Handforth A. Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 1999;53(4):666-9.
13. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010;51(4):676-85.
14. Berg AT, Millichap JJ. The 2010 revised classification of seizures and epilepsy. Continuum (Minneap Minn) 2013;19(3 Epilepsy):571-97.
15. McHugh JC, Singh HW, Phillips J, Murphy K, Doherty CP, Delanty N. Outcome measurement after vagal nerve stimulation therapy: proposal of a new classification. Epilepsia 2007;48(2):375-8.
16. Torun G, Midi İ, Ağan K, Zaimoğlu S, Bingöl CA. The effects of vagus nerve stimulation on seizure, cognition and mood. Epilepsi 2007;13(1):21-24.
17. Elliott RE, Morsi A, Kalhorn SP, Marcus J, Sellin J, Kang M, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy Behav 2011;20(1):57-63.
18. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998;51(1):48-55.

19. Englot DJ, Chang EF, Auguste KI. Efficacy of vagus nerve stimulation for epilepsy by patient age, epilepsy duration, and seizure type. Neurosurg Clin N Am 2011;22(4):443-8.
20. Elliott RE, Morsi A, Tanweer O, Grobelny B, Geller E, Carlson C, et al. Efficacy of vagus nerve stimulation over time: review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS > 10 years. Epilepsy Behav 2011;20(3):478-83.
21. Hajnsek S, Petelin Z, Poljaković Z, Mrak G, Paladino J, Desnica A. Vagus nerve stimulation in the treatment of patients with pharmacoresistant epilepsy: our experiences. Coll Antropol 2011;35(3):755-60.