Vagus Nerve Stimulation in Depression

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Summary

Vagus nerve stimulation (VNS) is an established palliative treatment method for resistant epilepsy. Studies of VNS for treatment-resistant depression were started after reports about VNS effect on mood improvement in epileptic patients, independent of its effect on seizures. Data from these studies suggest VNS being significantly effective for treatment-resistant depression. Mood improvement has been achieved in 30-40% of evaluated patients and about 15% have reached complete remission. The response rate did not decrease and remission rate even increased over time. VNS is a safe and well tolerated treatment method with mild side effects which usually taper down during prolonged stimulation. Taking all these findings together, data from the studies indicate that VNS has a potential to become a long-time antidepressant treatment for resistant depression, although control studies are needed. Further studies of mechanisms of VNS and its effects on the central nervous system could broaden the spectrum of application of VNS. Studies of VNS for other neuropsychiatrical disorders such as anxiety, chronic pain, rapid cycling bipolar disorder, post-traumatic stress are being discussed.

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Vagusnervstimulation bei Depression

Die Vagusnerv-Stimulation (VNS) ist eine etablierte palliative Therapie der pharmakoresistenten Epilepsie. VNS-Studien zur Behandlung von Depressionen wurden durchgeführt, nachdem eine Verbesserung der Stimmung unabhängig von der Wirkung auf die Anfallsdichte in Epilepsie-Patienten beobachtet wurde. Diese Studiendaten zeigen einen signifikanten Effekt der VNS auf pharmakoresistente Depressionen. In 30-40% aller evaluierten Patienten fand sich eine deutliche Verbesserung, in etwa 15% eine komplette Remission. Die Zahl der Patienten, die auf die Therapie ansprachen, verringerte sich nicht, die Zahl der Patienten mit kompletter Remission erhöhte sich sogar. VNS ist ein sicheres Verfahren und gut toleriert mit wenigen Nebenwirkungen, die im Allgemeinen weniger werden im Verlauf der Therapie. Nimmt man alle Studien zusammen, erscheint VNS als ein Antidepressivum mit Langzeit-Wirkung; Kontrollstudien sind jedoch notwendig. Weitere Untersuchungen zu VNS und ihrem Effekt auf das zentrale Nervensystem könnten ihre Anwendungsbereiche noch erweitern. VNS-Studien zu anderen neuropsychiatrischen Störungen wie Angststörungen, chronischer Schmerz, bipolare Syndrome und posttraumatischer Stress werden diskutiert.

La stimulation du nerf vague aux depressions

La Stimulation du Nerf Vague (SNV) est une méthode de traitement palliatif établie pour les épilepsies résistantes. Les études d'application de la SNV aux dépressions réfractaires ont été débutées après que des améliorations thymiques par la SNV aient été rapportés chez les patients épileptiques, indépendamment de l'effet sur les crises. Ces études suggèrent que la SNV ait une efficacité significative sur les dépressions réfractaires au traitement. Une amélioration thymique a été obtenue chez 30-40% des patients et une rémission complète chez 15%. Au cours du temps, le taux de réponse n'a pas diminué et le taux de rémission a même augmenté. La SNV est un traitement sûr et bien toléré avec peu d'effets secondaires, qui habituellement diminuent rapidement en cas de stimulation prolongée. Tous ces éléments pris en compte, les données des études indiquent que la SNV a un potentiel pour devenir un traîtement anti-dépresseur à long terme, bien que des études contrôles soient encore nécessaires. Des études complémentaires concernant les mécanismes à la base de l'effet de la SNV sur le système nerveux central pourraient élargir le spectre des applications. Des études d'application de la SNV sont discutées pour d'autres troubles neuropsychiatriques, tels que l'anxiété, la douleur chronique, les troubles bipolaires à cycles rapides et l'état de stress post-traumatique.

Introduction

Vagus nerve stimulation (VNS) is an invasive non pharmacological procedure, during which the activity of nervus vagus is modified. VNS is an established palliative treatment of refractory partial epileptic seizures. Functional neuroimaging methods provided additional data in understanding the widespread effects of VNS, providing evidence of its effect on cortical and subcortical structures including mood regulating systems. Improvement of mood, independent of seizure activity, was reported during studies of VNS for epileptic patients and led to research of VNS as treatment of depressive disorders resistant to other treatment strategies. Results from open-label studies of VNS for the treatment of resistant depression suggest that VNS may be effective.

Vagus nerve and possible mechanisms of VNS

Vagus nerve, the 10th cranial nerve, originates in the medulla. Both left and right vagus nerves include afferent and efferent fibers, innervating also visceral organs in the neck, thorax and abdomen. The right nerve is more essential in regulating cardiac rhythm. VNS is thus performed on the left nerve to avoid influence to the chronotrophic function [1]. The cell bodies of the afferent cells are in the nodose ganglion and project to the nucleus of tractus solitarius. Through the nucleus of tractus solitarius the vagus nervus has reciprocal connections with cortical and limbic structures. Consequently extracranial electrical stimulation of vagus nerve influences the corresponding cerebral regions [2]. Recent functional imaging studies have shown that stimulation of the vagus nerve results in cerebral blood flow reduction in amygdala, hippocampus, cingulate cortex, brain stem and thalamus [3, 4]. Krahl et al have demonstrated the importance of locus coeruleus in the mechanism of action of VNS [5]. It appears that via locus coeruleus VNS can modify limbic function and influence mood modulation [6]. The exact mechanisms of VNS effect however are still poorly understood and require further research.

Principle of VNS

VNS is performed using two electrodes, implanted through an incision in the neck and wrapped over the left vagus nerve. A bipolar programmable pulse generator, implanted subcutaneously in the left chest wall provides the electrical impulses to the electrodes by the leads in the subcutaneous tunnel. A software device is used to program the generator, modify current intensity, frequency, pulse width and "on - off" time parameters. The software allows making further functional assessment and retrieving data [1, 7]. Stimulation frequencies from 20 to 30 Hz are approved for clinical use, on the basis of experimental data showing that high frequencies may damage the nerve irreversibly [8, 9]. Other parameters have been: pulse width 250-500 ms, current intensity 0.5-1.5 mA, "on" cycle is 30 s, "of" cycle is 3-5 min. These parameters were approved for VNS for epilepsy treatment and have been applied to clinical studies for VNS for resistant depression treatment [10, 11]. In the experimental studies various parameters are used. A small powerful magnet is given to the patient that enables him to stop or launch stimulation when needed.

Historical data

A relationship between vagal nerve function and seizure reduction was first suspected by the American neurologist, James L. Corning, in 1883 [2, 12]. It was believed that seizures are caused by cerebral hyperemia and carotid artery compression, resulting in reduced cerebral vascularization, was used to treat seizures. J.L. Corning designed instruments for compression of carotid artery. Later he combined them with devices for nervus vagus and cervical sympathetic transcutaneous electrical stimulation in order to decrease the cardiac output and to obtain a vasoconstriction of cerebral vessels. It resulted in a decrease of cerebral blood-flow and a reduction of seizures was observed [12]. These methods however remained unappreciated by his contemporaries and were not used for a century until Bailey and Bramer (1938) observed that VNS aborted synchronized cortical activity in a cat and claimed that VNS had a direct influence to the CNS [2]. During later decades application of VNS was studied, but it took until the middle of the 20th century to confirm that VNS could have a long term effect on seizure reduction [2]. In 1988 Penry et al. implanted the first VNS device in man as a long term treatment of drug-resistant epilepsy [7]. Long-term effects of VNS showed a ≥50% seizure reduction in 37% of the patients at one year, which increased to 43% at three years in an open-label study [13]. VNS was established as an effective and safe treatment for epilepsy. It was approved for the treatment of epilepsy in Europe in 1994 [2] and in 1997 approved by U.S. Food and Drug Administration as adjunctive therapy for treatment of partial epileptic seizures, refractory to antiepileptic medications [14]. Until 2004 VNS device has been used in more than 29,000 patients [2].

Application of VNS for the treatment of depression

Since complete recovery from seizures had been achieved only for a small portion of patients treated with VNS, other effects became object of a number of studies. During a VNS study for epilepsy mood improve-

ments were noticed and a study to evaluate the effect of VNS on depressed mood of epileptic patients was conducted by Elger et al (2000). Significant mood improvement was observed after 3 months of VNS treatment. This effect persisted after 6 months without correlation to seizure activity [15]. Another study evaluated patients treated with VNS for epilepsy after 6 months using standardized self-reported questionnaires. Mood improvement was reported corresponding to a mild antidysphoric effect (30% lowering compared to the threshold of anxiety scales) of VNS in about 30-40% [16]. These findings were encouraging and motivated studies of VNS for patients with depressive disorders only. Rush et al. (2000) published results of an open-label study of VNS therapy for 30 patients without a history of epilepsy, but who had depression that was resistant to 2-5 drugs or more. The results of this study suggested a marked antidepressant effect of VNS: 40% of patients had improvement in mood and 17% showed a complete remission after up to ten weeks of VNS. Responders were followed-up and response status maintained after 4-9 months of VNS [10]. This study was continued enrolling a total of 60 patients. Significant clinical response was reported in 30-37% and full remission was achieved in 15.3%. It is worth mentioning that patients who were not responding to more than seven antidepressant drugs did not respond to VNS either [11]. The data suggests that VNS is not effective for those extremely resistant patients who did not respond to multiple previous treatments. In 2002 Marrangel et al. published the results of an additional nine-month VNS treatment for patients with major depression following the acute three-month study. They reported that after long-term VNS a response rate remained unchanged compared to short-term results (40 to 46%), whereas the remission rate increased significantly (17 to 29%) [17]. The same group of patients was evaluated after two-years of VNS and the results showed an unchanged response rate compared to one-year VNS (42%) and a slightly reduced remission rate (22%) [18]. Recently, an open study of VNS for treatment-resistant depression evaluating 205 patients was carried out. After one year, a significant response (reduction of ≥50% in the score compared with the baseline for the 24-item Hamilton Rating Scale for Depression ($HRSD_{24}$) was achieved in 27.2% and remission (score 9 for the $HRSD_{24}$) was achieved in 15.8%. Results on other depression scales were similar. It is important to note that response rates were increasing over time significantly [19], similar to response rates in epileptic patients. Another study compared the same group of 205 patients receiving VNS and antidepressant treatment with the group of 124 patients receiving only antidepressant treatment. It was observed that the VNS-group was associated with greater antidepressant benefit after twelve months with no difference between bipolar or unipolar depression patients [20]. Taking all findings together, these studies indicate that VNS has a potential to become a long-time antidepressant treatment for unipolar or bipolar depression, although control studies are needed. VNS was approved in Europe Union countries and Canada for adult patients for treatment-resistant chronic or recurrent depression in 2001, including major depressive disorders (unipolar) and manic depression (bipolar) [1, 14].

Other clinical applications of VNS

The vagus nerve is partly involved in anxiety regulation [2, 21] and data from Rush et al. (2000) study suggests that VNS has also an anti-anxiety effect [10].

VNS potency in treating cognitive disorders is also being evaluated. Some data from VNS studies for depression treatment showed that motor speed, psychomotor function, language and executive functions could be improved, but the authors stated that cognitive improvement was correlated with improvement of depression [22]. Thus, controlled studies are needed. Some trials on treatment of Alzheimer's disease included a few patients, but they were too short to conclude that VNS may be effective to treat a progressive degenerative disorder [2]. Pilot studies of VNS for other disorders such as treatment-resistant obesity, chronic pain, rapid cycling bipolar disorder, post-traumatic stress and other neuropsychiatric disorders are still ongoing [23].

Side effects of VNS

Side effects of VNS may be divided into two major groups: complications 1) during the implantation procedure or directly related to it; 2) related to the stimulation itself [24, 25].

Adverse effects related to implantation are: infection, reported from 1% to 6% of implantations [7, 24, 25]; nerve damage, which could be reduced if stimulation is not started earlier than 10-14 days after implantation; wound pain, which usually lessens over the time. Left cord paralysis and lower facial weakness are now extremely rare because of appropriate surgical technique. During implantation procedure transient asystole can occur in about 0.1% of implantations [23], but there was no asystolic events reported after the implantation procedure [24]. Although no significant changes in cardiac function from clinical studies in epilepsy were reported [7], VNS should be recommended with caution for patients with known cardiac conduction disturbances or sleep apnea [23].

The commonest adverse effects related to stimulation procedure are voice alteration, headache, neck pain, cough, dyspnea, difficulty in swallowing and pain [11]. Usually the symptoms are mild and have a tendency to taper down during prolonged VNS [7, 11, 24, 25] and should not lead to discontinue stimulation.

Conclusions

Depression disorders altering quality of life and leading to increased morbidity and mortality are very common. Despite new pharmacological opportunities, a considerable number of patients do not show an adequate response, and 5-10% of patients become resistant to multiple treatments [6]. Results from VNS for treatment-resistant depression studies seem very promising and VNS is about to become another treatment option, although VNS has failed as treatment of those extremely resistant depressions. Randomized control trials are necessary to confirm the efficacy of VNS for pharmacoresistant depression. Results from published studies [7, 11, 24, 25] show that VNS is safe and well tolerated, with mild adverse effects that have tendency to decrease during time. Further research to understand mechanisms of action of VNS are needed to investigate the benefit also for other neuropsychiatric disorders.

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