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The Neuromodulator Effect of Vagal Nerve Stimulation as the Treatment of Medically Refractory Epilepsy in Comparison with Surgical Approach: A Systematic Review

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Abstract

Background: Restorative options in medically refractory epilepsy are restricted to ablative brain surgery, the trial of antiepileptic medications, or palliative procedures. Vagal nerve stimulation (VNS) is an accessible palliative method of which the mechanism of action isn't well understood.
Methods: We searched for relevant studies published in 2016-2021 with PRISMA charts. For English published statistical analyses, we include all studies conducted on pediatric epileptic patients who have undergone epilepsy surgery and VNS.
Results: Antiepileptic impacts of VNS incorporate expanded movement of the locus coeruleus (LC) neurons with a raised norepinephrine (NE) discharge in the hippocampus, cortex, and amygdala. VNS-modulatory consequences for other synapse frameworks such as cholinergic, GABAergic, and glutamatergic depend on the activation of the LC-NE pathway. While in pediatric epilepsy, early surgical intervention is frequently recommended to work on cognitive and behavioral outcomes that unequivocally portray the epileptogenic zone.
Conclusion: The general rate of complication caused by epilepsy surgery was sensibly low (5%), suggesting primarily temporal lobe resection, can be safe preferably with recent procedure options, while VNS could be more effective as therapy begins at early stages pre- or post-seizure onset.
Keyword: Refractory Epilepsy, Epilepsy Surgery, Vagal Nerve Stimulation

Introduction

Epilepsy is a well-known chronic neurological disorder that is devastating for neuronal cells and affects approximately 50 million people worldwide. Although more than half of the patients can control it well with the help of antiepileptic drugs (AEDs), one-third of patients are unable to do that.[1] This is defined as refractory epilepsy. While epileptic focus resection can be curative for dozens of candidates, many individuals cannot undergo surgery because of the high risk of functional deficiency or multifocal seizure origin. In addition, patients who underwent epileptic focus resection may continue to have seizure onset post-operatively due to surgical failure.[2]

For the remaining patients, vagus nerve stimulation (VNS) has provided a new adjunctive treatment for epilepsy and has been well established since it was approved by the US Food and Drug Administration in 1997. The main neurobiological mechanisms of VNS are still poorly understood. However, some studies on animals and humans indicated that VNS might cause

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desynchronized activity and determine abnormal spiking patterns on electroencephalography. Besides, it is widely believed that the nucleus tractus solitarius plays a vital role in treating epilepsy using VNS. Approximately 50% of patients treated with VNS had the seizure frequency reduced by over 50%.[3] However, VNS may cause some inconvenience due to the electrode implantation device and a series of safety problems such as hemorrhage and infection. VNS is a newly developed therapy and overcomes the disadvantages of surgical procedures. The cymbal conchae is supplied by the auricular branch of the vagus nerve (ABVN), the only region of the outer ear exclusively innervated by the ABVN.[4] Several studies have proved that VNS is an effective procedure to control seizure onset and avoid the side effects of surgery. Here, we provided a systematic review of clinical studies examining the efficacy of VNS in treating medically refractory epilepsy in comparison with a surgical approach.

Methods

The results of the present systematic review were reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and adhere to a structured review protocol. Two authors (M.A.A. and D.H.R.) performed a search of PubMed, ScienceDirect, and British Medical Journal databases using the following search strategy: (“VNS” OR “vagal nerve stimulation” OR “vagus nerve stimulation”) AND (“refractory epilepsy” OR “medical refractor epilepsy” OR “medically refractory epilepsy”). We search the articles from inception to September 2021. The authors then independently excluded non-relevant articles based on a review of the full-text articles before comparing selected publications reporting on outcomes of patients with any medically refractory epilepsy that were implanted with a vagus nerve stimulator published in the English language were included. Upon uncertainty of inclusion of a publication, we consulted an additional author.

The authors extracted the primary endpoint of cessation from each article or not of the epilepsy episode in which VNS was implanted. A positive outcome was defined as either cessation of the epilepsy episode in which a VNS was invested and no report of later death or a significant (>50%) reduction in the most debilitating seizure type or seizure-freedom/no reoccurrence of medically refractory epilepsy. Grading of the level of evidence was carried out using the American Academy of Neurology's (AAN) classification scheme. The AAN defines a Class I and a Class II study as a randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment with a Class II study lacking one criterion a-e of Class I or a prospective matched cohort study meets Class I criteria. Class III trials are all other controlled trials (e.g., natural history controls or patients serving as their controls) in a representative population, where the outcome is independently assessed or derived by objective outcome measurements. Class IV studies do not meet Class I, II, or III criteria, including consensus or expert opinion. The PRISMA flowchart can be seen in Figure 1.

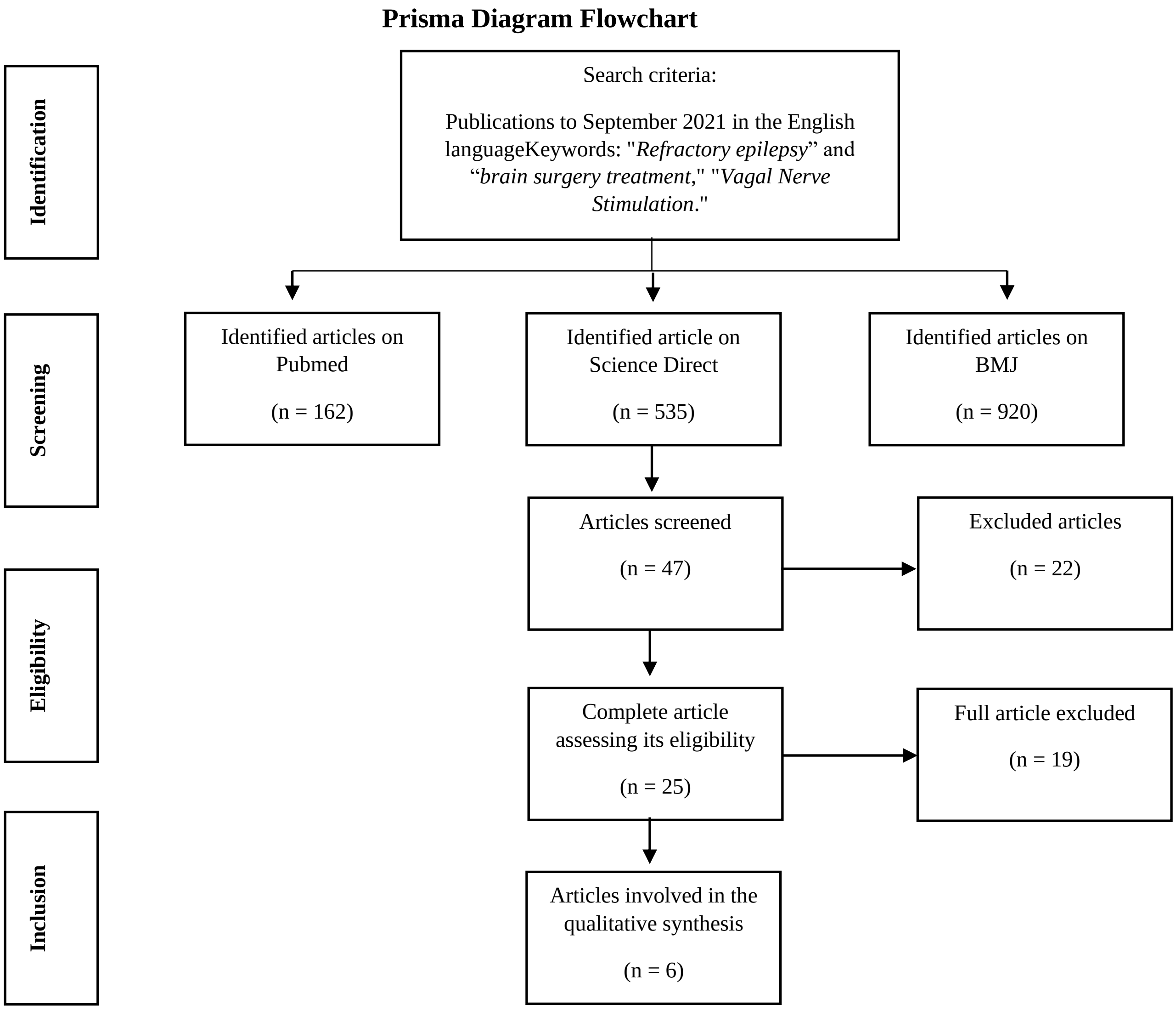

Figure 1. The PRISMA flowchart in identifying the literature included

Results

1617 articles were enrolled from the preliminary literature search: 162 papers from PubMed, 535 from ScienceDirect, and 920 from British Medical Journal. We excluded studies without data about the difference between good and poor responders from this initial screening. Finally, we identified 25 articles as relevant after reading the titles and abstracts, and after reading the complete text, six studies were selected for inclusion in our systematic review. The population of several studies was pediatric patients with drug-resistant epilepsy. Afra et al. analyzed patients to predict the outcome with>90% seizure reduction after VNS.[5] Villarreal et al. researched the predictor for seizure-free after VNS in follow-up. There was no randomized controlled trial among the included studies, and most were retrospective studies. Follow up was for at least one year.[6]

All identified studies reporting Class I, II, and III evidence of VNS efficacy in medically refractory epilepsy are summarized. Three blinded, randomized controlled trials

(Class I) have been published. In the first trial, Fetzer and colleagues randomized 114 patients with partial epilepsy at multiple centers to undergo either a high-frequency (presumed therapeutic) or a low-frequency (presumed sham) stimulation paradigm. Three months after surgery, the authors reported that high stimulation reduced seizure frequency by 25% compared with 6% in the sham group. Moreover, 31% of patients receiving high stimulation had ≥ 50% reduction in seizures.[7] Sen et al. performed a similar multicenter trial involving 196 patients with partial epilepsy. They documented a 28% reduction in seizures with high stimulation versus a 15% reduction with sham stimulation, with 23% of individuals in the therapeutic group attaining ≥ 50% reduction in attacks at three months after surgery. Finally, Amar and colleagues reported more dramatic results in a smaller VNS trial of 17 individuals, with 57% of treated patients attaining ≥ 50% decrease in seizures.[8]

We identified two nonblinded, randomized controlled trials (Class II evidence) by Tzadok et al. and Muthiah et al., who studied the response of 28 and 61 patients, respectively, to various VNS stimulation paradigms. Across all paradigms, a mean seizure reduction rate between 26% and 30% was reported, with 29% to 45% of patients experiencing ≥ 50% decrease in seizures. Finally, we identified one prospective observational clinical study (Class III evidence) examining 16 patients, with follow-ups for one year. Most investigators examined patients suffering from partial or mixed seizure types, revealing 17%–55% seizure reduction rates, with 21%–50% of patients experiencing ≥ 50% decrease in seizures. This study also reported a mean 50% decrease in seizure frequency.[9,10] Thus, several high-quality studies have suggested that VNS is efficacious in reducing seizure frequency by a modest but clinically significant amount in patients with various seizure types, as can be seen in Table 1.

Table 1. Summary of studies included VNS efficacy in treating medically refractory epilepsy in comparison with the surgical approach

Research	Cases	Seizures type	Follow-up	Seizure reductions (%)
Class I evidence				
Fetzer et al.	114	Partial seizures	Three months	25 vs 6
Sen et al.	196	Partial seizures	Three months	28 vs 15
Amar et al.	17	Partial seizures	Three months	71 vs 6
Class II evidence				
Tzadok et al.	28	Mixed seizures	3-64 months	30 overall
Muthiah et al.	61	Partial seizures	Three months	26 overall
Class III evidence				
Mertens et al.	16	Mixed seizures	>1 year	50

Discussion

With all its limitations, this systematic literature review found acute VNS implantation associated with the cessation of medically refractory epilepsy. Understanding this adjunctive surgical therapy for refractory epilepsy is vital given both the significant proportion of people with epilepsy who have exhausted medical therapy options and the devastating effects of ongoing seizures on the quality of life. We identified six clinical studies of VNS in epilepsy, including 432 patients. These studies consisted of 3 blinded, randomized controlled trials (Class I evidence); 2 nonblinded, randomized controlled trials (Class II evidence); 1 study reporting prospective data (Class III evidence). Among future studies (Class I–III evidence), seizure reduction rates were 25%–50% after 3–64 months of VNS therapy. Across all studies, VNS reduced seizure frequency by approximately 45%, although the seizure reduction rate increased from 36% at the 3- to 12-month follow-up to 51% after > 1 year of therapy. [11][12]

Notably, we found a more modest seizure reduction in the initial two large blinded, randomized controlled trials (25%–28% seizure decrease), compared with noncontrolled observational studies (approximately 50% seizure decrease). One possible reason for this finding is that follow-up was limited to 3 months in the controlled studies, potentially failing to capture a delayed benefit from therapy. Nevertheless, we must consider the possibility of author bias in noncontrolled observational series. A randomized controlled study examining the long-term effects of VNS in epilepsy would be helpful to clarify this issue further.[13][14]

That is to say, the mechanisms by which VNS causes changes in neurochemistry and prevents epileptic seizures are not yet known, although some evidence suggests the vagus nerve plays a role in quenching kindling of seizures in regions susceptible to heightened excitability.[15][16] These regions include the limbic system, thalamus, and thalamocortical projections. VNS may also affect structures in the midbrain and hindbrain, contributing to seizure suppression, although the specific changes in these cortical circuits remain unknown. VNS also increases activity in the locus coeruleus and the raphe nuclei and moderates the downstream release of norepinephrine and serotonin, both of which have been shown to have antiepileptic effects.[17][18]

VNS's success in treating refractory epilepsy with few side effects justifies its expansion to additional conditions and broader populations. VNS may also be helpful as a treatment for expecting mothers with treatment-resistant epilepsy. One study showed that women with epilepsy had a significantly higher risk of mortality during delivery when compared to women without epilepsy.[19] The goal of current epilepsy treatment is to optimize seizure control and minimize in utero fetal exposure to antiepileptic drugs, which, during the perinatal period, are associated with primary congenital malformation, growth retardation, and neurocognitive developmental deficits. VNS has been used successfully to treat medically refractory epilepsy in pregnant women, and physicians have concluded that VNS is a viable option for treatment during pregnancy. As a non-pharmacological treatment, VNS seems beneficial for seizure control in the expecting mother, and there is no evidence of harm to the developing fetus. [20]

A possible mechanism by which VNS appears to exert antiepileptic effects might be reducing damage to GABAergic inhibitory neurons within the cerebral cortex and possibly the hippocampal formation. In addition, in patients with partial epilepsy, VNS causes an increase in the inhibitory neurotransmitter levels of GABA in the CSF and normalizes cortical GABA-receptor density.[21] VNS treatment in another study did not alter GABA levels in the hippocampus. These data suggest that an enhanced GABA receptor-mediated neuronal inhibition may contribute to the therapeutic efficacy of VNS. VNS also might affect the glutamate system in epileptic states. Because it has been reported that VNS causes a reduction in glutamate levels in the CSF of patients with partial seizures.[6][22] Since epilepsy is associated with an excessive increase in glutamate (primary excitatory neurotransmitter in CNS) levels, reduced glutamate content in the CSF suggests an antiepileptic effect of VNS through modulation of glutamate release.[5][23]

Conclusion

Vagus nerve stimulation should be considered in patients in whom medical therapy has failed but who remain poor candidates for resection or continue to experience seizures after resection. Despite its initial approval in the US only for adults and adolescents with partial epilepsy, children and patients with generalized epilepsy have benefited significantly from VNS. However, it is essential to recognize that complete seizure freedom is rarely achieved with VNS and that one-quarter of patients do not receive any benefit from therapy. The general rate of complication caused by epilepsy surgery was sensibly low (5%), suggesting that epilepsy medical procedures, particularly primarily temporal lobe resection, can be safe, preferably with recent procedure options. At the same time, VNS could be more effective as therapy begins at early stages pre- or post-seizure onset to decide the preventative role of VNS in human epileptogenesis when the treatment is given promptly.

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