Chapter 48

Vagus nerve stimulation

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Overview

Vagal nerve stimulation (VNS) was first delivered to patients over 25 years ago with the first patient being implanted in 1988. European Community approval was granted in 1994 and USA (FDA) commercial approval in 1997[1]. VNS currently has a licence in Europe and the UK for the adjunctive treatment of epilepsy refractory to antiepileptic medication. The UK NICE Guidelines for Epilepsy (2012) suggest VNS is indicated 'for use as an adjunctive therapy in reducing the frequency of seizures in adults (and children) who are refractory to antiepileptic medication but who are not suitable for resective surgery'. NICE specifies that VNS is indicated for patients in whom focal or generalised seizures predominate. The US licence is for refractory focal epilepsy in patients over the age of 12.

VNS is implanted to reduce the frequency and severity of seizures. That the VNS magnet can be used to administer an extra stimulation at the onset of the seizure can be additionally beneficial in some patients. Since its initial implantations for epilepsy, VNS has been trialled in a variety of other medical conditions. In particular, the observation that co-existing depression in epilepsy patients seemed to improve with VNS led to VNS now also being licensed for treatment-resistant depression in adults and the American Academy of Neurology recently recommended that VNS may be considered for improving mood in adults with epilepsy[2]. Other potential therapeutic roles in anxiety, dementia, tremor, heart failure, obesity and even rheumatoid arthritis are being explored.

Mechanism of action

Theories as to how VNS mediates its effect include direct activation, neurotransmitter and neuropeptide modulation influencing ictal discharge, pre-ictal changes and arousal[3,4]. As many as 80% of vagus fibres are afferent and the parameters used in clinical practice preferentially stimulate these smaller fibres over the efferents. Afferent pulses reach the nucleus tractus solitaris (NTS), synapsing bilaterally. The NTS projects to the thalamus, hypothalamus, locus coeruleus, reticular activating system, midline raphe, limbic system and secondarily to the cortex. In a kindling model of epilepsy, VNS was shown to prevent lowering of seizure threshold compared to control animals[5], while in rodents treated with kainic acid VNS promoted neurogenesis in the dentate gyrus of the hippocampus. In a maximal electroshock rat epilepsy model, VNS therapy was no longer effective as an anticonvulsant when noradrenergic pathways were depleted by lesioning of the locus coeruleus. A cat amygdala kindling seizure model suggested a partial anti-epileptogenic effect of VNS. Positron emission tomography (PET) scanning showed increased blood flow in the thalamus, hypothalamus, and the insular cortex with decreased blood flow in the amygdala, hippocampus, and posterior cingulate. VNS induced forebrain Fos, a nuclear protein expressed under conditions of high neuronal activity. Further, VNS has also been

shown to reduce anhedonia in rats treated with kainic acid, lending support to the use of VNS in depression[6]. However, the exact molecular mechanism by which VNS exerts its effect is uncertain.

Some interesting insights into the action of VNS in humans have been explored with EEG recording. A small study compared five patients who had responded well to VNS implantation to five patients in whom VNS had not been beneficial. EEG recordings five years after implantation showed that patients who had benefited had a decrease in gamma band frequency desynchronisation[7]. More recently another small study has shown that patients who respond to VNS therapy demonstrate a shift in EEG architecture towards a more efficient configuration[8] raising the possibility that chronic VNS offers some stabilisation of neuronal networks. Studies have also begun to explore whether there are EEG signatures that might better predict response to VNS[9].

VNS – device and process

Originally only a single manufacturer (Cyberonics) had rights to produce the device but this restriction has now expired and a number of devices are becoming available. In some experimental animal models stimulating the right vagus nerve produces cardiac dysrhythmias so VNS is only licensed for implantation on the left in humans. The generator is usually implanted in the left upper chest with the electrodes placed around the left cervical vagus. Afferent pain fibres may be activated, especially at higher levels of clinical stimulation, producing discomfort in the throat, but even at normal therapeutic levels patients are usually aware when the device activates due to a sensation in the throat.

An electrical test of the device is performed intra-operatively but the device is usually activated some time post-operatively, often at the first outpatient follow-up. Continuous electrical stimulation of the vagus nerve in animal models has been shown to produce fibrosis and ultimately failure of the nerve, so stimulation is provided in an intermittent manner. Typically the VNS device is initially set to provide 30 seconds' stimulation every five minutes. The device is programmed externally (output current, signal frequency, pulse width, signal on- and off-times) and adjustments are made on the basis of tolerability of side effects and clinical efficacy.

In addition to the continuing cycling on and off, it is possible to manually activate the device by passing a magnet over the generator box. Patients or carers can use this when a seizure starts, and in some the magnet seems to shorten or limit the extent of the attack. Commonly the current delivered following magnet-induced activation is set slightly higher than the baseline level. The magnet also provides a means for the patient to deactivate the device. If the magnet is placed over the generator box and it remains there for more than a few seconds the VNS switches off. When the magnet is subsequently removed, it reactivates at the previous settings. This may be used by patients to investigate whether a symptom such as cough is related to the device or to some unrelated cause. Similarly, the device can be switched off for certain occasions when patients may wish, for example, to make a speech, when they are keen to avoid any fluctuation in voice quality.

Regular follow-up is needed, with gradual current adjustment to achieve maximum benefit in a similar way to adjustments of antiepileptic drug (AED) dose. Battery life, which depends on output and magnet use, is likely to exceed six years even at higher output levels, after which the pulse generator will need to be replaced. The device should be checked regularly and an early replacement indicator (ERI) or 'near end of service' (NEOS) alert will warn the clinician of impending battery exhaustion. A rechargeable battery is in development but is not yet in mainstream use.

Precautions and adverse effects

As with all surgical procedures in epilepsy, patients must be fully informed of the potential risks and the long-term consequences of VNS insertion. Despite little vagal viscero-effector activity during therapeutic VNS in humans, caution is advised in patients with heart disease and severe asthma. One study concluded that 'long-term vagus stimulation in patients without concomitant lung disease does not induce any significant changes in FEV1. However, in patients with obstructive lung disease, intense vagus stimulation can cause a deterioration of lung function'[10]. It is recommended that there is minimal handling of the vagus intra-operatively. Transient bradycardia or sinus arrest may occur during the lead test in 0.1% of cases but is not necessarily a contraindication to switching on the device after an interval. Infection of the lead or generator site, likely the most serious adverse effect, may occur in up to 3% requiring removal of the device in about 1%. Lead breakage may occur. Horner's syndrome, unilateral facial weakness and vocal cord paresis have been reported. Stimulation and, to a lesser extent, implantation may be associated with hoarseness, cough, dyspnoea, pharyngitis, paraesthesia and pain. Pre-existing dysphagia may be exacerbated, as can obstructive sleep apnoea, although these features do not seem to emerge *de novo* following VNS.

If a patient requires removal of the device for infection or if removal is requested due to lack of efficacy, it is usual to remove the generator box only and to leave the lead in place. The lead can be removed but this entails more difficult surgery and carries some risk of a hoarse voice owing to injury to the vagus nerve.

Common side effects of ataxia, dizziness, fatigue, nausea and somnolence as may be seen with AEDs were absent from the list of statistically significant side effects of VNS in a Cochrane review[11].

Practical considerations

Strong electric or magnetic fields may damage the generator and should be avoided. A detailed account regarding risks associated with defibrillation, lithotripsy, therapeutic ultrasound and therapeutic and surgical diathermy can be found on the website www.cyberonics.com. The system is not affected by home microwave ovens or mobile phones. Airport security systems and shop theft detectors may be activated by VNS although there are no reports of the VNS itself being affected.

There is some concern regarding limitations of new generation MRI in those with VNS implantation, including those where the battery pack has been removed but the wire remains. The potential risks of performing MRI on patients with an implanted VNS include heating effects, especially of the stimulation electrodes, inadvertent resetting of the device or magnet mode activation, image distortion and artefacts, magnetic field interactions and device malfunction or damage. If performing an MRI scan, VNS output should be set to zero beforehand and reset afterwards, meaning that an appropriately trained person must be available. VNS is approved in MRI scanning using only transmit-and-receive type head coils at both 1.5 and 3 Tesla field strength. Some modern head coils are of the phased-array type which should not be used.

In practice, good diagnostic quality brain scanning can be achieved if appropriate precautions are in place, however body or extremity imaging (receive-only coils) and experimental brain protocols may not be risk-free, even if the generator has been explanted and only the wire remains. Work is being carried out to develop full MRI compatibility but restrictions remain

at present. It is advisable to consult the device manufacturer if there is any doubt before performing MRI.

Effect in epilepsy

VNS appears to have an abortive and a prophylactic effect, both acutely and chronically in epilepsy. It is effective in various animal seizure models. Although the double-blind studies were in partial epilepsy, it appears to be broad spectrum. It has been implanted in a variety of syndromes, including idiopathic generalised epilepsy and Lennox-Gastaut syndrome[12], with broadly similar results[13].

A Cochrane review (2001) addressed the efficacy of high-level versus low-level stimulation, the latter as active control[11]. The review only included the two early short-term randomised and double-blind trials[14,15]. The review concluded that 'results of the overall efficacy analysis show that VNS stimulation using the high paradigm was significantly better than the low stimulation'. The overall odds ratio (OR) for 50% responders was 1.93 (1.1, 3.3). Any beneficial effect of low stimulation would tend to reduce the high stimulation OR compared to placebo. Although direct comparisons may not be valid, of interest are ORs reported in meta-analysis of studies of some add-on AEDs. For example ORs reported for 50% responders relative to placebo were, in order of increasing magnitude: 1.59 (0.91, 2.97) for remacemide, 2.29 (1.53, 3.43) for gabapentin, 2.32 (1.47, 3.68) for lamotrigine, 2.46 (1.61, 3.79) for zonisamide, 2.51 (1.88, 3.33) for oxcarbazepine, 3.78 (2.62, 5.44) for levetiracetam and 4.22 (2.80, 6.35) for topiramate[16,17,18,19]. Thus VNS in early studies appears to have a short-term effect in refractory patients approaching that of some of the AEDs. It is less effective, however, in the short or long term, than resective surgery in well-selected cases, including temporal lobectomy for mesial temporal sclerosis.

More recently there has been an updated Cochrane review (2015) of the role of VNS in focal epilepsy[20]. Again the objective was to determine the efficacy of high-level to low-level stimulation. Four trials were included in the meta-analysis and high-level stimulation was shown to be 1.5 times more effective than low-level stimulation. Overall VNS was well tolerated, with the side effect profile very similar to that previously reported. Hoarseness and dyspnoea were amongst the more common side effects and these were seen more frequently with higher levels of stimulation[20]. Similar findings have also been reported elsewhere[21], although some have been more circumspect as to whether VNS does offer significant patient benefit above best drug therapy[22].

Patients are generally aware of stimulation due to a feeling in the throat, so it is not possible to fully blind patients to whether VNS is on or off. Nevertheless the two double-blind randomised controlled trials in partial epilepsy were carried out when the device was first introduced and presumably the patients may have been less informed as to the expected effects[14,15]. Later studies involve large numbers of patients but are open label. The mean reductions of seizure frequencies of 24.5% and 28% observed at three months in the randomised trials indicate rather modest benefits.

However, by contrast with AEDs, whose benefits tend to reduce with time, open studies consistently show an increasing effect of VNS with time. For example, at one year a median seizure reduction of 45% has been shown, with 20% of patients achieving a greater than 75% reduction[1,15,16]. Most striking however are the longer-term studies with progressive improvement in the seizure frequency for more than ten years. For example Kuba et al found 85 out of 90 patients implanted continued VNS at five years with a median seizure reduction of 56% and with 64% enjoying a 50% or greater reduction[23]. By ten years Elliott et al found a 75% reduction in 65 patients[13]. However periods of seizure freedom greater than one year

are only experienced by about 5–10% of patients in the open studies and may be subject to publication bias[24].

Interestingly, a mortality study by Annegers[25] showed that the excess mortality associated with refractory epilepsy was lower with longer-term follow-up (standardised mortality ratio, or SMR, of 3.6 with extended follow-up compared to the previous finding of an SMR of 5.3). Moreover, when VNS experience was stratified by duration of use, the rate of sudden unexpected death in epilepsy (SUDEP) was 5.5 per 1000 over the first two years and 1.7 per 1000 thereafter. This finding was not, though, confirmed in a more recent study showing that VNS did not appear to lower the risk of premature death or rate of SUDEP[26].

In a cost analysis study[27], unplanned direct hospital costs before and after VNS implantation showed an annual reduction of some $3000 US per study patient, irrespective of whether the patient was classified as a responder (in this study defined as experiencing 25% or greater reduction in seizure frequency). Other studies have reported a significant decrease in epilepsy-related direct medical costs in VNS-treated patients[28] and recently a large study has confirmed a progressive and substantial reduction in healthcare costs following implantation, with the surgery and device costs being offset by the savings by 18 months[29].

Special groups

There are many case series of the use of VNS in particular syndromes, often purporting benefit that is not necessarily replicated in other studies. Notably, a recent review concluded that VNS could not currently be recommended in refractory status epilepticus[30]. There does, though, appear to be some evidence of specific benefit in Lennox-Gastaut Syndrome[2,31] and there are repeated reports of improvement in alertness and mood, most noticeable in those with learning difficulty. Patients with learning difficulties, both adults and children, may therefore be especially suitable for VNS insertion[32].

Future advances

A potentially promising development in VNS technology is the development of the new Aspire SR VNS device. Aspire SR is responsive to heart rate, giving an extra stimulation when detecting ictal tachycardia. The device is somewhat larger than the previous model, therefore requiring a larger skin incision, and intra-operative testing can take somewhat longer. However, the possibility of automated additional stimulation at the onset of a seizure would seem worthwhile, especially as this facility can be deactivated if necessary

Another novel development is of transcutaneous VNS. This stimulates the auricular branch of the vagus, which supplies the skin of the concha of the ear, and is a non-invasive device. Benefit has been shown to seizure profile in small studies and there are minimal reported complications or side effects[33,34]. However, larger studies are needed to fully evaluate the effect of transcutaneous VNS

Summary

VNS is now established as a safe procedure with clear, clinically useful and sustained benefits, particularly in the medium to long term. It is recommended that VNS is considered in patients with pharmacoresistant epilepsy who are not suitable for resective surgery. VNS may have a particular benefit in patients with learning difficulties and may also offer benefit to mood in patients with epilepsy. Caution however should still be exercised in older populations with potential co-existing cardiopulmonary disease where experience is still limited

VNS offers different advantages and disadvantages to standard AEDs and its profile may preferentially suit certain patients. Compliance is ensured and VNS does not typically associate with central nervous system side effects. VNS is unlikely to render patients seizure free and continued use of antiepileptic medication is usually necessary. The cost-benefit analyses in severe epilepsy are particularly compelling and may lead to a more widespread use in patients with frequent hospital admissions or who are on polypharmacy.

The increasing utilisation of responsive VNS and further development of transcutaneous VNS offer exciting possibilities. These advances, coupled with deep brain stimulation in epilepsy, mean that the role of neurostimulation in drug-refractory epilepsy is likely to continue to expand.

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