Use of Vagal Nerve Stimulation for the Treatment of Migraine

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Current Methods of Treatment

There is no single standard of care for patients presenting with migraine symptoms, and treating acute migraine is challenging because of substantial nonresponse rates among medication users and difficulty in predicting individual’s responses to a specific agent or dose. Abortive therapy is typically suggested as early as possible after the onset of symptoms. Effective first-line therapies for mild to moderate migraine are nonprescription nonsteroidal anti-inflammatory drugs and combination analgesics containing acetaminophen, aspirin, and caffeine.\(^5\)

Triptans (a class of serotonin receptor agonists) are first-line therapies for moderate to severe migraine, or mild to moderate migraine that has not responded to adequate doses of simple analgesics. Triptan intake must be carefully restricted as excess consumption can result in medication overuse headache. Additionally, triptan administration has been seen to elicit a behavioral syndrome of enhanced sensitivity to surrogate triggers of migraine that is maintained for weeks following discontinuation of drug, a phenomenon termed triptan-induced latent sensitization.\(^6\) Due to their potential side effects, triptans should be avoided in patients with vascular disease, uncontrolled hypertension, or hemiplegic migraine.\(^4\)

Agents that interact with the GABAergic system seem to have a positive effect in reducing migraine attacks.\(^1\) Divalproex sodium (Depakote) and topiramate (Topamax) are most commonly used and are FDA-approved for migraine prophylaxis. Both drugs have class I evidence supporting their effectiveness in decreasing the frequency of migraine attacks. Other anticonvulsants with weaker evidence for effectiveness include gabapentin, lamotrigine, carbamazepine, and zonisamide. Intravenous antiemetics, with or without intravenous dihydroergotamine, are effective therapies in an emergency department setting. Dexamethasone may be a useful adjunct to standard therapy in preventing short-term headache recurrence. Intranasal lidocaine may also have a role in relief of acute migraine. Isometheptene-containing compounds and intranasal dihydroergotamine are also reasonable therapeutic options. Injections of botulinum toxin (BOTOX®) around the scalp, neck, and shoulders have been used as a treatment in some patients who are intolerant of, or refractory to, other pharmacologic interventions.\(^12\)

Despite significant advancements in the medical management of this challenging disorder, clinical data have revealed a proportion of patients who do not adequately respond to pharmacologic or surgical intervention and remain symptomatic. Approximately 40% of all attacks do not respond to a given triptan or any other
substance. The limitations to current migraine medications present a clinical need for alternative treatment options.

**Vagus Nerve Stimulation**

The vagus nerve serves an important function in mediating pain signals to the sensory cortex. Vagus nerve stimulation (VNS) is a procedure that has been used for the treatment of epilepsy and medication-resistant depression and recently has shown a decreased incidence and severity of migraine symptoms. The GammaCore™ device from NeuroCore utilizes non-invasive neurostimulation of the vagus nerve in order to treat the symptoms associated with migraines.

In animal models, VNS decreases the activity of nociceptive neurons in the trigeminal nucleus as well as the spinal cord. Several studies of long-term VNS humans have shown a decreased incidence and severity of migraine. While the mechanism has not been verified in humans, the literature proposes a hypothesis for how VNS may alleviate migraine symptoms.

Functional neuroimaging studies confirm that VNS alters the activity of pain-regulating cortical structures including the locus coeruleus (LC) and trigeminal nucleus. In a rat model, VNS increased the firing activity of LC neurons releasing norepinephrine. Norepinephrine signals to the dorsal horn of the spinal cord to minimize pain perception. Studies also suggest that stimulation of the vagus nerve may inhibit secretion of calcitonin gene-related peptide and substance P from the trigeminal nucleus. A reduction in these inflammatory substances would decrease the pain signals to the thalamus and sensory cortex, resulting in an analgesic effect.

**Implantable VNS for Treatment of Migraines: Clinical Data**

Published clinical data and animal studies clearly demonstrate the safety and efficacy of vagus nerve stimulation devices. Mauskop et al (2005) found that 3 out of 6 patients with refractory migraine and chronic headache treated with implantable VNS showed significant improvement in headache symptoms. Kirchner et al (2006) evaluated the mechanism by which VNS reduces pain perception. Eleven patients’ pain responses were evaluated before and after VNS implantation using a visual analogue scale and brain imaging. VNS was found to significantly reduce pain to tonic pressure with a moderate reduction of blood flow within the axon reflex. The results suggest that VNS may inhibit peripheral nociceptor functioning in humans, leading to its analgesic effects.

**Implantable VNS for Prevention of Migraines: Clinical and Safety Data**

Lenaerts et al (2008) conducted a retrospective study on the effects of VNS therapy for migraine in epileptic patients. Lenaerts determined that 80% of migrainers.
experienced decreased frequency of migraines by at least 50%, with 5 out of the 10 patients reporting that after three months of VNS treatment they were completely headache free.\textsuperscript{11} Morris et al performed a long-term efficacy and safety follow-up of 454 epilepsy patients treated with an invasive VNS device. After three years, VNS remained safe and well tolerated with nearly three-quarters of patients choosing to continue therapy.\textsuperscript{12} In 5 separate studies conducted using a transcutaneous VNS device, no adverse effects were reported for the 110 healthy enrolled subjects.\textsuperscript{15-19} While implantable VNS has shown to be efficacious in the treatment and prevention of migraine, many patients are deterred from this option due to the costs and co-morbidities associated with a surgical procedure.

**Noninvasive VNS for Prevention of Migraine**

The GammaCore device utilizes short term non-invasive electrical stimulation of the vagus nerve to deliver relief from migraine pain without the complications and costs of an invasive surgical procedure. Recently, Oshinsky investigated the effect of non-invasive VNS in an accepted animal model of recurrent headaches.\textsuperscript{20} Rats were first administered infusions of an “inflammatory soup” to simulate the repeated activation of dural afferents believed to reduce pain threshold in patients with recurrent migraine headaches. After the pain threshold was lowered, rats received 60 seconds of noninvasive VNS (nVNS) delivered through a miniature GammaCore device. Pain threshold was measured using pressure sensory testing. As shown in Figure 1, rats treated with nVNS showed a significant increase in trigeminal pain threshold that persisted at least 2.5 hours. The results of this study demonstrate that short term noninvasive VNS has a positive effect on trigeminal pain threshold in the rat model of recurrent migraine headache.

In conclusion, results from clinical and pre-clinical studies indicate that noninvasive VNS may be effective in the prevention and treatment of migraine with minimal adverse effects.

\begin{figure}[h]
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\includegraphics[width=\textwidth]{gamma-core-device.png}
\caption{Effect of non-invasive VNS with the GammaCore device on trigeminal pain thresholds}
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De Felice M (Aug 2010) Triptan-induced enhancement of neuronal nitric oxide synthase in trigeminal ganglion dural afferents underlies increased responsiveness to potential migraine triggers. Brain 133(Pt 8):2475-88