Peripheral Neuromodulation for Treatment of Chronic Migraine Headache

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KEYWORDS

• Migraine • Neuromodulation • Occipital nerve stimulation • Headache

KEY POINTS

- Chronic migraine affects a large proportion of the population and is a significant source of disability and lost productivity.
- Traditional neurosurgical procedures that favor lesioning or decompressing the greater occipital nerve have not gained favor.
- Occipital nerve stimulation provides an attractive nondestructive alternative, but its degree of efficacy remains to be fully elucidated in randomized controlled trials.
- Mechanism of action is unknown but it has been attributed to the gate theory of pain or modulation of the trigeminocervical complex in the rostral spinal cord.

Between 25 and 45 million Americans experience migraine headaches; approximately 2.0% have chronic migraine (CM) headaches.[1,2] CM is characterized by a minimum of 15 headache days per month, and approximately half of the headache days meet the diagnostic criteria for migraine without aura or respond to a migraine-specific acute medication.[3] Individuals with CM are 4 times more likely to have major depression with more frequent suicide attempts than in the general population.[4–6] Furthermore, compared with episodic migraine, CM is associated with significantly greater disability, economic burden, and impairments in health-related quality of life.[7–10]

Pharmacotherapy for migraine headaches includes medications to relieve the acute pain (abortive agents) and medication to prevent the onset of headache (preventative agents). Abortive agents include nonsteroidal antiinflammatory agents, triptans, opioids, ergot compounds, and sedatives. Preventative agents include anticonvulsants, antidepressants, β-adrenergic blockers, and serotonin antagonists. In addition, recognition and prevention of exposure to precipitating agents such as caffeine, many foods including cheeses and red wines, and stress can provide significant relief and reduce medication intake.

Historically, neurosurgical therapies for headache have included destructive procedures including dorsal root entry zone (DREZ) lesioning, dorsal root ganglionectomy, peripheral neurolysis, and neurectomy. These therapies, however, have not been effective for migraine headaches and such techniques may result in secondary neuropathic pain in the distribution of the surgically treated nerve(s). For example, ganglionectomy at the second cervical level has been reported to be 80% effective at 3 year follow-up in posttraumatic second cervical pain syndromes.[11] Nontraumatic pain in this region, however, was not significantly relieved by ganglionectomy. Ventrolateral DREZ lesioning at the first, second, or third cervical level has been variably effective for occipital neuralgia but is highly invasive and has

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significant risks.[12] Greater occipital nerve neurolysis has demonstrated short-term efficacy, however, there was a significant recurrence rate within 2 years.[13] In addition to neurolysis and neurectomy, fusion of the first and second cervical vertebrae has relieved pain in some patients with occipital neuralgia.[14]

Initially, peripheral nerve stimulation using a cuff electrode or direct stimulation of the greater occipital nerve was found to be effective for treating occipital neuralgia.[15,16] More recently, peripheral neuromodulation in the occipital region has emerged as a promising treatment modality for a variety of chronic headache disorders, including CM.[17–25] Weiner and Reed[26] first reported the use of occipital nerve stimulation (ONS) for the treatment of occipital neuralgia. However, positron emission tomography (PET) imaging of these patients demonstrated activation patterns more consistent with CM than with occipital neuralgia, leading Matharu and colleagues[17] to suggest that Weiner and Reed's patients suffered from CM. Since then, ONS has been reported to be efficacious for the treatment of several headache disorders including migraine headaches,[4,5] cluster headache,[6] hemicrania continua,[25] and true occipital neuralgia.[24]

An extensive literature search was performed with a specific focus on high-quality clinical trials of peripheral neuromodulation for the treatment of intractable CM. This search revealed 6 independent and 3 industry-sponsored clinical trials, the results of which are listed here.

INDEPENDENT CLINICAL TRIALS

- Weiner and Reed.[26] This open-label trial included 13 patients implanted with percutaneous occipital leads for CM. Twelve patients reported a good to excellent response and required minimal oral analgesic medications at follow-up ranging from 18 months to 6 years.
- Popeney and Alo.[25] This open-label trial included 25 patients implanted with percutaneous occipital leads for CM. At the 18-month follow-up, 88% of patients showed a positive response, with an overall 50% reduction in the number of headache days per month.
- Oh and colleagues.[27] This open-label trial included 20 patients with transformed migraine headaches implanted with paddle-type occipital nerve stimulating leads. At 6 months, 80% of patients reported greater than 75% pain relief and 95% reported improvement in their quality of life and their willingness to undergo the procedure again.
- Slavin and colleagues.[28] This open-label trial included 10 patients with CM implanted with percutaneous occipital nerve stimulating leads. At the 22-month follow-up, 70% of patients had pain reduction ranging from 60% to 90% with a corresponding decrease in the use of analgesics.
- Levy.[29] This open-label prospective trial included 45 patients treated with peripheral nerve stimulation for CM. At the 2-year follow-up, 83% of patients reported good to excellent (>50% relief) results with an additional 9% of patients reporting fair (30%–50%) results; 92% of the patients reported satisfaction with the therapy, a willingness to have the device implanted again based on their treatment experience, and their unwillingness to have the device removed even at no cost.
- Silberstein and colleagues.[30] This prospective, randomized, double-blind study included 157 patients with CM randomized 2:1 between active (n = 105) and sham (n = 52) ONS. At 12 weeks, there was no statistically significant difference between the groups in terms of responder rate, defined as greater than 50% pain reduction, which was their primary end point. There was, however, a statistically significant difference between groups at the level of 30% pain reduction. Furthermore, the active group had a statistically significant reduction in the number of headache days and in the degree of migraine-related disability.

INDUSTRY-SPONSORED CLINICAL TRIALS

In 2013, peripheral neurostimulation for the treatment of CM has been approved for use in the European Union and in Australia. However, it has not yet been approved by the US Food and Drug Administration (FDA). ONS for CM is therefore used by physicians in the United States on an off-label basis. Industry is not allowed to market or promote the use of their products for off-label indications. Because of this limitation and the significant potential of this therapy for the treatment of migraine headache, the 3 major device manufacturers in this sector (Medtronic, Boston Scientific, St. Jude Medical) have sponsored research trials to investigate the safety and efficacy of their neurostimulation products for the treatment of migraine headaches.

Medtronic ONSTIM Trial

The Occipital Nerve Stimulation for the Treatment of Intractable Migraine (ONSTIM) trial, sponsored