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REVIEW

Clinical utility of implantable neurostimulation devices in the treatment of chronic migraine

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Abstract: Chronic migraine is a disabling disorder that is costly to individuals and society. Occipital nerve stimulation has been used to treat refractory cases of primary headache disorders including drug-resistant chronic cluster headaches and chronic migraine. The Food and Drug Administration (FDA) off-labeled application of equipment used for peripheral nerve (occipital) stimulation is borrowed from FDA-labeled spinal cord stimulation. Manufacturer-sponsored randomized trials include a feasibility study (ONSTIM-Medtronic) and a safety and efficacy study (St Jude). A non-industry sponsored prospective, randomized crossover study by Serra and Marchiotretto suggests improved quality of life and a significant reduction in medication use. Though preliminary studies suggest occipital nerve stimulation is safe and efficacious in treating chronic migraine headache, complication rates, including lead migration, lead fracture, and surgical site infections remain high. Further studies are needed to demonstrate long-term outcomes, while improved surgical techniques and site-specific equipment are needed to minimize complications.

Keywords: headache, occipital nerve stimulation, peripheral nerve stimulation, neuromodulation, electrical stimulation therapy

Introduction

This review will discuss the anatomy, equipment, adverse events and outcome measures of occipital nerve stimulation (ONS) trials, with an emphasis on the clinical utility of implantable neurostimulation devices in the treatment of chronic migraine. Headache can be a chronic disabling disorder with profound personal and societal impact. Headache disorders are a worldwide problem, affecting people of all ages, ethnicities, socioeconomic classes, and geographical areas.[1] Up to 4% of the world's adult population is affected by 15 or more headache days every month.[2]

Early civilizations must have recognized the impact of headache on their families and groups and sought relief through external intervention. Crude instrumentation and external manipulation is estimated to have occurred as early as 7,000 BC. Skull perforation through trepanation is evident not only in Neolithic skulls but continues to be practiced by some African tribes without anesthesia.[3]

In his 46 AD text *Compositiones Medicae*, Scribonius Largus, a roman court physician to the emperor Claudius, described the use of torpedo fish (electric ray) to treat headache.[4] This ancient account effectively demonstrates the earliest known use of primitive neuromodulation in headache.

In the late 20th century, progress was made by pioneers in neuromodulation. Picaza described his observational experience and patient outcomes who had undergone

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surgical procedures to expose and stimulate peripheral (sciatica, ulnar, and occipital) nerves.[5] Based on this early work, a number of physicians have reported their experience with direct and indirect ONS. Subcutaneously implanted leads for occipital (peripheral) nerve stimulation have been used to treat headache disorders refractory to drug therapy.[6–12] This includes chronic cluster headache,[13–15] hemicrania continua, posttraumatic, occipital neuralgia,[16,17] C2-mediated headaches,[18] and occipital region pain after surgery.[9]

The greater (GON) and lesser (LON) occipital nerves are the distal branches of C2–C3.[19–23] These peripheral nerves ascend to the skull vertex by traversing an imaginary line between the mastoid processes. Cadaveric studies show the GON between 5 and 28 mm and the LON 32–90 mm from midline. Subcutaneous leads are placed along the intermastoid line at the occipital base (C1 arch) and fixed subcutaneously to span this interval. Successful stimulation is achieved when the patient reports a "buzzing," "tingling," or pleasant vibratory sensation in the expected GON/LON dermatome.[24] Painful paresthesias or shock can occur.[13,15] Unilateral ONS in drug-resistant chronic cluster headache resulted in improvement; the attacks, however, shifted sides requiring bilateral stimulation. Unilateral ONS has also been linked with painless autonomic attacks and rapid recurrence with discontinuance of therapy.[13] Literature review suggests that only bilateral ONS has been applied in CM.

Methods

The medical literature relevant to this review was identified by searching the Scopus, Embase (1988–2013 Week 12), and Ovid Medline reference databases for English-language articles published between 1996 and 2013 (last search Week 12). Search terms included "electrodes," "peripheral nerves," "electrical stimulation therapy" or "occipital nerve stimulation," "occipital stimulation," "electric stimulation therapy," "neuromodulation" and "headache," and "migraine disorders" or "neuralgia."

Equipment

The equipment used for ONS in the treatment of chronic migraine relies on the same technology as that used for spinal cord stimulation. The universal components include an implantable power source (ie, a battery) termed an internal pulse generator (IPG) or internal neurostimulator (INS), which is coupled with a programmable radiofrequency receiver. Rechargeable and non-rechargeable (ie, primary cell) batteries are available and are the approximate size and weight of cardiac implantable devices. Like the rechargeable batteries in many personal electronic devices, ONS rechargeable batteries will require more frequent recharging as they age. The IPG/INS for stimulation is implanted in a subcutaneous pocket in the chest, abdomen, or low back of the patient.[25]

The IPG is connected to insulated leads (ie, inert polyurethane-coated wires) that connect to an array of 4–16 metallic electrodes (ie, platinum iridium contacts) typically measuring between 3.0 and 6.0 mm in length, with interelectrode spacing (edge to edge) of 1–16 mm. These electrodes are designed to function as non-charged (neutral) space, as anodes, or as cathodes. The configuration of arrays transmits an electrical current to the stimulation site. As previously noted, ONS is applied over the distal fibers of the C2–C3 dorsal rami GON and LON. Percutaneous leads with tubular contacts create a circumferential electrical field. They are inserted through a 14-gauge introducer needle. The leads may also be flat paddle leads, which are shorter and create a unilateral electrical field. Flat paddle leads require surgical dissection for placement and anchoring to the fascia. This may lead to additional bulk, wound complications, discomfort, or poor cosmetic outcome.

Migration of the leads (ie, bundled wires) can be prevented by suturing them to subcutaneous fascia with flexible anchors. In some cases, an extension cable (ie, a thin, coated wire) is required during implantation. This allows the surgeon to span an anatomical distance and/or provide coiled strain-relief loops during implantation of the leads connected to the distant IPG. Splitters can be used to divide electrical current to an additional anatomical site, such as right and left ONS or simultaneous occipital nerve and terminal trigeminal nerve stimulation.[26,27]

The IPG power source and programmable elements are activated by a handheld radiofrequency transmitter (ie, programmer). The programmer used by the clinician allows for the designation of cathodes and anodes as well as the programming of stimulation parameters and features including amplitude, pulse width, and frequency. A simplified programmer is used by the patient to turn the neurostimulator on or off, adjust power (amplitude), and select a preset program with set parameters in amplitude, pulse width, and frequency. Charging the IPG is completed via an external transmitter coil aligned over the device. Major manufacturers of the equipment in the United States include Boston Scientific Neuromodulation Corporation (Natick, MA, USA), Medtronic Inc. (Minneapolis, MN, USA), and St Jude Medical, Inc. (St Paul, MN, USA).

Some promising investigational ONS equipment that advanced to clinical trials has not been approved and is

therefore not commercially available. For example, the Bion microstimulator (Boston Scientific Neuromodulation Corporation) was investigated for its use for chronic migraine.[28,29] This "bionic neuron" contained a single anode/cathode configuration with a programmable microchip and a rechargeable lithium ion battery. The small size (27.5 mm × 3.2 mm) of the self-contained microstimulator allowed it to be deployed adjacent to nerves via an introducer needle, and no additional internal hardware was required.

Clinical indications

The Food and Drug Administration (FDA) has approved neurostimulation technology for spinal cord stimulation in trunk and limb pain syndromes associated with failed back surgery syndrome and radiculopathy or limb pain associated with it. Additional approved indications include epidural fibrosis (ie, arachnoiditis) and complex regional pain syndromes (ie, reflex sympathetic dystrophy). The use of neurostimulator and microstimulator devices for ONS in the treatment of headache disorders such as chronic or transformed migraine is considered off-label use by the FDA. The ideal candidate for ONS is an adult with no contraindications who has well defined chronic migraine as defined by the International Headache Society's second edition International Classification of Headache Disorders. The patient would present with headache more than 15 days each month for longer than 3 months in the absence of medication overuse, would have pain involving the occipital or suboccipital region, and would be proven refractory to behavioral, preventive and abortive pharmacologic therapies.[30] Diagnostic occipital nerve blocks have not been found to predict the efficacy of ONS.[31]

Contraindications

Contraindications to the use of ONS for chronic migraine include local or systemic infection, anticoagulant use, bleeding abnormalities, terminal illness, prior skull-based surgery, or anatomical abnormalities (eg, Chiari malformation). Patients with concurrent conditions requiring a demand cardiac pacemaker or automatic implantable cardioverter-defibrillator are precluded. Women who are pregnant, of childbearing age but not on contraception, or nursing are also not candidates for ONS. Additional ONS exclusion criteria include the probable future need for magnetic resonance imaging.[30,32] The relationship between migraine and mood disorders is well researched. Many chronic migraineurs suffer from anxiety, depression, impulsive behaviors, and personality disorders.[33] Specific pathologic psychiatric comorbidities that should be considered relative or absolute contraindications to ONS include personality disorders, suicidal tendencies, somatization or somatoform disorder, active substance abuse, or marked cognitive impairment; in these patients, psychological testing should be performed before initiating ONS.[34]

Literature review

In 2009, Boston Scientific presented preliminary results of the PRISM (Precision Implantable Stimulator for Migraine) study at societal meetings (Table 1).[35] This multicenter, double-blind, randomized, sham-controlled study evaluated ONS for prevention of treatment-refractory migraine. Of 132 randomized subjects, 125 completed a 12-week period of either active or sham stimulation. However, active ONS did not prove to be superior to sham ONS. Pain relief during the pre-implantation 5- to 10-day trial was suggestive of benefit at the 12-week follow-up after permanent implantation. Adverse events included infection, sensory abnormalities, and pain.

In 2011, the findings from the ONSTIM (ONS for the treatment of intractable chronic migraine headache) trial were reported.[30] This industry-sponsored, international, multicenter, randomized, blinded, controlled feasibility study was conducted to obtain preliminary safety and efficacy data on ONS in chronic migraine. Of 110 enrolled subjects, 75 were randomized to three treatment groups by a 2:1:1 ratio: (1) adjustable stimulation (AS [n = 33]), preset stimulation (PS [n = 17]), and medically managed (MM [n = 17]). A fourth, ancillary group (AG [n = 8]) met inclusion criteria but failed to respond to a diagnostic occipital nerve block. Three-month follow-up was available for all but two subjects (in the AG group). Stimulation parameters were variable in the ONSTIM feasibility study and were reported as pulse amplitude: 0.0–10.5 V, pulse width 60–450 μs, and frequency 3–130 Hz.

Results for the 67 subjects who completed the 3-month blinded study showed ONS to be relatively safe with promising efficacy. The subsequent 36-month, open-label, long-term follow-up (with potential crossover) is yet to be completed and published as of this writing.

Safety objectives were measured by reporting adverse device-related events (ADEs) and non-ADEs. ADEs were collected on intraoperative testing and on scheduled and nonscheduled visits. Non-ADEs were collected at scheduled and nonscheduled visits. ADEs were subclassified into system components, surgical implant procedure, device programming, or device stimulation. Thirty-six of 51 (71%) patients experienced a total of 56 ADE, the most frequent being lead migration (n = 12), infection of the lead or extension

tract/site (n = 8), ineffective stimulation (n = 6), intraoperative incision site complication (n = 4), and INS pocket infection (n = 3).

Efficacy data (eg, headache days, headache-free days, and days with prolonged and severe headache) were collected by having each patient keep a daily diary. Additional observational data included headache pain intensity, headache duration, "responder rates" to ONS therapy, functional impairment (disability), Migraine Disability Assessment (MIDAS), SF-36, and subject satisfaction. Responder rates were defined as the percentage of subjects achieving a 50% or greater reduction in the number of headache days per month or a three-point or greater reduction in overall pain intensity compared with baseline. The responder rates were: AS 39%, PS 6%, MM 0%, and AG 40%. Exploratory analysis suggested mixed results for mood states, satisfaction, disability, and quality-of-life measurements. The AS group tended to have improved moods compared with their PS and MM counterparts. Most (60%) AS subjects were satisfied, compared with only 25% of the MM subjects. Though the majority of the outcome measurements for disability and quality of life numerically favored the AS group, preliminary statistical analyses showed no clear advantage over the control groups.

Several randomized trials of ONS have been conducted recently. In 2011, Ellens and Levy described their experience with 2-year follow-up.[36] Fifty prospective nonrandomized patients (45 of whom had chronic daily headache or chronic migraine) were implanted with ONS in an attempt to reduce pain and topographically map out which headache phenotype responded best to stimulation therapy. Most (83%) reported "good to excellent" pain relief, and 9% reported "satisfactory" pain relief. These patients reported they would be unwilling to have the device removed. A notable finding of this study was a lead migration or fracture rate of 66%.

In 2012, Serra and Marchioretto[32] published the results of their prospective crossover design randomized study of ONS for chronic migraine. Albeit a small, single-center study, patient outcomes at 1 year were encouraging, and the authors suggested that ONS was an immediately effective intervention for chronic migraine.

Patients enrolled in the study met diagnostic criteria for chronic migraine, and 85% underwent 2 months of drug detoxification for concomitant medication overuse headache. Of 34 enrolled patients, 30 proceeded to implantation if they experienced a successful trial with a quadripolar percutaneous lead, documented by their recording of a decrease of 50% or more in the number or severity of attacks. Following permanent implantation of the INS (without lead revision), subjects were randomized 1:1 into "Arm A: INS ON" (active stimulation) or "Arm B: INS OFF" (inactive stimulation). The active stimulation parameters were frequency of 50 Hz, pulse width 330–450 μs, and adjustable amplitude up to 10.5 V. Crossover from "on" to "off" and vice versa occurred after 1 month. Patients in the "off" group were allowed to cross back to treatment ("on") at 2 months or sooner if they experienced a worsening of attacks of 30% or more on the Numeric Rating Scale (NRS-11). All patients ultimately finished in the "on" group.

Follow-up examinations were scheduled at months 1, 3, 6, and 12. Measures of improvement included the MIDAS, the SF-36 (quality of life), the (NRS-11), and a headache diary. Of the 29 subjects who completed the 1-year study, all had improvement on all measures, including drug intake documented in the diary. MIDAS scores improved from 79 at baseline to 10. The greatest improvements in the Short Form-36 domains were in the areas of Role Physical, Bodily Pain, Social Functioning, Role Emotional, and Mental Health. The median monthly dose of triptans per month decreased from 20 at baseline to 3. The doses per month of nonsteroidal anti-inflammatory drugs decreased from 25.5 at baseline to 2.0. Adverse events were minimal, with only five recorded: two severe implantation site infections (ie, presumed INS pocket), and 3 of 30 (10%) lead dislocations (ie, migration) that required repositioning without apparent long-term complications or nerve injury.

A second 2012 report with positive support for ONS as a headache treatment was Silberstein et al's[37] summary of their findings from a prospective, controlled study of PNS for migraine. Of 268 subjects enrolled over a 5-year period, 157 were permanently implanted with a percutaneous (cylindrical) lead after a successful temporary trial. These patients then underwent block randomization 2:1 into an active group (n = 105) and a control group (n = 52). The primary outcome measure at 12 weeks in both groups was the visual analog scale (VAS). "Responders" were those subjects who experienced 50% or greater improvement in VAS without an increase in headache duration. Secondary outcome measures were the reduction in the number of headache days, MIDAS questionnaire; patient-reported headache pain relief, and adverse events. No patients were lost to follow up; four, however, discontinued the study due to adverse events, including lead migration (20/157; 18.7%) and persistent pain or numbness at the IPG/lead site (23/157; 21.5%).

Silberstein et al reported no statistical difference for the primary endpoint. There were 18 responders (17.1%) to PNS/

Table 1 Summary of prospective controlled trials of occipital nerve stimulation for migraine

Author, (study)	Study design	Number of enrolled/ randomized patients	Primary outcome measure	Secondary measures	Results
Saper et al (ONSTIM)[30]	Multicenter, randomized, blinded, controlled feasibility study	110/75 Randomized/implanted/ 3-month follow up Active stim 33/29/29 Preset stim 17/16/16 Medical 17/0/17 Ancillary 8/6/5	Observational data collection via diary: number of headache attacks; number of days per week with headache; and headache severity and duration	Observational data collections via diary: responder rates, POMS, MIDAS, SF-36, functional MIDAS, quality of life, functional impairment, disability and subject satisfaction scores	68 patients implanted 67 analyzed at 3 months. ONS for chronic migraine warrants further investigation
Silberstein et al (safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine)[37]	Randomized, multi-center, double-blind, placebo-controlled	268/157 Two active/one sham	≥50% decrease in VAS at 12 weeks	Number of headache days, MIDAS, headache pain relief, and AEs	153 completed the study, 157 analyzed at 12 weeks. Study failed to meet primary endpoint
Serra and Marchioretto (Occipital nerve stimulation for chronic migraine: a randomized trial)[32]	Prospective, randomized crossover design	34/30	Data collection via diary: number of headache attacks; number of days/ week with headache; headache severity	MIDAS, SF-36, medication intake, and AEs	29; 1-year endpoint ONS appears safe and effective for chronic migraine

Abbreviations: AE, adverse event; MIDAS, Migraine Disability Assessment; ONS, occipital nerve stimulation; POMS, Profile of Mood States; SF-36, Short Form-36; VAS, visual analog scale.

ONS in the active group compared with seven (13.5%) in the control group. The authors argued, however, that a clinically significant difference was seen between the groups at the 30% reduction in VAS level, which the International Headache Society has established as clinically meaningful. Secondary outcome measures favored the active group because more of those subjects rated their headache pain relief as "good" or "excellent."[35]

Clinical implications and future directions

Chronic migraine is a complex phenomenon with both peripheral and central manifestations. The pathophysiology of chronic migraine is not well defined, and the mechanism by which patients with chronic migraine respond to ONS is unknown. Extrapolation of Melzack and Wall's[38] 1965 Gate Theory of Pain would suggest that wide-dynamic range neurons from the C2-innervated somatic structures affect trigeminal afferent nerves, hence modulating dura-vascular nociception.[30,39,40] ONS is of great interest to the pain management and neurology headache communities because of its potential benefit to otherwise-refractory headache patients. Patients considered for ONS therapy have failed psychological, medical, and other interventional approaches to pain relief. Significant obstacles remain before ONS can be considered a routine option in patients affected with this difficult problem. Large controlled studies showing durable benefit over placebo are needed. The response to placebo is likely high in any intervention, especially ONS, as the patient may or may not perceive stimulation after implantation.[41] Future studies and technical reviews should demonstrate surgical techniques to reduce the incidence of lead migration. Medical device manufacturers should develop equipment (leads, anchors, extensions, and pulse generators) specific to the application, which may minimize complications such as lead migration, fracture, infection, and poor cosmetic outcome.

This clinical review suggests that ONS has a viable place in the management of chronic migraine. Currently, expense for this non-FDA-approved indication is a significant barrier. The relatively fixed surgical and device cost of ONS must be measured against the financial expense of chronic pharmacologic therapy and the societal cost in lost work, impaired quality of life and disability. Future application of ONS may also include concomitant stimulation of the trigeminal nerve distal division including the supraorbital, the supratrochlear, and the temporal auricular nerves associated with refractory, severe headache disorders.[40,42,43] Specialists from multiple disciplines should participate and contribute to this growing fund of knowledge.

Disclosure

The authors report no conflicts of interest in this work.

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