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Clinical Report

Greater Occipital Nerve Stimulation via the Bion® Microstimulator: Implantation Technique and Stimulation Parameters Clinical Trial: NCT00205894

Terrence L. Trentman, MD[1], David M. Rosenfeld, MD[1], Bert B. Vargas, MD[2], Todd J. Schwedt, MD[3], Richard S. Zimmerman, MD[4], and David W. Dodick, MD[5]

From: Departments of [1]Anesthesiology, [5]Neurology, and [4]Neurosurgery, Mayo Clinic Arizona, Scottsdale, AZ, [2]Center for Neurosciences, Tucson, AZ, and [3]Department of Neurology, Washington University School of Medicine, St Louis, MO.

Address correspondence:
Terrence L. Trentman, MD
Mayo Clinic
Department of Anesthesiology
5777 E Mayo Blvd
Phoenix, AZ 85054
E-mail:
trentman.terrence@mayo.edu

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Background: Millions of patients suffer from medically refractory and disabling primary headache disorders. This problem has led to a search for new and innovative treatment modalities, including neuromodulation of the occipital nerves.

Objectives: The primary aim of this study is to describe an implantation technique for the Bion® microstimulator and document stimulation parameters and stimulation maps after Bion placement adjacent to the greater occipital nerve. The secondary aim is to document outcome measures one year post-implant.

Design: Prospective, observational feasibility study.

Methods: Nine patients with medically refractory primary headache disorders participated in this study. Approximately 6 months after Bion insertion, stimulation parameters and maps were documented for all patients. At one year, outcome measures were collected including the Migraine Disability Assessment Score.

Results: At 6 months, the mean perception threshold was 0.47 mA, while the mean discomfort threshold was 6.8 mA (stimulation range 0.47 – 6.8 mA). The mean paresthesia threshold was 1.64 mA and the mean usage range was 16.0. There were no major complications reported such as device migration, infection, or erosion. One patient stopped using her Bion before the 12-month follow-up visit. At one year, 7 of the 8 patients were judged as having obtained fair or better results in terms of reduction of disability; 5 patients had greater than a 90% reduction in disability.

Limitations: Small, heterogeneous patient population without control group. Not blinded or randomized.

Conclusion: The Bion can be successfully inserted adjacent to the greater occipital nerve in an effort to treat refractory primary headache disorders. This microstimulator may provide effective occipital stimulation and headache control while minimizing the risks associated with percutaneous or paddle leads implanted subcutaneously in the occipital region.

Key words: Chronic headache, migraine, cluster headache, peripheral nerve stimulation

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Migraine is the most common form of disabling primary headache, affecting 12% of Caucasian populations (1). Cluster headache and hemicrania continua, although much less common, also have a significant negative impact on quality of life (2,3). Subcutaneous occipital nerve stimulation (ONS) has been reported to effectively treat medically refractory primary headache disorders. A number of recent studies have documented efficacy outcomes and stimulation parameters associated with ONS (4-10). These studies document off-label use of spinal cord stimulation technology to stimulate the distal branches of the C1-3 nerve roots. Prospective, multicenter studies are underway to determine the safety and efficacy of this modality (11).

The implantable Bion microstimulator was initially developed as a radiofrequency (RF) powered functional electrical stimulator (12). However, the Bion microstimulator (from Boston Scientific Neuromodulation Corporation, Valencia, CA) (Fig. 1) used in this study is the only battery powered microstimulator of its type and as such does not require an external RF power source. It includes a single cathode on one end and a single anode on the other. Currently an investigational device, the Bion contains a programmable microchip, stimulating electrodes, telemetry capability, and a transcutaneously rechargeable (3 milliamp hours) lithium ion battery (13). It is expected that the battery will lose no more than 30% of its capacity after 500 cycles of full charge and discharge.

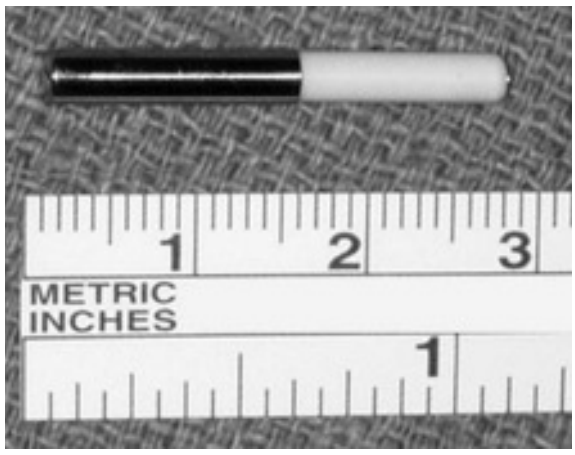

Fig. 1. *The Bion microstimulator.*

The Bion microstimulator's small size (27.5 mm x 3.2 mm) allows implantation adjacent to nerves via a less invasive technique than utilizing spinal cord stimulation technology. Previous studies have evaluated Bion implantation for pudendal nerve neuromodulation in the setting of refractory detrusor overactivity incontinence (14,15). At our institution, we have implanted 9 Bion microstimulators adjacent to the greater occipital nerve (GON) in an effort to treat refractory headache disorders.

The primary aim of this feasibility study is to describe an implantation technique for the Bion microstimulator and document stimulation parameters and stimulation maps after Bion placement adjacent to the GON. The secondary aim is to document outcome measures one year post-implant.

Methods

After the United States Food and Drug Administration (IDE G030225) and Institutional Review Board approval of this feasibility study, 9 patients diagnosed with chronic migraine or chronic cluster headache presenting to our clinic were screened for inclusion and exclusion. All 9 patients met the inclusion and exclusion criteria and all agreed to participate. Written informed consent was obtained from each. Inclusion criteria included 18 years of age or older, 12 or more months of chronic migraine or chronic cluster headache, refractory to at least 4 preventative medications used at adequate dosage for adequate duration of time, willingness to maintain current pain medication regimen during the study, and willingness and ability to maintain a headache diary for the duration of the study. Exclusion criteria included pregnancy or planned pregnancy, previous surgery in the occipital region, and participation in a device or drug trial within the previous 30 days.

All patients underwent a detailed neurologic exam and were assigned a diagnosis based on the International Classification of Headache Disorders – II (16). Six patients had chronic cluster headache including one with migraines and one with hemicrainia continua, and 3 patients had chronic migraine only (Table 1). Each patient underwent a psychiatric evaluation to determine their psychological stability to undergo the procedure. The patients did not undergo a trial of stimulation or occipital nerve block before implantation of the Bion.

For the purposes of this study, and consistent with our previous study on occipital stimulation mapping

Table 1. *Patient demographics, 6-month Bion microstimulator usage and Migraine Disability Assessment Scores (MIDAS).*

Patient	Diagnosis	Stimulator Usage	Pulse Width (us)	Rate (PPS)	Baseline MIDAS**	1 year MIDAS**	Response*
1 – 72f†	Migraine	0.5-1.5 hrs/day	250	60	130-85-4		Did not complete study
2 – 39f	Migraine	0.5 hrs, 2-3 days/wk	300	55	235-80-4	5-5-5	Excellent
3 – 44f	Cluster	0.5-0.75 hrs/2 wks	350	60	270-90-6	260-87-6	Poor
4 – 66f	Cluster	5-6 hrs/day	200	45	147-82-7	8-40-7	Excellent
5 – 46m	Cluster	22 hrs/day	250	55	225-90-7	130-80-5	Fair
6 – 44f	Cluster / hemicrania continua	16 hrs/day	350	45	87-90-5	8-25-4	Excellent
7 – 60m	Migraine	18 hrs/day	250	45	108-90-6	6-90-4	Excellent
8 – 44m	Cluster	24 hrs/day	300	60	120-88-6	10-85-3	Excellent
9 – 35m	Cluster/Migraine	20 hrs/day	200	45	110-90-7	70-60-7	Fair

*Response key:
> 90% reduction in disability = excellent
70–90% reduction in disability = very good
50–69% reduction in disability = good
25–49% reduction in disability = fair
< 25% reduction in disability = poor

PPS = pulse per second
†4 month visit

** The first number of each 3 digit series is the Migraine Disability Assessment Score, the second number is the number of headache days over a 3-month period, and the third number is the average severity of each headache.

(9), the following definitions were used: perception threshold is the lowest current amplitude that elicits sensation. Perception threshold is assumed to represent local tissue stimulation, while the upper end of the stimulation range (discomfort threshold) is defined as the current amplitude where patients feel stimulation strongly and do not wish the stimulation to be increased any further. The stimulation range (perception through discomfort threshold) represents the useful amplitudes for any given electrode combination while the usage range (discomfort threshold divided by perception threshold) "represents the relative size of the therapeutic stimulating window" (17). Paresthesia threshold is the current amplitude where the patient first noted stimulation traveling toward the vertex of his head, suggesting direct GON stimulation. The maximum stimulation tested during the study was 10 milliamps (mA).

The Bion implantation procedure was carried out under monitored anesthesia care in the prone position. Antibiotic prophylaxis was given to each patient before incision. The goal of each implant was to position the Bion microstimulator subcutaneously in the occipital region at a right angle to the GON, with the cathode immediately adjacent to the nerve. The anatomy of this region has recently been reviewed (8,18), and a cadaver study noted that in 10 specimens (20 nerves), the GON ascended between 5 and 28 mm from the midline at the level of the intermastoid line (19).

First, using fluoroscopic guidance, a line was drawn between the tips of the mastoid processes (intermastoid line) and in the midline. After sterile prep and injection of local anesthetic for skin wheal, a small (< 1 cm) incision was made 3 cm contralateral to the side of intended GON stimulation. Next, a 20-gauge, 15 cm insulated stimulating needle was inserted through the incision and across the midline toward the side to be stimulated. The ideal depth was estimated to be below the dermis but superficial to the fascia, in the subcutaneous fat layer. The location of the GON was marked as the point where the patient experienced maximal stimulation induced paresthesia towards the vertex of their head, at least to the level of the top of the ear.

Next, the stimulating needle was removed and the Bion introducer with the dissector/stimulator was inserted through the incision. The Bion dissector/stimulator was used to confirm the location of the GON, after which the Bion was deployed adjacent to the GON using the Bion placement tool and holder (Figs. 2,3).

Post implantation management included device activation 7–10 days postoperatively in 7 of the patients and activation on the day of implant in 2 patients. The timing of device activation was based on patient preference and travel considerations. The patients were initially given a radiofrequency "pillow" charger; a smaller "butterfly" charger subsequently became available that could be attached to a hat, allowing the patient to recharge while upright. The patients were instructed to initially use the Bion constantly at low amperage and then to increase the amperage as needed to treat intermittent headache exacerbations. However, they were given the prerogative to adjust use to comfort and effect. Patients turned stimulation on or off, and adjusted the amplitude of stimulation, via a wireless remote control.

Approximately 6 months after implantation, the following data were gathered in addition to the data collected as part of the sponsored study: headache location, average number of hours of Bion use per day, frequency of recharging, pulse width and rate, perception threshold with associated paresthesia map, discomfort threshold with associated paresthesia map, and paresthesia threshold. The patients were given a map of the head (Fig. 4) to allow them to identify the location of their baseline headaches and areas where they perceived stimulation. Mean values with standard deviation (SD) were used to summarize the data.

Migraine Disability Assessment Scores (MIDAS) were obtained prior to and at 12 months after implantation of the stimulator. The MIDAS questionnaire is a validated headache-related disability instrument that is increasingly used as a surrogate measure of outcome in episodic and chronic migraine trials (20). The 5-question instrument quantifies time lost due to headache from work, school, household work, and social/family or leisure activities over the preceding 3 months. The score is typically reported in a 3-digit format (e.g. 106-75-7): The first number is the MIDAS (greater than 20 is considered severe), the second number is the number of days in the past 3 months that the patient had a headache (max 90), and the third number is the average severity of each headache (0–10 scale).

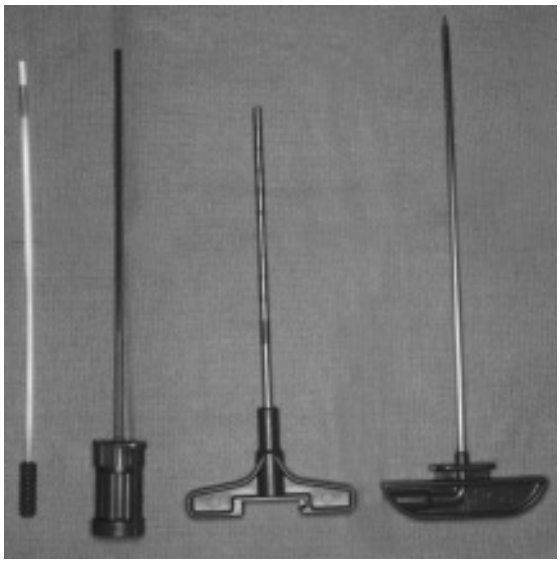

Fig. 2. *The Bion placement tools and holder.*

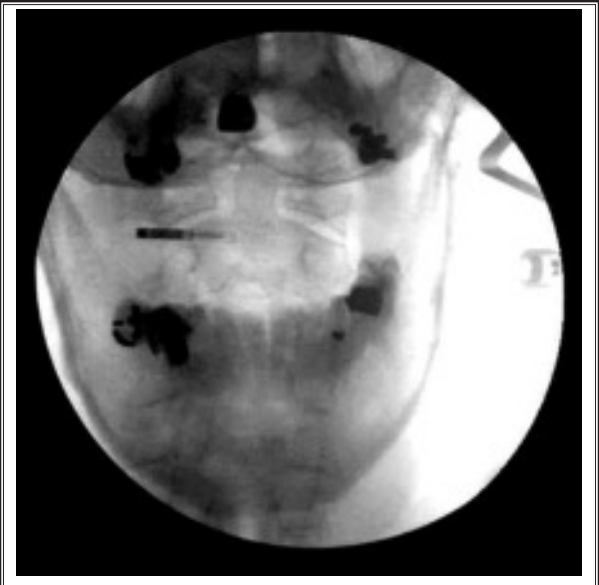

Fig. 3. *AP skull film showing Bion after insertion. The device is subcutaneous in the occipital region.*

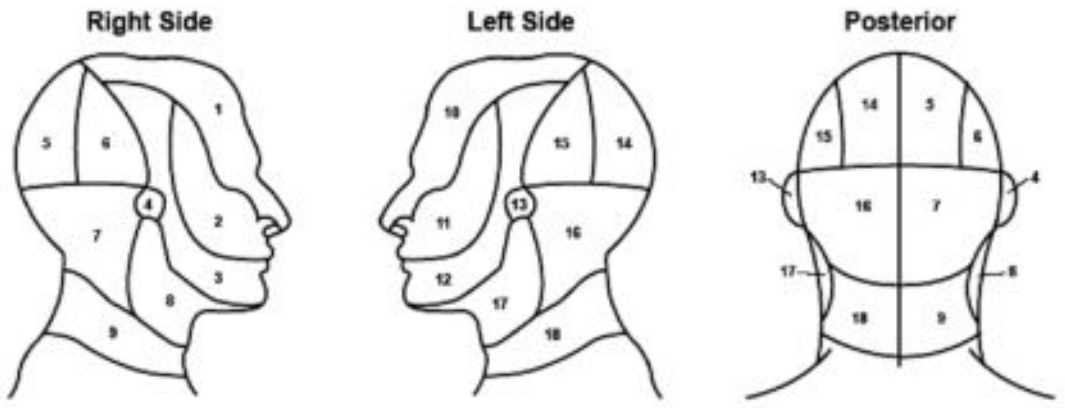

Fig. 4. *Head maps used to identify areas of baseline headache, perception threshold, and discomfort threshold. Used with permission. Trentman et al (9) and the International Neuromodulation Society.*

Results

All 9 patients invited to participate signed informed consent. One patient completed the headache maps approximately 4 months after implant. She subsequently did not appear for her 6-month follow-up and stopped using the Bion before study completion at 12 months. She stated the battery recharging schedule was too demanding, specifically that she was spending 1.5 hours recharging her Bion for every 1.5 hours of use. Patient demographics, baseline usage data, and MIDAS are summarized in Table 1. The mean decrease in number of days with headache for the 8 patients who completed the study was 28.5 (SD 29.6), while the average headache severity score decreased by 0.88 (SD 1.36). More detailed outcome data continues to be analyzed and will be presented separately.

Self-reported stimulator usage ranged from 30 minutes every 2 weeks to 24 hours/day (mean 12.2 hours/day, median 16 hours/day), and recharging frequency ranged from 35 minutes per week to 4 hours per day (mean 1.67 hours/day, median 1.5 hours/day). Distribution of baseline headache and stimulation thresholds (perception and discomfort) are shown in Table 2 (see Fig. 4 for maps). The zones of stimulation as noted in Table 2 are not meant to imply that the patients felt paresthesia throughout the entire zone; rather, they recorded stimulation in some part of each area noted. Table 3 summarizes stimulation parameters, including a mean perception threshold of 0.47 mA and a mean discomfort threshold of 6.8 mA (stimulation range 0.47 – 6.8 mA). The mean paresthesia threshold was 1.64 mA, and the mean usage range was 16.0. The average tissue impedance was 1.34 kilo-ohms.

No patients reported major device-related complications during the 12-month duration of the study

Table 2. *Headache and Stimulation Distribution (See Fig. 4). This data was obtained at the 6-month follow-up visit (except where noted) in addition to the data collected as part of the sponsored study.*

Patient	Location of Baseline Headache	Location of Perception Threshold	Location of Discomfort Threshold
1†	1,2,10,11	7,9,18	7
2	5 – 7,9	9	5,7,9
3	10 – 12,14 – 16	16,18	16,18
4	2 – 7, 9,18	7,9	5 – 7,9
5	10,16	16	14 – 16
6	10 – 12,14,16	16	7,14,16
7	10,12,15	18	14,16,18
8	10 – 12	18	7,9,16 – 18
9	1,5,6	1,5 – 7, 9	1,5 – 7,9

†Four month visit.

Table 3. *Bion Tested Stimulation Parameters. This data was obtained at the 6-month follow-up visit (except where noted) in addition to the data collected as part of the sponsored study.*

Patient	Perception Threshold (mA)	Discomfort Threshold (mA)	Paresthesia Threshold (mA)	Usage Range*
1†	0.6	10.0	1.8	16.67
2	0.2	5.4	1.6	27.0
3	0.4	1.6	1.2	4.0
4	0.2	2.2	0.6	11.0
5	0.8	10.0	1.6	12.5
6	0.4	10.0	4.0	25.0
7	0.4	6.2	1.6	15.5
8	0.8	5.8	1.6	7.25
9	0.4	10.0	0.8	25.0
Mean (SD)	0.47 (0.22)	6.8 (3.4)	1.64 (0.97)	16.0(8.2)
Median	0.4	6.2	1.6	15.5

*Usage range = discomfort threshold divided by perception threshold. †Four month visit.

such as infection, migration, or erosion. Adverse events reported after the study was complete at 12 months included loss of stimulation (N = 1). The patient's Bion had malfunctioned and was unrechargeable, requiring replacement. This patient subsequently experienced an infection necessitating explant and reimplant of a third Bion. Minor adverse events included 2 patients who complained of muscle stimulation at high amplitudes, and one patient who complained of pain near the implant site.

Discusson

Millions of patients suffer from primary headache disorders; a portion of them, like the patients in this study, endure severe, medically refractory pain. This problem has led to a search for new and innovative treatment modalities, including neuromodulation of the occipital nerves.

A number of recent studies have suggested that stimulation of the distal branches of the C1-2-3 nerve roots can produce pain relief in patients with otherwise refractory headache disorders (21-24). The mechanism of analgesia may be due to inhibition of nociceptive specific neurons in the trigeminal-cervical complex. Electrical stimulation of the GON may also result in mobilization of central pain modulatory centers (25,26). Of note, we previously reported pain relief despite persistent cranial autonomic activity (lacrimation, rhinorrhoea, conjunctival injection) in 2 of these patients implanted with Bions (27). One patient was diagnosed with cluster headache, while the other was diagnosed with hemicrania continua. This separation of autonomic signs from analgesia suggests that the autonomic features and first division pain are dissociated and separately controlled from a supranuclear generator.

While previous occipital stimulation techniques have resulted in diffuse distal C1-2-3 stimulation via cylindrical (percutaneous) or paddle (surgical) spinal cord stimulator (SCS) leads (4-7), the Bion was used here to stimulate a limited area and a specific nerve (GON). Our approach assumed that GON stimulation will have the same central analgesic affect as more diffuse C1-2-3 stimulation via percutaneous stimulator leads. If this assumption is correct, clinicians may be able to achieve the benefits of occipital stimulation via a microstimulator while circumventing the technical problems associated with occipital percutaneous leads and remote power sources.

In terms of stimulation parameters and the Bion, all of the patients had a sensory threshold of less than one milliamp, suggesting local tissue stimulation, while several patients had discomfort thresholds at the maximum tested amplitude of 10 mA. The mean paresthesia threshold of 1.64 mA suggests that at this amperage the GON was being stimulated directly. The large usage range (16.0, SD 8.2) indicates wide variation between these patients in terms of the size of their therapeutic stimulating windows. Lengthy daily usage time and high rates of stimulation (pulses per second) will increase recharging frequency.

Our previous study on occipital paresthesia mapping in patients with subcutaneously implanted SCS leads provides several points for comparison (9). In that study, the mean perception threshold was higher (1.07 V), while the discomfort threshold (3.63 V) was lower than the Bion (Table 3). The average tissue impedance in this study (1.34 kilo-ohms) is close to 1.0 kilo-ohms, allowing us to assume that the mA recorded for the Bion are roughly equivalent to the volts recorded in our previous study of SCS leads. The Bion's proximity to the GON may explain its lower perception threshold, while the reason for the higher discomfort threshold for the Bion is more obscure. Diffuse tissue stimulation produced by SCS leads may increase the likelihood of patient discomfort.

In terms of paresthesia mapping, it is difficult to determine if a correlation exists between distribution of paresthesia (Table 2 and Fig. 4) and outcome, but a pattern did not appear to emerge. Despite the Bion's small size, we were able to produce paresthesia in remote areas of the head, including at least one patient who noted trigeminal distribution paresthesia. It is unknown if outcome is improved by covering patient's baseline headache regions with paresthesia, analogous to spinal cord stimulation.

The MIDAS was used as a measure of outcome in this study. At one year, 7 of the 8 patients were judged as having obtained fair or better results in terms of reduction of disability; 5 patients had greater than 90% reduction in disability. All patients with excellent outcomes experienced a > 50% reduction in headache days and/or 30–50% reduction in average headache severity, while patients with a fair response experienced a reduction in headache days or severity of 25–50%.

The Bion's small size and low profile may help minimize or eliminate device displacement and lead breakage problems associated with SCS equipment implanted subcutaneously in the occipital region. As recently reviewed (10), complications of SCS systems implanted in the occipital region can occur frequently with lead migration rates as high as 100%. Other reported complications include lead fracture or disconnection, infection, erosion, and allergic reaction.

The Bion microstimulator requires no anchoring or tunneling of extensions to remote power sources; as such, much of the mechanical stress on the occipital stimulator system is eliminated. However, it is possible that a foreign body such as the Bion can move within tissue planes or become encapsulated, hence increasing the energy required to stimulate the occipital nerve. As a current controlled device, the Bion has the (limited) ability to automatically adjust the voltage to maintain the current amplitude despite encapsulation.

Disadvantages of a microstimulator system include the need for frequent recharging and limited choices in terms of electrode combinations. Future versions of this device may include a larger battery and multiple electrodes.

Limitations of this feasibility study include its small and heterogeneous patient population without a control group. It was neither randomized nor blinded. This however was a pilot study to ascertain the feasibility of the technique and potential for this modality in the treatment of refractory primary headache disorders. Thus far, there are no randomized controlled studies published on the safety or efficacy of any occipital nerve stimulation device for the treatment of primary headache disorders. The results of this feasibility study would support randomized controlled trials with the Bion microstimulator in this patient population. Potentially, a blinded study could be carried out wherein Bion microstimulators would be inserted in both a treatment and a placebo group. The treatment group would receive stimulation immediately after implant, while the placebo group would not have their Bion microstimulators activated for several months. A blinded, head to head comparison of the Bion microstimulator to other ONS systems that use spinal cord stimulation equipment could be more difficult to carry out, as the spinal cord stimulators systems require a remote battery implant. In this scenario, it would not be possible to "blind" the patient as to which system was implanted.

Conclusion

In conclusion, we have documented paresthesia maps and stimulation parameters for 9 patients after permanent implantation of a Bion microstimulator, with one year outcome data. There were no major adverse events during the study period, including device migration or infection. One patient did not complete the study. Further studies are needed to evaluate the safety and efficacy of subcutaneous C1-2-3 stimulation for headache disorders, including the use of microstimulators to stimulate specific nerves. If this novel microstimulator is shown to be effective in randomized trials, it may be possible to achieve headache control via neurostimulation with a low incidence of long-term complications.

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