ORIGINAL ARTICLE

Safety and Efficacy of Occipital Nerves Stimulation for the Treatment of Chronic Migraines: Randomized, Double-blind, Controlled Single-center Experience

Nagy A. Mekhail, MD, PhD*; Emad Estemalik, MD†; Gerges Azer, MD‡; Kristina Davis, PhD†; Stuart J. Tepper, MD§

*Pain Management Department, Cleveland Clinic, Cleveland, Ohio; †Center for Neurological Restoration, Cleveland Clinic, Cleveland, Ohio; ‡Evidence Based Pain Medicine Research, Cleveland Clinic, Cleveland, Ohio; §Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio U.S.A.

■ **Abstract**

Background: A recent multicenter study presented 52-week safety and efficacy results from an open-label extension of a randomized, sham-controlled trial for patients with chronic migraine (CM) undergoing peripheral nerve stimulation of the occipital nerves. We present the data from a single center of 20 patients enrolled at the Cleveland Clinic's Pain Management Department.

Methods: In this single center, 20 patients were implanted with a neurostimulation system, randomized to an active or control group for 12 weeks, and received open-label treatment for an additional 40 weeks. Outcomes collected included number of headache days, pain intensity, Migraine Disability Assessment (MIDAS), Zung Pain and Distress (PAD), direct patient reports of headache pain relief, quality of life, satisfaction, and adverse events (AEs).

Results: Headache days per month were reduced by 8.51 (±9.81) days ($P < 0.0001$). The proportion of patients who achieved a 30% and 50% reduction in headache days and/or pain intensity was 60% and 35%, respectively. MIDAS and Zung PAD were reduced for all patients. Fifteen (75%) of the 20 patients at the site reported at least one AE. A total of 20 AEs were reported from the site.

Conclusion: Our results support the 12-month efficacy of 20 CM patients receiving peripheral nerve stimulation of the occipital nerves in this single-center trial. ■

Key Words: spinal cord stimulation, complex regional pain syndrome, complex regional pain syndrome, neuromodulation, reflex sympathetic dystrophy, causalgia

INTRODUCTION

Chronic migraine (CM) affects approximately 2% of the general population and tends to be the most disabling of the four types of primary chronic daily headaches.[1] Pharmacological interventions in the treatment of CM include acute therapy, with the goal of terminating or reducing exacerbations, and daily preventive therapy, with the goal of reducing the frequency of headaches. Despite aggressive pharmacological intervention for CM, up to and including the only U.S. Food and Drug

Address correspondence and reprint requests to: Nagy A. Mekhail, MD, PhD, Pain Management Department, Cleveland Clinic, 9500 Euclid Ave. C25, Cleveland, Ohio 44195, U.S.A. E-mail: mekhain@ccf.org.

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Administration (FDA)-approved treatment, onabotulinumtoxinA, many patients continue to suffer.[2]

Published reports of peripheral nerve stimulation, in particular occipital nerve stimulation (ONS), suggest that this therapy is a promising intervention for those patients with refractory headaches who have failed to respond to pharmacologic interventions. The use of ONS for pain suppression was reported as early as 1977.[3] It has been utilized in the treatment of a variety of headache disorders. These include occipital neuralgia,[4–8] cervicogenic headache,[9] migraine,[10–12] hemicrania continua,[13] and cluster headache.[14]

Adverse events (AEs) associated with ONS reported in the European Union resulted in rescinding of the Conformite Europeane (CE) Approval Mark for ONS for CM in 2014. The study designed to obtain FDA approval reported meaningful reductions in number of headache days and pain, but having a high rate of AEs.[12,15] Questions remain about the reasons for the lack of success in gaining regulatory approval. Proposed issues for lack of success with the larger trial include the possibility of implanter experience to affect the safety profile and/or efficacy of the therapy and the possibility that patient selection criteria may need refinement. Specifically, Sharan and colleagues reported that increased implanter experience was associated with lower rates of AEs.[11] Therefore, despite promising early results, ONS failed to gain FDA approval, and the high number of Adverse Events Analysis was executed for subjects in the larger, multicenter CM trial from one particular investigational center, Cleveland Clinic's Pain Management Department, which enrolled a high number of subjects and for which the implanters had a high level of experience with ONS. The aim of this analysis was to investigate safety and efficacy without incurring the potential influence of heterogeneity on implanter skills, potential influences of the heterogeneity in implanter skill, and patient selection inherent to the larger multicenter study.

METHODS

Detailed methods for the full multisite study are described elsewhere.[12] Briefly, participants who met inclusion criteria and had a successful temporary ONS trial received a permanent implant and were randomized to either active stimulation or no stimulation for a period of 12 weeks. After 12 weeks, all patients were provided active stimulation for the remaining 40 weeks, resulting in 52 total weeks of study participation. The purpose of this analysis is to provide results from a single, high-enrollment study site, the Cleveland Clinic's Pain Management Department.

The FDA approved the study protocol, the study was reported on clinicaltrials.gov (NCT00615342), and all sites received institutional review board approval prior to study initiation. The dates for the participation at the Cleveland Clinic were May 2006 to August 2008. The last follow-up was in 2009.

Participants and Devices

Detailed inclusion and exclusion criteria have been previously published.[12,15] Key criteria included meeting modified criteria for CM (see ICHD -2), in addition to having tried and failed two migraine-specific acute medications and two different classes of prophylactic medications. Patients with a history of medication overuse headache (also known as rebound headache) were excluded.

Using the guidelines defined by the International Headache Society in section 1.5.1 of The International Classification of Headache Disorders, 2nd edition (ICHD-2),[16] patients were evaluated for CM prior to enrollment. These ICHD-2 criteria were different from current criteria and required migraine-level headache at least 15 days per month. Therefore, enrolled patients completed a 1-month diary to confirm that they met modified criteria for CM using the Silberstein–Lipton diagnostic criteria for transformed migraine (TM), which shortens the diagnostic evaluation period from 3 to 1 month.[16] What is unique about this cohort of patients is that they were referred to the Pain Management Department from the Headache Center at the Cleveland Clinic, where proper migraine diagnosis was well established and inclusion criteria for the study were accurately met.

Prior to the initiation of any study procedures, all patients provided written informed consent. If already in use 8 weeks before baseline, patients were permitted to continue pain medications and other treatment modalities at their current dose, but new methods of pain control were prohibited.

The implant procedures have been previously described.[12,15] Briefly, patients had percutaneous quadripolar leads (Quattrode™; St. Jude Medical, Plano, TX, U.S.A.) placed on either side of the midline, across the course of the occipital nerves. Depending on the pain distribution, leads were placed

either unilaterally or bilaterally. The Genesis™ (St. Jude Medical) nonrechargeable implantable pulse generator (IPG) was implanted in a subcutaneous pocket created so that the IPG was parallel to and not more than 4 cm (1.5 inches) below the skin surface. The site of the IPG pocket was in the upper outer quadrant of the right left buttock, depending on the patient's preference. The lead or extension was tunneled subcutaneously to the pocket, connected to the IPG, and the incisions were closed.

Randomization and Study Visits

A successful temporarily ONS trial was defined as ≥ 50% reduction in pain with adequate paresthesias to cover the painful areas. The trial period varied from a minimum of 3 days to a maximum of 5 days. Patients meeting criteria for temporary trial success proceeded to permanent implantation. After permanent implantation, patients were randomized using a 2:1 ratio with a block size of 3 (SAS® version 9.2; SAS Institute Inc., Cary, NC, U.S.A.). This randomization scheme was chosen to maximize capture of AEs related to active stimulation and to minimize the number of patients who did not receive stimulation after implantation. Both investigator and patients were blind to the randomization results. Patients in the active group were programmed with appropriate, comfortable paresthesias over the distribution of the occipital nerves; patients in the control group were provided a sham programmer that did not communicate with the IPG. At the end of the 12-week control phase, all patients were provided active stimulation for an additional 40 weeks.

Patients were assessed at baseline (just before permanent implantation), and at 4, 12, 24, and 52 weeks after permanent implantation. At all follow-up visits, patients completed the Migraine Disability Assessment Scale (MIDAS) questionnaire and provided patient-reported headache pain relief in both categorical and percentage ratings, quality of life (QoL) ratings measured on a 3-point categorical rating of "improved," "stayed the same," or "deteriorated," and satisfaction measured as a dichotomous rating of "yes" or "no." Electronic diaries captured headache frequency, duration, and intensity during 4-week periods preceding the baseline, 4-, 12-, and 52-week study visits. If a patient completed less than 14 days of any 4-week diary period, the patient's value was considered missing for that period.

Data Analysis and Statistical Methods

The primary outcome for the controlled phase (baseline to 12 weeks) was mean daily visual analog scale (VAS) measurements from the patient diary, and the primary endpoint was a comparison of the proportion of responders in the active group to those in the control group at 12 weeks. Primary responder analysis included 2 responder categories calculated as a change in VAS between baseline and 12 weeks: (1) patients achieving at least a 50% reduction in VAS from baseline, and (2) patients achieving at least a 30% reduction from baseline (inclusive of category 1).

Secondary endpoints investigated were the reduction in number of headache days with a duration of > 4 hours and peak intensity reported as moderate or severe (normalized to 28 days), the MIDAS questionnaire, direct patient reports of headache pain relief (categorical and percentage), QoL, satisfaction, and AEs. A secondary responder analysis examined the proportion of patients who achieved at least a 30% and 50% reduction in headache days. Change from baseline scores was computed for 12 and 52 weeks for the number of headache days, MIDAS, and Zung Pain and Distress (PAD) scores.

Summary statistics for AEs are reported for the entire study period (enrollment to 52 weeks). AEs were classified as stimulation related, nondevice related, hardware related, and biological, as determined by the investigators. AE rates, calculated as the number of patients reporting an event divided by the total number of patients in the study, are presented. The rate of occurrence for specific AE types is also presented, calculated as the number of a specific type of event divided by the number of total events reported during the study. Proportions tests were used to investigate statistical differences in AE rates.

The last observation carried forward (LOCF) approach for missing data was used. For the responder analysis, patients who dropped out prior to the 12-week or 52-week visit were considered nonresponders for the missed visit.

Statistical analyses were performed using MiniTab version 16 (Minitab Inc., State College, PA, U.S.A.). An alpha level of 0.05 was adjusted, using the Bonferroni correction for multiple comparisons, to control family-wise error. Adjustments to alpha for specific sets of comparisons are described in the Results section. For all continuous measures, independent *t*-tests were used to examine active vs. control groups at each study visit.

Paired *t*-tests examined the change from baseline for each study visit for continuous measures. Responder analyses and examinations of categorical variables were performed using a test of proportions comparing the active and control groups. Summary descriptive statistics are provided as appropriate for the level measurement of each assessment tool.

RESULTS

Patients

A total of 20 patients at the Cleveland Clinic met inclusion criteria and were enrolled in the study. Site participants were, on average, 44.6 (±12.6) years old, and the majority were female (n = 15, 75%). A majority of site participants reported unknown causes for their headache (n = 14, 70%), which is consistent with CM being a primary daily headache. However, there were patients included with secondary chronic daily headache, including trauma (n = 3, 15%) or other reasons (n = 3, 15%) as the cause of their headache condition. Site participants more commonly reported bilateral headaches (n = 13, 65%) than unilateral headaches (n = 7, 35%). As shown in Table 1, the subjects at the site did not differ from the pooled multisite data and therefore comprise a reasonable subset of the larger cohort.

At the site, 14 patients were randomized to the active stimulation group and 6 patients were randomized to the control group.

Controlled Phase

At the conclusion of the first 12 weeks of the study, 60% of site patients who were in the active group reported a ≥ 30% reduction in pain intensity on the VAS; 20% of patients in the control group reported a VAS reduction of ≥ 30%. The rate of 30% response in active vs. control groups was not statistically different (all $P > 0.05$; Table 2). Approximately 30% of patients in the active group reported a ≥ 50% reduction in VAS scores at the end of 12 weeks; no patients in the control group reported a ≥ 50% reduction in VAS. The rate of 50% response at 12 weeks was statistically higher in the active group than the control group ($P = 0.018$).

Average daily VAS at 12 weeks from the headache diary was higher for patients in the control group (mean = 67.85 [±18.58] mm) than for patients in the active group (mean = 29.98 [±14.64] mm), representing approximately an 8-mm increase and 23-mm decrease from baseline in average daily VAS, respectively (all $P < 0.001$; Table 3).

Open Phase

At 52 weeks, 12 site patients (60%) reported ≥ 30% reduction in VAS scores; 7 (35%) reported a reduction of ≥ 50% in pain intensity (see Table 2). At the 52-week visit, the mean of each patient's average daily VAS scores was 36.74 mm (±21.70), which represented a decrease from baseline of 16.90 (±21.50) mm. The change from baseline to 52 weeks was statistically significant ($P = 0.002$; see Table 3).

Secondary Outcome Measures

Headache Days from Pain Diary. At baseline, patients had an average of 16.95 (±9.56) and 17.04 (±8.73) headache days per month in the control and active groups, respectively. At the 12-week study visit, patients receiving active stimulation reported an average reduction of approximately 12 headache days per month, while patients in the control group reported an average reduction of less than 1 headache day per month. At the

Table 1. Subject Demographics for Single- and Multisite Cohorts

	Single-Site Cohort	Multisite Cohort
Age (mean years [SD])	44.6 (12.6)	44.9 (11.0)
Female gender (n [%])	15 (75%)	33 (79%)
Cause of headaches (n [%])		
Trauma	3 (15%)	17 (11%)
Unknown	14 (70%)	118 (75%)
Other	3 (15%)	22 (14%)
Headache duration (mean hours [SD])	18.5 (15.1)	21.6 (7.1)
Headache type (n [%])		
Unilateral	7 (35%)	50 (31.8%)
Bilateral	13 (65%)	107 (68.2%)

Table 2. Patients with 30% and 50% Average Daily Visual Analog Scale (VAS) Reduction and No Increase in Headache Duration or Frequency

	Control (n = 6)	Active (n = 14)	All (N = 20)	P value
30% Reduction in VAS (n [%])				
12 weeks	4 (20%)	12 (60%)	16 (80%)	0.373*
52 weeks			12 (60%)	
50% Reduction in VAS (n [%])				
12 weeks	0 (0%)	4 (29%)	4 (20%)	0.018*
52 weeks			7 (35%)	

*Obtained using a test of proportions comparing the frequency of response for active vs. control groups.

Table 3. Mean Average Daily Visual Analog Scale Scores (±SD) from the Diary for Each Visit

	Control (n = 6)	Active (n = 14)	All (N = 20)	P value	Significant*
Baseline	59.94 ± 23.39	50.94 ± 17.95	53.64 ± 19.55	0.36†	No
4 weeks	63.36 ± 25.24	32.81 ± 15.91		0.004†	Yes
Change from baseline	3.42 ± 9.89	−21.59 ± 10.22		< 0.001†	Yes
12 weeks	67.85 ± 18.58	29.98 ± 14.64		< 0.001†	Yes
Change from baseline	7.91 ± 10.56	−23.03 ± 11.54		< 0.001†	Yes
52 weeks			36.74 ± 21.70		
Change from baseline			−16.90 ± 21.50	0.002‡	Yes

*Alpha = 0.0125 after Bonferroni correction for multiple comparisons.
†P value obtained using t-tests to compare active and control groups.
‡P value obtained using paired t-test comparing change from baseline to 52 weeks.

52-week visit, patients at the site collectively reported a mean of 8.51 (±9.18) headache days per month, representing a reduction from baseline of 8.50 (±9.99) days (see Table 4 for additional details).

Patient-reported Percentage of Pain Relief. As shown in Table 5, patients in the active group reported a ≥ 50% level of pain relief in response to ONS at all study visits. Patients in the control group reported significantly lower pain relief than patients in the active group at both study visits occurring within the control phase (all $P < 0.001$). After all patients were switched to active stimulation, active and control groups did not report statistically different pain relief at either the 24- or 52-week study visit ($P > 0.05$). After at least 40 weeks of stimulation, site participants reported an average of 60% (±30) pain relief.

Migraine Disability Assessment Scale. Nineteen of the 20 patients at the site completed the MIDAS questionnaire. At baseline, the control group (n = 6) reported a mean of 183.33 (±60.43) interference days, a mean of 73.67 (±29.78) headache days, and a mean of 7.33 (±1.97) headache intensity on a scale of 0 to 10. At the end of the controlled phase, patients in the control group reported a mean reduction of 12.17 (±69.27) interference days, a mean reduction of 14.83 (±30.80) headache days, and no reduction of pain intensity (mean = 0.00, SD = ±1.55). Patients in the active group (n = 13) reported, at baseline, mean interference days of 168.00 (±55.36), mean headache days of 77.86 (±25.40), and mean headache intensity of 7.29 (±1.20). At 12 weeks, the active group reported a mean reduction of 85.210 (±40.63) interference days, a mean reduction of 32.71 (±33.31) headache days, and a mean reduction of 2.14 (±2.28) for headache intensity. At 12 weeks, the change in interference days and headache days was significantly larger for those in the active group compared to the control group (all $P < 0.0125$; see Table 6 for more details).

At the 52-week study visit, participants at this site reported a mean reduction of 92.32 (±65.21) interference days and of 31.16 (±48.13) headache days on the MIDAS (see Table 6).

Quality of Life and Satisfaction

At the 12-week visit, all the patients in the active group (n = 14) reported improved QoL and all the control patients (n = 5) reported that their QoL stayed the same. No patients reported deteriorated QoL. At 52 weeks, 13 active group patients had available QoL data; one patient had missing data for this measure. Eleven (85%) patients in the active group reported improved QoL, and 2 (33%)

Table 4. Mean and Mean Reduction in Headache Days (Diary) for Each Visit

	Control (n = 6)	Active (n = 14)	All (N = 20)	P value	Significant*
Baseline	16.95 ± 9.56	17.04 ± 8.73	17.01 ± 8.73	0.98†	No
4 weeks	16.00 ± 13.19	6.88 ± 6.56		0.05†	No
Change from baseline	−0.95 ± 5.93	−11.50 ± 6.29			
12 weeks	16.80 ± 12.31	5.42 ± 7.35		0.02†	No
Change from baseline	−0.15 ± 5.27	−12.32 ± 8.88			
52 weeks			8.51 ± 9.18	0.001‡	Yes
Change from baseline			−9.10 ± 10.13		

*Alpha = 0.0125 after Bonferroni correction for multiple comparisons.
†P value obtained using t-tests to compare active and control groups.
‡P value obtained using paired t-test comparing change from baseline to 52 weeks.

Table 5. Mean Reported Percentage Pain Relief by Study Visit

	Control (n = 6)		Active (n = 14)		All (N = 20)			
	Mean	SD	Mean	SD	Mean	SD	P value*	Significant†
4 weeks	6.67	16.33	56.79	18.67			< 0.001	Yes
12 weeks	1.67	4.08	58.21	22.75			< 0.001	Yes
24 weeks					54.74	26.53	0.32	No
52 weeks					60.26	33.48	0.18	No

*P value obtained using t-tests to compare active and control groups.
†Alpha = 0.0125 after Bonferroni correction for multiple comparisons.

Table 6. Mean and Reduction for Migraine Disability Assessment for Each Visit

	Control (n = 6)	Active (n = 13)	All (n = 19)	P value*	Significant†
Sum items 1 to 5 (interference days)					
Baseline	183.33 ± 60.43	168.00 ± 55.36		0.587	No
12 weeks	162.67 ± 109.00	86.43 ± 73.58		0.082	No
Change from baseline	−12.17 ± 69.27	−85.21 ± 40.63		0.008	Yes
52 weeks			75.95 ± 69.9	0.993	No
Change from baseline			−92.32 ± 65.21	0.778	No
Headache days					
Baseline	73.67 ± 29.78	77.86 ± 25.40			
12 weeks	88.5 ± 2.35	45.14 ± 33.50		0.006	Yes
Change from baseline	14.83 ± 30.80	−32.71 ± 33.31		0.007	Yes
52 weeks			44.74 ± 38.40	0.02	No
Change from baseline			−31.16 ± 48.13	0.48	No
Headache intensity (scale of 0 to 10)					
Baseline	7.33 ± 1.97	7.29 ± 1.20		0.956	No
12 weeks	7.33 ± 1.51	5.14 ± 2.25		0.044	No
Change from baseline	0.00 ± 1.55	−2.14 ± 2.28			
% Change from baseline	12.96 ± 11.77	33.72 ± 25.63		0.077	No
52 weeks			5.74 ± 2.35	0.751	No
Change from baseline			−1.58 ± 2.63		
% Change from baseline			33.76 ± 20.07	0.995	No

*P value obtained using t-tests to compare active and control groups.
†Alpha = 0.0125 to determine significance after Bonferroni correction for multiple comparisons.

patients in the control group reported improved QoL at the 52-week visit; rate of improved QoL was significantly higher for active group patients (P = 0.041). Two (15%) of the active group patients reported that their QoL remained the same, and 4 (67%) of the control group patients reported that their QoL stayed the same; rate of stable QoL was significantly higher for the control group (P = 0.014). For the available QoL data from both groups (n = 19), at least 40 weeks of stimulation resulted in 13 patients (68%) reporting in improved QoL, with 6 (32%) reporting that QoL stayed the same, and no patients reporting deteriorated QoL.

All 20 patients at the site had available data for the satisfaction measure. At the 12-week study visit, 8 patients (57%) in the active stimulation group reported that they were satisfied with the device. None of the patients in the control group reported satisfaction at 12 weeks. At the 52-week visit, 14 (3 control group + 11 active group) of the site's patients reported satisfaction with the device.

Adverse Events

A total of 8 patients reported 8 AEs during the controlled phase of the study. Of the 8 events, 1 (12.5%) was a stimulation-related event, 4 (50%) were hardware related, and 3 (37.5%) were biological. The occurrence of biological events was significantly higher for the active group than for the control group during the first 12 weeks (P = 0.006). The rate of hardware-related and stimulation-related events was similar for active and control groups during the controlled phase (all P > 0.05; see Table 7 for a detailed listing of AEs during the controlled phase).

By the end of the 52-week study, 15 (75%) of the 20 patients at the site reported at least 1 AE. A total of 20 AEs were reported from the site. Two stimulation-related events were reported as nausea (n = 1) and unintended stimulation effects (n = 1). Both stimulation-related events were reported by patients in the control group, and no significant differences existed

Table 7. Adverse Events (AEs) by Category and Type for the Control Phase

	Control (n = 6)	Active (n = 14)	All (N = 20)	P value*
Total AEs	3	5	8	
No. of patients with AE	3	5	8	
AE by category and type				
Stimulation related	1	0	1	
% of total events	12.50%	0.00%	12.50%	0.221
Nausea/vomiting	1	0	1	
Unintended stimulation effects	0	0	0	
Hardware related	2	2	4	
% of total events	25.00%	25.00%	50.00%	0.445
Lead migration	1	2	3	0.849
Device malfunction—disconnection	1	0	1	
Lead breakage/fracture	0	0	0	
Normal battery depletion	0	0	0	
Device malfunction—programmer	0	0	0	
Biological	0	3	3	
% of total events	0.00%	37.50%	37.50%	0.006
Persistent pain or numbness	0	1	1	0.264
Wound site complication	0	1	1	
Allergic reaction	0	1	1	

*P value obtained using proportions test comparing active vs. control.

between the active and control groups for the rate of stimulation-related events (P = 0.08). A total of 4 nondevice-related events were reported, 2 from the active group and 2 from the control group, representing a 20% rate of nondevice-related events.

Nine events, or 45% of all AEs, were hardware related. Hardware-related events included lead migration (n = 5), device malfunctions (1 disconnection, 1 programmer malfunction), lead breakage/fracture (n = 1), and normal battery depletion (n = 1). For patients in the active group, the rate of hardware-related events was 35% (7/20), while the control group reported hardware-related events at a rate of 10% (2/20). The rate of hardware-related events was not statistically different between active and control groups (P = 0.48).

A total of 5 biological events were reported during the study, representing 25% of all AEs at the site. Biological events reported were persistent pain or numbness at the IPG or lead site (n = 3), wound site complication (n = 1), and allergic reaction (n = 1). All biological events were reported by patients in the active group, and the rate of biological events was significantly higher in the active vs. the control group (P = 0.005).

The overall rate of AEs during the controlled phase did not differ significantly from the open-label phase for stimulation-related, hardware-related, or biological events (all $P > 0.05$).

During the 52-week study, 11 (55%) of the 20 AEs required an additional surgical intervention. Of the AEs leading to surgical intervention, 8 (73%) were hardware related and 3 (27%) were biological.

DISCUSSION

Occipital nerve stimulation is emerging as a promising treatment modality for medically intractable headache disorders, in particular CM. The results from this study support other published findings, suggesting a role for ONS in the treatment of CM.[11,12,15,17,18] It is important to summarize the broader randomized, multicenter, double-blinded study under which our center's experience occurred, in order to compare and contrast results from the whole to the part.[12,15]

As shown in Table 8, patients at our site reported an average reduction of approximately 9 headache days per

Table 8. Summary of Selected Measures for the Single- and Multisite Cohorts

Through 12 Weeks (Controlled Phase)	Single-site Cohort		Multisite Cohort*	
	Control (n = 6)	Active (n = 14)	Control (n = 52)	Active (n = 105)
30% reduction in VAS [n (%)]	4 (20%)	12 (60%)	6 (12%)	37 (35%)
50% reduction in VAS [n (%)]	0 (0%)	4 (29%)	5 (10%)	18 (17%)
Mean change in headache days (diary) [mean (95% CI)]	−0.2 (−4.4, 4.0)	−12.3 (−16.9, −7.6)	3.0 (not reported)	6.3 (−5.4, −0.8)

Through 52 Weeks (Open-Label Phase)	Single-site Cohort (N = 20)	Multisite Cohort† (N = 111)
30% reduction in VAS (n [%])	12 (60%)	66 (60%)
50% reduction in VAS (n [%])	7 (35%)	53 (48%)
Mean change in headache days (diary) (mean [SD])	−9.1 (10.1)	−6.7 (8.4)

*From Silberstein et al.[15]
†From Dodick et al.[12]

month after 52 weeks. The proportion of patients who achieved a 30% and 50% reduction in headache days at the end of 1 year of therapy was 60% and 35%, respectively. Headache days for the multisite cohort were significantly reduced by 6.7 days in the intent-to-treat population and by 7.7 days in the intractable CM population. The proportion of patients who achieved a 30% and 50% reduction in headache days and/or pain intensity was 59.5% and 47.8%, respectively. Thus, the total headache day reduction was higher at our center, the 30% responder rate the same, and the 50% responder rate lower compared with the group as a whole.

At our site, the overall rate of AEs during the control phase did not differ significantly from the open-label phase for stimulation-related, hardware-related, or biological events. Despite improvement in surgical techniques, AEs remain prominent, thus warranting enhancements in both technology and implantation procedures.

At our site, 9 events, or 45% of all adverse effects, were hardware related. These again included lead migration, device malfunctions, lead breakage/fracture, and normal battery depletion. Biological events occurred in 5 patients, accounting for 25% of all adverse effects. Lead migration remains the most common hardware-related adverse reaction. Overall, during the 52-week study, 11 (55%) of the 20 AEs required a surgical intervention. Of the AEs leading to surgical intervention, 8 (73%) were hardware related and 3 (27%) were biological. In the 2015 multisite cohort, a total of 183 device/procedure-related AEs occurred, of which 18 (8.6%) required hospitalization and 85 (40.7%) required surgical intervention; 70% of patients experienced an AE. Lead migration accounted for 13.9% of all AEs.[12]

Lead migration is detected by patients when they experience a change in stimulation and requires imaging for confirmation. Surgical intervention is often necessary, and referral to a neurosurgeon can be necessary. Again, the single-center AE rate reported here was not markedly different from the multisite cohort, suggesting that implanter experience, which was high at our site, may not appreciably reduce AE rates in the context of other factors that may affect the incidence of AEs. A need remains for technique or hardware improvements. We adopted the use of paddle leads instead of cylindrical leads for ONS, which has decreased the incidence of lead migration.

The exact mechanism by which ONS exerts its effect in CM remains unknown. The area of interest in migraine pathophysiology relates to the trigeminocervical complex (TCC).[18,19] The TCC is formed by the caudal trigeminal nucleus and portions of the upper cervical dorsal horns.[20] In one study, 8 patients receiving ONS treatment and showing marked benefit had activation in some of these centers when positron emission tomography scans were performed in conjugation with the ONS treatment.[21] Such studies are crucial in determining the mechanism of action of ONS to further refine the appropriate patient selection.

CONCLUSION

Occipital nerve stimulation is an emerging treatment modality for patients with CM who have failed various treatment modalities. Patient-centered outcomes are important measures in patients with CM. Elements such as QoL, disability, and patient satisfaction scores should be taken into account in addition to meeting other primary endpoints such as headache days and reduction in severity of episodes. Despite advancements in surgical techniques, AEs with ONS remain prominent, thus warranting further research into both technology and implantation techniques.

This analysis compared the outcomes of a multicenter study of ONS to one site, in hopes of elucidating differences in outcomes and AEs. The analysis underscores the value of proper patient selection with a definitive diagnosis as well as the experience of the implanting physician and the infrastructure to support large clinical studies. Certain outcome measures showed better results at our center; many did not. An overall advantage to our center trial may have been the collaboration between the Headache and Pain Management Departments within the Cleveland Clinic, allowing for optimal patient selection.

DISCLOSURES

All authors listed contributed intellectually to the article whether in the study design, laborious data collection, statistical analysis, literature review, or manuscript writing.

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