Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: Initial experience

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Abstract

A novel approach to the treatment of chronic migraine headaches based on neurostimulation of both occipital and supraorbital nerves was developed and reduced to clinical practice in a series of patients with headaches unresponsive to currently available therapies. Following positive trials, seven patients with chronic migraine and refractory chronic migraine headaches had permanent combined occipital nerve–supraorbital nerve neurostimulation systems implanted. The relative responses to two stimulation programs were evaluated: one that stimulated only the occipital leads and one that stimulated both the occipital and supraorbital leads together. With follow-up ranging from 1 to 35 months all patients reported a full therapeutic response but only to combined supraorbital–occipital neurostimulation. Occipital nerve stimulation alone provided a markedly inferior and inadequate response. Combined occipital nerve–supraorbital nerve neurostimulation systems may provide effective treatment for patients with chronic migraine and refractory chronic migraine headaches. For patients with chronic migraine headaches the response to combined systems appears to be substantially better than occipital nerve stimulation alone.

Keywords

Migraine, chronic migraine, refractory migraine, peripheral nerve stimulation, occipital nerve stimulation, supraorbital nerve stimulation

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Introduction

Following our initial report in 1999 on occipital nerve stimulation (ONS) treatment for refractory occipital neuralgia (1), the development of peripheral nerve stimulation (PNS) for head pain has proceeded along two general diagnostic avenues: certain cephalic neuralgias (occipital neuralgia and certain trigeminal neuralgias) and the distinct, more general primary headache syndromes. Regarding the cephalic neuralgias, numerous subsequent investigators have supported our initial findings for occipital neuralgia (2–6), whereas others have successfully extended this treatment methodology to the frontal region and various trigeminal neuralgias (7–9). Importantly, the results of studies on cephalic neuralgias were consistent with the well-documented effectiveness of implanted neurostimulation for neuropathic pain syndromes over the rest of the body, including the torso and limbs. Indeed, neuropathic pain remains possibly the best documented indication for implantable neurostimulators, regardless of anatomical location (10).

As the evidence base for PNS in the treatment of cephalic neuralgias has increased, attention has shifted to its potential in treating primary and secondary headaches. In 2003, Popeney and Alo observed strongly positive responses in a series of patients with headaches with migrainous symptoms (11), and Dodick observed a similar response in a patient with cluster headaches (12). Subsequent investigations have reported that various headache syndromes responded variably to ONS, with the majority of studies involving three general diagnostic

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categories: occipito-cervical headaches (3,7,13,14), cluster headaches (15–21) and chronic migraines (22–25). Although summaries of these studies reveal a consistently high (average 88%) response rate for occipital neuralgia and cervicogenic headaches, they indicate only roughly a 40–50% rate for primary migraines and cluster headaches (Tables 3–5), which suggests that a substantial subset of patients with these types of primary headache may indeed not respond to ONS.

Importantly, the historical trajectory of PNS treatment has evolved differently over the frontal and occipital regions. Over the occipital region the indications studied for ONS treatment progressed, as noted, from solely occipital neuralgia to the more general primary headaches, whereas over the frontal region the indications remained largely limited to various trigeminal neuralgias. While a report by Slavin in 2006 included headache patients treated with supraorbital nerve stimulation (SONS) along with ONS (7), a corresponding effort to evaluate specifically the potential effectiveness of SONS for primary headaches was not made until 2007, when Narouze described a positive response in a patient with cluster headaches (26). This is interesting, as a consideration of the final common neuroanatomical pathway for all cephalic afferents suggests potential for a salutary effect from SONS. Specifically, both the trigeminal and greater occipital nociceptive afferents converge on the same second-order sensory neurons in the trigeminocervical complex (TCC), and thus on a final common pathway to the higher structures, including nuclei felt to be important in pain modulation (27–29). Acknowledging this common neurosubstrate begs the question as to the potential effectiveness of SONS as a treatment for frontal headaches analogous to ONS and occipital headaches.

Another rationale for considering the potential for SONS in the treatment of headaches is based on the generally accepted clinical approach to treating pain with neurostimulation, whereby the goal is to produce a concordant paraesthesia, i.e. to cover the painful region as best as possible with the stimulator-induced paraesthesia. This is the clinical indicator that the appropriate portion of the nervous system is being stimulated and is the recognized approach to neurostimulation and pain over the torso and limbs (30). For example, one would not generally consider treating chronic abdominal wall pain by an induced paraesthesia localized to the lumbar region. However, that is indeed what is being suggested for certain headache types and is thus a relevant concern, as several studies have reported improvements in patients with holocephalic/hemicranial migraine and cluster headaches (thus a fronto-temporal distribution of pain) by stimulating the anatomically distant occiput (3,11,12,15–25). This methodology of treating distant pain, outside of the distribution of the stimulated nerve, is therefore novel; however, as the clinical results are persuasive, it needs to be explained. Otherwise, the traditional clinical approach of seeking a concordant paraesthesia suggests that combining SONS with ONS may provide for a better treatment response in patients with hemicranial/holocephalic primary migraines than would be seen with ONS alone, where the paraesthesia would cover only the occipital portion of the pain. Or, more generally, it suggests that ONS may be best for occipital pain, SONS for frontal pain and combined ONS–SONS for holocephalic pain.

Noting a subset of patients with primary migraine headaches that may be non-responsive to ONS, and based upon the historical clinical approach of covering the painful area as best as possible with the paraesthesia, as well as the potential neuroanatomical substrate of the TCC with its final common pathway for both trigeminal and occipital nociceptive afferents, we hypothesized that patients with hemicranial/holocephalic, primary migraine headaches would respond better when both occipital and supraorbital stimulation were applied together as opposed to occipital stimulation alone. We report on seven patients with severe, chronic migraine headaches (three had refractory headaches) that benefited from combined ONS and SONS. This is the first report on the use of combined frontal and occipital neurostimulation for primary headaches.

Materials and methods

Patient population

Patients were referred by experienced neurology headache specialists. Diagnoses conformed to criteria of the International Classification of Headache Disorders, 2nd edn, of the International Headache Society (IHS) (31) and satisfied appendix criteria for chronic migraine (32). All patients had well-documented histories of severe (disabling), chronic migraine headaches (Table 1). Additionally, three patients (cases 1, 2 and 6) satisfied Schulman's proposed criteria for refractory headaches (33). The other four had headaches unresponsive to extended courses of medical management but did not strictly meet the Schulman criteria. The headaches were either hemicranial or holocephalic in extent, having specifically no history suggesting a primary occipital focus (it cannot have initiated from or be localized to the occiput). For the three patients with refractory headaches, the medications listed were provided at optimal dosages and over sufficient periods (over 2 months) to be consistent with the criteria for refractory headache. Several patients were taking small doses of opiates at presentation; however, these were of

Table 1. Patient demographics

No	Age/sex	Occupation	HA Dx Init	HA Dx HA Recat	Dur CM	Neuro Symp	HA meds summary Current & (previous)	Functional status
1	36/F	Homemaker	MoA	RCM	5 years	None	Topiramate, sertraline, tizanidine, nadolol, sumatriptan (propranolol, ergotamine, ibuprofen, elitriptan)	Impaired
2	49/F	Corp. Exec.	HM	RCM	2 years	Sc, vis loss, limb numb	Valproic acid, propranolol, hydrocodone, naproxen, (divalproex, amitriptyline, sumatriptan)	Incapacitated
3	50/F	Supervisor	MoA	CM	1.5 years	None	Hydrocodone, butorphanol, alprazolam, pregabalin, ibuprofen, Fioricet (sumatriptan, rizatriptan, topiramate)	Incapacitated
4	71/F	Retired	CDH	CM	4 years	None	Oxycarbazine (gabapentin, pregabalin, nortriptyline)	Limited
5	57M	Underwriter	CDH	CM	1 year	Tinnitus, foul smell	Hydrocodone, topiramate, duloxetine, (naproxen, pregabalin, sumatriptan)	Limited
6	20/F	Student	MA	RCM	1 year	None	Hydrocodone, verapamil, amitriptyline, ibuprofen, Fioricet (nadolol, topiramate, sumatriptan, zolmitriptan, DHE)	Incapacitated
7	24/F	Unemployed	MA	CM	6 months	None	Sumatriptan (zolmitriptan, divalproex, hydrocodone, ibuprofen, amitriptyline)	Homebound

HA DX Init/Recat (Initial/Recategorized)—the initial diagnoses were those set at initial patient referral. Prior to submission the diagnoses were recategorized by the neurology headache specialist according to International Classification of Headache Disorders, 2nd edn criteria.
Meds Summary—medications out of parentheses were current at presentation; medications in parentheses were accumulated summary of previous medications.
CDH, chronic daily headache; CM, chronic migraine; Dur CM, duration of chronic migraine; HM, hemiplegic migraine; MA, migraine with aura; MoA, migraine without aura; RCM, refractory chronic migraine; Sc, scotoma.

the order of only a few pills a week and were initiated only after the headaches became refractory and the patients were awaiting evaluation for neurostimulation. This was carefully taken into consideration to ensure that there were no associated rebound headaches. Furthermore, based upon the clear clinical presentations, the diagnostic clinicians were confident that none of the patients had hemicrania continua, so that an indomethacin trial was not considered necessary. Although some patients had severe, daily headaches that often began unilaterally, ultimately they all developed holocephalic pain and none had autonomic features. Those agreeing were provided full and detailed information on the procedure, and informed consent was obtained.

Trial stimulation; procedure technique

Utilizing C-arm fluoroscopy, Axxess or Quatrode [St Jude Medical (St Jude), Dallas, TX, USA] wire lead arrays were placed subcutaneously across the supraorbital nerves just over the eyebrow and across the greater occipital nerves just above the occipital ridge. Following placement, patients were provided with two programs for the unit: one that stimulated only the occipital nerves and another that stimulated both the occipital and supraorbital nerves. Extensive instructions on the use of the equipment and how to monitor and document the response appropriately were provided. Following a 3–5-day trial period, the leads were removed and the patient interviewed as to the response. During approximately half of the trial period, the unit was programmed to stimulate only the occipital nerves, and for the other half both the supraorbital and greater occipital nerves were stimulated. A minimum criterion for a positive trial was at least 50% overall improvement in pain, The relative response to occipital stimulation alone and combined occipital–supraorbital stimulation was determined and, based upon the results, the final system configuration for the permanent implant was accordingly planned. Based upon the patient's usage pattern during the trial, as reflected in the total energy required as determined by the St Jude programming computer, a determination was made as to which specific implantable pulse generator (IPG) would be best. Options included rechargeable Eon or Eon Mini (St Jude; life expectancy of 10 years) and non-rechargeable Eon-C (St Jude; life expectancy of 5 years) units (Table 2).

Permanent implant: operative technique

Following positioning, prep and general anaesthesia (patients were not intubated), small incisions were

Table 2. Patient responses to combined ON–SON stimulation

No	F/U Months	IPG (ANS)	Uni v Bil System	% of time combined ON–SONS	HA Freq/Mo Mild/Severe	HA % Imp	Neuro. Symp.	HA Meds	Functional status
1	35	Eon	Bil	100	3/0	90	NA	Topiramate, sumatriptan	Normal
2	29	Eon	Bil	100	0/0	90–100	Resolved	None	Full; Ret to work
3	19	EM	Bil	75	0/0	90–100	NA	None	Full; Ret to work
4	15	Eon	Bil	100	0/0	90–100	NA	None	Normal
5	12	Eon	Bil	100	30/0	60	Resolved	NSAIA	Normal
6	10	Eon	Bil	100	0/0	90–100	NA	None	Full; Ret to university
7	1	EM	Bil	100	0/0	90–100	NA	None	Normal

% of time ON–SONS—percent of time the patients currently use the full combined ON–SONS vs. ONS alone.
EM, Eon Mini; NA, not applicable; NSAIA, non-steroidal anti-inflammatory agent; ON–SONS, occipital nerve–supraorbital nerve stimulation.

made over the patient's forehead and upper cervical region to accept introducer needles, which were advanced subcutaneously across the bases of the supraorbital and greater occipital nerves. Quatrode (St Jude) wire lead arrays were then placed per the frontal introducers and passed to an incision over the right ear, where they were anchored, looped and further advanced to the occipital incision. In a similar fashion quatrode leads were also placed across the occipital nerves and anchored, whereby strain relief loops were fashioned in all leads. Prior to anchoring, the patient was awakened to confirm appropriate placement by their description of the stimulator-induced paraesthesia pattern and, as necessary, the leads were adjusted to optimize this pattern. Following re-induction of anaesthesia, an incision was made over the upper outer gluteal region, where a pocket was fashioned to accept an IPG. The leads were tunnelled to the pocket and connected to the IPG. Following closure, a sterile dressing was applied. Following recovery from anaesthesia, the neurostimulator was programmed by a representative of the manufacturer. While fully implanted, the IPG was capable of responding to an external, programming computer through a radiofrequency couple. The goal of programming was to provide the patient with the most effective paraesthesia pattern possible, which was accomplished by optimizing various parameters including signal amplitude, pulse width and frequency, temporal signal variation, negative/positive terminal settings, and active lead combinations. The patient received and was fully instructed in the use of a portable handheld programmer, which provided the patient the continuous option of adjusting signal strength, frequency and location. Disposition included prophylactic antibiotics and instructions on temporary activity restrictions.

For the first 2 months the patients were re-evaluated at frequent intervals and ongoing responses were documented. A representative of the manufacturer was available at each visit and, as necessary, would reprogram the neurostimulator to re-optimize the settings. Importantly, each patient was continually provided with at least two specific programs: one that would stimulate only the occipital leads and another that would stimulate both the occipital and supraorbital leads. The patients were repeatedly instructed to evaluate both programs intermittently to determine which one worked best, and their relative preferences were reported. Following this initial 2-month stabilization period, the patients returned every 2–3 months thereafter for general re-evaluations, including assessments both of their ongoing clinical response and of which programs (ONS vs. combined ONS–SONS) they preferentially used.

Results

Trial stimulator

Using a subjective criterion of 50% improvement in the pain as the standard for a positive trial, seven of eight patients had positive trials as all reported 80–100% improvement in pain and neurological symptoms. These positive results came only with the combined frontal–occipital lead combination, as all had markedly inferior responses (much less than 50%), when only occipital neurostimulation was applied. All seven patients who reported a positive response ultimately had the full system implanted.

Permanent stimulator

All patients received bilateral combined occipital nerve–supraorbital nerve (ON–SON) combined systems. Even the patients with primarily unilateral pain would often ultimately have the pain globalize, and all thus preferred the bilateral system. Based upon the energy requirements observed during the trial period, all patients had rechargeable Eon or Eon Mini IPG units (St Jude) recommended and implanted, which was not surprising due to the multi-lead systems. The seven patients with permanent implants had a median follow-up of 15 months (range 1–35 months) following placement of the permanent neurostimulator system (Table 2). All seven continue to use their stimulators, with each continuing to describe almost identical results to those achieved during the trial. Five were able to discontinue their medications completely, and the other two noted marked reductions. All returned to fully functional lifestyles including college and work. As indicated and on an ongoing basis, the patients would intermittently evaluate and report the results of the relative efficacy of the two programs (occipital stimulation alone vs. combined supraorbital and occipital stimulation). The results remained consistent in that all continue to greatly prefer the combined program, and indeed most use it exclusively.

Case reports

Case 1

A 36-year-old White woman presented in June 2005 with a history of migraine headaches since childhood, which 5 years previously had progressed to daily severe, throbbing headaches, associated with nausea, vomiting and photophobia. Often heralded by blurred vision, they usually began on the left side and progressed to a holocephalic distribution. In 2004, when they began to seriously affect her activities, an extensive neurological evaluation, including magnetic resonance imaging (MRI) and vascular studies, by a neurology headache specialist was unremarkable, and a diagnosis of migraine without aura was made. The headaches came under control with topiramate, sertraline and sumatriptan. A year later, when the pain became refractory (failed extended trials of ergotamine, propranolol, ibuprofen, naproxen and other triptans), transdermal fentanyl was added, and she was referred to our facility with a diagnosis of chronic migraine headaches. Supraorbital and greater occipital nerve blocks provided temporary relief. In April 2006 a bilateral combined ON–SON stimulation system was implanted with immediate, near-complete resolution of the headaches. In June 2006 signs of infection developed in one supraorbital lead, but remarkably cleared with local debridement and prolonged antibiotics. Thereafter, the headaches remained under excellent control with the stimulator and topiramate as a prophylactic agent. At her last evaluation in January 2009 she reported being largely headache free, indicating about three mild headaches per month, which respond to sumatriptan.

Case 2

In September 2006 a 49-year-old White woman presented with daily incapacitating headaches. They had begun as a teenager and were controlled well with various prophylactic and abortive agents. Over the 2 years prior to presentation they had progressed to severe daily, unilateral throbbing headaches interspersed with fleeting, knifelike pains in her eye and jaw. Flashing lights and transient paresis of her left arm were a common prodrome approximately 2 h before headache onset. Significant visual loss occurred with 50% of the headaches, and photophobia and phonophobia were common. These ultimately became refractory to extended courses of various prophylactic (topiramate, valproate, propranolol, amitriptyline) and abortive (multiple triptans, naproxen) medications. The headaches were incapacitating to the point of full disability, as she was forced to resign her corporate executive position. In early 2006 she came under the care of a local neurology headache specialty group, who diagnosed hemiplegic migraine and referred her to our office in July 2006. In September 2006 bilateral occipital leads were placed with moderate but, on the whole, inadequate relief. With the addition of supraorbital leads in October 2006, the headaches and all neurological symptoms (visual loss, paresis) resolved. In March 2007 an occipital lead migrated and was repositioned. Thereafter, she remained headache free off medications and back to full functional status.

Case 3

A 50-year-old White woman presented with a 30-year history of progressively severe migraine headaches.

Various regimens including anti-inflammatory medications, triptans, topiramate and botulinum toxin injections initially helped; however, in 2005 the situation had progressed to severe, daily headaches, unresponsive to all measures, at which point an occipital nerve decompression was performed with no response. Rendered completely disabled, she was forced to resign her supervisory position at work. She had then come under the care of an experienced neurology headache specialist, whose diagnostic evaluation was unremarkable. When the pain proved unresponsive to botulinum toxin injections and medication management (hydrocodone, butorphanol, alprazolam, and pregabalin), she was referred to our clinic with a diagnosis of migraine without aura headaches. She was found to be suffering from daily, severe, throbbing right hemicranial headaches, noting occasional left supraorbital pain. Nausea and vomiting were commonly associated. Greater occipital and supraorbital nerve blocks provided only temporary relief. In August 2007 a bilateral combined ON–SON stimulation system was implanted, and the headaches promptly and completely resolved. In early 2008 she presented with local swelling and tenderness at the IPG site. Studies ruled out infection, and a diagnosis of allergy to titanium was determined by skin testing. The pulse generator was ultimately replaced with an Eon Mini (St Jude), around which a surgical mesh wrap provided a successful safeguard to the allergy. Thereafter, she remained completely headache free off medications and returned to a full activity schedule, including work. She uses the stimulator about 50% of each day and occasionally can go a day completely without it. If a headache does start, it promptly resolves with resumption of the stimulation. She uses the full frontal and occipital system about 75% of the time and just the occipital leads 25% of the time.

Case 4

A 71-year-old White woman presented in November 2007 with a 4-year history of daily holocephalic headaches for which she had variously tried gabapentin, pregabalin, nortriptyline, oxycarbazine and butalbital. She was evaluated by an experienced neurologist, who obtained a full imaging panel and diagnosed chronic daily headaches. Chiropractic care and regional injections were not beneficial. The headaches became unresponsive to medical management, and she was referred to our centre, taking only oxycarbazine. In December 2007 she responded well to a bilateral combined ON–SON stimulation system and has remained headache free off medications thereafter.

Case 5

A 57-year-old White man presented in January 2008 with a 1-year history of severe, daily, holocephalic headaches that were associated with tinnitus and a foul taste and smell. After a period of ineffective dental and chiropractic treatment, he had come under the care of an experienced neurology headache specialist. A full radiographic and laboratory evaluation was unremarkable, and a diagnosis of chronic daily headaches was established. When the problem was unabated by an extensive course of medical management, including naproxen, sumatriptan, hydrocodone, topiramate and duloxetine, a bilateral combined ON–SON stimulation system was implanted in March 2008. Subsequently, the headaches and neurological symptoms completely resolved off medications. Months later he developed some recurrent daily head pain, but this stabilized to a current low daily pain level that was 60% improved over presentation. The frequency of severe headaches decreased to once every 3 months.

Case 6

A 20-year-old White woman noted the onset of migraine headaches at age 12 years and until age 15 years experienced migraines with aura two to three times a week. In 2003 the headaches had escalated in severity and responded well to dihydroergotamine. In March 2005 the headaches again escalated, and she was admitted to an in-patient headache specialty hospital, where she underwent an extensive diagnostic evaluation and treatment protocol. The headaches responded to zolmitriptan, and in September 2006 she enrolled in college. A year later, however, they progressed to the point that she had to withdraw from college and return home. She was experiencing severe daily, throbbing hemicranial headaches, associated with nausea, vomiting and photophobia that became refractory to all therapeutic measures. Over the year prior to presentation various medication regimens, including combinations of nadolol, topiramate, various triptans, dihydroergotamine, mixed analgesics and hydrocodone, were tried without benefit. At the time of referral she was completely disabled (homebound and unable to participate in even brief family outings) and was taking only hydrocodone twice weekly. In May 2008 a bilateral combined ON–SON stimulation system was implanted, which provided prompt and complete resolution of the headaches. Thereafter, she remained headache free and returned to college that autumn. At her last evaluation 10 months post implantation she was completely headache free off medications.

Case 7

A 24-year-old White woman developed headaches as a teenager, which were controlled with regimens including various triptans, divalproex, amitriptyline and

anti-inflammatory medications. Six months prior to presentation they progressed to severe daily headaches. Visual changes typically heralded the onset, whereupon a severe, throbbing right hemicranial (occasional holocephalic) headache would rapidly develop and associate with nausea, vomiting and noise intolerance. It generally lasted the rest of the day and forced her to bed. She had ultimately come under the care of an experienced neurology headache specialist, when an MRI scan of the brain and spine were unremarkable, and a diagnosis of migraine with aura was made. All treatment efforts ultimately failed, as she became completely disabled and homebound. When there was no response to a medication change to sumatriptan and tizanidine, she was referred to our centre. A set of occipital nerve blocks was not helpful. A bilateral combined ON–SON stimulation system was fully implanted in February 2009, whereupon the headaches promptly resolved, and she remained headache free off medications thereafter.

Discussion

All of the patients reported marked improvement in headache frequency and severity, resolution of associated neurological symptoms, and return to a fully active lifestyle. Furthermore, all remained convinced that combined ON–SON stimulation benefited their headaches much more than ONS did alone. The 88% trial-to-permanent stimulator ratio suggests that a high percentage of patients with chronic migraines may respond to combined neurostimulation. Perhaps most impressive were the improvements in patient function, particularly notable in the three patients who were functionally incapacitated, yet responded so well that all returned to their full pre-morbid lifestyle including college or work. Problems included a single lead migration, an infected lead, and an allergic reaction to the IPG. Furthermore, the study is clearly limited due the small sample size, with other weaknesses including the lack of a diary and the open-label, non-randomized structure. Given the structure of the report, a placebo effect cannot be completely excluded; however, given the uniform continuation of such dramatic responses across all patients and for the duration of their implants, we feel that there is probably minimal placebo effect.

When considering neurostimulation and headaches, in addition to diagnosis we suggest that it is particularly helpful to classify headaches according to the anatomical location of the pain. Accordingly, we distinguish three groups of patients who historically have aroused most interest amongst researchers concerned with neurostimulation—one group with headaches localized primarily to the occipital region (occipitally focused headaches; Table 3) and two groups with headaches

Table 3. Summary of reports on patients with occipitally focused headaches treated with occipital nerve stimulation

Study	Dx	Trial: Pos/Tot	No Perm Imp	Perm: Resp Rate (no pts)	Resp magnitude
Weiner & Reed (1)	ONa	13/13	13	80% (10)	80% had good to excellent relief
Weiner et al. (2)	IC2H	?	62	80% (50)	80% had good to excellent relief
Popeney & Alo (11)	TM	25/25	25	100% (25)	100% responded
Oh et al. (3)	ONa/TM	20/20	20	95% (19)	90% had > 75% improvement at 3–6 months
Melvin et al. (14)	ONa	11/14	11	100% (11)	73% rated relief as good to excellent
Kapural et al. (4)	CEH	6/6	6	100% (6)	70% average decrease in VAS
Rodrigo-Royo et al. (13)	ONa	4/4	4	100% (4)	97% average decrease in VAS
Slavin et al. (6)	ONa	10/14	10	90% (9)	All had excellent pain relief at 6 months
Johnstone, Sundaraq (5)	ONa	7/8	7	71% (5)	73% average decrease in VAS
Summary	OFH	96/104 (92%)	158		88% (139/158) of pts implanted had > 50% relief

Weiner & Reed's initial report indication of 100% response rate (1) was later modified to 80% (2).
Whereas subsequent authors (47–49) have recategorized the diagnoses in Weiner & Reed's initial study (11) to chronic migraines, we retain the original diagnosis of occipital neuralgia. Author Reed (also co-author of the original report) was the primary pain physician for the original patients and maintains the original diagnoses of occipital neuralgia as correct.
CEH, cervicogenic headaches; Dx, diagnosis; IC2H, Intractable C-2 headaches; OFH, occipitally-focused headaches; ONa, occipital neuralgia; Pos/Tot, positive responses/total patients; TM, transformed migraine.

Table 4. Summary of reports on patients with cluster headaches treated with occipital nerve stimulation (ONS)

Study	No implants	Response rate and magnitude
Dodick (12)	1	> 90% improvement
Magis et al. (15)	8	7/8 (63%) had > 50% improvement in frequency or severity
Schwedt et al. (16)	1	> 70% improvement in frequency and severity
Schwedt et al. (23)	3	HA frequency: 0% improved; HA severity: 1/3 had > 50% improvement
Burns et al. (17,18)	14	5/14 (36%) of patients had > 50% improvement in frequency, severity or duration
Lainez et al. (19)	5	4/5 (80%) had 100% improvement
Vargas et al. (20)	4	3/4 (75%) had an average of 65% improvement in frequency
Leone et al. (21)	10	3/10 (30%) of patients responded
Summary	46	54% (25/46) of patients responded to ONS with > 50% improvement

Table 5. Summary of reports of patients with chronic migraines treated with occipital nerve stimulation (ONS)

Study	No implants	Response rate and magnitude
Schwedt et al. (23, 24)	8	4/8 (50%) had > 50% improvement in severity or freqeuncy
Saper et al. (25)	51	20/51 (40%) had > 50% improvement in pain
Summary	59	47% (24/59) of patients responded to ONS with > 50% improvement in severity or frequency

As there was no trial for the Medtronic Study, the 40% response rate is the rate of responders to the full implant.

classically localized to the fronto-temporal regions (migraine and cluster headaches; Tables 4 and 5). Occipitally focused headaches is not a term used by the IHS, and we define it here to be any headache (regardless of specific headache diagnosis) that either is localized primarily to the occipito-cervical region or begins there and subsequently progresses to involve other anatomical regions, e.g. hemicranial or holocephalic headaches. Examples of occipitally focused headaches include occipital neuralgia and cervicogenic headaches; however, headaches with migrainous features may also be occipitally focused (3, 11). The clinical importance of distinguishing these from the fronto-temporal migraine and cluster headache groups (Tables 4 and 5) relates to the fact that for migraine and cluster headaches pain is perceived most commonly in the distribution of the trigeminal nerve, as opposed to occipitally focused headaches, where pain perception is primarily in the distribution of the greater occipital nerve. Therefore, recognizing that these two neural distributions are anatomically distinct and that ONS stimulates only one of them allows for critical comparisons between the groups on the relative response rates to ONS.

Indeed, a review of the historical response rates for ONS and headaches as set forth in these three tables provides perspective for analysis of our data. The highest patient response rate to ONS is seen with the occipitally focused headache group, with 88% of patients overall reporting a positive response. In contrast, in the two patient groups with pain classically focused over the frontal-temporal regions (migraines and cluster headaches) only 47 and 54%, respectively, responded. Indeed, the largest migraine study to date, Saper's report on data abstracted from Medtronic's (Medtronic Inc., Minneapolis, MN, USA) ONSTIM study, found that only 40% of patients responded to ONS over the long-term (25). As Saper went directly to permanent implant without antecedent trials, the results may be skewed compared with the series on occipitally focused headaches, which all began with stimulator trials (Table 3). However, even if the results of the occipitally focused studies are extrapolated to determine a long-term response rate based upon the initial pre-trial patient number, which more closely approximates Saper's protocol, a 77% long-term rate is still derived, which remains markedly higher than Saper's 40% response rate. Therefore, the data suggest that although patients with classic fronto-temporal headaches (migraine and cluster headaches) may respond to ONS, the response rate is considerably lower than that for occipitally focused head pain. The question arises how best to understand why migraine and cluster headaches should have such a substantially lower response rate to ONS than occipitally focused headaches or, alternatively, why combined ON–SON stimulation may be more effective for these headache types than ONS alone.

These questions and our data should be considered in the context of the current understanding of the neuroanatomy and neurophysiology of head pain. Neuroanatomical studies of the TCC and brainstem

suggest possible sites of action for neurostimulation and may provide a potential substrate for understanding the evidence base for ONS and headaches. Migraines and cluster headaches are understood to be disorders of the brain, whereby pain is most commonly perceived in the distribution of the trigeminal nerve (34, 35). Occipital neuralgia, cervicogenic headaches and other occipitally focused secondary headaches (e.g. post-traumatic headaches) differ in that in these groups pain is perceived primarily in the distribution of the greater occipital nerve (36–38). The first division of the trigeminal nerve innervates the frontal regions of the head, including the forehead and supratentorial meninges and vasculature (34). The greater occipital nerve derives largely from the C2 root and provides the primary innervation for the occiput and upper posterior cervical region, including the skin, soft tissue and the infratentorial dura (37). The nexus of these two systems occurs at the TCC, which is formed by the caudal trigeminal nucleus and portions of the upper three cervical dorsal horns (27–29). The pivotal interface here is where nociceptive afferents from both the trigeminal nerve and the greater occipital nerve converge on the same second-order neurons in the TCC and thus to a final common pathway to higher centres for cephalic nociception and modulation. Bartsch and Goadsby's meticulous animal studies convincingly demonstrated both this discrete convergence as well as subsequent sensitization of second-order TCC neurons following a sensory barrage, findings that probably underlie the clinical observations of allodynia, hyperpathia and spreading pain seen with primary headaches (27, 28, 39). In 2003 Popeney and Alo suggested that this nociceptive convergence at the TCC may be significant with respect to the mechanism of action for ONS and migraine headaches (11) and thus help explain the clinical puzzle of how paraesthesia limited to the occiput could affect pain over the distant fronto-temporal regions, as is seen with migraine headaches. It is interesting to consider that the convergence was found to be partial (48% of both trigeminal and occipital neurons terminated unilaterally on TCC neurons) (27) and speculate on the possibility that this partial convergence may be mechanistically related to the apparent lower response rates of the headaches with pain in the front-temporal region (migraine, cluster) compared with occipitally focused headaches (Tables 3–5). Whereas for occipitally focused headaches the stimulation is applied directly to the nerves that are transmitting the pain signals, for the fronto-temporal pain of migraine headaches ONS only indirectly influences the nociceptive system (trigeminal afferents at the TCC). Therefore, the TCC may provide a potential mechanism for both questions—why the fronto-temporal pain of migraine headaches may respond at all to stimulation of the distant occipital nerves, and why that response may be less pronounced than that seen with occipital pain.

The brainstem and higher structures also play a key role in migraine pathogenesis (34, 40–43), as well as a likely one in pain modulation from neurostimulation (22, 44, 45). Matharu's elegant positron emission tomography (PET) studies documented specific areas of brainstem activation in patients with migraines treated by ONS and provide the best evidence to date of neurostimulation-induced activation of higher neural centres (22). Paraesthesia-correlated activation was observed in the cuneus, pulvinar and anterior cingulate cortex. Activation of the rostral dorsal pons demonstrated a covariable response with pain scores and may be particularly important in the genesis of chronic migraines. Activation of the pulvinar has also been reported in a patient with a thalamic stimulator for chronic pain (44) and another with a spinal cord stimulator for angina (45). Matharu hypothesized that activation of these structures may be important in pain modulation, including the affective dimension of pain (22). Taken together, the discovery of partial nociceptive convergence at the TCC and the PET documentation of neurostimulator-induced brainstem activation provide an attractive model that may help explain why migraine headaches apparently respond to stimulation of the distant occipital nerves but in a less marked fashion than the responses seen with occipitally focused head pain.

The clinical analogue to the thesis of stimulating the appropriate portion of the nervous system is the topographic coverage of the neurostimulator-induced paraesthesia. We feel that the location of the paraesthesia in relation to the pain is a central issue and suggest that during the course of the historical evolution of investigations into ONS and headaches, a paradigm shift occurred from the traditional approach to neurostimulation and pain. Over the decades the vast bulk of investigational work on neurostimulation and pain involved spinal cord stimulation for back and extremity pain, and throughout this period the clinical approach has always been to produce a paraesthesia over the part of the body that hurt, which indicated that the correct portion of the nervous system was being stimulated. Even reports of salutary effects from spinal cord stimulation for such pain problems as intractable angina and abdominal visceral pain still have the paraesthesia covering the related anatomical areas of pain (e.g. a precordial paraesthesia was found to be best for angina) (10, 45, 46). Indeed, prior to 2003 we can find no evidence, regardless of anatomical location, that neurostimulation reliably eased pain that was significantly outside the area of paraesthesia. The departure thus came with head pain, where in 2003 investigators

began evaluating the response of cluster headaches to an occipital paraesthesia (12). The shift in the paradigm was that we went from treating pain with neurostimulation based on producing an anatomically concordant paraesthesia, irrespective of diagnosis, to treating pain with neurostimulation based on diagnostic categories (e.g. migraines, cluster headaches), irrespective of paraesthesia coverage. Therefore, the application of ONS to occipitally focused headaches was fully consistent with the traditional method, as ONS produced a paraesthesia localized to the painful area (occiput), with resultant high reported response rates (Table 3). On the other hand, the application of ONS to migraine and cluster headaches departed from this standard, as the pain over the fronto-temporal regions was being treated with a distant paraesthesia localized solely to the occiput (no fronto-temporal paraesthesia is produced by ONS), and the response rates were correspondingly lower. Therefore, from this viewpoint, which is consistent with the preceding discussion of the neuroanatomy, while it is actually noteworthy that there is a positive response rate at all, the prediction is that we should have a markedly lower response rate, which the early results indeed indicate (Tables 4 and 5).

The results of Popeney and Alo's 2003 report on transformed migraines (TM) (11) and Oh's 2004 report on ONS for both occipital neuralgia and TM (3) support our thesis of the importance of a concordant paraesthesia. While TM is generally understood to be a primary headache disorder with pain that is not anatomically focused, the patients in these studies suffered from a 'neuropathic subset' of TM manifested by a 'radiating posterior headache pain syndrome' with 'symptoms within the C1 through C3 neural distribution' (and thus occipitally focused) (3, 11, personal communication with co-author Alo). Some questions have arisen regarding the appropriateness of using TM as a diagnosis in these patients (7); however, that does not affect our analysis relating to the clinical aspects of these patient groups. Oh's patients were divided equally into two groups: those with classical occipital neuralgia (lancinating neuritic pain over the occipito-cervical region) and those with 'neuropathic' TM (primary headaches with migrainous features focused over the occipito-cervical region). At 3 months the results were similar, as 90% of the occipital neuralgia group and 100% of the TM group reported positive responses. Thus, we have two groups of patients with pain primarily localized to the occipito-cervical region, yet with different neurophysiological underpinnings (solely neuropathic head pain vs. headaches with migrainous symptoms). The pain from both sets was perceived in the distribution of the occipital nerves, and both groups responded to a concordant paraesthesia over the occiput. Similar observations may be made on Popeney and Alo's report on ONS for TM headaches (all had migrainous features but clinically had a neuropathic quality over the distribution of the C1 through C3 roots), where all of the patients responded to a concordant paraesthesia (11). Contrast these 90–100% response rates of patients with an occipitally focused migraine variant to a concordant paraesthesia (3, 11) with the roughly 50% rate reported for primary (fronto-temporal) migraines to a non-concordant (occipital) paraesthesia (23, 25) (Table 5). These findings suggest that the presence or absence of migrainous features (neurophysiological diagnosis) may be less important than the topographical distribution of the pain, which is exactly what would be expected from the traditional approach to neurostimulation, where we find optimal results from a concordant paraesthesia over the painful area, irrespective of specific diagnosis.

We therefore suggest that when considering the potential responsiveness of various types of headaches to neurostimulation, it may be beneficial to return to the traditional approach of concordant paraesthesia. That is not to say that ONS is ineffective for migraine and/or cluster headaches, as clearly there is a group that responds. Rather, it is to draw attention to the issue and recommend that in addition to subsuming patient outcomes under diagnostic categories (e.g. studies evaluating the relative response rates for cervicogenic and migraine headaches to ONS), it would be helpful if the topographical coverage of the paraesthesia in relation to the pain was also considered. The results of our study as well as the literature database support the argument and prediction that, irrespective of specific diagnosis, pain localized primarily over the occipital region (occipital nerve-mediated pain) will probably respond best to ONS; pain over the frontal region (trigeminal nerve-mediated pain) will probably respond best to SONS; and that hemicranial/holocephalic pain will tend to respond best to combined ONS–SONS. Acknowledging the early and thus limited historical database, these inferences stand as conjectures, yet ones that can be tested based upon their predictive value. Further studies will hopefully further illuminate these issues.

In summary, our patients reported strongly positive clinical responses to combined ONS–SONS. ONS alone was inadequate, a finding consistent with the historical data's indication of a substantial subset of patients with migraine headaches that may not respond to ONS. While not exclusive, the TCC convergence model along with the PET scan documentation of activation of higher central nervous system sites with ONS may provide a potential substrate for the clinical puzzle of how distant, occipital stimulation may ease the frontal pain of trigeminal nerve-mediated

primary migraine headaches, yet with a response rate that appears to be lower than for occipital nerve-mediated cervicogenic headaches. The clinical analogue to this issue of directly stimulating the appropriate portion of the nervous system is that of a concordant paraesthesia. Recent studies on ONS and migraine and cluster headaches suggest a paradigm shift from the traditional approach here, and evidence adduced in this report suggests that it may be helpful to reconsider this position. The accumulated data thus indicate that although a substantial proportion of patients with migraine headache may not respond to ONS alone, they may respond well to combined ON–SON stimulation. An appreciation of these considerations may be important when it comes to patient care decisions, as well as in the development and analysis of future clinical investigations.

Conclusions

The results of our study indicate that combined ON–SON stimulation systems appear to markedly ease the pain, neurological symptoms and disability in some patients with severe, chronic migraine and refractory chronic migraine headaches. The degree of clinical response to these combined systems was found to be uniformly much better than single modality ONS treatment alone, and the high trial-to-permanent implant ratio suggests that a high percentage of patients with chronic migraine headaches may respond to a combined system. The findings appear to be in concert with our current understanding of neuroanatomy and physiology, as well as with the traditional approach to neurostimulation and pain, i.e. the importance of a concordant paraesthesia. Taken together, they underpin our initial rationale to consider the potential of combining SONS with ONS in patients with hemicranial/holocephalic migraine headaches and further may help explain why ONS appears to help the frontal pain component of only a portion of holocephalic migraine headaches. Recognizing these considerations may affect the analysis of clinical studies of ONS and headache responsiveness, as they emphasize the importance of both the appropriate anatomical coverage of the neurostimulator-induced paraesthesia, as well the appropriate diagnostic grouping with respect to outcomes. Further studies are warranted.

Competing interests

All four authors serve as consultants for St Jude Medical and are co-investigators in St Jude Medical's ongoing study evaluating occipital nerve stimulation for migraine headaches. No advice, direction, or assistance (financial or otherwise) was received for this paper.

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