

Occipital Stimulation for Chronic Migraine: Patient Selection and Complications

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ABSTRACT: Background: Chronic migraine is a significant cause of disability world-wide and occipital region stimulation (OS) has been proposed to treat it. While participating in an industry-sponsored pilot trial of OS, we aimed to collect data regarding our surgical complications and long term usage of OS in our chronic migraine patients. **Methods:** Ten patients (8 female, median age 46.5 years) were enrolled based on criteria established by the sponsoring company, screened in the headache clinic, and followed for a median of 33 months. We did not access data collected by industry for this report and instead collected our own data prospectively, including predominant location of headache, location of paresthesia evoked by OS, and complications. **Results:** Adverse events included three possible early infections requiring antibiotics but not hardware removal, one late implantable pulse generator erosion requiring removal, one generator malfunction requiring revision, and loss of paresthetic coverage requiring four revisions in four patients. Two patients experienced new symptoms requiring psychiatric intervention. Five patients had no benefit and have been explanted. Of those who remain using their device, the proportion of their pre-operative pain located in the occipital region was 0.62 ± 0.14 , whereas in those patients who have been explanted, the proportion was 0.31 ± 0.18 ($t = 3.15$, $p=0.01$). **Conclusions:** Complication rates with OS are higher than those seen with other stimulation techniques, despite identical hardware and similar surgery. The location of migraine pain did predict outcome, and suggests that only those with primarily occipital region headache are candidates for this therapy.

RÉSUMÉ: Stimulation occipitale dans la migraine chronique : sélection des patients et complications. Contexte : La migraine chronique est une cause importante d'invalidité à l'échelle mondiale et la stimulation de la région occipitale (SO) a été proposée comme traitement de cette maladie. Lors de notre participation à un projet pilote sur la SO, commandité par l'industrie, nous avons recueilli des données sur les complications chirurgicales que nous avons observées et sur l'utilisation à long terme de la SO chez nos patients atteints de migraine chronique. **Méthode :** Dix patients dépistés à notre clinique de la céphalée, qui satisfaisaient aux critères de sélection déterminés par le commanditaire, ont été inclus dans l'étude dont 8 femmes et dont l'âge moyen était de 46,5 ans. La durée médiane du suivi a été de 33 mois. Nous n'avons pas eu recours aux données recueillies par le commanditaire pour effectuer cette étude. Nous avons plutôt recueilli nos propres données de façon prospective, dont la région prédominante de la céphalée, l'endroit des paresthésies provoquées par la SO et les complications de l'intervention. **Résultats :** Parmi les incidents thérapeutiques, nous avons noté 3 infections précoces ayant nécessité l'administration d'antibiotiques sans retrait de l'appareillage, une érosion tardive du neurostimulateur implantable ayant nécessité son retrait, un dysfonctionnement du neurostimulateur ayant nécessité une révision et la perte de la couverture paresthésique ayant nécessité 4 révisions chez 4 patients. Deux patients ont présenté de nouveaux symptômes qui ont nécessité une intervention psychiatrique. Cinq patients n'ont pas éprouvé de bénéfice et leur dispositif a été retiré. Chez ceux dont le dispositif est encore en place, la proportion de la douleur préopératoire localisée à la région occipitale était de $0,62 \pm 0,14$, alors que chez les patients explantés, la proportion était de $0,31 \pm 0,18$ ($t = 3,15$; $p = 0,01$). **Conclusions :** Les taux de complications de la SO sont plus élevés que ceux observés avec d'autres techniques de stimulation, malgré un appareillage et une chirurgie similaires. La localisation de la douleur migraineuse prédisait le résultat thérapeutique, ce qui suggère que seulement ceux qui ont une céphalée principalement occipitale sont des candidats à ce traitement.

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Headache, and specifically migraine, is one of the biggest causes of lost productivity in developed countries^{1,2}. While there are numerous medical options to treat migraine, some patients progress to a chronic daily headache syndrome, chronic migraine. Diagnostic criteria for chronic migraine include headache on 15 days or more per month, with at least eight of these days continuing to meet migraine diagnostic criteria, or be successfully treated with migraine-specific drugs³. The development of chronic migraine is now considered one of the complications of migraine⁴. A recent management approach is occipital nerve stimulation, although more precisely should be called occipital region stimulation (OS) because the electrodes are placed in the subcutaneous tissue near the nerve, not on the nerve itself⁵. Success rates ranging from 50-90%⁶⁻⁸ have been

reported in open label single centre studies, including reduced headache days, severity of pain, disability, depression and pain impact scores⁹.

Three recent industry sponsored clinical trials reported different results at three month follow-up. The ONSTIM study¹⁰ reported a 39% responder rate, defined as a 50% reduction from

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baseline in headache days per month or a 3-point drop in severity of pain on a 10 point visual analog scale, in chronic migraine patients treated with OS in comparison to 6% in the sham OS and 0% in the medically managed groups. The PRISM trial was larger, was published only in abstract form, but failed to identify a difference in number of headache days in migraine sufferers with sham vs. active stimulation¹¹. Interestingly the complications seen in these two trials were also different. The third large trial funded by yet another industry competitor, has also only been reported in abstract form¹², finding a very low complication rate of 1% and significant improvements in number of headache days, pain/distress scales and quality of life in those receiving active stimulation. In the ONSTIM study, 24% of subjects experienced lead migration at the three month time point. The PRISM group¹¹ reported infection (15.1%), non-target area sensory symptoms (18.0%), implant site pain (17.3%) and 6.8% lead migration over two years of follow-up. Both trials suggested that specific subgroups may have better response to therapy than others, although only in the PRISM trial did a specific subgroup undergo separate analysis¹¹. Similarly a recent retrospective study identified the types of headache classes more likely to respond to this therapy⁷.

There are several questions about OS for migraine that remain to be resolved. These include (i) who are the migraineurs most likely to respond to this surgery, and (ii) what are the complications of this procedure. We participated in the industry sponsored trial reported by Saper et al¹⁰ and collected data in our patients in a prospective manner as part of routine medical care to address these two questions.

METHODS

The patient sample reported here is from the multicentre study¹⁰ registered with National Institutes of Health (NIH)

ClinicalTrials.gov (NCT00200109). We obtained institutional ethics approval for this trial.

Details of the study protocol, inclusion and exclusion criteria, outcome measures are reported in the multicentre trial¹⁰. Briefly all patients were screened in the headache clinic, deemed to be refractory to medical management (more than 15 headache days per month over three months) and had pain located in the occipital or suboccipital regions. However the amount of pain located in this region was not specified. The protocol did not require psychological screening, but did require the absence of medication overuse. Patients and evaluating clinicians were blinded for the first three months and the two groups consisted of patients who were allowed to control their own OS with their patient programmer and patients that was set to sham stimulation (1 minute of stimulation every 24 hours).

The surgical technique was dictated by the multicentre protocol. Briefly, patients were positioned awake in the lateral decubitus position and fluoroscopy in the AP plane utilized to pass spinal cord stimulation electrodes (PISCES QUAD 3487A, Medtronic, Minneapolis, MN) bilaterally from a midline incision at C2. Local anaesthesia and intravenous sedation allowed intra-operative testing to confirm adequate paresthetic coverage of the greater and lesser occipital nerve territories bilaterally. The Touhy needle provided in the kit was bent into a slight curve and passed from midline towards each mastoid process in the suprafascial plane. After confirming that the patient felt paresthesia in the greater and lesser occipital nerve territories, the lead was secured with a specially designed device (TITAN anchor, Medtronic Inc. Minneapolis, MN) to the fascia after leaving a loop of wire for strain relief in a subcutaneous pocket. The spinal cord leads were then tunnelled towards a scapular incision. Implantable pulse generators (IPG, Synergy 7427, Medtronic, Minneapolis, MN) were placed in the abdomen and

Table: Demographics and details of outcomes

Subject	Sex	Age	Other conditions	Location of pain	Trigger points	Complications	Paresthesia	Outcome
1	F	37		0.66 occipital: 0.33 temporal	5		Almost full coverage	Using at 36.1 m
2	F	36		0.75 occipital: 0.25 frontal	3	IPG failure, replaced	Full coverage	Using at 38.2 m
3	F	55		0.6 occipital: 0.3 temporal: 0.1 orbital	4	Revision of leads due to inadequate coverage	Inadequate coverage	Removed at 14.9 m
4 *	F	32		0.35 occipital: 0.65 frontal	1	Psychiatric treatment	Full coverage	Removed at 7.2 m
5	M	49	Diabetes, obesity	0.7 occipital: 0.1 frontal: 0.2 temporal	1	Incisional infection / inflammation, Revision of L lead due to loss of coverage	Almost full coverage after revision	Using at 35.9 m
6	F	44	Bipolar disorder	0.2 occipital: 0.4 temporal: 0.4 orbital	0	Incisional infection / inflammation Narcotic addiction requiring psychiatric admission	Full coverage	Removed at 33.9 m
7*	F	58	Fibro-myalgia	Everywhere (see Fig 3)	10	Revision to regain coverage & correct extension tightening	Local coverage only	Removed at 27.0 m
8	M	54		0.6 occipital: 0.4 frontal	1		Partial coverage	Using at 33.2 m
9	F	38	Morbid obesity	0.4 occipital: 0.6 frontal	0	Incisional infection / inflammation, late erosion requiring removal, delayed re-implantation	Full coverage	Using 31.2 m after first, 6 m since re-implant
10	F	50		0.2 occipital: 0.8 frontal	6	Only R side implanted during first surgery, L side implanted 4 m later	Full coverage	Removed at 27.7 m

Subjects continuing to use their OS are shaded grey. Subjects in whom the IPG was placed in the buttock instead of abdomen are starred*.

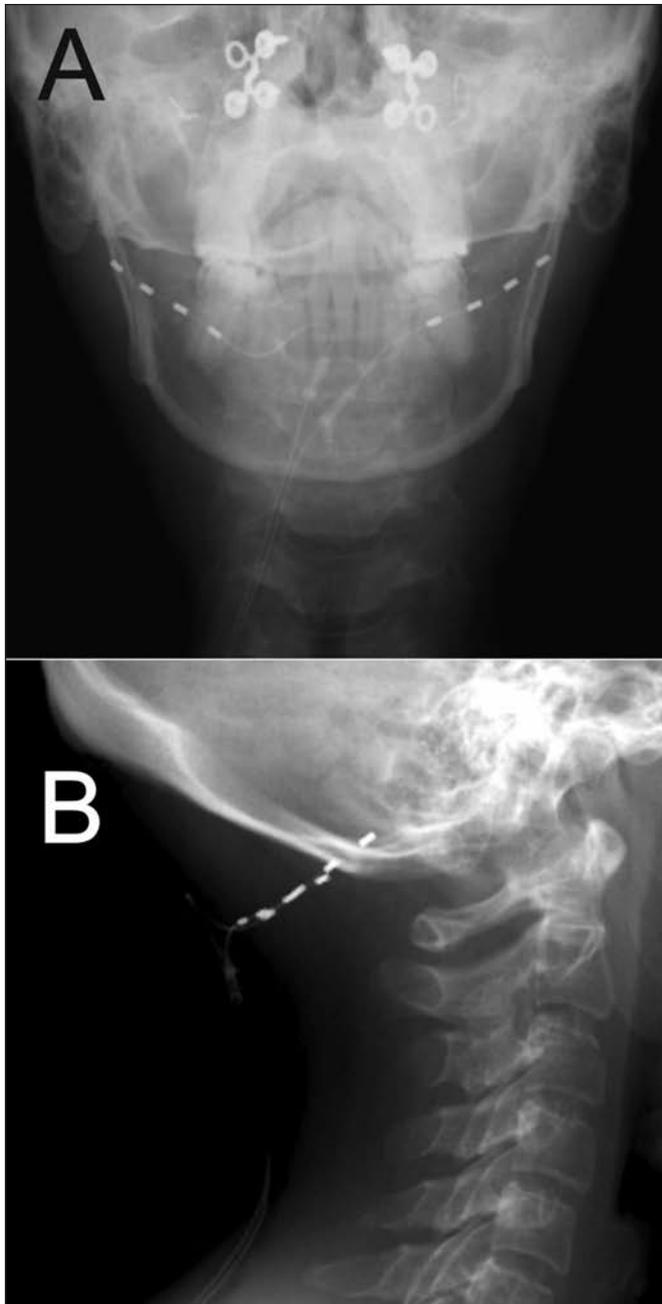


Figure 1: Skull and cervical spine radiographs showing example of ONS electrode location in AP (A) and lateral (B) views.

extensions were tunneled from the scapular connector site to the IPG. Buttock placement of the IPG was allowed under exceptional circumstances and this was the case for two of our patients (Table). Three passes of the occipital electrode was allowed before a failure to achieve adequate paresthetic coverage ensued and the procedure aborted. Radiographs confirmed correct placement of the electrodes in the immediate post-operative period, at each follow-up, or if there was a change in paresthetic coverage (Figure 1).

Ten patients (8 female, median age 46.5 years) were enrolled and followed for a median of 33 months (range 7-38) (Table). We did not access the data collected through the multicentre trial for this report and instead collected our own data prospectively, as part of routine neurosurgical care. These data included predominant location of pain, location of paresthesia evoked by OS, surgical details, stimulation parameters utilized, and complications. Pre-operatively patients were questioned about the percent of their usual headache pain located in each part of the head or neck, and this was recorded on figurines (Figures 2, 3). Trigger points in the upper body and co-morbidities were recorded at baseline. Paresthesia induced by OS was noted on figurines at each follow-up appointment. The ONSTIM study protocol required three years of follow-up and we saw all patients yearly while they had an implanted system. Patients were not followed after device removal. For the purposes of this report, we defined responders as those patients who continue to use the ONS systems three years post-implant, and non-responders as those who do not and/or have had their systems electively removed.

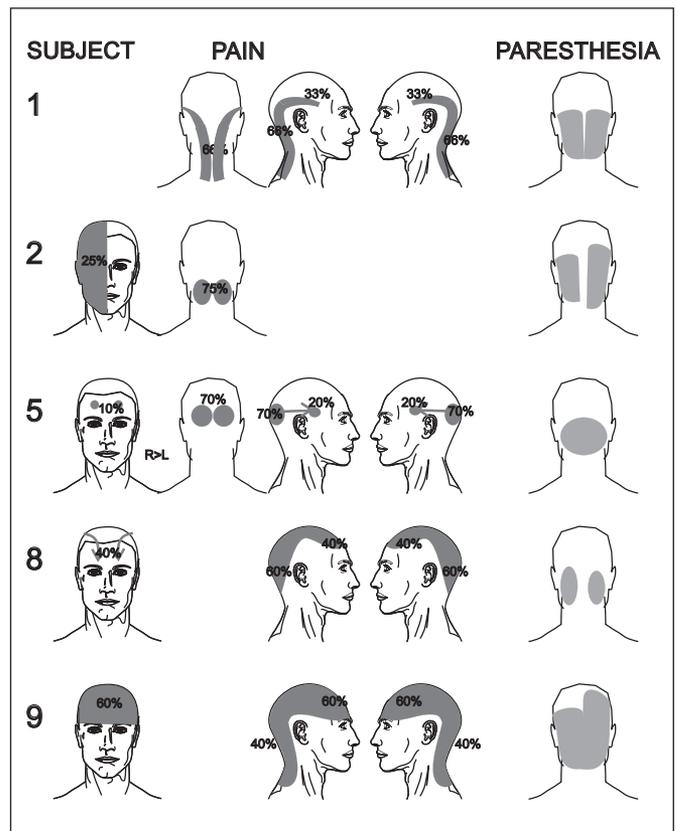


Figure 2: Examples of migraine headache pain locations (A) and paresthesia coverage (B) in patients continuing to use OS. The arrows indicate that the pain travelled in the direction shown. For example, subject 8 described 60% of pain in the occipital region, but when headache became very severe occipitally, it travelled to the frontal region 40% of the time.

RESULTS

The Table reports the demographic details and outcomes in our ten patients. Two patients had buttock placement of the IPG because of multiple abdominal procedures and hernias in one and plans for pregnancy in another. In one patient adequate paresthesia could not be obtained in the operating room during the initial procedure, therefore only one lead was implanted. The patient returned four months later for a delayed surgical placement on the other side.

Surgical complications

In the immediate post-operative period three patients experienced inflammation at surgical sites: two at the suboccipital and one at the abdominal incision. All three received intravenous followed by oral antibiotics although neither blood nor wound cultures identified bacterial growth and none required removal of hardware.

There was one delayed skin erosion in a morbidly obese patient, 21 months after initial implantation. This was the same patient who had an inflammation at the IPG site in the immediate post-operative period. The erosion likely occurred because the IPG rotated in the subcutaneous fat of her abdomen. The system was removed, and re-implanted 11 months later in the subclavicular region. In one patient, the IPG malfunctioned and was replaced 17 months post-operatively. This same patient complained about intermittent non-painful swelling at the IPG and occipital sites, however this was never witnessed by a health care professional.

Other adverse events

The most common adverse event was loss of paresthetic coverage requiring four revisions in four patients. These occurred at variable time points, from immediately to two years post-operatively. The most troubling adverse events involved psychiatric complications. One patient who had apparently stable bipolar disorder pre-operatively, required a three week hospital stay for narcotic addiction ten months post-implant. Another patient who had no prior psychiatric issues, experienced significant depression requiring in-patient management.

Predictors of outcome

Five patients experienced no benefit and their systems were explanted at 7.2-33.9 months. These five subjects were compared to the five who continue to use OS. Details of their outcomes are described in the multicentre study¹⁰ and are not the focus of this article. Instead we compared location of migraine pain on figurines, number of trigger points in the upper body, and co-morbidities at baseline in these two groups, as well as paresthesia coverage of the greater and lesser occipital nerve territories.

There was no significant difference in number of trigger points in the responders (as defined by continuing to use OS three years post-implant) in comparison to the non-responders (as defined by removed OS systems). However of the responders, the proportion of their pain located in the occipital region was 0.62 ± 0.14 , whereas in the failures the proportion was 0.31 ± 0.18 ($t = 3.15$, $p=0.01$). Of the five responding to OS, four had complete or almost complete paresthesia covering both

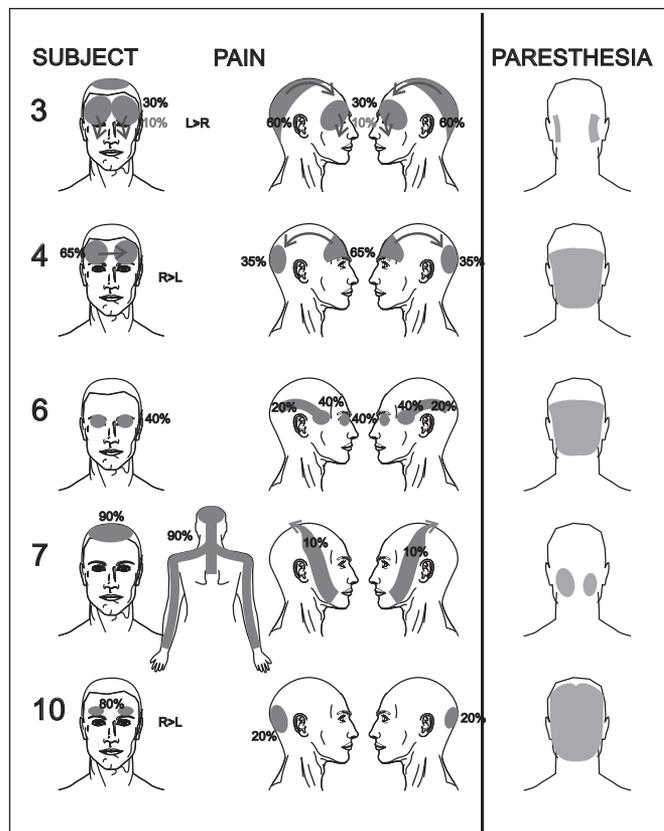


Figure 3: Examples of migraine headache pain locations (A) and paresthesia coverage (B) in patients who failed to achieve benefit with OS.

greater and lesser occipital nerve territories, however in three of the five failures coverage was complete as well, but benefit was not realized. Pre-morbid medical issues, did not always predict outcome. For example, despite more complications in the two obese patients, they both continue to use OS. However, the one subject with a significant prior psychiatric history did not respond and had additional psychiatric issues arise.

DISCUSSION

In summary, based on our experience with ten patients, OS is more likely to provide benefit to migraineurs with predominantly occipital pain. Adverse events associated with OS for migraine are higher than what is usually encountered with spinal cord stimulation¹³⁻¹⁵ despite identical hardware and similar surgery.

There are several possible reasons for the higher complication rate in these patients. There is a learning curve for any new procedure for both surgeons and referring physicians. Also the use of pre-operative psychological screening may reduce the number of psychiatric/psychological complications we encountered. The hardware used for OS was designed for epidural placement. The length of the lead and extension to an abdominal IPG site is long, thereby placing the system at higher risk for displacement. Ideally a shorter lead length, closer placement of the IPG to the site being stimulated or an IPG located within the leads themselves^{8,16} could reduce the risk of

displacement. Presumed infection or inflammation occurred in 30% of patients, far higher than the 5% reported in the SCS population^{15,17}. The midline C2 insertion site may have contributed to infection risk, especially in obese patients with overlapping skin layers. This may be reduced by placement of the leads from lateral mastoid region incisions¹⁸. We can only speculate on the reasons why one large study reported a 24% lead displacement rate over the first three months post-operatively¹⁰ and another study reported only a 8% rate over two years¹¹. While it may have to do with hardware specific to each company, it may also relate to how lead displacement was defined. For example, the PRISM study reported ‘non-target area sensory symptoms’ as a complication. It is possible that this was also related to lead displacement because if stimulation parameters were changed to cover the target territory, the region of paresthesia may also have altered and resulted in “non-target area sensory symptoms”.

There has been minimal discussion in the literature about pain locations responding to OS. Originally OS was used to treat occipital neuralgia and the technique was to stimulate the nerve directly by exposing it and placing the stimulating lead beside it¹⁹. Later these patients were reclassified as suffering from chronic migraine rather than primary occipital neuralgia²⁰. Recent studies seem to have expanded the indications for OS and include everything from fibromyalgia²¹ to unclassifiable facial pains²². In addition, the larger studies have not defined location of pain clearly in their inclusion/exclusion criteria. That is why we operated on patients with such variable locations of pain. We found that those patients with primarily occipital pain were more likely to keep their OS systems after three years than those whose pain was more diffuse or located in other parts of the head and neck. While this should not be surprising, it has not been previously reported. Exact location of pain may not have concerned the trial designers because of the convergence of afferent input from dura supplied by trigeminal nerve and greater occipital C2 fibres onto the trigeminocervical complex in the brainstem and upper spinal cord²². Our finding that those patients with primarily occipital pain were more likely to keep their OS systems after three years than those whose pain was more diffuse or located in other parts of the head and neck requires confirmation in a larger patient group. If confirmed, it could provide prognostication, suggest appropriate patient selection, and may even suggest alternative hypotheses about OS mechanisms of action. Most recently electrodes have been placed in other head and neck sites^{23,24}, likely because OS alone was not covering the area of pain. Perhaps patients with a lot of pain outside the occipital region may still be candidates for neuromodulation, but other regions may need to be stimulated as well.

CONCLUSIONS

In summary, while OS may be a reasonable treatment option for intractable migraine, the location of headache pain is an important determinant of long term outcome. In addition, complication rates, both surgical and psychiatric are higher than those seen with SCS and suggest that the instrumentation for OS as well as the screening criteria should be optimized for future clinical trials.

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DECLARATION

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