

Peripheral occipital nerve stimulation to treat chronic refractory migraine

Peripheral nerve stimulation of the occipital nerve has a favourable efficacy to safety profile for chronic migraine, which is notoriously difficult to treat. This article covers the rationale, surgical procedure and clinical data for this treatment option.

Migraine is the most common neurological disorder in the developed world. National and international prevalence surveys have estimated the adult prevalence of migraine at approximately 12%; 17% in women and 6% in men (Stovner et al, 2007). This means that approximately eight million people have migraine in the UK. Migraine is characterized by attacks of moderate-to-severe, often unilateral headache, frequently accompanied by non-headache symptoms such as nausea, photophobia, phonophobia and, less frequently, vomiting. Patients are typically symptom free between attacks (Headache Classification Committee of the International Headache Society, 2004). Multiple therapies exist for the symptomatic management of migraine, including over-the-counter medications, prescription-only drugs and complementary therapies. However, migraine remains under-diagnosed and under-treated, despite the high prevalence and the therapeutic options available to sufferers (Lipton et al, 2000).

Migraine not only imparts a significant burden on the patient as a result of the symptoms and reduced quality of life, but also on the patient's family and the health-care system. Migraine negatively affects family relationships, social lives and productivity (Lipton et al, 2003a). There is also a significant effect on the national economy. Steiner et al (2003) estimated that there are 190 000 migraine attacks daily in the UK and for every 10 000 migraine patients the health-care resource use amounted to 28 000 GP visits, 5000 emergency room visits and six hospitalizations per year. In any given year a GP practice of 2000 patients had 40 existing migraine patients and five new patients. UK migraine costs have been estimated to be £1.913 billion, representing 0.5% of GDP or a 1 p increase on the basic rate of tax. In 2001, prescription drug costs within primary care were more than £60 million, and lost work time and work effectiveness amounting to £1.5 billion (Lipton et al, 2003b).

In some migraine sufferers, the condition becomes chronic as a result of biological factors or the overuse of symptomatic medications (Dowson et al, 2005). In the latest classification of the International Headache Society (Olesen et al, 2006), chronic migraine is classified as a complication of migraine with sufferers experiencing ≥ 15 headache days per month for ≥ 3 months without medication overuse and with ≥ 8 days per month with migraine

symptoms. Population-based studies give estimates of chronic migraine prevalence of 1.3–2.4% (Natoli et al, 2010) and it is the most common disorder encountered in headache specialist clinics (Dowson, 2003). The progression of episodic to chronic migraine was estimated as varying between 3 and 14% per year (Katsarava et al, 2004).

Chronic migraine is more severe and more difficult to treat than episodic migraine (Blumenfeld et al, 2011), where attacks occur on < 15 days per month (Headache Classification Committee of the International Headache Society, 2004). Until recently, no specific and licensed therapy for chronic migraine was available. Patients were usually prescribed preventive therapies used for episodic migraine, e.g. a beta-blocker, antiepileptic drug or antidepressant. While these therapies may be effective for chronic migraine, there is little evidence for their efficacy in large randomized, placebo-controlled clinical trials. A large controlled trial demonstrated the effectiveness of botulinum toxin type A (Botox, Allergan, Marlow, UK) in chronic migraine (Dodick et al, 2010) and it is now licensed in the UK for use in patients who have failed on other preventive therapies.

More treatments are urgently required for this refractory condition, and peripheral nerve stimulation of the occipital nerve or greater occipital nerve stimulation may offer a viable therapeutic option. This article reviews the rationale behind this treatment, details the surgical procedure and summarizes available clinical data in chronic migraine and other headache subtypes.

Rationale for using occipital nerve stimulation in chronic migraine

Migraine is now recognized as a brain disorder rather than one of blood vessels. Current theories indicate that migraine results from an abnormal neuronal excitability within the cerebral cortex, in part possibly because of reduced magnesium levels and increased levels of glutamate and calcium, which creates susceptibility for cortical

Mr Keyoumars Ashkan is Neurosurgeon in the Department of Neurosurgery and **Dr Andrew Dowson** is Headache Specialist in the Department of Neurology, King's College Hospital, London SE5 9RS

Correspondence to: Mr K Ashkan (k.ashkan@nhs.net)

spreading depression and peripheral sensitivity of the trigeminal vascular system (Pietrobon and Striessnig, 2003). Each trigeminal ganglion cell projects to the pia arachnoid, its blood vessels and the dura mater. The dura and blood vessels generate pain that is escalated by plasma protein extravasation mediated by neuropeptides. Central projections of trigeminal ganglion cells lie in the trigeminal nucleus caudalis. The pathway then follows a reflex arc to the parasympathetic outflow and passes through the superior salivatory nucleus, the cranial ganglia and sphenopalatine ganglia before finally reaching the meninges, resulting in vasodilatation and pain. Therefore, central modulation of migraine occurs in addition to the mechanisms of cortical depression and extravasation. Activation of the brainstem during migraine has been demonstrated by positron emission tomography studies (Weiller et al, 1995; Bahra et al, 2001).

The greater occipital nerve is the medial branch of the posterior C2 and C3 primary sensory divisions of the cervical nerves, along with the lesser occipital nerve (C3). It emerges between the posterior arch of C1 and the lamina of C2, ascending and piercing the semispinalis and trapezius muscles near their attachment on the occipital skull medial to the occipital artery. These nerves supply the posterior scalp over the vertex via the superficial fascia. The occipital nerves provide access into the trigeminocervical pathways of migraine and cluster headache, and neuromodulation via occipital nerve stimulation is hypothesized to inhibit the system.

Mechanism of action

Currently there are two proposed theories for the potential mechanism of action of occipital nerve stimulation in the alleviation of chronic migraine.

The first theory states that occipital nerve stimulation is clinically effective through the same mechanisms proposed to explain the clinical efficacy of spinal cord stimulation for chronic pain management, i.e. the gate control theory of pain (Melzack and Wall, 1965). In this theory, stimulation of large diameter nerve fibres (touch, pressure and vibration) counteracts the nerve transmission within the small diameter pain nerve fibres. The large diameter transmission excites the inhibitory cells within the dorsal horn, 'closing' the gate to transmission of pain signals to the brain.

The second theory proposes that retrograde activation of the C2 and C3 nerve roots through occipital nerve stimulation modulates the brainstem nuclei involved in the trigeminal vascular system, thereby dampening or inhibiting migraine attacks. A positron emission tomography study evaluating eight patients who underwent occipital nerve stimulation demonstrated significant blood flow changes in the dorsal rostral pons, anterior cingulate cortex and cuneate nucleus, suggesting that occipital nerve stimulation induced modification of the brainstem trigeminal vascular system involved in migraine attacks (Matharu et al, 2004).

Surgical procedure

Occipital nerve stimulation is a minimally-invasive surgical procedure involving subcutaneous placement of electrodes in the sub-occipital region of the scalp. The electrodes are connected to an implantable pulse generator similar in appearance to a cardiac pacemaker, which is usually placed in a subcutaneous pocket below the clavicle. The electrodes deliver mild electrical stimulation to the occipital nerves.

The procedure may be performed under general or local anaesthesia (with or without light sedation). A 2 cm vertical skin incision is made at the level of the C1 lamina in the midline. Then a Touhy type needle is inserted subcutaneously through the incision in the back of the neck, aiming laterally towards the midpoint of a line joining the external occipital protuberance and the mastoid process. The electrodes are advanced through the needle and positioned superficial to the cervical musculature and fascia transversing the occipital nerves, unilaterally or bilaterally, usually at C1 vertebral level and often under fluoroscopic control. The electrodes are then connected to the pulse generator which is most commonly placed in a subclavicular subcutaneous pocket. Other potential sites for the pulse generator, based on the patient's choice, include the abdomen or the buttocks, in which case an extension cable is required to connect the electrode to the generator. The total procedure time is typically 1 hour, allowing the treatment to be offered as a day case.

Once the patient has recovered from the surgery, the stimulation parameter set is programmed by radiofrequency waves using a physician programmer to generate pleasant paraesthesia over the distribution of the occipital nerves. Multiple parameters and electrode combinations can be chosen to optimize the stimulation, which is readily adjustable. It is usual for the patient to require a number of reprogramming sessions in an outpatient setting to optimize the stimulation.

The patient is usually provided with a hand-held personal programmer allowing him/her to adjust the stimulation within predefined physician-set limits, with the aim of maintaining therapeutic stimulation.

Clinical data

Two randomized, double-blind, controlled studies have investigated the efficacy and tolerability of occipital nerve stimulation in chronic migraine.

In a prospective, multicentre, double-blind, randomized and controlled study, patients received active stimulation ($n=105$) or non-active stimulation ($n=52$) for 12 weeks and then continued in an open-label phase until a 52-week evaluation (Silberstein et al, 2012). Outcome assessments used the Zung Pain and Distress Scale, the Migraine Disability Assessment (MIDAS) questionnaire, visual analogue scale (VAS), and patient-reported headache relief, satisfaction, quality of life, procedure assessment and adverse events.

A total of 153 patients completed the 12-week double-blind period. Significantly more patients in the active group than in the control group reported an improvement on the Zung Pain and Distress Scale (20% *vs* 8%), MIDAS scale (41% *vs* 13%) and headache relief assessments. A total of 35.2% of patients in the active group achieved a 30% reduction in their VAS score compared with 11.5% of the control group. Statistical significance was demonstrated across most outcome measures at 12 weeks. The primary end point (specified by the US Food and Drug Administration) of a minimum of 50% pain reduction as measured by VAS was not met, but a significant difference was observed between the groups at the 40% VAS reduction level.

Patients in the active group reported 43.3% and 49.5% headache relief at 24 and 52 weeks post-implant respectively, and the majority of patients scored their headache relief as either good or excellent and reported improved quality of life (67% *vs* 17% on non-active treatment) at both time points. The active stimulation group reported a 28% reduction of headache days, which represented an additional seven headache-free days per month compared with one additional day of headache in the control group. A total of 76.1% of patients indicated they would undertake the procedure again, 88.2% that they would recommend the therapy to other chronic migraine sufferers, and 67% of patients were either satisfied or very satisfied with their outcome. One per cent of patients reported serious adverse events, which were related to the device or the procedure.

The ONSTIM prospective, multicentre, randomized, placebo-controlled, double-blind feasibility study (Saper et al, 2011) enrolled 110 migraine patients to recruit 75 assigned to the treatment group. Patients had suffered from migraine for an average of 22 years, of which 10 years were defined as chronic migraine. They had approximately 23 days of headache per month with pain in the distribution of the occipital nerves and were intractable to two or more classes of preventive medications. Patients were randomized into three groups: adjustable stimulation (33 patients), pre-set stimulation for 1 minute daily (sham stimulation, 17 patients), and medical management (17 patients). The patients are currently being followed up for 36 months in an open-label study.

Diary data were available for 66 patients at the 3-month follow up to evaluate the primary end point of a minimum 50% reduction of headache days per month or a minimum 3-point reduction in average overall pain intensity compared with baseline. Three-month responder rates meeting the primary end point were 39% (adjustable stimulation), 6% (pre-set stimulation) and 0% (medical management) respectively, demonstrating that active occipital nerve stimulation had a better clinical effect than sham stimulation or no stimulation. At 3 months the reduction of actual headache days per month in the adjustable stimulation, pre-set stimulation and medical management groups were 6.7 ± 10.0 , 1.5 ± 4.6 and $1.0 \pm$

4.2 respectively. The reduction in pain intensity was 1.5 ± 1.6 , 0.5 ± 1.3 and 0.6 ± 1.0 respectively, and the reduction of actual days living with prolonged severe headaches was 5.1 ± 8.7 , 2.2 ± 6.4 and 0.8 ± 5.6 respectively.

A case series in 25 patients with chronic migraine showed substantial reductions in pain and disability following treatment with occipital nerve stimulation (Popeney and Aló, 2003). Before treatment, all patients experienced severe disability and reported an average of 75.6 headache days per 3 months. Following treatment, 16 patients reported mild or no disability and the mean MIDAS score reduced from 121 to 15. The number of headache days per 3 months was reduced to 37.5.

One study reported on the long-term efficacy of occipital nerve stimulation in 15 patients (eight with chronic migraine and three with chronic cluster headache) with refractory headaches for a mean of 19 months' (range 5–42 months) treatment (Schwedt et al, 2007). All six mean headache measures used were statistically improved from baseline. Headache frequency per 90 days improved by 25 days from a baseline of 89 days, headache severity (on a 0–10 scale) improved 2.4 points from a baseline of 7.1 points, MIDAS disability improved 70 points from a baseline of 179 points, Headache Impact Test-6 scores improved 11 points from a baseline of 71 points, depression (assessed by Beck's Depression Inventory-II) improved eight points from a baseline of 20 points and the mean subjective improvement in pain was 52%.

A prospective non-randomized study investigated a cohort of 50 patients (45 with chronic headache or chronic migraine) treated with occipital nerve stimulation for 2 years (Ellens and Levy, 2011). Non-interested third parties stated that 83% of patients reported good to excellent pain relief. All patients were willing to undertake the procedure again and all refused to have the neurostimulation system taken out.

Occipital nerve stimulation has also demonstrated efficacy against other headache subtypes. Three small studies in patients with medically refractory chronic cluster headache demonstrated that occipital nerve stimulation was a potentially effective treatment for this serious condition (Magis et al, 2007; Burns et al, 2007, 2009a). Two studies showed efficacy was maintained after 18 (Burns et al, 2009a) and 20 (Burns et al, 2007) months of treatment. Occipital nerve stimulation was also shown to be effective over 13.5 months of treatment among a small group of six patients with hemicrania continua (Burns et al, 2009b).

A long-term retrospective study in 26 patients with refractory headaches evaluating clinical efficacy also examined the phenotypes that responded well to occipital nerve stimulation (Paemeliere et al, 2010). The mean duration of follow up was 36 months (range 7–87 months). Patients reported a mean long-term pain relief of 63% (range 0–100%) and 81% of patients experienced a minimum of 50% long-term pain relief. A detailed examination of the pain relief data revealed significant improvement in the 'actual pain', 'lowest pain last week', 'mean pain last week'

and 'percentage of time pain free'. There was also significantly improved sleep quality, significant reduction of daily medication intake and increased social activities among the patients. After phenotyping, two main groups of responders emerged: eight patients had 'migraine without aura' and eight patients 'constant pain caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions'.

Four small studies of patients with occipital neuralgia also showed that most patients reported pain relief after occipital nerve stimulation treatment (Weiner and Reed, 1999; Oh et al, 2004; Slavin et al, 2006; Melvin et al, 2007).

These studies indicate that occipital nerve stimulation has potential in the treatment of several types of chronic intractable headaches. The best evidence derives from studies in chronic migraine, but the technique may also be effective in chronic cluster headache and occipital neuralgia. However, randomized, placebo-controlled studies are needed to confirm efficacy in the latter two indications.

Adverse events

In the large controlled study of occipital nerve stimulation in chronic migraine (Silberstein et al, 2012), the most common adverse events in the active group were lead migration (14.3%) and persistent pain or numbness at the lead site (13.3%). The ONSTIM Study (Saper et al, 2011) reported the most frequent adverse events as lead migration (24%) and infections (14%) within the initial 3-month follow-up period.

Lead revisions were reported to be the most frequently recorded adverse event in other studies (Weiner and Reed, 1999; Oh et al, 2004; Burns et al, 2007; Magis et al, 2007; Melvin et al, 2007; Schwedt et al, 2007). Lead revisions may be related to procedural learning technique, since established centres gaining on incremental experience plus improved anchoring and procedural improvements reported significantly reduced lead migration complications.

Role of occipital nerve stimulation in therapy

Occipital nerve stimulation is indicated in chronic migraine sufferers who are either refractory to, have failed or are unsuited to alternative therapies. Suitable chronic migraine patients for occipital nerve stimulation should be selected by a multidisciplinary team comprising at least a headache specialist and a neurosurgeon skilled in neuromodulation surgery. The following criteria may prove useful in the clinic when selecting patients:

- The patient has a diagnosis of chronic migraine according to the latest International Headache Society criteria (Olesen et al, 2006)
- The headache pattern has been present for a minimum of 12 months
- The patient is managed appropriately for medication overuse by the withdrawal of overused medications and appropriate treatment of withdrawal symptoms (Dowson et al, 2005)

- The patient is refractory to or intolerant of at least three different classes of preventive medications
- Pain is characterized as migraine pain limited between C3 and the vertex, pain located within occipital and sub-occipital areas within the fields of the greater and/or lesser occipital nerves, and unilateral or bilateral pain.

Once patients undergo occipital nerve stimulation, it is important that they are kept under long-term follow up. The following pointers may be useful when considering the effects of stimulation:

- If there is an early response, i.e. a reduction in headache frequency, occipital nerve stimulation treatment can be continued without change.
- If there is no early response, adjustments can be made, e.g. retuning and checking the battery and wires. This can also be done if there is an early response and a failure later.
- If treatment fails in the long term or there are intolerable side effects, then occipital nerve stimulation treatment can be stopped. It is unusual to have to remove the device itself.

Occipital nerve stimulation may also be a suitable treatment for patients with refractory chronic cluster headache. *Figure 1* suggests a management algorithm for occipital nerve stimulation in chronic migraine and chronic cluster headache. If the procedure is performed within the already established neuromodulation services experienced in managing headaches and pain, it is unlikely that any significant additional resources would be needed. Patients may then be referred locally, regionally and possibly nationally to such teams.

Conclusions

Occipital nerve stimulation is a relatively non-invasive surgical procedure with a favourable efficacy to safety profile for chronic migraine. There are numerous publications on its clinical effectiveness on all features of the headache, including improvements in pain, disability, headache days, headache severity and headache frequency, and the device is well accepted by patients. A surgical device for occipital nerve stimulation was approved for chronic migraine in the UK by the Medicines and Healthcare Products Regulatory Agency in September 2011, and is likely to be indicated for chronic migraine sufferers who are refractory to or are unsuited to alternative therapies. Occipital nerve stimulation, together with other innovative therapies (e.g. botulinum toxin type A), offers the promise of effective treatments for this often intractable condition, improving patients' lives and reducing the burden of the illness on society. **BJHM**

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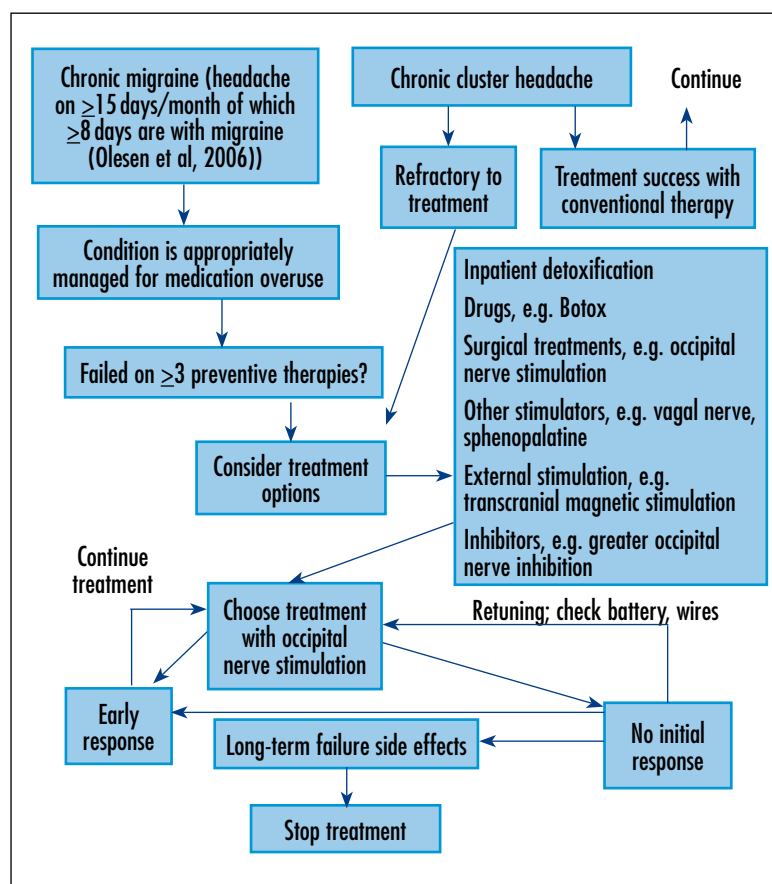
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Figure 1. Proposed algorithm for use of occipital nerve stimulation in chronic migraine and chronic cluster headache.



KEY POINTS

- Chronic migraine is a disabling condition which is more severe and more difficult to treat than episodic migraine.
- Few approved treatments are available for this condition.
- Occipital nerve stimulation is a relatively non-invasive surgical procedure with the scientific rationale to be effective in a range of headache disorders.
- Occipital nerve stimulation is effective for the treatment of chronic migraine and possibly also in other disabling headache disorders.