



Occipital nerve stimulation for chronic headache—long-term safety and efficacy

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Cephalalgia

Schwedt TJ, Dodick DW, Hentz J, Trentman TL & Zimmerman RS. Occipital nerve stimulation for chronic headache—long-term safety and efficacy. *Cephalalgia* 2007; 27:153–157. London. ISSN 0333-1024

The aim of this study was to examine the safety and efficacy of occipital nerve stimulation for medically intractable headache. Electrical stimulation of large sensory afferents has an antinociceptive effect. Occipital nerve stimulation may be effective for the treatment of medically intractable headache. Retrospective analysis was performed of 15 patients with medically refractory headache who underwent implantation of an occipital nerve stimulator. Pre- and postimplant data regarding headache frequency, severity, disability, depression and post-stimulator complications were collected. Twelve patients were female and three male. Ages ranged from 21 to 52 years (mean 39 years). Eight patients had chronic migraine, three chronic cluster, two hemicrania continua and two had post-traumatic headache. Eight patients underwent bilateral and seven had unilateral lead placement. Patients were measured after 5–42 months (mean 19). All six mean headache measures improved significantly from baseline ($P < 0.03$). Headache frequency per 90 days improved by 25 days from a baseline of 89 days; headache severity (0–10) improved 2.4 points from a baseline of 7.1 points; MIDAS disability improved 70 points from a baseline of 179 points; HIT-6 scores improved 11 points from a baseline of 71 points; BDI-II improved eight points from a baseline of 20 points; and the mean subjective percent change in pain was 52%. Most patients (60%) required lead revision within 1 year. One patient required generator revision. Occipital nerve stimulation may be effective in some patients with intractable headache. Surgical revisions may be commonly required. Safety and efficacy results from prospective, randomized, sham-controlled studies in patients with medically refractory headache are needed. □ Cluster headache, hemicrania continua, migraine, occipital nerve stimulation, post-traumatic headache

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Introduction

Occipital nerve stimulation (ONS) may be useful for the treatment of patients with chronic and disabling head pain that is unresponsive to medical therapy. Electrical stimulation of the occipital nerves may have an antinociceptive effect in the direct territory of these nerves as well as in trigeminally innervated locations. Herein we report safety and efficacy data on 15 patients who underwent

ONS placement for the treatment of medically refractory chronic headaches.

Methods

This study was approved by the Mayo Clinic institutional review board. Fifteen patients underwent ONS for the treatment of chronic and disabling headaches that were recalcitrant to medical therapy. Patients considered for ONS were identified in our

headache specialty clinic. Each of the patients had failed to respond to prophylactic medications from several different classes, including combination pharmacotherapy, and none was felt to be suffering from rebound headaches. Each patient suffered from head pain that involved the C2 distribution with or without pain in other regions of the head. A neurologist specializing in headache was responsible for headache classification according to International Headache Society (IHS) diagnostic criteria. Each subject was also evaluated by one neurosurgeon and one anaesthesiologist specializing in pain, and all underwent psychiatric evaluation. Thirteen of 15 patients underwent occipital nerve blockade prior to temporary stimulator placement. All subjects underwent a percutaneous stimulator trial prior to permanent placement. During this 5–7-day trial, efficacy and tolerability were measured. Permanent ONS implant was performed within 1 month of the trial.

Implantation technique was modelled after the procedures described by Weiner (1). Subjects were implanted with Pisces Quad Plus leads and Synergy implantable pulse generators (IPGs) from Medtronic Inc.[®] (Minneapolis, MN, USA). Stimulation was unilateral in subjects with strictly ipsilateral head pain and bilateral in all others. Leads were secured to fascia at the C1 level with a spacing of 12 mm. Leads were tunneled to an extension connector site in the periscapular region. Extensions were then tunneled to the IPG in the upper buttocks, lower abdomen, or in the infraclavicular region. All patients underwent intraoperative stimulator testing during permanent placement.

Subjects were able to control their stimulator use and adjust their stimulation amplitude and frequency. Subjects were instructed to use and adjust their stimulator per effect. Stimulator settings including amplitude, pulse width and frequency were collected. Data regarding the duration of daily ONS were collected. As this was an open-label study, patients made changes in their headache medications during the period of follow-up.

Data including patient demographics, frequency and severity of headaches, Migraine Disability Assessment (MIDAS) disability scores, Headache Impact Test 6 (HIT-6) scores and Beck Depression Inventory II (BDI-II) scores were collected pre and post ONS. Headache frequency was measured by asking the patient to report the number of days with headache during the previous 3 months. Headache severity was measured by asking the patient to rate how painful the headaches were during the previous 3 months on a scale from 0

(none) to 10 (worst) points. In addition, all subjects were asked to rate subjectively their percentage change in overall pain with ONS. Post-stimulator complications and adverse events were collected. The data were collected at clinic visits and via telephone interviews.

The primary outcome measures were the six headache measures. The mean level at follow-up was compared with the mean at baseline and the statistical significance was calculated using the paired *t*-test. The mean percent change in pain was compared with 0% and the statistical significance was calculated using the one-sample *t*-test. We accounted for six multiple comparisons by using the Holm method. Assumptions about the sampling distributions were checked by using bootstrap resampling. The relationships between the changes and follow-up time were explored using scatterplots. We also report the percentage of patients whose disability score changed by at least one grade and confidence intervals (CI) were calculated using the exact binomial method. The incidence of adverse events was calculated using the Kaplan–Meier method.

Results

Fifteen patients underwent a temporary stimulator trial. All tolerated stimulation and had significant analgesia and thus all had ONS implantation. IHS headache diagnoses were as follows: eight chronic migraine, three chronic cluster, two post-traumatic headache and two hemicrania continua. Indomethacin was effective in both hemicrania continua patients, but had to be discontinued secondary to adverse side-effects including bleeding and nausea/vomiting. There were 12 females and three males with an age range from 21 to 52 years (mean 39 years). Follow-up measurements were collected at 5–42 months (mean 19 months).

Ten of 13 patients who had undergone occipital nerve blockade prior to temporary stimulator placement had C2 analgesia for 24 h to 7 days. Eight subjects had bilateral electrode placement and seven had unilateral placement. Datasets were available from all patients with the exception of HIT-6 and BDI-II scores, which were available from 14. Twelve patients stimulated continuously, whereas three used intermittent stimulation. Specific data regarding stimulator settings in these patients will be reported elsewhere. However, a representative group stimulated with a mean amplitude of 2.6 V (range 0.1–6.7 V), a mean pulse width of 399 μ s (range 240–450 μ s) and a mean

Table 1 Change from baseline headache measures among patients treated with occipital nerve stimulation

| | N | Baseline, mean (SD) | Follow-up, mean (SD) | Change | | |
|--------------------------|----|------------------------|-------------------------|-------------|------------|--------|
| | | | | Mean (SD) | 95% CI | P |
| Frequency (/90 days) | 15 | 88.8 (4.6) | 63 (39) | -25 (40) | -48, -3 | 0.03 |
| Severity (0-10) | 15 | 7.1 (1.3) | 4.7 (2.2) | -2.4 (1.7) | -3.4, -1.4 | <0.001 |
| MIDAS Disability (0-450) | 15 | 178 (80) | 109 (92) | -70 (77) | -112, -27 | 0.004 |
| HIT-6 (36-78) | 14 | 71.4 (5.4) | 60 (11) | -11.1 (9.6) | -17, -6 | 0.001 |
| BDI (0-63) | 14 | 20 (12) | 12.4 (7.6) | -8 (12) | -15, -1 | 0.03 |

MIDAS, Migraine Disability Assessment; HIT-6, Headache Impact Test 6; BDI, Beck Depression Inventory.

Table 2 Incidence of adverse events (and number at risk) among patients with occipital nerve stimulation

| | Post-op | 6 months | 1 year | 2 years | 3 years |
|-------------------------------|----------|----------|----------|----------|----------|
| Lead migration | 0% (15) | 33% (14) | 60% (10) | 60% (10) | 100% (8) |
| Battery died | 0% (15) | 0% (14) | 19% (10) | 42% (7) | 42% (5) |
| Neck stiffness | 13% (15) | 13% (14) | 13% (11) | 13% (7) | 13% (5) |
| Battery site pain | 7% (15) | 7% (15) | 7% (10) | 7% (6) | 7% (4) |
| Contact dermatitis | 7% (15) | 7% (14) | 7% (10) | 7% (6) | 7% (4) |
| Lead site pain | 7% (15) | 7% (14) | 7% (9) | 7% (6) | 7% (4) |
| Myofascial incision site pain | 7% (15) | 7% (14) | 7% (10) | 7% (6) | 7% (4) |
| IPG revision | 0% (15) | 7% (14) | 7% (10) | 7% (6) | 7% (4) |

IPG, implantable pulse generator.

pulse rate of 38 Hz (range 25-60 Hz). Follow-up ranged from 5 to 42 months with an average of 19.5 months (Table 1).

All six headache measures were significantly better at follow-up than at baseline (Table 1). None of the measures showed a strong relationship with the duration of follow-up.

Headache frequency per 90 days decreased by nearly one-third from the baseline mean of 89 days. Headache severity decreased by a mean of 2.4 points, which is more than 20% of the range of the scale for severity.

The mean patient-reported change in headache pain was a 52% reduction (SD 35%, 95% CI 43, 61; $P < 0.001$). Sixty percent of the patients reported at least 50% reduction in headache pain (95% CI 32, 84). None of the patients reported worsening of pain (95% CI 0, 22).

MIDAS Disability scores improved by a mean of 70 points from a baseline mean of 178 points. Two-thirds of the patients had Grade IV disability at baseline. This change was substantially larger than the 21-point difference between the cut-off levels for Grade I and Grade IV disability. The midpoints for Grades I-III differ by less than eight points. The improvement was 16% of the maximum range of the scale. Despite the high mean score at

baseline, one-third of the patients improved by at least one grade level (95% CI 12, 62). No patient advanced to a higher grade level (95% CI 0, 22). In terms of the mean number of days per item of the MIDAS scale, a change of 70 points corresponds to 14 fewer days of disability per item per 90-day period.

HIT-6 scores improved by a mean of 11 points from a baseline mean of 71 points. The improvement was 26% of the range of the scale. In comparison, a change of three points has previously been correlated with significant clinical change (2).

BDI-II scores also improved by a mean of eight points from a baseline mean of 20 points. Changes of five to nine points have been defined as 'minimal change', 10-19 points as 'moderate change', and ≥ 20 points as 'large change' (3). According to these definitions, four of 14 patients had minimal reduction, three had moderate reduction, two had large reduction, three had no change and two had a minimal increase.

The most common adverse event was lead migration (Table 2). While 8/15 patients required surgical revision due to lead migration, the need for such a revision may depend on the length of follow-up. All patients who had 3 years of follow-up had lead migration and required revision. Therefore, lead

migration requiring surgical revision may be even more common after an adequate length of follow-up. Using current methods, most patients are expected to have lead migration within 1 year. Approximately 20% of patients are expected to require battery replacement within 1 year and 40% are expected to require battery replacement within 3 years.

Discussion

The results of this study suggest a role for ONS in the treatment of medically refractory headaches. There were significant reductions in headache frequency, severity, headache-related disability and depression with ONS therapy. Nine of 15 patients (60%) had $\geq 30\%$ reductions in headache severity and/or frequency, with eight of the nine having $\geq 50\%$ reduction in severity and/or frequency. Subjectively, nine of 15 (60%) subjects reported a $\geq 50\%$ reduction in their overall pain. Surgical revisions were common in this study. Nine of 15 patients required a surgical revision, including eight lead revisions and one IPG revision.

Although all six headache measures were significantly better at follow-up, some individuals did not have headache improvement after permanent ONS implantation, despite improvement during the temporary stimulator trial. Although it is not clear why these patients did not respond to permanent implantation, it is hypothesized that the therapeutic effect of stimulation simply did not endure to the time of outcome measurement. Outcomes related to the temporary stimulator trial were measured at 5–7 days, while outcomes from permanent implantation were measured at 5–42 months (mean 19 months). Second, the non-specific effects of therapy may have been greater during the stimulator trial and may have waned during the longer follow-up after permanent implantation.

Previous studies have analysed the safety and efficacy of ONS for the treatment of occipital neuralgia and migraine (1, 4–8). Each of these studies has suggested significant improvement in the frequency and/or severity of pain with the use of ONS. Minor adverse events and surgical revisions were common. This study adds to our existing body of knowledge by providing a larger number of patients with a variety of headache types, longer duration of follow-up, and other clinical outcome variables measuring headache-related disability (MIDAS, HIT-6), depression (BECK) and patient global assessment of change in pain scores.

The mechanism(s) of action of ONS in headache is unclear. However, electrical stimulation of large sensory afferents has an antinociceptive effect, which is likely to be due in part to the suppression of small c-fibre and a-delta fibre nociceptive input at the level of the spinal dorsal horn (9–13). In addition, because the occipital nerve represents the peripheral (C2) anatomical and functional extension of the trigeminal cervical complex, its stimulation may inhibit central nociceptive trafficking (14–17). In addition, functional brain imaging in chronic headache patients undergoing ONS has demonstrated the possibility that central pain-modulating circuits are activated in these patients during stimulation (4).

The limitations of this analysis are several, including those inherent in any unblinded study. However, these results support previous observations in the literature and lend support to the need for prospective, randomized, blinded, controlled studies using this modality in patients with chronic headache. Though patients with several different headache subtypes were evaluated, the numbers within each group were too small to draw any conclusions on the differential effect of ONS in any single population. The data were incomplete for one patient (HIT-6 and Beck scores were unavailable), but this patient had a $>50\%$ reduction in headache severity and an 80% reduction in the subjective global impression of change in pain, so the overall benefit with regards to headache-related disability and depression for the group was likely to be underestimated rather than amplified. Lastly, surgical methods and placement of the device differed slightly among patients and evolved over time due to changes in technique to anchor the leads securely so as to prevent migration. Lead anchoring techniques, methods of stress relief of the leads and the location of IPG placement are likely to alter the risk of lead migration and the need for surgical revisions.

Conclusion

The results of this retrospective study are preliminary, but suggest the possibility that some patients who have medically refractory headache respond to ONS. Larger samples are needed in order to measure accurately the effect of treatment for specific types of headache. Controlled studies are needed in order to separate the effect of treatment from the possibility of regression to mean. The need for surgical revision was high, required in all patients who were followed for 3 years. If this

modality proves effective for severe chronic headache, engineering and/or surgical improvements will undoubtedly be required to reduce the chance of technical failure and the need for surgical revisions.

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