Phenotype of patients responsive to occipital nerve stimulation for refractory head pain

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Abstract

Occipital nerve stimulation (ONS) has been employed off-label for medically refractory head pain. Identification of specific headache diagnoses responding to this modality of treatment is required. Forty-four patients with medically refractory head pain and treated with ONS were invited to participate in a retrospective study including a clinical interview and, if necessary, an indomethacin test to establish the headache phenotype according to the International Classification of Headache Disorders Second Edition (ICHD-II). We gathered data from questionnaires before implantation, at one month after implantation, and at long term follow-up. Twenty-six patients consented and were phenotyped. At one month follow-up and at long term follow-up a significant decrease in all pain parameters was noted, as well as in analgesic use. Quality of sleep and quality of life improved. Patient satisfaction was generally high as 80% of patients had ≥ 50% pain relief at long term follow-up. The overall complication rate was low, but revisions were frequent. After phenotyping two main groups emerged: eight patients had “Migraine without aura” (ICHD-II 1.1) and eight patients with “Constant pain caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions” (ICHD-II 13.12). Overuse of symptomatic acute headache treatments was associated with less favourable long term outcome in migraine patients. We conclude that careful clinical phenotyping may help in defining subgroups of patients with medically refractory headache that are more likely to respond to ONS. The data suggest medication overuse should be managed appropriately when considering ONS in migraine. A controlled prospective study for ONS in ICHD-II 13.12 is warranted.

Key words: occipital neurostimulation, refractory headache, neuropathic pain, migraine
Introduction

Headache is among the most common reasons for patients to seek medical care. Migraine, the most common form of disabling primary headache, has been estimated to be the most costly neurological disorder in the European Community (1). While considerable developments have been made in understanding and treating primary headache, there remains a group of patients with difficult to treat headache problems, labeled generically as medically intractable headache (2). In general terms these patients have frequent, daily or near-daily headache unresponsive to medical therapy. Neuromodulation methods may offer an opportunity to address the needs of these highly disabled patients. In a landmark paper, Weiner and Reed described excellent outcomes with occipital neurostimulation (ONS) in twelve patients, described as having occipital neuralgia (3). On clinical review of this patient cohort and using the International Classification of Headache Disorders, Second Edition (ICHD-II) (4), it became clear that most of them had chronic migraine and one had hemicrania continua. A subsequent PET study in those with chronic migraine (5) demonstrated persistent activation of the dorsolateral pons, as is seen in other imaging studies of migraine (6), and activation of thalamus structures when the device was activated.

Given that there has been off-label use of ONS on compassionate grounds in highly disabled patients, there is an opportunity to classify those patients using the ICHD-II in order to identify potential patient groups for systematic study. Recent experience with chronic cluster headache suggests that ONS may be helpful that disorder (7, 8). Indeed other modalities of stimulation have begun to be used in chronic cluster headache, specifically deep brain stimulation and these are also proving highly promising (9). Data from the first randomized, controlled, prospective trial for ONS for the Treatment of Intractable Migraine headache
(ONSTIM trial) have recently become available in abstract form (10). The results indicate that ONS may be a promising treatment for some intractable chronic migraine patients, and further controlled trials are required. Interestingly, given the hemicrania continua patient in Weiner and Reed’s initial cohort (3), there are nine cases of hemicrania continua treated with ONS now reported in the literature and seven benefited from the therapy (11-13). These cases are important since hemicrania continua is an indomethacin-sensitive headache, which broadens still the range of headache types that may benefit from this approach.

In this retrospective study a cohort of patients, implanted with occipital neurostimulators at a single site were invited to attend a clinical evaluation and, if necessary, to undergo an indomethacin test in order to clarify the diagnosis. We confirm other reports that chronic migraine patients can be treated with this approach adding a note of caution around medication overuse, and identify a previously unreported group, Upper Cervical Neuropathic Pain (ICHD-II, 13.12), who have a promising outcome. This work was presented in preliminary form at the 10th Congress of the European Federation of Neurological Societies (14).
Methods

Forty-four patients were consecutively treated with ONS for medically refractory headache between April 2000 and December 2006 at the AZ Nikolaas Pain Clinic (JPVB, Figure 1). All patients underwent a preoperative psychological evaluation. Informed consent was sought from all patients by letter to review their clinical data, including a pre-implantation questionnaire, a questionnaire at one month following trial stimulation (i.e. before the definitive implantation procedure), as well as technical details: implantation date and procedure; complications such as dislocations, lead fractures, electrical leakage at the connections and infection; and battery replacement. The patients were invited by letter to be interviewed by an independent and blinded headache neurologist at the Department of Neurology of the Ghent University Hospital (KP). If necessary to make a specific headache diagnosis, patients were invited to give their informed consent to undergo an indomethacin test, either intramuscular or oral. The indomethacin tests were performed by the treating physician at AZ Nikolaas Pain Clinic (JPVB). Patients that entered the study were finally invited to fill out the post-implantation questionnaire for a second time at their last visit at AZ Nikolaas Pain Clinic, to obtain long term follow-up data. The Ethics Committees of the Ghent University Hospital in Ghent and the AZ Nikolaas in Sint-Niklaas approved the study (EC/2006/383).

Implantation technique

Initially, the implantation technique described by Weiner and Reed (3) was used. A subcutaneous lead was inserted towards the midline via a lateral incision close to the mastoid process. The procedure was done under propofol sedation with a wake up during the procedure in order to check the area of paresthesia. With growing experience the technique
was adapted and the ONS procedure is now performed under general anesthesia with the patient in the prone position and the head in a horseshoe headrest. The incision is made close to the occiput, where there is more fat tissue that affords a subcutaneous pocket substantial enough for adequate fixation of the lead and leaving a loop. A curved needle (custom made by Medtronic Inc., Bakken Research Center, Maastricht, The Netherlands) is pushed from the occiput towards the mastoid process in the subcutaneous tissue, to cross the greater, lesser and least occipital nerve. The position of the lead is checked with fluoroscopy after the needle has been pulled out. An intermediate incision is made in the suprascapular area, again creating a pocket, and a second loop is left behind. A third incision is made parallel to the spine at the high thoracic level to bury the connection between the lead and the temporary extension lead. The connection is fixated to the underlying tissue. The temporary extension lead is tunneled laterally over the thoracic wall. After a successful trial period of at least one month, a pocket is created in the gluteal area for the implantable pulse generator, a new extension lead is tunneled towards the connector and the new connector is secured to the underlying tissue. Stimulation parameters, including frequency, pulse width and voltage, were adjusted such that all patients experience mild paresthesia in the stimulated area.

Pain questionnaires

The pre- and post-implantation questionnaires were developed by the Belgian Pain Society, and include data on regional distribution of the pain using a pre-printed drawing of the head and body, pain severity scores on a visual analogue scale or VAS from 0-10 indicating ‘pain at present’, ‘worst pain last week’, ‘lowest pain last week’, ‘average pain last week’, percentage pain-free time (0-100%), average daily number of analgesics used, quality of sleep on a scale from 1-5, influence of pain on activities of daily living, social activities, independence of others, hobbies and need for bed rest (all the five using VAS scores on a
scale from 0-10). The post-implantation questionnaire was filled out by every patient after one month of stimulation and by twenty-one patients at long term follow-up. This questionnaire included data on the subjective area of stimulation on a pre-printed drawing, perceived pain relief (‘worse’, ‘too little’, ‘moderate’, ‘largely’, ‘almost complete’, ‘complete’), patient satisfaction (‘excellent’, ‘very good’, ‘good’, ‘moderate’, ‘poor’, ‘no effect’ or ‘worse’), and the question whether the patient would undergo the procedure again for the same indication, but was otherwise identical to the pre-implantation questionnaire.

Clinical interview

During the clinical interview demographic data, analgesic use, all necessary information to make a headache diagnosis according to ICHD-II (4), as well as percentage of pain relief at long term follow-up were recorded. To make a diagnosis of medication-overuse headache the Appendix Criteria were used (15). Patients were instructed not to discuss their pre-implantation diagnosis. All clinical data were made available to a second blinded headache neurologist (PJG) before clinical diagnoses were assigned.

Indomethacin testing

To exclude a diagnosis of paroxysmal hemicrania or hemicrania continua an intramuscular indomethacin test was performed in some patients with strictly unilateral (attacks of) head pain (16). Intramuscular indomethacin tests were performed at the Pain Clinic of AZ Nikolaas. Patients had their stimulator turned off in the morning and recorded pain on a VAS from 0-10 for three hours in a diary. If the head pain reached an intensity of ≥ 5/10 on the VAS, 100 mg indomethacin was injected intramuscularly. Pain scores were recorded each hour afterwards for the rest of the day. Afterwards the patients received instructions to switch the stimulator back on. If the head pain reached an intensity of < 5/10 during the three hours observation
period, instructions were given to perform an ambulatory oral indomethacin test. Patients would record headache intensity on an hourly basis in a headache diary while under indomethacin. Indomethacin was started at 25 mg three times per day for three days. If the patient was not pain-free, the indomethacin dose was increased to 50 mg three times per day for three days. If the patient was not pain-free, the indomethacin dose was further increased to 75 mg three times per day for three days. If the patient was not completely pain-free at that point in time, the oral indomethacin test was deemed negative. Exclusion criteria for an indomethacin test were asthma, renal disease, allergy to acetylsalicylic acid or NSAIDs, active peptic ulcer disease and pregnancy.

Data analysis

The statistical analysis of the data was performed by an independent statistician (GVM) with R, a language and environment for statistical computing (17). Univariate comparison of unpaired groups was done with the Fisher’s Exact test for categorical data and the non-parametric Mann-Whitney U-test for the comparison of continuous variables. The non-parametric Friedman two-way ANOVA test with Wilcoxon matched-pairs signed-ranks test as multiple range test was used to compare measurements over the three time intervals. The significant level was set at $\alpha = 0.05$, two-tailed.
Results

All forty-four patients consented to have their data used from the questionnaires pre-implantation and at one month post-implantation. Twenty-six patients consented to undergo clinical interview, which took place at the Neurology Department of the Ghent University Hospital between December 2006 and April 2007. Data from the questionnaire at long term follow-up were additionally obtained from twenty-one of these twenty-six patients.

Overall safety in all 44 patients

The mean age of all forty-four patients at implantation was 48 years (range 29-75). All forty-four patients had an occipital component to their head pain and eighteen also had a trigeminal component. Twenty-one patients underwent unilateral neurostimulation, ten on the left, eleven on the right, and twenty-three patients had bilateral neurostimulation, using one electrode in nineteen and two electrodes in four. The mean duration of follow-up was 36 months (range 7-87 months). The total device time was 1592 months. Fourteen of the forty-four patients had a total of eighteen revisions. Eleven patients had to have a new lead put in place, in two patients because of dislocation, using the initial technique with a lateral incision (cf. Methods section), and in the other nine patients because of lead fracture, with four of these patients undergoing a second revision again lead replacement. In three cases there was a problem with the connection, with pain due to local current leakage, requiring opening of the connection and cleaning it. There were two instances of infection, one at the level of the lead insert during the trial period, and one later after implantation at the level of the connector due to a small skin defect. Both infections were solved with short term antibiotic treatment.
**Pooled results for the 26 phenotyped patients**

Twenty-six of the forty-four patients (59 %) agreed to be phenotyped. Pooled outcome data for this group are summarized in Table 1. Statistically significant improvements were obtained on all outcome parameters, both at one month follow-up and at long term follow-up when compared to pre-implantation data. The mean percentage long term pain relief was 63 % (range 0-100 %), and 81 % (21 of 26 patients) of the patients had at least 50 % long term pain relief. The outcome on three parameters was significantly worse at long term follow-up compared to data at one month post-implantation, including increased ‘lowest pain last week’, increased ‘average pain last week’ and decreased percentage time spent pain-free. Data from questionnaires on all available parameters were compared between patients that volunteered for a clinical interview (n = 26) and those that did not (n = 18) at baseline and at one month follow-up. There were no significant differences except for the included patients being older (average of 51 versus 44 years old), having less influence of pain on activities of daily living and hobbies at baseline, and having less influence of pain on hobbies at one month follow-up.

**Clinical phenotyping**

The mean age of the twenty-six patients that were phenotyped was 51 years at the time of implantation (range 29-75). There were fourteen women and twelve men in this group. An indomethacin test was proposed to six patients of whom two refused. All four indomethacin tests, of which two were oral and two intramuscular, were negative. The clinical diagnoses for all 26 patients fell into nine ICHD-II categories (figure 1). Two main subgroups were identified: eight patients with migraine without aura (ICHD-II 1.1) and eight patients with “Constant pain caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions” (ICHD-II 13.12). All patients with migraine without aura
had an additional diagnosis of medication-overuse headache prior to implantation. All migraine patients failed at least four classes of preventive medicines, of which at least three were a β-blocker, anticonvulsant, calcium channel blocker or tricyclic antidepressant thus fulfilling current criteria for medical intractability (2). We compared all available data between both groups ICHD-II 1.1 and ICHD-II 13.12 and found that there were few significant differences, except that patients with ICHD-II 13.12 had significantly more pain relief (mean 80% versus 47%; \( n = 8 \) in both groups) at long term follow-up, and that migraine patients were more independent of others at one month follow-up (\( n = 8 \) in both groups). The latter difference was not seen at long term follow-up.

**Patients with migraine**

The eight migraine patients had a mean follow-up of 24 months following implantation (range 12-60 months). Patient satisfaction at 1 month follow-up was rated excellent by one, very good by two and good by five. At long term follow-up one patient indicated no effect, one only moderate effect, one a good effect, three very good and one excellent (missing data in one patient). At one month follow-up every patient would undergo redo the procedure, but at long term follow-up two out of seven patients would not (missing data in one patient).

Grouped data from the questionnaires at one month and long term follow-up were compared with the data pre-implantation. There was a significant reduction on most pain parameters (‘actual pain’, \( p = 0.00557 \); ‘least pain last week’, \( p = 0.0118 \); ‘mean pain last week’, \( p = 0.00952 \); ‘% pain-free’, \( p = 0.00298 \)) except for the ‘worst pain in the last week’ (\( p = 0.0539 \)). The absolute average value for ‘mean pain last week’ decreased from 7/10 VAS score pre-implantation to 2.4/10 and 4/10 at one month and long term follow-up respectively. Five out of seven patients (missing data in one) had at least a three point drop in ‘mean pain last week’ at long term follow-up. The use of analgesics was significantly diminished (\( p = 0.0469 \)).
Influence of pain on most activity parameters was not significantly changed, except for an increase in social activities \((p = 0.0262)\). Quality of sleep was not significantly changed.

There were no significant differences between the data at one month follow-up versus at long term follow-up, except for a decrease in percentage of time spent pain-free at long term follow-up, that went down from 71 to 51\% \((p = 0.04983)\).

We considered migraine without aura patients with respect to presence \((n = 5)\) or absence \((n = 3)\) of medication overuse headache (see Table 2) at long term follow-up. The average percentage pain relief at long term follow-up was 47\% for the entire group of eight patients (range 0-95\%). Despite the small numbers patients with medication overuse had a significantly less percentage pain relief at long term follow-up when compared to those without (mean of 28\% versus 78\%; \(p = 0.0498\)).

**Head pain of cervical origin**

The eight patients suffering from “Constant pain caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions” had a mean follow-up of 53 months following implantation (range 32-74 months). All but one patient suffered for at least five years from “Constant pain caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions” despite conventional treatments, which illustrates the intractable nature of their condition \((2)\). Patients (missing data for one patient) rated the procedure as excellent \((n = 2)\), very good \((n = 2)\), or at least good \((n = 3)\) at one month post-implantation. At long term follow-up (missing data for one patient) satisfaction with the technique was at least good \((n = 4)\), but also very good \((n = 1)\) and excellent \((n = 2)\). All patients indicated they would redo the procedure at one month and at long term follow-up (with data missing for one patient). From our retrospective interview we ascertained that two
of eight patients had maximal pain relief within 24 hours after implantation, five of eight patients had an average of 70% (range 40-100%) pain relief within the first 24 hours, all eight patients had an average pain relief of 70% (range 20-100%) within seven days. Most patients within this group \((n = 5)\) find that switching the stimulator off leads to exacerbation of the pain very quickly, within ten minutes to one hour. Delay of pain relief upon switching the stimulator back on varies between ten minutes and days. However, two patients are able to switch the stimulator off part of the day to save on battery, but switch it on when the pain exacerbates. Grouped data from the questionnaires at one month and long term follow-up were compared with the data pre-implantation. There was a significant reduction on all pain parameters: ‘actual pain’ \((p = 0.0211)\), ‘worst pain in the last week’ \((p = 0.00841)\), ‘least pain last week’ \((p = 0.0160)\) and ‘mean pain last week’ \((p = 0.0135)\); the ‘% pain-free’ increased from an average pre-implantation value of 13% to 68% and 53% at 1 month and long term follow-up respectively \((p = 0.0193)\). The absolute average value for ‘mean pain last week’ decreased from 7.4/10 VAS score pre-implantation to 2.9/10 and 4.4/10 at one month and long term follow-up respectively. Six out of seven patients (missing data in one) had at least a three point drop in ‘mean pain last week’ at long term follow-up. The use of analgesics was significantly diminished \((p = 0.0244)\) and quality of sleep improved \((p = 0.0468)\). Influence of pain on most activity parameters was significantly diminished, specifically activities of daily living \((p = 0.0331)\), social activities \((p = 0.0295)\), dependency on others \((p = 0.0246)\) and need for bed rest \((p = 0.0220)\), except for hobbies \((p = 0.0941)\). There were no significant differences between the data at one month follow-up versus at long term follow-up. The overall average percentage pain relief at long term follow-up was 80%. There was no significant difference in percentage pain at long term follow-up (see Table 3) between those patients with medication overuse \((n = 5)\) and those without medication overuse \((n = 3)\) at long term follow-up.
Other headache diagnoses

Diagnoses according to ICHD-II in the remaining ten patients were diverse (see Table 4) and included new daily persistent headache (ICHD-II 4.8; \( n = 2 \)), chronic post-traumatic headache attributed to mild head injury (ICHD-II 5.2.2; \( n = 1 \)) and chronic headache attributed to whiplash injury (ICHD-II 5.4; \( n = 2 \)). One patient suffered from chronic cluster headache, probable migraine and medication-overuse headache (ICHD-II 3.1.2, 1.6.1 and A8.2; \( n = 1 \)).

Two patients had a combination of migraine with aura (ICHD-II 1.2.1) and ICHD-II 13.12 and two patients are not classifiable at present because they refused an indomethacin test.

These ten patients had an average follow-up of 27 months (range 9-68 months). All patients scored the efficacy at least good at one month follow-up (\( n = 8 \), missing data in two). At long term follow-up (missing data in three) only four of seven patients still scored the efficacy at least good. The patients experienced on average 62% pain relief at long term follow-up (range 0-95%). At long term follow-up six of seven patients would redo the intervention (missing data in three).
Discussion

The data presented suggest that for some subgroups of patients with relatively medically refractory headache occipital neurostimulation (ONS) offers an effective, well tolerated and comparably safe approach to management. Certainly in this very disabled group such a development would be welcome. The data provide support for the further study of ONS in migraine and caution investigators to carefully monitor for the potential effects of medication overuse when studying ONS. Perhaps more important a cohort of patients with that may be described as Upper Cervical Neuropathic Pain (ICHD-II, 13.12). This finding is important first, because the patients did well, and secondly, because such patients may not always come to attention of neurology and headache specialists thinking about this new treatment modality. An important feature of our cohort has been the very careful phenotyping of the cases, including indomethacin testing, to provide as clear diagnoses as possible. ONS is a promising therapy for a range of patients with challenges to both identify candidates and conduct appropriately blinded randomised controlled trials.

Peripheral nerve stimulation, which is a minimally invasive and reversible procedure, is increasingly employed in the treatment of certain forms of chronic neuropathic pain and certainly preferred over nerve ablation procedures (18). The mechanism of action is incompletely understood, but includes an inhibitory input within pain pathways, gate control of pain as well as modulation of neurotransmitters in the central nervous system (18, 19). The technique of implantation of a occipital neurostimulator was pioneered by Weiner and Reed (3) to treat patients with pain that had an occipital focus. Off-label use of ONS has been employed on a compassionate basis for highly disabled patients with intractable headache, suffering from occipital neuralgia (20), chronic migraine (5), or transformed migraine (21),
chronic cluster headache (7, 8), hemicrania continua (12), post-traumatic headache and headache of C2 origin (22). ONS is considered a minimally invasive procedure and safety data are good (11). The rationale behind the technique in primary headache syndromes, such as migraine and cluster headache, is to modulate sensory traffic from the trigeminocervical complex (23, 24), either at the level of the second order neurons (25, 26), or possibly in the thalamus (5). Given the loss of spatial specificity at the level of the trigeminocervical complex, electrical stimulation of the occipital nerve may have an anti-nociceptive effect in the territory of the trigeminal as well as the occipital nerves. Interestingly, stimulation of the greater occipital nerve in the rat reduces calcitonin gene-related peptide in the jugular blood, which is a biomarker of inhibition of the trigeminal system (27). In case of neuropathic pain in the occipital territory (ICHD-II 13.12), electrical stimulation of the sensory afferents may lead to suppression of Aδ- and C-fibres at the level of the spinal dorsal horn (28, 29).

We embarked on this retrospective study to try to identify subgroups of patients with medically refractory headache with an increased likelihood of responding to ONS. Response to an occipital nerve block certainly is not useful in predicting therapeutic effect of ONS (8, 10, 30). In this uncontrolled series all 44 patients had at least an occipital component to their head pain, and received uni- or bilateral ONS, mirroring the clinical distribution of the pain.

At one month follow-up post-implantation, patient satisfaction was generally high and all patients would theoretically undergo the intervention again for the same indication. Given the mean duration of follow-up of three years and a total device time of almost 1600 months, the overall complication rate of two infections. However, at least one revision was needed in about 30% of patients because of technical problems, which included lead fracture, dislocation and connector current leakage. Some of these problems are due to the fact that the
material used has not been designed for this purpose but for Spinal Cord Stimulation. It is reassuring that not a single neurological deficit was created by the intervention. We only had two patients with a dislocated lead and not a single dislocation occurred after the technique was adapted by doing a medial incision, leaving loops at two stages and fixing the connector. These results are very favourable when compared to earlier results with lead dislocation in all patients after 3 years (11).

Twenty-six patients were phenotyped according to the ICHD-II criteria. At long term follow-up twenty-one individuals indicated they experienced at least 50% pain relief. These twenty-six patients had a mean VAS reduction for ‘average pain last week’ of 4.7 at one month post-implantation and of 3.4 at long term follow-up. The overall satisfaction with the technique was high, except for three patients that had no pain relief at long term follow-up. All three individuals, two migraine patients and one patient with new daily persistent headache, had ongoing medication overuse. When we compared available data from the eighteen that were not phenotyped and the twenty-six that were, only few statistically significant differences were found, and these did not seem clinically important. For the rest of the discussion we speculate that our findings in the phenotyped patients are representative for the entire group.

After subanalysis two main groups of patients were identified, i.e. migraine without aura and occipital neuropathic pain, coded in the ICHD-II under 13.12 “Constant pain caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions”. Even though both groups only consist of eight patients, and thus statistical power is low, some significant differences were found. It appears that ICHD-II 13.12 patients had higher percentage pain relief at long term follow-up. This result is influenced by two migraine patients with ongoing medication-overuse headache that experienced no pain relief at long
term follow-up and that indicated they would not redo the intervention at that time. Indeed, the presence/persistence of medication overuse at long term follow-up is a negative predictor in migraine patients as the average pain relief for patients with medication-overuse was much less than for those without at long term follow-up. This finding is certainly consistent with the general concept that medication overuse renders migraine patients more resistant to prophylactic therapy. It appears thus that close monitoring of acute headache treatment is mandatory to assure long term benefit from the technique. Withdrawal of migraine patients from medication overuse is necessary prior to implantation, as it may account for a large part of the improvement by itself.

These findings need to be corroborated in randomized, blinded and controlled trials, as a placebo effect, regression to the mean and spontaneous improvement certainly may play a role in the observed effect. Some individuals did not have long term headache improvement after occipital neurostimulator implant, despite improvement in the temporary stimulator trial, as has previously been observed (11). Non-specific effects may have waned after permanent implantation. An important weakness of the study is that it is retrospective with regard to the pain aspects, although this is offset by the long term follow-up and the careful approach to phenotyping the cases that has been employed.

Conclusion

Results of ONS for refractory headache are promising, although the concept of intractable headache itself needs to be further refined. It must be clear what the purpose of the definition of refractory is for as the bar to a referral to an expert should be less than for a new therapy that is non-invasive versus an invasive treatment. A number of issues need to be resolved to
optimise ONS including stimulus parameters, battery life, and the stimulator itself with regard to implantation techniques and associated side effects, such as lead migration. An external rechargeable battery would certainly be welcome. Moreover, patient selection criteria, as well as predictors for outcome need to be further refined, and tested in clinical trials. Our retrospective study and a recent pilot study (22) generate the hypothesis that ICHD-II 13.12 may be an excellent indication for ONS and a well powered controlled trial would certainly be welcome. Careful clinical phenotyping will require close collaboration between pain specialists and neurologists, to assign diagnosis according to the ICHD-II. In particular migraine patients need to be closely monitored for medication overuse, as is appears to be a negative predictor for long term outcome in our study. ONS is promising and challenging for all concerned, although the prospect of finding therapies for our most disabled patients is a crucial and rewarding pursuit.
References


Figure 1. Study outline.

44 patients with occipital neurostimulator for medically refractory headache

Informed consent to use data from pre- and post-implantation questionnaires (n=44)

Informed consent for independent clinical interview ± INDO test (n=26)

26 patients in study 18 patients not in study

± INDO test

Informed consent to use data from questionnaire at long term follow-up (n=21)

ICHD-II diagnosis

1.1 Migraine without aura
1.2.1 Typical aura with migraine headache
1.6.1 Probable migraine without aura
3.1.2 Chronic cluster headache
4.8 New daily persistent headache
5.2.2 Chronic post-traumatic headache attributed to mild head injury
5.4 Chronic headache attributed to whiplash injury
13.12 Constant pain caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions
A8.2 Medication-overuse headache

Subanalysis
1.1 ± A8.2 (n=8)
13.12 ± A8.2 (n=8)
Table 1: Pooled results for the twenty-six phenotyped patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-implantation</th>
<th>At 1 month follow-up</th>
<th>At long term follow-up</th>
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<tbody>
<tr>
<td>1. Pain VAS scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain at present</td>
<td>7.3 (2.5-10)</td>
<td>2.6 (1-6)</td>
<td>2.6 (1-7)</td>
</tr>
<tr>
<td>Worst pain last week</td>
<td>8.9 (5.5-10)</td>
<td>4.8 (1-10)</td>
<td>5.7 (1-9)</td>
</tr>
<tr>
<td>Lowest pain last week</td>
<td>5.3 (1-10)</td>
<td>1.8 (1-4)</td>
<td>2.5 (1-6)</td>
</tr>
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<td>Average pain last week</td>
<td>7.3 (3.5-10)</td>
<td>2.6 (1-5.5)</td>
<td>3.9 (1-7)</td>
</tr>
<tr>
<td>2. Long term pain relief</td>
<td></td>
<td></td>
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<td>Mean percentage (range)</td>
<td>63% (0-100%)</td>
<td>72.2% (0-100%)</td>
<td>56.7% (0-100%)</td>
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<td>3. Time spent pain-free</td>
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<tr>
<td>Mean percentage (range)</td>
<td>7.3% (0-40%)</td>
<td>72.2% (0-100%)</td>
<td>56.7% (0-100%)</td>
</tr>
<tr>
<td>4. Analgesic consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number (range) of analgesics/day</td>
<td>2.9 (1-4)</td>
<td>1.5 (0-4)</td>
<td>1.6 (0-4)</td>
</tr>
<tr>
<td>5. Quality of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range) VAS score</td>
<td>6.3 (2-9)</td>
<td>3.6 (1-8)</td>
<td>3.6 (1-9)</td>
</tr>
<tr>
<td>Influence of pain on activities of daily living</td>
<td>7.4 (2-10)</td>
<td>3.2 (1-8)</td>
<td>3.8 (1-9)</td>
</tr>
<tr>
<td>Influence of pain on social activities</td>
<td>3.7 (1-10)</td>
<td>1.9 (1-5)</td>
<td>2.1 (1-9)</td>
</tr>
<tr>
<td>Influence of pain on Independence of others</td>
<td>7.4 (1-10)</td>
<td>3.9 (1-9.5)</td>
<td>4 (1-9)</td>
</tr>
<tr>
<td>Influence of pain on hobbies</td>
<td>5.8 (1-10)</td>
<td>2.7 (1-8.5)</td>
<td>2.7 (1-5)</td>
</tr>
<tr>
<td>Influence of pain on need for bedrest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean percentage scoring sleep at least good</td>
<td>56%</td>
<td>83%</td>
<td>86%</td>
</tr>
</tbody>
</table>

*: significant change (p<0.05) in parameter at 1 month follow-up compared to pre-implantation status

**: significant change (p<0.05) in parameter at long term follow-up compared to pre-implantation status

***: significant change (p<0.05) in parameter at long term follow-up compared to 1 month follow-up status
Table 2. Detail of migraine patient outcomes

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Baseline ICHD-II diagnosis*</th>
<th>VAS scores for pain pre-implantation actual/worst/least/mean</th>
<th>VAS scores for pain at 1 month actual/worst/least/mean</th>
<th>VAS scores for pain long term actual/worst/least/mean</th>
<th>% pain relief long term</th>
<th>MO long term</th>
<th>Redo long term</th>
</tr>
</thead>
<tbody>
<tr>
<td># 1</td>
<td>1.1, A8.2</td>
<td>8.5 9.5 7.5 7.5</td>
<td>1 8 1 2</td>
<td>3 8 2 3</td>
<td>0</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td># 5</td>
<td>1.1, A8.2</td>
<td>3.5 7 2.5 3.5</td>
<td>2 3 1 2</td>
<td>MD 7 3 6</td>
<td>0</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td># 12</td>
<td>1.1, A8.2</td>
<td>4 10 2 6.5</td>
<td>2 9 1 3</td>
<td>1 5 1 2</td>
<td>80</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td># 14</td>
<td>1.1, A8.2</td>
<td>9 10 5 8</td>
<td>1 1 1 1</td>
<td>1 8 1 1</td>
<td>95</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td># 16</td>
<td>1.1, A8.2</td>
<td>8 2 2 5</td>
<td>3 5 1 2</td>
<td>2.5 6.5 2 5</td>
<td>60</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td># 17</td>
<td>1.1, A8.2</td>
<td>9 10 6.5 9.5</td>
<td>4 10 1 4</td>
<td>MD MD MD MD</td>
<td>30</td>
<td>yes</td>
<td>MD</td>
</tr>
<tr>
<td># 24</td>
<td>1.1, A8.2</td>
<td>7 7 7 7</td>
<td>4.5 9 4 4</td>
<td>4.5 9 3 6</td>
<td>60</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td># 26</td>
<td>1.1, A8.2</td>
<td>9 6 6 9</td>
<td>1 2 1 1</td>
<td>1 5 5 5</td>
<td>50</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICHD-II 1.1, 8.2</th>
<th>Number of patients</th>
<th>% pain relief long term</th>
</tr>
</thead>
<tbody>
<tr>
<td>MO+</td>
<td>5</td>
<td>28%*</td>
</tr>
<tr>
<td>MO-</td>
<td>3</td>
<td>78%*</td>
</tr>
</tbody>
</table>

*p=0.0498

*1.1: Migraine without aura; A8.2: Medication-overuse headache
MD = missing data
MO+/- = with or without medication overuse at long-term follow-up
### Table 3. Detail of outcome of patients suffering from ICHD-II 13.12- Upper Cervical Neuropathic Pain

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Baseline ICHD-II diagnosis</th>
<th>VAS scores for pain pre-implantation actual/worst/least/mean</th>
<th>VAS scores for pain at 1 month actual/worst/least/mean</th>
<th>VAS scores for pain long term actual/worst/least/mean</th>
<th>% pain relief long term</th>
<th>MO long term</th>
<th>Redo long term</th>
</tr>
</thead>
<tbody>
<tr>
<td># 2</td>
<td>13.12</td>
<td>2.5 10 1 3.5</td>
<td>6 9 1 4.5</td>
<td>1 6 1 3</td>
<td>95</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td># 3</td>
<td>13.12</td>
<td>8 9 7 8</td>
<td>1 1 1 1</td>
<td>4 9 3 6</td>
<td>75</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td># 7</td>
<td>13.12</td>
<td>10 10 10 10</td>
<td>4 7 4 4</td>
<td>7 9 6 7</td>
<td>80</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td># 8</td>
<td>13.12</td>
<td>7 7.5 4 6.5</td>
<td>4 4 4 3</td>
<td>5.5 5.5 5.5 5.5</td>
<td>100</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td># 9</td>
<td>13.12</td>
<td>7.5 9 4 6</td>
<td>1.5 2.5 1 1</td>
<td>1 1 1 1</td>
<td>100</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td># 13</td>
<td>13.12</td>
<td>7 10 6 8</td>
<td>4.5 4.5 2 3</td>
<td>3 6 3 4.5</td>
<td>72.5</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td># 19</td>
<td>13.12</td>
<td>9.5 9.5 9.5 9.5</td>
<td>3 3 3 3</td>
<td>MD MD MD MD</td>
<td>65</td>
<td>yes</td>
<td>MD</td>
</tr>
<tr>
<td># 23</td>
<td>13.12</td>
<td>5 9 4 8</td>
<td>3 5.5 2.5 4</td>
<td>3.5 5 3.5 4</td>
<td>56</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICHD-II 1.1, 8.2</th>
<th>Number of patients</th>
<th>% pain relief long term</th>
</tr>
</thead>
<tbody>
<tr>
<td>MO+</td>
<td>5</td>
<td>73%*</td>
</tr>
<tr>
<td>MO-</td>
<td>3</td>
<td>93%*</td>
</tr>
</tbody>
</table>

*not sign.

13.12: Constant pain caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions
MD = missing data
MO+/− = with or without medication overuse at long-term follow-up
Table 4. Outcome data for all other patients

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Baseline ICHD-II diagnosis*</th>
<th>VAS scores for pain pre-implantation actual/worst/least/mean</th>
<th>VAS scores for pain at 1 month actual/worst/least/mean</th>
<th>VAS scores for pain long term actual/worst/least/mean</th>
<th>% pain relief long term</th>
<th>MO long term</th>
<th>Redo long term</th>
</tr>
</thead>
<tbody>
<tr>
<td># 4</td>
<td>4.8</td>
<td>8 8 1 7</td>
<td>1 2.5 1 1</td>
<td>1 7.5 1 5</td>
<td>0</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td># 6</td>
<td>5.2.2</td>
<td>MD MD MD MD</td>
<td>MD MD MD MD</td>
<td>MD MD MD MD</td>
<td>52.5</td>
<td>no</td>
<td>MD</td>
</tr>
<tr>
<td># 10</td>
<td>3.1.2, 1.6.1, A8.2</td>
<td>7 10 5 8</td>
<td>4 9 4 5.5</td>
<td>4.5 9 2.5 6</td>
<td>55</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td># 11</td>
<td>1.2.1, A8.2, 13.12</td>
<td>7 9 7 8</td>
<td>2 4 2 3</td>
<td>2 3 2 2.5</td>
<td>75</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td># 15</td>
<td>5.4</td>
<td>5.5 5.5 5.5 5.5</td>
<td>2 2 1 2</td>
<td>2 2 2 2</td>
<td>87.5</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td># 18</td>
<td>5.4</td>
<td>8 9 6 8</td>
<td>MD MD MD MD</td>
<td>MD MD MD MD</td>
<td>55</td>
<td>no</td>
<td>MD</td>
</tr>
<tr>
<td># 20</td>
<td>NC</td>
<td>8 9 2.5 6</td>
<td>1 5 1 2</td>
<td>1 3 1 3</td>
<td>95</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td># 21</td>
<td>4.8</td>
<td>10 10 10 10</td>
<td>2 2 1 1.5</td>
<td>2.5 2.5 3 3</td>
<td>85</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td># 22</td>
<td>NC</td>
<td>8.5 9.5 6.5 8</td>
<td>3 6 2 2.5</td>
<td>MD MD MD MD</td>
<td>15</td>
<td>yes</td>
<td>MD</td>
</tr>
<tr>
<td># 25</td>
<td>13.12, 1.2, A8.2</td>
<td>6.5 7 5 6.5</td>
<td>2 2 1 2</td>
<td>2 2 2 2</td>
<td>95</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

*1.2.1: Typical aura with migraine headache; 1.6.1: Probable migraine without aura; 3.1.2: Chronic cluster headache; 4.8: New daily persistent headache; 5.2.2: Chronic post-traumatic headache attributed to mild head injury; 5.4: Chronic headache attributed to whiplash injury; 13.12: Constant pain caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions; A8.2: Medication-overuse headache; NC = not classifiable
MD = missing data