

Randomized Trial

Occipital Nerve Stimulation for Chronic Migraine: A Randomized Trial

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Background: Chronic migraine (CM) and medication overuse headache (MOH) are disabling conditions that may be only partially managed with conservative treatments. Occipital nerve stimulation (ONS) is an innovative treatment for headache disorders.

Objectives: To investigate the safety and efficacy of ONS for CM and MOH patients and to evaluate changes in disability, quality of life, and drug intake in implanted patients.

Study Design: Prospective, randomized cross-over study.

Methods: Eligible patients who responded to a stimulation trial underwent device implantation and were randomized to "Stimulation On" and "Stimulation Off" arms. Patients crossed over after one month, or when their headaches worsened. Stimulation was then switched On for all patients. Disability as measured by the Migraine Disability Assessment (MIDAS), quality of life (SF-36), and drug intake (patient's diary) were assessed over a one-year follow-up.

Results: Thirty-four patients (76% women, 34% men, mean age: 46 ± 11 years) were enrolled; 30 were randomized and 29 completed the study. Headache intensity and frequency were significantly lower in the On arm than in the Off arm ($P < 0.05$) and decreased from the baseline to each follow-up visit in all patients with Stimulation On (median MIDAS A and B scores: baseline = 70 and 8; one-year follow-up = 14 and 5, $P < 0.001$). Quality of life significantly improved ($P < 0.05$) during the study. Triptans and nonsteroidal anti-inflammatory drug use fell dramatically from the baseline (20 and 25.5 doses/month) to each follow-up visit (3 and 2 doses/month at one year, $P < 0.001$). A total of 5 adverse events occurred: 2 infections and 3 lead migrations.

Limitations: Single-centre study, relatively small number of patients, absence of a control group.

Conclusions: According to the results obtained, ONS appears to be a safe and effective treatment for carefully selected CM and MOH patients.

Key words: Occipital nerve stimulation, chronic migraine, headache attacks, quality of life, cross-over

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Chronic daily headache (CDH) refers to a group of very disabling painful headache disorders and has an estimated prevalence of 3% to 5% worldwide (1). According to the International Classification of Headache Disorders (ICHD-II) (2),

chronic migraine (CM) is characterized by migraine episodes ≥ 15 days/month for ≥ 3 months; it affects 1.4% to 2.2% of the general population (3). In patients with CM, pain usually interferes with work performance, social relationships, and everyday activities, seriously

affecting quality of life (QoL) (4). Medication overuse headache (MOH) is associated with drug use for ≥ 15 days/month (2) and affects approximately 1% to 2% of the general population (5).

A controversial issue is the role of medication overuse in the classification of CM. Though it is clear that CM and medication overuse are connected and relatively common in these patients, making a single diagnosis in patients with daily or near-daily migraine attacks and drug intake is problematic. The current approach consists of first diagnosing CM and then ascertaining fulfillment of the criteria for MOH (6).

In patients with CM, a prophylactic therapy should be administered (7) and attacks managed with non-specific medications (analgesics and nonsteroidal anti-inflammatory drugs [NSAIDs]) or specific medications (ergot-related compounds and triptans), alone or in combination with other treatments (8,9).

In patients with MOH, treatment is even more complex (10), as the overused drugs need to be gradually withdrawn before an effective therapy can be determined (11,12).

When conservative therapies fail, occipital nerve stimulation (ONS) may provide an alternative approach to managing migraine episodes. First introduced by Weiner and Reed (13) for the treatment of patients with occipital neuralgia, ONS was later described as an effective therapy for different types of chronic headaches (14). Despite the good outcomes reported in literature, ONS is still considered an experimental therapy because of limited evidence in published works (15). Recently, the ONSTIM feasibility study (16) provided the first encouraging results of ONS in a randomized trial. The aim of our study was to investigate the safety and efficacy of ONS in a selected population. In addition, we evaluated changes in QoL, disability and drug intake.

METHODS

Patient selection

Outpatients from the Pain Unit and the Headache Center at Sacro Cuore Don Calabria Hospital, Negrar, Italy were evaluated in accordance with common clinical practice. Patients received a diary to record headache days/month and drugs taken to manage the attacks. A month later, patients were enrolled in the study if they had a diagnosis of CM or MOH and fulfilled the following inclusion criteria:

- refractoriness to at least 2 prophylactic treatments or intolerable side effects due to these treatments

- no ongoing prophylactic treatments at the beginning or during the study
- age ≥ 18 years
- ability and willingness to participate in the study
- written informed consent signed.

Patients were excluded if they met the following exclusion criteria:

- previous surgical procedure in the occipital area
- destructive ganglionectomy, local drug injection, nerve-blocks in the last 90 days
- participation in other clinical trials in the last 3 months
- confirmed pregnancy or desire to get pregnant during the study period
- significant psychological problems and/or serious drug habituation
- frequent need for MRI or diathermy.

In addition, MOH patients underwent a period of at least 2 months of drug withdrawal before the ONS trial. For these patients the baseline assessment was performed at the end of this period in order to avoid interference with the assessment of stimulation outcomes.

Once patients had been enrolled, they underwent Migraine Disability Assessment (MIDAS) (17,18) and SF-36 (19) questionnaires to assess headache-related disability and QoL. Headache intensity was also measured by means of the Numeric Rating Scale (NRS-11). Enrolled patients were asked to fill in their "headache diary" over the entire study period and were put on the waiting list for the ONS trial.

Study Design

A temporary ONS system was first implanted. If the number or severity of attacks decreased by 50% within 15-30 days, patients received an internal neurostimulator (INS) and were randomized (1:1) as follows:

- Arm A: INS On
- Arm B: INS Off.

After randomization, the severity of attacks was assessed by means of the NRS-11.

Patients randomized to Arm B could switch stimulation on if their headache attacks increased in severity or frequency by 30% or more. Follow-up examinations were carried out according to a regular schedule.

After 4 weeks, patients crossed over from Arm A to Arm B and from Arm B to Arm A, except for those

Arm B patients who had already switched stimulation on. Once again, the severity of attacks was assessed by means of the NRS-11. This situation was also maintained for a month, unless the health conditions of pa-

tients worsened (severity or frequency of headaches increased by 30% or more). Follow-up examinations were scheduled one, 3, 6, and 12 months after the INS implantation. The study design is summarized in Fig. 1.

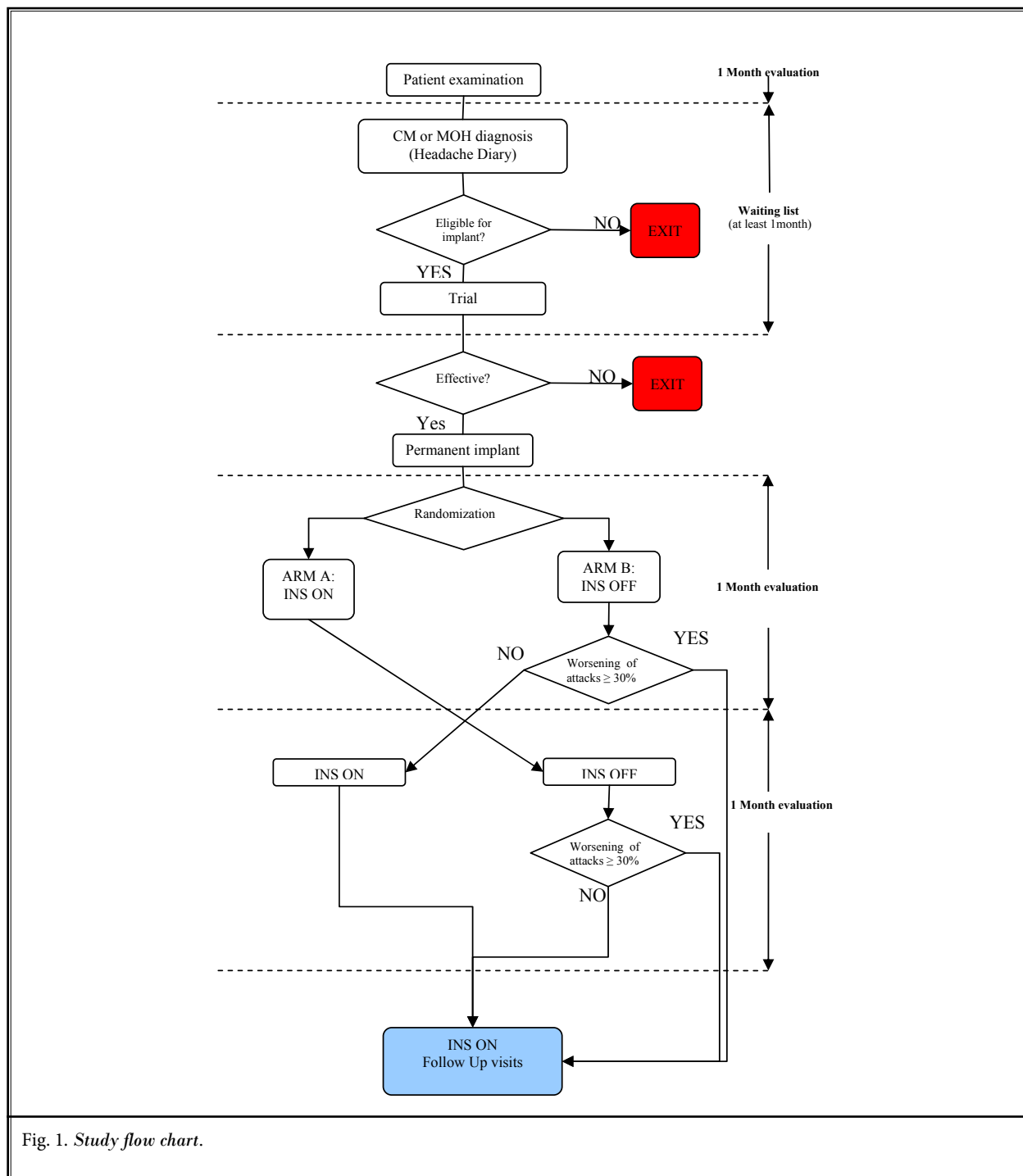


Fig. 1. Study flow chart.

Surgical Technique

Trial test or temporary implant

A percutaneous quadripolar lead (Medtronic Inc., Minneapolis, MN) was implanted under local anesthetic and mild sedation with the aid of an image intensifier. The lead was fixed to the fascia and then connected to a temporary extension in a pocket under the skin. The same technique was used to place the second lead to stimulate the contralateral nerves.

Permanent Implant

Under local anesthesia and mild sedation, a subclavicular or laterodorsal incision was made to form a pocket to house the INS, Synergy Versitrel (Medtronic Inc., Minneapolis, MN). The leads were connected to definitive extensions. To create strain-relief loops, in order to prevent lead migration, extensions were placed in the neck area forming circular coils, then were anteriorly tunneled and later connected to the INS.

All surgical procedures were performed by the same surgeon.

Stimulation Parameters

Parameter settings were variables in order to improve the effectiveness of stimulation in accordance to patients' specific needs. A bipolar configuration (one anode and one cathode) was usually used. The stimulation frequency was 50 Hz, the pulse width ranged between 330 μ s and 450 μ s while the stimulation amplitude could be modified to a maximum value of 10.5 V.

Follow-up Visits

At follow-up visits, headache diaries were examined and drug use recorded. MIDAS and SF-36 questionnaires were administered. If necessary, the stimulation parameters were adjusted in order to optimize the perception of paresthesia. Patients were, however, provided with remote controls to modify the stimulation amplitude, except in the period when stimulation was off.

Adverse Events

The safety of ONS was assessed by recording the number and the type of adverse events which occurred during the study period. For each event, the severity and the remedial action taken were recorded.

Sample Size and Statistical Analysis

A total of 34 patients were enrolled. This sample

size was calculated by means of the program STATA 9.0 (StataCorp LP, College Station, TX): .samps1 0.1 0.6, p(0.8), assuming the following hypotheses :

1. During the trial, 10% of patients with stimulation On would report worsening of headache symptoms
2. During the trial, 60% of patients with stimulation Off would report worsening of headache symptoms
3. Type I error, $\alpha = 5\%$
4. Power, $p = 80\%$.

The data collected were analyzed in order to assess the baseline characteristics of patients in the 2 arms and changes from the baseline to follow-up examinations. Continuous data are presented as mean \pm standard deviation (or median with interquartile range, if not a Gaussian distribution) and categorical variables as absolute and relative frequency. Differences between groups were evaluated by means of Student's t test or nonparametric Mann-Whitney U test for continuous variables and Cramer's V test or Fisher's exact test for categorical variables. A general linear model for repeated measures was used to compare the results of NRS-11 and questionnaires administered over time. Statistical comparisons between groups were carried out by one-way analysis of variance (ANOVA). All 2-tailed *P* values < 0.05 were considered statistically significant.

RESULTS

Characteristics of the Population.

A total of 34 patients (76% women, 34% men) with a mean age of 46 ± 11 years (range 26 – 66 years) were enrolled.

All patients met the criteria for CM and 85% also for MOH. Familial recurrence was found in 71% of cases, and the mean age of CM onset was 16 ± 9 years (range 4 – 44 years). At the baseline, patients reported an average frequency of 5.8 ± 1.6 days per week, with migraine episodes of medium (9%), high (59%) or very high (32%) intensity. The median value of headache severity was 8 (1st-3rd quartile: 7-8). Pain was classified as throbbing (65%), heavy (23%), dull (6%), burning (3%), or sharp (3%). Migraine attacks worsened with movement in 82% of cases and were accompanied by neurovegetative crises, such as nausea (79%), vomiting (65%), phonophobia (77%), photophobia (74%), and osmophobia (62%). Before enrollment, all patients had experienced the failure of at least 2 prophylactic therapies.

Phases of the Study

All patients underwent the stimulation trial. After the test, one patient withdrew informed consent and another suffered an infection; both dropped out of the study. Thirty-two patients were assessed at an average time of 45 ± 23 days (range: 12 – 122 days) after lead implantation: 9% reported a reduction $\geq 50\%$ in the number of attacks, 22% a reduction $\geq 50\%$ in the severity of attacks, 66% a reduction $\geq 50\%$ in both the number and severity; only 3% (one patient) did not achieve a reduction $\geq 50\%$ in the number or severity of attacks. This patient was considered nonresponsive to the ONS treatment and, following explantation, exited the study. All 31 patients who successfully responded to the trial underwent permanent implantation. The INS was placed in a laterodorsal (71%) or subclavicular (29%) subcutaneous pocket. Thirty patients were randomized 1:1, and one withdrew informed consent. Patients in Arm B, with stimulation switched Off, activated the generator after an average of 4.9 ± 3.8 days (range 1-12 days), because of $\geq 30\%$ worsening in the number (33%), severity (13%) or both number and severity (54%) of attacks. After cross-over, stimulation was switched Off in Arm A and switched On in Arm B.

Patients in Arm A required stimulation On after a mean of 4.4 ± 2.8 days (range 2-10 days), owing to $\geq 30\%$ worsening in the number (20%), severity (20%) or both number and severity (60%) of attacks. There was no significant difference in the period of stimulation Off between the 2 groups.

In order to compare the number of attacks between Arm A and Arm B, the number of days per week and the proportion of days with attacks (ratio) were extracted from headache diaries. Headache severity was also assessed in the 2 arms. Results of the comparison are shown in Table 1.

After every patient in Arm A had turned the INS on, all 30 patients had received the stimulation. One patient developed an infection after 3 months and withdrew from the study. Consequently, a total number of 29 patients completed the one-year follow-up.

MIDAS Questionnaire

The MIDAS total score and questions A and B scores improved during follow-up visits (Table 2). Significant changes were recorded between the median scores at the baseline and each follow-up visit, while changes between different follow-up visits were not always significant.

Table 1. Median (1st -3rd quartile) number of days per week, Ratio and severity of migraine attacks in arms A and B (Test U-Mann -Whitney)

Headache Attacks	Number of days/ week	Ratio	Severity (0-10)
INS ON – ARM A	2.1 (1.2 – 3.3)	0.3 (0.2 - 0.5)	5 (5 - 6)
INS OFF – ARM B	6.3 (3.6 - 7)	0.9 (0.5 - 1)	7.5 (7 - 8)
P - value	< 0.001	< 0.001	< 0.001
	Number of days/ week	Ratio	Severity (0-10)
INS OFF – ARM A	6 (4.2 - 6.3)	0.86 (0.6 - 0.9)	8 (7.5 - 9)
INS ON – ARM B	2.3 (1.5 - 2.8)	0.32 (0.2 - 0.4)	6 (4 - 8)
P - value	< 0.001	< 0.001	< 0.05

Table 2. Median (1st -3rd quartile) Midas total score, Midas question A and Midas question B scores at the baseline and at FU visits (N=29, Friedman test)

	MIDAS TOTAL SCORE	MIDAS - A	MIDAS - B
Baseline	79 (30-135)	70 (50-88)	8 (7-8)
1-month FU	27.5 (0- 52)	25 (17-40)	6 (5-7)
3-month FU	19 (0-44)	20 (12-35)	6 (5-6)
6-month FU	10 (0-27)	19 (12-28)	6 (4-7)
12-month FU	10 (0-20)	14 (8-16)	5 (4-6)
P- value	< 0.001	< 0.001	< 0.001

SF-36 Questionnaire

All the SF-36 domains improved during follow-up examinations (Fig. 2), while no significant changes were found among the various follow-up visits.

Drug Intake

During the study period, 13 (45%) of the 29 patients who completed the trial took triptans, 7 (24%) took NSAIDs and 9 (31%) patients took both triptans and NSAIDs. The median monthly dose of triptans and NSAIDs significantly decreased. Triptans doses/month went from 20 at baseline to 3 at the one-year follow-up while NSAIDs doses/month went from 25.5 at baseline to 2 at the one-year follow up ($P < 0.001$). Figure 3 shows the drug intake of the population assessed.

Adverse Events.

A total number of 5 adverse events were recorded: 2 severe implantation site infections (one after the trial test and one prior to the 6-month follow-up visit)

and 3 lead dislocations (2 classified as severe and one as mild). The patients with infections exited the study and received the required medical treatment. In the patients with lead migration, the electrodes were repositioned and no further complications occurred. No adverse events led to long-term complications or nerve damage.

Discussion

ONS is an innovative and promising treatment for intractable chronic headaches and facial pain. Encouraging preliminary results have been reported for the management of occipital neuralgia (20-23), chronic migraine (24-26), transformed migraine (27), chronic cluster headache (28-31), and hemicrania continua (32).

The mechanism of action is not completely understood. The stimulation of C2-C3 nerves may reduce the activity of nociceptive fibers (33), providing pain relief according to the theory of "gate control" introduced by Melzack and Wall (34). It also seems that the excit-

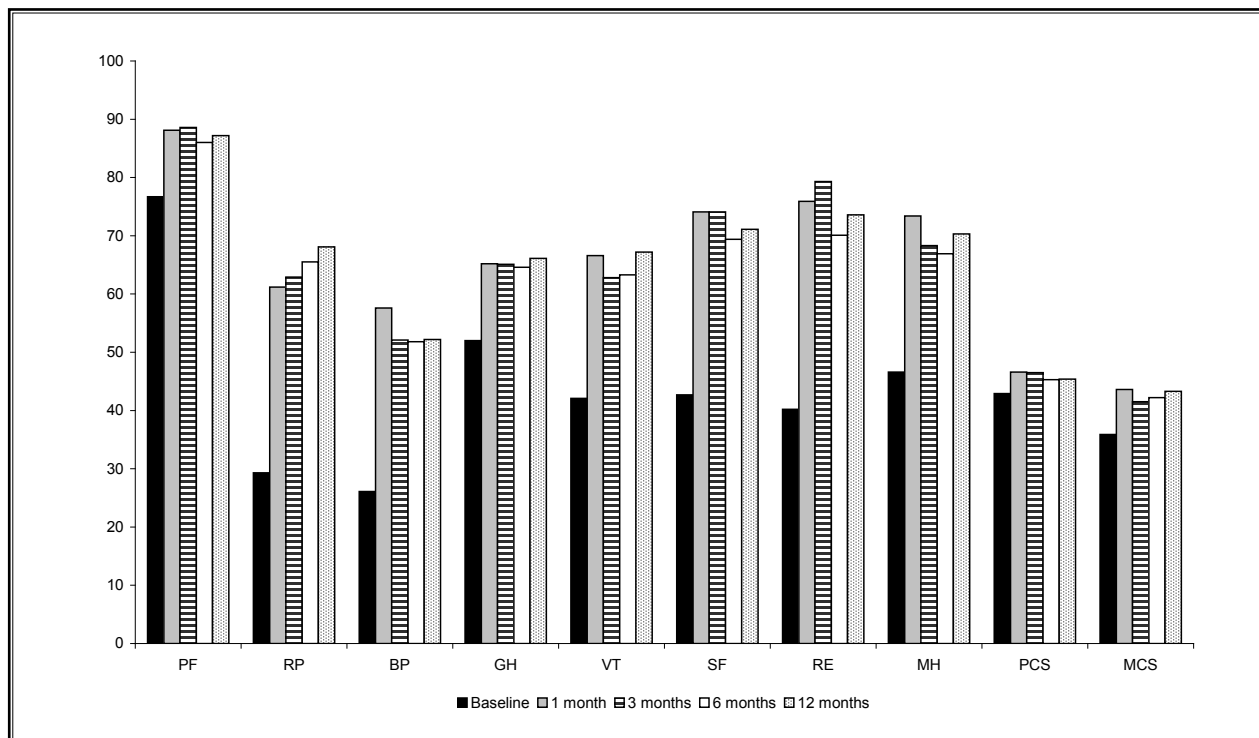
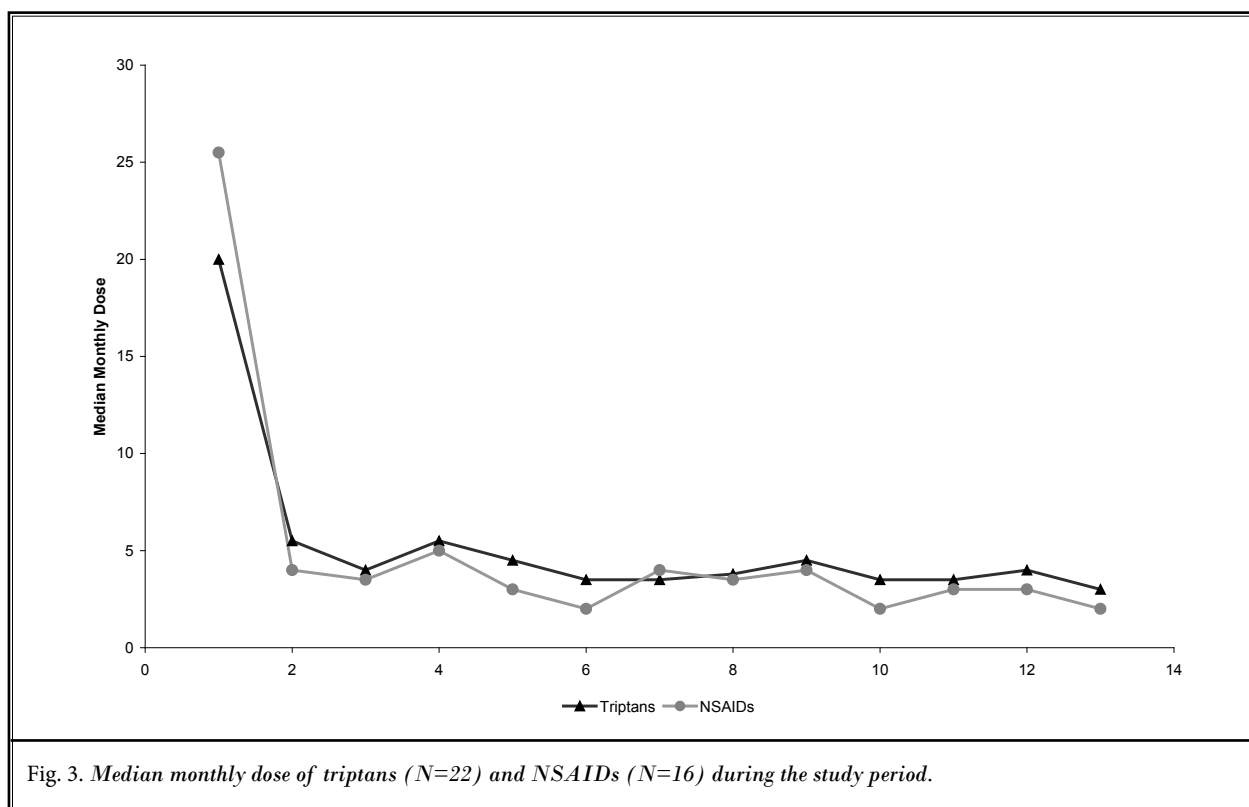


Fig. 2. SF-36 mean scores at the baseline and at FU visits. PF=Physical Functioning, RP: Role Physical, BP: Bodily Pain, GH: General Health, VT: Vitality, SF: Social Functioning, RE: Role Emotional, MH: Mental Health, PCS: Physical Component Summary, MCS: Mental Component Summary (Generalized linear model for repeated measure, $P < 0.05$, $N = 29$). The MCS and PCS increased from a mean of 35.9 ± 8.2 and 42.9 ± 5.8 at the baseline to 43.3 ± 5.8 and 45.4 ± 4.8 at the 12-month FU visit, respectively ($P < 0.05$).



ability of peripheral fibers may be altered by the electrical stimulation, thereby relieving pain (35,36). Furthermore, a positron emission tomography (PET) study in patients with CM has shown that ONS may have a central effect involving thalamic structures, resulting in pain alleviation (24).

Nevertheless, this therapy remains experimental, owing to the lack of robust studies providing strong clinical evidence (16,37). In this context, we conducted the first randomized cross-over trial involving a carefully selected cohort of patients.

All our patients suffered from intractable CM. The criteria for MOH was met by 85%, while the remaining 15% took triptans at very high dosages (mean monthly intake: 13.5 ± 0.6 doses), revealing that drug overuse needs to be managed in these patients, too.

In the patients enrolled, CM had begun very early (16 ± 9 years) showing a long history of severely disabling headache pain. ONS was well accepted by all the patients enrolled, since it is a minimally invasive, reversible technique.

The safety of ONS was evaluated in terms of adverse events. Infections occurred in about 6% (2 patients) of the population. This value is in good agree-

ment with the data reported in a review by Jasper and Hayek (15), in which 7 cases of infection were recorded in 150 patients (4.7%), while it is lower than the values recorded in the ONSTIM study (16), in which infections occurred in the INS pocket in 4% and in the implant site in 14% of cases. The patient who suffered infection after the permanent implantation in our study asked to continue ONS treatment once recovery was complete.

The literature shows that lead migration is the most frequent adverse event during ONS; in the papers reviewed by Jasper and Hayek (15), this complication arose in 26% of patients (30 of 115) and in the ONSTIM trial in 24% (12 of 51). In our population, lead migration was recorded in 10% (3 patients) with an INS. This lower rate may be attributed to the surgical technique used, which is specifically intended to reduce the strain on leads. Furthermore, these events declined in the later phases of the study, as the learning curve improved.

The efficacy of ONS was assessed by comparing headache frequency and intensity between the 2 groups (stimulation On and Off) before and after cross-over, and by evaluating changes from one follow-up visit to another when all patients had stimulation On (after cross-over), up to the one-year follow-up visit.

When stimulation was On, whether after randomization or after cross-over, the frequency and intensity of migraine episodes were significantly lower than when stimulation was Off.

In this preliminary study, the trial test was administered in order to avoid the implantation of an INS without indications on the possible effects of the stimulation for the enrolled patients. In addition, the period of stimulation Off had not been previously established, because, from a deontological point of view, leaving patients free to interrupt the stimulation Off period was considered the most suitable choice for those who responded positively to the stimulation trial. Hence, when patients are aware of paresthesia, the placebo effect cannot be discounted during the first phase of the study (comparison between the Stimulation On and the Stimulation Off groups). However, concerning the 29 patients with the stimulation On who completed the one-year follow-up, analysis showed a statistically significant change in all parameters from the baseline to each follow-up visit, but not among different follow-up visits. This reveals that ONS provided a dramatic improvement, which was maintained throughout the study period.

The MIDAS score fell from a median value of 79 (grade IV: severe disability) at the baseline to 10 (grade II: mild disability) at the one-year follow-up visit ($P < 0.001$); this shows an improvement in patients' productivity.

MIDAS question A scores decreased from a median value of 70 at the baseline to 14 at the one-year follow-up visit ($P < 0.001$), indicating a dramatic reduction in the frequency of attacks. Furthermore, this median value shows that in our population the criterion for CM

(migraine episodes on ≥ 15 days/month for ≥ 3 months) had not yet been fulfilled. MIDAS question B scores decreased from a median value of 8 at the baseline to 5 at the one-year follow-up visit ($P < 0.001$), indicating a significant reduction in patients' impairment due to headache.

The efficacy of ONS also resulted from the marked reduction in drug intake ($P < 0.001$), which fell from almost daily use to occasional use; this positively affected patients' QoL by reducing severe drug-related side effects.

Study Limitations

This study has some limitations. It is a single-center study with a relatively small number of patients. In addition, a control group over the one-year study period was not provided.

CONCLUSIONS

According to the results of our study, ONS appears to be a safe and effective treatment for well-selected patients with CM or MOH. Indeed, only a small number of therapy-related adverse events occurred, and these were solved without long-term complications for the patients. The therapy is easy to implement and to manage, and optimizing the surgical procedure may help to prevent adverse events. The severity and frequency of headache pain were significantly lower in all patients when stimulation was On than when it was Off, and improved from the baseline to the one-year follow-up visit. In addition, QoL and disability scores dramatically improved, while drug intake fell markedly. Further analyses on larger populations in multicenter trials may strengthen these promising findings.

REFERENCES

1. Coeytaux RR, Linville JC. Chronic daily headache in a primary care population: Prevalence and headache impact test scores. *Headache* 2007; 47:7-12.
2. Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 2nd edn. *Cephalalgia* 2004; 24(Suppl 1):9-160.
3. Lantéri-Minet M, Duru G, Mudge M, Cottrell S. Quality of life impairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: A systematic review. *Cephalalgia* 2011; 31:837-850. Epub Apr 4.
4. Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. *Neurology* 2008; 71:559-566.
5. Stovner LJ, Andree C. Prevalence of headache in Europe: A review for the Eurolight Project. *J Headache Pain* 2010; 11:289-299.
6. Manack AN, Buse DC, Lipton RB. Chronic migraine: Epidemiology and disease burden. *Curr Pain Headache Rep* 2011; 15:70-78.
7. Goadsby PJ, Sprenger T. Current practice and future directions in the prevention and acute management of migraine. *Lancet Neurol* 2010; 9:285-298.
8. The British Association for the Study of Headache. Guidelines for all health-care professionals in the diagnosis and management of migraine, tension-type headache, cluster headache, medica-

- tion-overuse headache 2010
http://217.174.249.183/upload/NS_BASH/2010_BASH_Guidelines.pdf
9. Ellens DJ, Levy RM. Peripheral neuromodulation for migraine headache. *Prog Neurol Surg* 2011; 24:109-117.
 10. De Felice M, Ossipov MH, Porreca F. Update on medication-overuse headache. *Curr Pain Headache Rep* 2011; 15:79-83.
 11. Mathew NT. Dynamic optimization of chronic migraine treatment: Current and future options. *Neurology* 2009; 72: S14-S20.
 12. Evers S, Marziniak M. Clinical features, pathophysiology, and treatment of medication-overuse headache. *Lancet Neurol* 2010; 9:391-401.
 13. Weiner RL, Reed KL. Peripheral neurostimulation for control of intractable occipital neuralgia. *Neuromodulation* 1999; 2:217-221.
 14. Paemeleire K, Bartsch T. Occipital nerve stimulation for headache disorders. *Neurotherapeutics* 2010; 7:213-219.
 15. Jasper JF and Hayek SM. Implanted occipital nerve stimulators. *Pain Physician* 2008; 11:187-200.
 16. Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ; ONS-TIM Investigators. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONS-TIM feasibility study. *Cephalalgia* 2011; 31:271-285. Epub 2010 Sep 22.
 17. www.americanheadachesociety.org
 18. Stewart WF, Lipton RB, Kolodner KB, Sawyer J, Lee C, Liberman JN. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. *Pain* 2000; 88:41-52.
 19. www.SF-36.org
 20. Johnstone CSH, Sundaraj R. Occipital nerve stimulation for the treatment of occipital neuralgia—eight case studies. *Neuromodulation* 2006; 9:41-47.
 21. Oh MY, Ortega J, Bellotte JB, Whiting DM, Alo K. Peripheral nerve stimulation for the treatment of occipital neuralgia and transformed migraine using a C1- 2-3 subcutaneous paddle style electrode: A technical report. *Neuromodulation* 2004; 7:103-112.
 22. Rodrigo-Royo MD, Azcona JM, Quero J, Lorente MC, Acin P, Azcona J. Peripheral neurostimulation in the management of cervicogenic headache: Four case reports. *Neuromodulation* 2005; 8:241-248.
 23. Slavin KV, Nersesyan H, Wess C. Peripheral neurostimulation for treatment of intractable occipital neuralgia. *Neurosurgery* 2006; 58:112-119.
 24. Matharu MS, Bartsch T, Ward N, Frackowiak RS, Weiner R, Goadsby PJ. Central neuromodulation in chronic migraine patients with suboccipital stimulators: A PET study. *Brain* 2004; 127:220-230.
 25. Dodick DW, Trentman T, Zimmerman R, Eross EJ. Occipital nerve stimulation for intractable chronic primary headache disorders. *Cephalalgia* 2003; 23:701.
 26. 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.
 27. Popeney CA, Alo KM. Peripheral neurostimulation for the treatment of chronic, disabling transformed migraine. *Headache* 2003; 43:369-375.
 28. Burns B, Watkins L, Goadsby PJ. Treatment of medically intractable cluster headache by occipital nerve stimulation: Long-term follow-up of eight patients. *Lancet* 2007; 369:1099-1106.
 29. Burns B, Watkins L, Goadsby PJ. Treatment of intractable chronic cluster headache by occipital nerve stimulation in 14 patients. *Neurology* 2009; 72:341-345.
 30. Magis D, Allena M, Bolla M, De Pasqua V, Remacle JM, Schoenen J. Occipital nerve stimulation for drug-resistant chronic cluster headache: A prospective pilot study. *Lancet Neurol* 2007; 6:314-321.
 31. Magis D, Bruno MA, Fumal A, G erardy PY, Hustinx R, Laureys S, Schoenen J. Central modulation in cluster headache patients treated with occipital nerve stimulation: An FDG-PET study. *BMC Neurol* 2011; 11:25.
 32. Burns B, Watkins L, Goadsby PJ. Treatment of hemicrania continua by occipital nerve stimulation with a bion device: Long-term follow-up of a crossover study. *Lancet Neurol* 2008; 7:1001-1012. Epub 2008 Oct 7.
 33. Goadsby PJ, Schoenen J, Ferrari MD, Silberstein SD, Dodick D. Towards a definition of intractable headache for use in clinical practice and trials. *Cephalalgia* 2006; 26:1168-1170.
 34. Melzack R, Wall PD. Pain mechanisms: A new theory. *Science* 1965; 150:971-979.
 35. Ignelzi RJ, Nyquist JK. Direct effect of electrical stimulation on peripheral nerve evoked activity: Implications in pain relief. *J Neurosurg* 1976; 45:159-165.
 36. Ignelzi RJ, Nyquist JK. Excitability changes in peripheral nerve fibers after repetitive electrical stimulation. Implications in pain modulation. *J Neurosurg* 1979; 51:824-833.
 37. Paemeleire K, Van Buyten JP, Van Buynder M, Alicino D, Van Maele G, Smet I, Goadsby PJ. Phenotype of patients responsive to occipital nerve stimulation for refractory head pain. *Cephalalgia* 2010; 30:662-673. Epub 2010 Mar 31.

