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Long-term occipital nerve stimulation for drug-resistant chronic cluster headache

Massimo Leone[1], Alberto Proietti Cecchini[1], Giuseppe Messina[2] and Angelo Franzini[2]

Abstract

Introduction: Chronic cluster headache is rare and some of these patients become drug-resistant. Occipital nerve stimulation has been successfully employed in open studies to treat chronic drug-resistant cluster headache. Data from large group of occipital nerve stimulation-treated chronic cluster headache patients with long duration follow-up are advantageous.

Patients and methods: Efficacy of occipital nerve stimulation has been evaluated in an experimental monocentric open-label study including 35 chronic drug-resistant cluster headache patients (mean age 42 years; 30 men; mean illness duration: 6.7 years). The primary end-point was a reduction in number of daily attacks.

Results: After a median follow-up of 6.1 years (range 1.6–10.7), 20 (66.7%) patients were responders (≥50% reduction in headache number per day): 12 (40%) responders showed a stable condition characterized by sporadic attacks, five responders had a 60–80% reduction in headache number per day and in the remaining three responders chronic cluster headache was transformed in episodic cluster headache. Ten (33.3%) patients were non-responders; half of these have been responders for a long period (mean 14.6 months; range 2–48 months). Battery depletion (21 patients 70%) and electrode migration (six patients – 20%) were the most frequent adverse events.

Conclusions: Occipital nerve stimulation efficacy is confirmed in chronic drug-resistant cluster headaches even after an exceptional long-term follow-up. Tolerance can occur years after improvement.

Keywords

Cluster headache, treatment, neurostimulation, occipital nerve, drug-resistant, chronic

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Introduction

Cluster headache (CH) is characterized by severe strictly unilateral headaches lasting 15–180 minutes, accompanied by agitation and ipsilateral autonomic phenomena, including rhinorrhoea, lacrimation and conjunctival injection (1). Due to the excruciating nature of pain, CH is also known as suicide headache (2). The most common form is episodic CH characterized by pain periods lasting about 1–2 months (1). The chronic form of CH is rare and its attacks recur over- > 1 year without remission periods or with remission periods lasting < 1 month (1). Some chronic CH patients become drug-resistant and continue to suffer daily-almost daily attacks for long periods: this condition is highly disabling. In such patients a number of destructive surgical procedures mainly on the trigeminal nerve have been tried with poor results (3). Since 2000, hypothalamic stimulation has been employed to successfully treat many drug-resistant chronic CH patients but it is an invasive and high-cost procedure (4,5). Recently, a less invasive procedure, occipital nerve stimulation (ONS), has been shown to be a promising treatment for drug-resistant chronic CH in case series (6–10). An ongoing randomized controlled trial is investigating ONS efficacy in CH (11); paraesthesia is

[1]Department of Neurology, Headache Centre and Pain Neuromodulation Unit, Italy
[2]Department of Neurosurgery, Fondazione Istituto Nazionale Neurologico Carlo Besta, Italy

Corresponding author:
Massimo Leone, Department of Neurology and Headache Centre, Fondazione Istituto Nazionale Neurologico Carlo Besta, Via Celoria 11, 20133 Milano, Italy.
Email: leone@istituto-besta.it

necessary to achieve the clinical effect and blinding with ONS is a challenge. Previous open studies on ONS in chronic CH have a median follow-up of 13.3 months (range 6.0–36.8 months) with up to 15 implanted patients at one centre (12). Chronic CH is fluctuating in nature (2) and, in order to better establish ONS efficacy, long-term follow-up in a large group of patients is needed.

Results from a long-term follow-up of > 6 years in a large group of chronic drug-resistant CH patients treated by ONS are presented.

Methods

Patient selection

This is a monocentric experimental open label study on 35 consecutive patients with chronic CH, diagnosed according to International Headache Society criteria (1), who received ONS in the period from March 2004 to February 2014 at our Institution. Clinical characteristics are reported in Table 1. Selection criteria for ONS were daily/almost daily attacks in the last year and resistance to all known prophylactic drugs for CH (13) (Table 2) including verapamil, lithium carbonate, methysergide, valproate, topiramate, gabapentin, melatonin, pizotifen, indomethacin and others, and repeated sphenopalatine ganglion blockade (14). We used stricter than usual selection criteria (15) because our Institutional Review Board (IRB) does not give permission to perform this experimental invasive high-cost treatment unless all drugs have been tried (or contraindicated). Before ONS, all patients tried repeated long-term steroid cycles to control the condition and all developed at least one of the clinically relevant steroid-induced side effects, including peptic ulcers, bone fractures, arterial hypertension, weight increase, insomnia, psychosis, glaucoma, skin eruptions. Occipital nerve blockade as well as external ONS trials were not used as selection criteria due to their high uncertain effect as a predictive test for ONS (5). Medication overuse headache was not present in our patients prior to implantation. All patients had a normal neurological examination and normal cerebral magnetic resonance imaging. Patients underwent a psychiatric and psychological assessment and their profile was considered normal. The five women were not pregnant. The procedure was in accordance with the IRB rules. Patients gave written informed consent.

Number of headache attacks and sumatriptan injection consumption, as well as other acute treatments, were recorded in headache diaries with a very good compliance throughout the follow-up. In the first year after ONS, visits were on a monthly basis; thereafter visits were at 2–4 month intervals. Additional visits were guaranteed at patients' request at any time. When diaries were incomplete, information was directly collected during the follow-up.

The primary end-point was reduction in number of daily attacks (headache frequency). The mean number of daily attacks before and after ONS was compared; the reference periods were the 6 months before the operation as baseline vs. the last year of observation. Responders were patients with a headache frequency reduction $\geq 50\%$.

In many cases, reduction of both intensity and duration of pain accompanied a reduction in the number of headache attacks; in the long run, patients did not regularly report intensity and duration of headache and could not be considered in the analysis.

The first five implanted patients received ONS for less than 6 months with poor results and were then shifted to hypothalamic stimulation because at that time it was shown that in neurovascular headaches ONS produced benefit with very short latency (16). These five patients are not considered in the per protocol analysis.

Surgery and follow-up

The procedure described herein has also been described in a previous report (17). The patient is placed on the operating table in a prone position with his/her head fixed in the Mayfield head holder system. Bony prominences, the chest wall and iliac crests must be adequately padded in order to prevent post-operative skin and peripheral nerve lesions. The head is slightly flexed and positioned in line with the chest to avoid skin creases and curvatures We then position the three-pin Mayfield head holder in the parietal region bilaterally. Bilateral electrode placement only is described. Quadripolar bilateral electrodes or one longer octopolar electrode have been employed. After shaving of the occipital hairline, a small vertical incision is made in the posterior cervical region in the midline from 1 cm above to 1 cm below the external occipital protuberance (EOP). The greater occipital nerve (GON) is usually present about 4 cm lateral to the midline turning in a slight medio-lateral direction before dividing into a medial and a lateral branch about 1 cm above the EOP (17). Two symmetric vertical incisions are then made 4 cm lateral to the EOP on both sides for bilateral placements. A blunt dissection of subcutaneous tissue is then performed exposing the cervical fascia located superficial to the trapezius and splenius capitis muscles. Then a Tuohy needle is inserted from each lateral incision to the midline incision in a lateral-to-medial direction, allowing the insertion of the electrode. The lead is 4 cm lateral from the midline where the main GON trunk is usually located. The wires connected to the

Table 1. Clinical characteristics and main ONS results in chronic drug-resistant CH patients.

Patient no.	Age	Gender	Duration of chronic CH (years)	Follow-up (years)	No. of attacks per day before ONS (median)	No. of attacks per day at last follow-up (median)	% change in attack frequency after ONS	Time to improvement (weeks)	M SJ	ONS on both sides	Steroids after ONS	Battery depletion	Relapse when stimulator off (latency)	Adverse events
1	56	Male	4	NA	4	3	NA	NA	M	No	NA	NA	NA	–
2	69	Male	4	NA	2	2	NA	NA	M	No	NA	NA	NA	–
3	24	Male	1	NA	4	4	NA	NA	M	No	NA	NA	NA	–
4	27	Male	3	NA	6	6	NA	NA	M	No	NA	NA	NA	–
5	45	Female	5	NA	5	5	NA	NA	M	No	NA	NA	NA	–
6	56	Male	3	9.1	5	5	0	–	M	No	Yes	N*	NA	–
7	44	Male	9	8.4	4	episodic CH	NA	12	M	Yes	No	Yes (1)	Yes (8 days)	electrode migration
8	53	Male	18	9.8	3	0.1	96.7	14	M	Yes	No	Yes (1)	Yes (9 days)	–
9	53	Male	3	8.2	4	0.07	98.3	18	M	Yes	No	Yes (1)	Yes (hours)	wire decubitus
10	37	Female	5	8.7	6	episodic CH	NA	9	M	Yes	No	Yes (2)	Yes (2 and 4 days)	–
11	43	Male	5	8.6	6	6	0	–	M	Yes	Yes	Yes (1)	Yes (3 days)	electrode migration
12	33	Male	7	10.7	3	3	0	–	M	No	Yes	Yes (2)	Yes (8 and 1 days)	–
13	33	Male	10	7.6	4	0.1	97.5	32	M	Yes	No	Yes (1)	Yes (1 day)	–
14	31	Male	11	7.4	3	0.03	99	12	M→SJ	Yes	No	Yes (2)	Yes (14 days)	electrode migration
15	53	Male	11	7.3	7	6	14.3	–	M	Yes	Yes	No*	NA	–
16	48	Male	3	7.1	8	0.1	98.8	2	M→SJ	Yes	Yes	Yes (2)	Yes (3 and 2 days)	wire decubitus
17	38	Male	2	6.9	8	8	0	–	M	Yes	Yes	Yes (1)	NA	–
18	33	Female	3	6.8	8	0.03	99.6	9	M	Yes	No	Yes (2)	Yes (5 days both)	–
19	35	Male	4	6.6	4	4	0	–	M	Yes	Yes	Yes (1)	NA	
20	33	Male	4	6.1	10	9	10	–	M	Yes	No	No	NA	electrode migration
21	49	Male	10	6.0	6	0.1	98.3	8	M	Yes	No	No	NA	–
22	54	Male	27	4.9	6	0.1	98.3	1	M	Yes	No	No	NA	–

(continued)

Table 1. Continued.

Patient no.	Age	Gender	Duration of chronic CH (years)	Follow-up (years)	No. of attacks per day before ONS (median)	No. of attacks per day at last follow-up (median)	% change in attack frequency after ONS	Time to improvement (weeks)	M	SJ	ONS on both sides	Steroids after ONS	Battery depletion	Relapse when stimulator off (latency)	Adverse events
23	30	Male	4	5.6	7	episodic CH	NA	37	M		Yes	No	Yes (1)	Yes (1 day)	electrode migration
24	53	Male	2	5.6	7	0.07	99	3	M		No	No	No	NA	–
25	29	Male	10	5.0	8	8	0	–	M		Yes	Yes	No	NA	electrode migration
26	44	Male	10	3.4	4	0.1	97.5	9		SJ	No	No	Yes (2)	Yes (3 and 1 days)	–
27	53	Male	5	3.4	6	0.07	98.8	21		SJ	Yes	No	Yes (2)	Yes (2 and 3 days)	electrode *plus* wire malfunctioning
28	50	Male	3	3.2	3	1.2	60	3		SJ	Yes	No	Yes (1)	Yes (1 day)	–
29	27	Female	3	3.2	6	0.03	99.5	12		SJ	No	No	Yes (1)	Yes (3 days)	–
30	55	Female	16	3.1	3	3	0	–		SJ	No	No	Yes (1)	NA	–
31	37	Male	4	2.9	8	1.6	80	1		SJ	No	No	Yes (2)	Yes (3 and 2 days)	–
32	44	Male	2	2.6	5	1.3	74	22		SJ	No	Yes	Yes (1)	Yes (3 days)	–
33	29	Male	8	2.4	6	6	0	–		SJ	No	No	No	NA	–
34	43	Male	8	1.9	5	1	80	1		SJ	Yes	No	Yes (1)	Yes (4 days)	electrode decubitus
35	43	Male	6	1.6	7	1.4	80	5		SJ	Yes	Yes	No	NA	–
MEAN	42		6.7	6.1	5.7	2.4		9.0							

ONS: occipital nerve stimulation; CH: cluster headache; M: Medtronic; SJ: Saint Jude; NA: not applicable (follow-up less than 6 months).
Note: In the Battery depletion column, the number in brackets refers to the number of battery changes.

Table 2. Inclusion and exclusion criteria for occipital nerve stimulation in drug-resistant chronic cluster headache (CH) patients.

Inclusion criteria
• Age 18–70 years
• Chronic CH according to International Headache Society criteria (1)
• Daily/almost daily attacks in the last year
• Resistance to all known prophylactic drugs for CH (13) including verapamil, lithium carbonate, methysergide, valproate, topiramate, gabapentin, melatonin, pizotifen, indomethacin and other drugs and repeated sphenopalatyne ganglion blockade (14)
• Normal neurological examination
• Normal cerebral magnetic resonance imaging
• Normal psychiatric and psychological profile
Exclusion criteria
• Pregnancy
• Any condition contraindicating positioning of neurostimulator, such as cardiac pathologies
• Patients implanted with other stimulators, e.g. pacemaker, defibrillator etc.
• Patients who have undergone a destructive procedure affecting C2/C3/occipital distribution

electrodes are then tunnelled together in a caudal direction along the occipital and neck midline until about the middle dorsal level. At subcutaneous cervical level, we anchor both electrodes to the underlying fascia with non-resorbable stitches to prevent their caudal dislodgement and relief loops are made at both this site and at more caudal sites along tunnelling passages to prevent excessive tension, with possible discomfort to the patient, and fracture of the leads (17). The age of the patient and his/her individual anatomy will determine the rostro-caudal level of the location of the lead connectors. We use 60 cm or 95 cm length connection wires in order to prevent, again, any excessive strain on the whole system. It is important at this point to create a little subcutaneous pocket at this level in order to allow enough room for both of the connectors and to avoid skin erosions. Another incision is then made in the midline at the lumbar level. Both dorsal and lumbar incisions serve as guides for midline tunnelling of both wires. The two connection wires may then diverge with one on each side if two single-channel impulse generators (IPGs) (Soletra, Medtronic, Libra, St Jude) are used or may run on the same side if a dual-channel IPG is positioned on one side (Activa PC, Medtronic, Libra xp, St Jude) (both Medtronic and St Jude devices are unlabelled for the treatment of CH). We consider the possibility of converting ONS into hypothalamic deep-brain stimulation (DBS), thus leaving intact the implanted IPGs and lead extensions.

Subcutaneous pockets for IPGs are made approximately 4 cm above the iliac crest at the level of the external oblique muscle, paying attention not to jeopardize the latter muscle in order to prevent excessive bleeding and post-operative pain.

Patients were provided with a remote control to turn the stimulator on/off. All other parameters were adjusted during follow-up visits to achieve comfortable paraesthesia in the occipital region.

Results

The summary of results is shown in Table 1.

After a median follow-up of 6.1 years (range 1.6–10.7), the mean number of daily attacks dropped from 5.7 to 2.4 (two-tail paired t-test, $p < 0.001$; Table 1). Twenty out of the 30 (66.7%) patients in the per protocol analysis were responders ($\geq$50% reduction in headache number per day); 12 (40%) of the responders showed a stable improvement characterized by sporadic attacks (i.e. $\leq$3 headache attacks per month); five had a 60–80% reduction in headache number per day; in the remaining responders ($N = 3$) chronic CH was transformed in episodic CH and the condition was stable in the last 3 years follow-up (Table 1). Fluctuation in headache frequency was usually observed before improvement. Sumatriptan injection was the abortive agent in the large majority of CH attacks and its consumption mirrored changes in headache attack frequency (data not shown).

Ten (33.3%) patients were non-responders. Five of these previously showed a $\geq$ 50% reduction in headache number per day lasting a mean of 14.6 months (range 2–48 months); in four of these patients the initial improvement lasted up to 12 months after ONS and in the remaining patient (patient no. 12) improvement lasted 4 years before losing clinical benefit.

After ONS, 20 (66.7%) patients did not take steroids anymore while the remaining 10 received short-term steroid courses. All patients needed to maintain prophylactic treatment for CH.

Following implant, patients remained unstimulated for a median of 3.3 days (range 0–14 days) because attacks were not present in that period. Once attacks reappeared, stimulation was started and improvement occurred after a median of 9 weeks (range: 1–37 weeks; Table 1).

Adverse events

A total of 32 adverse events (AEs) in 23 patients were observed (Table 1). Battery depletions occurred in 21 patients (65.6%) (Table 1): in all cases, the headache worsened when the battery had run down and

improved after battery change. The same happened in the case of malfunction.

The remaining 11 (34.4%) AEs were observed in 10 patients; eight (25%) AEs with regard to the electrodes were: six (18.8%) were electrode migration, one (3.1%) electrode malfunctioned; one (3.1%) decubitus. Three (9.4%) concerned the wire: two (6.3%) were wire decubitus; one (3.1%) malfunctioned (Table 1). In all cases, an intervention was necessary.

All patients perceived paraesthesia in scalp areas innervated by the occipital nerve. Stimulation parameters were set according to the patient's tolerability. In nine patients, stimulation produced unbearable paraesthesia at some time and amplitude was reduced (0–0.3 mA) for periods less than 2 weeks but in no case was it necessary to stop ONS. When reducing amplitude in patients experiencing improvement, headaches relapsed after a few days.

According to previous observations (6–10), many stimulation adjustments were necessary but no single pattern of stimulation parameters was found to predict efficacy. In this study, parameters were set according to tolerability. For Medtronic devices: the range was 30–60 Hz; pulse width 60–120 μs; amplitude 3–8 V. For Saint Jude devices: the range was 30–60 Hz; pulse width 210–350 μs; amplitude 2.5–7 mA. No difference between bipolar and monopolar stimulation was observed in terms of efficacy (data not shown).

Discussion

After a median follow-up of more than 6 years, ONS produced long-lasting improvement in a good fraction of patients (66.7%) and, in 40% of patients, a stable condition characterized by sporadic attacks is maintained.

The main limitation of this study is that it is an open study and the placebo effect is well known in CH (18). So it is not possible to rule out that the observed improvement is the consequence of the natural history of the disease (19). On the other hand, the very long-term follow-up in a large number of patients, worsening in the case of battery depletion, improvement after battery replacement, worsening both when amplitude had to be reduced and in cases of malfunctioning as well are arguments in favour of a true ONS effect. In one patient (no. 10) episodic CH turned back to chronic CH when the battery ran down.

In previous studies, a higher percentage of responders has been reported (12). In Magis et al. (7), study responders were 78.6% (11 out of 14 patients) after a mean follow-up of 36.8 months. Similar good results have been reported by Fontaine et al. (10), 11 responders out of 13 patients (76.9%) after a mean follow-up of 14.6 months and Muller et al. (8), nine responders out of 10 patients (90%) after a mean follow-up of 12 months). In another study, a lower percentage of responders, 35.7% (five of 14 patients) after a median follow-up of 17.5 months has been reported (6). At least part of the discrepancy could be due to short follow-up. Responders to the more invasive hypothalamic DBS were 69.2% after a 2.2 years mean follow-up (20) pointing to ONS as first choice neurostimulation procedure for drug-resistant chronic CH (5).

It is of note that in our study half of the non-responders ($N = 5/10$) showed a sustained improvement after ONS lasting several months up to years before failure; in three of these patients improvement lasted from 2 to 6 months and in the remaining two patients improvement lasted 12 and 48 months respectively. Natural course (fluctuation) (19) of the disease could explain initial benefit particularly when it is short-lasting; while tolerance to ONS could explain loss of efficacy in patients with long-lasting sustained improvement. In the patient with 48 months duration benefit headache worsened when the battery ran down and improved after battery change. In the patient with 12 months sustained improvement after ONS, the headache worsened after battery depletion but did not improve after battery change.

In previous studies side-shift has been noted in 36% of drug-resistant chronic CH patients implanted with ONS, suggesting bilateral implantation also in patients with one-sided CH (without side-shift) (for review, see 12). In our study, 70% of patients suffered bilateral CH before ONS and received bilateral ONS; this high percentage of bilateral CH before ONS is much higher than in previous studies (6–10) so it is difficult to compare the proportion of side-shift. In hypothalamic DBS the rate of side-shift is lower ($N = 1/17$, 6%) (21). One can argue that DBS may protect against side-shift while ONS can facilitate it. None of our patients with unilateral ONS developed contralateral attacks. Long-term studies are needed to disclose the relationship between side-shift and surgical procedures in CH.

In DBS studies, bilateral CH has been suggested to predict poor response (21) while in the present study 71.4% (15/21) of patients with bilateral ONS improved (Table 1). This observation suggests ONS as first choice surgical treatment in bilateral chronic drug-resistant CH.

Unfortunately, we did not find any predictors to tolerance or to failure. Future long-term studies on ONS will possibly identify predictive factors affecting ONS outcome.

All responders in our study could stop frequent steroid use, dramatically reducing its use for short limited periods. Also, the daily sumatriptan injection consumption was markedly reduced after ONS. In the long run the persistent reduction of both steroid and

sumatriptan injection consumption may decrease the risks of severe AEs associated with prolonged use of these drugs (22). We suggest that prolonged steroid consumption and/or daily use of multiple doses of sumatriptan injection should be taken in consideration among criteria suggesting the need for ONS in chronic drug-resistant CH patients with the aim of preventing life-threatening irreversible side effects.

Battery depletion is the most common AE. This is because of the high amplitude voltage necessary to obtain constant stimulation of the occipital nerve (6–10). This problem can be solved by inserting rechargeable batteries; we do this only in responders. Future studies focused on long-term ONS cost effectiveness will clarify if implanting a rechargeable battery should be implanted from the start of the treatment.

Mueller et al. (23) evaluated direct treatment costs of bilateral ONS over a mean follow-up period of 20 months and found a cost of €28,000 per patient. An estimate of the cost of 1 year daily consumption of sumatriptan injection in a chronic drug-resistant CH patient using a mean of four injections per day is €36,500 (one sumatriptan injection costs €25 × four injections × 365 days). Hence, costs of ONS are easily covered in our patients, both those improved to sporadic attacks as well as in patients whose chronic CH is transformed in episodic CH.

In conclusion, our data on long-term follow-up seem to temper earlier ONS results in chronic drug-resistant CH but nevertheless show long-lasting benefit in two-thirds of patients. ONS is well tolerated and safe and has to be offered before proposing the more invasive hypothalamic stimulation. Some responders can develop tolerance even a long time after ONS-related improvement: this phenomenon has never been reported before and has to be considered when planning and interpreting future studies.

Clinical implications

- After a 6-year follow-up (range 1.6–10.7 years) ONS efficacy is confirmed in about two-thirds of chronic drug-resistant cluster headache patients. Prospective studies are further needed
- Some responders can develop tolerance even a long time after ONS-related improvement.

Declaration of conflicting interests

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