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Occipital nerve stimulation for intractable chronic cluster headache: new hope for a dreadful disease?

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Abstract

Chronic cluster headache (CCH) is one of the most painful primary headaches. A small percentage of CCH become intractable (iCCH) and is refractory to the majority of preventing drugs. Various invasive and sometimes destructive procedures have been tempted to help these patients, but none gave satisfactory results for the long term. Hypothalamic deep-brain stimulation (hDBS) has recently raised expectations with an average improvement of 50 to 70%, but is not a riskless procedure. Harmless methods were therefore warranted, and in this perspective occipital nerve stimulation (ONS) trials were undertaken. Up to now, nearly 38 iCCH patients benefited from ONS in the available literature and the technique appears to give results similar to hDBS, having the advantage to have much milder side effects. The mechanism by which ONS is efficient in iCCH remains unknown but preliminary results of neurophysiological and imaging studies suggest ONS is just a symptomatic treatment which does not act on the disease generator. We would however advocate ONS as first choice alternative therapy in iCCH.

Key words: Cluster headache; chronic; drug-resistant; neurostimulation; treatment; occipital nerve stimulation; pathophysiology.

Introduction

Cluster headache is among the most painful primary headaches and is defined by the 2nd Edition of the International Classification of Headache Disorders (1) as attacks of unilateral orbital, supraorbital and/or temporal pain associated with ipsilateral autonomic signs (ptosis, miosis, conjunctival injection, tearing, rhinorrhoea, nasal congestion) and/or restlessness occurring in bouts (clusters) of weeks or months, separated by headache-free intervals of variable length (months or years) in its episodic form (ICHD-II 3.1.1). Chronic cluster headache (CCH, ICHD-II 3.1.2) is a disabling condition affecting 10% of cluster headache patients, which develop it over time or have it from onset (2). Patients are considered as 'chronic' when attacks occur during at least one year without remissions or with remissions lasting less than one month (1). Beside acute therapies – sumatriptan injection, oxygen inhalation or zolmitriptan nasal spray in decreasing order of efficacy –, CCH sufferers most often require one or more preventive drugs to be relieved, the most effective being verapamil, lithium carbonate, steroids (oral or as suboccipital infiltrations), and methysergide (3) (the latter needing regular drug holiday, as the risk of adverse events due to long-term use is significant).

A proportion of patients with CCH are refractory to medical management (intractable CCH or iCCH), although it is unclear how large this problem is since guidelines have only been recently defined (4). iCCH is a dreadful condition which ruins the patients' social, family and professional life, and may push some of them to commit suicide as the ultimate pain-relieving solution. Hence, various invasive and sometimes destructive procedures have been tempted in the last decades, targeting the trigeminal or cranial parasympathetic pathways, among them radiofrequency lesions, glycerol injections or balloon compressions of the Gasserian ganglion, gamma knife surgery or root section of the trigeminal nerve, trigeminal tractotomy, lesions of the nervus intermedius or greater superficial petrosal nerve, blockade or radiofrequency lesions of the pterygopalatine ganglion, and microvascular decompression of the trigeminal nerve combined with nervus intermedius section (5). None of these sometimes mutilating procedures gave long-term satisfactory results.

In the last decade, neurostimulation methods have raised a new hope for iCCH patients. The most

convincing and larger studies performed so far (around 55 published cases) concern hypothalamic deep brain stimulation (hDBS), with an average improvement of 50 to 70% depending on the series (6). Minor and manageable adverse effects are due to the stimulation of the hypothalamus and neighbouring areas (oculomotor disturbances, dizziness, panic attacks) or to the local tissue irritation at the site of stimulator implantation. Unfortunately, as with the implantation of stimulation electrodes in other sites, haemorrhage may occur. hDBS-induced haemorrhage may be minor and asymptomatic, but it was massive and fatal in one chronic cluster headache patient of our series (7). Less risky efficient procedures were therefore warranted. Hence, occipital nerve stimulation (ONS) was considered to help iCCH patients.

Rationale for ONS

Peripheral neurostimulation is a non-destructive and minimal invasive way to control drug-resistant pain (8). Experimental studies have demonstrated that trigeminal and cervical afferents converge on 2nd order nociceptors in the spinal trigeminal nucleus (9). Suboccipital injections of steroids or/and local anaesthetics in the region of the greater occipital nerve have shown efficacy in cluster headache (10). Finally, there were anecdotal reports of clinical benefit with occipital nerve stimulation (ONS) in various types of intractable headache including some cluster patients (11-12). In line with these observations, ONS studies were undertaken in iCCH patients.

Available efficacy studies of ONS in iCCH

Two open-label trials (13-16) and 9 case reports (12, 17-18) with encouraging results have been published up to now. Burns *et al*. implanted 14 iCCH patients (14-15). Efficacy on attack frequency and intensity was assessed according to an estimate of percentage change and subjective satisfaction made by the patients. The first patient was implanted unilaterally and improved, after which the attacks shifted side; hence all subsequent patients were implanted bilaterally. After a mean follow-up of 17 months, 3 patients described a marked improvement ≥ 90%, 3 a moderate improvement of 40 to 60%, and 4 a mild improvement of 20 to 30%.

We performed the other large study and published on 8 iCCH patients prospectively followed at baseline and after implantation using headache diaries (13). We found a mean 79.9% reduction of attack frequency and 50% of intensity; 2 patients

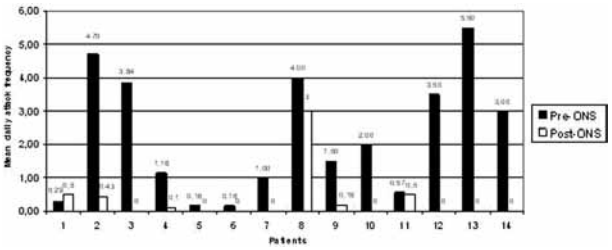

FIG. 1. — Average frequency of cluster headache attacks/day before (pre) and after (post) 4 to 60 months occipital nerve stimulation in individual patients.

became pain-free and 3 had an improvement around 90%. Our patients were implanted unilaterally on the cluster side and only a transient side shift of attacks occurred in 2 patients. All of our patients were treated with several preventive medications at high doses before ONS. After ONS all of them were able to reduce preventive medication, but not to interrupt it completely.

We have presently included 15 iCCH patients with a follow-up ranging from 4 to 60 months (mean 29 months (16) (Fig. 1). One patient had an immediate post operative infection of the material which had to be removed. Nine of the 14 remaining patients are totally pain-free (64%), 2 patients have an improvement in frequency exceeding 90% and one patient a 89% amelioration. Two patients are not responding or describe mild improvement, though the latter is rather satisfied by ONS. Intensity of residual attacks is not improved by ONS. Four patients (29%) were able to reduce their prophylaxis. Subjectively, nine patients are very satisfied by ONS and one patient moderately satisfied.

Finally, a few ONS-treated iCCH patients were also reported by Schwedt *et al* (17). In 1 patient there was a 70% of attack frequency and intensity, with persisting autonomic attacks, in 3 others a 33% improvement in headache days and 20% in intensity. Trentman *et al*. reported 6 cases of cluster headache patients treated with ONS, among them 3 showed an excellent response (18).

Adverse events

Only mild and reversible side effects are reported with ONS.

Batteries run flat rather rapidly because of the high stimulations intensities compared to deep brain stimulation (range 2.4-10 V in our study). In our recent long term follow-up, battery depletion occurred in 8/14 patients i.e. 57%. However, recurrent battery

replacement (until 2/ year in one patient) can now be avoided by the availability of rechargeable systems.

The other main adverse event is local infection of the material. In our trial of 15 patients, 1 had an acute postoperative infection whereas 2 other patients developed delayed infectious signs after 21 and 38 months respectively. The origin of this late appearing infection is unknown, it could be due to cutaneous erosion (mainly in thin subjects) or hematogenous contamination.

Local discomfort, such as neck stiffness, pain at the myofascial incision or the stimulator sites, was a common adverse effect. ONS-induced paresthesias in the territory of the greater occipital nerve (GON) are felt by all patients and may vary in intensity with head and neck position. They are used to assess lead positioning preoperatively if local anaesthesia is used (14), and to select or adjust the stimulation parameters. Their disappearance is often the first sign of a flat battery. In our study, two patients found the stimulation-induced paraesthesias unbearable and decided to switch their stimulators off after 4 months, however one of them was objectively improved by ONS. If general anaesthesia is required for technical reasons, or for the patient's comfort, the surgeon has to rely on anatomical landmarks (13). Hence, close contact of the lead with the GON may be lacking, which probably explains why high stimulation intensities are needed in several patients.

In our experience ONS is also associated with clinical peculiarities like side shift and isolated autonomic paroxysms in around 50% of responders. However, we confirm our first observation that contralateral attacks in implanted iCCH patients remain infrequent (a few per year on average) and does not appear to bother patients at all. Our interpretation for the occurrence of autonomic paroxysms without pain is that ONS does not act on the pathology's generator but is only a symptomatic treatment (see below).

As for hypothalamic deep brain stimulation, there are no known prognostic factors for ONS efficacy. In particular, the response to GON blocks with steroids and local anaesthetics does not seem to be predictive of the therapeutic effect of ONS (12-13). There is at present no placebo-controlled trial of ONS because blinding of the patients is difficult to achieve due to the paraesthesias. An alternative might be to use low voltage stimulations barely producing paraesthesias as a control. However, the lowest effective stimulation intensity able to produce an effect of ONS has not been determined yet. It is nonetheless unlikely that the clinical improvements of iCCH found with ONS are due to a placebo effect or to the natural evolution of the disease, since most patients responding to the neurostimulation severe attacks resumed rapidly after cessation of the stimulation due to an empty battery (13).

Mode of action of ONS

The precise neurobiological mechanisms by which ONS can improve iCCH are still obscure, but our recent findings are providing new insights in their understanding. We found no change in pain thresholds after ONS (13), which argues against a direct non-specific analgesic effect. As mentioned above, one of the rationale for ONS in headaches was the experimental evidence of convergence of cervical and trigeminal nociceptive afferents on 2nd order nociceptors in trigeminal nucleus caudalis (9). The nociception-specific blink reflex, mediated by a polysynaptic network in the medulla, increased with duration of ONS in our study (13) which could be due to sensitisation in trigeminal nucleus caudalis and is probably not related to the clinical effect of ONS. A more likely explanation for the therapeutic effect of ONS in iCCH is the induction of slow neuromodulatory changes in centres belonging to the pain matrix or playing a pathogenic role in the disorder. For instance, in a functional imaging study of ONS in chronic migraine, activity of an area in the dorsal rostral pons, known to be activated during migraine attacks, was modulated proportionally to the pain, whereas activity in the left pulvinar was correlated with ONS-induced paraesthesias (11). Such slow plastic changes might explain why the therapeutic effect after ONS takes some time to appear.

Interestingly, the preliminary results of a study in which we explored cerebral metabolism with 18-fluoro-deoxyglucose PET scanning in 10 iCCH patients before and after implantation (19), show a metabolic normalization in various regions of the so-called pain neuromatrix after several months of ONS, and a lack of short-term changes induced by the stimulation, supporting the previous hypothesis that ONS acts through slow neuromodulatory processes. Moreover, ONS responders exhibit a selective activation of perigenual cingular cortex, a pivotal structure in the control of the endogenous opioid system, suggesting that ONS may restore balance within dysfunctioning pain control centres. That ONS is nothing but a symptomatic treatment is illustrated by the discovery of a persistent hypothalamic hypermetabolism ipsilateral to the headache that is not modified by the stimulation. This persistent hypothalamic activation could explain why autonomic attacks may persist despite pain relief and why cluster attacks recur shortly after stimulator arrest.

Conclusions

Occipital nerve stimulation offers new hope for patients suffering from intractable chronic cluster headache. ONS has the advantage to be a relatively safe and effective procedure. Hence, 2 recent studies of a total of 29 patients show that ONS appears effective in the treatment of iCCH: 90% or more improvement in 14 patients, among them 9 are pain-free. These long-term results are similar to those of the more invasive hypothalamic DBS. Only minor local adverse effects are reported. However, preliminary physiopathological studies and clinical observation suggest that ONS does not act on the disease generator, but is just a symptomatic treatment, and placebo-controlled trials are lacking. At present, we advocate that ONS should nonetheless be recommended for iCCH patients before more invasive procedures like hDBS.

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