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SESSION III LOCAL TREATMENTS

Peripheral neurostimulation in primary headaches

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Abstract Peripheral neurostimulation techniques have emerged as promising treatments for patients with medically intractable, highly disabling chronic daily headaches including chronic migraine (CM) and chronic cluster headache (CCH) besides other less common headache syndromes. Encouraging controlled and open label data in medically intractable CM and trigeminal autonomic cephalalgias (TACs) have suggested a meaningful therapeutic role for occipital nerve stimulation (ONS). In view of the frequent occurrence of pain in the first branch of trigeminal nerve, percutaneous supraorbital nerve stimulation alone or in combination with ONS has been used successfully in open label series of CM and CCH patients. In view of its connections with the trigeminovascular system, the stimulation of the sphenopalatine ganglion has been used as a therapeutic target for the treatment of acute cluster headache attacks, with promising results. Preliminary data in patients with epilepsy and migraine have suggested a potential efficacy of vagus nerve stimulation in the treatment of primary headaches. Non-invasive devices targeting peripheral nerves have been developed and initial experience is emerging for the acute and preventive treatments of primary headache disorders. This review analyses the available evidence on the efficacy and safety of the different peripheral neurostimulation techniques.

Keywords Occipital nerve stimulation · Sphenopalatine ganglion stimulation · Vagus nerve stimulation · Chronic migraine · Trigeminal autonomic cephalalgias

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Introduction

Chronic daily headache is a major worldwide health problem that affects 3–5 % of the population [1] and results in substantial disability. Advances in the management of headache disorders have meant that a high proportion of patients can be effectively treated with medical treatments. However, a significant minority of these patients are intractable to conventional medical treatments. There is, therefore, a clear need for novel approaches for the management of this patient group. Neurostimulation therapies that entail peripheral or central nervous system targets are emerging as very promising approaches. The most widely used peripheral target is the occipital nerve. Open label studies in medically intractable trigeminal autonomic cephalalgias (TACs) have shown good tolerability and significant, long-term benefit of occipital nerve stimulation (ONS) [2, 3]. Encouraging open label results in chronic migraine (CM) patients have led to three multicenter randomized trials [4–6]. The benefits of ONS shown in these trials were less dramatic than hoped for. However, the studies had methodological flaws, unmitigated placebo effects and high rates of surgical complications, which may have obscured the full beneficial effect of ONS. More recently the use of different peripheral nervous targets, such as the sphenopalatine ganglion (SPG), supraorbital nerves and vagus nerves, has shown promising results. This

article reviews the available evidence for the use of stimulation of the occipital, supraorbital and vagus nerves as well as the sphenopalatine ganglion in the management of headache disorders.

Occipital nerve stimulation

The rationale for the use of ONS in headaches came from animal studies showing the convergence of cervical, somatic and dural afferents on second-order nociceptors in the trigeminocervical complex [7]. In recent years, ONS has been used in various primary headache syndromes, including migraine, cluster headache (CH), hemicrania continua (HC), SUNCT (Short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) and SUNA (Short lasting unilateral neuralgiform headache attacks with autonomic symptoms) [2, 3].

Open-label studies on the use of ONS in medically intractable CM showed very encouraging outcomes. Forty-three of 51 patients treated (84 %) reported at least 50 % improvement [2]. Based on this initial experience, three randomized controlled trials (RCTs) in the use of ONS for the prevention of CM were undertaken. The ONSTIM feasibility trial (ONS for the Treatment of Intractable chronic Migraine) was a multicentre, randomized, single-blind, controlled study [5]. The study recruited 66 patients who met the revised International Classification of Headache Disorders (ICHD-II) criteria for CM [8] and had responded to occipital nerve blocks. Patients were randomized in a ratio of 2:1:1 to adjustable stimulation, preset stimulation and medical management. The responder rate was defined as 50 % reduction in headache days/month or at least a three-point drop (on VRS 0–10) in pain intensity at 3 months. The responder rate was 39 % in the adjustable stimulation group compared with 6 % in the preset stimulation group and none in the medical management group. Lead migration occurred in 12 of 51 patients (24 %). In the PRISM trial [4], available in abstract form only, 125 drug-refractory CM patients were treated with ONS or sham. The study showed a mean decrease of 5.5 migraine days/month in 63 patients who received active stimulation and a decrease of 3.9 days in 62 patients who received sham stimulation at 12 weeks. This difference was not statistically different. In the third RCT by Silberstein et al. [6] 157 CM patients were treated with ONS. Responders were defined as patients with a reduction of the mean daily pain intensity from baseline of 50 % or greater. The study failed to achieve the primary endpoint, with the proportion of responders in the active group (17.1 %) not differing significantly compared to the control group (13.5 %). However, the number of headache days was significantly reduced in the ONS group compared to the sham group (−27.2 % vs. −14.9 %). The migraine-related disability also decreased with active ONS.

These studies tried to explore the safety and efficacy of ONS in CM using rigorous study designs but have some methodological flaws. The follow-up of 12 weeks may not be a sufficient timeframe to assess the outcome of a surgical procedure in primary headaches. From the open label experience with ONS, some patients report meaningful improvement a few months after the implant [2]; hence a longer follow up period may be more appropriate. As part of the inclusion criteria of some of these studies, only patients with pain centred in the C2–C3 territory were included. This subpopulation of patients may not be representative of the CM population that report pain in the trigeminal territories as well as in the cervical ones in the majority of cases. Additionally, these studies included patients who have failed to respond to at least two classes of preventive treatments. One of them was the class of beta-blockers [6]. There is no evidence for efficacy of beta-blockers in CM. This raises the possibility that the subgroup of CM patients selected and treated in these trials may not have been medically intractable, as defined by international consensus [9]. Finally, the study by Silberstein et al. [6] cannot be considered double-blind, since the patients underwent a trial phase during which ONS-induced paraesthesia were induced before being randomized thereby potentially unblinding the study population.

Future studies should focus on selection criteria that include the highly disabled patients seen in tertiary care headache centres. The surgical treatment should be offered only to patients with CM that cannot otherwise be managed with medical treatments, thus defined medically intractable [9]. On this note, due to the demonstrated efficacy of Onabotulinum toxin A in the prophylaxis of CM [10], Onabotulinum toxin A should be included within the list of medication that CM patients must fail to respond to in order to be suitable for surgery. Patients with concurrent medication overuse headache need to be studied separately. In addition, the blinding process should be addressed more carefully; long-term follow-up should be reported to provide more stable estimates of outcome measures.

ONS seems to be slightly more effective in the treatment of chronic medically intractable TACs than CM. To date, open label data in 91 medically intractable CCH patients treated with ONS have shown a favourable outcome in 67 % of cases [2]. However, no RCTs have been performed yet. A novel study design in headache neuromodulation has been suggested for a double blind RCT in the prevention of medically intractable CCH [11]. Blinding in peripheral neuromodulation studies is difficult because stimulation is felt by the patient as paraesthesia in the occipital region; therefore, it is not possible to perform a blinded study in which active stimulation is compared to no (sham) stimulation. Using the same principle

of a vagal nerve stimulation study in epilepsy [12], the authors proposed a way to perform a blind study in neuromodulation by comparing high- and low-amplitude stimulation and establishing a dose–response curve in a blinded way. The study would compare patients treated with ONS at high stimulation intensity (100 %), which corresponds to the sub-pain threshold with patients treated at low stimulation intensity (30 % of the range between perception and sub-pain thresholds). Although innovative in trying to reduce blinding issues, it should be noted that this kind of design will ultimately be unable to answer the paramount question of whether ONS is more effective than placebo. The results of the study will only help clarify whether high-intensity stimulation is superior to low-intensity stimulation. Notably, studies using spinal cord stimulation (SCS) for the treatment of angina and neuropathic pain showed that even sub-threshold stimulation can lead to some degree of pain relief [13, 14].

ONS has also been shown to be effective in hemicrania continua (HC) [15, 16]. Lambru et al. [3] recently reported the outcome of nine medically intractable SUNCT ($n = 6$) and SUNA ($n = 3$) patients treated with bilateral ONS. Data on frequency, intensity and duration of attacks were obtained from headache diaries at baseline and after implantation, along with data on disability, anxiety and depression and quality of life scales administered pre and post implantation. At a median follow-up of 38 months (range 24–55 months), all but one patient showed substantial improvements: four patients became pain free, two almost pain free and two had a remarkable reduction in attack frequency and severity. The implant was well tolerated overall with only one patient developing lead migration and one patient developing erosion of the electrode.

Sphenopalatine ganglion stimulation

The sphenopalatine ganglion is an extracranial parasympathetic ganglion located in the pterygopalatine fossa. Postganglionic parasympathetic fibres from the SPG innervate facial structures such as the salivary and lacrimal glands, the nasopharyngeal mucosa and the cerebral and meningeal blood vessels [17]. It has been suggested that the trigemino-autonomic reflex plays an important role in the pathophysiology of primary headaches [18]. The SPG is an important structure of this anatomo-functional reflex, responsible for the ipsilateral cranial autonomic features typical of TACs and, to a lesser degree, of other primary headaches such as migraine.

Based on this assumption, the SPG has been targeted over the years to treat CH by various lesional techniques (anaesthetic blocks, radiosurgery and gamma knife, alcohol injections, pulsed radiofrequency ablations). The success rates seem promising (varying from 46 to 85 %), but the benefits have been transient [19]. Because of this transient effect and the irreversible complications of the lesioning interventions, a non-destructive approach using acute percutaneous SPG stimulator with a removable electrode was examined in five patients with CH. SPG stimulation resulted in complete resolution of the CH attack in 11/18 attacks (61 %), partial resolution (>50 % VAS reduction) in 3/18 attacks and minimal to no relief in 4/18 attacks. Stimulation also resolved the associated autonomic features of CH [20]. Spontaneous or induced migraine attacks were treated with a percutaneous removable SPG stimulator in 11 migraine patients. Two patients had complete abolition of their induced headaches within 3 min of SPG stimulation, three had reduction in pain, five had no response and one was not stimulated [21].

Based on these preliminary findings, a new implantable microstimulator was developed and a multicenter randomised double-blind and sham-controlled trial has been conducted to examine the efficacy of acute SPG stimulation in refractory CCH [22]. This device is powered and controlled transcutaneously by electromagnetic waves. In this study, 32 CCH patients experiencing a minimum of four attacks per week were included. The design of the study consisted of a 4-week baseline period, followed by a post-implant stabilization and therapy titration period. The experimental period lasted until 30 CH attacks were treated or, if attack frequency was not high enough, for a maximum of 8 weeks. During this period, patients were instructed to use the stimulator to treat each attack for 15 min. The pain score was recorded using an electronic headache diary prior to each use and after the start of stimulation. Three stimulation doses were randomly applied when treatment was initiated by the patient for a CH attack: full stimulation, sub-perception stimulation and sham stimulation. The primary endpoint of pain relief after 15 min of stimulation was achieved in 67.1 % of full stimulation-treated attacks compared to 7.4 % of sham stimulation treated attacks. Remarkably, 43 % of patients experienced an attack frequency reduction of ≥50 % from baseline. Given the slight tingling sensation that accompanies stimulation of the SPG, a placebo effect cannot be excluded. In view of the apparent preventive effect of SPG stimulation, a multicentre trial currently underway aims to explore the efficacy of SPG stimulation in the preventive treatment of CM (NCT01540799).

Vagus nerve stimulation

Vagus nerve stimulation (VNS) is a well-established treatment for intractable epilepsy and depression. The mechanism of action still needs to be fully elucidated. In

animal studies, it has been demonstrated that electrical, chemical and physiologic activation of vagal afferents produces analgesic effects. A study using left VNS in animal models showed a significant decreased of fos-immunoreactivity in trigeminal nucleus caudalis neurons [23]. Initial positive data on the efficacy of VNS in migraine was gathered from retrospective analysis of patients implanted for the treatment of epilepsy [24, 25]. In another study, two of four patients with refractory CM and depression improved significantly with VNS [26]. Similarly, a positive effect of VNS was reported in two CCH patients who also suffered from severe depression [27].

Initial experience using non-invasive VNS has been presented at the European Headache and Migraine Trust International Congress (London, 2012). The transcutaneous VNS device (tVNS Gammacore®) was used in 18 patients: 12 migraine, two CCH patients and two HC patients. The stimulation was applied 3 times/day for 90 s each time. Ten patients out of 13 with data available stopped tVNS due to lack of efficacy and/or side effects [28]. In another pilot study, seven episodic and seven chronic CH patients were treated with tVNS. An improvement after 13 weeks of trial was reported by 13 patients [29]. Two patients with HC initially treated with ONS, who subsequently had to have the stimulator explanted, were treated successfully with tVNS [30]. Currently, some RCTs are ongoing to validate this therapeutic approach in the acute and preventive treatments of chronic headaches (NCT01667250, NCT01701245, NCT01792817).

Supraorbital nerve stimulation

Percutaneous supraorbital nerve stimulation (SON) produced almost complete resolution of symptoms in a patient with refractory CCH. The continuous stimulation led to a dramatic reduction in the frequency of attacks. Moreover, the patient was able to abort a CH attack by switching the stimulator programme [31]. In a retrospective study of five patients with refractory TACs (four patients had CH and one SUNCT), an implantable supraorbital and supratrochlear neuromodulation system led to a substantial reduction in pain intensity. Adverse events included skin erosion and wire infection [32].

Percutaneous SON has also been used in combination with ONS. The rationale of this combination was to try to cover the painful area as best as possible, according to the proposed mode of action of PNS [33]. Reed et al. [34] used combined ONS and SON in seven CM patients. All patients derived significant benefit and preferred the combined stimulation as opposed to the ONS stimulation alone. Recently, the efficacy of a novel transcutaneous supraorbital electrostimulation device (Cefaly, STX-Med, Liège, Belgium) in the prophylaxis of migraine was studied in a double-blind, randomized, sham-controlled trial [35]. Sixty-seven migraine patients with at least two attacks/month were recruited. Verum or sham stimulation was applied daily for 20 min during the three-month trial. The primary outcome measures were achieved. Patients treated with the verum stimulation obtained a significant reduction in the mean migraine days and the responder rate (50 % reduction of monthly migraine days between run-in and third month of treatment) was significantly higher in the verum compared to the sham group.

Conclusions

PNS techniques have emerged as potential meaningful management options in primary headache disorders. A growing armamentarium of different devices is becoming available; however, their clinical use is limited by the lack of proper controlled data [36]. Since peripheral nerve stimulation is always perceived by patients, a proper sham group is practically impossible. For this reason, PNS should be considered only in patients with primary chronic headache disorders, in whom the therapies recommended by the international guidelines have failed to produce significant benefit. Candidates for PNS should be carefully evaluated in tertiary care headache centres, preferably with a multidisciplinary set up. More effective and less invasive procedures should be offered first [37].

Based on published evidence, the use of ONS and SPG are advisable for the preventive and abortive treatment, respectively, of medically intractable CCH [2, 22]. However, properly controlled double blind trials are needed to ultimately confirm the open label evidence, especially for ONS. The use of ONS in CM seems acceptable albeit that the treatment effect is relatively modest in the trials. Future trials in CM should only include patients that fulfill the definition of medically intractable chronic headache [9]. Additionally, since Onabotulinum toxin A is the only medication approved for the prophylaxis of CM in adults [10], future neurostimulation study designs for CM should consider patients that have failed or not responded adequately to Onabotulinum toxin A. Furthermore, since medication overuse headache is relatively common in CM the role of neurostimulation therapies in this subgroup of patients needs to be studied.

References

1. Scher A, Stewart WF, Liberman J, Lipton RB (1998) Prevalence of frequent headache in a population sample. Headache 38:497–506
2. Magis D, Schoenen J (2012) Advances and challenges in neurostimulation for headaches. Lancet Neurol 11:708–719

3. Lambru G, Shanahan P, Watkins L, Matharu MS (2014) Occipital nerve stimulation in the treatment of medically intractable SUNCT and SUNA. Pain Physician 17(1):29–41
4. Lipton R, Goadsby P, Cady R, Aurora SK, Grosberg B, Freitag F et al (2009) PRISM study: occipital nerve stimulation for treatment-refractory migraine. Cephalalgia 29:30
5. Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ (2011) Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia 31:271–285
6. Silberstein S, Dodick D, Saper J, Huh B, Slavin KV, Sharan A et al (2012) Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia 32(16):1165–1179
7. Kerr FW, Olafson RA (1961) Trigeminal and cervical volleys. Convergence on single units in the spinal gray at C-1 and C-2. Arch Neurol 5:171–178
8. The International Classification of Headache Disorders: 2nd edition (2004) Headache Classification Subcommittee of The International Headache Society Cephalalgia 24(Suppl 1):1–160
9. Goadsby PJ, Schoenen J, Ferrari MD, Silberstein SD, Dodick D (2006) Towards a definition of intractable headache for use in clinical practice and trials. Cephalalgia 26:1168–1170
10. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, Diener HC, Brin MF, PREEMPT Chronic Migraine Study Group (2010) Onabotulinum toxin A for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 50(6):921–936
11. Wilbrink LA, Teernstra OP, Haan J et al (2013) Occipital nerve stimulation in medically intractable, chronic cluster headache. The ICON study: rationale and protocol of a randomised trial. Cephalalgia 33(15):1238–1247
12. Ben-Menachem E, Mañon-Espaillat R, Ristanovic R et al (1994) Vagus nerve stimulation for treatment of partial seizures. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. Epilepsia 35:616–626
13. Eddicks S, Maier-Hauff K, Schenk M, Muller A, Baumann G, Theres H (2007) Thoracic spinal cord stimulation improves functional status and relieves symptoms in patients with refractory angina pectoris: the first placebo-controlled randomised study. Heart 93:585–590
14. Wolter T, Kiemen A, Porzelius C, Kaube H (2012) Effects of sub-perception threshold spinal cord stimulation in neuropathic pain: a randomized controlled double-blind crossover study. Eur J Pain 16(5):648–655
15. Schwedt TJ, Dodick DW, Trentman TL, Zimmerman RS (2006) Occipital nerve stimulation for chronic cluster headache and hemicrania continua: pain relief and persistence of autonomic features. Cephalalgia 26:1025–1027
16. Burns B, Watkins L, Goadsby PJ (2008) Treatment of hemicrania continua by occipital nerve stimulation with a bion device: long-term follow-up of a crossover study. Lancet Neurol 7:1001–1012
17. Ruskell GL (2003) Orbital passage of pterygopalatine ganglion efferents to paranasal sinuses and nasal mucosa in man. Cells Tissues Organs 175:223–228
18. Goadsby PJ, Lipton RB (1997) A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic feature, including new cases. Brain 120(Pt 1):193–209
19. Blumenfeld A, Ashkenazi A, Napchan U, Bender SD, Klein BC, Berliner R et al (2013) Expert consensus recommendations for the performance of peripheral nerve blocks for headaches—a narrative review. Headache 53:437–446
20. Ansarinia M, Rezai A, Tepper SJ, Steiner CP, Stump J, Stanton-Hicks M et al (2010) Electrical stimulation of sphenopalatine ganglion for acute treatment of cluster headaches. Headache 50:1164–1174
21. Tepper SJ, Rezai A, Narouze S, Steiner C, Mohajer P, Ansarinia M (2009) Acute treatment of intractable migraine with sphenopalatine ganglion electrical stimulation. Headache 49:983–989
22. Schoenen J, Jensen RH, Lantéri-Minet M, Láinez MJ, Gaul C, Goodman AM (2013) Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. Cephalalgia 33(10):816–830
23. Kirchner A, Birklein F, Stefan H, Handwerker HO (2000) Left vagus nerve stimulation suppresses experimentally induced pain. Neurology 55:1167–1171
24. Hord ED, Evans MS, Mueed S, Adamolekun B, Naritoku DK (2003) The effect of vagus nerve stimulation on migraines. J Pain 4:530–534
25. Lenaerts ME, Oommen KJ, Couch JR, Skaggs V (2008) Can vagus nerve stimulation help migraine? Cephalalgia 28:392–395
26. Cecchini AP, Mea E, Tullo V et al (2009) Vagus nerve stimulation in drug-resistant daily chronic migraine with depression: preliminary data. Neurol Sci 30(suppl 1):S101–S104
27. Mauskop A (2005) Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches. Cephalalgia 25:82–86
28. Magis D, Gérard P, Schoenen J (2013) Transcutaneous vagus nerve stimulation (tVNS) for headache prophylaxis: initial experience. J Headache Pain 1(Suppl 1):P198
29. Nesbitt AD, Marin JCA, Tomkins E, Ruttledge MH, Goadsby PJ (2013) Non-invasive vagus nerve stimulation for the treatment of cluster headache: a case series. J Headache Pain 1(Suppl 1):P231
30. Nesbitt AD, Marin JCA, Goadsby PJ (2013) Treatment of hemicrania continua by non-invasive vagus nerve stimulation in 2 patients previously treated with occipital nerve stimulation. J Headache Pain 14(Suppl 1):P230
31. Narouze SN, Kapural L (2007) Supraorbital nerve electric stimulation for the treatment of intractable chronic cluster headache: a case report. Headache 47:1100–1102
32. Vaisman J, Markley H, Ordia J, Deer T (2012) The treatment of medically intractable trigeminal autonomic cephalalgia with supraorbital/supratrochlear stimulation: a retrospective case series. Neuromodulation 15(4):374–380
33. Doubell T, Mannion RJ, Woolf CJ (1999) The dorsal horn: state dependent sensory processing, plasticity and the generation of pain. In: Melzack PDWR (ed) Textbook of pain, vol 59, 4th edn. Churchill Livingstone, London, pp 165–180
34. Reed KL, Black SB, Banta CJ II, Will KR (2010) Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: initial experience. Cephalalgia 30:260–271
35. Schoenen J, Vandersmissen B, Jeangette S, Herroelen L, Vandenheede M, Gérard P, Magis D (2013) Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology 80(8):697–704
36. Palmisani S, Al-Kaisy A, Arcioni R, Smith T, Negro A, Lambru G, Bandikatla V, Carson E, Martelletti P (2013) A six year retrospective review of occipital nerve stimulation practice - controversies and challenges of an emerging technique for treating refractory headache syndromes. J Headache Pain 14(1):67
37. Martelletti P, Jensen RH, Antal A, Arcioni R et al (2013) Neuromodulation of chronic headaches: position statement from the European Headache Federation. J Headache Pain 14(1):86