Review

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Invasive pericranial nerve interventions

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Abstract

Background: In many patients suffering from primary headaches, the available pharmacological and behavioural treatments are not satisfactory. This is a review of (minimally) invasive interventions targeting pericranial nerves that could be effective in refractory patients.

Methods: The interventions we will cover have in common pericranial nerves as targets, but are distinct according to their rationale, modality and invasiveness. They range from nerve blocks/infiltrations to the percutaneous implantation of neurostimulators and surgical decompression procedures. We have critically analysed the published data (PubMed) on their effectiveness and tolerability.

Results and conclusions: There is clear evidence for a preventative effect of suboccipital injections of local anaesthetics and/or steroids in cluster headache, while evidence for such an effect is weak in migraine. Percutaneous occipital nerve stimulation (ONS) provides significant long-term relief in more than half of drug-resistant chronic cluster headache patients, but no sham-controlled trial has tested this. The evidence that ONS has lasting beneficial effects in chronic migraine is at best equivocal. Suboccipital infiltrations are quasi-devoid of side effects, while ONS is endowed with numerous, though reversible, adverse events. Claims that surgical decompression of multiple pericranial nerves is effective in migraine are not substantiated by large, rigorous, randomized and sham-controlled trials.

Keywords

Migraine, cluster headache, treatment, surgical decompression, percutaneous neurostimulation, nerve blocks

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Introduction

Primary headaches altogether represent the most common neurological disorders and are usually associated with disability, decreased quality of life and financial costs both for the affected individual and for society. Among primary headaches, migraine and cluster headaches are the ones that more often affect quality of life, especially their chronic forms, which are frequently associated with acute medication overuse and low responsiveness to preventative pharmacological treatments. Approximately 11% of all migraine patients and approximately 1% of chronic cluster headache (CCH) patients become refractory to all available pharmacological treatments (1).

The management of migraine and cluster headache is multifaceted. Besides advice on lifestyle, the management of cluster headache is based on acute interventions in order to alleviate the attack and preventative treatments in order to reduce attack frequency and disability. However, the efficacy of preventive drugs is limited in many patients, and most of these pharmacological treatments can have cumbersome adverse effects (2). Alternative treatments have thus been used for some time, but they have received increasing attention only recently because of the lack of new advances in pharmacotherapy.

Migraine and cluster headache are considered to be central neurovascular disorders. The headache is likely generated in the trigeminovascular system that cortical (migraine) or subcortical (cluster headache) dysfunctions are thought to activate (3). It was recently shown that trigeminovascular meningeal afferents project through the skull (4) and that activation of these extracranial afferents in rats causes the release of calcitonin gene related peptide (CGRP) from the dura,

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suggesting that extracranial noxious signals may influence meningeal nociception (5). Despite the scarcity of data favouring a role for pericranial nerves in primary headaches, these findings may offer a rationale for the various therapeutic interventions based on pericranial nerves that have been used in refractory patients for some time. Many patients indeed state that their pain is localised to the surface of the head or neck, which is in close anatomical relationship with branches of the pericranial nerves. Although these superficial pain locations were likely to represent referred pain from the visceral part of the ophthalmic division of the trigeminal nerve, they led to surgical interventions on superficial cranial nerves for the treatment of migraine and other headache types by as early as the first half of the 20th century. Renowned physicians such as Cushing, Penfield or Rowbotham pioneered subtotal ophthalmic nerve or cervical root rhizotomies, sections of supraorbital, supratrochlear or occipital nerves, excisions of the stellate ganglion or pericarotid sympathectomies, and even craniotomies (6). Various invasive lesional procedures have also been performed over time in cluster headache, targeting the trigeminal or cranial parasympathetic pathways and using radiofrequency lesions, glycerol injections or balloon compressions of the Gasserian ganglion, Gamma Knife surgery or section of the trigeminal root, trigeminal tractotomy, lesions of the nervus intermedius or greater superficial petrosal nerve, blockade or radiofrequency lesions of the sphenopalatine ganglion and microvascular decompression of the trigeminal nerve combined with nervus intermedius section (7). Although spectacular results were reported in some patients, most of them had a mixture of different headache types and few showed satisfactory long-term results, despite the mutilating character of the procedures (6).

We will focus here on some of the invasive interventions that are used to treat migraine and cluster headache and are supposed to act on pericranial nerve branches. We have schematically ordered them according to their increasing invasiveness from infiltrations/blocks to percutaneous neurostimulations and surgical decompressions.

Blocks and infiltrations

Peripheral nerve blocks have been used for some time in order to treat headaches (8). In most studies they targeted the greater occipital nerve (GON) because of the known anatomo-physiological convergence of C2 dermatoma and trigeminovascular afferents in the spinal trigeminal nucleus that underlies referred pain from the neck to the orbitofrontal regions innervated by the ophthalmic nerve (9). Local anaesthetics are commonly injected alone or in combination with corticosteroids. The procedure is minimally invasive, inexpensive, safe and it can be performed on an outpatient basis.

Migraine

The most relevant studies are summarized in Table 1 (10–14). Five controlled trials are available, but unfortunately no standardised methods were used. The selection criteria of patients varied between studies (some had fixed unilateral headache, others not) and so did the timing of the procedure (ictal or inter-ictal), the technique of infiltrations or blocks (unilateral or bilateral, associated blocks of other pericranial nerves or trigger point injections, one or more interventions), the compounds used for the blocks (local anaesthetics alone or combined with different types and dosages of steroids) and the outcome measures (number of headache-free days, percentage reduction of headache days or attacks, non-standardised pain indices). A comparison of results between studies is therefore challenging.

Overall, a complete or partial benefit for migraine prevention was reported in 48–100% of adult migraineurs, lasting from a few days to several months. A retrospective study also found a partial benefit (<35%) from GON injections in paediatric chronic migraineurs (15). In none of the controlled studies on GON blocks was the addition of steroids found to be superior to the injection of a local anaesthetic alone, commonly used as placebo. In one controlled single-blinded study, the benefit was quite modest (10). Similarly, in a placebo-controlled randomized double-blinded trial performed in episodic ($n = 54$) and chronic ($n = 9$) migraineurs, the block with steroids showed a non-significant percentage of >50% responders (~30%) (11). In a third randomised trial in episodic migraine patients, 1.0 mL of lidocaine 2% injected suboccipitally induced a similar decrease of pain severity and frequency for up to 8 weeks, whether it was combined with 0.5 mL saline (control group: $n = 24$) or with 0.5 mL triamcinolone ($n = 24$) (12).

Two recent double-blind placebo-controlled studies comparing GON injections of saline (placebo) with 0.5% bupivacaine (verum) found that the latter provided partial benefit in migraine patients. In the first study, chronic migraine patients received four weekly injections (13). The number of headache days decreased from 16.9 ± 5.7 to 13.2 ± 6.7 in the placebo group ($p = 0.035$), but from 18.1 ± 5.3 to 8.8 ± 4.8 ($p < 0.001$) in verum-treated patients, and the superior effect of bupivacaine was confirmed in an open 2-month extension study. In the second study, patients suffering from chronic refractory migraine had a single ultrasound-guided GON block of saline or bupivacaine 0.5%. Four weeks later, the average pain intensity score on the injected side was significantly decreased in the

Table 1. Preventive effects of GON blocks in migraine and cluster headache (prospective controlled studies).

References	Type of study	Number of migraine patients	U/B headache	U/B treatment	Number of treatments	Medications used	Outcome	Follow-up (weeks)	Outcome evaluation
MIGRAINE									
10	Single-blinded RCT	37 TM (20 MOH)	?	B (plus 12 "trigger points")	1	P : 0.9 mL lidocaine 2% + 0.9 mL bupivacaine 0.5% + 0.2 mL saline V: 0.9 mL lidocaine 2% + 0.9 mL bupivacaine 0.5% + 0.2 mL triamcinolone 40 mg/mL	Acute pain relief Headache-free for 2.7 or 1 ± 1.1 days (V) No difference between the two groups	4	Modest/good
11	Double-blinded RCT	54 EM and 9 CM (30 P + 33 V)	U (7 V; 7 P) B (26 V; 23 P)	U (7 V; 7 P) B 26 V; 23 P)	1	P : 0.25 mL lidocaine 1% + 2.75 mL saline V: 2.5 mL bupivacaine 0.5% + 0.5 mL methylprednisolone 40 mg/mL	≥50% responders: P: 30%; V: 30% No difference between the two groups	4	Modest/good
12	Double-blinded RCT	48 EM (24 P + 24 V)	?	B	1	P : 1 mL lidocaine 2% + 0.5 mL saline V: 1 mL lidocaine 2% + 0.5 mL triamcinolone ? mg/mL	Reduced pain severity (~27–28%) and pain frequency (~18–28%). No difference between the two groups	8	Modest/good
13	Double-blinded RCT	72 CM (33 P + 39 V)	?	?	4	P: 2.5 mL saline V: 1.5 mL of 0.5% bupivacaine + 1 mL saline	Reduced number of headache days (~51.4%) and VAS pain score (~36.9 %) in the V group Reduced number of headache days (~21.9%) and VAS pain score (~17.3 %) in the P group Significant difference between groups	4 (after the last GON blockade)	Good
14	Double-blinded RCT	23 CM (refractory) (12 P + 11 V)	?	U	1	P: 1.5 mL saline V: 1.5 mL bupivacaine 0.5%	Reduced VAS pain score on the injection side (~60% in the V group, ~34% in the P group) Trend for significant difference between the two groups	4	Good

(continued)

Table 1. Continued.

References	Type of study	Number of migraine patients	U/B headache	U/B treatment	Number of treatments	Medications used	Outcome	Follow-up (weeks)	Outcome evaluation
CLUSTER HEADACHE									
29	Double-blinded RCT	16 ECH and 7 CCH (10 P + 13 V)	–	–	1	P : 2 mL saline + 0.5 mL xylocaine 2% V: 2 mL long-acting + rapid-acting betamethasone + 0.5 mL xylocaine 2%	Attack-free patients 1 week after GON injection: P: 0.0%; V: 84.6% Attack-free patients at the 4 weeks follow-up: P with additional prophylactic treatment: 80.0%; V: 69.2%	1 and 4	Very good
31	Double-blinded RCT	28 ECH and 15 CCH (22 P + 21 V)	–	–	3 (in 4–6 days)	P: 1.5 mL saline V : 1.5 mL cortivazol 3.75 mg	Reduction of attacks (≤2/day) in the 4 days after last GON injections: P: 55%; V: 95% Pain-free patients at 4 weeks after last GON injection: P:18%; V: 52%	4 days after last GON injection + 4 weeks + 12 weeks	Good

EM: episodic migraine; CM: chronic migraine; TM: transformed migraine; MOH: medication overuse headache; ECH: episodic cluster headache; CCH: chronic cluster headache;; GON: greater occipital nerve; RCT: randomised controlled trial; U: unilateral; B: bilateral; P: placebo; V: verum; ?: data not available; VAS: visual analogue scale.

verum ($n = 11$; $p = 0.003$) but not in the placebo group ($n = 12$; $p = 0.110$) (14).

Medication overuse was not associated with an increased risk of failure of GON blocks in two studies (16,17), but it tripled this risk in another study (18). The presence of GON palpation tenderness was associated with better outcome in one study (16), but not in two others (12,17). The effect of GON blocks on headache frequency and intensity does not predict the success of GON neurostimulation in chronic migraineurs (19).

GON blocks were also tested as a symptomatic treatment for migraine attacks. In 14 patients who received combined lidocaine blocks of the greater occipital nerve and supraorbital nerve (SON), pain reduction after 30 minutes was almost significant, but 50% of patients did not respond at all (20). By contrast, in an open study in which a GON block with 1 cc of a 50/50 mixture of 2% lidocaine and 0.5% bupivacaine was administered to patients with unilateral episodic or chronic migraine and brush allodynia, headache intensity decreased on average by 46.8% in 89.5% of patients after 20 minutes and ipsilateral allodynia decreased by 65.7% in all patients (21). The same group reported that the procedure produced 64% and 75% reductions of pain and allodynia scores, respectively, after 5 minutes and that the benefit lasted on average for 4 days, both in episodic and chronic migraineurs (22). In a single case report, GON infiltration with 3 mL of 0.25% bupivacaine and 1 mL of 40 mg/mL triamcinolone induced partial resolution of aura symptoms and complete disappearance of the headache after a few minutes in a patient with basilar-type migraine who was treated during an attack (23).

SON blocks have rarely been studied without concomitant GON blocks, so that their proper efficacy is difficult to assess. The combination of GON and SON blocks with 0.5–1.5 mL of lidocaine (20 mg/mL and 12.5 µg/mL adrenaline) had no beneficial effect in one study (20). By contrast, in an open trial comparing SON and GON blocks alone and their combination, SON blocks alone reduced headache frequency by 50% in 68.75% of patients after 1 month and in 75% of patients after 6 months (24). A further study reported that three consecutive bilateral SON and infraorbital nerve blocks with 1.5 mL of 1% lidocaine in episodic migraine patients were able to decrease significantly the mean headache frequency and migraine disability assessment (MIDAS) score (25).

In a recent randomized, double-blind, placebo-controlled trial, repetitive 0.5% bupivacaine blockades of the sphenopalatine ganglion with the Tx360® device twice a week for 6 weeks were compared to saline injections in chronic migraine patients (26). Slight but non-significant reductions in headache days and average pain scores were found in the bupivacaine group.

Cluster headache

A large number of open studies – reviewed in Leroux and Ducros (27) – found that GON blocks with steroids were beneficial as a transitional treatment during active bouts in episodic cluster headache (ECH) and in CCH patients who had an insufficient response to classical oral preventative drugs, while GON blocks solely with local anaesthetics were ineffective (28–30). At present, only two randomized, placebo-controlled studies are available on GON blockade in cluster headache. In the first study, CCH ($n = 7$) and active ECH ($n = 16$) patients were included (29). The verum group ($n = 13$) received a single GON infiltration on the side of attacks with a mixture containing a long-acting salt and a rapid-acting salt of betamethasone (dipropionate 12.46 mg and disodium phosphate 5.26 mg, respectively) mixed with 0.5 mL of lidocaine 2%, while the placebo-treated group received physiological saline and 0.5 mL of lidocaine 2%. The stringent outcome measure of sustained attack-free state within 72 hours for 4 weeks was fulfilled by 61.5% of steroid-injected patients, contrasting with none of the placebo-treated patients. A total of 85% of steroid-injected patients had a remission after 72 hours for at least 1 week. Only three patients out of the 11 who initially responded had recurrence of attacks within the 4-week duration of the trial. One additional patient was considered to be a non-responder because his attacks did not disappear within 72 hours of the injection, but he became asymptomatic 1 day later. Five out of eight responders remained in total remission for at least 6 months. Among the ten patients who were injected with physiological saline–lidocaine, none was attack-free after 1 week, and all of them needed additional prophylactic treatment.

The second randomised controlled trial (RCT) included 43 patients (28 ECH, 15 CCH) who received three unilateral suboccipital injections 48–72 hours apart of either cortivazol 3.75 mg (verum group, $n = 21$) or physiological saline (placebo group, $n = 22$) (31). In the first 2 weeks, patients in the cortivazol-treated group had on average a significant reduction of attack frequency ($p = 0.004$), and there was a trend for a higher percentage of patients with a > 50% reduction of attacks compared to the placebo group (86% vs. 59%; $p = 0.064$). At day 30 after the injections, 76% of cortivazol-treated and 59% of saline-treated patients were in remission.

Comments

Most observational studies suggest that GON infiltrations with local anaesthetics or steroids and, to a lesser degree, SON blocks may be beneficial in some

migraine patients, but further studies are needed in order to determine in which subgroups this beneficial effect occurs. By contrast, in three out of five controlled trials, the effect of GON blockade was marginal. Given the available evidence, GON blocks cannot be considered a first-line treatment in migraine. They are at best useful as an add-on therapy for the treatment of status migrainosus or for short-term prophylaxis in chronic migraine with medication overuse, with the aim of reducing the consumption of symptomatic drugs until preventative treatments become effective (32).

In two RCTs, GON infiltrations with steroids were clearly superior to physiological saline (31) or a local anaesthetic alone (29) in terms of interrupting a bout of cluster headache. This contrasts with migraine, for which some studies also reported a positive effect of the injection of a sole local anaesthetic.

Overall, GON blocks are well tolerated. Adverse effects are rare and minor, and include dizziness, local pain and vaso-vagal pre-syncope. Alopecia was reported in some patients who were injected superficially with triamcinolone; this can be avoided completely by injecting steroids in a deeper location close to the anatomical area where the GON has a latero-medial trajectory before becoming superficial next to the midline (33).

Invasive peripheral nerve neurostimulation

Electrical stimulation of peripheral nerves (PNS) is a well-known and efficacious way to relieve pain within the territory of the stimulated nerve. Its effect is thought to be due to activation of afferent Aβ fibres and subsequent gate control mechanisms in the spinal cord dorsal horn and/or activation of descending supraspinal pain controls from the periaqueductal grey and rostral ventromedial medulla (34,35).* Visceral trigeminovascular afferents converge with cervical (C2) and somatic ophthalmic nerve afferents on second-order nociceptors in the spinal trigeminal nucleus (36). There is thus, in theory, a rationale for stimulation of the GON and/or the SON in migraine and cluster headache.

Migraine

Invasive PNS was studied as a preventative therapy quasi-exclusively in patients suffering from drug-resistant chronic migraine.

In addition to a small, randomized open trial, only three randomized sham-controlled trials have been published, two *in extenso* and one in abstract form (37–40).

In the open-label trial, 29 patients who did not respond to at least two prophylactic treatments and had benefited from a preliminary temporary occipital nerve stimulation (ONS) system were ameliorated when the ONS device was switched on as compared to when it was switched off, and these benefits were confirmed in a 1-year follow-up (37). In the ONSTIM trial that included 66 patients with a 12-week follow-up, 39% of patients who received the active ONS had at least a 50% decrease in headache frequency and headache intensity, while there were no improvements in the sham-stimulated and medically treated groups (Table 2) (38). Unfortunately, ONSTIM was not powered to demonstrate efficacy, but rather feasibility and safety. By contrast, in the sham-controlled PRISM study, in which 125 patients with drug-resistant chronic migraine with or without medication overuse were enrolled, there was no superiority of active ONS over sham stimulation (39). The hitherto largest RCT of ONS in 157 chronic migraine patients failed to reach the primary endpoint (at least 50% reduction in mean daily headache intensity), but a higher percentage of patients in the active than in the sham arm achieved a 30% reduction in mean headache days ($p < 0.05$) and a decrease in migraine-related disability score (MIDAS) ($p < 0.01$) (40). After the 3-month randomised phase, an open-label phase of 40 weeks showed a significant 6.7-day reduction in monthly headache days in the intention-to-treat group and a 7.7-day reduction in a subgroup of patients with 'intractable' chronic migraine ($p < 0.01$); 59.5% of patients had a 30% reduction in headache days and/or pain intensity and 47.8% had a 50% reduction (41).

In order to test whether unblinding due to local paresthesias may influence outcome in ONS trials, suprathreshold, subthreshold and no stimulation were compared in a small randomised cross-over study of eight patients suffering from chronic migraine. The suprathreshold stimulation was found to be more effective than the subthreshold one, but the latter was also superior to no stimulation (42).

A meta-analysis of the available RCTs and seven case series (total of 517 patients) suggests a superiority of real ONS over sham stimulation in chronic migraine patients, but the average effect size is modest and seems to be smaller than that found in cluster headache (43).

The effect of combined ONS and SON stimulation (SNS) was assessed retrospectively in an open study of 44 patients with chronic migraine. The combination was reported to reduce the frequency of severe headaches by 81% (44,45), with a nearly complete headache disappearance in half of the patients (45). This impressive result needs to be confirmed in a RCT. Combined ONS–SNS was found to be superior to ONS alone in a small retrospective study of chronic migraineurs (44),

Table 2. Preventative effects of occipital nerve stimulation in migraine (prospective controlled studies).

References	Type of study	Number of migraine patients	U/B intervention	Type of stimulation	Type of control	Duration of follow-up (months)	Outcome (% reduction in headache days/month)
38	Blinded RCT	61 CM responsive to GON blocks (AS group, $n=28$; PS group, $n=16$; MM group, $n=17$; ancillary group received AS, although not responding to a prior ONS trial, $n=5$)	U or B	AS PS	MM	3	AS: $-27.0 \pm 44.8\%$ PS: $-8.8 \pm 28.6\%$ MM: $-4.4 \pm 19.1\%$ Ancillary group: $-39.9 \pm 51.0\%$ (NS)
39	Double-blinded multicentre RCT	125 EM or CM drug-refractory responders to a previous percutaneous stimulation trial Active stimulation: $n=63$ Sham stimulation: $n=62$	B	Active stimulation	Sham stimulation (lower pulse duration, frequency and intensity than the active one)	12	Active stimulation: approximately -27.2% Sham stimulation: approximately -20.3% (NS)
40,41	Double-blinded multicentre RCT	157 CM responders to a previous percutaneous stimulation trial Active stimulation: $n=105$ Sham stimulation: $n=52$	U or B	Active stimulation	Sham programmer (who did not communicate with the implantable pulse generator)	3 (+9 months open label)	Active stimulation: -27.2% Sham stimulation: -14.9% ($p=0.008$) (open-label follow-up: active stimulation (all): approximately -31%)

EM: episodic migraine; CM: chronic migraine; AS: adjustable stimulation; PS: pre-set stimulation; MM: medical management; GON: greater occipital nerve; ONS: occipital nerve stimulation; RCT: randomised controlled trial; U: unilateral; B: bilateral; NS: non-significant; EM: episodic migraine; CM: chronic migraine; RCT: randomized controlled trial; U: unilateral; B: bilateral.

but patient selection and follow-up biases may have influenced the results (46). The combined stimulation was found to be useful in a case series of four drug-resistant sporadic hemiplegic migraine patients (47). This result also needs confirmation, but it was hypothesised that PNS might inhibit cortical spreading depression (48).

Cluster headache

The evidence for the effectiveness of ONS in intractable CCH (iCCH) comes from several open-label prospective studies (49–53) and three long-term follow-up studies of the same patients (54–56). The first sham-controlled trial (ICON) is still ongoing (57). In one trial, eight iCCH patients were implanted bilaterally: six patients reported 20–95% ameliorations of attack frequency and intensity after a follow-up of 6–27 months (49). In another pilot study, eight iCCH patients were implanted unilaterally on the attack side and prospectively followed for 3–22 months using headache diaries (50). Two patients became pain-free, three had a decrease in attack frequency of approximately 90% and two had a decrease in attack frequency of approximately 40%. Overall attack intensity decreased by 50%. With ONS, all of the patients could reduce preventative medications, but not interrupt them completely. Transient side shift of attacks occurred only in two patients. In both studies, a clinical benefit occurred after a delay ranging from several weeks to several months post-surgery.

In a multicentre prospective study involving 13 iCCH patients who were implanted bilaterally and followed for 3–34 months, ten patients reported an amelioration of attack intensity within a few days of the surgery (51). Among the seven patients with a follow-up of 12 months, two were headache-free, four had a $\geq 50\%$ reduction of attack frequency and one had a 30% reduction of attack frequency. At the long-term follow-up, the treatment response was lost in two out of these seven patients. In a small study of three patients, two had a $> 50\%$ reduction in headache frequency already at 1 month post-surgery, whereas the last one responded after 3 months (52).

A trial with bilateral ONS including ten iCCH patients showed beneficial effects in nine subjects, with a mean overall improvement over time of 44% (range: 20–90%) in terms of attack frequency; eight patients also reported a decreased intensity of any remaining attacks. ONS became effective on average at 20 days after surgery (53).

Three of these trials were subsequently extended to other patients and longer follow-up (49,50,53). In the study by Burns et al., nine out of 14 patients were followed up for more than 12 months (54). Four of them reported sustained a $\geq 50\%$ improvement of their headache. Magis et al., after long-term follow-up (range: 11–64 months), reported complete remission of attacks in eight patients out of 13 who had a follow-up exceeding 12 months, and about 90% amelioration in two patients, but most patients continued preventative drugs and the intensity of residual attacks was not significantly reduced (55). Among the 17 patients who were followed for at least 12 months during ONS, Mueller et al. demonstrated that 15 showed a $\geq 50\%$ amelioration (56).

Some case reports of unilateral ONS-treated iCCH patients with moderate to high benefits were also published (58,59). In one young patient, ONS was combined with SNS and infraorbital nerve stimulation, which was reported to produce a dramatic improvement for up to 3 years (60).

SNS alone (three patients) or combined with infraorbital neurostimulation (one patient) was found to be effective in a small retrospective study (61).

Comments

There is strong evidence from uncontrolled studies that ONS is effective for patients suffering from drug-resistant CCH, and the effect size is greater than in chronic migraine, in which the moderate advantages from ONS are not confirmed in all RCTs. A $\geq 50\%$ decrease in attack frequency is reported in 44–88% of iCCH patients, compared to 39–48% in chronic migraine. In a long-term follow-up retrospective study, 80% of iCCH patients reported experiencing a benefit from ONS compared to 42% of refractory chronic migraine patients (62).

The effect of ONS in iCCH is no more than symptomatic, however, since the majority of patients are unable to stop taking preventative drugs and attacks recur after interruption of the stimulation (e.g. when the battery goes flat). There is no known predictive factor for ONS efficacy; response to GON blocks (see above) does not predict response to ONS (50,58,63). Nonetheless, medication overuse may be associated with a less favourable outcome after ONS (64).

Adverse effects are frequent in ONS-treated patients. The most prevalent are local pain and/or intolerable paresthesias, infections, electrode displacement and battery replacements. The latter cannot be considered an adverse effect *per se*, but may further increase the cost of ONS, which is estimated at €28,000 per patient (56). In one study, 58% of patients required at least one lead revision (62). Because of the paresthesias produced by the stimulation, true blinding is difficult to achieve in clinical trials, and it is thus challenging to establish the

placebo effect with confidence. As mentioned before, however, the superiority of subthreshold ONS over no stimulation in chronic migraine studies and the rapid recurrence of attacks after cessation of the stimulation in cluster headache trials suggest that the clinical benefit is due to a genuine effect of ONS and not to a placebo effect or to the natural history of the disease (50,63).

The precise mode of action of ONS needs to be determined. In a fludeoxyglucose positron emission tomography study of iCCH patients treated with ONS for more than 6 months, the only difference between responders and non-responders was increased metabolism in the subgenual anterior cingulate gyrus, suggesting that ONS modulates central pain control centres (65).

Taken together, the available evidence suggests that invasive ONS could be a treatment option for drug-resistant iCCH patients. Future studies should try to determine its advantages and disadvantages with respect to sphenopalatine ganglion stimulation (see Lainez, this issue) and with respect to the upcoming non-invasive transcutaneous and transcranial neurostimulation methods (see Schoenen et al., this issue). Based on published studies, the evidence favouring ONS in chronic migraine is less convincing, and further studies are clearly needed in order to identify the predictors of response. According to the position statement of the European Headache Federation, ONS is advisable in iCCH; in refractory chronic migraine patients, it is only considered to be acceptable, although this is based on limited evidence (66).

Surgical decompressions for migraine

As mentioned in the introduction, there is scarce evidence that nervous structures in the pericranium or face play a primary causative role in headache pathogenesis, although pain felt on the surface of the head or neck tends to be attributed merely to referred pain from the visceral part of the ophthalmic nerve (see above). Nonetheless, surgical procedures to treat headache acting directly on cranial nerves have been used for a long time.

In the last 15 years, decompression of pericranial nerves by sectioning adjacent muscles and sections of superficial nerve branches was repeatedly proposed as a possible treatment for migraine patients (67–79). Up to now, this procedure has not been attempted for other primary headaches. In the first retrospective study, resection of the corrugator supercilii muscle for rejuvenation was reported to improve migraine patients (67). It was followed by a prospective study in which the intervention was performed in headache patients with hypertrophy of the corrugator supercilii muscle who had at least 50% amelioration after one injection of 25 U botulinum toxin type A into this muscle (68). Disappearance of headaches was reported in 66.7% of subjects, and partial improvement was reported in the remaining 33.3%. The latter also underwent a transection of the zygomaticotemporal branch of the trigeminal nerve and repositioning of the temple soft tissues. After follow-up (222–494 days), all patients except one had supplementary improvement. In a subsequent unblinded prospective study, patients were allocated, depending on the origin of pain and botulinum toxin effect, to one or a combination of four surgical procedures: removal of corrugator supercilii, depressor supercilii and procerus muscles (90% of patients); endoscopic removal of 3 cm of the zygomaticotemporal branch of the trigeminal nerve (80%); resection of the semispinalis capitis muscle and shielding of the GON (38%); and septoplasty and inferior and/or middle turbinectomies (70%). Outcomes were compared to a non-operated control group after a 1-year follow-up (69). In the operated group, 92% of patients were reported to have a $\geq$50% reduction in migraine headache frequency and duration, while only 15.8% of controls improved. At the end of a 5-year follow-up period, 88% of patients, 69.5% of whom were operated on at three to four sides, experienced beneficial effects from the surgical treatment, according to the authors (70).

The only sham-controlled study included 75 patients with migraine with or without aura, who reported a so-called ''trigger site'' (i.e. a predominant site ''where the migraine headache begins and settles and corresponds to the anatomical zone of potential irritation of the trigeminal nerve'') and had at least 50% amelioration after injection of 25 U botulinum toxin into the ''trigger'' area (71). They were operated on according to their ''trigger sites'' (''frontal'', ''temporal'' or ''occipital'') and followed for 1 year. In each group, a third of patients underwent a sham operation. In the verum arm ($n = 49$), 83.7% of subjects from the three groups demonstrated significant amelioration or elimination of headaches, whereas in the sham arm ($n = 26$), 57.7% had a similar positive outcome.

Several retrospective studies reported possible predictors of favourable outcome (72–74) or benefit from additional surgical procedures such as supraorbital foraminotomy (75) or ligation of the occipital artery (76).

Some other retrospective studies of the effects of surgery in the frontal area in migraine are available. In the largest one using resection of corrugator and depressor muscles, 58.3% of 60 chronic or episodic migraineurs had a $\geq$ 50% reduction in headache days at the 6-month follow-up (77). Another study reported a $\geq$ 50% amelioration of headaches in 16 out of 18

migraine patients responding to botulinum toxin and operated on at multiple sites in various combinations (78). Improvement after corrugator muscle resection was also reported in nine out of ten patients who suffered from frontally located ''chronic daily headache'' and improved by $\geq$50% after at least two frontal injections of botulinum toxin (79).

Comments

The proposed rationale for surgical decompression of pericranial nerves in migraine is that compression of these nerves induces inflammation and peptide release, which may reach the meninges and hence trigger headaches. This rationale may gain support from recent studies demonstrating extracranial projections of meningeal afferents (4).

With one exception, however, the evidence for the effectiveness of peripheral nerve decompressions in migraine stems mostly from retrospective or prospective uncontrolled studies. A critical point is that the migraine patients included in these studies all had some uncommon clinical features (80), such as strictly side-locked unilateral headache and the presence of ''trigger sites'' that are much more typical of cranial neuralgias and tension-type headaches than of migraine (81). Similarly, some additional symptoms that have been used to determine the site of the interventions are commonly found in other primary or secondary headaches such as neuralgias, headaches attributed to temporomandibular dysfunction, chronic tension-type headaches, chronic/recurring rhinosinusitis, mucosal contact points or concha bullosa and whiplash. All of these causes of head or facial pain can aggravate migraine and sometimes mimic it. An intervention that is able to influence them has the potential to improve migraine indirectly.

In addition, the strategy of selecting for surgery patients who respond to botulinum toxin type A injections at ''trigger sites'' is rather puzzling and has no scientific basis. In fact, most patients who were included had episodic migraine and were reported to respond to botulinum toxin in proportions ranging from 58% to 90% (68,69,71,79), which clearly contrasts with RCTs of multiple pericranial and facial injections of botulinum toxin that show no difference with saline injections (82). Hence, it is likely that many patients were selected for surgery on the basis of a placebo response. This is supported by the very high placebo response of 58% found in the only sham-controlled study of peripheral nerve decompression. Without scientific evidence, the authors hypothesize that this placebo response may be due to the fact that the incision and the undermining of pericranial tissues may have altered neurosensory functions and that some patients may have exaggerated their preoperative symptoms in order to increase their chances of being selected for surgery (68,69,71,79). It is well established, however, that the placebo response in headaches is greater with invasive procedures than with drug treatments (83).

Given these confounding factors and methodological uncertainties, surgical decompression of peripheral nerves cannot be considered at the present time as an established treatment for migraine. It remains to be determined in future sham-controlled trials whether such procedures may have a lasting clinical benefit that exceeds a placebo effect in clinical subgroups of selected patients.

Conclusions

Invasive interventions on pericranial nerve branches have been used for a long time to treat headaches. Although current knowledge on primary headache pathophysiology favours a central nervous system dysfunction (84), such interventions could modulate the neuronal circuits that are involved in central sensitisation and pain control, merely producing a symptomatic non-specific effect. Among primary headaches, cluster headache appears to respond best to both GON blocks and peripheral neuromodulation, but the treatment responses are not necessarily correlated. In migraine, both procedures are only marginally effective, but this may improve in the future with advances in patient selection and treatment protocols.

Larger better-designed and comparative trials are needed in order to evaluate the long-term effects of the invasive implantation of neurostimulators or nerve decompressions. Effective blinding is a major challenge in such trials, as will be the comparison with the upcoming non-invasive neurostimulation methods.

Literature search methods

English-language publications were searched for in PubMed up to July 2015.

The following search terms were used: ''migraine neurostimulation'', ''cluster headache neurostimulation'', ''migraine neuromodulation'', ''cluster headache neuromodulation'', ''migraine injection'', ''cluster headache injection'', ''migraine nerve infiltrations'', ''cluster headache nerve infiltrations'', ''migraine nerve blocks'', ''cluster headache nerve blocks'', ''migraine surgery'', ''cluster headache surgery'' and ''migraine decompression''. All of the identified publications were individually assessed according to their relevance to the topic. Specific exclusion criteria included publications on single case reports and

editorials and other review articles unless of exceptional importance. The reference lists of identified publications were also scrutinised for further relevant publications.

Clinical implications

- Suboccipital infiltrations (or greater occipital nerve blocks) are effective, evidence-based, safe and inexpensive treatments for short-term prophylaxis in cluster headache patients; they may also have some effect in selected migraine patients, particularly those with fixed unilateral headaches and ipsilateral autonomic symptoms.
- Percutaneous occipital nerve stimulation (ONS) has long-term efficacy in refractory chronic cluster headache, but it has frequent, though reversible, adverse effects, and a sham-controlled trial is not yet available. By contrast, the evidence that ONS is effective in chronic migraine is weak, although some randomised controlled trials (RCTs) indicate that it might be beneficial in subgroups of patients.
- Surgical decompression of pericranial nerves in migraine patients was reported to be superior to sham surgery in one study, and most case series are non-controlled and published by the same group. The heterogeneity of included patients, selection bias and questionable inclusion criteria are major shortcomings of these studies and do not allow us to rule out the notion that the greater part of the reported benefits is due to a placebo effect. Further better-designed RCTs are needed before surgical decompressions can be recommended in the treatment of selected migraine patients.

Declaration of conflicting interests

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