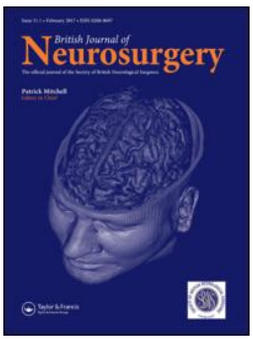

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ORIGINAL ARTICLE

Percutaneous electrical nerve stimulation (PENS) therapy for refractory primary headache disorders: a pilot study

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ABSTRACT

Purpose: Primary headache disorders are common, but many patients are refractory to medical treatment. Percutaneous electrical nerve stimulation (PENS) therapy involves the stimulation of one or more individual nerves or dermatomes using needle probes. We assessed whether a 'single shot with single probe' strategy would benefit patients with refractory headache disorders, including chronic migraine (CM), and chronic cluster headache (CCH).

Materials and methods: Service evaluation of 36 patients treated with PENS therapy between September 2012 and June 2016. Follow-up data were available for 33 patients, of whom 16 had CM, nine had CCH, and six had secondary headache disorders. PENS was given using Algotec® disposable 21 gauge PENS therapy probes (8 cm) to the occipital nerve ipsilateral to the pain (or bilaterally in cases of bilateral pain). Stimulation was delivered at 2 Hz/100 Hz, at 3 cycles/s, between 1.2 and 2.5 V depending on patient tolerability, for 25–28 min.

Results: Six of nine patients with CCH improved significantly after the first session. In all patients with CCH, PENS therapy was well tolerated, with no significant adverse events reported. One patient with CCH reverted to episodic cluster. Only four patients with CM experienced any benefit.

Conclusion: PENS therapy shows potential as a relatively non-invasive, low-risk, and inexpensive component of the treatment options for refractory primary headache disorders, particularly CCH.

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PENS therapy; cluster headache; neurostimulation

Introduction

Headache disorders are the commonest causes of neurological disability on a global basis.[1,2] Over the course of a lifetime, migraine affects 33% of women and 13% of men; the one-year prevalence of cluster headache is about 0.1%.[3,4] Approximately 2% of the population in developed countries have chronic daily headaches.[5] The treatment of patients with headaches is often compromised by the common and serious side effects of available medications; in addition, some patients prove refractory to multiple attempts at medical treatment.

In the last two decades, new techniques of headache treatment have been introduced that aim to modify pain and other mechanisms involved in headache by targeting the central or peripheral nervous system. This group of techniques comprises invasive and non-invasive neurostimulation, and non-invasive neuromodulation. High-quality randomised controlled trials (RCTs) are technically difficult, and remain sparse; further studies are needed. In addition, techniques such as percutaneous electrical nerve stimulation (PENS) therapy, which have proven safety and efficacy in other pain disorders (including secondary headache disorders) should be trialled in primary headache disorders.

PENS therapy involves the stimulation of one or more individual nerves or dermatomes using needle probes. A single probe with a grounding pad or pairs of fine-gauge needles are inserted into soft tissue near the targeted nerves or into the affected dermatomes. The needles are connected to a low-voltage pulse generator and an electrical current is then applied. This may generate a sensation of paraesthesia and muscle contraction. The duration of treatment varies but each session of stimulation typically lasts between 15 and 60 min. RCTs have shown that PENS may be effective in neuropathic pain conditions such as lower back pain, sciatica, post-operative pain, and diabetic neuropathic pain.[6–12] PENS is generally safe and well tolerated. Reports exist of exacerbation of pain, bruising and bleeding as immediate adverse events. Theoretical adverse events include local vascular or nerve damage; pneumothorax; possible interaction with a cardiac pacemaker if used above the waistline; possible epileptogenic effect if used near the head; and possible adverse effects if used in pregnancy. No published reports exist of any of these theoretical problems actually arising, however.

Very few reports exist of the use of PENS therapy to treat primary headache disorders, and those that do comprise focus on episodic migraine, and use programs of stimulation lasting several weeks.[13,14] We therefore sought to assess whether a 'single shot with single probe' strategy would provide any short-term or lasting benefit to patients with a range of refractory headache disorders, including chronic migraine (CM), and chronic cluster headache (CCH).

Materials and methods

Patients with primary and secondary headache disorders were considered for treatment if they were refractory to standard preventive treatments, that is, if standard treatments did not work at

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Table 1. Demographic details of patients with primary headache disorders ($n = 25$).

	CM/NDPH ($n = 16$)	CCH ($n = 9$)
Average age	42 (18–64)	40 (29–63)
Gender	11 F; 5 M	5 F; 4 M
Average # failed preventive meds	4.1 (1–6)	4.8 (2–8)
Response to GON		
Good (weeks)	3 (19%)	1 (11%)
Modest (days)	5 (31%)	6 (67%)
None	8 (50%)	2 (22%)
Response to Botox		
Poor (weeks)	4/9	N/A
None	5/9	N/A
Response to DHE		
None	4/4	1/1
Mean # PENS sessions	1.8	3.2
≥1 PENS sessions	4/16 (25%)	6/9 (67%)

all, or only provided transient relief. No formal criteria were used, but many of the patients would have been referred for consideration of an implantable occipital nerve stimulator had that treatment not been temporarily unavailable through the British National Health Service (NHS).

We performed a service review of 36 patients treated with supraorbital or occipital PENS therapy at Charing Cross Hospital between September 2012 and June 2016. A retrospective review of their medical records was undertaken. Follow-up data was available for 33 patients. Of these, 25 had a primary headache diagnosis, of whom 14 had CM, nine had CCH, and two had new daily persistent headache (NDPH) with migrainous features. One patient was thought to have hemicrania continua, though this diagnosis was later revised when her headaches resolved completely after cardiac angioplasty. The other secondary headaches comprised occipital neuralgia (2), cervicogenic headache (2), and trigeminal neuropathy (3).

PENS was given using Algotec® disposable 21 gauge PENS therapy probes (8 cm) to the occipital nerve ipsilateral to the pain (or bilaterally in cases of bilateral pain). In some cases supraorbital PENS was tried on a second or subsequent occasion if the patient had failed to respond to occipital stimulation. Stimulation alternated every 12 seconds between 2 Hz and 100 Hz, at 3 cycles/s, between 1.2 and 2.5 V depending on patient tolerability, for 25–28 min. No immediate complications were recorded during stimulation, apart from one patient who experienced pain during stimulation. In most cases the treating neurosurgeon (DN) recorded good coverage and radiation of effect during stimulation.

Results

Demographic details of patients are given in Table 1. All the patients had previously failed to respond to between one and eight oral preventive medications (typically at least four), and had at best experienced temporary benefit from greater occipital nerve (GON) blocks with local anaesthetic and steroids. In reviewing the outcomes following PENS therapy, the patients with NPDH have been assessed alongside those with CM, as both patients had clear migrainous features during exacerbations of their persistent headache disorder.

Six out of the nine patients with CCH improved significantly after the first session, with reduced frequency and/or severity of attacks lasting at least 4 weeks (Table 2). Following further treatment, four of these patients derived similar benefits on second and subsequent occasions, one patient experienced only transient benefit, and one patient declined further treatment. One additional patient, who had experienced only a transient benefit at first, did much better on subsequent occasions. In all patients with CCH, PENS therapy was well tolerated, with no significant adverse events reported. One patient with CCH reverted to the episodic form of the disorder; this improvement was maintained for more than two years following the cessation of therapy. By way of contrast, only four of the patients with CM/NDPH experienced any noticeable benefit with PENS therapy; one patient with CM/NDPH experienced pain during stimulation, two patients with CM/NDPH experienced severe neck pain, and three patients with CM/NDPH experienced an exacerbation of their condition lasting days to weeks.

Previous response to GON blockade does not seem to have been predictive of response to PENS in patients with CM: of the six CCH patients who benefited from PENS, two had previously experienced prolonged benefit from GON blocks (3–5 weeks, although one patient had become intolerant of the injections), three had derived only transient benefit (3–4 days), and one had not found GON blockade helpful; of the three CM patients who improved with PENS, one had previously had a prolonged response to GON blockade (2 months), one a transient response (4 days only), and one no response at all.

Discussion

The first report of the use of GON injection in the management of headache was published in 1940.[15] Since the early 1990s, many studies have shown that targeting peripheral nervous system inputs into the trigeminocervical complex (TCC; initially with anaesthetic blockade, and subsequently with neurostimulation) can be a viable option for treating intractable headache disorders. The pathophysiological basis for the responses to blockade or stimulation of the occipital nerve in patients with primary headache disorders is not definitively established, but is believed to relate to the modulation of input into neuronal processing in the TCC, where second order neurons have input from both trigeminal and cervical afferents. The TCC comprises the trigeminal nucleus caudalis in the caudal medulla and the neurons of the dorsal horns at C1 and C2.[16–19] Experimental stimulation of structures innervated by the trigeminal nerve, such as the superior sagittal sinus and middle meningeal artery, activates neurons in this complex.[20] The fibres of the GON originate predominantly from the C2 dorsal root.[21] Stimulation of the nerve activates neurons in the TCC, and in some cases can elicit ipsilateral conjunctival injection, eye watering, and ptosis.[22,23] Stimulation of the C1 and C2 nerve roots can elicit frontal pain, especially in patients with migraine.[24] Even transient alterations to the input from the GON may therefore precipitate a central modulatory change involving the TCC.[17,19,25,26] However, stimulation of the occipital nerve does not necessarily alter trigeminal processing; at least one study suggests that low frequency (3 Hz, 2-10 mA) short-time stimulation of the nerve has no discernible central effect. The authors suggest this lack of effect may be responsible for their observation – not borne out by the results of this study – that the beneficial effect of occipital nerve stimulation in CCH can take some weeks to become apparent.[27]

Anaesthetic blockade of the GON, with or without a steroid moiety, was reported to be a useful treatment for occipital neuralgia,[28] and subsequently for a number of primary headache disorders, including migraine,[28,29] cluster headache,[30–32] CCH,[31,33] hemicrania continua,[29] cervicogenic headache,[34] coital cephalalgia,[35] and trigeminal neuropathy.[36] Recent placebo-controlled trials – in migraine, CM, and medication overuse headache – are

Table 2. Response to PENS therapy in patients with chronic cluster headache.

Patient #	Age	Sex	Years CH	Years CCH	# PENS RX	Previous preventive treatments	Best response to GONB	Response to 1st pens RX	Subsequent course	Outcome
1	32	F	13	3	7	VER, TOP, LI, MEL, SVP, MTH, VNS	2–3 weeks, itching & localised alopecia	6 weeks pain free	Up to 3 months pain free	Ongoing PENS therapy & GONB
2	39	M	4	3	2	VER, TOP, LI, MTH, PIZ	3–4 days	4 weeks pain free	Only 3 days pain free	Referred for ONS
3	45	F	22	3	1	VER, TOP	Unhelpful	Unhelpful	N/A	Ongoing medical treatment
4	49	M	9	9	1	VER, TOP, LI, MEL, DHE, INDO	3–4 days	4 days reduced severity	N/A	Ongoing medical treatment
5	42	F	2	1	8	VER, TOP, LI, MEL, MTH, INDO	Up to 5 weeks, but less effective over time	5 days pain free	Up to 2 months pain free	Reverted to episodic CH
6	63	M	7	5	3	VER, TOP	3–4 days	6 weeks pain free	Up to 3 months pain free	Ongoing PENS therapy
7	33	F	6	6	4	VER, TOP, LI, MEL, MTH, PRG, AMI, INDO, VNS	3–4 days, painful	6 weeks pain free	6–8 weeks pain free	Ongoing PENS therapy & referred for ONS
8	32	F	1	1	2	VER, TOP, LI, INDO	Unhelpful	6 months reduced severity	3 months pain free	Ongoing PENS therapy
9	29	M	12	12	1	VER, TOP, LI	3–4 days	6 months reduced severity	N/A (declined further PENS Rx)	Ongoing medical treatment

less consistent, though meta-analysis suggests a probable overall benefit.[37–42]

Following a report of positive results of occipital nerve stimulation in patients with intractable occipital neuralgia,[43] successful peripheral stimulation of the occipital nerve for medically refractory headache was subsequently reported in open label trials and series for migraine,[44,45] occipital neuralgia,[46–48] hemicrania continua,[49,50] and CCH.[51–54]

There are very few reports of PENS therapy *per se* being used in headache disorders. The first such report was that of PENS therapy being used to treat post-ECT headaches.[55] More recent studies of the utility of single-shot PENS in neuropathic pain conditions have included significant numbers of patients with secondary headache and facial pain disorders, including occipital neuralgia and post-herpetic trigeminal pain.[56] As noted above, two trials exist of repeated PENS therapy, delivered over a number of weeks to patients with headache. Ahmed *et al.*[13] treated patients with tension-type headache, migraine, and post-traumatic headache with 2-week courses of PENS (15/30 Hz, 30 min, 3 days/week), finding a ≥50% reduction in headache intensity in the 48 hours after treatment in all three headache groups. Li and Xu[14] studied the effects of a 12-week course of PENS therapy (2/100 Hz, 30 min, 5 days/week) on headache frequency in patients with episodic migraine. They demonstrated a modest mean reduction of 2.2 headache days/month from a baseline of 7.0 in the verum group, with a ≥50% responder rate of 37.9%.

With a different purpose in mind, Kinfe *et al.* investigated whether the response to PENS therapy could be used to predict ultimate response to ONS in patients with refractory headache disorders. In this paper 3/8 patients with CM experienced a reduction in the intensity of pain after three PENS sessions, each separated by 1 week, as did their sole patient with CCH, and one patient with post-traumatic headache. 5/8 patients with CM did not respond, and neither did their sole patients with occipital neuralgia and episodic CH. They concluded that response to PENS was not a useful predictor of likely response to ONS.[57]

Our study provides support for further study of a 'single shot with single probe' strategy for the treatment of CCH. Prolonged benefit from a single session of PENS therapy was seen in a significant proportion of our patients. Regular but infrequent sessions of PENS therapy may for some patients be preferable to a permanent implantable stimulator, with its uncertain outcome, and attendant risks of infection, lead migration, and battery failure.[58]

It does not, however, suggest this approach is likely to be generally helpful for patients with CM. This is perhaps unsurprising given the reported modest effects of repeated PENS therapy, and indeed of ONS, in this condition. In addition a significant number of patients with CM worsened after the procedure; all of these patients reported allodynic symptoms. Allodynia is a recognised clinical marker for central sensitisation, and its presence is regarded as a predictor of migraine chronification, as well as poor prognostic indicator for response to triptan therapy.[59,60] Central sensitisation engenders hypersensitivity to TCC afferent inputs, and impaired descending inhibition of trigeminal activity, and it is perhaps unsurprising that some patients would react adversely to prolonged stimulation of one of the main inputs into the TCC. In this regard stimulation – or at least short-term stimulation – seems to work differently from GON blockade: whereas animal studies raise the possibility that occipital nerve stimulation might actually reduce allodynia,[61] and one study has shown an immediate effect of GON blockade on reducing allodynia in patients with migraine,[62] the presence of allodynia reduces the response to transcutaneous occipital stimulation in CM.[63] The presence of allodynia may therefore be a poor prognostic indicator when CM patients are being considered for PENS therapy. As far as CCH is concerned, central sensitisation is not regarded as a cardinal feature of this condition, though recent work suggests that allodynia may be more common than previously realised in cluster headache, and future studies should look at this question in more detail.[64]

Conclusion

PENS therapy shows great potential as a relatively non-invasive, low-risk, and inexpensive component of the treatment options for refractory primary headache disorders, particularly CCH. Further trials of the technique in this debilitating condition are warranted.

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Disclosure statement

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