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Percutaneous nerve field stimulation (PENS) of the occipital region as a possible predictor for occipital nerve stimulation (ONS) responsiveness in refractory headache disorders? A feasibility study

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Abstract

Background: Occipital nerve stimulation (ONS) has been reported to diminish pain levels in intractable chronic headache syndromes of different origin. No reliable objective markers exist to predict ONS responsiveness. This study investigated the predictive value of occipital percutaneous nerve field stimulation (PENS) prior to ONS.

Methods: This trial included 12 patients (CCH, CM, PTH, CH) with chronic refractory headache syndromes eligible for ONS. Repetitive PENS (3 × /10 days) was performed and the headache severity/frequency monitored over four weeks before ONS implantation. Further assessment of PENS/ONS outcomes were stimulation-related complications, perception/tolerance stimulation threshold, the Migraine Disability Scale (MIDAS) and the Beck Depression Inventory (BDI).

Results: All PENS responders benefited from ONS. Of the seven PENS-nonresponders with VAS 6.1(±1.1), six experienced significant pain relief from ONS after three months and one patient failed the PENS/ONS trial (VAS 3.7 (±1.6)); (95% CI 3.6 to 5.7, $p < 0.001$). The VAS baseline was 8.4 (±0.5) and decreased significantly (50% reduction in severity/frequency) in five patients after PENS, while seven failed to improve (VAS 4.9 (±1.1); (95% CI 2.5 to 4.5, $p < 0.001$). BDI baseline (from 22.6 (±4.2) to 10.6 (±5.9) (95% CI 7.4 to 16.6, $p < 0.001$)) and MIDAS baseline (from 143.9 (±14.5) to 72.8 (±28.7) (95% CI 1.17 to 2.3, $p < 0.001$)) significantly declined after ONS. No PENS/ONS-related complications occurred.

Conclusions: Presurgical applied occipital PENS failed to identify ONS responders sufficiently according to our study protocol, thus requiring further specific investigations to determine its predictive usefulness.

Keywords

Occipital nerve stimulation, refractory chronic headache disorders, percutaneous nerve field stimulation, presurgical predictive factor

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Introduction

Chronic intractable headache disorders remain a challenge for diagnosis and treatment; they constitute one of the leading chronic neurological diseases impairing the quality of life and causing severe disability in affected individuals, and resulting in a high economic impact (1). Among primary headache disorders, migraines occur more frequently than cluster headaches or other trigeminal autonomic cephalalgias, such as short-lasting, unilateral neuralgiform headache or

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hemicrania continua (1–6). Notably, the most common diagnosis among chronic headache sufferers remains medication-overuse headache derived from medical management in the first instance, which in the majority of conservatively treated patients diminishes in severity and/or frequency (2,7). In addition, posttraumatic headache (PTH) and cervicogenic headache (CH) were found with a relatively moderate incidence within the group of patients with secondary headache disorders (3).

In some circumstances, medical and/or behavioral therapeutic strategies fail to significantly suppress the pain levels. The refractory state in conservatively pretreated patients with chronic headache remains a pivotal point for deciding toward noninvasive and/or invasive neuromodulation approaches. Thus, appropriate and clinically applicable definitions have been recommended (8).

Based on their refractory headache state, a large number of patients become eligible for a neuromodulation attempt (8). Electrical stimulation has been applied in a noninvasive manner (transmagnetic stimulation, direct current stimulation, vagal nerve stimulation) or by using invasive neurostimulation methods at different target sites (deep brain stimulation, occipital nerve stimulation (ONS), spinal cord stimulation (SCS), and ganglion sphenopalatinum stimulation) to provide relief in such conditions (2).

ONS has been investigated in detail in randomized controlled studies and in smaller series with an open-label design. These studies have yielded a broad range of ONS outcomes in chronic cluster headache (CCH), chronic migraine (CM), other trigeminal autonomic cephalalgias, and secondary headache diseases like PTH (9–24). ONS, as a minimally invasive implantation technique, still bears the risk of non-responsiveness and complications (the most common being dislocation, infection and stimulation-related discomfort) (9–22), and can result in high costs although battery replacement is no longer required since the introduction of rechargeable devices (2,21). To date, no reliable and objective predictor for ONS success has been identified. In the past, presurgical occipital nerve block (ONB) performed prior to ONS yielded no predictive value and no randomized controlled study exists as yet (25).

These facts argue the obvious need for reliable and predictive presurgical assessment tools to determine eligible patients in terms of ONS responsiveness, thus meriting further specific investigations to identify objective and reliable predictors. The present study attempted to provide a practical and easy tool to predict ONS responsiveness in refractory chronic headaches of different origin using presurgical percutaneous nerve field stimulation of the occipital region (PENS) according to a standardized reproducible stimulation and implantation paradigm.

Material and methods

Study design

This study is a prospective, observational single-center trial investigating the possible usefulness and reliability of repetitively performed PENS prior to ONS implantation. It aims to predict ONS responsiveness in refractory chronic headache syndromes of different origin with regard to frequency and severity.

The study protocol including patient data collection/evaluation for investigational purpose was reviewed and approved by an independent, internal, local ethics research board/committee (no. 099/14).

Study population

Twelve patients suffering from chronic headache disorders and eligible for neuromodulation treatment by ONS were prospectively included, after they provided informed consent, to undergo repetitive standardized PENS ($3 \times /10$ days) of the occipital region prior to ONS implantation. The enrollment period was from May to September 2014. The patients were referred by a headache specialist (anesthesiologist) to our university hospital. In addition, the diagnosis of a refractory and chronic headache disorder was confirmed by an interdisciplinary internal pain board (including a neurologist, an anesthesiologist, a neurosurgeon, psychiatrist, and pain nurse) in cooperation with a tertiary level headache center according to the International Classification of Headache Disorders, third edition beta (ICHD-3 beta) (26). A detailed delineation of inclusion and exclusion criteria is given in Table 1.

In the majority, diagnosis was established in a neurological clinic specializing in headache disorders. The challenge of achieving a reliable diagnosis, for instance, the term refractory has been refined in the past and still reflects an issue of ongoing discussion, emphasizes the need for headache specialists combined with a multidisciplinary assessment. The patients with CM were refractory to preventive medication (β-blockers, anticonvulsants, tricyclic antidepressants, calcium channel blockers) while patients with CCH were refractory to verapamil, corticosteroid and lithium. Headache medication was unchanged in all patients at least four weeks prior to PENS (Table 1).

Out of the 12 patients, 10 were women and two were men with a median age of 50 years (range 23 to 71). Chronic refractory migraine was diagnosed in eight patients; the remaining study population consisted of

Table 1. Overview of patient selection criteria.

Inclusion criteria	Exclusion criteria
• Chronic refractory headache disorder according to the ICHD-3 beta • Age equal to/greater than 18 • Informed consent (study, PENS, ONS) • Refractory to medical and/or behavioral therapy • Medication-overuse headache has been ruled out • Eligible for occipital nerve stimulation • Willingness to follow a defined follow-up interval • Intracranial and cervical pathologies ruled out by MR scan • Stable pain medication four weeks prior to PENS	• No informed consent • Other concomitant neuropsychiatric comorbidity not adequate classified and/or requiring specific diagnosis/treatment Pregnancy • Previously performed invasive, noninvasive and ablative procedure • Not willing to complete pain diary regarding severity and frequency

ICHD: International Classification of Headache Disorders, third edition beta; PENS: percutaneous nerve field stimulation; ONS: occipital nerve stimulation; MR: magnetic resonance.

one participant with PTH, one with CH, one with occipitalis neuralgia, and one with CCH (Table 2).

Data acquisition and follow-up evaluation

Severity and frequency (headache days per month) prior to each PENS were recorded using patient diaries and continued at baseline and within the observation period (at least three months). Onset and severity of any adverse event (dislocation, infection and stimulation-induced side effects) related to the PENS and ONS procedure were evaluated. The perception and tolerance threshold were assessed for all three PENS and ONS procedures, comparing left and right ONS electrodes for reproducibility of the observed stimulation effects. The study did not include a sham-treated control group to objectively determine PENS efficacy and exclude placebo effects (feasibility) of the study protocol, which indeed might lead to uncertain interpretation of the obtained data. In addition, headache-related scores were used to further determine ONS success using the Beck Depression Scale (BDI) and Migraine Disability Scale (MIDAS) at baseline, after one month and after three months. The median observational follow-up period for the described study was five months (range, three to nine months).

Stimulation and implantation protocol of performed PENS and ONS

PENS. After inclusion in our study protocol, patients received repetitive PENS three times in 10 days (every third day). The stimulation parameters chosen for PENS were bipolar configuration, 300 μs, 100 Hz; stimulation intensity was selected according to individual comfort. Of note, all patients received stimulation at least at perceptional or supraperceptional thresholds to provide a standardized protocol. As described, three sessions were performed across 10 days with a duration of 30 minutes per PENS treatment. PENS was performed using an external current-driven stimulator (Pierenkamp GmbH, Wetzlar, Germany) connected to four acupuncture needles (Figure 1). Commercially available acupuncture needles (DMC International Trading GmbH, Düsseldorf, Germany) were percutaneously placed following a strict protocol to avoid uncertainty. In total, four needles were placed subcutaneously transversely at the level of C1, which was defined as 3 cm below the protuberantia occipitalis, 1.5 cm paramedian (first needle), and 3.5 cm (second needle) paramedian to ensure that it reached the occipital afferent distribution area (Figure 1) (27).

ONS. Four weeks after PENS, visual analog scale (VAS) score was re-assessed prior to ONS implantation. According to a standardized implantation technique, the patient was positioned prone under general anesthesia. In general, a 3-cm long median skin incision starting 2 cm below the protuberantia occipitalis was performed.

To avoid lead traction, a subcutaneous pocket was prepared to loop the implanted wire. Using a tuohy needle, the electrode was inserted bilaterally (Octrode®, St Jude Medical Inc) toward the mastoid (at 3 cm below the protuberantia). The electrode placement achieved at the transition of C1 was confirmed by intra-operative radiography. To inhibit lead migration, electrodes were sutured to the muscle fascia (Figure 1).

After connecting to an extension wire, the electrodes were externalized for postoperative test/stimulation purposes (7–10 days under intravenous (i.v.) antibiotic administration). Within the trial period, data related to the intensity/frequency and distribution of paresthesia (patient comfort) were collected. In a second procedure, a rechargeable implantable pulse generator (IPG) (Eon Mini, St Jude Medical Inc) was placed in the left

Table 2. Study population with demographic characteristics, baseline pain assessment, pain outcome after PENS as measured on the VAS and pain assessment after prior, 1 month and 3 months after ONS including BDI (Beck Depression Scale) and MIDAS (Migraine Disability Scale) evaluation.

Population				Baseline					PENS Outcome				ONS three months							
Patient	Age (years)	Pathology	Gender	VAS	Headache-days/month	MIDAS Score	MIDAS Grade	BDI Score	1. PENS VAS	2. PENS VAS	3. PENS VAS	Pre ONS VAS	VAS/ONS one month	Headache-days/month	MIDAS Score	MIDAS Grade	BDI Score	VAS	Follow-up (months)	Medication pre-PENS	PENS-ONS outcome
1	47	CM	w	9	21	34	4	19	7	7	5	9	3	6	16	3	6	3	9	NSAID	NR-R
2	50	CM	w	8	17	41	4	20	7	5	5	8	4	7	9	2	10	3	7	TRIP, NSAID	NR-R
3	49	CCH	w	9	28	34	4	19	8	5	4	8	8	8	40	4	19	8	7	AC, NSAID, O_2	R-R
4	48	CM	w	8	19	45	4	24	7	4	3	8	4	3	3	1	2	2	4	NSAID	R-R
5	71	CH	m	8	22	37	4	23	8	8	8	8			37	4	23			NSAID, AC	NR-NR
6	60	ON	m	9	26	39	4	20	6	5	5	9	4	5	4	1	7	2	3	NSAID, AC	NR-R
7	49	CM	w	9	21	42	4	19	7	6	6	9	7	10	10	2	7	4	3	NSAID, AC	NR-R
8	51	CM	w	8	21	35	4	32	6	4	4	8	6	9	13	2	10	4	3	TRP	R-R
9	23	CM	w	8	24	39	4	25	7	4	4	8	3	4	6	2		3	3	NSAID	R-R
10	47	CM	w	8	22	32	4	26	7	7	7	8	5	12	8	2	11	4	3	TRP	NR-R
11	52	PTH	w	9	21	41	4	19	3	3	2	9	5	6	18	2	6	3	3	NSAID, AC	R-R
12	49	CM	w	8	20	36	4	27	7	6	6	8	5	10	9	2	15	5	3	TRIP, NSAID	NR-R

PENS: percutaneous nerve field stimulation; ONS: occipital nerve stimulation; VAS: visual analog scale; NSAID: nonsteroidal anti-inflammatory drug; BDI: Beck Depression Inventory; MIDAS: Migraine Disability Scale; TRIP: triptan; R: responder; NR: non-responder; AC: anticonvulsant drugs.

Figure 1. Illustration of the anatomical landmarks to determine PENS needle placement as described 3 cm below the protuberantia and 1.5 cm/3.5 cm paramedian toward the mastoidal direction as indicated. The external current driven stimulator is connected to the acupuncture needles with a standardized stimulation program as reported in the Methods section. On the left side the ring demonstrates the PENS needle location, and on the right side the permanent ONS system with the stars indicating contact location. PENS: percutaneous nerve field stimulation; ONS: occipital nerve stimulation.

abdominal wall, via tunneling using an extension wire. The stimulation parameters used for ONS (300 µs, 100 Hz, bipolar configuration) were similar to those of the previously performed PENS.

Statistical analysis

ONS and PENS success was defined as a 50% reduction in headache severity and/or frequency on the VAS. We analyzed the data unvaried to reveal the differences between baseline pain intensity (VAS), headache frequency (headache days/month, MIDAS), and depressive comorbidity (BDI and MIDAS) after PENS and ONS treatment. These were measured for PENS after each session, and for ONS after one and three months after implantation. In the second step, the study population was dichotomized according to treatment success or failure after PENS treatment. ONS outcome of the two groups at the three-month follow-up was compared using the Fisher exact test for binominal data and *t*-test for continuous data. A p value lower than 0.05 was considered significant. All patients were included in the analyses. One patient did not receive implantation and was defined as a non-successful PENS/ONS trial. Statistical analyses were performed using Excel (Microsoft, Seattle, WA, USA) and QuickCalc (GraphPad Software Inc) software.

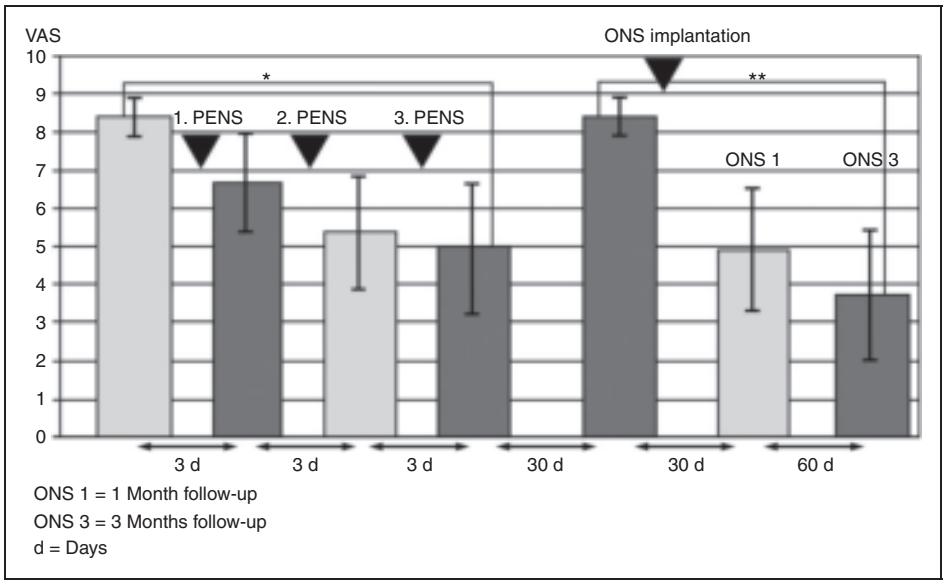

Figure 2. Mean pain score on the VAS at baseline and pre-ONS, during PENS and ONS treatment presented by columns, the corresponding standard deviation indicated by bars and the significant pain decrease between baseline and after the third PENS session and the significant pain decrease between the preoperative level and after three months ONS marked with * (p value < 0.001), respectively.** (p value < 0.001). VAS: visual analog scale; PENS: percutaneous nerve field stimulation; ONS: occipital nerve stimulation.

Results

Pre-treatment pain severity was high in our collective with a mean score of 8.4 (±0.51) on the VAS; all included patients were classified as MIDAS IV prior to treatment initiation.

After each PENS session, there was a decrease in the mean pain score on the VAS. This decrease was reinforced in the last two PENS sessions reaching a mean score of 4.9 (±1.6) (95% confidence interval (CI) 2.5 to 4.5, $p < 0.001$) down from a mean VAS score of 6.6 (±1.3) after the first PENS session (Figure 2). However, one patient with PTH experienced significant pain reduction after the first PENS session. Increased PENS effects, in terms of suppressed headache levels, could be observed in four patients (one PTH, one CCH, two CM) after the second PENS session with a mean VAS score of 5.3 (±1.4) and in five patients after the third/last PENS procedure with a mean VAS score of 4.9 (±1.6) (one PTH, three CM, one CCH).

A successful ONS trial (defined as 50% reduction in severity and/or frequency) was achieved in seven of 12 patients (four CM, CCH, PTH, ON), while four CM patients reported an improvement of 35%. In one patient (CH), no change occurred after the PENS sessions or in the ONS trial; after internal review and consulting, the ONS electrodes were removed with patient consent. Sufficient paresthesia coverage was achieved in all ONS trials with no complication related to the ONS trial. Out of the five PENS responders, the extent of pain suppression observed after PENS was comparable to that achieved by the ONS trial in three patients (CCH, PTH, CM), but not for the remaining two PENS responders with CM (ONS trial 35% reduction). The three-month ONS outcome was comparable to the results observed in the ONS-trial in seven patients (four CM, CCH, PTH, ON), while the remaining four patients (CM) achieved a higher level of headache reduction (≥50%) at the three-month follow-up, which negates the usefulness of ONS trials in patients with CM according to our study protocol.

In total, 11 patients could be classified as having achieved ONS treatment success after three months, defined as a 50% reduction in headache severity and frequency. Pain intensity ameliorated one month after ONS treatment and significantly decreased after three months, reaching a mean VAS score of 4.9 (±1.5) and 3.7 (±1.6) (95% CI 3.6 to 5.7, $p < 0.001$), respectively. ONS treatment was successful in five out of 11 patients (45.5%) after one month and in all 11 patients after three months (Figure 2). Of the 11 ONS responders after three months, five (45.5%) also experienced significant pain reduction from presurgical PENS treatment (50% reduction in headache severity) with a mean VAS score of 4.9 (±1.6) (95% CI 2.5 to 4.5, $p < 0.001$) after PENS application, indicating a certain possible predictive value. The other six PENS non-responders (established diagnosis: chronic migraine) showed a gradual improvement (severity pre-PENS 8.4 (±0.5) versus severity post-PENS 6.3 (±1.13); nevertheless, failed to reach the 50% threshold, but

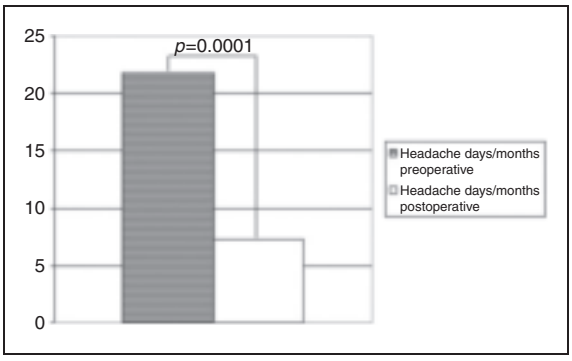

Figure 3. Comparison with a student *t*-test of the preoperative and postoperative mean headache-days/month (frequency) in 11 patients implanted with ONS. ONS: occipital nerve stimulation.

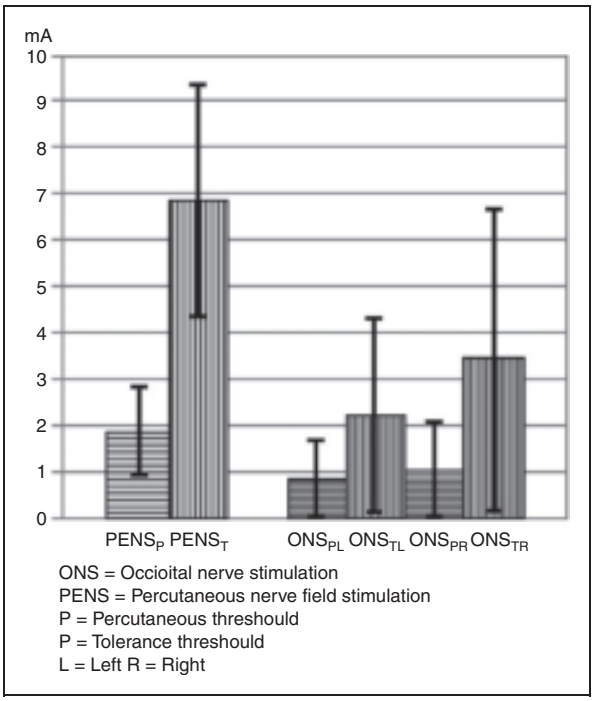

Figure 4. Mean stimulation intensity (mA) for perception and maximal tolerated stimulation thresholds evaluated for PENS and ONS electrodes per side represented by columns and standard deviation indicated by bars. PENS: percutaneous nerve field stimulation; ONS: occipital nerve stimulation.

achieved significant pain reduction at the three-month follow-up in terms of ONS responsiveness 3.7 (±1.6), which may neglect the true efficacy of the presurgical PENS procedure in patients with CM (Figure 2). In total, eight patients with CM were included, of whom three were classified as PENS responders and five as PENS nonresponders; in the later course, all experienced pain relief by ONS after three months. As neuromodulation effects in chronic migraine develop over a longer time span, the described and used PENS paradigm in our protocol should be refined in terms of PENS-duration (45 minutes) and PENS application (six to eight applications in 30 days). One patient did not benefit from either PENS or ONS trial stimulation, which might indicate a negative predictive value. The mean pre-ONS headache frequency was 21.8 (±2.9) days/month and decreased significantly to an average of 7.3 (±2.7) (95% CI 12.2 to 17, $p < 0.001$) after three months of ONS treatment (Figure 3).

Regarding stimulation thresholds for perception and tolerance values, there was no significant ($p = 0.7$) difference between the parameter used for PENS (perception threshold mean 1.9 (±0.9) mA; tolerance threshold mean, 6.9 (±2.5) mA; compared with ONS (perception—left ONS electrode 1.4 (±0.8) mA; right ONS electrode 1.5 (±1) mA; tolerance threshold—left ONS electrode 6.6 (±2.1) mA, right ONS electrode 6.5 (±3.2) mA), in which we evaluated ONS electrodes separately per side to detect individual differences with no significant side-related differences. However, the parameters used for ONS treatment did not differ with regard to side and were slightly lower for perception and tolerance threshold levels compared to those used for the PENS procedure (Figure 4).

The BDI value declined significantly after three months of ONS from a baseline mean of 22.6 (±4.2) to 10.6 (±5.9) (95% CI 7.4 to 16.6, $p < 0.001$) (Figure 5). Similar findings were obtained in the MIDAS score, which dropped down from 143.9 (±14.5) to a three-month follow-up score of 72.8 (±28.7) (95% CI 1.17 to 2.3, $p < 0.001$) (Figure 5).

Overall, the prescription of analgesic medication was reduced, but was not analyzed in detail. The median follow-up observation period was five months (range, three to nine months). No hardware or stimulation-related complications occurred for either stimulation methodology during the treatment course (Table 2).

Discussion

Several approaches using noninvasive and invasive devices have been used at peripheral or central neural targets to provide pain relief in such refractory circumstances. However, some issues remain poorly understood and robust data are still lacking to objectively predict the treatment course of ONS in headache syndrome (2,12–21,25). In a position statement, the Expert Group on Neurostimulation of the European Headache Federation (EHF) has recommended ONS for treatment of chronic refractory cluster headache and has classified ONS as an acceptable option for chronic migraine because of a lack of data (2). To date, neuromodulation responsiveness relies on self-report of pain.

There are well-designed literature data, guidelines and recommendations for conservative treatment

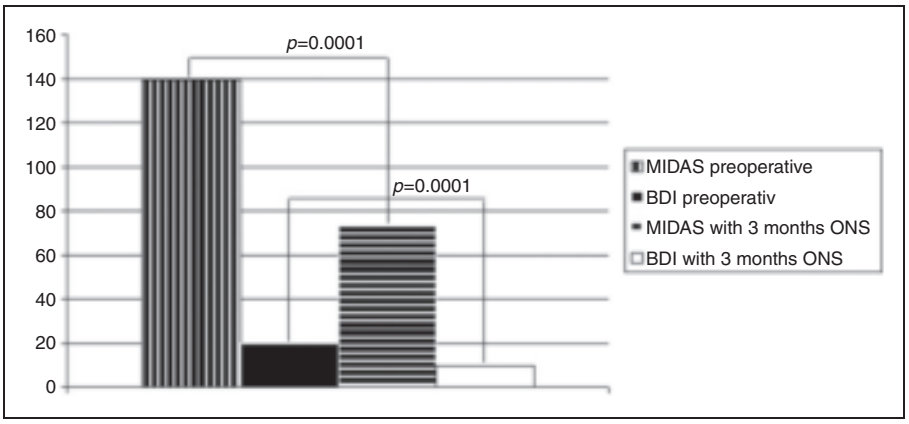

Figure 5. Comparison of the mean BDI and MIDAS scores before and after three months ONS treatment demonstrating significant decline ($p < 0.001$). BDI: Beck Depression Inventory; MIDAS: Migraine Disability Scale; ONS: occipital nerve stimulation.

approaches (medical/behavioral). In addition, there are a large number of patients with chronic refractory headache who have failed to achieve sustained pain relief after minimally invasive neuromodulation like ONS. Several questions remain unanswered with regard to presurgical predictors, objective biomarkers at the pre-treatment and treatment stage, and standardized protocols for implantation and stimulation technique (chronic vs. cyclic stimulation mode) in treating refractory headache disorders (27–34).

In our investigated population of 12 individuals with chronic headache, five obtained significant pain reduction from PENS, while seven were nonresponders. Those who responded to PENS also responded to ONS (combined with pharmacotherapy). Except for one patient (CH) with a negative response to both modalities (PENS/ONS), six of the patients with CM who did not respond to PENS demonstrated sustained pain relief after conventional pharmacotherapy and minimally invasive therapy. The common diagnosis in the PENS-nonresponder/ONS-responder patients was chronic refractory migraine. As stated in an earlier publication, ONS effects on chronic migraine occur over a longer time period compared to those observed in other primary or secondary headache disorders (2). The authors speculate that PENS performed over a longer period as in our study protocol may reliably parallel the effects of ONS in chronic migraine. At least, a gradual improvement could be observed in the six PENS nonresponders.

The specificity of ONS trials in predicting long-term ONS responsiveness has been critically discussed in the past for several reasons. Neuromodulation of the afferent properties of occipital nerves has been assumed to occur over a longer time span (weeks rather than days) to affect the pain-processing intracranial structures. ONS trial results obtained in seven to 10 days must be interpreted with caution as a reliable predictor. Some of the observed effects may be due to a placebo effect related to the high expectations of headache sufferers (2,32–34). Brewer et al. observed a trial success rate of 89%, while ONS outcome dropped down to 56% in the short term, and further decreased to 42% after 34 months (21). The obtained ONS-trial results and enhanced ONS-outcome after three months in our study may illustrate this important unmet criterion.

The outcome of minimally invasive ONS may also depend on whether the patient is treated with a subperceptional, perceptional, or supra-perceptional threshold stimulation intensity. All three stimulation modalities provided pain reduction, with supra-perceptional stimulation threshold being superior in a smaller case series (29,30). In general, the stimulation paradigm in our study consisted mainly of a suprathreshold stimulation mode. Regardless of the ONS outcome, the observed decline of pain levels in five PENS responders enables the development of a standalone noninvasive neuromodulation headache treatment using PENS, as a safe and well-accessible methodology still requiring refinement related to the underlying headache disorder.

No immediate response, like those observed in ONB, occurred after PENS, suggesting a longer time span depending on the headache disorder (days to weeks) necessary for headache pain reduction. The PENS effects relapsed after four weeks, reaching a gradually declined VAS compared to pre-PENS baseline VAS. Although not investigated in detail in our study, a priming effect may occur in ONS patients if PENS was administered prior to ONS. The authors speculate that the extent of head pain decline demonstrated cannot only be preserved, but also increased, if PENS is applied for a longer duration as in our study protocol.

ONB provided prior to ONS implantation yielded no clear predictive value for ONS responsiveness as no randomized controlled trial exists on this issue.

As ONB is assumed to diminish trigeminal hyperexcitability and suppress nociceptive transmission, it is suggested to work on a segmental and short-term pattern. This may explain why ONB failed to serve as a predictive methodology before ONS (16,17,19,25).

A cadaver-based ONS study, scoping to identify anatomic landmarks for reproducible stimulation assessment of the occipital nerves, observed no correlation between ONS outcome and the distribution and extent of the ONS-induced electrical field. This anatomic study investigated the correlation between the anatomic course of the occipital nerves and ONS lead placement. Mueller et al. stated that stimulation of the main trunk of the occipital nerves might be more important than the achieved paresthesia coverage (27). The needle placement chosen in our PENS procedure intended to reach the main trunk of the occipital nerves (Figure 1).

In order to enhance the stimulation setting, Göbel and colleagues introduced a computer-based assessment tool permitting the quantitative and qualitative acquisition of ONS-induced paresthetic distribution. Sensory mapping may allow reliable and objective stimulation paradigms, analyzing such standard obtained data in the neuromodulation treatment course (30). The same frequency (100 Hz) and amplitude (300 μsec) parameters were defined in our stimulation paradigm in order to obtain comparable and reproducible data. The obtained perception and tolerance threshold values in our trial were lower for both ONS electrodes compared to the PENS procedure with no significant difference.

The mechanism of ONS remains unclear. In primary headache disorders, neuromodulation of the occipital afferents may inhibit nociception on a segmental level (occipital afferents) and suprasegmental level (trigemino-cervical complex and thalamic nuclei), thus modulating the headache pathways as well as affecting pain-processing transmitter systems within the intracranial space (31,35). ONS is thought to suppress the presynaptic, nociceptive and a-delta fibers, which contribute to pain processing. Afferent fibers of the cervical segment C1–3 and dural afferents converge with fibers of the trigeminal nucleus caudalis anatomically (cervico-trigeminal complex), which may be a possible hint for the mechanism of ONS (35). As the stimulation patterns (amplitude width, frequency and intensities) derived from our stimulation protocol did not differ significantly in the perception and tolerance thresholds for both modalities, it seems reasonable that the electrical fields within the afferent properties of the occipital nerves evoked by PENS may modulate the trigemino-cervical complex. An important difference between both modalities (PENS/ONS) is the treatment time pattern as the PENS paradigm constituted a cyclic stimulation mode in contrast to the chronic pattern-driven ONS setting. The required duration of PENS treatment for inducing a measurable effect remains difficult to define and may depend on the underlying headache disorder.

The impact of PENS and ONS responsiveness could be enhanced by multidisciplinary based clinical phenotyping. Medication overuse in migraine was found to predict less favorable ONS outcome in an earlier study by Paemeleire and colleagues. They reported that migraine without aura and CH might be a better indication for ONS (31). Different PENS stimulation paradigms should be considered for different headache indications as the above-mentioned headache disorders were based on different pathophysiological mechanisms. Interestingly, patients with CH responded within hours to seven days to ONS, while a decline of the short-term effects was observed in patients with migraine in the long-term follow-up, indicating CH is a suitable target for PENS/ONS modulation (31). Although beneficial ONS outcome was reported for cervicogenic head pain (ICHD-II 13.12), the only PENS/ONS non-responder in our study suffered from sharp and burning persistent pain within the upper cervical and occipital region (31). The importance of interdisciplinary pre-implantation assessment was underlined in a review by Palmisani and colleagues in 25 patients with refractory headache (19 CM, three ON, one CCH, one CH). Out of 25 included patients, nine patients with CM (of note, 11 out of the 19 patients with CM were previously classified as ON) and three ON patients were evaluated for long-term pain relief. Pain catastrophizing (PCS) was found to be a positive predictor for ONS outcome among other clinical features like headache duration, neuropsychiatric distress, cognitive decline and personality disorder (negative predictors). Depression as a clinical comorbidity was found to be one of the most important positive pre-SCS predictors, while factors like anxiety, somatization and poor coping determined poor neuromodulation outcome in patients treated with SCS. Multidisciplinary-based pre-implantation assessment intended to monitor headache-related disability (possible predictor) is highly recommended to achieve a reliable diagnosis, ensure proper selection and enhance ONS outcome (32).

Based on the observations made in this study, the PENS procedure may be a well-tolerated, stand-alone treatment strategy and/or pre-surgical tool for predicting neuromodulation success in terms of ONS with the intent to prompt randomized, controlled, blinded multicenter trials. In addition, the authors recommend including PENS in an appropriate multidisciplinary approach to sufficiently identify other positive and negative predictors contributing to long-term ONS outcome. The study design lacks sham-treated

subgroups in order to exhibit placebo effects, and requires randomization, prolonged duration of the observational period, and a larger sample size with a homogeneous cohort of the study population.

Under-investigated issues remain regarding the stimulation mode (specifically related to the headache disorder), location of needle placement, number of treatments and duration of treatment. These reflect the main limitations of the described trial, as the authors intended to investigate the proof of principle of PENS prior to ONS.

Future targeted research to identify predictive factors and objective biomarkers may be seen in neuroimaging using functional magnetic resonance imaging (fMRI) and computational-based modeling studies (28,36–39).

The concept of using resting-state brain activity as a biomarker is of importance, urging investigations to provide data in determining its potential feasibility and specificity (28). A randomized controlled trial investigated acupuncture therapy in 80 migraine sufferers receiving active or sham treatment. A negative correlation of decreased VAS scores and increased activity can be seen as a predictor; however, it is not feasible to predict response in the individual patient (28,38,39). Conclusively, no data exist to support the hypothesis that using resting-state brain measurements is reliable as a biomarker for ONS-induced headache pain suppression (28).

The dorsal root ganglia cells (DRGs) have been suggested to be involved in the genesis of nociceptive and neuropathic pain. An animal model investigating the distribution of serotonin $(5\text{-HT})_{1B/1D/1F}$ receptor agonists (triptans) in the afferent and sensory ganglia demonstrated $5\text{-HT}_{1B/1D/1F}$ receptor agonists at different spine levels, supporting the possibility of ONS screening by percutaneous, interventional treatment of the DRGs C1–C3 (40,41).

Conclusion

The provided study protocol may illustrate an appropriate and useful methodology that may merit further clinical pain research to assign the predictive value of PENS prior to ONS and in addition its value as a standalone treatment approach in refractory headache disorders.

Clinical implications

- The predictive value of percutaneous nerve field stimulation (PENS) prior to occipital nerve stimulation (ONS) is low.
- PENS protocols should be designed related to specific headache disorders.
- In addition PENS may serve as a standalone noninvasive neuromodulation treatment option.
- PENS should be incorporate in a multidisciplinary pre-implantation setting to detect further possible or negative predictive factors.

Declaration of conflicting interests

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