Stimulation of the Greater Occipital Nerve: Anatomical Considerations and Clinical Implications

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Background: Stimulation of the greater occipital nerve has been employed for various intractable headache conditions for more than a decade. Still, prospective studies that correlate stimulation of the greater occipital nerve with outcome of patients with respect to alleviation of headache are sparsely found in literature.

Objective: To identify anatomical landmarks for a reproducible stimulation of the greater occipital nerve. For the clinical implication, the individual response to therapy of patients with refractory chronic cluster headache undergoing occipital nerve stimulation was correlated with the postoperative localization of the electrodes and with the distribution of the stimulation field.

Study Design: Prospective observational study, approved by the local research ethics board (09-4143).

Setting: University hospital, departments of neurosurgery and neurology, institute of anatomy and radiology.

Methods: Ten formaldehyde fixed human cadavers were dissected to identify the passage of the greater occipital nerve through the trapezius muscle. The distance to the external occipital protuberance was triangulated measuring the distance of the nerve from the nuchal midline and the protuberance.

Between December 2008 and December 2011, 21 consecutive patients suffering from chronic cluster headache underwent surgery in terms of bilateral occipital nerve stimulation, with electrodes placed horizontally at the level of C1. The postoperative x-rays were compared with the acquired landmarks from the anatomical study. The distribution of the stimulation field was correlated to the individual response of each patient to the therapy and prospectively analyzed with regard to reduction of daily cluster attacks and relief of pain intensity at 3 months and at last follow-up.

Results: The greater occipital nerve crosses the trapezius muscle at a mean distance of 31mm below the occipital external protuberance and 14mm lateral to the midline as found in the anatomical subjects. The electrodes were targeted at this level in all of our patients and stimulated the greater occipital nerve in all patients. Eighteen of the patients (85.7%) reported a significant reduction of the frequency of their cluster attacks and/or declined intensity of pain during the attacks. Yet, 3 of 21 patients (14.3%) did not benefit from the stimulation despite an adequate spread of the stimulation over the occiput. The spread of the stimulation-induced paraesthesias over the occiput was not correlated to a reduction of cluster attacks, to the intensity of attacks, or to the response to treatment at all.

Limitations: Single center non-randomized non-blinded study.

Conclusions: From our study we conclude that a reproducible stimulation of the greater occipital nerve can be achieved by placing the electrodes parallel to the atlas, at about 30mm distance to the external occipital protuberance. The response to the stimulation is not correlated to the field width of the paraesthesia. We, therefore, consider stimulation of the main trunk of the greater occipital nerve to be more important than a large field of stimulation on the occiput. Still, an individual response to the occipital nerve stimulation cannot be predicted even by optimal electrode placement.

Key words: Greater occipital nerve, occipital nerve stimulation, anatomical study, chronic cluster headache
stimulation of the great occipital nerve has come into common praxis for the treatment of various intractable headache disorders since the publication by Weiner and Reed in 1999 (1). First applied to occipital neuralgia, occipital nerve stimulation (ONS) was soon found to be effective in other headache disorders as well (2-5).

Amongst headache disorders subjected to ONS, cluster headache (CH) is generally accepted to be the most devastating. Eighty-five percent of the affected patients suffer from an episodic CH with attacks lasting for up to 6 weeks. Fifteen percent of the afflicted subjects experience a secondary chronification defined as pain-free intervals of less than 4 weeks in one year according to the diagnostic criteria of the International Headache Society (IHS 2004) (6). CH attacks show a strict unilateral appearance with additional typical vegetative-autonomic accompanying symptoms in the majority of patients and last from 15 to 180 minutes (IHS 2004). Despite intensified treatment and combination of prophylactic medications, a certain number of patients cannot satisfactorily control their CH attacks or suffers from severe side effects of the drugs (7). In some, occipital blocks may prove helpful (8). For refractory patients an invasive treatment of the cluster headache is proposed (9,10).

In 2007, Burns et al (11) published their prospective study on patients undergoing ONS for chronic cluster headache. Their patients showed a promising response rate in the short and mid-term follow-up with up to 90% reduction of cluster attacks (11,12). The effectiveness of ONS for chronic CH was confirmed in numerous studies with a steadily growing number of patients (13-15).

It is of note that ONS is rather a subcutaneous stimulation in the region of the greater occipital nerve (GON) than a true peripheral nerve stimulation (16,17). Still, randomized prospective studies of the ONS are sparse and, regardless of various reports on the effectiveness of the stimulation, questions remain about the localization of electrode placement, field-width of the paraesthesia, and intensity of the stimulation and their probable correlation with a response to treatment (18-20).

The present study was conducted to identify a defined anatomical destination for electrode placement in order to achieve a reproducible stimulation of the GON. Furthermore, the major interest of this study lies in the analysis of a possible correlation between field-width of the occipital paraesthesia and the response to ONS in means of reduction of frequency and/or intensity of cluster attacks. Finally, long-term follow-up data on complications of the implanted electrodes and generators were analyzed. The trial design of this observational study and acquisition of patients’ data for study purposes were approved by the local research ethics board (09-4143).

Methods

Anatomical Cadaver Studies

For anatomical study purposes 10 human cadavers fixed with formaldehyde were dissected at the Institute of Anatomy to determine the course of the GON through the trapezius muscle, before it divides into its epifascial branches. The external occipital protuberance (EOP) was skeletonized, the trapezius as well as the semispinalis muscle were separated, and the traversing nerve was located on both sides of the midline in each cadaver (Fig. 1). The distance to the EOP was measured downwards along the midline and laterally to the piercing point of the GON through the muscles.

Radiological Study

In addition to the anatomical study, we examined magnetic resonance imaging (MRI) scans of the craniocervical region of 20 randomly chosen patients, who underwent an MRI scan for other reasons than pathological conditions of the craniocervical junction, to determine the mean distance of the EOP to the atlas. Furthermore, we analyzed the mobility of the atlas in correlation to the EOP to evaluate a possible negative impact on the stimulation by dislocating the electrodes. The data of 5 patients who participated in a previously published radiological MRI study were analyzed to determine the maximum motion ranges of the atlas and the EOP in passive anteflexion (50°) and retroflexion (60°) (21).

Clinical Investigations

Patients Collective

Twenty-one patients suffering from refractory chronic CH consecutively underwent ONS between December 2008 and December 2011 and were prospectively enrolled in the observational study after informed consent was granted. There were 15 men and 6 women (mean age at operation was 38 years, range 18 to 54 years). The CH was diagnosed refractory in all patients, if the attacks were not controlled by medication ac-
according to predefined criteria (isoptine ≥ 450mg/diem, topiramate ≥ 150mg/diem, lithium plasma level within therapeutic range, drugs alone or in combination). All patients assessed a headache diary 30 days prior to operation and continuously during the follow-up. By this, an individual baseline of the frequency and intensity of the attacks could be established for each patient. Informed consent for the operation and, separately, the study participation were obtained from all patients.

Implantation Techniques

All implantations were done in a standardized manner under general anaesthesia, with the patients in the prone position (14). After sterile scrubbing and dressing of the operation field, an incision, a thumb's breadth distal to the EOP, measuring 20mm in length, was made down to the fascia plane. A subcutaneous pocket was created to contain a small loop of the stimulation lead after fixation to the fascia with silicone anchorage using Ethibond Excel 2.0® (Ethicon, a Johnson & Johnson company, Norderstedt, Germany). The electrodes (Piscos Quad® or Quad Plus®, Medtronic, Sofamor Danek, USA; 10 patients December 2008 until April 2010; Octrode®, St. Jude Medical, Inc., St. Paul, Minnesota, USA; 11 patients from May 2010 on) were positioned subcutaneously by advancing a Tuohy needle towards the mastoid tip. Positioning of the electrodes at the level of C1 was intraoperatively checked by fluoroscopy. A strain relief loop was interposed via a small pocket above the ipsilateral scapula, before connecting the stimulation electrode to the extension lead. The extension was externalized at the flank using a tunneling passage as long as possible. The leads were secured to the skin with Prolene 2.0® (Ethicon, a Johnson & Johnson company, Norderstedt, Germany).

All patients underwent a test phase with externalized leads for 30 days. After this period, the response to, and the effectiveness of, the stimulation were assessed. Patients were submitted to implantation of a permanent generator if a discernible effect of the stimulation could be read from the headache diary.

Fig. 1. Picture of the anatomical dissected craniocervical region. A: Asterisk marks the external occipital protuberance, the right greater occipital nerve is shown piercing the m. semispinalis (arrow). B: Forceps defines the midline, and the greater occipital nerves are marked bilaterally, passing the muscles symmetrically.
In the case of a successful response to the stimulation, a permanent generator was implanted (Synergy®, Medtronic, Sofamor Danek, USA, or EonC®, St. Jude Medical, Inc., St. Paul, Minnesota, USA, respectively).

**Stimulation Parameters**

All patients were set with the same stimulation parameters as follows: pulse width 390us (387us) and a frequency of 40Hz. The intensity of the stimulation was individually chosen by the patients according to their preference.

**Follow-up Examinations and Data Analysis**

Patients were seen in regular follow-up intervals of 3 months, or in between if required. Patients residing at greater distances were seen after 3 months and from then on semi-annually. These patients were contacted regularly by email or phone.

To find a clinical correlation of the anatomical data, the postoperative x-rays of the patients were analyzed with respect to positioning of the electrodes. Postoperatively, biplanar x-rays of the cranio-cervical junction were obtained to document correct placement of the electrodes.

Field-widths of the paraesthesias were estimated and divided into 3 zones (nuchal, up to the retroauricular region, up to the vertex) for each patient with respect to previously suggested head zones of paraesthesia (22) (Fig. 2). To assess the possible effectiveness of the stimulation, data on frequency and intensity of the CH attacks were recorded at 3 months follow-up for each subject. Any adverse event was recorded with a maximum follow-up of 39 months, so far.

The mean transsection point of the GON through the muscles assessed in our anatomical study was compared to the localization of the electrodes on the postoperative x-rays. Deviations were correlated to field-width of the stimulation in each patient.

Correlations (Pearson’s correlation coefficient) were made between response to treatment, distribution of stimulation, usage of voltage- or constant current-gated implantable permanent generators (IPGs) and application of subthreshold-stimulation. Student’s t-test analysis for dependent paired samples were performed for reduction of daily attacks, improvement on the numeric rating scale (NRS), and usage of triptanes at baseline, after 3 up to 6 months, and at last follow-up, respectively. Statistical analysis was performed using SPSS 18.0®.

**Results**

**Anatomical Study**

In the 10 formalin-fixed human cadavers, the GON was found at a mean of 31mm (range 25 - 35mm) distal to the external occipital protuberance and on average 14mm (range 8 - 25mm) distant from the midline traversing the trapezius muscle. There was no substantial difference in distances from the right to left side within one subject. Once piercing through the fascia of the trapezius muscle, the GON spreads manifold and proceeds with various branches on its way up to the vertex. The course of these smaller subcutaneous branches cannot be reliably predicted.

**Radiological Study**

Mean distance of the dorsal vertebral arch of the atlas to EOP was 57mm (range 45 – 68mm) for all subjects. Subgroup analysis for gender revealed that the female population showed a smaller distance (mean 53mm, range 45 – 59mm, standard deviation [SD] 4mm) than the male subjects (mean 62mm, range 58 – 68mm, SD 5mm). In passive ante- and retroflexion using the NeuroSwing system, we determined a motion range of an average of 2mm (range 0 – 4mm, SD 2mm) (21).
Clinical Study

With the above described implantation technique, the electrodes can be reproducibly placed parallel to the level of C1, which is easily controlled by intraoperative fluoroscopy. This in turn hits the region determined above where the GON penetrates the trapezius muscle. Therefore, we were able to stimulate the GON in all 21 patients only by relying on anatomical landmarks (EOP) and the triangulated points of optimal lead placement.

Out of the 21 patients, 18 responded to the stimulation with a relief of their cluster headache by means of diminished attacks, pain intensity (measured with NRS) or usage of triptanes. The effect of the ONS was evaluated from the patients’ headache diaries on average after 20 days of stimulation. Prior to that, the possible effects were not conclusive and might have also been assigned to the sham effect of any operation. This accounts for the non-responders as well, who were only able to tell after that period of time that they did not benefit from the stimulation.

The initially achieved stimulation zone was not predictive of success of the therapy (Pearson’s -0.220, significance 0.337). Of the 3 non-responders, one patient felt a substantial relief of the accompanying migraine. The subject was regarded as a non-responder but was kept in regular follow-up as he received an IPG, and consecutively was listed in the current statistic as non-responsive but participating. In the other 2 non-responders, the electrodes were removed and they were not evaluated for further analysis.

Nine subjects received a voltage-gated IPG (Synergy, Medtronic®, Sofamor Danek, USA), and 10 were implanted with a constant current working IPG (EonC, St. Jude Medical, Inc., St. Paul, Minnesota, USA). The mode of acting of the applied IPG was neither predictive of the response to treatment (Pearson’s 0.117, significance 0.614) nor of the percentage of subjective reluctance of the cluster as rated by the patients (Pearson’s -0.211, significance 0.358).

Stimulation parameters (40Hz, 390us impulse width) were fixed for all patients. Yet, the intensity of the stimulation was freely adjustable by the patients. Ten patients preferred to stimulate near to subthreshold (prickling sensation only lightly noticeable at certain movements, or not at all), while 9 used the stimulation achieving a well-noticeable paraesthesia. The effect of the stimulation did not correlate with the adjusted intensity (Person’s -0.356, significance 0.113).

At 3 months follow-up, the mean rate of cluster attacks (n = 2.9) had significantly declined compared to the baseline rate (n = 5.6; P < 0.001). This result was confirmed at latest follow-up (attacks: n = 2.8; P < 0.05).

The intensity of the cluster attacks also relieved significantly. From a mean NRS score of 8.3 (baseline), we observed a drop to a mean NRS score of 5.7 (3 months follow-up, P < 0.01), and 5.6 (latest follow-up, P < 0.01), respectively.

Patients responsive to ONS were mostly able to reduce their amount of acute medication. Initially, a mean consumption of 1.58 doses of triptanes daily (zolmitriptan nasal spray or sumatriptan applied subcutaneously in most patients) was recorded, dropping to a mean of 0.55 daily triptane doses at 3 months follow-up (P < 0.05), yet increasing slightly to a mean daily need of 0.96 doses of triptanes at latest follow-up, but still significantly diminished (P < 0.05).

Results are depicted in Figs. 3 to 5.

There were several severe adverse events during the study period. We observed a total of 4 local infections (in 3 patients), requiring explantation of the leads and replantation after antibiological eradication. One patient was not included in the study, because it was not possible to implant the electrodes without recurrent systemic septicaemic-like infections despite prolonged substitution of antibiotics after the operation. This might be explained by impaired skin conditions due to severe preceding acne of the upper thorax and neck region.

Fig3. Daily cluster headache attacks are depicted in boxplots at (1) baseline, and at (2) 3 months follow-up, and at (3) latest follow-up.
In 2 patients the extension leads broke and had to be replaced. We observed one iatrogenic lead dislocation during the IPG implantation. Fortunately, the electrode dislocated only 2cm and the stimulation field was not altered by this maneuver.

Three patients experienced a change of side of their CH. The attacks on the other side were far less intense and occurred seldom, yet they only started after initiation of ONS.

All patients with a follow-up comprising more than 6 months experienced at least one severe recurrent episode of CH, regardless of their response to the ONS. On further follow-up we observed that these episodes culminated in spring and autumn/early winter, just like episodic CH semiannually does (23,24).

**DISCUSSION**

The GON derives from the second and, partially, third cervical nerve root, turning backwards and traversing the lamina of the axis before ascending toward the occiput (25). It runs between the muscles of the erector spine and pierces the semispinalis capitis muscle and the trapezius muscle (26). Though the GON spreads into several highly variable branches which serve the skin of the occiput, its common trunk generally takes a constant course until leaving the fascia of the m. trapezius (26,27). Landmarks have been proposed before where anaesthetic blocks can be applied to infiltrate the GON (8,28). In chronic CH this infiltration helps to interrupt or relieve episodes of cluster attacks (29-31). In the present study the GON ran in a very constant fashion on its way through the semispinalis capitis muscle and the trapezius muscle in all examined human cadavers, before passing the fascia of the trapezius muscle and branching multiple. Measuring from the external occipital protuberance, the GON was constantly found at an average 31mm distal and 14mm laterally to the midline (to both sides). These data are in accordance with a previous study (27). This triangulated anatomical point of the passing GON resembles the level of the atlas. Thus, placing an electrode epifascial at the level of the atlas should allow for a reproducible stimulation of the GON, which was proved right in all of our patients. According to the findings from the present radiological study we conclude that even wide ranges of motion in ante- and retroflexion will not diminish the stimulation as the mean relative mobility of the atlas to the EOP measures 2mm only in a 110° passive mobility setting (21).

It has to be debated, whether it is helpful to apply intraoperative ultrasound to guide the electrodes subcutaneously. Recently, 2 studies have advocated the intraoperative use of ultrasound for secure positioning of the leads (32,33). Even though we did not apply it and have not experienced problems with lead misplacements, we would advise the use of ultrasound with respect to their findings. Noteworthy, a subfascial misplacement of the electrodes will possibly cause inconvenient spasm of the high cervical muscles, whereas a too superficial implantation might lead to consecu-
Several reports suggest distinct points on the occiput for stimulation of the GON as well as to apply anesthetic blocks to it. Blockade of the GON is an effective treatment option in many patients with CCH (29,36). The neuromodulative stimulation of the GON has been reported in numerous clinical series as a beneficial adjunctive therapy for various headache disorders (2,12,13,16,18,37). Patients suffering from CH, occipital neuralgia, and chronic migraine achieve satisfactory relief of their disabling pain with regard to intensity, frequency of attacks, and duration of attacks (10,14,38,39). Nevertheless, the underlying pathology and mechanism of action have not been clarified despite multiple laboratory and clinical studies (3,40-42). It is not surprising that even the placement of the electrodes, the destined localization, and number of electrodes are still debated controversially (1,2,17,38). Some authors propagate the intraoperative testing of the stimulation, and proceed with the operation only, if the GON is adequately stimulated by means of the distribution field of the achieved paraesthesia (19). This is somehow contradictory to the common finding that the effect of the stimulation will build up over several months (12,40,43). It is questionable whether intraoperative testing of the GON is of any value to the patient. In the ONSTIM study, patients were excluded when intraoperatively the GON could not be stimulated (19). Placing electrodes in the suboccipital subcutaneous tissue is a painful act for the patient regardless of the local anesthesia. Furthermore, if the operation field is extensively anesthetized, chances are high that the GON will be blocked by this and, therefore, stimulation of the nerve will be inhibited. Implanting the electrodes under general anesthesia, as it was done for the present study in a standardized manner, may expose the patient to the risks of general anesthesia. Nevertheless, stimulation of the occipital nerve could be achieved in all of our patients. Hence, it seems to be important to clarify if the achieved paraesthesia, its intensity and field-width, correlates with the efficiency of the stimulation.

The present study shows that GON stimulation is possible with a standardized placement of the electrodes bilaterally from the midline at the level of C1, which can be easily found approximately a thumb's breadth beneath the external occipital protuberance. Yet, a successful stimulation of the GON will not predict a therapeutic benefit for the ONS. An adequately long test period of stimulation is the only way to elucidate whether a subject responds to ONS according to our experience. From our data we conclude, that the response rate to ONS is approximately 80%, which is in accordance with recent literature (5,11,16,44,45).

The width of the stimulation field covering the occiput is not correlated with the response to therapy at all, or a superior reduction of cluster attacks, as far as we can tell from our data. We are not even sure whether the patient needs to sense the stimulation to experience a relief of the CH. Half of our patients, who benefit from the ONS, do so by stimulating with subthreshold or near to subthreshold amplitude. Lowering the amplitude of the stimulation toward subthreshold stimuli did not impact the outcome negatively in our patients. This may even have a ponderable effect on the capacity of the generators implanted. Still, the small sample size of the study excludes a generalization of the results. More prospective studies are required to evaluate further the necessary extent and effect of the stimulation.

Patients responding to ONS report of various effects, ranging from a faster onset of acute medications to a total decline of attacks over weeks. From our data we could neither predict if a patient responds to the stimulation, nor to what extent a possible effect builds up. Yet, we learned from this prospective study that the effect of the ONS is fluctuating intra-individually over time. On follow-up examination it became clear that the underlying semi-annual course of CH is not affected by the ONS. ONS might provoke a change of side of CH as reported before (12). And even though possible adverse events might be restricted to the epifascial plane, there are numerous complications, namely lead migrations, skin erosions, or infections that can be possibly minimized when keeping strictly to a standardized implantation procedure (16,34,35).

Nevertheless, the overall acceptance of ONS for chronic CH is rated good to excellent; and our patients invariably recommend the operation to other CH patients. The small sample size and the study restriction to refractory CH patients have to be kept in mind and, therefore, results should not be generalized to all different headache disorders. Yet, despite negative selection bias by only proposing refractory patients to ONS so far, the results are convincing.

**Conclusion**

The GON runs on a constant course through the craniocervical muscles before fanning out into branches. It can be reproducibly stimulated at the level of C1.
Intraoperative testing of the stimulation is therefore superfluous. Yet, successful stimulation of the GON does not warrant a successful response to the treatment with regard to a reduction of cluster attacks, intensity of attacks, or usage of acute medication such as triptanes. From our data we suggest that non-responders can be identified after a decent period of test stimulation, so that implantation of an IPG is only performed in the responders with a minimal rate of consecutive therapy failures. Still, for refractory CH patients ONS is a promising therapy alternative that combines promising results with an acceptable operative morbidity.

References


