Accuracy of Electrode Position in Sphenopalatine Ganglion Stimulation in Correlation With Clinical Efficacy

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ABSTRACT

Introduction: Sphenopalatine ganglion (SPG) stimulation is an efficient treatment for cluster headache. The target for the SPG microstimulator in the pterygopalatine fossa lies between the vidian canal and foramen rotundum, ideally two contacts should be placed in this area. However, placement according to the manufacturers recommendations is frequently not possible. It is not known whether a suboptimal electrode placement interferes with postoperative outcomes.

Materials and Methods: SPG stimulation was performed in 13 patients between 2015 and 2018 in a single center. Lead location was determined by intraoperative computed tomography scan and correlated with the planned lead position as well as clinical data and stimulation parameters. Patients with a reduction of 50% or more in pain intensity or frequency were considered responsive.

Results: Eleven patients (84.6%) responded to SPG stimulation with eight being frequency responders (61.5%). In seven cases, there were less than two electrodes between vidian canal and foramen rotundum, there was no significant correlation with negative stimulation results (p = 0.91). The mean distance of lead location between pre- and postoperative images did not correlate with clinical outcomes (p = 0.84) and was even bigger in responders (4.91 mm vs. 4.53 mm). The closest electrode contact to the vidian canal was in the stimulation area in all but one patient, regardless of its overall distance to canal. The distance of the closest electrode to the vidian canal was, however, not significantly correlated to the percentage of frequency (p = 0.68) or intensity reduction (p = 0.61).

Conclusion: There was no significant correlation regarding aberrations of lead position from the planned position with clinical outcome. However, this study might be underpowered to detect such a correlation. The closest electrode contact to the vidian canal was in the stimulation area in all but one patient in the final programming. This indicates that, overall, the lead location does play a crucial role in SPG stimulation for cluster headache.

Keywords: Chronic pain, cluster headache, electrode placement, neuromodulation, sphenopalatine ganglion

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INTRODUCTION

Cluster headache is a clinical entity characterized by recurrent and excruciating unilateral headache attacks associated with parasympathetic autonomic features ipsilateral to the headache. The pain typically affects the region around the eye, untreated lasts for 15–180 min and recurs once every other day up to eight times a day (1). Despite best pharmacological therapy involving triptans, oxygen, and prophylactic drugs like verapamil, some patients show no or little improvement and therefore are diagnosed with refractory cluster headache.

Sphenopalatine ganglion (SPG) stimulation was suggested as a new approach to refractory cluster headache for the first time by Ibarra in 2007 (2). Ansarinia described in a small study of six patients how SPG stimulation during a cluster attack resulted in a complete relief of 11 out of 18 pain crises (3). Partially based on these results, an implantable microstimulator system for SPG stimulation was developed (Fig. 1). The system consists of a rechargeable and implantable stimulator that is activated by the
patient with a remote controller when cluster attacks begin. SPG stimulation on-demand—exclusively during a cluster attack—achieved pain relief in 67.1% and pain freedom in 34.1% of the attacks in a multicentric study of 32 patients (4). It was later shown that SPG stimulation could not only abort cluster attacks, but also prevent new ones for reasons still not completely understood.

There is no official definition for the ideal lead position, but a generally accepted standard used by ATI for the preoperative planning states that at least two electrodes should be placed between the vidian canal and the foramen rotundum. The vidian canal and the foramen rotundum are landmarks of the approximate location of the SPG, usually located inferior to the vidian nerve. The microstimulator body should be placed no deeper than 3.5 cm under the skin, otherwise the communication with the remote controller could be disturbed. The fact that the lead cannot be directly seen during the insertion, as well as the frequent difficulties that each patient's anatomy may pose, make SPG stimulation surgery a challenging procedure. It is not uncommon that the lead deviates from the planned position. A possible correlation between suboptimal (meaning not in the planned location based on the implantation guidelines) lead placement and worse clinical outcomes has not yet been investigated.

This study reviews data of 13 patients who underwent SPG stimulation. We analyzed whether a suboptimal overall electrode position results in worse clinical outcomes in SPG stimulation. Additionally, programming parameters and the electrode location in relation to the vidian canal were analyzed.

**MATERIAL AND METHODS**

From May 2015 to December 2018, a total number of 13 patients with refractory chronic cluster headache and indication for SPG stimulation presented at the Department of Neurosurgery of the Heinrich Heine University of Düsseldorf. The patients’ hospital records, outpatient charts, operative reports, pre-, intra- and postoperative radiologic studies, stimulation parameters, and demographic information were subjected to retrospective analysis and review. Dates for follow-up examinations were scheduled by the responsible surgeon at 3, 6, and 12 months follow-up. No patients had a change in medications in the four weeks prior to surgery. No patient previously had ablative procedures or other surgical interventions in the pterygopalatine fossa.

Midface anatomy was evaluated with a computed tomography (CT) scan, which provided important information for the choice of the leads length. CT data were analyzed by the ATI. Using the software Mimics (Materialise, Leuven, Belgium), they provided a preoperative plan of the presumably ideal lead position based on the patients’ anatomy (Fig. 2).

The only commercially available product for SPG stimulation was Pulsante™ SPG Microstimulator System, developed by Autonomic Technologies, Inc. (ATI, Redwood City, CA, USA). Leads were implanted under fluoroscopy and in cooperation with an experienced otolaryngologist. An incision is made 5 mm superior to the mucogingival junction above the maxillary first or second molar with a length of 1.0–1.5 cm. After elevation of the maxillary periosteum, the edge of the zygomaticomaxillary buttress is exposed. The Pulsante Surgical Introducer is advanced into the pterygopalatine fossa using fluoroscopy and the length of the lead is confirmed. The lead blank is inserted to create a trajectory from inferior to superior in the soft tissue. After loading the Microstimulator to the Pulsante Shielded Tip Surgical Introducer, the tip of the lead is advanced under fluoroscopy until it is very close to the SPG, which cannot directly be seen. A measure of electrode impedance is performed and an intraoperative CT is done to show the lead position. Following verification of correct lead position, the microstimulator body is anchored to the maxilla using the fixation plate and then the incision may be closed. After four weeks, the patients present for the first programming session. Active contacts and stimulation parameters are selected to induce paresthesia in the root of the nose, indicating stimulation of the SPG and not of surrounding structures.

Lead placement was assessed using PACS, the Picture Archiving and Communication System, and Mimics®, a software developed by Materialise, Inc. that elaborates three-dimensional reconstructions of intraoperative CT data. The first parameters evaluated compared the position of the implanted lead with the planned electrode position based on the manufacturers’ recommendations. The distances between each individual electrode of the implanted lead and their respective ideal positions as planned were assessed. Mean, minimum, and maximum distances measured the accuracy of lead placement. Furthermore, lead position within the pterygopalatine fossa is classified as anterior, mid-fossa, and posterior. In a second step, the anatomic relation of the

![Figure 1. Pulsante SPG microstimulator system with its microstimulator body and an integrated lead with six electrodes, the most proximal of them being two separate contacts. Used with permission from ATI.](image-url)
implanted lead with osseous landmarks of the fossa was studied. The distance between individual electrodes and the superior aspect of the middle point of the vidian canal and the inferior aspect of the middle point of foramen rotundum are measured as well, the closest electrodes to the vidian canal and to the foramen rotundum were identified for each patient. To evaluate conformity with the manufacturer’s definition, following parameters also were assessed: number of electrodes between vidian canal and foramen rotundum, depth of the microstimulator body, and presence of electrodes in nasal sinuses.

The evaluation of clinical outcomes was based on pre- and postprocedural pain intensity and frequency and were collected at each follow-up appointment. The mean duration of cluster attacks could not be assessed. Preprocedural baseline was the last appointment prior to the implant. Pain intensity was assessed using the Visual Analog Scale (VAS) that ranges from 0 to 10. A patient was considered frequency responsive when the frequency of cluster attacks decreased at least 50% after the procedure, a phenomenon attributed to the repeated use of SPG stimulation. Acute response was defined as a mean intensity reduction of at least 50% after 15 min of SPG stimulation during cluster attacks.

This study was approved by the local IRB (2018-150-RetroDEuA).

RESULTS

The population of this study consists predominantly of male patients (9/13, 69.2%) and has a mean age of 44.4 years, which is consistent with epidemiological data for the general population (5). The baseline attack frequency was 23.9 attacks per week (standard deviation [SD] = 18.5) and baseline pain intensity was 8.6 (SD = 1.5) in the VAS scale. Cluster attacks were predominant on the left side (nine patients, 69.2%) and were present for a mean time of 13 years (SD = 10.9 years).

Lead Position

In three cases, a second intraoperative CT was performed after unsatisfactory lead position and immediate revision was performed. Lead position could be successfully corrected in two of these cases. Figure 3 shows a three-dimensional view of the implanted lead in the pterygopalatine fossa. Figure 4 compares the individual electrodes of the implanted lead with their planned position and the respective mean distances are listed in Table 1. The lead position in the pterygopalatine fossa is obtained from the evaluation of axial CT images at the vidian canal (Fig. 5). A comparison between final lead placement and the planned lead position also is done in Table 1. Planned lead position included at least two electrodes between vidian canal and foramen rotundum, no electrodes in paranasal sinuses and a microstimulator body no deeper than 3.5 cm in relation to the skin.

The mean distance between implanted lead and planned ideal position for all patients was 4.85 mm (SD = 2.41 mm). Leads were placed in the anterior portion of the pterygopalatine fossa in six cases (46.2%), four leads were inserted posteriorly (30.8%), and two were in the mid-fossa (15.4%). In one case, the lead placement was virtually identical to the preoperative planning, in another case the lead remained outside of the pterygopalatine fossa after multiple attempts.

Three-dimensional reconstructions of the sphenoid bone with the implanted lead give a more precise impression of lead
placement and are the basis for the following assessments (Fig. 6). Distances between each individual electrode and the superior aspect of the middle point of the vidian canal are given in Table 2, which also displays stimulation parameters at the last follow-up for each patient. Distances to the inferior aspect of the middle point of the foramen rotundum also were assessed.

The minimum distance from one electrode to the vidian canal for all patients had an average of 8.20 mm (SD = 1.86 mm). The first electrode was most frequently the closest electrode to the vidian canal (6/13, 46.1%). In 12 cases, the closest electrode to the vidian canal was in the stimulation area, regardless of the overall distance between electrode and canal. The average of minimum distances from one electrode to the foramen rotundum was 13.17 mm (SD = 2.49 mm), and electrodes one, two, and five were in closest contact in three cases each.

Overall, five patients (38.5%) had their lead inserted exactly as suggested by ATI. A minimum of two electrodes between the vidian canal and the foramen rotundum could be placed in six cases (46.2%) and the remaining of them only had one (six patients) or none (one patient) in the indicated region. In one patient, one electrode was located in the paranasal (maxillary) sinus. A microstimulator implantation depth of more than 3.5 cm was found in one case; this is against the implantation guidelines as it might disturb telemetry.

Clinical Outcomes

After the implantation of an SPG microstimulator, patients were followed up for an average of 8.3 months (SD = 3.0 months). As this surgery is performed only in selected centers in Germany, most patients have a long journey and are therefore followed-up in the long term by a local specialist. However, all patients completed at least six months of follow-up at our clinic and pain frequency and intensity were evaluated at each appointment. The
The mean frequency reduction was 61.3% (SD = 33.8) at three-month follow-up and 67.8% (SD = 35.5) at the last follow-up (Table 3). This is a reduction from a mean baseline of 23.9 (SD = 18.5) to 8.0 (SD = 12.8) attacks per week. Most patients showed a consistent response to stimulation, in only one case a significant frequency response just appeared at the second follow-up. A total of ten patients (76.9%) had a frequency reduction of at least 50% and were considered frequency responders. Among these patients, mean frequency reduction was 84.2% (SD = 16.6%); four patients had a complete remission of cluster attacks. Patients that were frequency responders had an average of 20.3 (SD = 13.6) attacks per week at baseline and 2.4 attacks per week at the last follow-up.

Acute response to SPG stimulation was found in a lower proportion of patients. Excluding the four cases of complete remission, acute response to SPG stimulation was found in 54.5% of patients. The majority of patients showed a consistent response, with only one case showing a significant frequency response just appearing at the second follow-up. A total of ten patients (76.9%) had a frequency reduction of at least 50% and were considered frequency responders. Among these patients, mean frequency reduction was 84.2% (SD = 16.6%); four patients had a complete remission of cluster attacks. Patients that were frequency responders had an average of 20.3 (SD = 13.6) attacks per week at baseline and 2.4 attacks per week at the last follow-up.

### Table 1. Accuracy of Lead Placement Compared to Preoperative Planning and to the Standard Definition of Ideal Lead Position.

| Patient number | Mean distance (mm) | Position in PPF | Electrodes between VC and FR | No electrodes in paranasal sinuses | Microstimulator body depth (cm) | Conformity to standard definition |
|----------------|-------------------|----------------|-----------------------------|-----------------------------------|---------------------------------|----------------------------------|
| 1              | 3.54              | Mid-Fossa      | E1                          | +                                 | 3.0                             | -                                |
| 2              | 4.20              | Posterior      | E3 and E4                   | -                                 | 3.2                             | -                                |
| 3              | 3.54              | Anterior       | E4 and E5                   | +                                 | 3.2                             | +                                |
| 4              | 7.39              | Anterior       | E1                          | +                                 | 2.9                             | -                                |
| 5              | 5.18              | Anterior       | E1                          | +                                 | 4.0                             | -                                |
| 6              | 6.10              | Anterior       | E1                          | +                                 | 2.8                             | -                                |
| 7              | 5.36              | Mid-Fossa      | E5 and E6                   | +                                 | 2.8                             | +                                |
| 8              | 2.62              | Posterior      | E1 and E2                   | +                                 | 2.9                             | +                                |
| 9              | 2.96              | Posterior      | E3 and E4                   | +                                 | 2.7                             | +                                |
| 10             | 0                 | Anterior       | E2 and E3                   | +                                 | 3.4                             | +                                |
| 11             | 9.09              | Outside        | None                        | +                                 | 3.0                             | -                                |
| 12             | 7.41              | Posterior      | E1                          | +                                 | 2.3                             | -                                |
| 13             | 5.68              | Anterior       | E1                          | +                                 | 2.8                             | -                                |

Mean distances between individual electrodes of the implanted lead and their planned ideal position are given in millimeters. The second column indicates the lead position in the PPF. Comparison of final lead placement with standard definition of ideal position from ATI (Autonomic Technologies, Inc.).

Microstimulator body depth is indicated in centimeters.

PPF, pterygopalatine fossa; VC, vidian canal; FR, foramen rotundum.

### Figure 5. Axial CT image at the VC. The first three electrodes of the implanted lead are indicated (E1–E3).
Figure 6. Anterior view of a three-dimensional reconstruction of the sphenoid bone. Implanted lead is depicted in yellow, and the preoperatively planned ideal position is shown in red. Vidian canal is indicated with a pink point and foramen rotundum in blue.

Table 2. Distances From Individual Electrodes to the Vidian Canal and Stimulation Parameters in the Last Follow-Up.

| Patient number | Distance to vidian canal | Anode   | Cathode | Stimulation parameters |
|----------------|--------------------------|---------|---------|------------------------|
|                | E1 | E2 | E3 | E1 | E3 | Frequency (Hz) | Maximum amplitude (mA) |
| 1              | 7.92 | 7.97 | 8.73 | E1 | E3 | 120 | 1.6 |
| 2              | 12.64 | 11.54 | 10.86 | E1 | E3 | 120 | 1.6 |
| 3              | 11.40 | 9.58 | 8.44 | E5 | E4 | 120 | 2.0 |
| 4              | 7.72 | 8.62 | 10.33 | E1 | E3 | 120 | 2.0 |
| 5              | 12.84 | 12.68 | 13.71 | E2 | E1 | 120 | 1.3 |
| 6              | 7.89 | 8.46 | 9.67 | E5 | E1 | 120 | 2.0 |
| 7              | 11.59 | 9.49 | 7.86 | E3 | E1 | 120 | 2.6 |
| 8              | 4.92 | 6.25 | 7.60 | E3 | E1 and E2 | 120 | 2.0 |
| 9              | 9.05 | 8.24 | 8.28 | E2 | E1 | 80 | 1.8 |
| 10             | 6.99 | 6.65 | 7.67 | E2 | E3 | 120 | 2.0 |
| 11             | 7.55 | 9.87 | 12.51 | E1 | E2 and E3 | 120 | 2.0 |
| 12             | 8.13 | 8.12 | 8.80 | E1 and E2 | E3 | 120 | 1.5 |
| 13             | 7.81 | 8.77 | 10.70 | E2 and E3 | E1 | 120 | 2.5 |

Distances from each of the first three individual electrodes (E1–E3) to the superior aspect of the middle point of the vidian canal. Distances are indicated in millimeters and the shortest one for each patient is in bold. Fifth and sixth columns indicate the electrodes used as anode and cathode from E1 to E6, the remaining electrodes are OFF. Signal frequency given in Hertz and maximum current amplitude in milliamperes.
remission, in which no acute response could be evaluated, three patients (23.0%) reported a pain relief of at least 50% after SPG stimulation. Mean pain reduction compared to baseline was of 35.8% in the last follow-up, from an average baseline intensity of 9.0 (SD = 1.2) to 5.7 (SD = 2.0) on the VAS. Overall, 11 patients (84.6%) responded to SPG stimulation, with eight (61.5%) being frequency responders, one (7.7%) being acute responder, and two (15.4%) being frequency and acute responders.

No permanent device- or procedure-related adverse events occurred. There were neither postoperative revisions, nor extant procedures, nor lead migrations. However, nine patients reported some form of adverse event (69.2%), most of them transitory or related to stimulation. The most common events were localized sensory disturbances, mostly hypoesthesia in the face, palate, and uvula, reported by seven patients (53.8%). In all cases, the sensory disturbance resolved in the first three months after the procedure, including the single cause of hypoguesia (7.7%). Patient 11, that had a lead implanted at the entrance of the pterygopalatine fossa, reported persistently paresthesia of the front of the nose during stimulation. There was one case of swelling that needed treatment with steroids (7.7%) and one case of trismus that was clinically observed and resolved within two months without specific treatment. One patient reported persistent nausea associated to stimulation, refractory to reprogramming, and treated with antiemetics.

The presence of at least two electrodes between vidian canal and foramen rotundum was not significantly associated with better clinical outcomes in this study. Out of 11 responders, six had one electrode or no electrode at all in the desired position, a Chi-squared test found no significant association (p = 0.91). The single patient with no electrodes between the vidian canal and the foramen rotundum had a frequency response of 93% and an acute response of 70% with stimulation, above the mean values for frequency and acute responders.

The mean distance between implanted lead and planned ideal position, obtained as average of the distances between each individual electrode of the implanted lead and their respective ideal positions as preoperatively planned, was not significantly associated with better clinical outcomes in this underpowered study.

Student’s t-test indicated no significant correlation in a setting where six patients had a mean distance above the average for the entire SPG group (p = 0.85). The mean distance was even higher in the group of responders rather than in the two patients that did not benefit from the therapy (4.91 vs. 4.53 mm).

When all the three main components of the ATI definition of ideal electrode position are considered, no correlation with clinical outcomes was found using a Chi-squared test (p = 0.72). In only one case, an electrode was detected inside a nasal sinus; this patient had no more cluster attacks after SPG stimulation and only a transient hypoesthesia as single side effect was found. Only one patient had a microstimulator body implanted deeper than 3.5 cm, no technical difficulties were observed and the patient reported a complete remission of his cluster attacks under stimulation.

The distance of the closest electrode to the vidian canal was not significantly correlated to the percentage of frequency or intensity reduction, Pearson’s correlation coefficient (R) was +0.13 for frequency reduction (p = 0.68) and –0.20 for intensity reduction for the eight subjects with evaluable intensity reduction (p = 0.61). The negative correlation between distance of the closest electrode to the vidian canal and maximum amplitude also was not statistically significant (R = –0.54, p = 0.06).

**DISCUSSION**

**Limitations of the Study**

Conclusions from the statistical results in this study have to be drawn with caution, mainly because of the small sample size. This makes the analysis susceptible to false negative results. Additionally, multiple other factors, as individual anatomy and the natural variability in cluster severity in each patient, add insecurity to the conclusions. Unfortunately, no more patients could be included in the analysis as the device lost approval in the European Union and currently no new procedures are performed.

The consequent data collection with headache diaries would have substantially helped to improve data quality in this study. Unfortunately, we did not routinely use diaries during the time

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**Table 3. Cluster Attacks Intensity and Frequency After SPG Stimulation.**

| Patient number | Baseline | 3 months f/u | 6 months f/u | 12 months f/u | Baseline | 3 months f/u | 6 months f/u | 12 months f/u |
|----------------|----------|-------------|-------------|--------------|----------|-------------|-------------|--------------|
| 1              | 9        | 6 (−33%)   | 5 (−44%)    | Not evaluable | 2.5      | 1 (−60%)    | 0.25 (−90%) | 0 (−100%)    |
| 2              | 5        | Not evaluable | Not evaluable | Not evaluable | 28       | 0 (−100%)   | 0 (−100%)   | 0 (−100%)    |
| 3              | 8        | 7 (−12.5%) | 4 (−50%)    | 3 (−62.5%)   | 10       | 10 (0%)     | 6 (−40%)    | 10 (0%)      |
| 4              | 8        | 5 (−37.5%) | 5 (−37.5%)  | 5 (−37.5%)   | 7        | 1.5 (−79%)  | 3 (−57%)    | 1.5 (−79%)   |
| 5              | 8        | Not evaluable | Not evaluable | Not evaluable | 35       | 0 (−100%)   | 0 (−100%)   | 0 (−100%)    |
| 6              | 10       | 9 (−10%)   | 8 (−20%)    | Not evaluable | 28       | 28 (0%)     | 28 (0%)     | Not evaluable |
| 7              | 8        | 7 (−12.5%) | 7 (−12.5%)  | Not evaluable | 17.5     | 4.5 (−74%)  | 4 (−77%)    | Not evaluable |
| 8              | 9        | Not evaluable | Not evaluable | 31.5        | 0 (−100%) | 0 (−100%)   | 0 (−100%)   | Not evaluable |
| 9              | 7        | 7 (0%)     | 7 (0%)      | Not evaluable | 70       | 42 (−40%)   | 42 (−40%)   | Not evaluable |
| 10             | 10       | 7 (−30%)   | 6 (−40%)    | Not evaluable | 4        | 2.5 (−38%)  | 1.5 (−63%)  | Not evaluable |
| 11             | 10       | 5 (−50%)   | 3 (−70%)    | Not evaluable | 28       | 7 (−75%)    | 2 (−93%)    | Not evaluable |
| 12             | 12       | 8 (−20%)   | 8 (−20%)    | Not evaluable | 10.5     | 3.5 (−67%)  | 4.5 (−57%)  | Not evaluable |
| 13             | 10       | 5 (−50%)   | 4 (−60%)    | Not evaluable | 38.5     | 14 (−64%)   | 10.5 (−73%) | Not evaluable |

Average pain intensity (VAS) and frequency (cluster attacks per week) after SPG stimulation at the baseline and after 3, 6, and 12 months follow-up. Percentage reduction compared to the baseline is indicated. Patients who did not have any cluster attack after microstimulator implantation were considered not evaluable for pain intensity.
this study was conducted. By now we have adapted the use of headache diaries in all patient with headache disorders treated in our department prior to treatment and during follow-up. Due to these limitations, we will cautiously discuss our findings and encourage different interpretations of the results based on the readers’ experience with SPG stimulation.

Results of a Young Therapy
In this study, 11 of the 13 patients responded to SPG stimulation (84.6%), a comparably higher rate than the 68% achieved in the landmark study Pathway CH-1 (4). This success rate was based mostly on frequency response, which was the case of eight patients (61.5%)—twice as much as in Pathway CH-1. A significant acute response in the absence or presence of frequency response was observed in three patients (23.1%), near to the reported 32%. Pathway CH-1 was a landmark clinical trial that compared full stimulation with subperception and sham stimulation. Main goal of the study was to prove the effect of SPG stimulation on cluster attacks and not to prospectively follow the clinical course. A mean of 6.8 attacks per patient was studied. The reported data comprise a maximum of two months of follow-up and therefore may not represent the long-term efficacy of repeated SPG stimulations on the attack frequency. Results regarding acute response were similar between CH-1 and our study, but it is noteworthy that the definition of acute response is broader in our study than in Pathway CH-1.

Barloese et al. analyzed a big cohort of patients submitted to SPG stimulation in ten different centers from three European countries. Clinical data from a group of 97 patients resulted in 68% of patients being responders (6). A total of 55% of the patients were frequency responders in this prospective study that collected 12 months follow-up data. Despite the discrepancy in the overall success rates, probably due to the lower number of patient in our study, proportions of frequency and acute response were comparable. Curiously, the long-term follow-up for 24 months of the same patients enrolled in the Pathway CH-1 did not show the expected increase in frequency response that was surpassed by the rate of acute response (7).

The mechanism of frequency response remains unclear. SPG stimulation was initially developed for acute treatment of cluster attacks. Repetitive short stimulation of a peripheral autonomic ganglion was not expected to have a long-lasting effect, especially in a chronic pain disorder that was thought to have its frequency controlled by the hypothalamus. Schoenen et al. mention the possibility of an exhaustion of parasympathetic neurotransmitters that mediate the pain. The existence of a parasympathethocio-trigeminal feedback that could silence pain triggers similar to the effect of occipital nerve stimulation via the trigeminocefalic complex also was discussed (4). This second possibility could explain the similar success rates between SPG stimulation and occipital nerve stimulation (ONS). Although the exact mechanism is still not clear, indication for a prophylactic SPG stimulation is normally given in patients that do not perform well with on-demand stimulation only.

Consequences for the Implantation Technique
This study has limited power due to the small sample size, mostly a consequence of the loss of approval and the missing option of including more patients. The results were unable to show any significant correlation between clinical outcomes and overall lead position, which raises a discussion about the implantation procedure. Intra- or postoperative CT scan does not belong to the standards for the SPG lead implantation procedure in many departments, some rely on with intraoperative navigation. The relevance of the preoperative CT, however, is widely accepted. Cases of facial pain similar to cluster headache and secondary to sphenoid sinus mucocele (8) and sphenoid ridge meningioma surgery (9) were reported. These conditions may be identified in the preoperative CT scan and are associated with intense fibrosis in the operative site, which poses big difficulty to the surgeon and is a contraindication for the SPG lead implantation procedure.

When it comes to the implantation technique, Kohlmeier et al. gave a valuable contribution analyzing lead implantation with intraoperative navigation, a familiar tool for neurosurgeons. Navigation gave to the surgeon live information about the exact location of the surgical instruments and of the ideal lead position according to the preoperative planning. Leads implanted using this method were compared with leads implanted with the classic technique. There was a significant reduction of the mean distance between implanted lead and preoperative planning (3.37 vs. 2.17 mm, p = 0.009), an increase of the average operation time (91.4 vs. 103.2 min) and nonsignificant reduction of the intraoperative fluoroscopy time (101.8 vs. 72.8 s, p = 0.054) (10). Although intraoperative navigation can significantly optimize lead position, the findings of the present study, limited by the small sample size, do not give any predictive value for the distance from the final lead to the preoperative planning. Intraoperative navigation, as live reference to the preoperative planning, may be very useful in patients with anatomic abnormalities in the pterygopalatine fossa and its nonsignificant reduction of fluoroscopy time is certainly an advantage, but its regular use according to the present study would not determine better postoperative outcomes.

In the absence of statistical support for a correlation between overall lead position according to ATI standard and clinical outcomes in this study, questions could be raised about the necessity of an intra- or postoperative CT documenting lead position. This study suggests that suboptimal lead placement in the pterygopalatine fossa could be compensated with reprogramming, but a final lead position in nasal sinuses or even outside the fossa should be actively avoided. Difficult surgical cases, that happened to three patients of this study needing a repeated intraoperative CT (23.1%), benefit from high-definition intraoperative imaging. Lead position could be successfully corrected in two of these three cases. Even when fluoroscopy indicates correct lead placement, an intraoperative CT scan can still optimize the lead position and avoid surgical revision, that appears with an incidence of around 9% in most studies (4,6). An intraoperative CT should be done after the placement of a first bone screw to hold the microstimulator in position, anchoring may cause a lead migration that otherwise would not be detected. It also still does not substitute the final electrode impedance testing.

The case of patient 11 is particularly interesting. After a difficult first lead implantation, an intraoperative CT showed the lead outside of the pterygopalatine fossa and a penetration of the posterior wall of the maxillary sinus. The lead was repositioned under fluoroscopy and a second intraoperative CT displayed the lead nearer to the entrance of the fossa, but still outside. Without a perspective of better results with another try, the lead position was accepted. Since the first stimulation programming, the patient reported uncomfortable paresthesia in the front teeth and in the front of the nose. This area is innervated by the alveolar or external nasal branches, nerves normally located superolateral to...
the SPG in the pterygopalatine fossa. Lead position in CT matches to the physiologically inferred position. Despite suboptimal placement, since the first follow-up appointment the patient had significant acute and frequency responses to the stimulation. Distance from E1 to the vidian canal in this case was 7.55 mm—closer than in ten other patients and a possible explanation for the good clinical response. The stimulation-dependent paresthesia did not resolve completely, but after a reduction of the pulse width it became less uncomfortable. Although this single case alone has little strength of evidence, it didactically illustrates that suboptimal lead positions, radiologic and even physiologically confirmed, may result in adequate response with minor changes in stimulation parameters. However, it does not exclude the possibility that better lead position would have led to even better results.

It is noteworthy that in 12 cases the closest electrode to the vidian canal was in the stimulation area, be it as cathode, anode, or between them. No significant correlation between the distance to vidian canal and the percentage of clinical improvement could be found in this study, possibly due to the small sample size. But the SPG lies next to the vidian canal and stimulation of this area may be important for clinical outcomes. In 38.5% of the patients, the closest electrode to the foramen rotundum was not in the area of most intense stimulation, which indicates that the best target for lead placement lies next to the vidian canal. Direct imaging of the SPG could help in this discussion. This study examines patients that had an intraoperative CT scan, which can display osseous structures of the pterygopalatine fossa with high definition, but no soft tissues like the SPG itself. Magnetic resonance imaging (MRI) imaging could properly address this issue and this possibility was studied by a group coordinated by Jakobs and Ahmadi, who found that postoperative CTs in patients submitted to SPG stimulation had a mean artifact volume of 0.73 cm$^3$. Depending on the sequence, artifacts in MRI due to the metallic implant were much bigger and ranged from 25.2 to 220.7 cm$^3$. Although MRI could be performed safely in the studied individuals, the artifacts caused by the lead render the anatomic evaluation of the pterygopalatine fossa inaccurate (11). More recently, Siakallis and Connor appointed computed tomography angiography as a new approach for SPG localization in the pterygopalatine fossa, which can pave the way for new studies comparing lead position with the real anatomic location of the ganglion (12).

CONCLUSIONS

In this study with a limited sample size, there was no significant correlation between the lead position according to the implantation guidelines and clinical outcome in SPG stimulation for chronic cluster headache. However, we did find that the closest electrode to the vidian canal was in the stimulation are in all but one patient in the final programming. Placing the lead close the vidian canal might therefore be crucial for the overall clinical outcome.

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Authorship Statement

Guilherme S. Piedade, Philipp J. Slotty, and Thomas Klenzner conceived the idea; Jan Vesper, Guilherme S. Piedade, Philipp J. Slotty, Rahel Hoyer, and Thomas Klenzner performed the procedures and follow-ups; Guilherme S. Piedade and Rahel Hoyer developed the project; Guilherme S. Piedade wrote the manuscript with input from all authors. All authors approved the final version of the manuscript.

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COMMENT

Sphenopalatine ganglion stimulation (SPGS) is a promising therapy in the management of cluster headache. Unfortunately, its development has been stalled since the device is not currently commercially available. In this small series of 13 patients, the authors report positive results with only minor adverse events. Although they did not find significant correlation between lead location and clinical outcome, the study is likely to be underpowered with regard to this question. The authors have acknowledged that failure to keep...
headache diaries is a significant limitation since symptoms reporting at clinical appointments is subject to significant recall bias. Moreover, headache duration is significantly affected by the abortive effect of SPGS, but this variable was not measured. Nevertheless, the positive effect of SPGS, and the observation that contacts closest to the Vidian canal within the pterygopalatine fossa were almost always involved in stimulation, are interesting findings.

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