Aus der Klinik für Neurochirurgie
der Heinrich-Heine-Universität Düsseldorf
Direktor: Prof. Dr. med. Daniel Hänggi

Postoperatives Outcome in Abhängigkeit von der Elektrodenposition im Ganglion Sphenopalatinum bei Patienten mit Cluster-Kopfschmerz

Dissertation

zur Erlangung des Grades eines Doktors der Medizin
der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

vorgelegt von
Guilherme Santos Piedade
2019

Als Inauguraldissertation gedruckt mit Genehmigung der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

gez.:
Dekan: Univ.-Prof. Dr. med. Nikolaj Klöcker
Erstgutachter: PD Dr. med. Philipp Jörg Slotty
Zweitgutachter: Prof. Dr. med. Bernd Turowski

Diese Arbeit wurde noch nicht veröffentlicht.

Zusammenfassung

Die Stimulation des Ganglions Sphenopalatinum (SPG) ist eine etablierte Therapie für Patienten mit Cluster-Kopfschmerz. Das Ziel für die Platzierung des ATI SPG Microstimulators in der Fossa Pterygopalatina entspricht der klassischen anatomischen Beschreibung der SPG Lokalisation: hinter der mittleren Nasenmuschel, zwischen Canalis vidianus (VC) und Foramen rotundum (FR). Obwohl die Platzierung von zwei Kontakten der Elektrode in dieses Bereich empfohlen wird, wird die optimale Elektrodenposition wegen der anatomischen Begebenheiten oft nicht erreicht. Es ist bisher nicht bekannt, ob eine suboptimale Elektrodenposition zu schlechteren postoperativen Ergebnissen führt. Die SPG Stimulation wurde bei 13 Patienten zwischen 2015 und 2018 in der Klinik für Neurochirurgie durchgeführt, intraoperative CTs dokumentierten die Elektrodenposition und die Daten wurden zur präoperativen Planung, zu klinischen Ergebnissen und zu Stimulationsparametern korreliert. Ein Ansprechen auf die Therapie wurde als mindestens 50-prozentige Reduktion der Attackenfrequenz oder der Schmerzintensität definiert.

Insgesamt sprachen elf Patienten (84,6%) auf die SPG Stimulation an, davon hatten acht eine Frequenzreduktion (61,5%), einer eine Intensitätsreduktion (7,7%) und zwei eine Frequenz- und Intensitätsreduktion (15,4%). In sieben Fällen wurden weniger als zwei Kontakten zwischen VC und FR implantiert, es gab keine signifikante Korrelation zu negativen Ergebnissen ($p = 0,91$). Der mittlere Abstand zur präoperativen idealen Elektrodenposition war 4,85 mm (SD 2,41 mm), es war keine signifikante Korrelation zu postoperativen Ergebnissen vorhanden ($p = 0,84$) und der Abstand war sogar höher bei Therapieansprechern (4,91 mm vs. 4,53 mm). In allen Fällen war der zum VC am nächsten gelegene Kontakt in Stimulationsbereich. Die häufigste Nebenwirkung waren transiente sensorische Störungen (53,8%). Es ergab sich keine Korrelation zwischen suboptimaler Elektrodenposition und schlechteren postoperativen Ergebnissen. Die präoperative Planung ist hilfreich, aber nicht für das Therapieansprechen determinierend.

Abstract

Sphenopalatine ganglion (SPG) stimulation is a well-established treatment for chronic cluster headache. The target for the ATI SPG microstimulator in the pterygopalatine fossa (PPF) corresponds to the classical anatomic description of SPG location: posterior to the middle nasal turbinate, between vidian canal (VC) and foramen rotundum (FR). Although it is recommended to insert at least two contacts in this position, the correct placement is due to particularities of the anatomical region in many cases not possible. It is not known whether a suboptimal electrode placement interferes with the postoperative outcomes. SPG stimulation was performed in 13 patients between 2015 and 2018 in the Department of Neurosurgery at the University Hospital in Düsseldorf, intraoperative CT documented lead placement in relationship with osseous structures and the data were correlated to the preoperatively planned electrode position, as well as to clinical data regarding characteristics of cluster attacks and to stimulation parameters. Patients with a reduction of 50% or more in pain intensity after stimulation or in pain frequency were considered responsive.

A total of eleven patients (84.6%) responded adequately to SPG stimulation, eight being frequency responders (61.5%), one acute responder (7.7%) and two frequency and acute responders (15.4%). In seven cases, there were less than two electrodes between VC and FR, there was no significant correlation with negative stimulation results ($p = 0.91$). The mean distance between pre- and postoperative images was 4.85 mm (SD 2.41 mm), no significant correlation with postoperative outcomes was found ($p = 0.84$) and mean distance was even greater in responders (4.91 mm vs. 4.53 mm). In all cases, the closest contact to VC was inside the stimulation area. The most frequent side effect were transitory sensory disturbances that resolved in 3 months after surgery (53.8%). Concluding, there is no significant correlation between the suboptimal lead position and worse postoperative outcomes. Preoperative planning may be helpful, but not determinant to patient's responsiveness to SPG stimulation.

Abbreviations

ATI	Autonomic Technologies, Inc.
CE	*Conformité européene*
CGRP	Calcitonin gene-related peptide
CT	Computed tomography
DBS	Deep brain stimulation
FDA	U.S. Food and Drug Administration
FR	Foramen rotundum
IPG	Implantable pulse generator
MRI	Magnetic resonance imaging
ONS	Occipital nerve stimulation
PACAP	Pituitary adenylate cyclase-activating peptide
PACS	Picture archiving and communication system
PET	Positron-emission tomography
PPF	Pterygopalatine fossa
SD	Standard deviation
SUNA	Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms
SUNCT	Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
SPG	Sphenopalatine ganglion
VAS	Visual analog scale
VC	Vidian canal
VIP	Vasoactive intestinal polypeptide

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1 Introduction

1.1 Cluster headache

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 is more common in males with a ratio of 2.5:1 (Bahra et al., 2002) and affects typically the region around the eye, lasts for 15 to 180 minutes untreated and recurs once to eight times a day (Headache Classification Committee of the International Headache Society (IHS), 2018). Common autonomic features are lacrimation, rhinorrhea, eyelid edema, facial sweating and miosis – present in about 97% of the attacks (Nappi et al., 1992). According to the last edition of the International Classification of Headache Disorders, at least five attacks are necessary for the clinical diagnosis (Headache Classification Committee of the International Headache Society (IHS), 2018). Duration and frequency of pain attacks are key points that discriminate cluster headache from other trigeminal autonomic headaches, such as paroxysmal hemicrania, SUNCT, SUNA and *hemicrania continua*. In opposition to migraine, cluster headache leads to important restlessness and agitation, patients are unable to lay down and rather pace the floor, as classically described (Dodick et al., 2000). Episodic cluster headache occurs in periods lasting up to one year intercalated with remission periods of at least three months, it affects 86% of the patients (Sjöstrand et al., 2000). Longer periods with headache attacks or shorter pain-free periods characterize chronic cluster headache.

The acute pain attack can be treated most commonly with a combination of subcutaneous sumatriptan (6 mg) (Ekbom et al., 1993) and inhalation of 100% oxygen at a rate of 12 L/min for 15 minutes (Cohen et al., 2009). Zolmitriptan was proven to be effective both in oral and nasal therapy (Bahra et al., 2000; Rapoport et al., 2007), sumatriptan in nasal spray showed also positive results (Schuh-Hofer et al., 2002). Lidocain has the potential to abort attacks of one third of the

patients and is mainly used as an adjunctive medication (Robbins, 1995). The first choice to prevent new attacks is verapamil, a calcium channel blocker that reduces the number of attacks and the use of analgesics starting from the second week (Leone et al., 2000). Corticoids are also an effective alternative, although with well-known side effects (Becker, 2013). Anticonvulsants, such as topiramate, valproic acid and gabapentin, may have a prophylactic effect (El Amrani et al., 2002; Förderreuther et al., 2002; Vuković et al., 2009). Despite maximal pharmacological therapy, some patients show no or little improvement and are considered refractory. In these cases, neuromodulation is a next step and addresses key anatomic regions involved in the pathophysiology of cluster headache.

1.2 Pathophysiology

The exact mechanism is not completely understood yet, but it is accepted that cluster attacks are a result of the interaction of three important systems: trigeminovascular, parasympathetic and hypothalamic.

Trigeminal nerves innervate cranial vessels and the dura mater and project to the trigeminal nerve nuclei in the brainstem. Afferents to the spinal trigeminal nucleus carrying information about deep touch, pain and temperature connect with the dorsal horns of the spinal cord at levels C1 and C2 – this region is therefore called the trigeminocervical complex (Figure 1). The activation of trigeminal neurons of the ophthalmic branch, leading to the secretion of calcitonin gene-related peptide (CGRT) and pituitary adenylate cyclase-activating peptide (PACAP) (Goadsby and Lipton, 1997), could be the causative event of cluster headache according to the trigeminal model. This explains the use of fremanezumab and galcanezumab, antibodies against CGRP being tested for chronic and episodic cluster headache (Bigal et al., 2015; Sun et al., 2016). This model further explains the effect of occipital nerve stimulation (ONS), that would dampen the trigeminocervical complex, and even the effect of triptans, known to inhibit cerebral vasodilatation and trigeminal neurotransmission (Plosker and

McTavish, 1994). Trigeminal nerve root section was not capable, however, of healing or even improving cluster symptoms (Matharu and Goadsby, 2002).

Figure 1. Anatomical and neurotransmitter components of cluster headache pathophysiology.

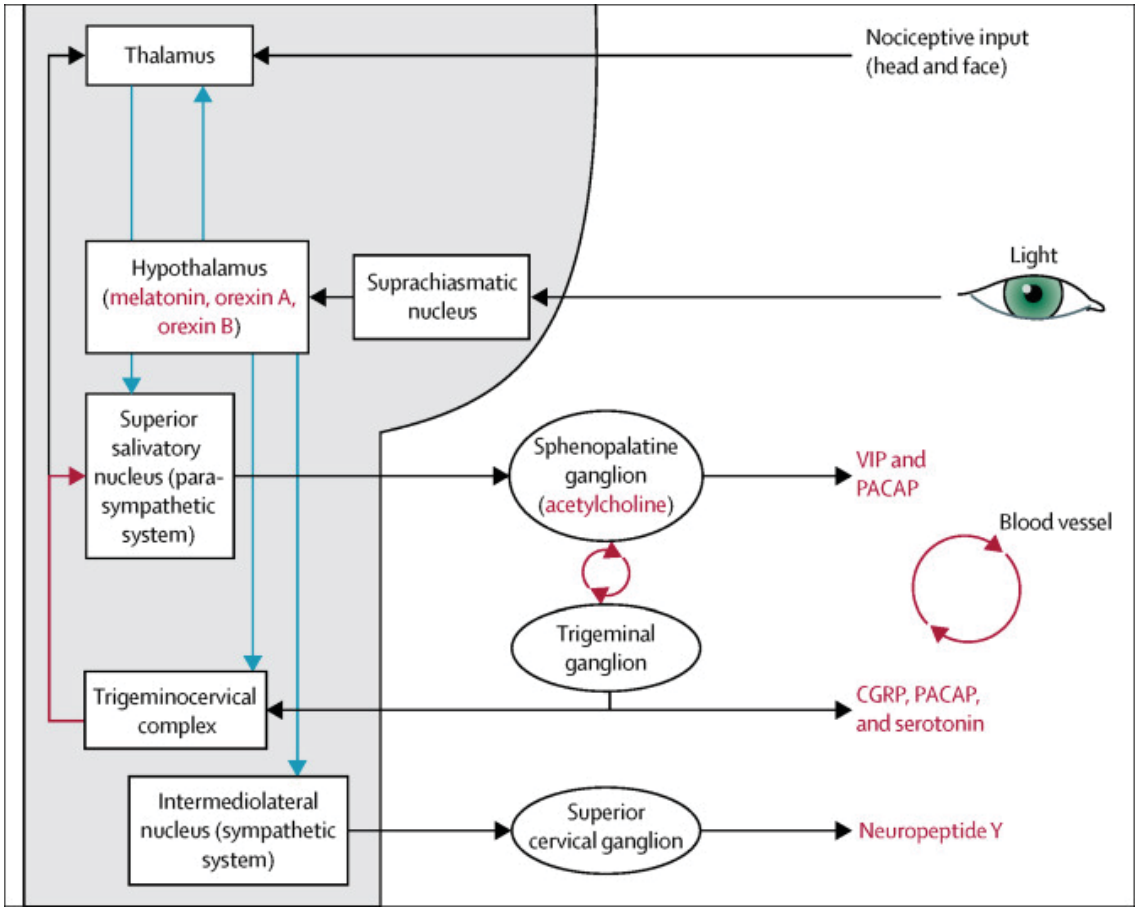

Fig. 1: Trigeminovascular, parasympathetic and hypothalamic components of the pathophysiology of cluster headache. Black arrows are connections between peripheral and central nervous systems, red arrows indicate connected structures within the brainstem. Red arrows in a circle illustrate the trigeminal autonomic reflex. CGRP: calcitonin gene-related peptide, PACAP: pituitary adenylate cyclase-activating peptide, VIP: vasoactive intestinal peptide. Used with authorization from Elsevier (Hoffmann and May, 2018).

The part of the parasympathetic system thought to be involved in cluster headache comprehends the superior salivatory nuclei, in intimate connection with the trigeminocervical complex. The activity of the first trigeminal branch could induce the trigeminal autonomic reflex (May et al., 2001; May and Goadsby,

1999), stimulating a parasympathetic response mainly mediated by the sphenopalatine ganglion. This key structure receives its parasympathetic component from the facial nerve and innervates the lacrimal gland, nasal cavity and pharynx, hard palate and paranasal sinuses. The resulting parasympathetic activity is marked by the release of vasoactive intestinal polypeptide (VIP) (Goadsby and MacDonald, 1985).

The above described fact that a complete trigeminal root section cannot heal the cluster headache (Matharu and Goadsby, 2002), as well as the documented existence of cluster attacks without autonomic symptoms (Nappi et al., 1992) led to the belief that the starting point of this complex mechanism may be another structure of the nervous system. The observation that patients follow a seasonal pattern of cluster attacks and pain-free periods pointed to the role of the hypothalamus, which connects to the trigeminal nerve via the trigemino-hypothalamic tract (Malick et al., 2000). The inferior hypothalamic gray matter has been proven in a PET study to have a high activity during cluster attacks (May et al., 1998) and this finding led to the first hypothalamic deep brain stimulation (DBS) in a patient with cluster headache (Leone et al., 2004, 2001). The risks of this procedure and the diminishing effect over time limit its application (Pedersen et al., 2013), but the complete remission of pain attacks in 60% of the patients indicated the importance of the hypothalamus in this yet incompletely understood pathophysiological mechanism.

1.3 Sphenopalatine ganglion and the pterygopalatine fossa

The pterygopalatine fossa is classically described as a pyramidal space below the orbital apex (Gray H, Williams PL, Bannister L., 1995). It is limited superiorly by the greater wing of the sphenoid, inferiorly by the pyramidal process of palatine bone, anteriorly by the posterior surface of maxilla, posteriorly by the pterygoid process, medially by palatine bone and laterally by the opening to the pterygomaxillary fissure. It connects with its eight foramina the middle cranial

fossa, orbit, nasal and oral cavities and is known as important neurovascular crossroad (Figure 2).

Figure 2. Maxillary nerve and the sphenopalatine ganglion.

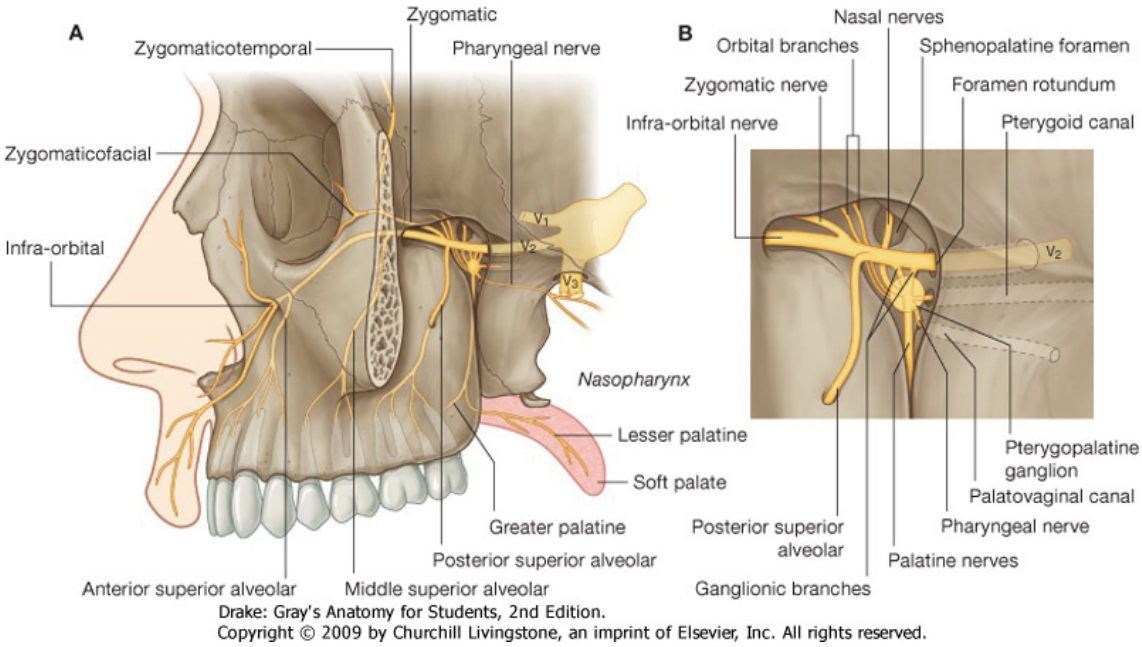

Fig. 2: A. Terminal branches of the maxillary nerve. B. The sphenopalatine ganglion in the pterygopalatine fossa. Used with permission from Elsevier (Drake, Vogl, Mitchell, 2009).

The sphenopalatine ganglion is a 3-4 mm structure with conical or triangular shape inside the pterygopalatine fossa (Lovasova et al., 2013). It is a location of postganglionic neurons of the parasympathetic nervous system and receives input from preganglionic neurons coming from the superior salivary nucleus. These fibers leave the brainstem with the facial nerve and later branch as greater petrosal nerve. Before it enters the pterygoid canal, greater petrosal nerve is joined by the deep petrosal nerve, which arises from the internal carotid plexus, formed by postganglionic sympathetic fibers from the superior cervical ganglion. This junction gives shape to the nerve of pterygoid canal, which leaves the middle cranial fossa through the pterygoid (vidian) canal together with artery of pterygoid canal. Although sympathetic fibers do not synapse in the sphenopalatine ganglion like the parasympathetic ones, sphenopalatine ganglion

remains as an important source of autonomic innervation to the structures described below.

The maxillary division of the trigeminal nerve leaves middle cranial fossa and passes through foramen rotundum, which lies superolateral to the pterygoid canal. Before the nerve enters the orbit via inferior orbital fissure, fibers from the sphenopalatine ganglion join the maxillary division and are later responsible for the innervation of the lacrimal gland. Pharyngeal nerve also connects with sphenopalatine nerve and leaves the pterygopalatine fossa with pharyngeal artery via palatovaginal canal to innervate the nasopharynx. The autonomic supply of the nasal cavity is made by the nasopalatine nerves, which pass through sphenopalatine foramen together with sphenopalatine artery. The innervation of the palate is carried out by greater and lesser palatine nerves, which descend through the greater palatine canal. Posterior teeth are also supplied with parasympathetic fibers from the sphenopalatine ganglion, these emerge as posterior superior alveolar nerve and leave the pterygopalatine fossa via pterygomaxillary fissure.

1.4 Sphenopalatine ganglion stimulation

Since the beginning of the twentieth century the sphenopalatine ganglion was seen as target of many ablative procedures for cluster headache (Goadsby, 2002). Sluder used cocaine to lesion the ganglion and treat headache in 1908 (Sluder G., 1908). Other therapies included percutaneous alcohol injection (Devoghel, 1981), radiofrequency lesioning (Salar et al., 1987) (Figure 2) and more recently stereotactic surgery (Lad et al., 2007).

Figure 3. Needle position during pulsed radiofrequency of the sphenopalatine ganglion.

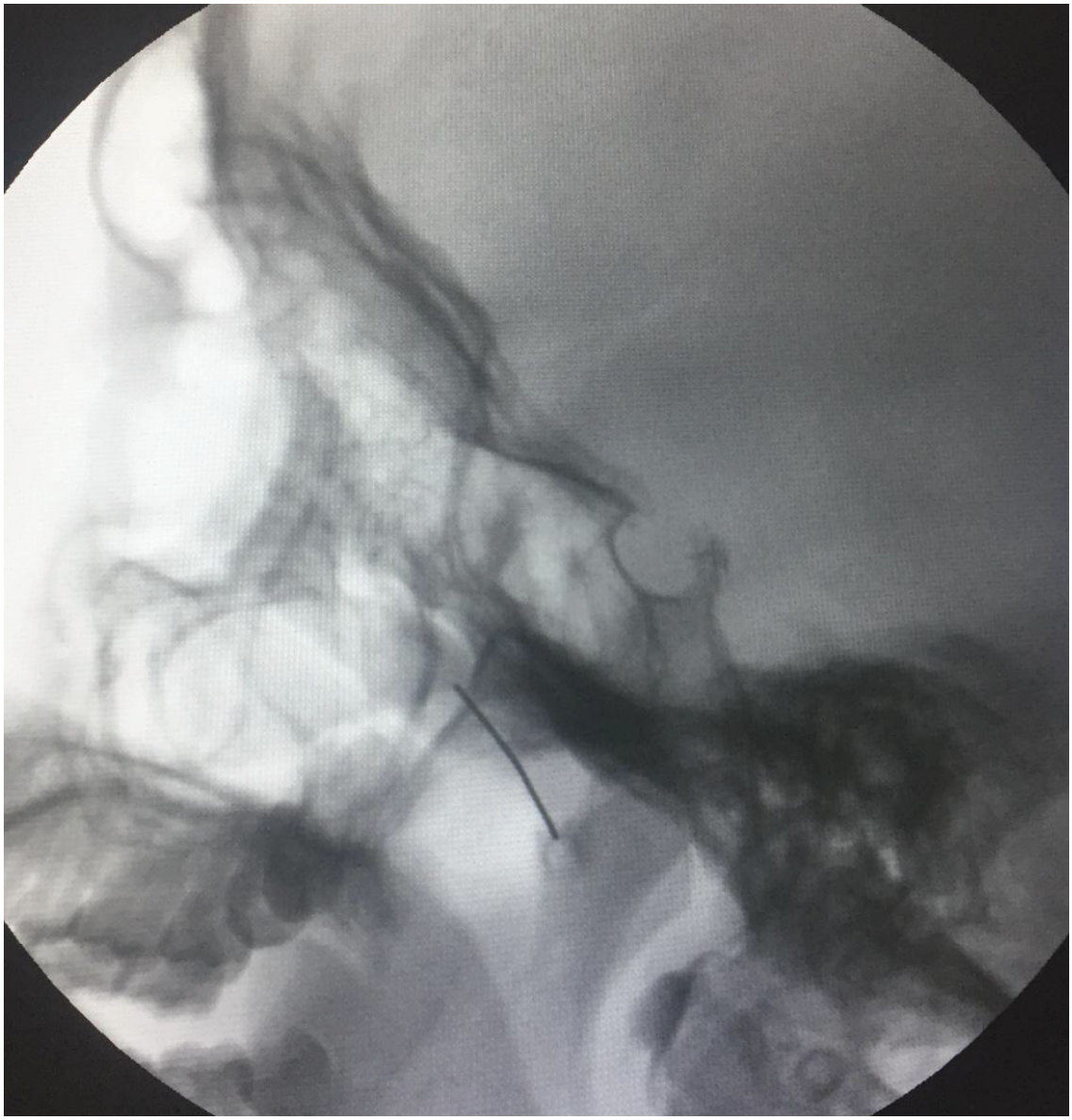

Fig. 3: Lateral fluoroscopic view of the skull, tip of the needle in the pterygopalatine fossa. Courtesy of Dr. Daniel Benzecry Almeida, MD.

In many countries, radiofrequency lesioning of the sphenopalatine ganglion is still the procedure of choice for refractory cluster headache (Figure 3). In a recent study, Salgado-López et al. performed both radiofrequency ablation and pulsed radiofrequency in 37 patients and followed them for a mean of 68.1 months. A total of 13.5% of the patients had complete pain relief, 56.8% had partial and transient relief, 29.7% did not improve (Salgado-López et al., 2019). The promising results of techniques addressing the SPG and the

development of technology led to a switch from irreversible ablative procedures to the modern neurostimulation (Leone M, Rapoport A., 2006; Matharu et al., 2003).

SPG stimulation was suggested as a new approach to refractory cluster headache for the first time by Ibarra in 2007 (Ibarra E., 2007). Ansarinia described in a small study of six patients how SPG stimulation during a cluster attack resulted in a complete relief of eleven out of eighteen pain crises (Ansarinia et al., 2010). These results motivated the development of the Pulsante™ SPG Microstimulator System by Autonomic Technologies, Inc. (ATI, Redwood City, CA, USA), the only commercially available system for SPG stimulation. The system consists of a rechargeable and implantable stimulator that is activated by the patient with a remote controller when cluster attacks begin. The efficiency of on-demand stimulation – exclusively during a cluster attack – was evaluated by Schoenen et al. in 2013 in a multicentric study of 32 patients. Standard stimulation achieved pain relief in 67.1% and pain freedom in 34.1% of the attacks, while not effective stimulation methods (sham) had significant worse results (7.4% pain relief, $p < 0.0001$; 1.5% pain freedom, $p < 0.0001$) (Schoenen et al., 2013). A total of nineteen patients out of 28 completed the study (68%). After 8 weeks, seven patients were identified as acute responders because of a pain relief greater than 50% during attacks, ten where characterized as frequency responders and had a reduction greater than 50% in attack frequency and two were both acute and frequency responders (Schoenen et al., 2013). A follow-up of the same group of patients showed that after 24 months 61% of all patients continued profiting from SPG stimulation, being 45% acute responders and 33% frequency responders (Jürgens et al., 2017). The importance of this treatment modality is represented not only by significant clinical improvement in patients with refractory pain, but also by mean annual drug cost savings of €7,484, majorly in acute medications, as calculated by Pietzsch et al (Pietzsch et al., 2018).

The study of Schoenen et al. reported mild-to-moderate sensory disturbances in distinct distributions of the maxillary nerve in 81% of the patients as the most common adverse event, resolving completely in 78.9% of the cases.

In 9.4% of the patients a lead revision was needed due to misplacement during the original implantation. Lead migration was reported in 6.3% of the cases and was associated to an incorrectly sized microstimulator. Infection occurs in other 6.3%, but no explant was required (Schoenen et al., 2013).

1.5 Pulsante™ SPG Microstimulator System

The Pulsante™ SPG Microstimulator System has been commercially available in the European Union since 2012, when it received a CE mark for acute pain relief of cluster headache. It electrically stimulates the SPG with a biphasic constant current of rectangular pulse that reaches up to 3.9 mA and consists of a rechargeable system with a microstimulator and a remote controller. The Pulsante™ Microstimulator has a body with 16 x 8 x 4 mm that is screwed with a fixation plate to the maxilla and an integrated lead with six electrodes, the most proximal of them being two separate contacts (Figure 4). Electrodes are configured as anode, cathode or OFF, signal frequency ranges between 1 and 200 Hz, pulse width per phase between 40 and 480 μs. The lead has a diameter of 1.0 mm and is available in four different lengths (3.6 to 6.0 cm). The appropriate size can be estimated in pre-operative CT scan and definitely confirmed using the centimeter scale of the Pulsante™ Surgical Introducers during the procedure. The handheld Pulsante™ Remote Controller is used by the patient on demand to activate the Pulsante™ Microstimulator and is used by the physician for changes in stimulation parameters (Figure 5). It also records anonymous and encrypted information about usage.

Figure 4. Pulsante™ SPG Microstimulator System.

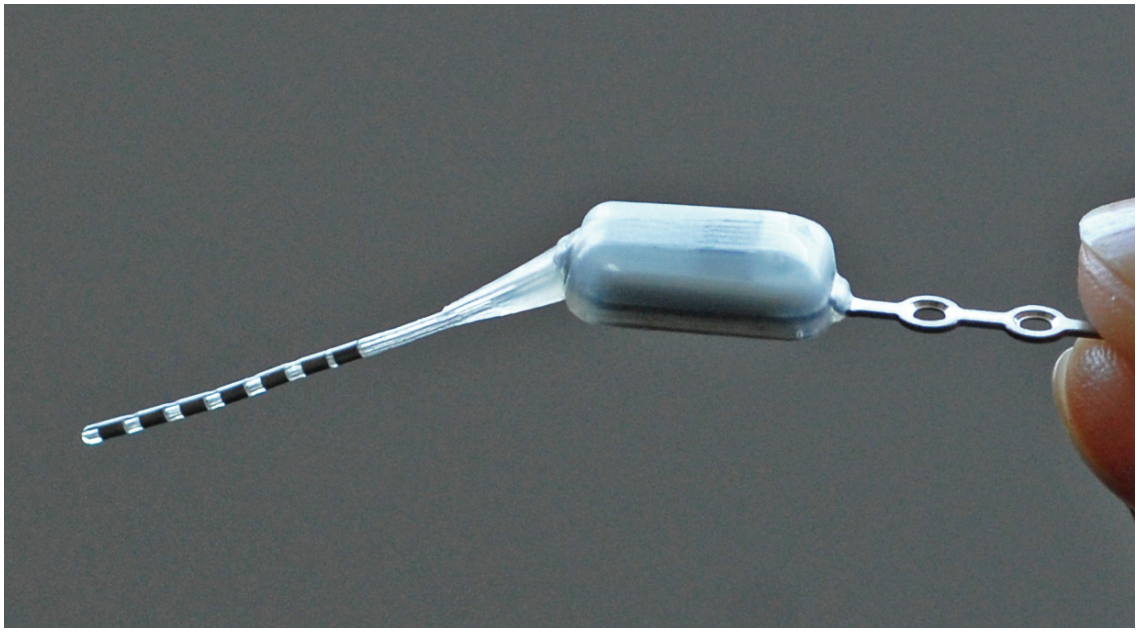

Fig. 4: Pulsante™ SPG Microstimulator System with its microstimulator body and an integrated lead with six electrodes, the most proximal of them being two separate contacts. Used with permission from ATI.

Figure 5. Stimulation with Pulsante™ Remote Controller.

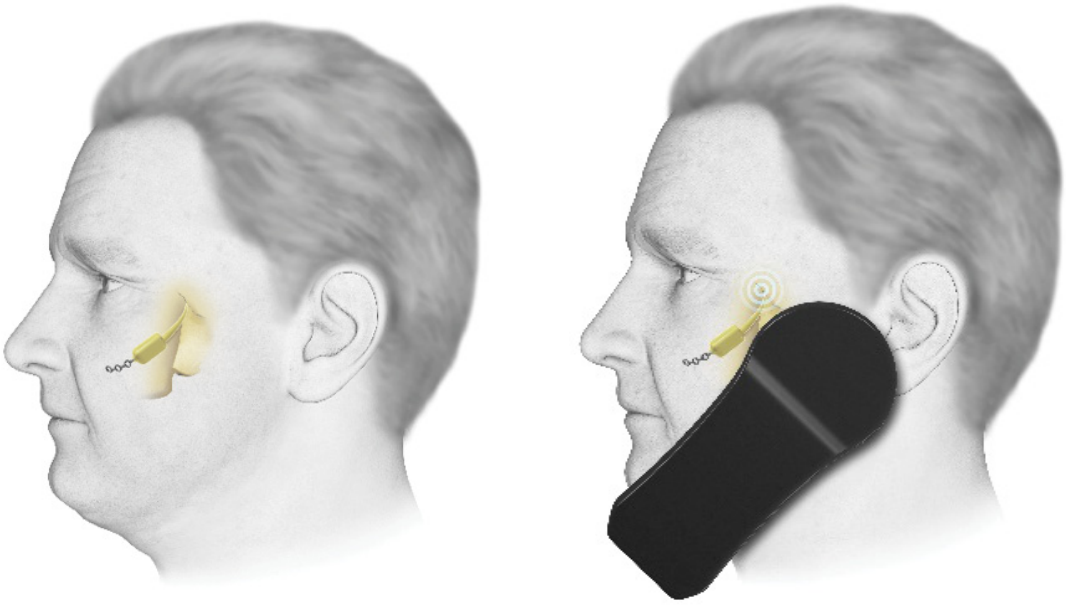

Fig. 5: View of the implanted Pulsante™ SPG Microstimulator System (left), during a cluster attack the Pulsante™ Remote Controller activates the stimulation. Used with permission from ATI.

Patients are submitted to a pre-operative CT scan for the procedure's planning, an ideal lead position based on the patient's individual anatomy is then provided by ATI. An incision is made 5 mm superior to the mucogingival junction above the maxillary first or second molar with a length of 1.0 to 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 Pulsante™ Lead Blank is then inserted to create a trajectory from inferior to superior in the soft tissue (Figure 6). After loading the Microstimulator to the Pulsante™ Shielded Tip Surgical Introducer, the tip of the lead is advanced also under fluoroscopy until it is very close to the sphenopalatine ganglion, which cannot directly be seen. A measure of electrode impedance is performed and an intraoperative CT documents lead position, after satisfying results the Pulsante™ Microstimulator is anchored to the maxilla using the fixation plate and then the incision may be closed.

Figure 6. Insertion of the Pulsante™ Lead Blank under fluoroscopy to create a trajectory.

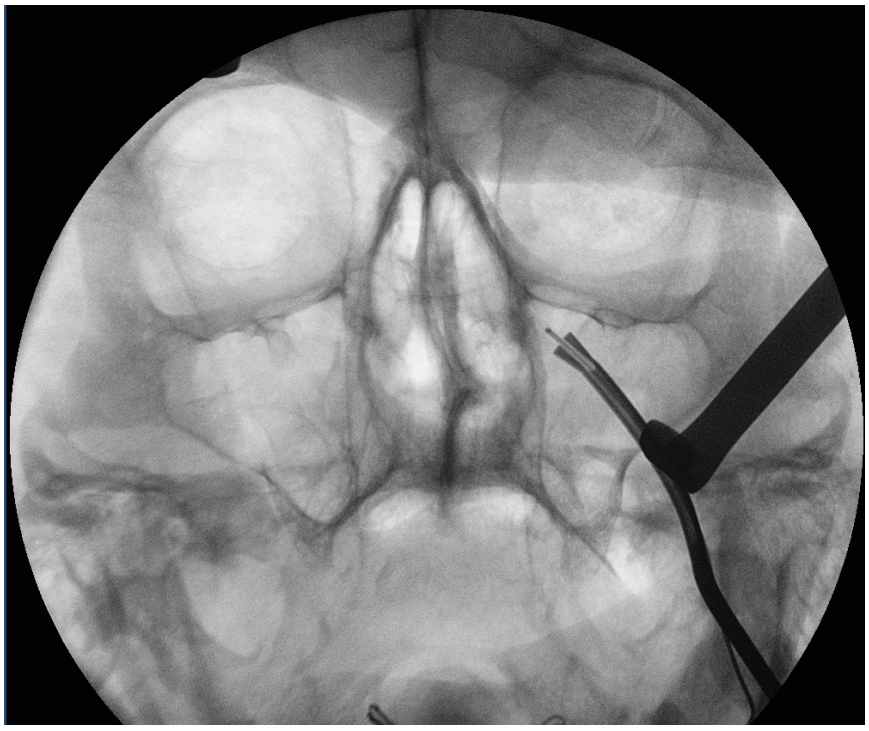

Fig. 6. View of the insertion of the Pulsante™ Lead Blank in the left pterygopalatine fossa under fluoroscopy. Used with permission from ATI.

There is no official definition of ideal position for lead placement, but a generally accepted standard used by ATI for the preoperative planning demands at least two electrodes between vidian canal and foramen rotundum and no electrodes in paranasal sinuses. The microstimulator body should lay no deeper than 3.5 cm in relation to 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, turn SPG stimulation into a challenging procedure. It is not uncommon that the lead deviates from the optimal position, but a possible correlation between suboptimal lead placement and worse postoperative outcomes has not yet been established.

More recently in 2017, Pulsante™ SPG Microstimulator System received the expansion of the CE mark for highly disabled migraine patients with one or more of the following characteristics: orbital or temporal pain, pain-free periods between attacks, autonomic symptoms.

1.6 Occipital nerve stimulation

Occipital nerves are considered, in terms of neurostimulation, a door to the trigeminocervical complex due to the connection between the spinal trigeminal nucleus and the dorsal horn of the spinal cord at levels C1 and C2 (Bartsch and Goadsby, 2003). ONS could silence an important system responsible for pain in cluster headache and in migraine as well. The procedure consists of the insertion of two subcutaneous electrodes near to the greater occipital nerve bilaterally, the electrodes are anchored to the underlying fascia and the wires are then tunneled caudally to connect with the impulse generator (Leone et al., 2017). In contrast to SPG stimulation, in ONS the stimulation is continuous and not controlled by the patient.

One of the first reports was done by in 2009 by Burns et al., who described positive clinical outcomes in 14 patients (Burns et al., 2009). A prospective study with 13 patients conducted in France was able to achieve 76.9% of responders

with a mean 14.6 months follow-up (Fontaine et al., 2011). Similar efficacy was obtained by the same group in a later study with 44 patients that also correlated ONS to significant improve in health-related quality of life (Fontaine et al., 2017) and by an italian experimental study of 35 patients with median follow-up of 6.1 years (Leone et al., 2017).

Noteworthy in ONS patients is the number of adverse events, with the most significant of them being lead migration because of the high mobility of the neck. This was the case in approximately 25% of the patients (Leone et al., 2017; Saper et al., 2011) and all cases require an operative revision. The study conducted by Fontaine et al. obtained an uncommon rate of 3.4% of lead migration and despite of that 25.8% of the patients required another surgery due to hardware infection, hardware dysfunction and wound healing disturbance (Fontaine et al., 2017). Battery depletion is also a common issue that requires a second operation and it may occur earlier depending on the amount of energy required by the patient.

There is to date no study comparing efficacy and safety of occipital nerve stimulation and sphenopalatine ganglion stimulation. Although the techniques have a similar success rate in the different isolated studies published so far, the existence of a significant difference in one study designed to compare both methods would have interesting consequences for the understanding of the pathophysiological mechanism of cluster headache. While occipital nerve stimulation targets the trigeminocervical complex, sphenopalatine ganglion stimulation addresses the parasympathetic system. The confirmation, however, of more frequent adverse events with occipital nerve stimulation would support the indication of sphenopalatine ganglion stimulation.

1.7 Objectives

The aim of this study is to analyze whether a suboptimal electrode position leads to worse postoperative outcomes in sphenopalatine ganglion stimulation.

This study will also compare postoperative outcomes between sphenopalatine ganglion stimulation and occipital nerve stimulation.

2 Patients and Methods

2.1 Study design and subjects

From August 2012 to December 2018, a total number of 22 patients with refractory chronic cluster headache presented at the Department of Neurosurgery of the Heinrich Heine University of Düsseldorf. Occipital nerve stimulation was performed between August 2012 and April 2016 in ten patients, sphenopalatine ganglion stimulation started being performed in May 2015 and is today the procedure of choice, with a total of 13 patients. Three patients were treated with ONS since May 2015 due to chronic migraine as important comorbidity or due to advanced age. The patients' hospital records, outpatient charts, operative reports, pre-, intra- and postoperative radiologic studies, stimulation parameters and demographic information were subjected to careful 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 preventive medications in the four weeks preceding the procedure. None were previously submitted to ablative procedures. No operated patients were excluded.

2.2 Insertion Procedure

After the indication for sphenopalatine ganglion stimulation, midface anatomy is evaluated with a CT scan, which provided important information for the choice of the lead's length. Patients with osteodestructive disease, osseous defects, severe dental pathology or signs of regional infection were excluded. Patients with secondary cluster headache following midface trauma are also excluded due to the intense fibrosis around the pterygopalatine fossa. CT data are analyzed by ATI, which used the software Mimics (Materialise, Leuven, Belgium) to provide a preoperative plan of the ideal position for lead insertion

considering the patients' unique anatomy (Figure 7). Both three-dimensional and two-dimensional images represent ideal lead position to guide the lead insertion.

Figure 7. Preoperative planning.

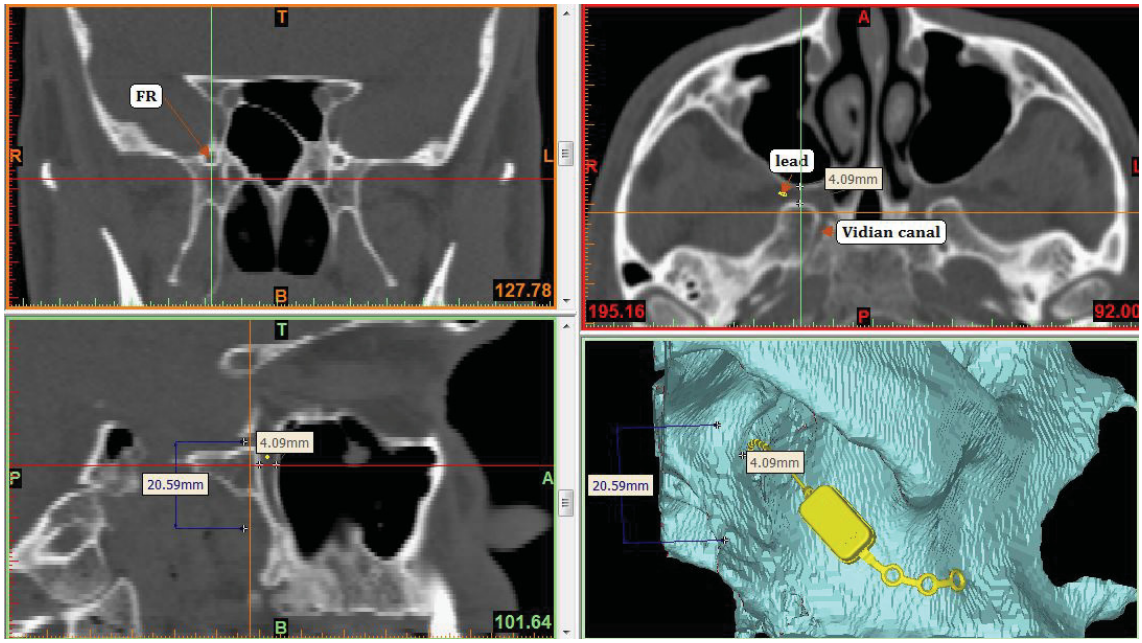

Fig. 7: Using preoperative CT data the ideal position for the lead is planned and documented in a three-dimensional reconstruction. In the superior left image, a coronal view passing through the foramen rotundum. Superior right an axial view of the pterygopalatine fossa at the level of the vidian canal, the anteroposterior dimension of the fossa is indicated in millimeters. In the inferior left image, a parasagittal view of the fossa, the projected vertical distance between the tip of the lead and the center of the microstimulator is indicated in millimeters along with the already mentioned anteroposterior dimension of the fossa. Finally, inferior right a three-dimensional reconstruction with the ideal lead position in yellow and the skull in blue. Used with permission from ATI.

Under general anesthesia and in a supine position, the patient's head is placed in a three-pin Mayfield skull clamp. An oral intubation is preferred over nasal intubation to better evaluate fluoroscopic images during the insertion. The patient receives a preoperative dose of prophylactic antibiotic, oral decontamination is also conducted. The buccal gingiva is infiltrated with local anesthesia to reduce postoperative pain. The procedure is performed with an experienced otolaryngologist, who normally does the surgical approach. The oral

mucosa along the molars is incised and the superior-lateral surface of the zygomaticomaxillary buttress is exposed. The following steps are done under fluoroscopy. Pulsante™ Surgical Introducer provided by ATI is inserted in the pterygopalatine fossa along the posterior maxilla and confirms the appropriate microstimulator length. Pulsante™ Lead Blank is then inserted in the fossa to create a path for the lead. Pulsante™ Surgical Introducer is once again introduced in the fossa targeting the ideal position of the lead's tip (Figure 8).

Figure 8. Transoral approach to the pterygopalatine fossa.

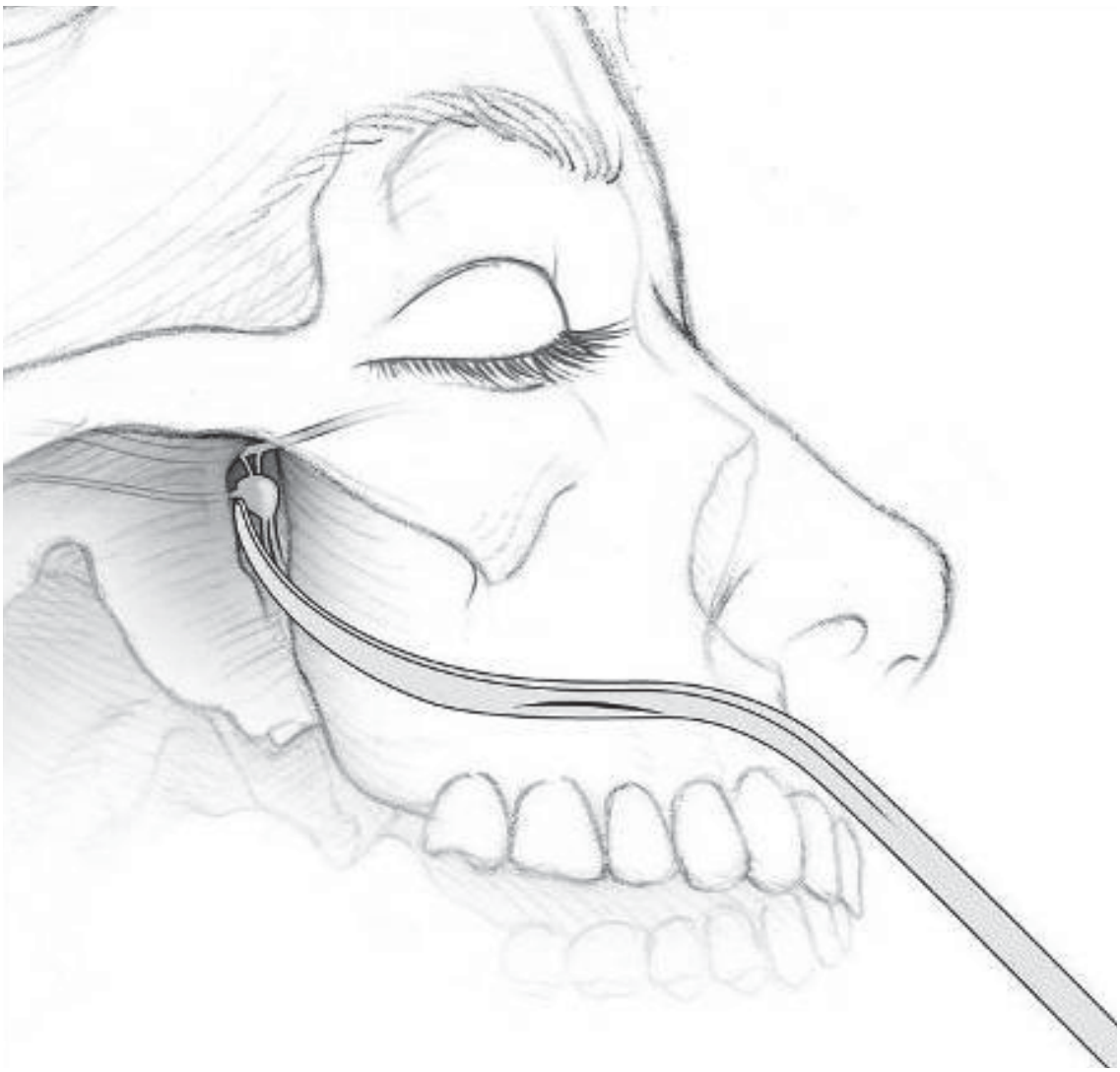

Fig. 8: Insertion of the Pulsante™ Surgical Introducer into the pterygopalatine fossa. Used with permission from ATI.

When fluoroscopic view indicated adequate position, the microstimulator, already loaded into the Pulsante™ Shielded Tip Surgical Introducer, is advanced into the pterygopalatine fossa using Pulsante™ Surgical Introducer as a guide. Instruments are removed, a first bone screw is placed to secure the position of the microstimulator and an intraoperative CT scan documents lead position. At this time, suboptimal lead positions can still be corrected and a final intraoperative CT scan is made. The microstimulator is then finally anchored to the maxilla with a second bone screw and, before the incision is carefully closed with resorbable suture, a final electrode impedance testing should be performed. Adequate wound healing is normally achieved within a month, after which the patients present for the first follow-up appointment to begin stimulation.

2.3 Analysis of lead position

Lead placement in patients treated with SPG stimulation 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 to be evaluated compared the position of the implanted lead with the ideal position of the preoperative planning. The distances between each individual electrode of the implanted lead and their respective ideal positions as planned by ATI were assessed. Mean, minimum and maximum distances measure the accuracy of lead placement. Furthermore, lead position within the pterygopalatine fossa is classified as anterior, mid-fossa and anterior. In a second step, the anatomic relation of the 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 ATI definition, following parameters were also assessed: electrodes

between vidian canal and foramen rotundum, depth of the microstimulator body and presence of electrodes in nasal sinuses.

2.4 Clinical outcome measures

The evaluation of clinical outcomes was based on pre- and post-procedural pain intensity and frequency. Pre-procedural baseline period included the four weeks preceding 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 minutes of SPG stimulation during cluster attacks. In the particular case of occipital nerve stimulation, when stimulation is continuously administered, there is no acute response, but intensity response. Complications were also assessed for both groups.

2.5 Stimulation parameters

Anonymous and encrypted data regarding stimulation usage collected by each device were analyzed. Of special interest are signal frequency, pulse width and amplitude of the produced wave and the electrode configuration among those used as anode, cathode or not used. Saved data regarding each stimulation, documented pain intensity at the start and at the end of stimulation and duration of stimulation were collected.

2.6 Statistical analysis

Associations among clinical outcomes, lead position and stimulation parameters were assessed using the chi-squared test in the case of two categorical variables and the Student's t-test to compare categorical and quantitative variables. The outcomes of sphenopalatine ganglion stimulation and occipital nerve stimulation were also compared.

2.7 Ethical issues

This study was registered at the *Universitätsklinikum Düsseldorf* under the number 2018064709 and was conducted after the IRB approval 2018-150-RetroDEuA, granted by the ethics committee of the Medical School of the *Heinrich-Heine-Universität Düsseldorf* on September 17, 2018. Patient data were anonymized, the decryption key was irreversibly destroyed after data collection. After an amendment to the original IRB approval, data collection reached data generated until January 3, 2019 (2018-150_1-RetroDEuA).

3 Results

3.1 Baseline characteristics

The population of this study is composed predominantly by male patients and has a mean age of 43.3 years (Table 1), which is consistent with epidemiological data for the general population (Bahra et al., 2002). Patients submitted to ONS had comparatively higher baseline pain intensity and frequency, but once again, the selection for either ONS or SPG stimulation was based on the Department's preference for SPG after May 2015, with a few exceptions due to special comorbidities or advanced age, when ONS was preferred.

Table 1. Baseline characteristics of SPG and ONS groups.

SPG group (n = 13 patients)		
Male (%)		69.2
Mean age (years)		44.4 (SD 9.4)
Baseline cluster attacks/week		23.9 (SD 18.5)
Baseline pain intensity (VAS)		8.6 (SD 1.5)
Cluster attack laterality (%)	Left dominant	69.2
	Right dominant	30.8
ONS group (n = 9 patients)		
Male (%)		55.6
Mean age (years)		41.7 (SD 16.6)
Baseline cluster attacks/week		34.7 (SD 22.5)
Baseline pain intensity (VAS)		9.2 (SD 1.3)
Cluster attack laterality (%)	Left dominant	55.6

	Right dominant	44.4

Table 1: Baseline characteristics of patients submitted to SPG (sphenopalatine ganglion) stimulation or ONS (occipital nerve stimulation). Pain intensity given in VAS (Visual Analog Scale). SD: standard deviation.

3.2 Lead placement

Patients submitted to SPG stimulation had their intraoperative CTs analyzed. In three cases a second intraoperative CT was performed after unsatisfactory lead position in a first attempt. Figure 9 and Figure 10 illustrate in a three-dimensional view of the implanted lead in the pterygopalatine fossa. Figure 11 compares the individual electrodes of the implanted lead and with their ideal position in the preoperative planning, distances are listed in Table 2. The lead position in the pterygopalatine fossa, also listed in Table 2, is obtained from the evaluation of axial CT images at the vidian canal (Figure 12).

Figure 9. Three-dimensional view of the implanted electrode.

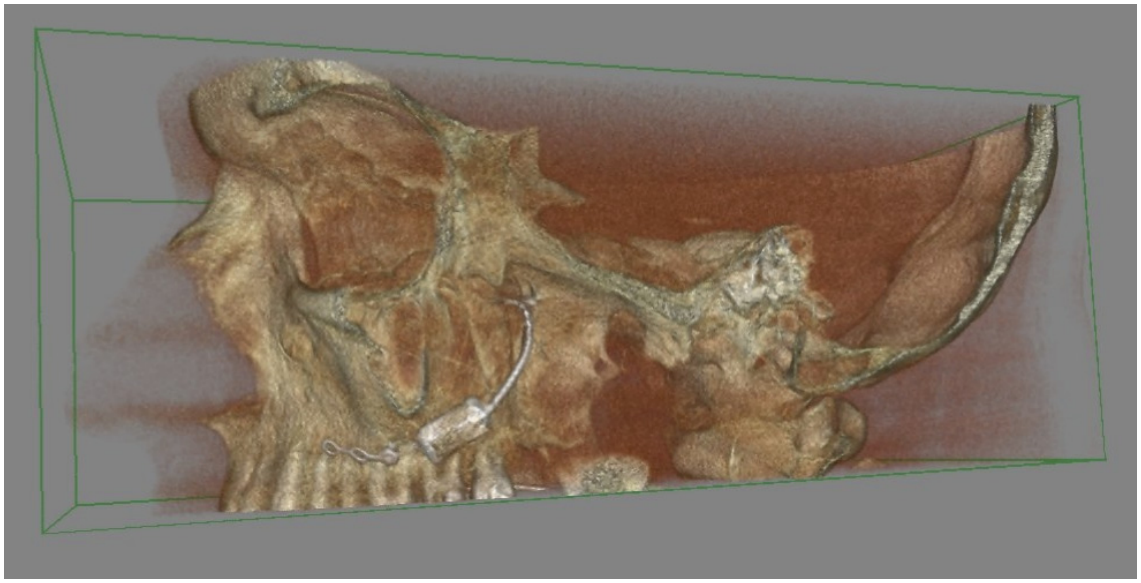

Fig. 9: Pulsante™ SPG Microstimulator System is depicted in white in this three-dimensional reconstruction. The microstimulator body is fixed to the maxilla and the lead is inserted in the pterygopalatine fossa.

The mean distance between implanted lead and planned ideal position for all patients had an average of 4.85 mm (SD 2.41 mm). Leads were placed in the anterior portion of the pterygopalatine fossa in 46.2% of the cases, 30.8% of the leads were inserted posteriorly and 15.4% of them were in the mid-fossa. 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.

Figure 10. Three-dimensional reconstruction of the skull with implanted microstimulator system.

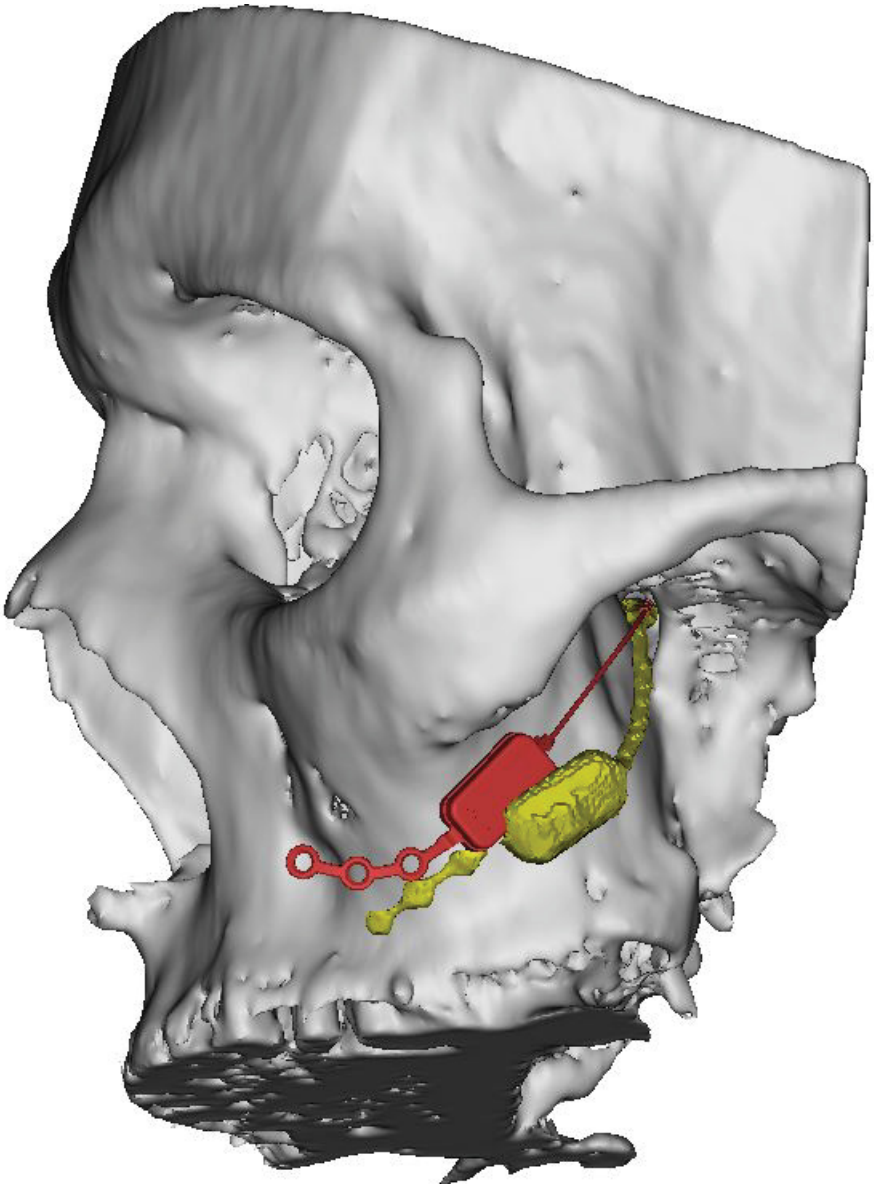

Fig. 10: The implanted microstimulator system is depicted in yellow, red indicates the preoperative planning. Used with permission from ATI.

Figure 11. Comparison between planned and final lead placement.

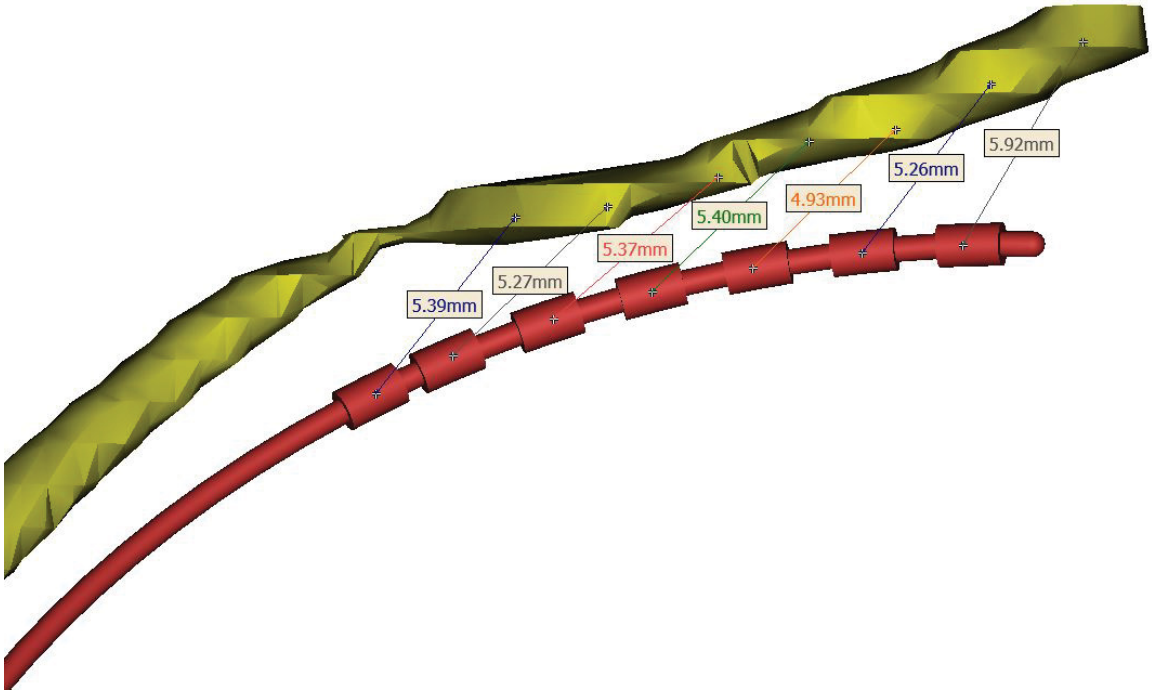

Fig. 11: Final lead placement is shown in yellow, planned lead placement in red. The indicated distances between individual electrodes are displayed in millimeters. Used with permission from ATI.

Table 2. Accuracy of lead placement compared to preoperative planning.

Patient number	Mean distance	Min Distance	Max distance	Position in PPF
1	3.54 mm	2.84 mm	4.74 mm	Mid-Fossa
2	4.20 mm	3.75 mm	4.85 mm	Posterior
3	3.54 mm	3.24 mm	3.81 mm	Anterior
4	7.39 mm	6.85 mm	7.94 mm	Anterior
5	5.18 mm	4.30 mm	5.91 mm	Anterior
6	6.10 mm	5.74 mm	6.83 mm	Anterior
7	5.36 mm	4.93 mm	5.92 mm	Mid-Fossa
8	2.62 mm	1.66 mm	3.82 mm	Posterior
9	2.96 mm	1.96 mm	5.15 mm	Posterior
10	0	0	0	Anterior
11	9.09 mm	7.96 mm	9.78 mm	Outside

12	7.41 mm	6.39 mm	9.78 mm	Posterior
13	5.68 mm	3.98 mm	6.48 mm	Anterior

Table 2: Mean, minimum and maximum distances between individual electrodes of the implanted lead and their planned ideal position are given in millimeters. The last column indicates the lead position in the pterygopalatine fossa (PPF).

Figure 12. Axial CT slice at the vidian canal.

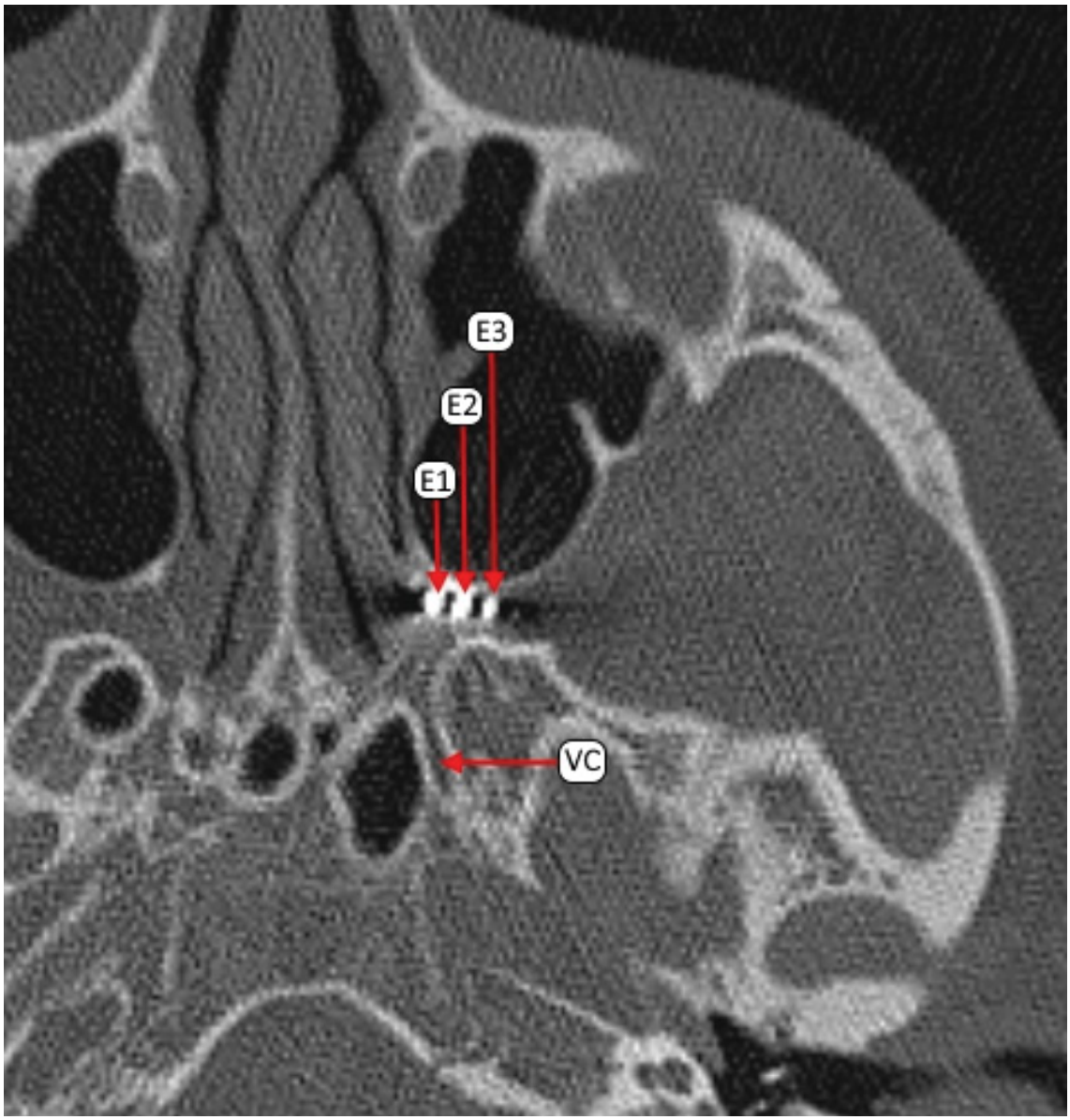

Fig. 12: Axial CT image at the vidian canal (VC). The first three electrodes of the implanted lead are indicated (E1-3).

Three-dimensional reconstructions of the sphenoid bone with the implanted lead give a more precise impression of lead placement and are the

base for the following assessments (Figures 13 and 14). Distances between each individual electrode and the superior aspect of the middle point of the vidian canal are listed in Table 3. Distances to the inferior aspect of the middle point of the foramen rotundum are indicated in Table 4.

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 (46.1%) was most frequently the closest electrode to the vidian canal. The average of minimum distances from one electrode to the foramen rotundum was 13.17 mm (SD 2.49 mm), electrodes one, two and five were in closest contact in 23.1% of the cases each.

Figure 13. Reconstruction of the sphenoid bone with implanted lead.

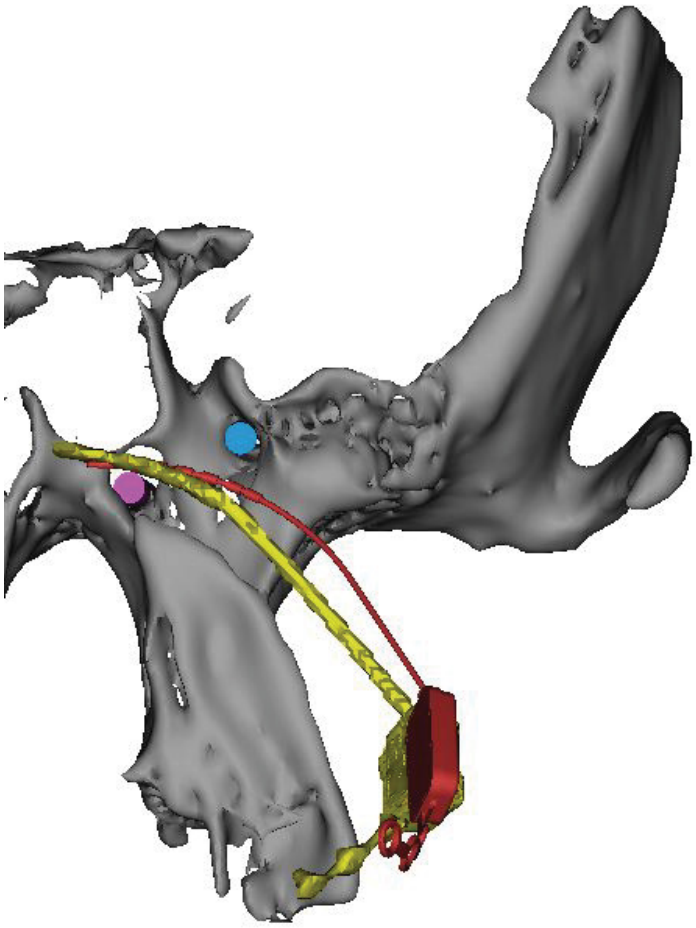

Fig. 13: Three-dimensional reconstruction of the sphenoid bone. Implanted lead is depicted in yellow, the preoperatively planned ideal position is shown in red. Vidian canal is indicated with a pink point, foramen rotundum in blue. Used with permission from ATI.

Figure 14. Three-dimensional view of the lead between vidian canal and foramen rotundum.

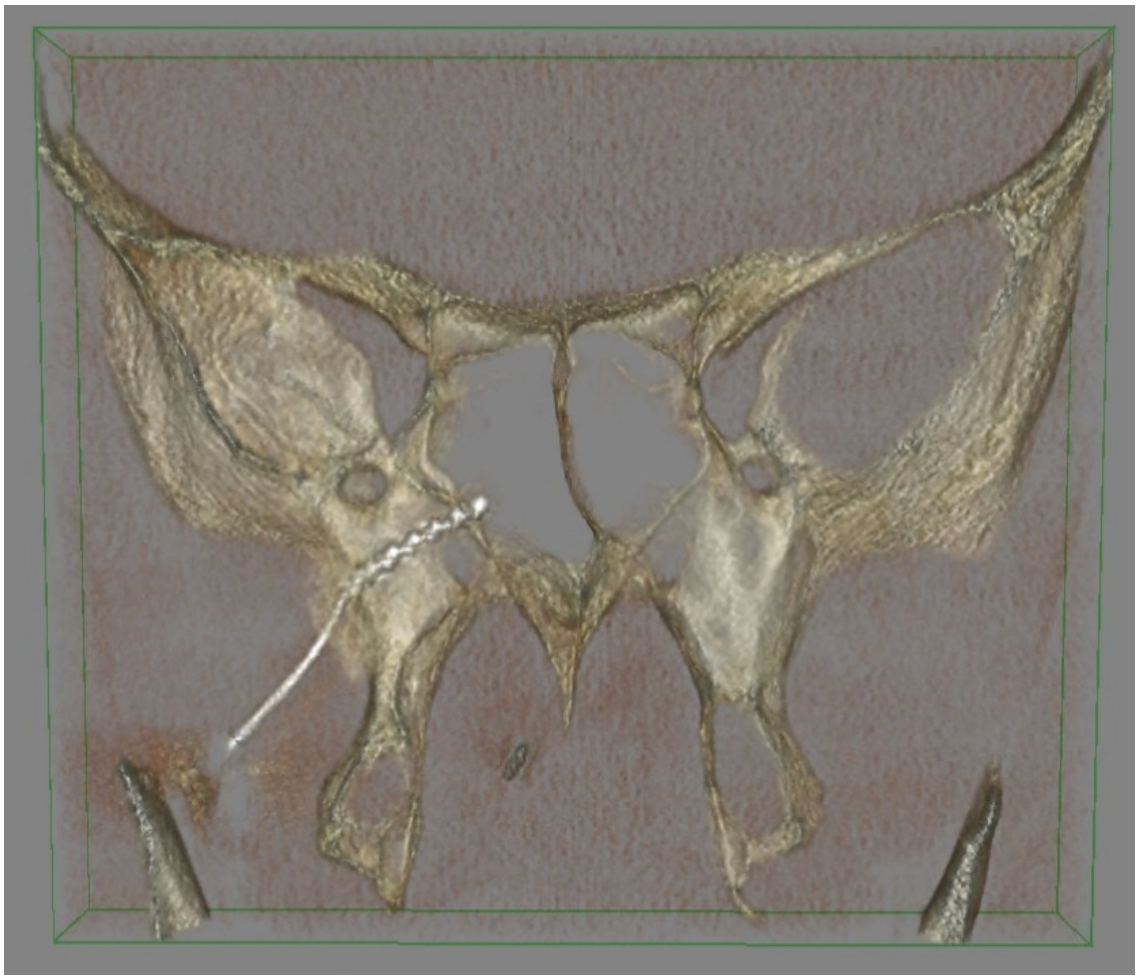

Fig. 14: Reconstruction of the skull at the level of the pterygopalatine fosse, implanted lead is depicted in white and lies between the vidian canal inferiomedial and the foramen rotundum superolateral. The tip of the first electrode is in the nasal cavity.

Table 3. Distances from individual electrodes to the vidian canal.

Patient number	E1	E2	E3	E4	E5	E6
1	**7.92**	7.97	8.73	9.53	11.92	14.37
2	12.64	11.54	**10.86**	11.94	13.18	15.22
3	11.40	9.58	**8.44**	8.64	10.37	12.44
4	**7.72**	8.62	10.33	12.20	14.86	17.43
5	12.84	**12.68**	13.71	14.27	15.92	17.90

6	**7.89**	8.46	9.67	11.94	14.37	16.52
7	11.59	9.49	**7.86**	8.17	10.04	12.18
8	**4.92**	6.25	7.60	9.56	11.45	13.58
9	9.05	**8.24**	8.28	9.88	12.54	14.58
10	6.99	**6.65**	7.67	9.96	12.73	15.29
11	**7.55**	9.87	12.51	14.94	17.44	19.88
12	8.13	**8.12**	8.80	10.14	12.85	15.17
13	**7.81**	8.77	10.70	13.74	15.22	17.18

Table 3: Distances from each of the six individual electrodes (E1 – E6) 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.

Table 4. Distances from individual electrodes to the foramen rotundum.

Patient number	E1	E2	E3	E4	E5	E6
1	11.67	**11.15**	12.27	14.08	16.30	18.77
2	21.73	19.58	17.73	16.44	**15.78**	16.33
3	23.44	21.00	18.16	15.97	13.63	**12.18**
4	**10.39**	11.36	13.48	15.97	18.88	21.76
5	13.74	**11.57**	12.63	13.69	15.72	18.12
6	17.53	**16.72**	17.32	18.52	19.93	21.54
7	18.54	16.39	14.08	12.18	**10.99**	11.46
8	18.22	15.99	**14.63**	14.94	16.33	18.79
9	19.27	17.25	14.76	13.83	**13.78**	14.95
10	19.47	18.23	17.40	**17.17**	17.73	19.07
11	**12.59**	13.64	15.55	17.78	20.45	22.21
12	**9.51**	10.62	12.93	15.59	18.14	10.56
13	16.87	15.44	**14.72**	15.16	16.13	18.27

Table 4: Distances from each of the six individual electrodes (E1 – E6) to the inferior aspect of the middle point of the foramen rotundum. Distances are indicated in millimeters and the shortest one for each patient is in bold.

Furthermore, a final comparison between final lead placement and the standard definition of ideal lead position was made (Table 5). This definition requires 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.

Overall, five patients (38.5%) had their lead inserted exactly as preconized by ATI. A minimum of two electrodes between vidian canal and foramen rotundum was achieved in six cases (46.2%), the remaining of them had only one (six patients) or none (one patient) in the indicated region. Electrodes found in paranasal sinuses were the case in one patient. Microstimulator body depth greater than 3.5 cm, that could possibly disturb the communication with the handheld remote controller, was found in one case. Figure 15 illustrates the final position the Pulsante™ SPG Microstimulator System.

Table 5. Accuracy of lead placement compared to the standard definition of ideal lead position.

Patient number	Electrodes between VC and FR	No electrodes in paranasal sinuses	Microstimulator body depth	Conformity to standard definition
1	E1	+	3.0 cm	-
2	E3 and E4	-	3.2 cm	-
3	E4 and E5	+	3.2 cm	+
4	E1	+	2.9 cm	-
5	E1	+	4.0 cm	-
6	E1	+	2.8 cm	-
7	E5 and E6	+	2.8 cm	+
8	E1 and E2	+	2.9 cm	+
9	E3 and E4	+	2.7 cm	+
10	E2 and E3	+	3.4 cm	+
11	None	+	3.0 cm	-
12	E1	+	2.3 cm	-
13	E1	+	2.8 cm	-

Table 5: Comparison of final lead placement with standard definition of ideal position from ATI (Autonomic Technologies, Inc.). Microstimulator body depth is indicated in centimeters. VC: vidian canal, FR: foramen rotundum.

Figure 15. Lead position after sphenopalatine ganglion stimulation.

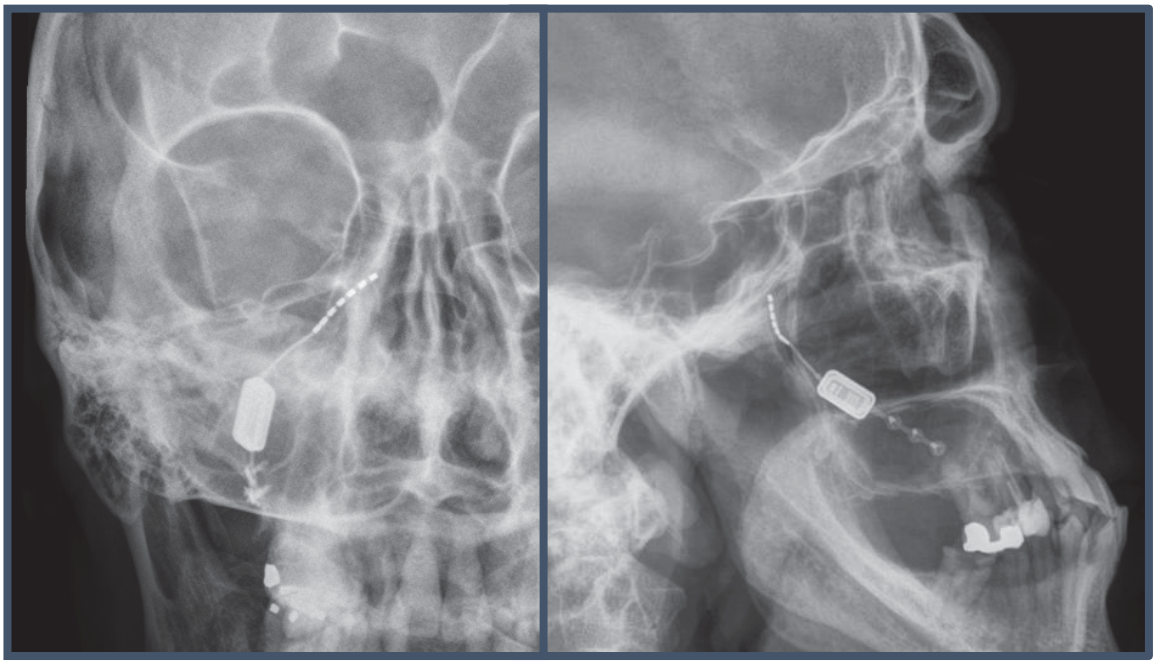

Fig. 15: Anterioposterior (left) and lateral (right) X-rays of the skull with views of the lead position in the pterygopalatine fossa. Used with permission from ATI.

3.3 Clinical Outcomes

After the implantation of an SPG microstimulator, patients were followed up for an average of 8.3 months. After three months, mean frequency reduction was 61.3% (SD 33.8). In the last follow-up, SPG group had an overall frequency reduction of 67.8% (SD 35.5) from a mean baseline of 23.9 (SD 18.5) to a mean frequency of 8.0 (SD 12.8) attacks per week (Table 6). Most patients showed a constant response to stimulation, in only one case a significant frequency response appeared later at the second follow-up appointment. A total of 10 patients (76.9%) had a frequency reduction of at least 50% and were considered frequency responders. Among these patients, mean frequency reduction achieved 84.2% (SD 16.6%), and in four cases SPG stimulation led to complete

absence of cluster attacks. Patients that were frequency responders had an average baseline of 20.3 attacks per week (SD 13.6) and 2.4 in the last follow-up.

Table 6. Cluster attacks frequency after SPG stimulation.

Patient number	Baseline frequency	3 months f/u	6 months f/u	12 months f/u
1	2.5	1 (-60%)	0.25 (-90%)	0 (-100%)
2	28	0 (-100%)	0 (-100%)	0 (-100%)
3	10	10 (0%)	6 (-40%)	10 (0%)
4	7	1.5 (-79%)	3 (-57%)	1.5 (-79%)
5	35	0 (-100%)	0 (-100%)	0 (-100%)
6	28	28 (0%)	28 (0%)	
7	17.5	4.5 (-74%)	4 (-77%)	
8	31.5	0 (-100%)	0 (-100%)	
9	70	42 (-40%)	42 (-40%)	
10	4	2.5 (-38%)	1.5 (-63%)	
11	28	7 (-75%)	2 (-93%)	
12	10.5	3.5 (-67%)	4.5 (-57%)	
13	38.5	14 (-64%)	10.5 (-73%)	

Table 6: Pain frequency given in cluster attacks per week at the baseline and after 3, 6 and 12 months follow-up. Percentage reduction compared to the baseline is indicated. SPG: sphenopalatine ganglion, f/u: follow-up.

Acute response to SPG stimulation was found in a lower proportion. Excluding the four cases of complete absence of cluster attacks, when no acute response could be evaluated, three patients (23.0%) reported a pain relief of at least 50% after SPG stimulation (Table 7). 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) in the visual analog scale. Overall, 11 patients (84.6%) benefited from SPG stimulation, being eight (61.5%) frequency

responders, one (7.7%) acute responder and two (15.4%) frequency and acute responders.

Table 7. Cluster attacks intensity after SPG stimulation.

Patient number	Baseline intensity	3 months f/u	6 months f/u	12 months f/u
1	9	6 (-33%)	5 (-44%)	Not evaluable
2	5	Not evaluable	Not evaluable	Not evaluable
3	8	7 (-12.5%)	4 (-50%)	3 (-62,5%)
4	8	5 (-37.5%)	5 (-37.5%)	5 (-37.5%)
5	8	Not evaluable	Not evaluable	Not evaluable
6	10	9 (-10%)	8 (-20%)	
7	8	7 (-12.5%)	7 (-12.5%)	
8	9	Not evaluable	Not evaluable	
9	7	7 (0%)	7 (0%)	
10	10	7 (-30%)	6 (-40%)	
11	10	5 (-50%)	3 (-70%)	
12	10	8 (-20%)	8 (-20%)	
13	10	5 (-50%)	4 (-60%)	

Table 7: Average pain intensity (VAS) 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. SPG: sphenopalatine ganglion, f/u: follow-up, VAS: visual analog scale.

3.4 Stimulation parameters

Patients submitted to SPG stimulation had their stimulation parameters from their last follow-up indicated in Table 8. Most patients (84.6%) need only the first three electrodes of the lead activated. Signal frequency, pulse width and current amplitude vary with tolerance. Except in patient 9, that required an

extensive reprogramming due to stimulation-dependent nausea, stimulation frequency was 120 Hz, as described in Pathway CH-1 (Schoenen et al., 2013).

Table 8. SPG stimulation parameters in the last follow-up.

Patient number	Anode	Cathode	Frequency	Pulse width	Maximum Amplitude
1	E1	E3	120 Hz	434 μs	1.6 mA
2	E1	E3	120 Hz	402 μs	1.6 mA
3	E5	E4	120 Hz	355 μs	2.0 mA
4	E1	E3	120 Hz	402 μs	2.0 mA
5	E2	E1	120 Hz	402 μs	1.3 mA
6	E5	E1	120 Hz	355 μs	2.0 mA
7	E3	E1	120 Hz	450 μs	2.6 mA
8	E3	E1 and E2	120 Hz	355 μs	2.0 mA
9	E2	E1	80 Hz	118 μs	1.8 mA
10	E2	E3	120 Hz	402 μs	2.0 mA
11	E1	E2 and E3	120 Hz	197 μs	2.0 mA
12	E1 and E2	E3	120 Hz	308 μs	1.5 mA
13	E2 and E3	E1	120 Hz	339 μs	2.5 mA

Table 8: The first two columns indicate the electrodes used as anode and cathode from E1-E6, the remaining electrodes are OFF. Signal frequency given in hertz, pulse width per phase in microseconds and maximum current amplitude in milliamperes. SPG: sphenopalatine ganglion.

3.5 Occipital nerve stimulation

The mean follow-up in the ONS group was 8 months. The frequency reduction achieved an average of 53.1% (SD 63.6) for all patients, from a baseline of 34.7 attacks per week to 14.1 (SD 24.5) in the last follow-up (Table 9). A frequency response was found in 66.7% of the patients, and among responders the frequency reduction was of 91.7% (SD 6.9) from a baseline of

40.8 (SD 23.0) to 4.2 (SD 4.1) attacks per week. Two patients had complete absence of cluster attacks after implantation.

Table 9. Cluster attacks frequency after ONS.

Patient number	Baseline frequency	3 months f/u	6 months f/u	12 months f/u
1	21	21 (0%)	21 (0%)	21 (0%)
2	24.5	5 (-79.6%)	2 (-91.8%)	2 (-91.8%)
3	38.5	10 (-74%)	6 (-84.4%)	
4	42	0 (-100%)	0 (-100%)	0 (-100%)
5	52.5	10.5 (-80%)	7 (-86.7%)	
6	77	0 (-100%)	10 (-87%)	
7	42	42 (0%)	77 (+83.3%)	
8	10.5	0 (-100%)	0 (-100%)	
9	4.5	2 (-55.6%)	4 (-11.1%)	

Table 9: Pain frequency given in cluster attacks per week at the baseline and after 3, 6 and 12 months follow-up. Percentage change compared to the baseline is indicated. ONS: occipital nerve stimulation, f/u: follow-up.

Excluded the two patients without postoperative cluster attacks, when intensity could not be evaluated, intensity reduction of at least 50% in headache crises was only achieved in one case (11.1%) (Table 10). From a baseline intensity of 9.1 (SD 1.3) to 6.4 (SD 2.2), intensity reduction corresponded to 29.2% (SD 22.6). Overall, six patients (66.7%) benefited from ONS, being five frequency responders (55.6%) and one frequency and intensity responder (11.1%). Figure 16 illustrates lead placement in an ONS case.

Table 10. Cluster attacks intensity after ONS.

Patient number	Baseline intensity	3 months f/u	6 months f/u	12 months f/u
1	9	9 (0%)	9 (0%)	9 (0%)
2	8.5	6 (-31.2%)	5 (-41.2%)	5 (-41.2%)

3	10	3 (-70%)	4 (-60%)	
4	10	Not evaluable	Not evaluable	Not evaluable
5	10	7 (-30%)	6 (-40%)	
6	10	Not evaluable	6 (-40%)	
7	10	10 (0%)	10 (0%)	
8	10	Not evaluable	Not evaluable	
9	6.5	5 (-23.1%)	5 (-23.1%)	

Table 10: Average pain intensity (VAS) after ONS 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 lead implantation were considered not evaluable. ONS: occipital nerve stimulation, f/u: follow-up, VAS: visual analog scale.

Figure 16. Final lead position after occipital nerve stimulation.

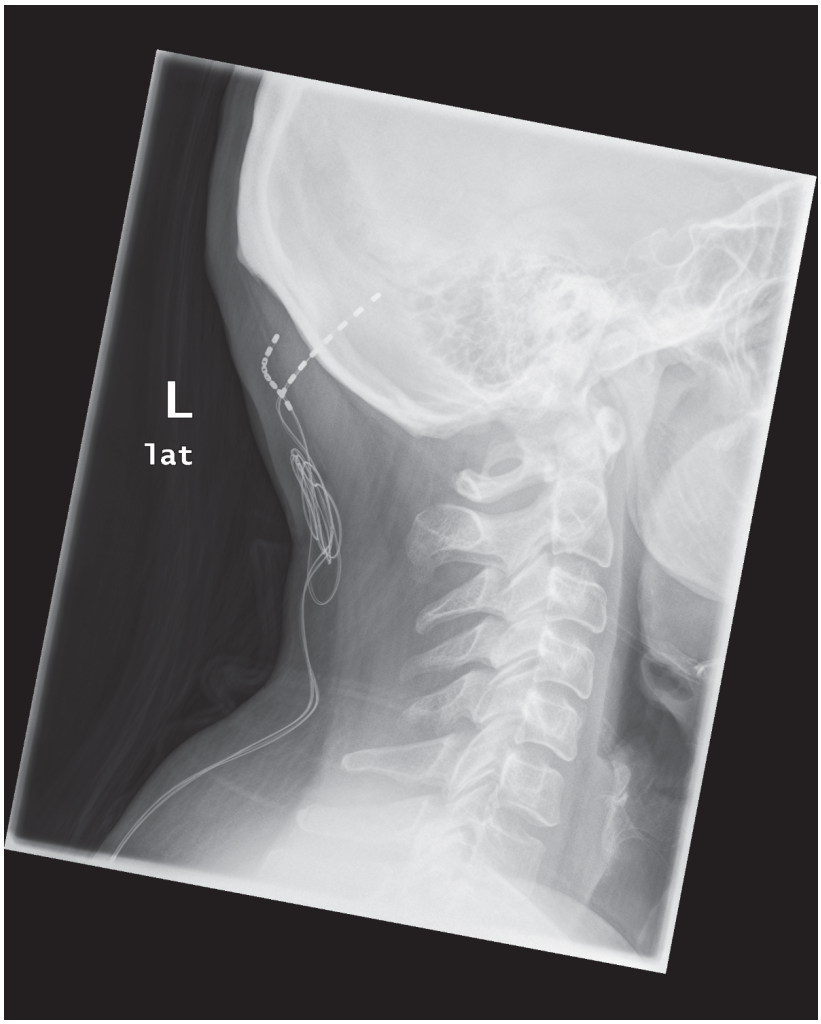

Fig. 16: Lateral X-ray of skull and cervical spine with a view of lead position after occipital nerve stimulation for cluster headache.

3.6 Adverse events

Across all SPG patients, no permanent device- or procedure-related adverse events occurred. There were no operative revisions, no explant procedures, no lead migrations. However, 69.2% of the patients reported some form of adverse event, most of them transitory. The most common event were localized sensory disturbances, mostly hypoesthesia in the face, palate and uvula, reported by seven patients (53.8%) and attributed to manipulation of the ganglion and its surrounding nerves. In all cases the sensory disturbance resolved in the first three months after the procedure, including the single cause of hypogeusia (7.7%). Patient 11, that had a lead implanted at the entrance of the pterygopalatine fossa, reported persistently paresthesia of the front teeth and of the front of the nose during stimulation. There was one case of swelling that needed treatment with corticoids (7.7%) and one case of trismus that was clinically observed and resolved within 2 months (7.7%). One single patient reported a persistent nausea associated to stimulation, refractory to reprogramming and treated with antiemetics.

In the ONS group, seven out of nine patients needed a second, eventually a third or even a fourth operation, not considered regular exchange of non-rechargeable implantable pulse generator. Device-related disorders, such as recharging problems with prolonged charging time or sudden battery failure, occurred in two patients and the implantable pulse generator was exchanged (22.2%). Lead migration was the case of a second procedure in two other patients (22.2%), one of them had later a lead breakage after a sudden movement of the head (11.1%). Two explant procedures were performed because of infection of the stimulation system (22.2%), in one case of the leads and in another one of the implantable pulse generator. There were two other explants because of inexistent pain relief after extensive reprogramming (22.2%). One operative revision due to deep implantation of the IPG was necessary (11.1%). A superficial wound dehiscence was present in one case (11.1%). In contrast to SPG stimulation, no immediate postoperative sensory disturbances were reported.

One case of stimulation-dependent lacrimation occurred and lasted for six months, until appropriate stimulation parameters were found (11.1%).

4 Discussion

4.1 Results of a young therapy

In this study, 84.6% of the thirteen patients benefited from SPG stimulation, a comparably higher rate than the 68% achieved in the landmark study Pathway CH-1 (Schoenen et al., 2013). This success rate was based mostly on frequency response, which was the case of 61.5% of the operated patients – 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%. Final results are summarized in Table 11, that shows statistically significant reductions of attack frequency and intensity with SPG stimulation. Pathway CH-1 was a landmark clinical trial that compared full stimulation of the sphenopalatine ganglion with sub-perception and sham stimulation, the main goal was to prove the effect of SPG stimulation over cluster attacks and not to prospectively follow their clinical course. A maximum of 30 cluster attacks for a maximum of eight weeks were analyzed for each patient in the phase of full stimulation, a mean of 6.8 studied attacks per patient was achieved. The reported data comprise a maximum of two months of follow-up and may not fully represent the long-term effect of repeated SPG stimulations over attack frequency. Results regarding acute response were similar, but it is noteworthy that the definition of acute response is broader in the present study than in Pathway CH-1. Comparable to Pathway CH-1 but considerably larger, Pathway CH-2 is the largest clinical trial underway currently, includes 22 clinical study centers, estimates an enrollment of 120 participants and its results are expected to lead to FDA approval in the United States.

Table 11. Clinical outcomes after SPG stimulation and ONS.

SPG group (n = 13 patients)						
	Baseline		Last Follow-up			
	Mean	SD	Mean	SD	Reduction	p value
Attack frequency (per week)	23.9	18.5	8.0	12.8	67.8%	0.001
Attack intensity (VAS)	8.6	1.5	5.7	2.0	35.8%	0.003
ONS group (n = 9 patients)						
Attack frequency (per week)	34.7	22.5	14.1	24.5	53.1%	0.076
Attack intensity (VAS)	9.2	1.3	6.4	2.2	29.2%	0.019

Table 11: Measures of clinical outcome after SPG stimulation and ONS at the baseline and at the last follow-up. Percentage reduction compared to the baseline is indicated. Patients who did not have any cluster attack after the procedure were considered not evaluable and therefore not included in the mean reduction. SPG: sphenopalatine ganglion, ONS: occipital nerve stimulation, SD: standard deviation, VAS: visual analog scale.

Barloese et al. were responsible for a big cohort of patients submitted to SPG stimulation in ten different centers from three European countries. Clinical data from an impressive group of 97 patients indicated again 68% of responders (Barloese et al., 2018), probably a golden number in terms of SPG stimulation. A total of 55% of the patients were frequency responders in this prospective study that lasted for 12 months. Despite the discrepancy in the overall success rates, probably due to the reduced patient number of this single-center study, proportions of frequency and acute response (32%) were comparable with the results of the present study. 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 (Jürgens et al., 2017).

The mechanism of frequency response remains unclear. SPG stimulation was initially developed with a view to the acute treatment of cluster attacks, short stimulations of a peripheral autonomic ganglion were not supposed to interfere with a 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 parasympathetico-trigeminal feedback, that could silence pain triggers similar to the effect of occipital nerve stimulation over the trigeminocervical complex, was also discussed (Schoenen et al., 2013). This second possibility could explain the similar success rates between SPG stimulation and ONS. Although the exact mechanism is still not clear, indication for a prophylactic SPG stimulation is normally given in patients that do not perform satisfactorily well only with on-demand stimulation.

Success rates achieved by SPG stimulation are similar to those reported for ablative procedures, namely for pulsed radiofrequency or radiofrequency ablation of the sphenopalatine ganglion. These techniques are easily available and are an important alternative to SPG stimulation in the countries where this newer therapy in still under consideration. Salgado-López et al. published recently the results of a long cohort of refractory cluster headache patients treated with either radiofrequency ablation or pulsed radiofrequency. A total of 37 patients were followed for a mean of 5.7 years, 13.5% reported complete pain relief, 56.8% experienced partial or transient relief and 29.7% did not improve. The overall improvement rate was 70.8%. No radiofrequency modality was superior to the other and for both of them there was a significant decrease of efficacy in the long-term follow-up (Salgado-López et al., 2019). The same effect observed by Narouze et al., who studied 15 patients submitted to radiofrequency ablation and reported a constant increase in attack intensity and frequency until the 18-month follow-up, the last evaluated by his group. Mean attack intensity at the last follow-up was 61.5% higher compared to the first month after the procedure, attack frequency increased 53.7% in the same period of time and surpassed the half of baseline attack frequency (Narouze et al., 2009) – parameter of the present study for frequency response. Radiofrequency lesioning

of the sphenopalatine ganglion is a safe technique that can be performed fast and its results in the short-term are comparable to those achieved by SPG stimulation, but the constant decrease in clinical efficacy favors the second. Compared to stimulation, radiofrequency lesioning is considerably cheaper, but a consistent study conducted by Pietzsch et al. showed that the more expensive SPG stimulation led to annual drug cost savings of €7,484, mostly due to acute medications (Pietzsch et al., 2018). It is known that there are no studies involving SPG stimulation with a follow-up time comparable to articles on radiofrequency lesioning, but if future studies confirm a sustained response to SPG stimulation without the need for second procedures, financial benefits may overcome the current price of an SPG stimulation device and surpass the advantages of radiofrequency lesioning.

As an interesting and costly alternative to neuromodulation techniques, antibodies against CGRT were already approved by the FDA for migraine and are being tested for the preventive treatment of chronic and episodic cluster headache. Fremanezumab targets CGRT and inhibits its potent vasodilatation. The clinical trial involving chronic cluster headache was discontinued for futility as reported by the company, its effects in episodic cluster headache are however still being tested. Galcanezumab achieved positive results in episodic cluster headache, 71% of the individuals had a significant frequency response vs. 53% in the placebo group, and the overall frequency reduction was 48.9% after 3 weeks vs. 30% in the placebo group ($p = 0.04$) in a trial with 106 patients (Goadsby et al., 2019). The company reported for galcenezumab also negative results in chronic cluster headache, which is the main indication for sphenopalatine ganglion stimulation. Immunomodulation of neural circuits is still a promising field and, in the particular case of cluster headache, expectations surround the development of monoclonal antibodies against PACAP, another important neurotransmitter involved in migraine and cluster headache (Waschek et al., 2018).

4.2 Consequences for the implantation technique

Parameters describing the lead position were confronted with clinical outcomes. The belief that the placement of at least two electrodes between vidian canal and foramen rotundum is associated with better clinical outcomes did not find significant statistical support. Out of eleven responders, six had one electrode or no electrode at all in the desired position, a chi-squared test found no significant association ($p = 0.91$). Curiously, the single patient with no electrodes between vidian canal and 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 as well. 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).

The minimal distance from one electrode to the vidian canal also could not predict better postoperative outcomes, Student's t-test ruled out a significant association ($p = 0.91$). 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, also in this case no more cluster attacks were documented after SPG stimulation.

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 penetrating lesion 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 result 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 supplied by the alveolar or external nasal branches, nerves normally located superolateral to the sphenopalatine ganglion 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 clear acute and frequency responses to the stimulation. 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.

It is noteworthy that in all 13 cases the closest electrode to the vidian canal was in the stimulation area, be it as cathode, anode or between them. In 38.5% of the patients, the closest electrode to the foramen rotundum was not in the area of most intense stimulation, what indicates that the best target for lead placement lies next to the vidian canal. 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 sphenopalatine ganglion itself. MRI imaging could properly address this issue and this possibility was studied by a group coordinated by Dr. Jakobs and Dr. Ahmadi, who found out 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 (Jakobs et al., 2018). The definition of a specific target in a three-dimensional space with the methods of the present study would require a significantly larger study population. One other possibility could be the evaluation of patients that already had a preoperative MRI and that had an

intraoperative or postoperative CT with the implant, in this case image fusion could precisely indicate lead position with reference to the sphenopalatine ganglion. Unfortunately, no patient in this study had a preoperative MRI.

The results were unable to show any correlation between clinical outcomes and lead position, which raises an inevitable discussion about implantation techniques. Patients in this study had a preoperative CT that allowed an anatomic evaluation of the pterygopalatine fossa and an estimation of the microstimulator length and was reference for the preoperative planning, later presented in X-ray-like and in three-dimensional models. The leads were implanted under fluoroscopy and in cooperation with an experienced otolaryngologist, an intraoperative CT was routinely performed. It is known that an intra- or postoperative CT does not belong to the standards of many neurosurgical and non-neurosurgical departments, others perform the implantation with intraoperative navigation and some neurosurgical centers do not recruit other medical specialties for the procedure. Although it is a pacific point, a first important consideration should highlight the relevance of the preoperative CT. Epidemiologic data of secondary cluster headache are relatively poor, but cases of post-traumatic cluster headache are not uncommon in specialized ambulant units. Cases of cluster headache secondary to sphenoid sinus mucocele (Branco et al., 2018) and to sphenoid ridge meningioma surgery (Kou et al., 2019) were reported, special attention should be payed particularly to post-traumatic cluster headache. These conditions are associated with intense fibrosis in the operative site, which poses big difficulty to the surgeon and is a contraindication for the procedure.

When it comes to the implantation technique, Kohlmeier et al. gave a precious 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) (Kohlmeier et al., 2017). Although intraoperative navigation can significantly optimize lead position, the findings of the present study do not give any predictive value to the distance from the lead to the preoperative planning, which is however very helpful during the procedure. 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.

As electrode position in the pterygopalatine fossa is not determinant to clinical outcomes, 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 23.1% of the patients of this study needing a repeated intraoperative CT, benefit from high-definition intraoperative imaging. Lead position could be successfully corrected in 66.7% of the 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 9.4% in the most studies (Barloese et al., 2018; Schoenen et al., 2013). An intraoperative CT should be done after the placement of a first bone screw to fixate the microstimulator, anchoring may cause a lead migration that otherwise would not be detected. Although minor deviations from the optimal position can be compensated with reprogramming, the operation for lead implantation is normally the only moment when a repositioning can be done without major inconveniences. Efforts should be done to achieve optimal lead position and an intraoperative CT plays an essential role, which however still does not substitute the final electrode impedance testing. Although this study has not addressed the effect of a multidisciplinary team during the procedure, the presence of experienced

otolaryngologists or oral and maxillofacial surgeons during the surgical approach in their areas of expertise is salutary.

4.3 Occipital nerve stimulation

Patients enrolled in the present study achieved a mean frequency reduction of 53.1%, being 66.7% of the patients frequency responders. Similarly as obtained for the SPG group, patients submitted to occipital nerve stimulation had a less expressive intensity reduction, in this case of 29.2%. Only one patient (14.3%) out of seven evaluable cases had a significant intensity response. Table 11 summarizes the final results and shows a significant intensity reduction without a significant frequency reduction. This particular result is mostly due to Patient 7, who exceptionally had an increase of cluster attacks with stimulation. The increase of attacks frequency happened gradually until the sixth postoperative month and was accompanied by severe paresthesia on the right side. Reprogramming alleviated the severity of the paresthesia, but no effect over the attack frequency was observed. The stimulation system was later explanted and, not considering this particular case, the ONS led to a significant decrease in pain frequency ($p = 0.013$).

The results of the present study were comparable to most cohorts in the literature. A large cohort of 44 patients conducted in France by Fontaine et al. obtained a mean decrease of attack frequency of 50.2% one year after the procedure, 59% of the patients had a frequency reduction of at least 50% (Fontaine et al., 2017). The findings of this work also showed a dramatic improvement in health-related quality of life in responders. Leone et al. found 66.6% of frequency responders in a cohort of 35 patients after a mean follow-up of 6.1 years, mean frequency reduction for all patients was 57.9% (Leone et al., 2017). In a last cohort by Miller et al., 32 subjects with chronic cluster headache alone were evaluated for a mean of 3.5 years, there were 53.1% of responders and the reported mean frequency reduction was of 49.5% across all patients,

significant improvements were also observed in pain intensity (25.0%) and duration (43.2%) (Miller et al., 2017).

The present study observed higher frequency responses in patients submitted to sphenopalatine ganglion stimulation. The SPG group had a similar proportion of frequency responders (69.2% vs. 66.7%) and a higher mean frequency reduction considering all patients, but this difference was not statistically significant (67.8% vs. 53.1%, p = 0.49). Intensity response was achieved in 35.8% of the patients of the SPG group, only one patient submitted to occipital nerve stimulation reported significant intensity decrease (14.3%). Mean intensity reduction was slightly higher with sphenopalatine ganglion stimulation, but no statistical significance was achieved (35.8% vs. 29.2%, p = 0.59). The slight superior mean frequency reduction in the SPG group may point to an eventual superiority of sphenopalatine ganglion stimulation, that however could not be demonstrated with the present number of subjects. Comparisons between SPG stimulation and ONS have not been reported in the literature yet, but there is a belief that treatments targeting the sphenopalatine ganglion could be superior because of the pathophysiological mechanism of cluster headache. Whereas occipital nerve stimulation acts over the trigeminocervical complex, that activates parasympathetic fibers to cause a cluster attack, sphenopalatine ganglion stimulation targets the parasympathetic output directly. Both being peripheral nerve stimulation techniques, it seems intuitive that the therapy that most directly addresses the pain should be more efficient.

Although no significant differences in the clinical outcomes could be demonstrated, patients of the ONS group did have considerably more complications than patients of the SPG group. Patients submitted to sphenopalatine ganglion stimulation reported mostly transitory side effects, which are explained by the manipulation of the maxillary nerve and its branches and required in most cases no treatment or just a reprogramming. As already reported, in the ONS group, seven out of nine patients needed a second, eventually a third or even a fourth operation. Device-related disturbs, lead migration, infection and absent pain relief were the main causes that triggered surgical revision or even explantation of the stimulation system. Fontaine et al.

reported the need for an additional surgery in 26% of the patients (Fontaine et al., 2017), Leoni et al. described 11 adverse events excluding expected battery depletions in 10 out of 35 patients (28.6%) and in all cases an intervention was necessary (Leone et al., 2017). In the cohort of Miller et al. there were 19 adverse events requiring surgery in a total of 35 patients, again excluding expected battery depletion (Miller et al., 2017).

Studies involving sphenopalatine ganglion stimulation normally report less adverse effects requiring surgical intervention. In Pathway CH-1, that did not foresee a CT but an X-ray for verification of lead position, 9.4% of the patients needed a lead revision due to misplacement during the original implantation, lead migration was reported in 6.3% of the cases and an infection occurred in other 6.3% (Schoenen et al., 2013). The infection cases did not require a second surgery. Barloese et al. reported 9.4% of lead revision due to suboptimal placement during the implantation and no other surgical complications, 73% of the patients experienced self-limiting mild to moderate adverse events like sensory disturbances and swelling (Barloese et al., 2018). It seems that sphenopalatine ganglion stimulation is less complication-prone and that an intraoperative CT scan could avoid the few cases of correction of lead position in a second surgery.

4.4 Strengths and limitations

As a limitation of this study we indicate the absence of systematic information about the area of paresthesia reported by the patients during the programming. It is known that typical positions of the contacts are associated with paresthesia in different regions of the face. Sensory disturbances reported in the posterior nasopharynx and in the back of the nose, innervated by palatine and greater palatine nerves, normally indicate an anterior or lateral caudal lead position. The front teeth and the front of the nose, area supplied by alveolar or external nasal branches, are affected when the lead is superolateral to the SPG. Finally, stimulation of SPG efferent posterior lateral nasal nerves leads to

paresthesia in the root of the nose and are indicative of correct lead placement. Identification of these areas when programming stimulation allows a physiological localization of the lead using SPG connections as a reference and could give precious information.

The number of study subjects may be considered a strength when considered that the present study was developed in a single center. Refractory cluster headache is rare entity and the few patients are seldom referred for sphenopalatine ganglion stimulation because it is a new and not well-known therapy, although scientifically very well established. Most studies discussed are multicentric and involve many European countries, however the number of subjects remains in two digits and each participant center hardly achieves ten patients.

Fortunately, a noncompliance was the case in only one patient due to professional reasons and, as that occurred after 12 months of follow-up, there was no interference with the study results. In this case, the patient had almost complete loss of the effects of stimulation over attack frequency and returned to the baseline. After reutilization of the stimulation, the patient described the same clinical effect observed before. Many patients treated in this center come from different states, so that a loss of follow-up restricted evaluation of SPG stimulation in an even longer period of time. Data regarding use of pain medication were also not disposable, as it could have been possible in a prospective study.

4.5 Conclusions

There was no correlation between electrode position in the pterygopalatine fossa with clinical outcomes following sphenopalatine ganglion stimulation. Preoperative planning is therefore helpful but not determinant for the clinical results. When programming stimulation parameters, the contact most closely related to the vidian canal should be in the stimulation area. In this study, clinical outcomes of occipital nerve stimulation were similar to those of patients treated

with Pulsante™ SPG Microstimulator System, but the complications rate was comparably higher.

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