



Neurostimulation for Cluster Headaches of the Sphenopalatine Ganglion (SPG)-Literature Review

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ABSTRACT

The current literature of the Sphenopalatine Ganglion (SPG) neurostimulation for cluster headache or other trigeminal autonomic cephalalgia is reviewed in this narrative paper. The authors published their experience with surgical transnasal approach with SPG ganglion as a target. SPG is a target in interventional pain medicine for headaches and orofacial pain and several approaches have been described. Cluster headache is a primary headache disorder, and it is classified as a Trigeminal Autonomic Cephalalgia (TAC). It is strictly unilateral, characterized for short excruciating pain attacks with autonomic symptoms. It has a huge impact in patient quality of life and functionality. Patient treatment and relief are challenges for physicians. Poor quality of life and disability are part of life in chronic cluster headache. Small group of patients are non-responders to pharmacological treatment or experience bothersome side effects, and they might be candidates for SPG neurostimulation. Neurostimulation is an alternative for patients with refractory chronic headache and new approaches and techniques have been published recently. Key words used for research were sphenopalatine ganglion, cluster headache, headache, neurostimulation, migraine. Pub Med, Embase, Cochrane Central Register of the Controlled Trials (Central) databases and clinicaltrials.gov were reviewed for the studies. There is no Cochrane systematic review for sphenopalatine ganglion neurostimulation and 21 clinical trials in the last 10 years (Jan 2023-June 2023). Diagnosis and treatment of cluster headache, neurostimulation, sphenopalatine ganglion anatomy and pathophysiology were also reviewed to write this paper. Neurostimulation is not new, however more studies are needed in the field of headache. Cluster headache brings high disability and low quality of life to the patient. Ablative procedures allow short term relief and more disable side effects, such as paresthesia. New studies evaluating disability, quality of life, medications intake, number of attacks and with long term follow up are needed. New devices are emerging and should be studied for headaches, especially for chronic cluster headache. The evidence of neurostimulation for cluster headache treatment is still low and treatment should be personalized.

Keywords: Sphenopalatine ganglion; Neurostimulation; Cluster headache; High frequency; Palliative care

INTRODUCTION

Chronic Cluster headache is described by the International Classification of Headache Disorders-3 (ICHD-3) as a headache

occurring for one year or longer without remission, or with remission periods lasting less than 3 months. An episodic cluster headache is defined by Cluster headache attacks occurring in periods lasting from 7 days to one year, separated by pain-free

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periods lasting at least 3 months (ICHD-3) [1]. The role of SPG in the pathophysiology of cluster headache is well established, with nasal congestion, lacrimation, rhinorrhea, and redness of the eye. Approximately 10%-15% of the patients have chronic cluster headache [1]. SPG is placed in the Pterygopalatine Fossa (PPF) and it is the target in pain intervention for orofacial pain and headache, such as TAC, post-puncture headache, trigeminal neuralgia and post-herpetic neuralgia. SPG has parasympathetic and sympathetic fibers and connections with cervical and trigeminal structures [1-5].

It is responsible for the glandular innervation and vascular tone of the nasal cavities, paranasal sinuses, lacrimal and palatine salivary glands, in addition to the sensitivity of the nasal mucosa. The PPF is delimited by bone parameters: Posterior wall of the maxillary sinus (anterior), pterygoid process and greater wing of the sphenoid (posterior), greater wing of the sphenoid and inferior orbital fissure (superior), vertical plate of the palatine bone (medial) and pterygomaxillary fissure (laterally) that communicates the PPF with the Infratemporal Fossa (ITF). Its content consists of fatty tissue, as well as terminal arterial vascular branches of the maxillary artery, in an anterior position, and autonomic nerves, posteriorly. It receives, through the pterygoid foramen, fibers of the vidian nerve, medially, while the maxillary division of the trigeminal, V₂, reaches this region through the foramen rotundum, more laterally, and follows as the infraorbital nerve after issuing sensory branches that pass through the SPG [4-7].

We emphasize the vascular anatomy of the PPF. Vascular structures are normally located in an anterior position in relation to the neural structures in the PPF: Careful endoscopic dissection and coagulation of fatty tissue in the PPF, in order to skeletonize the arterial branches, must be performed before puncture, allowing optimal visualization and management of the electrode tip by the surgeon, in order to place it perfectly over the SPG. The maxillary artery, terminal branch of the external carotid artery, enters the PPF through the pterygomaxillary fissure after crossing the ITF. Distally, the maxillary artery divides in descending palatine artery and sphenopalatine artery, which in turn subdivides in posterior lateral nasal artery and posterior septal artery [5,6].

Anatomical variations, both in neural and vascular structures, are extremely frequent in this narrow fossa, so that endoscopy-assisted accesses are safer due to magnification and wide-angle effect of the optics. This guarantees the preservation of neurovascular structures during the procedure, as well as their direct manipulation, through cauterization or clipping for immediate hemostatic control in case of iatrogenic injury [5-7].

Wu et al., studied the relationship of SPG volume and cluster headache. SPG volume was greater measured by MRI in patients with cluster headache compared to controls and it was larger on the side of pain. The ganglion was measured manually by MRI [8,9].

LITERATURE REVIEW

Cluster headache

Cluster headache is a primary headache disorder, which is an excruciating, strictly one-sided pain syndrome, belonging to the Trigeminal Autonomic Cephalalgias (TACs), affecting up to 0.1% of the population. The clinical features are detailed in the International Classification Headache Disorder-3 (ICHD-3). The male-to-female ratio is approximately 2:1,5:1 [3,9-12].

Patients with cluster headache experience multiple attacks of relatively short-lasting severe headaches. The pain ramps up quite quickly once it starts and typically remains for 15-180 min when untreated up to 8 times a day [13-17].

The attacks are characterized by the severe, excruciating, unilateral pain typically in the supraorbital, retro-orbital, temporal regions and arising from deep within, mainly in the first division of the trigeminal nerve, with associated prominent unilateral cranial autonomic symptoms, which include lacrimation, eye redness, eye discomfort such as grittiness, ptosis, nasal congestion, rhinorrhea, aural fullness, throat swelling and flushing and a sense of agitation and restlessness during the attacks [9]. This is a useful feature that can help in distinguishing cluster headache from migraine, in which patients prefer to lie still. In addition, sympathetic impairment presenting as miosis, and partial Horner syndrome may occur [13]. There is a tendency for the attacks to occur at night and patients report a sleep association. When in bout, cluster headache attacks can be triggered by alcohol, food containing nitrates, nitroglycerin, and strong odors such as petroleum, paint, and nail varnish [17].

Cluster headache is subdivided into episodic and Chronic Cluster Headache (CCH). Patients with episodic cluster headache have 'bouts' that tend to last 6-12 weeks and often have a circannual pattern, with more attacks in the spring or autumn. Episodic cluster headache can shift to chronic cluster headache and vice versa. CCH patients have persistent attacks occurring for more than one year without remission, or a remission period lasting less than three months, without preventive medication. About 15%-20% of patients suffer from chronic cluster headache and 33% of patients with initial CCH may shift to the episodic pattern during the disorder [3,15,17].

Longitudinally, cluster headache tends to remit with age with less frequent attacks and more prolonged periods of remission in between attacks.

Neurostimulation

Although subject of controversy, many studies have been addressed the role of neurostimulation in cluster headache treatment. Essentially, the neurostimulation may be either noninvasive or invasive. In the first group, it is worth mentioning Transcranial Magnetic Stimulation (TMS), which may act as a preventive therapy for cluster episodes. Differently, the invasive therapies, such as peripheral nerve stimulation, Vagal Nerve Stimulation (VNS) and Deep Brain Stimulation (DBS) might work as a treatment for the crises themselves. Acting as peripheral nerve stimulation, the sphenopalatine ganglion stimulation is one of the main invasive therapies applied in refractory cases of cluster headache [18-22].

Animal studies demonstrate that Low-frequency stimulation (10Hz) causes changes in the blood-brain barrier with vasodilation and triggering cluster pain. That is, the treatment with neurostimulation must be of high frequency [23]. The first description of the treatment of unilateral facial pain due to inflammation of the nasal sinuses was described by Sluder in 1908. The term Sluder Neuralgia was coined. We now know that Sluder's neuralgia and cluster headache are different entities and are classified differently [1,24].

Destructive procedures provide temporary relief. Neurostimulation acts on neural pathways without causing permanent damage and can be considered adjustable and reversible. The first report of neurostimulation for SPG was described by Ibarra in 2007. An

electrode was implanted in the SPG to provide electrical stimulation at a frequency of 50Hz. The patient was pain free [1,19].

Ansarinia et al., demonstrated the benefits of SPG neurostimulation in 6 cluster patients. The electrodes were positioned using the infra-zygomatic approach. Complete pain resolution was achieved in 60% of patients and an improvement in pain intensity (>50%) in 22% of patients. Benefits were achieved after 1 to 3 min of stimulation. The most common efficient frequency was 50Hz [1,20].

Systematic review to assess the level of evidence for the use of blockade, radiofrequency and neurostimulation of the sphenopalatine ganglion was published by Narouze et al., This group wrote a systematic review, where 83 articles were selected, 60 about pain blockades, 15 on radiofrequency and 8 on neurostimulation of these works, higher levels of evidence were achieved in 23 studies, 19 of which were about blockades, 1 studied the benefits of radiofrequency and 3 studies investigated benefits of neurostimulation [21].

The strongest evidence of intervention techniques was observed in studies for cluster headache, but they were also applied for trigeminal neuralgia, migraine and analgesic reduction after endoscopic nasal surgery. SPG block (nine studies regarding cluster headache) the publications mentioned agents used in blocking: Cocaine, local anesthetic and local anesthetic with corticoid, with second one being the most common. Double-blind studies demonstrated the benefit of using SPG blockade with transnasal swab soaked in anesthetic solutions with cocaine, lidocaine, bupivacaine or mepivacaine, aborting cluster headache crisis induced by nitroglycerin. In summary, SPG block has moderate evidence in the treatment of cluster headache (degree of recommendation B). The evidence is only for acute conditions and cannot be extended to CCH. The addition of corticosteroids, to prolong the benefit, has weak evidence (degree of recommendation C) [22].

There are 3 SPG block approaches described-transnasal, transoral and infrazygomatic. In the transnasal approach, a cotton swab, the TX-360 device and nasal spray can be used. Several local anesthetics can be used, with xylocaine and bupivacaine being the most common. Other medications include cocaine, alcohol, phenol, dexamethasone, triamcinolone and epinephrine. The needle approach can be guided by radioscopy or CT. The described side effects are paresthesia and hypoesthesia of the maxilla and palate regions, in addition to bad taste and anesthesia of the hypopharynx. In needle techniques, hematoma may occur.

SPG Radio Frequency (RF) (9 studies for cluster) of the 9 studies, one is a prospective cohort and the other 8 are case reports (3 on pulsed RF and 5 on conventional RF). The prospective cohort (Narouze et al-1) analyzed 15 cases of chronic cluster with treatment by conventional ablative RF, using the infra-zygomatic access, with injection of 2% lidocaine 0.5 mL, followed by 2 lesions by conventional RF at 80 degrees per 60 sec each. After the ablation, 0.5 mL of 0.5% bupivacaine and 5 mg of triamcinolone were injected. The study demonstrated improvement in pain intensity, frequency, and disability for up to 18 months. Sandres et al., reported the largest case series in the treatment of chronic cluster by RF. There were 66 patients evaluated for 12 to 70 months. The study demonstrated complete remission in just over 60% of patients with episodic cluster, and 30% of patients with CCH. The main adverse events mentioned in the studies were: temporary paresthesia in the palate and cheek for up to 3 months, epistaxis and hematoma. The grade of recommendation for treating clusters

with RF is grade B [23,24].

The first case report on the use of RF for the treatment of Sluder's neuralgia was from 1987 by Salar et al., There are several published articles demonstrating the effectiveness of RF for the treatment of clusters, however the vast majority are case reports. RF tends to have a longer result in pain control than simple SPG blockade as demonstrated for 18 months and work by Narouze et al. Most RF lesioning approaches were infrazygomatic, with temperatures of 80 degrees (ablative) or 42 degrees (pulsed), although there are no studies comparing the two RF techniques. In the studies, the positioning of the cannula was confirmed with a sensory stimulus perceived at the base of the ipsilateral nose. Adverse events were hypoesthesia and paresthesia of the maxillary territories and palate lasting a few months and complete reversal, in addition to hematoma and epistaxis. SPG neurostimulation is a newer treatment and applied in chronic and refractory cases [25].

Low frequency stimulation of SPG in humans can provoke autonomic symptoms due the activation of parasympathetic flow. In contrast, high frequency stimulation blocks parasympathetic outflow, alleviating the symptoms. In a double-blind sham controlled cross-over study with SPG low frequency stimulation with 16 patients, authors could demonstrate that low frequency stimulation (20 Hz) induces higher sympathetic tone preceding cranial autonomic symptoms and cluster headache attack [26,27].

One randomized controlled trial with other 2 long follow-ups of the same trial, and 2 case reports/series were published by the same group. First, Schoenen et al., published a randomized controlled trial, the Pathway CH-I, to study efficacy and safety of acute electrical stimulation of the SPG. They evaluated 28 patients with refractory cluster headache that were implanted neurostimulation devices, with 3 stimulation modalities by demand: Full stimulation, subperceptive and sham. A total of 566 cluster attacks were treated and complete relief was achieved in 67.1% of patients receiving full stimulation compared to 7.4% of sham group. The sub-perceptive stimulation group was not much different from the sham group. Rescue medication was used more often in the sham group (77.4%) and sub-perceptive group (78.4%) compared to the full stimulation group (31%). Furthermore, quality of life and headache disability improved with clinically significant difference, measured with Headache Impact Test (HIT-6) score and Short Form Health Survey (SF-36v2). The CH-I trial had incidence of adverse events like those reported in other oro-facial surgical procedures and the most common adverse event reported was transient paraesthesia in the maxillary territory (up to 3 months) [23].

Jurgens et al., published a series of cases followed by patients in Schoenen's work and showed 61% of patients with response in pain intensity improvement (>50%) and pain frequency improvement (>50%) in 24 months. The degree of recommendation for the treatment of chronic cluster with neurostimulation is B [24].

Barloese et al., enrolled 33 patients with chronic cluster headache refractory to conventional treatment. In this study, patients were followed for 24 months. Patients underwent to a transoral insertion of a micro-stimulator placed near to the SPG. 30% of these patients (10 patients) presented at least one month relief, one or more periods of relief. This study could show that stimulation can be abortive treatment during the cluster headache attack, to be preventive and induce a long-period remission in 30% of patients with CCH [27].

Goadsby et al., randomized 93 patients for a sham-controlled

double-blind trial. One group with 45 patients was assigned for SPG neurostimulation and 48 patients were assigned for control group. The SPG stimulation group had significantly pain relief after 15 minutes of stimulation during an acute attack. The number of responders in the clinical group was greater for relief of pain at 15 minutes, freedom of pain at 15 minutes and sustained pain relief after 50% or more of attacks compared to the control group [2].

Our group placed in a cadaver an epidural lead in the PPF. We divided this procedure into two approaches-transnasal endoscopic approach and cervico-facial approach. The dissection begins with a transnasal endoscopic approach using the reversible medial maxillectomy technique. After maxillary antrostomy, an oblique pre-lacrimal mucosal incision is made, continuing inferiorly to the inferior turbinate, up to the nasal floor. Then, the incision is extended posteriorly through the nasal floor to the inferior turbinate tail. Sub periosteal dissection is performed and, afterwards, a straight osteotome is used to fracture the maxilla along the already marked line. The medial wall of the maxilla is medially displaced, including the nasolacrimal duct and inferior turbinate. At the end of the entire procedure, the medial wall of the maxilla is repositioned, and the mucosal incisions are sutured with 3-0 Vycril sutures in two points. With total exposure of the posterior wall of the maxillary sinus, a new mucosal incision is made, with a pedicle in its most lateral region, allowing exposure of the bone wall. Osteotomies are performed and the bone wall is removed, exposing the periosteum of the posterior wall of the maxillary sinus. A careful incision of the periosteum is made with a sickle knife, thus exposing the fat and other contents of the pterygopalatine fossa. Fossa fat is retracted and partially removed, using bipolar cautery and blunt dissection, exposing the vascular branches, which must be dissected and preserved. A good tip for locating the ganglion is to follow the divisions of the vidian and maxillary nerves, after emerging through the pterygoid and round foramina, respectively. Next, the middle turbinate is dissected and a pedicled flap is created on the lateral wall of the nose (Figure 1) [28].

The cervico-facial approach begins with a skin incision: Retro

auricular arch, approximately 7 cm for detachment of the pocket under the muscle-periosteal flap, similar to the access described for the cochlear implant, in order to house the internal generating unit. This incision is extended inferiorly towards the mastoid tip, anteriorly to the sternocleidomastoid muscle, through which the passage of a trocar is made, in order to direct the electrode bundle into the fossa. At the end of the surgery, closure is performed by layers, suturing muscles with 3-0 Vycril and skin with 4-0 Nylon sutures. The trocar involved by a catheter enters the pterygopalatine fossa through its lateral communication with the infratemporal fossa, tangent to the lateral pterygoid lamina. Once inside the pterygopalatine fossa, under endoscopic visualization, the trocar is removed, maintaining the catheter position and the bundle of electrodes is introduced through it. Finally, the bundle is positioned anteriorly to the ganglion, avoiding gripping it. In the end, the ipsilateral middle concha flap is rotated from medial to lateral through the maxillectomy, in order to cover the electrode and the surgical defect of the posterior wall of the sinus. The mucosa of the posterior wall of the maxillary sinus that was previously reflected is used to cover the exposed bone, after rotation of the flap [28].

A transnasal endoscopy surgical approach is feasible for other lead models, allowing direct visualization to place the lead in the PPF and the vascular structures avoiding complications e mitigating possible migrations.

DISCUSSION

Cluster headache is certainly the most painful and incapacitating of primary headaches, particularly for patients who suffer from long bouts or for those who present with the chronic form. About 1% of patients become refractory to treatment. Defined as cluster headache that fails to respond to more than three typical preventive medicines. The condition is rare, but difficult to manage and invasive treatments may be needed. They are the main target population for extracranial implantable neuro-modulation devices, like occipital nerve or sphenopalatine ganglion stimulators (Figure 2) [29-32].

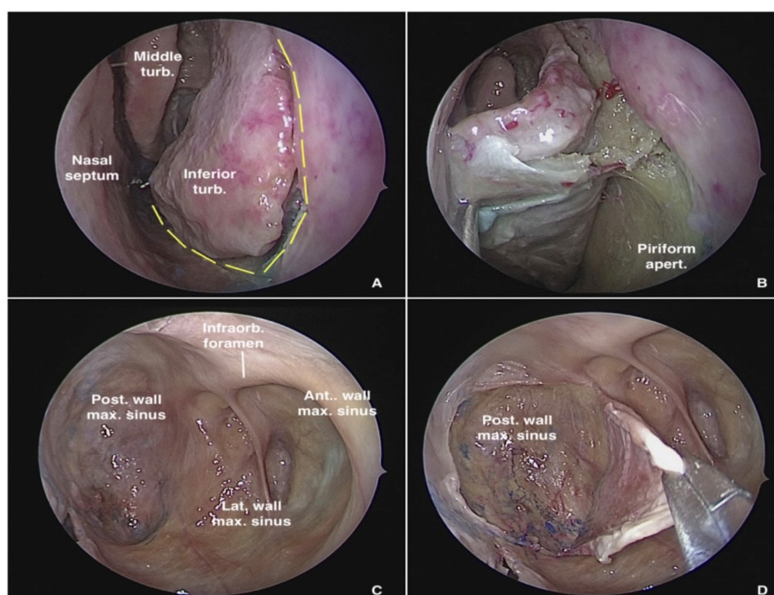


Figure 1: Transnasal approach to the left maxillary sinus a 00 endoscope. (A) Incisions on the lateral wall of the nose for medial displacement of the medial wall of the maxillary sinus. (B) Exposure of the piriform aperture and mucosal undermining before osteotomy. (C) Endoscopic control of all maxillary sinus walls. (D) Detachment of the mucosa from the posterior wall of the maxillary sinus for subsequent bone removal and access to the pterygopalatine fossa.

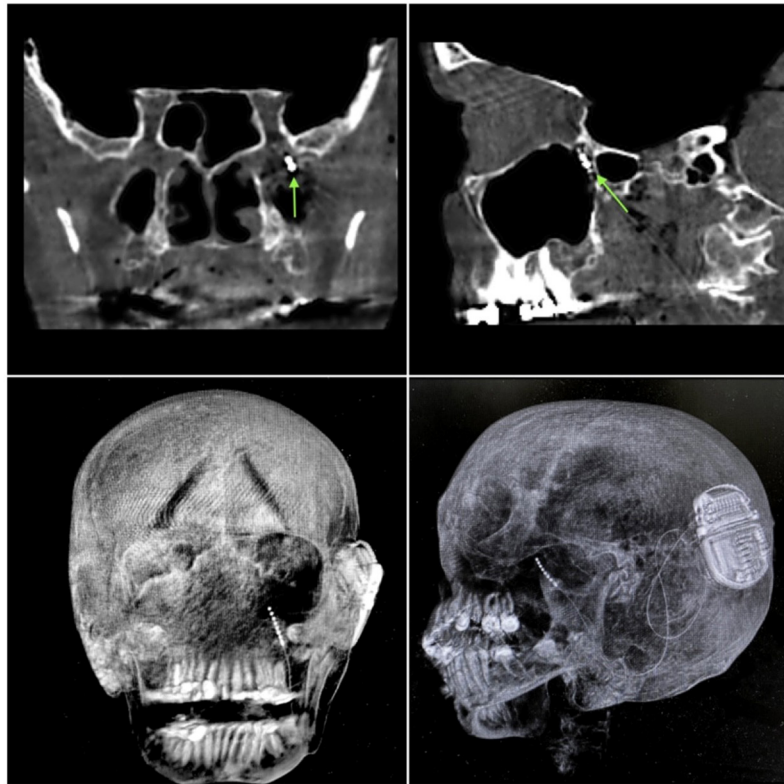


Figure 2: Control computed tomography obtained after neurostimulator implantation. (A and B) Bone window, coronal and sagittal sections respectively; green arrow represents the location of the electrode tip within the sphenopalatine ganglion. (C and D) Three-dimensional reconstruction, allowing visualization of the entire electrode path and location of the internal pulse generator.

SPG is a very complex structure with several connections, playing an important role in headaches pathophysiology, especially in cluster headache. Many interventional procedures have been performed targeting SPG for orofacial or headache pain relief. SPG trans mucosal nasal blocks or guided by image and radiofrequency have been performed to treat migraine, post-puncture headache, trigeminal neuralgia and cluster headache [1,2,19,23,24].

Neurostimulation is not new and few trials could demonstrate that is promising to offer pain relief during cluster headache attacks, prolongating pain free periods of chronic cluster headache and improving quality of life and patient satisfaction. In contrast to radiofrequency, that offer relief for short period of time, neurostimulation may be an alternative for years [2,23].

Pharmacological treatment of cluster headaches can be bothersome, with significant side effects. The brief duration of attacks and the number of them make abortive treatment a challenge. Preventive drugs side effects can limit the treatment. Drugs, such as sodium valproate, lithium carbonate, verapamil and topiramate are usually provided for these patients. However, many patients are always searching for new treatment options, because of the side effects or non-responsiveness to a standard treatment [1].

New devices without battery implant with remote control may be promising for these patients with CCH for attack abortion and to allow a long pain free period. High frequency neurostimulation induces less paresthesia compared to low frequency neurostimulation and ablation. Complications of these devices are lead migration, hematomas, infection and sensory disturbances and pain in area of maxillary nerve [1,23].

A device placed without surgery image guided with external battery was studied for knee pain, shoulder, cluneal nerves with significant pain relief and it can be promising for headaches. Peripheral nerve stimulation at SPG for cluster headache is evidence level III [33].

CONCLUSION

Neurostimulation surgery placed, or image guided, is a feasible and a low-risk treatment for patients with cluster headache. Acute attacks can be aborted with SPG stimulation and patients that suffer with CCH can have more pain free periods. High frequency stimulation is the most adequate option for these patients since low frequency may induce the attack.

Trials have a small number of patients, but could provide information about significant pain relief, quality of life improvement and reduction of disability. Number of complications is relatively low when these patients are followed up. However, the follow up of these studies is short, long-term benefit needs to be better evaluated.

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