Sphenopalatine ganglion stimulation for the treatment of cluster headache

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Abstract: Cluster headache is a severe, debilitating disorder with pain that ranks among the most severe known to humans. Patients with cluster headaches have few therapeutic options and further, 10–20% develop drug-resistant attacks. The often brief duration of cluster attacks makes abortive therapy a challenge, and preventive medications are almost always provided to patients, but the side effects of these preventive medications can be significant. The sphenopalatine ganglion (SPG) is believed to play a role in headache pain and cranial autonomic symptoms associated with cluster headache, which is a result of activation of the trigeminal-autonomic reflex. For over 100 years, the SPG has been a clinical target to treat primary headache disorders using pharmacologic and nonpharmacologic methods. Radiofrequency lesioning and nerve-resection therapies, while initially beneficial, are irreversible procedures, and the use of neurostimulation provides one method of interfacing with the neural pathways without causing permanent damage to neural tissue. SPG neurostimulation is both reversible and adjustable, and has recently been tested in both proof-of-concept work and in a randomized, sham-controlled trial for the treatment of cluster headache.
A randomized, sham-controlled study of 32 patients was performed to evaluate further the use of SPG stimulation for the acute treatment of chronic cluster headache. Of the 32 patients, 28 completed the randomized experimental period. Overall, 68% of patients experienced an acute response, a frequency response, or both. In this study the majority of adverse events were related to the implantation procedure, which typically resolved or remained mild in nature at 3 months following the implant procedure. This and other studies highlight the promise of using SPG stimulation to treat the pain-associated cluster headache. SPG stimulation could be a safe and effective option for chronic cluster headache.

Keywords: cluster headache, neurostimulation, sphenopalatine ganglion

Introduction

Cluster headache is a severe, debilitating disorder with pain that ranks among the most severe known to humans [Holland and Goadsby, 2009]. It is associated with accompanying autonomic symptoms ipsilateral to the pain including conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid or periorbital edema, forehead and facial sweating, miosis or ptosis, and a sense of restlessness or agitation. Cluster headaches can occur many times a day and typically last between 15 min and 3 h. Episodic cluster headache occurs in periods lasting 1 week to 1 year, separated by pain-free periods of 1 month or longer [International Headache Society, 2004]. Approximately 10–15% of patients suffering from cluster headache suffer from chronic cluster headache, with headaches occurring without remission or with remission lasting less than 1 month during a year.

Patients with cluster headaches have few therapeutic options and further, 10–20% develop drug-resistant attacks [May, 2005]. While subcutaneous triptan injections [Sumatriptan Cluster Headache Study Group, 1991; Gobel *et al.* 1998], and inhaled high-flow oxygen [Cohen *et al.* 2009], provide relief to some patients some of the time, many patients are severely affected and disabled. Sumatriptan is contraindicated in ischemic heart disease, uncontrolled hypertension, and peripheral vascular disease, may be associated with

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vascular events [Roberto *et al.* 2013], and is often limited to a maximum of twice-daily dosing. While oxygen-inhalation therapy (100%, 12 L/min for 15 min *via* a face mask) can be effective [Cohen *et al.* 2009], it may be associated with recurrence [Geerlings *et al.* 2011], and it has significant practical limitations due to the size and cumbersomeness of the required oxygen tanks.

The socio-economic burden of cluster headache on the individual and society is quite high due to the direct costs of healthcare services, and the indirect costs of lost work days and decreased work efficacy. A Danish report showed that 43.5% of cluster patients had seen specialists, approximately 30% had missed work, and 78% reported restrictions in daily living [Jensen and Stovner, 2008]. A recent German study showed that a single chronic cluster-headache patient could cost the healthcare system over €21,000 per year [Gaul *et al.* 2011].

The often brief duration of cluster attacks makes abortive therapy a challenge, and preventive medications, such as verapamil, lithium carbonate, divalproex sodium (valproate), and topiramate among others, are almost always provided to patients. The side effects of these preventive medications can be significant, ranging from nausea and fatigue to hypotension, bradycardia, atrioventricular block, and myocardial infarction, and may be better tolerated when used for cluster headache than other headache types [Lainez *et al.* 2003]. None of these preventive medications are approved by the US Food and Drug Administration for the treatment of cluster headache. Given the relentless nature of their disorder, cluster patients continue to search for new, less invasive therapies to treat their headaches [Beck *et al.* 2005].

Targeting the sphenopalatine ganglion for cluster headache

For over 100 years, the sphenopalatine ganglion (SPG) has been a therapeutic target to treat primary headache disorders [Sluder, 1908]. Since Sluder first described the application of cocaine or alcohol to the SPG for the treatment of headaches, the SPG has been the site for a variety of clinical interventions for the treatment of headaches due to the involvement of the SPG in the trigeminal-autonomic pain reflex associated with cluster headache [May and Goadsby, 1999]. Interventions include ganglionectomy [Meyer *et al.* 1970], percutaneous alcohol injection [Devoghel, 1981], lidocaine or corticosteroid application [Costa *et al.* 2000; Felisati *et al.* 2006; Maizels and Geiger, 1999; Maizels *et al.* 1996; Yang and Oraee, 2006; Morelli *et al.* 2010; Kudrow *et al.* 1995], cryosurgery [Cook, 1978], stereotactic radiosurgery [Lad *et al.* 2007; Effendi *et al.* 2011], radiofrequency (RF) lesioning [Narouze *et al.* 2009; Salar *et al.* 1987; Bayer *et al.* 2005; Shah and Racz, 2004; Sanders and Zuurmond, 1997], and more recently, neurostimulation [Tepper *et al.* 2009; Ibarra, 2007; Ansarinia *et al.* 2010; Schoenen *et al.* 2013].

Also referred to as the pterygopalatine ganglion, the SPG is a large extracranial parasympathetic ganglion with multiple neural roots, including autonomic, sensory, and motor [Lang, 1995]. Humans have two SPGs, located on each side of the mid face within the pterygopalatine fossa (PPF), which is a small inverted pyramidal space measuring approximately 2 cm high and 1 cm wide. Parasympathetic and sympathetic fibers are carried to the SPG *via* the vidian nerve, which is formed by the greater and deep petrosal nerves, respectively. Parasympathetic fibers synapse within the SPG, while sympathetic nerve fibers pass through the SPG. The maxillary division of the trigeminal nerve also sends neural projections (pterygopalatine nerves or ganglionic nerves) that pass through the SPG, and these nerves form the sensory component of the SPG [Norton, 2006]. Postganglionic parasympathetic fibers that arise within the SPG are distributed to the ophthalmic and maxillary divisions of the trigeminal nerve to the lacrimal gland, nasal glands, palatine glands, and pharyngeal glands. In addition, numerous postganglionic parasympathetic branches have been shown to course superior medially from the SPG into the orbital cavity, providing parasympathetic innervations to the meningeal and cerebral blood vessels [Larsson *et al.* 1976; Nozaki *et al.* 1993; Ruskell, 1970, 2003; Suzuki and Hardebo, 1993].

The SPG is believed to play a role in headache pain and cranial autonomic symptoms associated with cluster headache, which is a result of activation of the trigeminal-autonomic reflex. In cluster headache, postganglionic parasympathetic fibers from the SPG, which innervate the cerebral and meningeal blood vessels [Larsson *et al.* 1976; Nozaki *et al.* 1993; Ruskell, 1970, 2003; Suzuki and Hardebo, 1993], are activated and release neuropeptides that cause vessel dilation and/or activation of trigeminal nociceptor fibers in the meninges, which is perceived as referred pain

from the head by the sensory cortex [Goadsby, 2002; Goadsby *et al*. 2002; Moskowitz, 1990]. This neurogenic inflammation in the meninges has been observed during electrical stimulation of the trigeminal ganglion in the rat [Markowitz *et al.* 1987], presenting further evidence of the involvement of the SPG in these processes. These inputs also trigger a reflex connection between neurons in the pons, in the superior salivary nucleus, which results in an increase in cranial parasympathetic activity that is mediated through the SPG [Burstein and Jakubowski, 2005; Goadsby, 2002; Goadsby *et al.* 2002, 2009; May and Goadsby, 1999; Yarnitsky *et al*. 2003]. Neurogenic inflammation and the release of neuropeptides related to the activation of the trigeminovascular system and the cranial parasympathetic nervous system was first shown in humans in patients with cluster headaches [Goadsby and Edvinsson, 1994].

More recently, Akerman and colleagues described the mechanism of action of oxygen therapy for cluster headache by using facial nerve stimulation in rats and demonstrated that oxygen has no direct effect on trigeminal afferents, and instead acts specifically on the parasympathetic/facial nerve projections *via* the SPG to inhibit trigeminovascular and autonomic pathway activation [Akerman *et al*. 2009].

Owing to the role of the SPG in the manifestation of cranial autonomic symptoms, and in initiating and sustaining cluster headache pain, the SPG has been a target for preventive clinical treatment for headache pain. Local application of anesthetic agents has been attempted to control the pain of cluster attacks. In a study of alcohol injection through a percutaneous, suprazygomatic approach, pain relief was observed in 86% of cases (n = 120 patients), with follow up ranging from 6 months to 4 years [Devoghel, 1981]. In a study of 15 cluster patients, including both chronic and episodic sufferers, complete cessation of pain was achieved in all patients following intranasal application of cocaine (31 min) and lidocaine (37 min), compared with intranasal saline (59 min) [Costa *et al*. 2000]. In another study, anesthetics and steroids were applied locally over 2–4 weekly sessions in 20 chronic cluster patients, and 55% of patients achieved subsidence of symptoms or partial benefit [Felisati *et al.* 2006].

The SPG has also been targeted using nonpharmacologic methods. For example, RF lesioning of the SPG in 15 chronic cluster patients who had previously responded to SPG blocks resulted in decreased attack intensity and frequency at 18 months [Narouze *et al.* 2009]. Similarly, in 56 episodic and 10 chronic patients, complete pain relief was achieved in 61% and 30% of patients, respectively, and partial relief was achieved in 25% and 30% of patients, respectively [Sanders and Zuurmond, 1997]. Surgical removal of the SPG *via* ganglionectomy has also shown success at controlling cluster pain in a small number of patients. However, approximately half of the patients no longer received benefit at 6 months postganglionectomy [Meyer *et al.* 1970]. A large study of SPG cryosurgery in cluster and migraine patients also indicated > 50% improvement in more than half of the patients [Cook, 1978].

While, there is a long history of SPG interventions positively impacting cluster headache sufferers in a preventive manner, benefits are often transient and long-term relief requires that patients undergo repeated procedures.

SPG neurostimulation treatment for cluster headache

RF lesioning and nerve-resection therapies, while initially beneficial, are irreversible procedures, and the use of neurostimulation provides one method of interfacing with the neural pathways without causing permanent damage to neural tissue, and is considered both reversible and adjustable [Grill, 2005]. Recently, SPG stimulation for the treatment of cluster headache has been tested in both proof-of-concept work and in a randomized, sham-controlled trial for the treatment of cluster headache [Schoenen *et al.* 2013].

The first report of SPG stimulation for the treatment of cluster headaches was a case report published by Ibarra in 2007 [Ibarra, 2007). An implantable device was used to provide continuous SPG stimulation in a preventive manner to a 30-year-old male experiencing severe cluster pain with associated tearing, conjunctival injection, facial sweating, edema, ptosis, photophobia, phonophobia, and osmophobia. Prior pulsed RF ablation of the right SPG had been successful, though repeated ablations were required. However, RF ablation of the left SPG was unable to control the patient's left-sided pain. An electrode and pulse generator were implanted and programmed to deliver constant electrical stimulation to the SPG at a frequency of 50 Hz and a

pulse width of 247 μs. With these settings, the patient became pain free until an electrode failure occurred and resulted in a worsening of the patient's headaches. Following electrode replacement, chronic relief from the cluster attacks was again achieved. The unexpected hardware failure and temporally associated increase in headache symptoms provided an internal control that demonstrated the efficacy of chronic preventive SPG stimulation in this patient.

More recently, Ansarinia and colleagues demonstrated the acute benefits of SPG stimulation in six chronic cluster patients [Ansarinia *et al.* 2010]. Patients treated either spontaneous or triggered cluster attacks with SPG stimulation that was applied through an electrode placed using a standard infrazygomatic transcoronoid approach. Each patient was stimulated between zero and two times. About 61% of attacks achieved complete pain resolution and 22% of attacks achieved partial (> 50%) pain resolution within 1–3 min of initiation of stimulation. The most common frequency to achieve pain resolution was 50 Hz. Poor response appeared to be associated with the limitations of using an off-the-shelf stimulation system, including the inability to position the stimulating lead sufficiently close to the SPG.

A randomized, sham-controlled study of 32 patients was performed to evaluate further the use of SPG stimulation for the acute treatment of chronic cluster headache. In this study, the SPG neurostimulator (Autonomic Technologies Inc, Redwood City, CA, USA) was implanted through a minimally invasive gingival buccal incision. The neurostimulator contained an integral lead that was placed within the PPF proximate to the SPG. The body of the neurostimulator, which contained no battery, was placed along the maxilla and was powered on demand by the patients using an external hand-held remote controller. Patients were instructed to apply stimulation to moderate or severe cluster pain for up to 15 min. Mean stimulation frequency applied was 120 ± 15 Hz, mean pulse width was 390 ± 75 μs. Of the 32 patients, 28 completed the randomized experimental period. Pain relief was achieved in 67.1% of full stimulation-treated attacks at 15 min following the start of stimulation, compared with 7.4% of sham-treated attacks ($p < 0.0001$). A reduction in cluster attack frequency of at least 50% compared with baseline without any increase in preventive drugs was observed in 43% of patients, with the average cluster attack frequency reduction in these patients being 88%. Following the implant procedure, attack frequency remained unchanged through the start of stimulation, indicating that the frequency reduction was likely associated with the start of SPG stimulation. Overall, 68% of patients experienced an acute response (achieved pain relief in at least 50% of treated attacks), a frequency response (reduction in cluster attack frequency of at least 50% compared with baseline), or both. About 64% of patients experienced clinically significant improvement in headache disability and 75% experienced clinically significant improvements in the quality of life [Schoenen *et al.* 2013].

Overall, SPG stimulation has proven to be a safe and effective therapy option for cluster headache. In each of these studies, patients were tolerant of SPG stimulation and did not report any significant effects from the stimulation. In the randomized, sham-controlled study, the majority of adverse events were related to the implantation procedure, most often including localized reduction in or loss of sensation in distinct distributions of the maxillary nerve, which typically resolved or remained mild in nature at 3 months following the implant procedure [Schoenen *et al.* 2013].

Discussion and conclusion

The SPG is involved in the trigeminal-autonomic reflex associated with cluster headache pain. Further, numerous pharmacologic and surgical SPG interventions have been shown to relieve the pain and cranial autonomic symptoms associated with this disabling condition. More recently, SPG stimulation has been utilized as a reversible intervention that interrupts the trigeminal-autonomic reflex. Both acute and randomized studies have highlighted the promise of this therapy and suggest that SPG stimulation is a safe, effective option for cluster headache. With correct anatomical and physiologic placement of the stimulation lead, on-demand SPG stimulation can be used to relieve the acute pain associated with the cluster headache and may also be associated with a reduction in cluster headaches. Additionally, cranial autonomic systems, such as edema, lacrimation, and nasal congestion, can be resolved.

The next step is to confirm the results of SPG stimulation in long-term studies. In the future, SPG stimulation could be an alternative in patients with episodic forms of the disorder for which there is no response to preventive

treatments, and in patients with contraindications or poor tolerability to acute treatments.

SPG stimulation also may be a reasonable option to consider in other trigeminal-autonomic cephalalgias, including paroxysmal hemicranias, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms, and further studies in this direction may be necessary.

At the moment, a trial of SPG in frequent refractory migraine is in progress.

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